Mucocutaneous Manifestations of

VIRAL DISEASES

Second edition

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edited by

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Preface to the second edition

The skin is the window of the body. Many viral diseases express themselves through changes in skin appearance, skin lesions, edema, etc. Often the skin becomes a warning of internal manifestations signaling the physician to look beyond the window for other impacts. The contributors to the second edition of ***Mucocutaneous Manifestations of Viral Diseases*** interact on a regular basis with other dermatologists and virologists, or combinations thereof. The book is an outgrowth of those daily consultations and discussions with other colleagues in various fields of medicine. As family practitioners are increasingly being called upon to provide their diagnosis and treatment of a wider variety of illnesses (those previously referred to a specialist), a quick reference is needed. This book not only helps distinguish the cutaneous manifestations of one virus from another, but also helps differentiate viral diseases from other infectious and noninfectious diseases. It is intended for internists, dermatologists, pediatricians, and family practitioners worldwide.

The goal of this book is to enhance the expertise of physicians in the diagnosis, treatment and pathogenesis of viral diseases that express their presence in the skin and its affiliated mucous membranes. No other text currently addresses the issues of the skin manifestations of viral diseases. Photographs in other texts to aid diagnoses were previously black and white and of limited use to the physician. Many color atlases only encompass one or a few viral diseases, leaving the practioner with a desire for more detail and/or a better explanation of possible mimics of the diseases.

The contributing authors and editors have provided a text that serves as a central resource for each of the viral diseases described. It should be of interest to physicians worldwide as we have included many diseases previously known only in third world, developing countries. Given the global aspects of international transportation, social exchange and political boundaries, it is not only feasible that one or more of these rarer viral diseases could present itself at any physician's office in the world, many examples of this occurrence have been documented since the first edition of this book was published. Animal vectors and reservoirs are often immigrants on baggage or agricultural products. Each chapter includes, as appropriate, a timeline of infection and progress of the disease, numerous quality color illustrations of characteristic epidermal and cellular manifestations, a means to reference the differential diagnosis of viral diseases from other infectious or noninfectious diseases, a brief taxonomy and history of the disease, incidence among gender and age groups by geographical region, pathogenesis, clinical manifestations, dermatopathology, laboratory findings, differential diagnoses, and treatment/prophylaxis. To the extent possible, we have used tabular information for quick reference by the physician.

The second edition of ***Mucocutaneous Manifestations of Viral Diseases*** is unique in that it covers the field of viral diseases having mucocutaneous manifestations and offers the quality color photographs associated with an atlas. The book also serves as a bibliography for physicians wishing to broaden their knowledge of the primary literature. We envision the physician using the color photographs in considering the possible diagnoses. The differential diagnosis section helps the physicians narrow the search for the virus causing the epidermal insult. The text would then provide suggestions as to which laboratory tests might be useful to confirm the diagnosis. Finally, it outlines the appropriate treatment, including specific types of antiviral drugs and vaccines.

In summary, the editors hope that the second edition of ***Mucocutaneous Manifestations of Viral Diseases*** will fill a void in the medical literature and provide a valuable resource to a variety of practicing physicians worldwide.

Stephen K Tyring
Angela Yen Moore
Omar Lupi

1 Cutaneous Virology

Stephen K Tyring

Introduction

Viral diseases may produce mucocutaneous manifestations either as the result of viral replication in the epidermis or as a secondary effect of viral replication elsewhere in the body. Most primary epidermal viral replications result from three groups of viruses: human papillomaviruses (HPV), herpesviruses, and poxviruses. Secondary skin lesions are produced by such virus families as retroviruses, paramyxoviruses, togaviruses, parvoviruses, and picornaviruses. Rhabdoviruses, rotavirus, etc., rarely induce skin lesions and are beyond the scope of this book. The mucocutaneous manifestations of subviral agents, such as viroids and prions, are only beginning to be understood.

A number of cutaneous diseases appear to be viral exanthemas, but no virus has been proven to be the etiologic agent in some of these diseases. For example, pityriasis rosea (PR) is an acute, self-limiting, cutaneous eruption with a distinctive course. The initial lesion, the herald patch, is followed after 1–2 weeks by a generalized secondary rash, which typically lasts about 6 weeks (Fig. 1.1). Like most viral infections, PR shows seasonal variability, with an increased incidence in the autumn and winter and a decreased incidence in the summer. A preceding upper respiratory infection is often noted with PR, as are clusters of cases in time and space. Recently, PR was hypothesized to be due to infection with human herpesvirus 7, and most controlled studies have supported this hypothesis.

Likewise, asymmetric periflexural exanthem of childhood (APEC) or unilateral laterothoracic exanthem (ULE) is suspected to be of viral etiology. It presents in children, six months to five years of age, in the winter and spring. The rash is unilateral on the trunk, often in the axillae or large flexures of the limbs (Figs. 1.2 and 1.3). It spreads centrifugally and to the contralateral side over 2–4 weeks and resolves in 6 weeks. Initially, red, 3-mm papules appear, followed by a scarlatiniform or eczematous rash. There are no constitutional symptoms, but an enlarged lymph node is usually observed at the primary site. Viruses that are suspected, but not proven to be of etiologic significance, include parvovirus B-19, parainfluenza 2 or 3, and adenoviruses.

On the other hand, several new viral diseases, or viral diseases in new geographic areas have been described recently. These diseases include infections due to Lujo virus (an arenavirus), bocavirus (a parvovirus), bannavirus (a reovirus), TTV (a circovirus), Nipah virus and metapneumovirus (paramyxoviruses), and zika virus (a flavivirus). When cutaneous manifestations of such viruses are reported, the description in the general medical literature is rarely more specific than "rash" or "skin rash." More specific descriptions in the dermatology literature might aid in the more rapid diagnosis of these diseases.

Clinical Manifestations

Viral infections can result in a wide spectrum of skin lesions. HPV infection frequently results in verrucous papules, but the range of presentations includes erythematous macules in epidermodysplasia verruciformis, smooth papules in bowenoid papulosis, and fungating Buschke-Lowenstein tumors. The primary lesions in herpes simplex virus (HSV), varicella-zoster virus (VZV), and many coxsackievirus infections are vesicles. Erythema and papules often precede the vesicles, which are followed by pustules, crusts, or shallow ulcers. Cytomegalovirus (CMV) infections of the skin and mucous membranes, as well as HSV, VZV, or coxsackievirus infections of mucous membranes, can present as ulcers without other stages. Measles and rubella can be associated with both macules and papules. Epstein-Barr virus (EBV), human herpesvirus type 6 (HHV-6), and parvovirus B19 infections may result in macules that coalesce into larger erythematous patches. A spectrum of nonspecific skin lesions, such as erythema multiforme, urticaria, and petechiae, may be viral or nonviral in etiology. Mucocutaneous manifestations of viral diseases can range from very specific (e.g., dermatomal vesicles of herpes zoster) to very general (e.g., urticaria); thus, the differential diagnosis must take the total clinical presentation of the patient into consideration (Table 1.1). Some skin changes may be highly suggestive of a specific viral disease, such as the verrucous papules seen with papillomavirus infection or smooth umbilicated papules resulting from poxvirus infection. Often, further diagnostic tests may not be needed for these conditions. A differential diagnosis, including both viral and nonviral etiologies, may be suggested by vesicles induced by HSV-1 or -2 or VZV or they may be diagnostic. The diagnosis may not be obvious when any of these three viruses produce mucous membrane lesions and further diagnostic procedures may be required. Less frequent skin manifestations may be produced by other herpes viruses, such as EBV, CMV, and HHV-6. These infections are most accurately diagnosed only when the systemic manifestations of the viral infection are simultaneously considered. The cutaneous manifestations would indicate the need to evaluate systemic signs and symptoms and to institute appropriate diagnostic tests in other diseases where viral replication is not in the epidermis.

Pathophysiology

Three different routes are used by viruses to infect the skin: direct inoculation, local spread from an internal focus, or systemic infection. Papillomaviruses, most poxviruses, and primary HSV infect the skin by direct inoculation. The skin in primary VZV is infected from systemic infection, while recurrent VZV (shingles) or recurrent HSV reaches the skin from an internal focus.

Skin lesions may be the direct effect of virus replication on infected cells or the skin lesions may be the result of the host response to the virus. Alternatively, an interaction of viral replication and the host response may produce the lesions. Viruses that replicate in the epidermis, for example, are generally directly responsible for the lesions. Skin lesions of rubella and measles, on



Figure 1.1 Pityriasis rosea.

the other hand, are thought to be at least partly due to the cell-mediated immune response to the virus.

Diagnosis

Confirmation of suspected viral diseases is usually via one of five general methods of laboratory diagnosis: viral cultures, microscopic examination of infected tissue, detection of viral antigens, detection of viral DNA or RNA, or serology. The preferred



Figure 1.2 Asymmetric periflexural examthem of childhood (unilateral laterothoracic examthem).



Figure 1.3 Asymmetric periflexural examthem of childhood (unilateral laterothoracic examthem).

method of diagnosis is viral culture when a good culture system is available. A positive culture can be obtained in 1 or 2 days when HSV-1 or -2 is responsible for the lesion. Generally, however, high rates of positivity are seen only when lesions are in the vesicular stage, while later stages of healing are less likely to be positive. Even when fresh vesicular fluid is used to inoculate the appropriate cell culture, positive cultures are more difficult to obtain from VZV.

Papillomaviruses and many other common viral diseases of the skin do not have available culture systems. Microscopic examination of biopsy material can reveal changes consistent with a viral family in such cases, but it is usually not helpful in identifying the specific virus responsible. Histologic changes induced by HPV in benign warts, for example, have similar microscopic appearances. Similar microscopic changes are induced by HSV-1 and -2, as well as by VZV, but are distinctive from changes associated with other herpes viruses. The Tzanck smear is a more rapid procedure than microscopic examination of biopsy tissue to detect changes associated with HSV-1 and -2 and VZV. A smear containing cells scraped from the base of a vesicle is prepared on a glass slide and stained (e.g., with Wright's or Giemsa stain). Multinucleated giant cells will help to confirm that one of the three viruses is responsible for the vesicle, but they cannot specify which virus. Molluscum contagiosum (MC) is another viral infection that can be diagnosed directly from smears from a skin lesion. Intracytoplasmic inclusion bodies (Table 1.2) will help to distinguish papules associated with MC from skin lesions of *Cryptococcus neoformans*, which can appear very similar in HIV-infected patients.

Rapid diagnostic tests for viral antigens are widely available. Fluorescent antibody detection of HSV-1 and -2, as well as VZV, is frequently used in the detection of viral infections of the skin. The three viruses can be distinguished by this technique (in contrast to the Tzanck smear). HPV capsid antigens are sometimes detected by immunoperoxidase techniques, but this technique can be associated with false-negative results with oncogenic HPV types in which viral DNA may be present without capsid antigens. Viral antigens may also be detected by radioimmunoassay or enzyme-linked immunosorbent assay (ELISA). Viral particles or

Table 1.1 Viral Exanthems

Type of rash	Associated virus
Macular/maculopapular	Rubella
	Echovirus (especially 9, 16, 71)
	Coxsackievirus (especially A5, A9, A16, B5)
	Epstein-Barr virus (infectious mononucleosis)
	Human herpesvirus 6 (roseola)
	Rubeola
	Arboviruses (dengue fever)
	Parvovirus B19 (erythema infectiosum)
	Hepatitis B and C
	Human immunodeficiency virus 1
Papular	Human papillomaviruses
	Orf
	Human herpesvirus 8 (Kaposi's sarcoma)
	Milker's nodule
	Molluscum contagiosum
	Human immunodeficiency virus 1
Patches	Epstein Barr virus (oral hairy leukoplakia)
Petechial/purpuric	Coxsackieviruses A5, A9
	Hemorrhagic fever viruses
	Congenital rubella
	Congenital cytomegalovirus
	Echovirus 9
	Epstein-Barr virus
Urticarial	Human immunodeficiency virus 1
	Hepatitis B
	Coxsackieviruses A5, A9
	Epstein-Barr virus
Vesicular/vesiculopustular	Varicella-zoster
	Vaccinia
	Variola
	Herpes simplex virus types 1 and 2
	Coxsackievirus (hand, foot, and mouth disease) (Herpangina)
	Vesicular stomatitis
	Echovirus

viral antigens can also be detected by labor intensive techniques such as electron microscopy or immunoelectron microscopy.

Viruses for which no effective culture system (or serologic assay) is available can be identified by the use of assays to detect viral nucleic acid. HPV is an example, but any virus should be detectable with these methodologies if sufficient knowledge is available regarding the viral genome in order to design specific probes and primers. In situ hybridization is the most widely available technique for detection of viral nucleic acids. Detection of the viral nucleic acid and histologic localization of the virus to specific cells is possible with this technique. Southern hybridization is a more sensitive technique for viral nucleic acid detection and is the basis for greater than 100 HPV types described thus far. The polymerase chain reaction (PCR) is the most sensitive technique for viral nucleic acid detection. A range of viruses within a particular family (i.e., using consensus primers) can be detected or primers used in PCR can be designed to be specific for a particular virus (i.e., type-specific primers). In situ PCR that combines the sensitivity of PCR with specific histologic localization of the virus is even more sophisticated. The Hybrid Capture Assay II is a molecular technique with similar sensitivity as PCR that has become available commercially.

Table 1.2 Viral Inclusion Bodies in Human Diseases

Virus	Location	Eponym
Adenovirus	Nucleus	
Cytomegalovirus	Nucleus, cytoplasm	"Owl's eye"
Herpes simplex (types 1 and 2)	Nucleus	Cowdry type A, Lipschütz body
Measles	Cytoplasm	
Molluscum contagiosum	Cytoplasm	Henderson-Paterson body
Papillomaviruses*	Nucleus, cytoplasm	
Rabies	Cytoplasm	Negri body
Varicella	Nucleus	Cowdry type A
Variola, vaccinia	Cytoplasm	Guarnieri body

*Keratohyaline granules.

Serology provides a fifth technique for diagnosis by using the detection of antibodies elicited by the viral infection. A recent infection is indicated by a four-fold rise in serum antibodies to a specific virus between acute and convalescent sera (usually 4 weeks). A true primary herpetic infection (which would be associated with high levels of immunoglobulin [IgM]) can be distinguished from a first-episode nonprimary infection or a recurrence (i.e., high levels of IgG) by serology. Antibodies to viruses can be detected by a variety of techniques. The responsible virus determines, at least partly, the usefulness of a particular technique. ELISA is considered a screening test for antibodies against HIV, for example. Confirmation with Western blotting must be completed before a definitive diagnosis can be made due to the possibility of a false positive test. Specificity between HSV-1 and -2 antibodies is now adequate with the recently available ELISAs, but detection of IgG against HSV can be made accurately with this test only after 1–4 weeks following primary infection. Antibodies to HSV-1 can be distinguished with sensitivity and specificity from those to HSV-2 using the Western blot.

Differential Diagnosis

A spectrum of nonviral and viral conditions must be considered in the differential diagnosis of various types of viral exanthemata. HSV-1, HSV-2, VZV, poxviruses, hand-foot-mouth viruses, as well as other coxsackieviruses may produce vesicles. During the process of healing, most vesicles develop into pustules. Nonviral entities such as bullous impetigo, insect bite reactions, drug eruptions, contact dermatitis, and gonococcemia must be included in the differential diagnosis of vesiculopustules. Rubella, EBV infections (i.e., infectious mononucleosis), HHV-6 infection (i.e., roseola), as well as a variety of coxsackievirus (A and B) and echovirus infections may produce macules. Drug eruptions and bacterial infections (e.g., scarlet fever, Rocky Mountain spotted fever, erysipelas) are possible nonviral etiologies of macules. Measles, echovirus infections, and human parvovirus B19 infections (i.e., erythema infectiosum) may result in macules presenting with papules. Any of the macular or papular nonviral conditions noted above, as well as erythema multiforme, which is commonly of viral etiology (i.e., HSV), may produce maculopapular lesions or they may be associated with nonviral infections or with drug eruptions. A spectrum of poxvirus and HPV infections, as well as in Gianotti-Crosti syndrome, which may be a manifestation of hepatitis B or a variety of other viral infections, may manifest as papules. Bacterial infections (e.g., Bartonella, Mycobacterium), fungal infections (e.g., cryptococcus), and noninfectious

conditions (e.g., seborrheic keratoses, basal cell carcinomas) may also be papules. Poxvirus infections (e.g., orf, milker's nodules), HPV (e.g., squamous cell carcinomas associated with HPV-16), or herpesvirus 8 (e.g., Kaposi's sarcoma), mycobacterial and Bartonella infections (e.g., bacillary angiomatosis), and noninfectious tumors (e.g., basal cell carcinomas, squamous cell carcinoma, melanoma, pyogenic granuloma) may be nodular. Allergic reactions, including drug eruptions, as well as hepatitis B or coxsackie A9 virus infections, are usually associated with urticaria. Dengue fever and other hemorrhagic fevers (e.g., Lassa fever) may result in petechiae, but this finding may occur in nonviral conditions producing thrombocytopenia. Viral infections such as HSV-1, HSV-2, VZV, CMV, and hand-foot-mouth disease (HFMD) commonly cause ulcerations of the mucous membranes. Immunocompromised persons sometimes suffer oral or anogenital ulcers due to CMV, or such ulcers may involve a coinfection of CMV and HSV. Nonviral ulcers such as aphthous stomatitis must be distinguished from oral ulcers of viral etiology. Stasis dermatitis or other causes of decreased circulation may cause cutaneous ulcers.

DNA VIRUSES

Poxviruses

Poxviruses are large DNA viruses that are members of the family Poxviridae; those of clinical significance include smallpox, vaccinia, MC, orf, and milker's nodules (Table 1.3). The only one of these viruses with significant mortality, smallpox, has been eradicated via worldwide vaccination programs that resulted in the last patient with epidemic smallpox being treated in 1977 [1].

Smallpox

Although smallpox replicates in the epidermis, it is spread not only via direct skin contact and fomites, but also by respiratory transmission. Patients experience 3 days of apprehension, preceding development of skin lesions; this is followed by sudden prostrating fever, severe headache, back pain, and vomiting. Tense, deep-seated papules and vesicles are preceded by erythematous macules. Pustules follow the vesicles, then crusts, and finally scar formation. All lesions are in the same stage of development with the rash appearing in a centrifugal distribution. The hemorrhagic form of smallpox results in almost 100% mortality even before development of skin lesions, although the overall mortality rate with smallpox is approximately 30%.

Vaccinia

Vaccination against the vaccinia virus is no longer routinely used since smallpox has been eradicated (Tables 1.4 and 1.5). While use of the vaccinia virus to immunize against smallpox was one of the greatest success stories in medical history, use of this live virus occasionally led to complications in susceptible individuals, such as bacterial superinfection, abnormal viral replication, or altered reactivity [2].

Molluscum contagiosum

The most prevalent poxvirus is molluscum contagiosum (MC); the incubation period of MC is 2–7 weeks. MC presents as 3 to 6-mm skin-colored papules with a central umbilication. While two different strains of MC (I and II) have been identified (based on restriction endonuclease digestion patterns), both strains produce similar clinical pictures. MC often follows one of two patterns of clinical presentation in immunocompetent individuals: widespread papules on the trunk and face of children transmitted by direct skin-to-skin (nonsexual) contact or genital papules in adults spread by sexual contact. In either case, it is unusual to see more than 20 lesions per patient [3]. In immunocompromised persons, especially those who are HIV positive, MC can present with thousands of papules and be a major source of morbidity; prevalence rates in this population range from 9 to 18% [4].

Orf

Contagious ecthyma, orf, is a less common poxvirus that is transmitted from sheep, goats, etc., to the hands of humans. The cutaneous presentation of orf is usually nodules averaging 1.6 cm in diameter associated with regional lymphadenopathy, lymphangitis, and fever. Orf lesions spontaneously progress through six stages, resulting in healing in about 35 days [5].

Milker's nodules

A paravaccinia virus causes milker's nodules, which is similar to orf except that lesions result from manual contact with teats of infected cows, and milker's nodules have an incubation period of 4–7 days. The nodules heal in 4–6 weeks after progressing through six clinical stages similar to orf [6].

Primary viremia follows local multiplication in the respiratory mucosa and regional lymphoid tissue after contact with smallpox via the respiratory route. A secondary viremia is associated with the initiation of the prodrome after spreading throughout the reticuloendothelial system. Thrombocytopenia accompanies the development of skin lesions which, in hemorrhagic forms of smallpox, can become severe and result in disseminated intravascular coagulation with decreases in accelerator globulin, prothrombin, and proconvertin, ending with extensive hemorrhage and death.

Regional lymphadenopathy sometimes accompanies a local reaction to vaccinia replication in the epithelium. The host immune response limits systemic manifestations except in cases of depressed immunity or in diseases with inadequate epithelial barriers. Generalized vaccinia can result, but it is rarely a lethal disease like smallpox. Viral replication in MC, orf, and milker's nodules is generally limited to the epidermis, but dermal changes are also seen in milker's nodules.

Pathology. Lesional biopsy of smallpox reveals cytoplasmic eosinophilic inclusion bodies (Guarnieri bodies) along with papules, vesicles, or pustules. Electron microscopy or fluorescent antibody staining can identify smallpox, or the virus can be isolated with appropriate tissue culture systems. A history of vaccination along with the clinical presentation is usually sufficient for diagnosis of vaccinia, but diagnostic tools similar to those used for smallpox may be used to detect this virus.

Histologically, a hypertrophied and hyperplastic epidermis overlying a normal-appearing basal layer characterizes MC. Multiple Feulgen-positive intracytoplasmic inclusion bodies (Henderson Paterson bodies or molluscum bodies) are seen in the enlarged epidermal cells.

Laboratory Findings. Laboratory findings with orf and milker's nodules, as with MC, are generally limited to histology. The histopathology varies with the clinical stage in the case of the latter

Table 1.3 Taxonomy of Human Viruses

Family	Subfamily, genus	Type species or example	Morphology	Envelope	Chapter
DNA VIRUSES					
dsDNA viruses					
Poxviridae			Ovoid	+	3
	Chordopoxvirinae				
	Orthopoxvirus	Vaccinia virus, variola			
	Parapoxvirus	Orf virus			
	Molluscipoxvirus	Molluscum contagiosum virus			
	Yatapoxvirus	Yaba monkey tumor virus			
Herpesviridae			Icosahedral	+	
	Alphaherpesvirinae				
	Simplexvirus	Human herpesviruses (HSV) 1 and 2			4
		Cercopithecine herpesvirus 1 (herpesvirus B)			11
	Varicellovirus	Human herpesvirus 3 (VZV)			5
	Betaherpesvirinae				
	Cytomegalovirus	Human herpesvirus 5 (CMV)			7
	Roseolovirus	Human herpesvirus 6 and 7[a]			8,9
	Gammaherpesvirinae				
	Lymphocryptovirus	Human herpesvirus 4 (EBV)			6
	Rhadinovirus	(HHV-8)			10
Adenoviridae	*Mastadenovirus*	Human adenoviruses	Icosahedral	−	27
Papovaviridae	*Polyomavirus*	JC virus, Merkel cell polyomavirus	Icosahedral	−	
Papillomaviridae	*Papillomavirus*	Human papillomaviruses	Icosahedral	−	12
SsDNA viruses					
Parvoviridae	*Parvovirinae*				
	Erythrovirus	B19 virus			
	Dependovirus	Adeno-associated virus 2[a]			13
	Bocavirus	Human Bocavirus			
Circoviridae	*Circovirus*	TTB	Icosahedral		
DNA and RNA reverse transcribing viruses					
Hepadnaviridae	*Orthohepadnavirus*	Hepatitis B virus	Icosahedral	−	24
Retroviridae			Spherical	+	
	Deltaretroviruses	HTLV-I and II			15
	Lentivirus	Human immunodeficiency viruses			14
	Spumavirus	Human spumavirus[a]			
RNA VIRUSES					
DsRNA viruses					
Reoviridae			Icosahedral	−	
	Orthoreovirus	Reovirus 3[a]			
	Orbivirus	Kemerovo viruses			
	Rotavirus	Human rotaviruses			
	Coltivirus	Colorado tick fever virus			16
	Seadornavirus	Banna virus			
Negative Stranded SsRNA viruses					
Paramyxoviridae			Spherical	+	
	Paramyxovirinae				
	Respirovirus	Human parainfluenza viruses			
	Morbillivirus	Measles virus			
	Rubulavirus	Mumps virus			17
	Henipavirus	Nipah virus			
	Pneumovirinae	Human respiratory syncytial virus			
	Pneumovirus				
	Metapneumovirus	Human metapneumovirus			
Rhabdoviridae			Bacilliform	+	
	Vesiculovirus	Vesicular stomatitis virus			
	Lyssavirus	Rabies virus			
Filoviridae	*Filovirus*	Ebola virus, Marburg virus	Bacilliform	+	18
Orthomyxoviridae			Spherical	+	
	Influenzavirus A	Influenza A virus			
	Influenzavirus B	Influenza B virus			
	Influenzavirus C	Influenza C virus			

(*Continued*)

Table 1.3 (Continued)

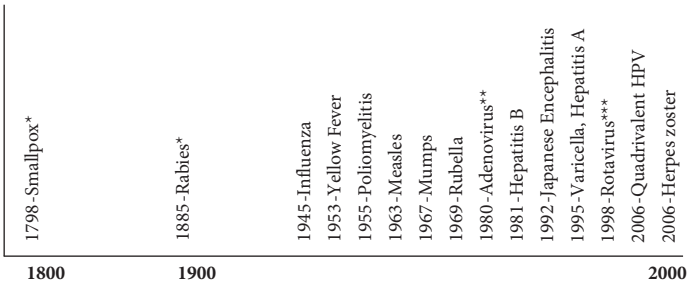
Family	Subfamily, genus	Type species or example	Morphology	Envelope	Chapter
Bunyaviridae			Amorphic	+	19
	Orthobunyavirus	Bunyamwera virus, LaCrosse virus			
	Hantavirus	Hantaan virus, Sin Nombre virus			
	Nairovirus	Crimean-Congo hemorrhagic fever virus			
	Phlebovirus	Rift Valley fever virus			
Arenaviridae			Spherical	+	
	Arenavirus	Lymphocytic choriomeningitis virus, Lassa fever virus, South American hemorrhagic fever viruses			20
Positive stranded ssRNA virus			Icosahedral	–	
Picornaviridae	*Enterovirus*	Polioviruses, Coxsackieviruses, Echovirus			21
	Rhinovirus	Human rhinoviruses			
	Hepatovirus	Hepatitis A virus			24
Caliciviridae	*Calicivirus*	Norwalk virus	Icosahedral	–	
Hepeviridae	*Hepevirus*	Hepatitis E		+	24
Astroviridae	*Astrovirus*	Human astrovirus 1	Icosahedral		
Coronaviridae	*Coronavirus*	Human coronavirus	Pleomorphic	+	
Flaviridae	*Flavivirus*	Yellow fever virus, Dengue virus	Spherical		22
	Hepacivirus	Hepatitis C virus			24
Togaviridae	*Alphavirus*	Western equine encephalitis virus, Chikungunya	Spherical		23
	Rubivirus	Rubella virus			
Subviral Agents: Satellites, Viroids, and Agents of Spongiform Encephalopathies					
Satellites (single-stranded RNA)	*Deltavirus*	Hepatitis delta (D) virus	Spherical	–	
Prion protein agents		Creutzfeld-Jakob agent	?	–	25

[a]Human virus with no recognized human disease.

two diseases. In the early stages, both intracytoplasmic and intranuclear inclusions may be observed.

Management. The only effective management of smallpox proved to be prevention via vaccination. Management of symptoms and prevention of bacterial superinfection were paramount for patients with smallpox or disseminated vaccinia. Thiosemicarbezone and antivariola or antivaccinia sera had limited effectiveness (Table 1.6). Liquid nitrogen, curetting, imiquimod or cidofovir can be used to treat MC. In immunocompromised persons, recurrences are common. Excision and cautery can remove lesions of orf or milker's nodules, but this is usually not necessary as spontaneous resolution can be expected in approximately 6 weeks.

Table 1.4 Timeline of Virus Vaccine Development*



*Dates for smallpox and rabies vaccines are of the first published results of vaccine usage. Remaining dates are of FDA approval of a vaccine.
**No longer available.
***Subsequently replaced by two new rotavirus vaccines.

Human Papillomaviruses

HPVs are nonenveloped, double-stranded DNA viruses that belong to the family Papillomaviridae. Regional tropism (i.e., whether they produce genitomucosal lesions, nongenital lesions in the general population, or lesions associated with epidermodyplasia verruciformis [EV]) can be used to categorize HPV. Location of the lesions, quantity of HPV in the lesion, degree and nature of the contact, and immune status of the exposed individual determine the transmission of HPV. Genital (venereal) warts, condyloma acuminatum, are the most prevalent clinical form of viral genitomucosal lesions; the incidence of these warts has risen six-fold during the past three decades. Classification of HPVs also may be according to their malignant potential. More than 90% of condyloma acuminatum are clinically benign and are due to HPV-6 or HPV-11. HPV types 31, 33, and 35 have intermediate malignant potential. By contrast, HPV types 16 and 18 have high malignant potential; over 70% of cervical and other anogenital cancers contain DNA from one of the latter two types [7–9]. Orogenital sex can transmit these HPV types to other mucous membranes resulting in oral condyloma acuminatum, or HPV may be transmitted nonsexually such as during vaginal delivery [10]. HPV from vaginal warts in the latter case may be transmitted to the oral or respiratory tract of the infant and present as respiratory (laryngeal) papillomas [11]. As a result of HPV acquired during vaginal delivery, anogenital warts may also develop in infants within a few months of birth. While sexual abuse can produce anogenital warts in children, a significant proportion of such warts results from incidental spread from cutaneous warts [12]. Oral warts not of genital origin can be seen in focal epithelial hyperplasia that

Table 1.5 Virus Vaccines: Recommendations for Administration*

Vaccine	Target population	Route	Dosage	Comments
MMR (measles, mumps, rubella)	Children	SC	2 doses at 12–15 mos and 4–6 yrs	Also available: Measles and Rubella (live): MRVAX II® Measles (live attenuated): ATTENUVAX® Mumps (live): MUMPSVAX Rubella (live): MERUVAX Rubella + Mumps (live): BIAVAX II
Varicella Zoster Varivax®	Children and susceptible adults	SC	2 doses: at ages 12–15 mos and at 4–6 yrs 2 doses (4–8 wks apart in susceptible persons ≥ 13 yrs	Proquad (MMR +Varivax)
Zostavax	Adults >60 years	SC	1 dose	
Influenza Flumist, FluLaval, Afluria, Fluarix Fluzone® Fluvirin® Fluogen® Flushield®	Persons ≥65 yrs, residents of chronic care facilities, those with chronic cardiopulmonary diseases, or those who may transmit the virus to high-risk persons	IM	6 mos – 8 yrs: 1 or 2 doses of split virus only, at least 1 month apart 9–12 yrs: 1 dose of split virus only >12 yrs: 1 dose of whole or split virus	Vaccinate from September to November Flumist is a live attenuated vaccine given intranasally
Hepatitis A	Children and susceptible adults	IM	2 doses: Havrix® - >2 yrs: 0 mos & 6–12 mos Vaqta® - 2–17 yrs: 0 mos & 6–18 mos >17 yrs: 0 mos & 6 mos	Havrix® is available in combination with Engerix-B® as Twinrix®
Hepatitis B Recombivax HB® Engerix B® Comvax®(with haemophilus influenza type B vaccine)	Children and susceptible adults	IM	3 doses: Infants: birth to 2 mos, 1–4 mos & 6–18 mos Children and adolescents: mos 0, 2, & 4 Adults: mos 0, 1, & 6	Infants with HbsAG-positive mothers receive 1st dose within 12 hours of birth. 2nd dose at 1 month, and 3rd dose at 6 months. Engerix-B® is now available in combination with Havrix® as Twinrix®.
Rabies Imovax, Rabavert **RABIE-VAX®**	Persons at risk of rabies exposure or those recently exposed		Preexposure: 3 doses on days 0, 7, & 21 or 28 HDCD: Imovax® PCEC: RabAvert™ Rabies Vaccine Absorbed HDCD: Imovax® Rabies ID Postexposure: 5 doses on days 9, 3, 7, 14, & 28 HDCV Rabies Vaccine Absorbed PCEC	 Previously vaccinated persons require only 2 doses after rabies exposure, on days 0 & 3.
		IM IM IM ID IM IM IM		
Poliomyelitis Poliovax® IPOL® Orimune® (live, oral)	Children	SC Oral	Sequential series: 4 doses 2 mos: IPC (inactivated polio vaccine) 4 mos: IPV 6–18 mos: OPV (oral polio vaccine) 4–6 yrs: OPV	Regimens with all IPV or all OPV are given in the same time frame. All IPV doses are indicated for immunosuppressed patients or contacts. All OPV dosing is accepted in certain circumstances only.
Yellow Fever YF-VAX®	Persons traveling to endemic countries (parts of Africa and South America)	SC	1 dose	Booster given every 10 years for recertification for travel into endemic countries
Japanese Encephalitis Ixiaro JE-VAX®	Persons traveling to certain parts of Asia	SC	3 doses, on days 0, 7, & 30	
Rotavirus Rotarix RotaTeq	Children	Oral		
Human Papillomaviruses types 6, 11, 16, 18 Gardasil	Females from 9 to 26 years	IM	3 doses on months 0, 2 & 6	Virus-like particle (VLP) vaccine made from recombinant L-1 major capsid proteins

IM=intramuscular; SC=subcutaneous; ID=intradermal; mos=months; yrs=years; HDCV=human diploid cell vaccine; PCEC=purified chick embryo cell culture vaccine.

*Vaccinia vaccine for prevention of smallpox not generally available (or recommended) and when available, limited to certain military forces.

Table 1.6 Immunoglobulins (IG): Indications for Administration*

Immunoglobulin	Generic/trade name	Approved indication
Intramuscular IG	BAYGAM	Exposure to measles or hepatitis A in susceptible persons; varicella (if VZIG unavailable); rubella
Hepatitis B-IG	BAYHEPB, NABI-HB, HYPER HEP	Hepatitis B exposure in susceptible persons
Human rabies IG	BAYRAB, IMOGAM-Rabies, HYPERAB	Rabies exposure in previously unvaccinated persons
Varicella-Zoster IG	VZIG	Susceptible persons exposed to varicella who have a high risk for complications (e.g. immunocompromised patients and neonates)
Respiratory syncytial virus IG	Respigam® (Palivizumab) Synagis®	Prophylaxis in high-risk infants (e.g. those with bronchopulmonary dysplasia or prematurity)
Cytomegalovirus	Cytogam	CMV prophylaxis in seronegative renal transplant recipients of a kidney from a CMV-positive donor

*Vaccinia immune globulin generally not available, and when available, limited to certain military forces.

contains such unique HPV types as 13 or 32 and they present most commonly in certain ethnic groups [13]. In the general population, cutaneous warts are very common and can present as verruca vulgaris (HPV-2), plantar warts (HPV-1), or verruca plana (HPV-3). These verrucous papules rarely lead to major medical problems, but can be annoying and difficult to eradicate.

On the other hand, cutaneous warts in EV can lead to major morbidity and mortality [14]. EV was the first model of cutaneous viral oncogenesis in humans and is a rare condition that can occur sporadically or in an autosomal recessive manner. During childhood, disseminated warty papules and erythematous macules develop in EV patients. Approximately one-half of these patients will develop cutaneous carcinomas in adulthood. EV is associated with at least 17 HPV types. HPV-3 and -10 are also found in flat warts in the general population, but most are unique to EV. Malignant transformation in EV is mostly associated with HPV-5 and -8. Oncogenic HPV in EV appears to be necessary but not sufficient for malignant transformation, which is analogous to the situation with HPV-16 and -18 in anogenital cancers in the general population. In both cases, cofactors appear to be necessary. Cofactors, including cigarette smoking, other transactivating viruses, genetics, and diet, may be important in anogenital malignancies, but the individual role of each cofactor is not clear [15]. The most important cofactor in EV is ultraviolet irradiation, which is illustrated by the fact that the highest incidence of carcinomas in EV patients is in areas of greatest sunlight exposure [16].

HPV DNA replication, RNA transcription, and late protein production are coordinated by the state of differentiation of the epithelial cell following infection of the basal layer of the epidermis. Early (E) proteins direct viral replication. Late (L) proteins, L1 and L2, are viral capsids, which are synthesized and assembled into virions in the nuclei of the granular layer [17]. Verruca are produced in approximately 2–9 months, but HPV DNA can remain in a latent state in normal-appearing skin or mucous membranes for much longer periods of time. Therefore, in some cases, the incubation time from infection to lesion development may be years.

Since newer warts tend to have more virions than do older verrucae, the copy number of HPV DNA varies according to the age of the lesions. Plantar warts usually have more virions than do condyloma acuminatum, and benign warts have more virions than do dysplastic or neoplastic HPV-related lesions.

Pathology. If the lesion is assumed to be HPV related and benign, often no laboratory tests are carried out. The following general patterns may be observed in tissues from biopsies of verrucae: acanthosis, papillomatosis, hyperkeratosis, parakeratosis, and prominent and often thrombosed dermal capillary vessels. Often such features as koilocytes, large keratinocytes with an eccentric, pyknotic nucleus surrounded by a perinuclear halo, are observed. A biopsy is sometimes taken to determine if the lesion is dysplastic or neoplastic. Such biopsies would most likely be taken in the anogenital region in the general population. Dysplastic or neoplastic lesions are most frequent on the cervix and would be detectable via cytopathology taken with the Papanicolaou smear.

Laboratory Findings. Immunohistochemical staining of HPV capsid antigens for more specific detection of HPV can be done. This method may give false-negative results with such lesions since dysplastic or neoplastic lesions contain few, if any, capsid antigens. The only specific method of diagnosing HPV is via DNA detection methods, since HPV cannot be readily grown in tissue culture nor is serology routinely available. Over 100 HPV types are recognized based on Southern hybridization [18]. A new HPV genotype is designated if the virus differs more than 10% in nucleotide sequence in the "late gene" L1 open reading frame from previously identified HPV types. Although in situ hybridization and Hybrid Capture Assay II have become widely available, detection of specific HPV types is more frequently a research tool than a routine laboratory procedure. Hybrid Capture Assay II and PCR, however, are by far the most sensitive methods of detecting HPV DNA [19].

Management. Treatment for most benign verrucae includes surgery, cryotherapy, or topical chemotherapy. The objective in each case is to eradicate the lesion and allow the immune system to hold latent HPV in surrounding (normal-appearing) tissue in check to prevent recurrences. Simple excision, electrodesiccation, and removal with a CO_2 laser are all types of surgical therapy. Liquid nitrogen for destruction of the lesion is a form of cryotherapy. Podophyllin resin, purified podophyllotoxin, 5-fluorouracil, retinoic acid, cantharidin, salicylic acid, lactic acid, sinecatechins ointment, bichloroacetic acid, and trichloroacetic acid are options for topical chemotherapy [20–22]. The size and location of the wart, as well as the history of previous therapies, are determinants in selection of the most appropriate therapy.

Interferon (IFN-α) for treatment of condyloma acuminatum is the only antiviral therapy approved for HPV (Table 1.7) [23].

Table 1.7 FDA-approved Anti-HPV Agents

Generic name	Trade name
Interferon-α	Roferon A
	Intron A
	Alferon
Imiquimod	Aldara*

*Approved as an immune response modifier since the antiviral activity is indirect. Veregen (sinecatechins) also approved, but mechanism of action unknown.

Although IFN-α is effective in eradicating 50–70% of genital warts, its most effective use is in combination therapy [24]. IFN-α given subcutaneously following laser excision of condyloma acuminatum, for example, markedly reduces the recurrence rate. Surgery is used for therapy of HPV-related malignant lesions; if metastases are present, chemotherapy is usually included. Antisense oligonucleotides and cidofovir (a broad-spectrum agent active against a variety of DNA viruses) are new treatments for HPV-related lesions currently under study [25,26]. An immunomodulatory agent demonstrated to be very effective for condyloma acuminatum is imiquimod [27]. The patient applies imiquimod topically and it produces minimal local inflammation and no systemic side effects. The mode of action of imiquimod is via induction of endogenous IFN-α as well as a wide variety of other cytokines. Recurrence rates following clearance of lesions with imiquimod are very low. HPV vaccines containing recombinant L-1 major capsid proteins in virus-like particles (VLPs) are approved for the prophylaxis of anogenital lesions due to HPV 6, 11, 16, and 18.

Human Herpesviruses

The family Herpesviridae is composed of double-stranded DNA viruses and is divided into three subfamilies: alphaherpesviruses (HSV-1, HSV-2, VZV, and B virus); betaherpesviruses (CMV, HHV-6, HHV-7), and gammaherpesviruses (EBV, HHV-8). Primary VZV reaches the skin as a result of a secondary viremia, but primary HSV infects the skin via direct inoculation. The skin is infected by local spread from an internal focus (i.e., the nerve) in recurrent HSV and VZV. Viral replication at nonepithelial sites can result in infrequent skin lesions secondary to EBV or CMV. Although HHV-6 infection frequently produces an exanthem, viral replication is occurring in the peripheral blood mononuclear cells (especially T cells). While no specific disease has yet been proved to be due to HHV-7 infection, PR has been closely associated with this virus. HHV-8 has been identified both in the endothelial cells of Kaposi's sarcoma and the epithelial cells of squamous cell carcinomas of organ transplant patients, but its role in the etiology of the latter tumor is not clear. Herpesvirus simiae, an animal herpes virus (B virus), can also cause human disease, most significantly a fatal encephalomyelitis. The virus can be recovered from vesicular skin lesions at the point of inoculation as well as from vesicles possibly arising from reactivation of latent B virus infection.

Herpes Simplex Viruses 1 and 2

Although most known for causing cold sores and genital herpes, respectively, HSV-1 and HSV-2 cause several other mucocutaneous infections, such as gingivostomatitis, herpes gladiatorum, eczema herpeticum, herpes whitlow, neonatal herpes, lumbosacral herpes, herpetic keratoconjunctivitis, and herpes encephalitis. Erythema multiforme is usually caused by HSV. These viruses typically cause a primary mucocutaneous infection followed by a latent infection when the virus remains dormant in the neuronal ganglia. Viral reactivation and movement down the nerve to produce active mucocutaneous infections is seen with recurrent disease.

Three to fourteen days following sexual exposure to an infected partner, primary genital herpes may occur. In most transmissions, the source partner may be shedding HSV asymptomatically. Widespread genital vesicles and ulcers, edema, pain, inguinal lymphadenopathy, discharge, dysuria, malaise, fever, photophobia, and occasionally aseptic meningitis can be seen during the primary episode. The severity of these signs and symptoms is usually greater in women than in men; 3–4 weeks are often required for complete healing. Viral shedding lasts up to approximately 10 days in men and 14 days in women [28], but can recur asymptomatically at any time.

The first recognized episode of genital HSV, however, is often not truly primary. This first clinical manifestation of a virus that has remained latent in the infected nerve for an extended period of time (i.e., months or even years) would be considered a first episode, nonprimary outbreak. In such cases, signs and symptoms are usually less severe than in true primary genital HSV and may require only 2–3 weeks for complete healing. The pre-existence of sufficient levels of IgG to attenuate the disease is the major reason for the decreased severity of first episode, nonprimary genital herpes.

An increasing proportion (e.g., 30%) of first-episode genital herpes is due to HSV-1, which is often attributable to orogenital contact. Outbreaks of genital herpes due to HSV-1, however, are usually less severe than those due to HSV-2.

While at least 45 million individuals in the USA are estimated to be seropositive for HSV-2, approximately 11 million persons have recognized recurrent genital herpes [29–37]. According to one study, approximately one-half of seropositive persons who deny a history of genital herpes can be taught to recognize signs and symptoms of the disease. Another investigation demonstrated that the majority of persons seropositive for HSV-2 via Western blotting shed the virus asymptomatically at least occasionally. Virus traveling down the sensory nerve first causes prodromal sensations of pruritus or tingling followed shortly by the formation of vesicles. This is the result of reactivation of HSV, which lies dormant in neuronal ganglia. A variety of factors, such as emotional or physical stress (e.g., menstrual periods) or mild trauma (e.g., sexual intercourse), may trigger recurrences. HSV recurrent episodes are usually less severe than initial outbreaks and often heal in 7–10 days without therapy. Genital herpes due to HSV-2 recurs more frequently than HSV-1-associated disease. Compared to men, women suffer 20% less recurrences of genital herpes, a factor that may contribute to the higher rate of herpes transmission from men to women than from women to men. HSV recurrences in immunocompromised patients may be chronic and result in large ulcerations if not treated.

HSV-1 is associated with greater than 90% of orolabial herpes, which is usually acquired early in life [32,33]. Primary HSV-1 infection may present as acute gingivostomatitis with a peak

incidence between the ages of 1 and 5 years. Five to ten days after exposure to HSV, primary gingivostomatitis often presents with sore throat, regional lymphadenopathy, fever, and widespread painful ulcerations of the oral cavity and lips.

Up to 90% of adults in various seroepidemiologic surveys have serologic evidence of HSV-1 infection [33]. Recurrent herpes labialis, however, is seen in 20–40% of the population. The majority of orolabial herpes infections remain asymptomatic, analogous to the situation with genital herpes. In certain susceptible individuals, not only stress and trauma, but also exposure to sufficient ultraviolet light, can induce recurrent episodes of herpes labialis. Erythema and vesicle formation are preceded by a few hours of prodromal symptoms of pruritus, tingling, and pain. Formation of vesicles usually occurs on the vermilion border of the lip, but occasionally may be seen around the lips. Such lesions contain culturable HSV for approximately 4 days. During the next 10 days, vesicles ulcerate, crust, and usually undergo complete healing.

Varicella Zoster Virus

The presentation of VZV can be as primary varicella (chickenpox) or as the recurrent form, herpes zoster (shingles) [34]. Children usually develop primary varicella, which presents with the simultaneous onset of rash, low-grade fever, and malaise. The exanthem is often preceded by up to 3 days of prodromal symptoms in older children and adults, including headache, myalgia, anorexia, nausea, and vomiting. The face and trunk first develop lesions that appear as erythematous macules and rapidly progress over the next 12–14 hours to papules, vesicles, pustules, and crusts. Most skin lesions are seen on the trunk and on proximal extremities. Pruritus is the most prevalent symptom. Varicella is characterized by the simultaneous presence of lesions in all stages of development in the same anatomic region due to the rapid evolution of successive crops of lesions. Shallow, painful ulcers develop from rapid erosion of vesicles that appear on mucous membranes. Scarring, which may be due to bacterial secondary infection, is the most common cutaneous complication of varicella in immunocompetent persons. Significant morbidity and occasional mortality can result from such complications as central nervous system (CNS) involvement, varicella pneumonia, or varicella hepatitis in adults and in immunocompromised individuals. A 2% risk of congenital malformations is associated with maternal varicella if infection occurs during the first 20 weeks of pregnancy.

VZV persisting in sensory ganglia reactivates, usually after many years, in 20% of immunocompetent persons and in 20–50% of immunocompromised patients. This reactivation causes a transient viremia and spreads down the sensory nerve, producing radiculoneuritis [35]. Vesicles appear along the distribution of the sensory nerve after a few days (to weeks) of pain. Fever, regional lymphadenopathy, malaise, and, occasionally, a flu-like syndrome can be associated with pain. It is not unusual for a few lesions to appear in neighboring dermatomes, although vesicles generally occur only along one dermatome. The areas usually affected most severely by primary varicella are those same anatomic regions (i.e., face and trunk) that have the greatest predilection for zoster. Pustules result after a few days when the vesicles are infiltrated by leukocytes. Pustules begin to dry after 1–2 weeks, resulting in crusts that are usually lost by 1 month after the appearance of the first vesicle.

Cutaneous complications are rare, although scarring can occur, particularly in darker skinned individuals [36]. Postherpetic neuralgia, which can be defined as any pain remaining after full cutaneous healing, is the most prevalent complication. The pain can be extremely severe, can be treatment resistant, and can last months to years. Disseminated herpes zoster, defined as more than 20 vesicles outside the primary and adjacent dermatomes, is rare in normal hosts; but severely immunocompromised patients have a risk of dissemination approaching 40%. Cutaneous dissemination can herald significant morbidity and mortality, because it may be a marker of visceral involvement (i.e., liver, lungs, CNS).

Vision impairment or blindness with involvement of the ophthalmic branch of the trigeminal nerve is another complication of herpes zoster, not uncommonly seen in normal hosts [37]. Involvement of the facial and auditory nerves can result in the Ramsey-Hunt syndrome. CNS involvement and motor paralysis less commonly can result from herpes zoster [38,39].

Cytomegalovirus

The seroprevalence for CMV increases with age such that most adolescents are seropositive and nearly 100% of older individuals are CMV seropositive. In immunocompetent persons, primary infection is asymptomatic and usually subclinical. In most normal hosts, the virus remains latent. However, it can produce clinical symptoms in neonates and in immunocompromised persons, but skin involvement is rare. During pregnancy, primary CMV infection results in intrauterine infection in 55% of fetuses. If infection occurs during the first trimester, sequelae are most severe [40]. Infection with CMV is the major infectious cause of mental retardation and deafness in the USA and is the most common congenital viral infection. CMV can produce purpuric macules and papules due to persistent dermal hematopoiesis, like other causes of the TORCH syndrome (i.e., toxoplasmosis, other [syphilis/bacterial sepsis], rubella, CMV, HSV), resulting in the clinical picture termed blueberry muffin baby [41]. A variety of skin lesions, from vesicles to verrucous plaques, have been reported in association with immunocompromised patients. The most prevalent cutaneous manifestation of CMV is ulceration, especially in the perianal area [42,43].

Epstein-Barr Virus

In immunocompetent individuals, the most prevalent clinical manifestation of EBV infection is infectious mononucleosis [44]. In infectious mononucleosis, the incubation period of EBV is 30–50 days followed by a prodrome characterized by malaise, headache, and fatigue followed by fever, sore throat, and cervical adenopathy. Small petechiae are observed at the border of the hard and soft palate in approximately one-third of patients. Cutaneous manifestations of infectious mononucleosis, such as macules or papules and, less commonly, erythema, vesicles, petechiae, or purpura, occur in 3–16% of patients [45]. These lesions are more common on the trunk and upper arms, last 1–7 days, and present during the first week of illness. A high percentage of patients develop erythematous macules and papules over the trunk and extremities after approximately 1 week if ampicillin or certain other penicillins are given to a person with infectious mononucleosis [46]. After about 1 week, these lesions are followed by desquamation.

Table 1.8 The Classic Childhood Exanthems (Named in Early 1900s)

First Disease:	Rubeola (Measles)
Second Disease:	Scarlet Fever
Third Disease:	Rubella
Fourth Disease:	Filatov-Dukes (staphylococcus scalded skin syndrome?)
Fifth Disease:	Erythema Infectiosum
Sixth Disease:	Exanthem Subitum (Roseola Infantum)

The epithelial cells of oral hairy leukoplakia, an oral lesion closely associated with HIV infection, also contain EBV DNA [47,48]. In addition, B-cell lymphomas of immunocompromised individuals often produce mucocutaneous lesions and contain EBV DNA. Symmetric, nonpruritic, lichenoid papules of the face, limbs, and buttocks, known as Gianotti-Crosti syndrome, have also been associated with primary EBV infection [49].

Human Herpesvirus Type 6

HHV-6 is presently recognized as the cause of exanthem subitum (roseola infantum), which was also termed sixth disease long before HHV-6 was isolated (Table 1.8) [50]. Exanthem subitum usually occurs after an incubation period of 5–15 days, in infants from 6 months to 2 years of age, with high fever lasting 3–5 days. The infant may not appear in distress despite the high fever, but can have such signs as palpebral edema, inflammation of the pharynx, and lesions of the soft palate. A macular to papular eruption appears on the trunk and neck as the fever resolves. Manifestations of the disease, including the rash, usually fade in 1–2 days without treatment [51–53].

Human Herpesvirus Type 7

HHV-7 has been associated with certain cases of roseola infantum as well as with PR, but it is not currently proved to be the etiologic factor in any disease.

Human Herpesvirus Type 8

HHV-8 has been detected both in Kaposi's sarcoma from HIV-infected persons as well as classic (HIV-negative) Kaposi's sarcoma and was termed Kaposi's sarcoma-related herpesvirus [54–57]. The same viral sequences have been reported from squamous cell carcinomas and other epithelial lesions from patients with organ transplants [58]. The role of HHV-8 in epithelial tumors is unknown, however, this virus is considered necessary, but not sufficient, to cause Kaposi's sarcoma. Cofactors for development of this tumor are under study.

B Virus (Herpesvirus simiae)

Many nonhuman herpesviruses exist, but B virus is of particular importance due to the high mortality rate from encephalomyelitis in humans infected with this simian herpesvirus [59]. Humans become infected with this virus following a bite or scratch from a macaque monkey. Fever, lymphangitis, lymphadenopathy, gastrointestinal symptoms, and myalgia follow development of erythema, induration, and vesicles at the inoculation site. Rapid progression to the neurologic signs and symptoms of encephalomyelitis follow these symptoms [60,61]. The prognosis is very poor with B virus infection.

Pathology. Ballooning degeneration and cell fusion are seen with HSV-1, HSV-2, and VZV infections, resulting in multinucleated giant cells. The uninfected stratum corneum is elevated to form a vesicle by degeneration of epithelial cells and influx of edema fluid. Infiltration by leukocytes forms pustules. Both intranuclear and intracytoplasmic inclusions may be seen in cells infected with CMV. Intranuclear inclusions in HSV or VZV infected cells are similar to those observed in cytomegalic cells, but the CMV intranuclear inclusions are larger, surrounded by a clear halo, and resemble "owls' eyes." Viral infection of the vascular endothelium and subsequent destruction of blood vessels cause cutaneous ulcerations in CMV.

It is not certain whether EBV enters epithelial cells by interaction with a specific receptor, e.g., CD21, or by fusion of the epithelial cell with an infected lymphocyte. It is not completely understood how EBV produces a rash in infectious mononucleosis (with or without ampicillin) or in oral hairy leukoplakia.

It is not fully known how HHV-6 produces an exanthem. The presence of HHV-8 sequences has been documented in endothelial cells of Kaposi's sarcoma. Ballooning degeneration, multinucleated cells, vesicle formation, and necrosis are seen in cutaneous lesions with B virus infection.

Laboratory Findings. The most definitive method of demonstrating a herpesvirus as the probable cause of a vesicle is viral culture. In 1–2 days, both HSV-1 and HSV-2 grow readily. VZV has a much lower recovery rate than HSV and requires 7–10 days to produce a cytopathic effect. Culturable virus is much less likely to be found in pustules than in vesicles; virus can only rarely be cultured from crusts. HSV or VZV can be grown in either fibroblast or epithelial (amnion) cell cultures, but CMV only grows in fibroblast cultures. EBV or HHV-6 grows in lymphocytes; growth of HHV-8 in the laboratory has been reported recently.

Multinucleated giant cells of HSV and VZV will be revealed by scraping the base of a vesicle and subsequent staining (Tzanck smear). The Tzanck smear can differentiate HSV- or VZV-associated changes from those associated with nonviral etiologies similar to a skin biopsy or electron microscopy, but it cannot distinguish among HSV-1, HSV-2, and VZV. Differentiation of skin lesions associated with each of these three viruses can, however, be accomplished using direct fluorescent antigen staining.

Diagnosis of infection with herpesviruses is possible via serologic tests. ELISA testing is used to detect antibodies to HSV-1 or HSV-2. Western blotting provides differentiation of antibodies with high sensitivity and specificity. True primary genital herpes can be differentiated from first episode, nonprimary genital herpes by the predominance of IgM in the former and IgG in the latter presentation. A four-fold or greater increase in the antibody titer to VZV between acute and convalescent titers can retrospectively diagnose herpes zoster.

Any of the eight human herpesviruses can be detected via PCR. While this technique is the most sensitive, it is also associated with a significant incidence of false positivity if proper controls are not used.

Management. Thirteen antiviral drugs are FDA approved for therapy of herpesvirus infections (Table 1.9) [62]. Ophthalmic preparations of trifluridine and vidarabine are used

Table 1.9 FDA-approved Anti-herpesvirus Agents

Human herpes virus	Generic name	Trade name
Herpes simplex virus 1 & 2 and/or herpes zoster virus	Acyclovir	Zovirax
	Valacyclovir	Valtrex
	Famciclovir	Famvir
	Foscarnet (Acyclovir resistant HSV and VZV)	Foscavir
	Penciclovir (topical only)	Denavir
	Trifluridine (optical only)	Viroptic
	Vidarabine (optical only)	Vira A
	n-docosanol (topical only)	Abreva*
Cytomegalovirus	Ganciclovir	Cytovene, Vitrasert
	Valganciclovir	Valcyte
	Foscarnet	Foscavir
	Cidofovir	Vistide
	Fomivirsen (intravitreal only)	Vitrasene
Human herpesvirus-8 (AIDS-related Kaposi's sarcoma)	Interferon-α	Roferon-A Intron-A

*Over the counter, has antiviral activity, but not specifically approved as an antiviral drug.

for treatment of HSV- and VZV-associated keratitis and keratoconjunctivitis. Topical, oral, and intravenous formulations of acyclovir are available. Topical acyclovir has very low efficacy, but continues to be used for therapy of HSV infections. Oral, genital, and other HSV infections are treated with oral acyclovir [63]. Primary varicella and herpes zoster require a four-fold higher dose of acyclovir [64,65]. Frequent dosing and low (i.e., 15–20%) bioavailability limit the efficacy of oral acyclovir. Therefore, the intravenous preparation is favored in immunocompromised patients with HSV or VZV infections, especially with disseminated disease. Acyclovir is not only very effective in suppressing signs and symptoms of genital herpes, but was also demonstrated to reduce asymptomatic viral shedding of HSV-2 by 95% [66–68].

Two additional drugs, famciclovir and valacyclovir [69,70], were approved for treatment of herpes zoster to overcome the limitations of oral acyclovir. More convenient dosing and greater bioavailability after oral dosing are provided by famciclovir and valacyclovir than with acyclovir. These newer drugs are also approved for episodic treatment of recurrent genital herpes. Penciclovir, a metabolite of famciclovir, and n-docosonal are approved in topical formulations for the therapy of herpes labialis. Fomivirsen is an antisense compound directed against CMV and is given via intraocular injection. Fomivirsen, valganciclovir, cidofovir, foscarnet, and ganciclovir are approved for treatment of CMV infections. The latter three drugs are administered intravenously and are associated with markedly higher rates of toxicities than the three antiviral agents approved for systemic therapy of HSV and VZV infections. Ganciclovir in oral and ocular implant forms is approved for CMV prophylaxis in immunocompromised patients; valganciclovir is approved for induction and maintenance therapy of CMV retinitis; foscarnet is also approved for therapy of acyclovir-resistant HSV infections.

VZV is the only herpes virus for which a vaccine is currently available for prophylaxis (Table 1.5) [71]. Approval for this live, attenuated viral vaccine (Oka strain) came in 1995 for prevention of primary varicella (chickenpox); the vaccine produces a 95% seroconversion rate. Approval of a more concentrated form for prevention of herpes zoster (shingles) came in 2006. Studies are ongoing with recombinant glycoprotein vaccines for the prophylaxis (and possible therapy) of HSV infections [72].

Parvoviruses

The only parvovirus know to infect humans is parvovirus B19, which is the cause of erythema infectiosum (Fifth disease) (Table 1.8) and papular pruritic socks and gloves syndrome [73]. Erythema infectiosum presents most commonly in children and often occurs in epidemics in late winter and early spring [74]. This syndrome begins with nonspecific symptoms approximately 4–14 days after exposure to parvovirus B19, which is transmitted primarily by the respiratory route. Erythematous confluent, edematous plaques appear on the cheeks after about 2 days of low-grade fever, headache, and coryza. A "slapped" appearance of the cheeks is accompanied by continuation of the above-mentioned symptoms and the appearance of cough, conjunctivitis, pharyngitis, malaise, myalgias, nausea, diarrhea, and occasional arthralgias. The facial rash fades after 1–4 days concomitant with the appearance of erythematous macules and papules with a reticulated pattern on the extensor surfaces of the extremities, neck, and trunk. The rash usually lasts for 1–2 weeks, but can persist for months and can be pruritic. Since parvovirus B19 is not usually found in respiratory secretions or in the serum after the appearance of cutaneous manifestations, patients with erythema infectiosum appear to be infectious only before the appearance of the rash.

Acute arthropathy, usually without rash, is often associated with primary parvovirus B19 infection in adults. Transient aplastic crisis in patients with chronic hemolytic anemias, parvovirus-related chronic anemia in immunocompromised patients, and nonimmune fetal hydrops are other clinical presentations of parvovirus B19 infection potentially much more serious than erythema infectiosum but, uncommonly accompanied by rash.

Pathology. Although the rash appears 17–18 days following infection, viremia appears 6–14 days after a susceptible patient contracts parvovirus B19 via the respiratory route. The pathogenesis of erythema infectiosum is not understood and may relate to immune complex formation, but the systemic manifestations of parvovirus B19 infection involve viral lysis of erythroid precursor cells. There are no diagnostic histologic changes in the skin of these patients.

Laboratory Findings. In erythema infectiosum recent infection is indicated by detection of serum IgM directed to parvovirus B19 via RIA or ELISA. After 1 month, serum levels of IgM start to decline, but are still detectable for 6 months after infection. One week following infection, parvovirus B19-specific IgG can be detected and persists for years. Less readily available tests exist for detection of the virus, such as RIA, CIE, ELISA, dot blot hybridization, and PCR. Human erythroid progenitor cells can be used to culture the virus.

Management. Treatment of erythema infectiosum is aimed at relief of symptoms since no antiviral therapy exists for parvovirus B19. Development of a vaccine appears feasible because one infection with the virus produces lifelong immunity.



Figure 1.4 Merkel cell carcinoma, which was rapidly fatal despite aggressive therapy and was found to contain DNA from the Merkel cell polyomavirus.

Polyomaviruses

Polyomaviruses are small DNA viruses with oncogenic potential, but they usually persist in the host without causing disease. The polyomavirus that has been most closely associated with serious disease in humans is the JC virus, which can cause fatal progressive multifocal leukoencephalopathy in AIDS patients and other immunocompromised persons. In 2008, a new species, the Merkel cell polyomavirus was described and has been associated with the majority of cases of the highly aggressive Merkel cell carcinoma studied thus far (Fig. 1.4).

RNA VIRUSES

Enteroviruses

Enteroviruses, such as coxsackieviruses, are small RNA viruses belonging to a subgroup of the family Picornaviridae. The two most distinctive clinical syndromes are HFMD and herpangina, although a variety of enteroviruses, particularly coxsackieviruses, cause mucocutaneous manifestations. Most epidemic cases of HFMD are associated with coxsackievirus A16, but HFMD may be associated with coxsackieviruses A4–7, A9, A10, B2, or B5 as well as echovirus 71. Coxsackieviruses A2, A4, A5, A6, A8, or A10 cause herpangina.

Hand-Foot-Mouth Disease

Persons in their preteen to early teen years are most susceptible to HFMD [76]. This disease should be distinguished from foot-and-mouth disease (FMD) or hoof-and-mouth disease, which is a viral disease of cloven-hoofed animals. Although FMD is due to a picornavirus, the disease very rarely affects humans. HFMD is spread via oral or fecal-oral routes. A prodrome characterized by low fever, malaise, and abdominal or respiratory symptoms develops after an incubation period of 3–6 days; this prodrome precedes the mucocutaneous lesions by 12–24 hours. Most common on the hard palate, tongue, and buccal mucosa, oral lesions begin as macules that rapidly progress to vesicles and then to shallow, yellow-to-gray ulcers with an erythematous halo. Concomitant with or soon after the oral lesions, cutaneous vesicles appear and are most prevalent on the hands and feet. Cutaneous and oral lesions are usually tender or painful. In 5–10 days, both types of lesions resolve without treatment.

Herpangina

Herpangina is caused by viruses spread via routes similar to those causing HFMD. Children from 1 to 7 years of age are most commonly seen with herpangina, which begins abruptly with fever, sore throat, dysphagia, and malaise [77]. Small gray-white vesicles surrounded by erythema appear on the posterior palate, uvula, and tonsils. The vesicles usually ulcerate. Within 4–5 days, systemic symptoms usually resolve, and the ulcers heal spontaneously within 1 week.

Pathology. Viral infection of the buccal mucosa extends to regional lymph nodes in HFMD or herpangina. A viremia carries the virus to mucocutaneous sites approximately 48 hours later, resulting in intraepidermal vesicles containing neutrophils, mononuclear cells, and proteinaceous eosinophilic material. A perivascular polymorphous infiltrate composed of lymphocytes and neutrophils is observed in the edematous subvesicular dermis.

Laboratory Findings. A mild leukocytosis (i.e., 10,000 to 15,000/mm^3) may be seen in both HFMD and herpangina. The responsible virus may be recovered using tissue culture techniques or type-specific serology can identify the responsible coxsackievirus.

Management. Since no vaccine or antiviral drug is available for HFMD or herpangina, management is symptomatic.

Paramyxoviruses

Paramyxoviruses (Paramyxoviridae), such as measles, are enveloped, single-stranded RNA viruses.

Measles

Measles (rubeola) is seen primarily in winter and spring and is most prevalent in children 5–10 years of age. An incubation period of 10–11 days precedes a prodromal phase. The prodrome is characterized by high fever, cough, coryza, conjunctivitis, malaise, and Koplik's spots on the buccal mucosa, which persist for 3–4 days. Developing first behind the ears and over the forehead, an erythematous macular and papular rash then spreads to the face, neck, trunk, and extremities within 3 days. The fever, cough, and conjunctivitis are most severe when the lesions reach confluence over the face and upper back. Two to three days after the appearance of the rash, the Koplik's spots disappear. The rash fades within 5 or 6 days, sometimes with fine desquamation. Encephalitis and purpura are uncommon complications. Subacute sclerosing panencephalitis is a rare, but usually fatal, complication of measles. Persons previously given killed measles virus vaccine, who are subsequently exposed to wild-type measles or to live attenuated measles virus vaccine, can develop atypical measles [78].

Pathology. Respiratory secretions spread the measles virus throughout the prodrome until 4 days after initiation of the rash. The appearance of skin lesions concomitant with detectable serum antibody suggests that virus-antibody complexes may initiate the damage, although the rash may be partly due to viral damage to epithelial and vascular endothelial cells. Likewise, immune complexes may cause the complications of encephalitis and thrombocytopenic purpura. Hyaline necrosis of epithelial cells, formation of a serum exudate around superficial dermal vessels, proliferation of endothelial cells followed by a leukocytic infiltrate of the dermis, and lymphocytic cuffing of vessels are seen in biopsies of the measles exanthem.

Laboratory Findings. In measles, routine laboratory tests are usually unremarkable, but specific tests can include viral culture or detection of viral antigens in secretions. Measles infection is confirmed more commonly via serology using ELISA, complement fixation, neutralization, or hemagglutination inhibition tests.

Management. Treatment is supportive therapy since no approved antiviral drug exists for measles. The live attenuated measles vaccine for prevention is effective (Table 1.5). If serum immunoglobulin is administered within 6 days of exposure to the virus, passive immunity may modify or prevent measles (Table 1.6).

TOGAVIRUSES

Togaviruses (Togaviridae), such as rubella and chikungunya, are enveloped, single-stranded RNA viruses.

Rubella

Between 14 and 21 days following exposure to the virus, the prodrome of rubella (German measles, 3-day measles) develops and becomes more prominent with the increasing age of the patient. Low-grade fever, headache, conjunctivitis, cough, sore throat, and marked lymphadenopathy can be observed during the prodrome; arthritis can be seen in adults. An erythematous macular to papular rash appears first on the face and then on the neck, trunk, and extremities from 1 to 4 days after initiation of the prodrome. The rash clears with fine desquamation after 2–3 days. During spring months, rubella is most common. Intrauterine infection produces congenital malformations in 50% of infected neonates, but the sequelae of rubella are rare in children and adults. The teratogenic findings, which can affect a wide variety of organ systems, especially the heart, eye, auditory system, bone, and CNS are most severe if the infection is early during pregnancy. The characteristic cutaneous findings of the TORCH syndrome, petechiae and ecchymoses, are produced by infection of the bone marrow [79,80].

Pathology. The virus can be recovered from the pharynx from 7 days before the rash until almost 2 weeks after the rash and is spread via the respiratory route. The initial measurable antibody response appears simultaneously with the rash, suggesting that the exanthem may be due to the inflammatory effects of antibody-virus complexes rather than direct viral infection of the vascular endothelium. Only nonspecific acute and chronic inflammatory changes are seen in skin biopsies of the rubella rash.

Laboratory Findings. The peripheral blood may contain increased numbers of atypical lymphocytes and plasma cells, but they are not diagnostic. Hemagglutination inhibition, RIA, ELISA, etc., are serologic tests to detect rubella antibodies. Viral RNA can be found with PCR, or the virus may be cultured. Direct immunofluorescence may detect viral antigen.

Management. Since no antiviral drug is approved for rubella, treatment is symptomatic. A live attenuated vaccine that is administered along with the mumps and measles vaccines (i.e., MMR) is used for prevention (Table 1.5).

Chikungunya

Chikungunya is a mosquito-borne togavirus that produces epidemics in countries in the area of the Indian Ocean and is being reported more recently from various other parts of the world. The morbidity of Chikungunya is frequently severe and is similar to that of Dengue fever. The acute fever lasts 2–5 days and is followed by prolonged arthralgias affecting the joints of the extremities. The joint pain associated with Chikungunya can persist for weeks or months.

RETROVIRUSES

Retroviruses (Retroviridae) such as human immunodeficiency virus (HIV) contain a central core surrounding two identical copies of the single-stranded viral RNA genome. An envelope formed by budding from the cell membrane covers the core. HIV, like other retroviruses, contains an RNA-dependent DNA polymerase (i.e., reverse transcriptase), which allows viral RNA to be converted into a proviral DNA sequence.

Human Immunodeficiency Virus

The most important retrovirus medically, epidemiologically, and in terms of cutaneous manifestations is HTLV-III, more commonly known as human immunodeficiency virus (HIV)-l. Other retroviruses, however, such as human T-cell leukemia virus (HTLV) types I and II can have cutaneous manifestations, particularly due to the association of HTLV-I with adult T-cell lymphoma/leukemia and infective dermatitis [81].

The signs and symptoms that lead to suspicion and serologic testing for HIV in individuals at high risk are often due to the mucocutaneous manifestations of HIV infection. Progression from asymptomatic HIV infection to full-blown acquired immunodeficiency syndrome (AlDS) may be reflected in a variety of mucocutaneous manifestations [82,83]. Sexual contact with an infected person, significant exposure to infected blood or blood products (including intravenous drug abuse), or perinatal exposure are the primary routes of transmission of HIV.

The incubation period in many persons infected with HIV may be 10 or more years before the appearance of signs or symptoms. Primary HIV infection is occasionally manifested by fever and mild systemic symptoms that may be accompanied by a papulosquamous exanthem that is similar to those seen with a variety of other viral diseases. Within 2 weeks, the exanthem and symptoms generally resolve spontaneously [84].

Over 90% of patients will develop secondary mucocutaneous manifestations of their infection as the disease progresses from asymptomatic HIV infection through advanced AIDS [85,86]. Infectious, neoplastic, or noninfectious/non-neoplastic signs may be observed. Herpesviruses, poxviruses (i.e., MC), and papillomaviruses are examples of opportunistic viral infections commonly presenting clinically in HIV-positive individuals. Not only are

relatively common organisms such as *Staphylococcus aureus*, *Streptococcus*, *Pseudomonas aeruginosa*, and *Treponema pallidum* responsible for opportunistic bacterial infections, but multiple species of Mycobacterium and unique infections, such as with *Bartonella quintana* and *B. henselae* (which cause bacillary angiomatosis), also have mucocutaneous manifestations. A variety of species of tinea as well as systemic fungi, including *Candida* sp., *C. neoformans*, and *Histoplasma capsulatum* produce mycotic infections. Kaposi's sarcoma is the most common neoplasm in HIV-positive patients and is associated with HHV-8. Inflammatory diseases (e.g., psoriasis and Reiter's disease), vascular diseases, hypersensitivities to drugs, insect bites, and ultraviolet light, pruritus, xerosis, ichthyosis, and seborrheic dermatitis are all common non-neoplastic/noninfectious mucocutaneous findings.

Pathology. The virus infects CD4+ T lymphocytes by attaching to the CD4 molecule. HIV also infects monocytes and macrophages that help to spread the virus to susceptible cells in the brain, lymph node, skin, lung, and gastrointestinal tract. Disease is produced by HIV killing CD4+ cells, by syncytia formation, and by induction of certain cytokines that may play a direct role in induction of malignancy, neurologic disease, and other clinical manifestations. Several weeks are usually required after infection for detectable antibody formation to HIV; in some cases, seroconversion may follow infection by more than 1 year. The exanthem associated with primary HIV infection usually demonstrates nonspecific changes such as a superficial perivascular and perifollicular mononuclear cell infiltrate predominately composed of CD4+ cells.

Laboratory Findings. Marked leukopenia, anemia, and thrombocytopenia may be found with progression of disease, as well as an elevated erythrocyte sedimentation rate and lymphocytic cerebral spinal fluid pleocytosis. Marked declines in CD3+ cells, CD4+ cells, and a reversed CD4/CD8 cell ratio accompany disease progression. Seropositivity to the virus using ELISA with confirmation by Western blotting documents HIV infection. Isolation of the virus from the blood or demonstration of HIV p24 antigenemia demonstrates the presence of HIV.

Management. Seven synthetic nucleoside analogs, zidovudine, zalcitabine, didanosine, stavudine, lamivudine, embricitabine, and abacavir, are approved for therapy of HIV infection (Table 1.10). All seven drugs work by inhibition of HIV reverse transcription [87–91]. Four non-nucleoside analogs, nevirapine, delaviridine, etravirine, and efavirenz, are also approved. The only nucleotide analogue is tenofovir. Saquinavir was the first protease inhibitor approved for treatment of HIV. Other available protease inhibitors include ritonavir, indinavir, nelfinavir, amprenavir, darunavir, atazanavir, tipranavir, fosamprenavir, and lopinavir. There is currently one fusion inhibitor available, enfuvirtid, one integrase inhibitor, raltegravir, and one entry inhibitor, maraviroc. Combinations of antiviral drugs from different classes appear to produce greater efficacy than higher doses of individual agents, thereby reducing both adverse events and viral resistance. Such combinations usually include at least one protease inhibitor and two drugs from the other classes, although combinations of nucleoside and non-nucleoside analogs have recently been demonstrated to be effective. Together, these agents form "highly active antiretroviral therapy" (HAART). HAART has produced marked reductions in morbidity and mortality of AIDS patients since 1996. Clinical trials are ongoing with a variety of other antiretroviral drugs, as are prophylactic and therapeutic HIV vaccines. Management of HIV-positive patients also requires treatment and prophylaxis of a variety of opportunistic infections and neoplasms, in addition to drugs aimed at the responsible retrovirus [92].

Table 1.10 FDA-approved Anti-retroviral Agents

Category of drug	Generic name	Trade name
Nucleoside analogues	Zidovudine	Retrovir
	Didanosine	Videx
	Zalcitibine	Hivid
	Stavudine	Zerit
	Lamivudine	Epivir
	Emtricitabine	Emtriva
	Zidovudine + lamivudine	Combivir
	Abacavir	Ziagen
	Abacavir + Lamivudine + Zidovudine	Trizivir
	Abacavir + lamivudine	Epzicom
Non-nucleoside analogues	Nevirapine	Viramune
	Delaviridine	Rescriptor
	Efavirenz	Sustiva
	Etravirine	Intelence
Nucleotide analogue	Tenofovir	Viread
	Tenofovir + emtricitabine	Truvada
	Tenofovir + emtricitabine +efavirenz	Atripla
Protease inhibitors	Saquinavir	Invirase
	Ritonavir	Norvir
	Indinavir	Crixivan
	Nelfinavir	Viracept
	Amprenavir	Agenerase
	Tipranavir	Aptivus
	Fosamprenavir	Lexiva
	Darunavir	Prezista
	Atazanavir	Reyataz
	Lopinavir + ritonavir	Kaletra
Fusion inhibitor	Enfuvirtide	Fuzeon
Integrase inhibitor	Raltegravir	Isentress
Entry inhibitor	Maraviroc	Selzentry

Miscellaneous Viruses

Hepatitis B, hepatitis C, several hemorrhagic fever viruses and a variety of other viral diseases have occasional cutaneous manifestations, but pathogenesis and histology of the rash in these diseases are often not well understood, or the eruption may not be specific for a particular viral infection (Table 1.11). Therefore, the rash of these viral infections may be of less diagnostic or prognostic significance as in the previously discussed viral diseases. Although these viruses are covered by individual chapters in this text, viruses having no (or very rare) mucocutaneous manifestations, such as rhinoviruses, influenza, respiratory syncytial virus, rabies, etc., are not discussed further (Table 1.12).

Recognition of characteristic mucocutaneous manifestations, however, of a variety of viral diseases either directly helps to determine the etiologic agent or assists the clinician in deciding which additional diagnostic tests to order. Proper management of the patient can be initiated from the results of such tests.

An important concept in the control of viral diseases is that antiviral drugs are generally virostatic, not virocidal.

Table 1.11 FDA-approved Anti-hepatitis Agents

Hepatitis virus	Generic name	Trade name
Hepatitis B virus	Interferon-alfa-2b	Intron A
	Peginterferon alfa-2a	Pegasys
	Lamivudine	Epivir-HBV
	Entecavir	Baraclude
	Adefovir	Hepsera
	Tenofovir	Viread
	Telbivudine	Tyzeka
Hepatitis C virus	Interferon-α	Roferon-A, Intron A, Infergen
	Interferon-α + ribavirin	Rebetron
	Peginterferon Alfa-2b + ribavirin	PegIntron + Rebetol
	Peginterferon alfa-2a + ribavirin	Pegasys + Copegus

Therefore, prevention of viral infections takes on an even greater level of importance. Such control includes good public health measures, such as sanitation, hand washing (and the use of disposable examination gloves), safe sex (abstinence, condoms), control of mosquitoes (and other vectors), testing of blood products, and single use of needles. Otherwise, the single most effective medical intervention is the use of vaccines. The prototype of a successful vaccine campaign was the eradication of smallpox. Since widespread vaccination of the general public stopped over 20 years ago, the majority of the world's population has no immunity to smallpox. Therefore, smallpox is considered to be a leading pathogen that could be used for bioterrorism.

Generally, the FDA-approved vaccines are several orders of magnitude safer, in terms of morbidity and mortality, than the diseases that they are designed to prevent. One vaccine, however, was removed from the market due to safety issues. Rotashield® was a live, oral tetravalent, rotavirus vaccine that was associated with several cases of intussusception and is considered to be causal [93]. It has been replaced by two new rotavirus vaccines, Rotarix and RotaTeq, which are not associated with increased rates of intussusception. Most associations between vaccines and adverse events are not, however, demonstrated to be causal. For example, the measles mumps rubella (MMR) vaccine was reported very recently not to have a causal relationship to autism [94,95]. Likewise, a causal relationship between the hepatitis B vaccine and a variety of autoimmune diseases has been disproven. This vaccine does not increase the risk of multiple sclerosis nor does it cause a relapse of pre-existing multiple sclerosis [96,97]. Nevertheless, suspected relationships between vaccines and adverse events need to be reported to the "Vaccine Adverse Event Reporting System" (1-800-822-7967) so that the excellent safety record of vaccines can be maintained.

Table 1.12 FDA-approved Anti-influenza Agents™

Generic name	Trade name	Indication
Amantadine	Symmetrel	Influenza A
Ramantadine	Flumadine	Influenza A
Oseltamivir	Tamilflu	Influenza A and B
Zanamivir	Relenza	Influenza A and B

It is anticipated that the future will bring safe and effective vaccines for a variety of viral diseases, e.g., HIV, hepatitis C, HSV, and new strains of influenza. Although no vaccine is available for the therapy of a viral disease, our concept of vaccines is now being expanded by ongoing clinical trials of therapeutic vaccines, e.g., for HIV, HSV, and HPV.

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2 Cutaneous Resistance to Viral Infections

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Introduction

The skin permits primary immune sensitization, retains immunologic memory, and houses immunocytes, and can be preferentially affected by T-cell malignancies. Based upon this information, Streilein proposed a specific relationship between the immune system and the integument, much like the gut-associated lymphoid tissue [1]. He then proposed the concept of skin-associated lymphoid tissue (SALT) [2]. SALT is composed of: (1) keratinocytes, which can phagocytize, release many cytokines, and even express major histocompatability complex (MHC) class II antigens upon incubation with interferon-γ (IFN-γ); (2) epidermal Langerhans cells (LC), dendritic cells that have surface expression of MHC class II, CD1, CD3, and CD4 molecules, and are the predominant scavenger antigen-presenting cells of the epidermis; (3) skin tropic T cells, which in the epidermis include mainly "inactive" memory T cells of predominantly CD8+ phenotype, although CD4+ and CD4−, CD8−, and γδ+ T cells are also present; and (4) skin endothelial cells, which direct cellular traffic in and out of the skin. The epidermis contains the basic elements needed for an immune response (T cells, antigen-presenting cells, and cytokines). This, in conjunction with its anatomic structure, serves as a primary line of defense against infections. Therefore, we review the components of SALT, and their interactions with viruses having cutaneous manifestations.

Langerhans Cells

LCs are the professional antigen-presenting cells of the epidermis. LCs capture exogenous antigens and process them into peptides for presentation to CD4+ T cells in the context of MHC class II. So far, two predominant methods of antigen capture have been described in LCs; one is micropinocytosis and the other involves a mannose receptor-mediated mechanism. Additionally, when infected with a virus such as human immunodeficiency virus (HIV), LCs present viral peptides to CD8+ T cells in the context of a different MHC class (class I).

Skin biopsies from 7 of 40 HIV-positive individuals reacted with anti-HIV-1 core protein in an indirect immunofluorescence assay [3]. The only cells infected with HIV that could be detected were LCs, although Heng et al. have shown that keratinocytes, which do not express CD4, can be co-infected with HSV-1 and HIV in vivo [4]. Berger et al. demonstrated that LCs could be infected with HIV in vitro, and that LCs from HIV-positive individuals could infect mononuclear phagocytes from HIV-negative individuals [5]. Cimarelli et al. quantified the proviral DNA in LCs and found that this value correlated with the frequency of peripheral blood CD4+ T cells infected with HIV in acquired immune deficiency syndrome (AIDS) patients [6]. Two important questions arise: how are the LCs infected? How do they contribute to the pathology associated with AIDS?

HIV, the causative agent of AIDS, is a retrovirus that can incorporate into cellular DNA through reverse transcriptase. Infection leads to a progressive weakening of cell-mediated immune function and a progressive decline in the numbers of peripheral blood CD4+ cells. The effect on the humoral immune system is the induction of hypergammaglobulinemia, which enables diagnosis but is not sufficient to eliminate HIV infection. HIV preferentially infects HIV-specific memory CD4+ T cells as evidenced by the fact that these cells contain more viral DNA than other memory CD4+ cells [7]. Additionally, antigen-specific T cells responding to antigens presented by dendritic cells are more likely to be infected with HIV than non-responding T cells [8].

LCs normally reside in the epidermis. Upon activation, these cells migrate to the draining lymph nodes and come in contact with T cells. By using the HIV animal model of simian immunodeficiency virus (SIV) and rhesus macaques, it was shown that dendritic cells of the lamina propria are the first to be infected with intravaginal inoculation of virus [9]. Four rhesus macaques were inoculated intravaginally and then sacrificed 2, 5, 7, and 9 days later. The animal sacrificed at 2 days post-inoculation showed productive infection only in the dendritic cells of the lamina propria. Conversely, no infection could be detected by polymerase chain reaction (PCR) in the epithelial layer, including in LCs. Interestingly, SIV-infected cells in the lamina propria were found only immediately beneath the single columnar epithelium of the endocervix. Paradoxically, other investigators have shown that up to 40% of infected cells of the vaginal tract in rhesus macaques with chronic infection of SIV are intraepithelial LCs [10]. Miller and Hue were the first to provide in vivo evidence that LCs of the genital tract are infected with SIV. These same investigators claim that the dendritic cells of the epithelial layer are the first to be infected with SIV during vaginal inoculation [10]. A later study, using an ex vivo human organ culture system, definitively showed that HIV-1 simultaneously penetrates both intraepithelial vaginal LCs and CD4+ T cells upon contact in situ [11]. HIV enters LCs mainly via endocytosis of intact virions, while CD4+ cells are infected directly via CD4 and CCR5 receptor-mediated fusion. This study further demonstrated that the majority of intraepithelial CD4+ cells express CCR5 and that LCs commonly express CD4 and CCR5 (Fig. 2.1). These findings explain the rapidity of initial HIV infection in these cell types.

Kawamura et al. found that R5 HIV infection of LCs is dependent upon the CCR5 co-receptor and that CCR5 receptor polymorphisms account for varying levels of genetic susceptibility to HIV. Specifically, individuals expressing the mutant CCR5 allele, *ORFΔ32*, in both homozygous and heterozygous forms were less susceptible to HIV infection of LCs compared to individuals who lacked the mutant allele [12]. In a later study, they found that HIV-infected LCs transmit R5 HIV to T cells in a process that is mediated by CD4 and CCR5 receptors (Fig. 2.2). Further, LCs are responsible for more than 95% of HIV dissemination to subepithelial tissues [13]. Fahrbach et al. found that activated LCs

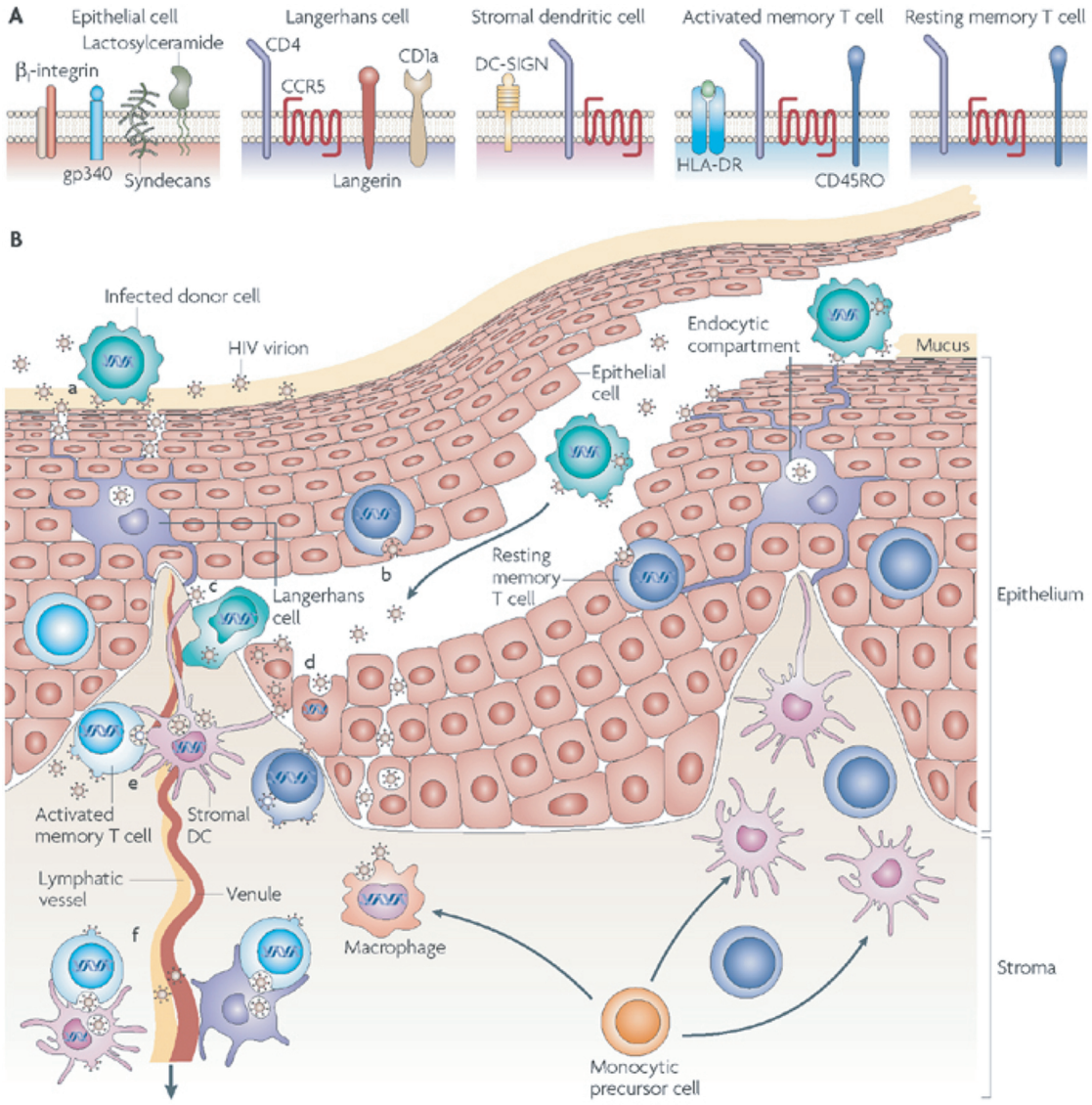


Figure 2.1 Pathways of HIV invasion in the mucosa of the vagina and ectocervix: characteristic phenotypic cell receptors and receptors relevant for HIV binding and infection are shown in A (top). The possible pathways of HIV penetration are summarized in **B**. (a) Free HIV virions or HIV-infected donor cells are trapped in mucus, resulting in penetration of the free virions into gaps between epithelial cells or attachment of HIV-infected donor cells to the luminal surface of the mucosa and secretion of virions on contact. The virions are then captured and internalized into endocytic compartments by Langerhans cells that reside within the epithelium. (b) HIV can also fuse with the surface of intraepithelial CD4+ T cells, followed by productive infection of these cells. (c) Infected donor cells or free virions can immigrate along physical abrasions of the epithelium into the mucosal stroma. There, they are taken up by lymphatic or venous microvessels and transported to local lymph nodes or into the blood circulation, respectively, or they make contact with stromal DCs, T cells, and macrophages. (d) Virions can transcytose through epithelial cells near or within the basal layer of the squamous epithelium, productively infect basal epithelial cells, be internalized into endocytic compartments, or penetrate between epithelial cells. (e) Once within the stroma, virions can productively infect stromal DCs or be internalized into the endocytic compartments of DCs and pass from the stromal DCs to CD4+ T cells across an infectious synapse where massive productive infection of CD4+ T cells ensues. In addition, virions can productively infect resting mucosal CD4+ memory T cells in the stroma and possibly stromal macrophages. (f) Productively infected CD4+ T cells and stromal DCs, and stromal DCs or intraepithelial LCs harboring virions in endocytic compartments, can emigrate into the submucosa and the draining lymphatic and venous microvessels. CCR5, CC-chemokine receptor 5; DC-SIGN, dendritic cell-specific ICAM-3-grabbing non-integrin. (Reprinted from F Hladik, MJ McElrath. Setting the stage: host invasion by HIV. Nat Rev Immunol 8: 450, 2008.)

are capable of transinfecting other target cells without becoming infected themselves. Activated LCs enhance transinfection at a rate 35 times higher than inactivated LCs. The authors suggest that transinfection is mediated by internalization of HIV virions into a trypsin-resistant compartment where they maintain infectivity and are later transmitted to target cells [14]. Blauvelt et al. propose that productive infection of dendritic cells by HIV-1 and the cell's ability to capture virus are mediated through separate pathways [15]. While productive infection is dependent on the CD4 ligand and co-receptor stimulation, HIV capture and transmission can take place independent of these factors. Epithelial LCs capture virus and deliver them to the draining lymph nodes. During activation by T cells, in the cytokine-rich lymph nodes, LCs may subsequently become productively infected. Recirculation of these LCs to the epithelial layer may explain the 40% composition of infected cells in the vagina [10].

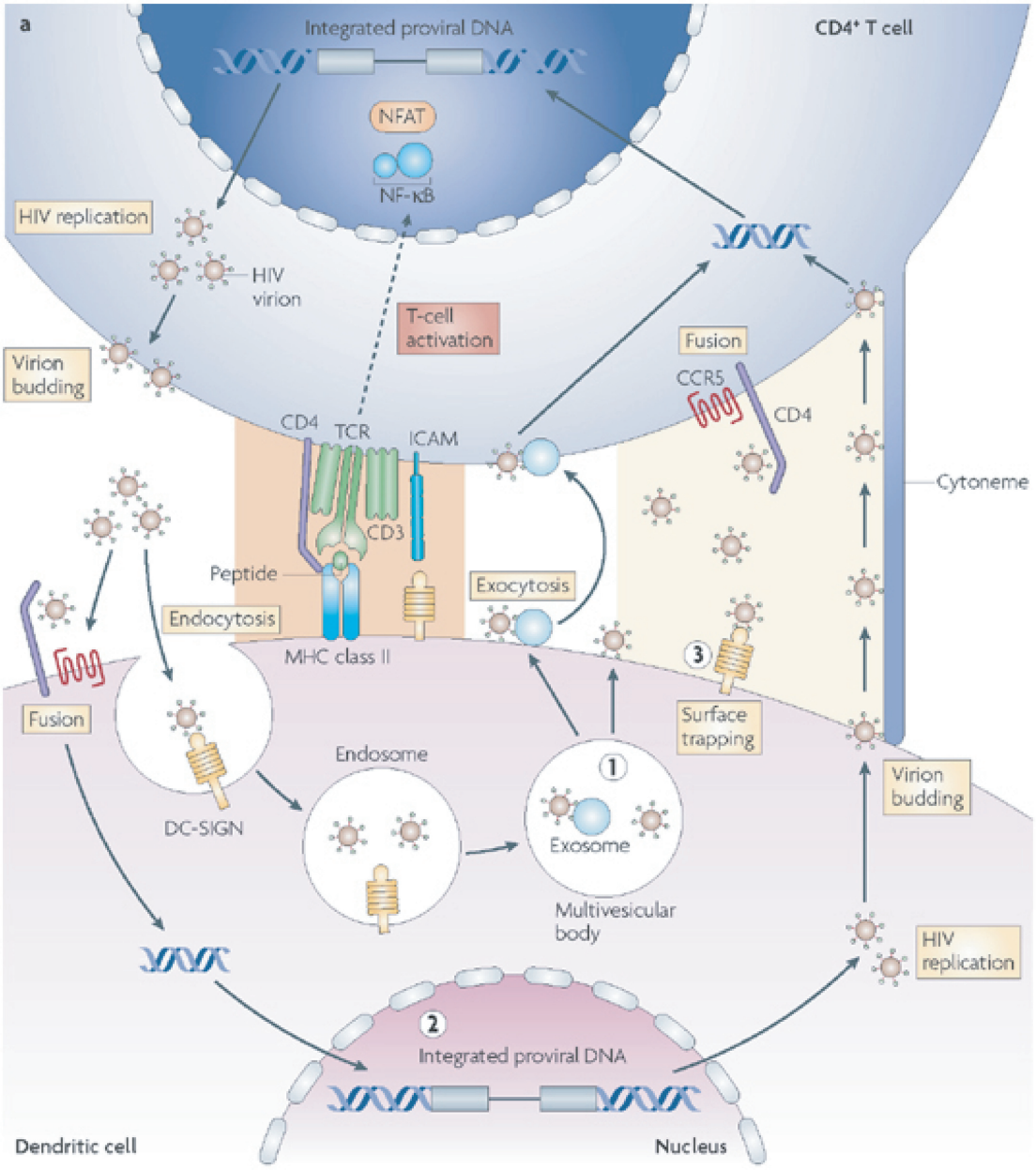


Figure 2.2 Pathways of HIV-1 passage between dendritic cells and CD4+ T cells: DCs can store HIV-1 in three forms for eventual infection of CD4+ T cells. (1) HIV can be stored as endocytosed intact virions in multivesicular bodies, following endocytic entry via C-type lectins such as DC-specific ICAM-3-grabbing non-integrin (DC-SIGN; also known as CD209). (2) HIV-1 can also be stored as an integrated provirus following entry by CD4− and co-receptor-mediated fusion, which leads to productive infection of DCs. (3) HIV can be stored as surface-bound intact virions by C-type lectins, such as DC-SIGN. Passage of HIV-1 from DCs to CD4+ T cells occurs most effectively across an infectious synapse (yellow shading), formed by a concentration of HIV-1 virions on the DC side and HIV receptors such as CD4 and CC-chemokine receptor 5 (CCR5) on the T-cell side. HIV is released into the infectious synapse either by exocytosis of stored virions from multivesicular bodies or by budding of newly formed virions following active viral replication. Virions trapped to surface receptors such as the C-type lectin DC-SIGN can also accumulate in the infectious synapse. Migration of HIV toward the T cell may be further enhanced by "surfing" of virions along the outer surface of filopodia or cytonemes that are extended from the T cell toward the DC. Coupling of virions to exosomes as they are being released from multivesicular bodies also increases their infectivity. Exosome-associated virions are likely to be transmitted to CD4+ T cells through membrane binding and fusion, either within the infectious synapse or over longer distances. In parallel with transmission of virus from the DC to the CD4+ T cell, the DC also presents antigenic peptides through MHC class II molecules to the T-cell receptor (TCR). During peptide recognition, additional receptor–ligand pairs that are important for T-cell stimulation accumulate in this region and form an immunological synapse (orange shading). Signals delivered through the immunological synapse lead to T-cell activation, which ultimately causes transcription factors such as nuclear factor-κB (NF-κB) and nuclear factor of activated T cells to translocate into the nucleus of the T cell. There, they bind to the enhancer region of the viral long terminal repeat and activate viral gene transcription, driving HIV-1 replication. (Reprinted from F Hladik, MJ McElrath. Setting the stage: host invasion by HIV. Nat Rev Immunol 8: 453, 2008.)

Consistent with this viral transfer model is the recent discovery of a new lectin, designated DC-SIGN. DC-SIGN binds ICAM-3 and HIV and maintains it on the cell surface for days, in a native conformation conducive to infection. However, LCs are not known to express DC-SIGN, but once in the dermis, dendritic cells express this lectin. Since epidermal, i.e., DC-SIGN-negative dendritic cells

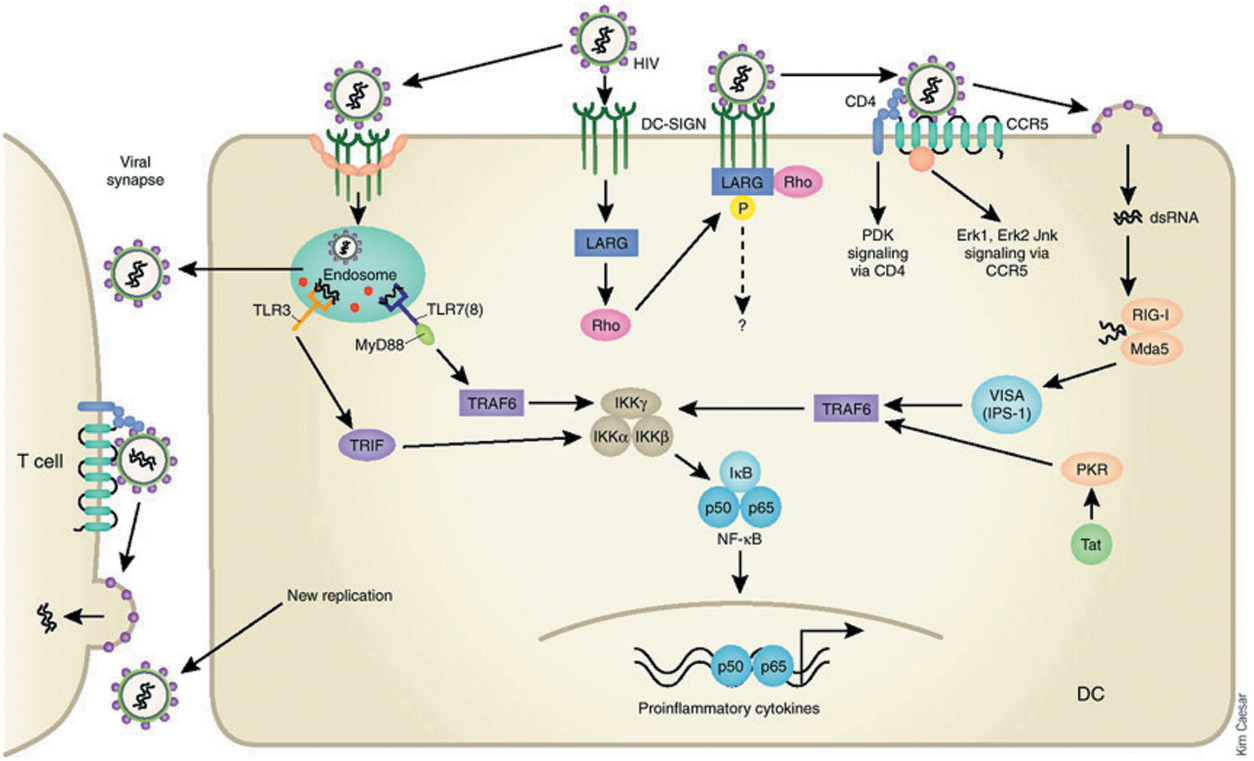


Figure 2.3 Binding of HIV-1 to DC-SIGN: binding of virus to DC-SIGN activates NF-κB through TLR3 and TLR7 (left) and/or leads to the phosphorylation of LARG and activation of Rho (middle). The LARG-Rho complex then becomes associated with DC-SIGN at the cell surface. Through an as yet unidentified mechanism ("?"), this inhibits the maturation of DCs and stimulates their ability to form synapses with T cells after HIV-1 infection. After binding to DC-SIGN, HIV can be transferred laterally ("*cis* transfer") to immature DC-expressed CD4 and CCR5 (top right); this is followed by fusion of the viral envelope (right) with the plasma membrane, delivery of double-stranded RNA (dsRNA) to RIG-1 or Mda5, and activation of NF-κB through VISA-TRAF6 (middle bottom). Transfer of HIV from DCs to T cells ("*trans* transfer") through the viral synapse (top left) occurs in two phases: first, from the DC endosome, and second, after new HIV replication (bottom left). IKK, inhibitor of NF-κB (IκB) kinase; p50 and p65, subunits of NF-κB. (Reprinted from AL Cunningham, AN Harmon, H Donaghy. DC-SIGN 'AIDS' HIV immune evasion and infection. Nat Immunol 8 (6): 557, 2007.)

are more selective for M-tropic HIV-1, the LCs likely transmit M-tropic HIV to the dermal dendritic cells, which become DC-SIGN positive to facilitate HIV transmission [16,17]. When HIV binds DC-SIGN, a virion may be endocytosed and destroyed within the dendritic cell, replicate within the dendritic cell, or be transferred from the dendritic cell to T cells (Fig. 2.3) [18].

It has been proposed that Langerin, a C-type lectin expressed on LCs, may have a function analogous to DC-SIGN on dendritic cells. However, de Witte et al. found that Langerin actually prevents HIV-1 infection of LCs by internalizing HIV virions into Birbeck granules and degrading these virions (Fig. 2.4) [19]. These results were confirmed by Kawamura et al.; however, they found that LCs may be infected when exposed to high concentrations of HIV. Thus, they suggest that Langerin may be saturated at high viral concentrations, rendering it unable to prevent HIV infection [13].

Alternatively, seeding of LCs may occur by direct inoculation and productive infection. This is particularly plausible in co-infection scenarios where, for example, a herpetic lesion has compromised the cornified layer of the epidermis. The lesions attract and activate CD4+ cells. This leaves LCs and other cells in the epidermis and possibly dermis vulnerable to primary infection. This idea is supported by the finding, in the rhesus macaques model, that the only DC-SIGN-positive cells of the lamina propria that were infected were those directly beneath the single columnar epithelium [9]. This epithelium barrier is an easier barrier to penetrate than that of squamous epithelium. Additionally, the epithelium of the vagina is not as tight and impenetrable as the skin. It is moist and fluid is continually passing through the intercellular spaces. These epithelial cells are connected by discontinuous patches of desmosomes, the weakest form of intercellular junction [9].

Another question that arises is the role of HIV on the status and function of LCs. A significant reduction of epidermal LCs in HIV-positive individuals has been demonstrated [20]. HIV infection can result in a milieu where levels of various cytokines, especially interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) are chronically elevated (Fig. 2.5) [21]. These cytokines are essential and powerful stimulators of LC migration out of the epidermis [22,23]. Cytokine stimulus may partly explain the reduction of epidermal LCs in HIV infection. LCs originate from CD34+ marrow-derived cells that can differentiate along two primary pathways. One pathway leads to the formation of a group of cells most known for their expression of CD1, and they go on to become the LC of the epidermis [24]. The alternative pathway leads to the dendritic cells of the dermis, noted for expression of CD14. While the CD1+ cells of the epidermis promote cell-mediated immunity (CMI), the CD14+ cells of the dermis tend to initiate a humoral response [24]. When the hypergammaglobulinemia in HIV and deficiency of CMI are considered, speculation is that

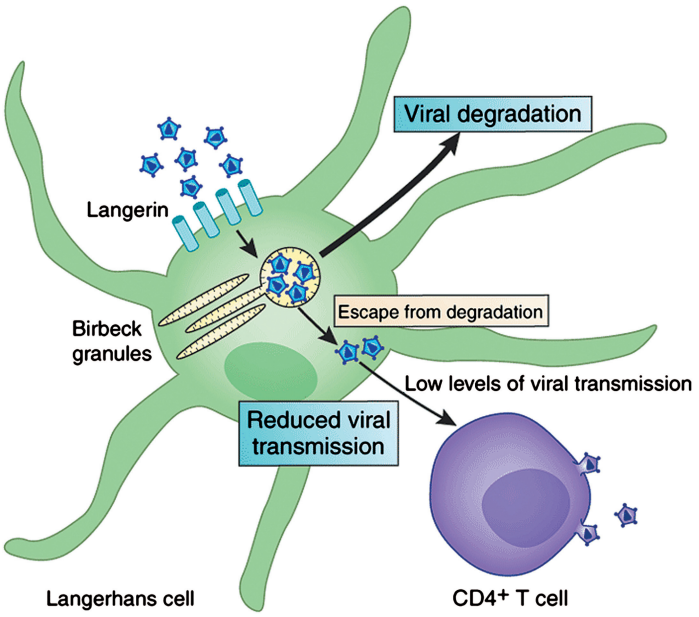


Figure 2.4 HIV-1 clearance by Langerhans cells: Langerhans cells in the mucosal epithelium are probably the first cells targeted by the virus during sexual transmission. Langerhans cells selectively express a C-type lectin, Langerin, which binds HIV-1 virions and drives them to Birbeck granules. Most of the captured virions are then rapidly degraded. Langerhans cells are thus responsible for virus clearance. However, a fraction of the incoming virions may escape degradation, in which case they will replicate at low levels in Langerhans cells and be transmitted to CD4+ T cells. (Reprinted from O Schwartz. Langerhans cells lap up HIV-1. Nat Med 13 (3): 246, 2007.)

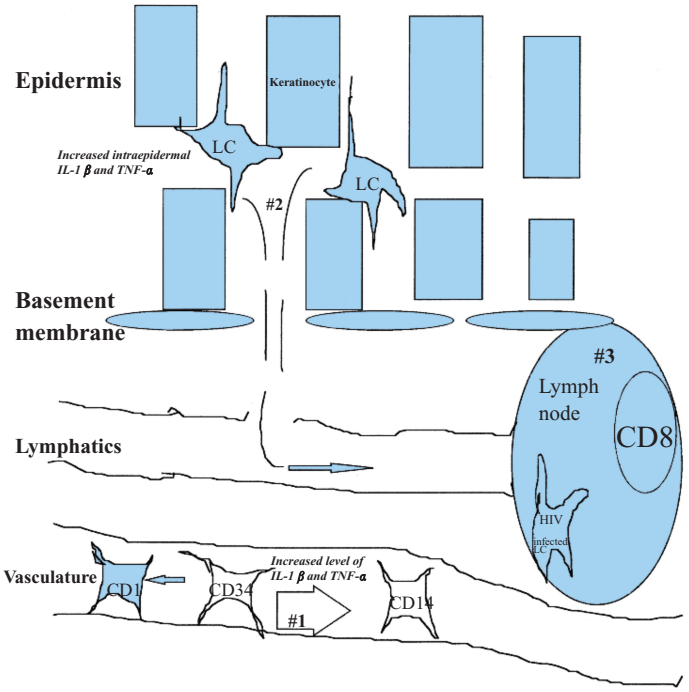


Figure 2.5 Intradermal depletion of Langerhans cells in HIV infection by three separate mechanisms: (1) IL-1β and TNF-α influence CD34 Langerhans cells precursors to differentiate towards CD14 dermal dendritic cells rather than CD1 LC; (2) Langerhans cells migrate toward the draining lymph nodes; (3) cytotoxic lymphocytes within lymph nodes destroy HIV-infected Langerhans cells. (Reprinted from AL Cunningham, Z Mikloska. The holy grail: immune control of human herpes simplex virus infection and disease. Herpes 8 (Suppl 1): 7A, 2001.)

direct or indirect cytokine manipulation by HIV results in a preference for the CD14+ pathway. This might be a second factor in the depletion of epidermal LCs. Lastly, HIV infection has definite cytopathic effects on LCs. After migrating to lymph nodes and activating T cells, dendritic cells do not leave the lymph nodes in the efferent lymphatics. In vitro studies have shown that HIV-infected dendritic cells could serve as targets of cytotoxic lymphocytes (CTL) [25]. In one study, as many as 50% of the dendritic cells were lysed after 3 days of HIV exposure, which was then followed by exposure to activated CTL.

Cytokines strongly influence HIV-infected LCs. Leonard et al. created a transgenic mouse with the HIV long terminal repeat (LTR), which contains all known HIV transcriptional response elements, linked to a reporter gene [26]. LCs from the mouse skin had a higher reporter gene activity when compared to other cells of the monocyte/macrophage lineage. This indicates that HIV provirus is easily induced in LCs. The transgenic mouse macrophages treated with a variety of cytokines (colony-stimulating factor-1, granulocyte-monocyte colony-stimulating factor (GM-CSF), IL-1α, and IL-2) had much higher reporter gene activity than macrophages incubated in the absence of these cytokines. These results indicate that the above cytokines are involved in modulating SALT, and it would be important to elucidate their role in human skin from HIV-positive patients.

In healthy skin, IL-1 is constitutively made by keratinocytes, whereas LCs make IL-1 upon activation and depend upon it for their proper maturation [27]. IL-1 upregulates IL-2 and IL-2 receptor production by T cells, a process necessary for an antigen-specific immune response. Stage of disease, by CDC classification, has been correlated with epidermal LC numbers. Subsequently, Dreno et al. have shown a relationship between intraepidermal levels of IL-1 in normal skin of HIV-positive patients and the stage of their disease [28]. All stage II patients had high levels of intraepidermal IL-1. Significant decreases in IL-1 were seen in stage III patients, with even lower or in some cases undetectable levels in stage IV^c and stage IV^d patients. It is likely that the paucity of intraepidermal LCs in these later stages is directly responsible for the lower levels of IL-1. These lower levels of IL-1 leave the epidermis devoid of T cells, vulnerable to infections, at risk for development of neoplasms, and anergic to recall antigens.

In addition to decreased epidermal LCs, symptom-free HIV-positive individuals have reduced intraepidermal CD4+ cell counts. After IL-2 injection, however, there is a local accumulation of T cells, monocytes, and LCs [29]. Although epidermal infiltration of CD4+ cells is normally reduced in HIV-positive patients, IL-2 induces a CD4+ infiltrative response equivalent to that seen in HIV-negative individuals and results in enhanced recall response to antigens [4]. Larsson et al. showed that dendritic cells can cross-present HIV antigens from both live and apoptotic monocytes carrying infectious and non-infectious HIV-1 in order to activate HIV-specific CD4+ and CD8+ T cells [30]. Maranon et al. found that dendritic cells can cross-present very small amounts of HIV proteins from both live and apoptotic HIV-infected CD4+ T cells. Therefore, inoculation of IL-2, which is usually made by T cells in response to IL-1, could be utilized to induce HIV expression and eradicate latently infected HIV reservoirs [31].

A great majority of T cells in the human epidermis have $\alpha\beta$ T-cell receptors. Some of these T cells lack the co-receptors CD4

and CD16 and their function in the epidermis is unknown. In humans, epidermal γδ+ cells are not dendritic and are involved in many diseases. CD1, which is expressed on LCs, can act as an antigen-presenting molecule for γδ+ T cells [32]. γδ+ cells, through non-MHC-restricted cytolytic activity, contribute greatly to immune surveillance against malignancies and viral infections [33]. In HIV infection, local γδ subtype ratios of bronchial-associated lymphoid tissue (BALT) are altered relative to HIV-negative individuals [34]. Hennier et al. observed higher γδ+ cells in the blood of relatively healthy HIV-positive patients than in symptomatic HIV-positive patients [35]. HIV-positive patients with oral candidiasis had even lower blood γδ T-cell counts. Numerous infectious, neoplastic and idiopathic cutaneous manifestations in HIV patients, along with the known effects of HIV on γδ+ cells in other lymphoid tissues, would suggest that γδ+ cells are functionally affected in the skin of HIV-positive patients. Unfortunately, it is not known whether γδ counts increase or decrease in the epidermis of HIV-positive individuals. Indirect immunofluorescence assays of punch biopsies of skin using pan-γδ antibodies should be a simple and direct method of answering this question.

A decrease in intraepidermal LCs is a common phenomenon of viral infections; however, some viruses have adapted other mechanisms of influencing LCs (Table 2.1). Mature dendritic cells release the cytokines necessary for T-cell activation and to ward off HSV infections [36,37]. Salio et al. showed that infected dendritic cells are unable to upregulate co-stimulatory molecules, do not produce cytokines and do not acquire responsiveness to those chemokines required for migration to secondary lymphoid organs [38]. Kruse et al. demonstrated that HSV infection of dendritic cells leads to impaired T-cell stimulatory capacity and degradation of the cell surface marker, CD83, which is upregulated during maturation of dendritic cells [39]. HSV infection of dendritic cells leads to their apoptosis. Bosnjak et al. showed that apoptotic HSV-infected dendritic cells are phagocytosed by uninfected dendritic cells, which then stimulate HSV-specific CD8+ T cells [40]. A recombinant replication defective HSV-1 encoding a green fluorescent protein is used to compare infected and uninfected dendritic cells. Normally, dendritic cells are the primary producers of IFN-α. It may be that the dysregulation of dendritic cells by HSV, as described above, allows HSV to evade the immune system [41].

Keratinocytes

Keratinocytes are squamous epithelia that take part in SALT by production of cytokines, presentation of endogenous viral antigens in the context of MHC class I to CD8+ T cells, and expression of MHC class II when stimulated with IFN-γ. Human papilloma viruses (HPV) are DNA viruses that can directly infect keratinocytes (Fig. 2.6). HPV gains entry into the epidermis through a break in skin and remains in the basal layer. It replicates just below the granular layer and gives rise to a slowly growing lesion. There are over 100 different recognized HPV genotypes [42]. HPV are categorized by regional tropism and potential for malignant transformation. For example, HPV-6 and -11 are tropic for the genital skin and mucous membranes, giving rise to condyloma acuminata, which has a low probability of undergoing malignant transformation. Epidermodysplasia verruciformis (EV) is characterized by persistent disseminated wart-like skin lesions associated with a variety of unique HPV types, e.g., HPV-5 and -8. One-third of patients with EV later experience malignant transformation of the HPV-infected lesions.

Recently, the active role of SALT in HPV infections has been further elucidated. Generally, regressing viral lesions are accompanied by CD4+ and CD8+ cellular infiltrates, an increase in epidermal LCs, an increase in dermal dendritic cells, and the appearance of human leukocyte antigen (HLA)-DR+ keratinocytes in the dermis. HPV lesions have a reduced number of epidermal LCs, which Drijkoningen et al. propose is likely due to direct cytotoxic effects of the virus [43]. Furthermore, lesions positive for HPV viral antigens are more likely to have reduced HLA-DR+ cell counts in the epidermis [44]. Keratinocytes are known to express

Table 2.1 Alterations in Langerhans Cells Following Viral Interaction

Virally-induced changes in Langerhans cell structure and function
Increased IL-1*β* in early stages of HIV infection
Increased TNF-*α*
Increased Langerhans cells migration out of epidermis
Decreased IL-1 in late stages of HIV infection
Decreased IL-2 in late stages of HIV infection
Decreased antigen presentation ability
Decreased T cell stimulatory capacity
Increased apoptosis of Langerhans cells

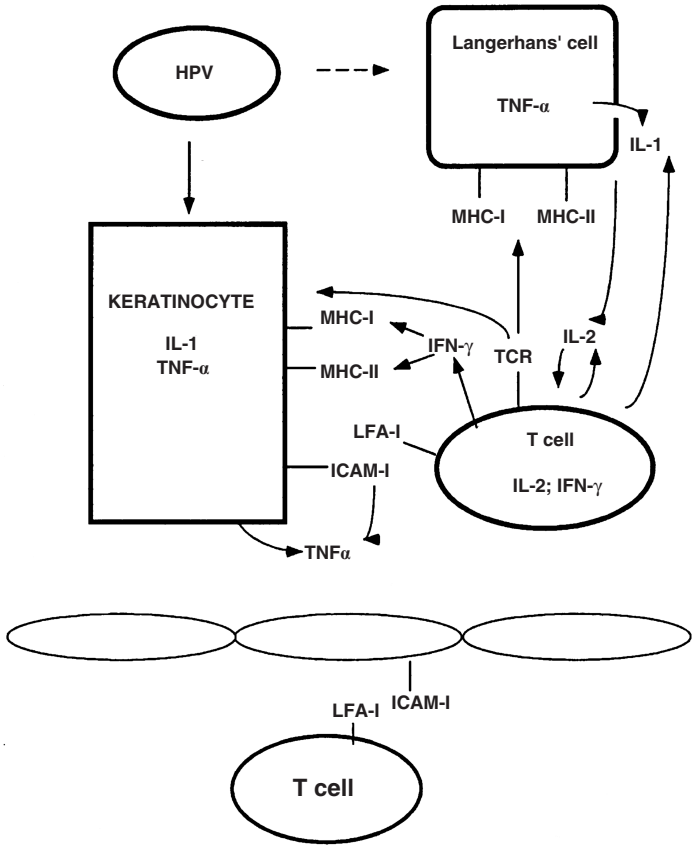


Figure 2.6 Necessary immune mechanisms for effective HPV clearance, including MHC-II presentation of HPV antigens to CD4 cells by Langerhans cells with co-stimulation by B7 and stabilization by ICAM-1. MHC-I and -II, IL-1, TNF-α, IL-2, ICAM-1, IFN-γ, and co-stimulatory molecules are commonly deficient in chronic HPV infections.

HLA-DR in HPV infections, but not HLA-DQ; therefore, staining for HLA-DR in the lesion reveals its expression on keratinocytes and not LCs. Viac et al. observed HLA-DR+ keratinocytes only in condyloma and laryngeal papillomas and not in palmar and plantar verruca [45]. HLA-DR expression directly correlated with the intraepithelial upregulation of intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) [45]. ICAM-1 is expressed on keratinocytes in condyloma and not in verruca plana. LFA-1, the natural ligand for ICAM-1, is expressed on lymphocytes and directs lymphocytes to the epidermis. Normally, ICAM-1 is expressed at low levels on dermal endothelial cells, not the epidermis. Upregulation of ICAM-1 and other adhesion molecules leads to lymphocytic infiltration. This, along with upregulation of HLA-DR in the epidermis, could facilitate antigen presentation to infiltrating CD4+ T cells and lead to clearance of infection [46–47].

We have addressed the role of HPV pathology in skin by identifying HPV gene products and immunological and cellular responses in patients. We probed for TNF-α and TGF-β1 levels in HPV-6 and -11 induced condylomas and found a dramatic reduction in their levels when compared to normal skin [48]. Majewski et al. found increased expression of TNF-α and TGF-β1 in EV lesions [49]. The disparity of TNF-α and TGF-β1 levels between EV and condyloma might indicate part of the underlying defect in EV patients. There may be a lack of proper T-cell repertoire [50], which is necessary to mount a regulatory or effector function, a cytokine receptor defect [51], or active neutralization of the cytokines by HPV products [52]. Ramoz et al. discovered that EV is associated with nonsense mutations in the genes EVER1 and EVER2 [53]. It was then determined that the gene products of EVER1 and EVER2 are transmembrane proteins in the endoplasmic reticulum (ER), which may act as ion transporters or channels or as modulators of these structures [54]. Orth later hypothesized that EVER proteins act as constitutively expressed restriction factors in keratinocytes and that EV is caused by a primary deficiency in HPV-specific intrinsic immunity [55]. This dysregulation at the level of the ER is also believed to be the cause of the pathologic finding of koilocytes (Koilo being Greek for hollow), which may be due to an enlarged ER. It is also interesting to note that, despite the presence of a mutation, treatment modalities around these defects are possible. For example, Berthelot et al. were able to successfully treat a patient with EV and an EVER2 mutation with topical imiquimod [56]. Imiquimod induces secretion of pro-inflammatory cytokines, predominantly IFN-α, TNF-α, and IL-12, thereby favoring a Th1 immune response, which is useful in the treatment of viral infections [57].

The viral oncoprotein/cellular protein interactions are well established in "high-risk" HPV types, but very little is known concerning lesions caused by "low-risk" HPV types. mRNAs of the early E2, E5, E6, and E7, as well as the late L1, can be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in "low-risk" HPV containing condylomas [48]. Especially important is the high abundance of E7 and E6 messages, since the former two can inhibit pRb and p53, respectively, two well-known tumor suppressor genes. Also important is E2, which regulates expression of HPV genes. The L1 gene encodes the major capsid protein and plays a critical antigenic role in cellular immunity. Viral oncoproteins, such as "high-risk" E6 and E7 interact with cellular regulatory proteins (e.g., p53, pRb, E2F) by displacing them in specific cellular pathways. "Low-risk" E6 and E7 proteins are probably not capable of binding cellular proteins, or at least bind with lower affinity, yet they are still able to transregulate certain host genes, as do their "high-risk" counterparts [58,59].

In condyloma lesions, there are decreased levels of growth-inhibitory genes (TGF-β1 and p53). Also, increased mRNA levels of hyperphosphorylated (inactive) retinoblastoma tumor suppressor gene product (pRB), reduced levels of p53 tumor suppressor gene product, increased levels of cdc2-kinase, and increased levels of c-myc are present [48]. Although HPV-6 and -11 are "low risk" for malignant progression, the condyloma lesional milieu is conducive to proliferation, i.e., a slow-growing lesion. Elevated cdc2 kinase levels lead to elevated cdc2 protein levels, presumably allowing for higher kinase activity. Elevated cdc2 protein most probably leads to hyperphosphorylation and inactivation of pRB. The underphosphorylated (i.e., active) pRB has strong transcriptional regulatory functions and can upregulate TGF-β1, as well as other growth control factors [60]. Underphosphorylated pRB also binds and inhibits the transcription factors for the enzymes of DNA replication. With reduced active pRB, the TGF-β1 levels would drop and the transcription factors necessary to produce the enzymes of DNA replication would be upregulated, leading to unregulated hyperproliferation of cells and subsequent growth of lesions.

The above data demonstrate an increase of proliferation, but a decrease in differentiation and growth suppressive signals by the presence of "low-risk" types of HPVs. Since experimental data suggest a negative effect of HPVs on cytokine/lymphokine secretion in vitro, these changes may be due to the expression of viral genes [61]. The downregulation of TGF-β, TNF-α, and IFN-β is particularly interesting as these cytokines and others (such as GMC-SF, IL-1s, etc.) have the capacity to influence MHC class I and class II expression, and, potentially, antigen presentation [62,63].

Condylomas have very low levels of MHC class I and II mRNAs compared with uninfected skin [64]. A study by Tao et al. found that condyloma acuminatum tissue had decreased expression of MHC class I and transporter associated with antigen processing-1 (TAP-1) compared to normal tissues. TAP-1 mRNA was also decreased in condylomas. They suggested that the downregulation of MHC-I is mediated by decreased TAP-1, and that this may lead to ineffective CD8+ T-cell clearance of HPV-infected cells [65]. A significant decrease of MHC mRNA, a marker for LCs, suggests a decline of LCs [66]. Quantitative and morphologic changes of cutaneous LCs have been observed in condylomas. Since HLA-DR is expressed chiefly by LCs and keratinocytes of condylomas, the reduced numbers of LCs must cause the net reduction. Diminished levels of IL-1α and IL-1β further affect the ability of epidermal cells to present antigens, thus influencing dendritic LCs. This lack of LCs probably hampers keratinocyte presentation of antigen and leads to a decrease in the immunological surveillance.

The very low levels of IL-2 mRNAs in condylomas further suggest a significant decrease in numbers of lymphocytes [67]. Indeed, CD4 and CD8 mRNA levels are significantly lower in infected skin than in uninfected skin. Tay et al. detected a lower helper/suppressor T-cell ratio in condyloma acuminatum compared to normal tissue [68]. Other data indicate that CD8 mRNA exceeds CD4 mRNA levels in infected skin and are in agreement

with these findings [48]. This depletion of intraepithelial lymphocytes, together with the depletion of LCs, the selective depletion of CD4+ cells, and the change in the ratio of CD4+ and CD8+ subsets, support the suggestion that there is a local intraepithelial immune deficiency associated with HPV infection. This might facilitate a prolonged HPV infection and expression of other long-term effects, such as malignancy.

The presence of HPV directly or indirectly can influence MHC gene expression. A direct influence might be elicited through the expression of E7 or E5 early genes, which seem to interact with the antigen processing system in in vivo studies [69]. Ashrafi et al. showed that E5 of HPV-16 causes retention of MHC class I complexes in the Golgi apparatus, thereby preventing their transport to the cell surface. Further, they found that E5 of HPV-16 selectively downregulates surface expression of HLA-A and HLA-B, preventing their ability to present viral antigens to CD8+ T cells [70]. In a later study, they proposed that downregulation of MHC class I is a common feature of all E5 papillomavirus proteins based on the discoveries that the E5 proteins of BPV-1, BPV-4, HPV-2, HPV-6, HPV-16, and HPV-83 all serve to downregulate MHC class I [71]. Indirect effects of E7 or other HPV early gene products may be exerted through different cytokines (TGF-β, TNF-α, IL-1, etc.) or oncogenes (c-myc), which can then influence MHC class I or II synthesis [72]. Another direct effect of HPV gene products on MHC levels and antigen presentation might relate to a high abundance of early viral genes (especially E7). This differential expression can have multiple effects, leading to immunological hyporesponsiveness. First, in vitro experiments demonstrate that the HPV E7 proteins are masked in the infected cell nuclei, likely due to complex formation with cellular proteins. The consequence of this masking might be an inappropriate immune recognition, which might be the case in non-responder tumors [73]. Second, keratinocytes, which lack co-stimulatory molecules, might render E7-specific T cells anergic through peripheral tolerance [74].

Upon an active immune response, HPV-infected keratinocytes release TNF-α, which is toxic to HPV replication. Patients with more advanced cervical carcinoma in situ were found to have lower levels of TNF-α in affected areas, while in areas of normal epidermis there was constitutively expressed TNF-α from keratinocytes. Another consistent finding was the lack of expression of any adhesion or co-stimulatory molecules by epithelial LCs [75]. The lack of TNF-α, a known stimulator of LCs, may have been responsible. TNF-α also normally upregulates the expression of ICAM-1 on keratinocytes, which attracts T cells. Therefore, ICAM-1 levels may also be inappropriately low. This, in combination with the decreased numbers of LCs in the epidermis, may be contributory. Keratinocytes were, however, found to have increased expression of HLA-DR, CD 54, and CD 58, thus increasing their antigen-presenting capacity (Table 2.2) [75]. This increased expression may be futile in light of the depressed activity of LCs secondary to decreased TNF-α and other LC-activating cytokines.

The deficiency in TNF-α, with subsequent downregulation of ICAM-1 and T-cells, results in decreased IFN-γ. Hence, MHC class II is not upregulated and antigen presentation is not facilitated (Fig. 2.2). Elevations of TGF-β1, IFN-β, underphosphorylated (active) pRB, and reduced levels of cdc2 kinase and c-myc follow intralesional IFN treatment of HPV-infected sites [76], indicating a more complicated role of IFN action. The IFN causes an initial immune modulatory effect, and stimulates the immune system to overtake the infection. Thus, the cytokine and antioncogene response reflects a normal status.

Table 2.2 Alterations in Keratinocytes Following Viral Interaction

Virally-induced changes in keratinocyte structure and function
Increased expression of HLA-DR in HPV
Increased CD 54 and CD 58
Increased antigen presentation capacity
Increased ICAM-1
Increased LFA-1
Decreased TNF-*α* in condylomas (increased TNF-*α* in EV)
Decreased TGF-*β*1 in condylomas (increased TGF-*β*1 in EV)
Decreased IFN-*β* and γ
Increased cdc2-kinase
Increased c-myc
Decreased MHC-I expression
Decreased TAP-1
Increased inactive retinoblastoma tumor suppressor gene product
Decreased p53 tumor suppressor gene product

Despite the wealth of knowledge regarding the virulence and oncogenic factors of HPV, some individuals continue to be more susceptible than others to these factors. The successful clearance of HPV from the epidermis is dependent upon an intact immune system. Among immunosuppressed transplant patients, 77% eventually develop viral warts [45]. Some recent investigations found a correlation between HLA type and HPV susceptibility and immunity [77–82]. Although a critical role for HLA antigens is likely, the results vary among investigators, and the data at this point are preliminary. One study has shown strong CTL responses following T-cell exposure to dendritic cells pulsed with recombinant E7 protein [83]. This may indicate that effective antigen presentation may be the area of deficiency in those with chronic HPV infection.

T Cells

T cells are an important regulatory and effector component in SALT. Herpes simplex virus (HSV) exemplifies the role of T cells in SALT, as T cells are necessary to prevent reactivation of HSV infection. Skin-homing lymphocytes express a sialyl Lewis a- and x- closely related antigen called cutaneous lymphocyte-associated antigen (CLA) [84]. CLA is a selectin ligand that is expressed on transition of T cells from the naive to the memory status in the presence of IL-12 and TGF-β and bind E-selectin of the endothelium [85]. Therefore, for memory T cells to traffic to skin, they normally express CLA.

HSV-1 and -2 are DNA viruses with extensive cutaneous manifestations, including interactions with SALT. This leads to modulation of immunocyte subsets and the epidermal upregulation of IL-1β, TNF-α, and IL-6 [86]. HSV types 1 and 2 cause a primary infection, and then retire to their respective neuronal ganglia to asymptomatically shed viral particles. In immunocompetent individuals, HSV remains in a latent phase, with only mild or subclinical reactivations. In immunocompromised patients, reactivation is more common and severe. Orr et al. determined that inhibition of MHC-I antigen presentation to CD8+ T cells by HSV is a major factor in the ability of HSV to reactivate [87]. One important question is the role of SALT in preventing HSV reactivation.

Overcoming a cutaneous HSV infection requires intact antigen presentation and both CD4+ and CD8+ T cells [88–90]. In most viral infections, including HSV, CD8+ CTL are major effector cells, but in HSV, CD4+ cells are involved in both immune modulation and direct cell killing. Jennings et al. reported the requirement of CD4+ T cells in mounting a primary CTL response to HSV infection and identified a similar requirement for the presence of CD4+ cells in a secondary CTL response [91]. Williams et al. demonstrated that although the epidermis is the primary site of inoculation and subsequent HSV infection, LCs failed to invoke a HSV-specific proliferation of T cells from naive animals [92]. This suggests that epidermal LCs may not invoke the primary T-cell response against HSV. Instead, they acquire the ability only after maturation in an extra-epidermal site where there is sufficient cytokine stimulation. This lag in time might allow the HSV viral infection to enter the protective dorsal ganglia. Also, LCs actively invoke a secondary T-cell proliferative response to HSV, abrogated by anti-MHC class II antibodies and complement [92]. Therefore, both the primary and secondary (i.e., memory) CD4+ T-cell response to HSV requires HSV presentation in the context of MHC class II. Because T cells do not have the ability to prevent latent or recurrent HSV infection, it has been proposed that HSV alters T-cell function. Sloan and Jerome investigated this hypothesis and found that HSV-infected T cells stimulated through the T-cell receptor selectively secreted IL-10, thereby favoring viral replication and suppressing cellular immunity. Further, they found that activation of p38 was necessary for IL-10 secretion by infected T cells [93].

The CD4+ Th cells have been categorized into two major subsets, Th1 and Th2 [94]. Th1 cells mainly secrete IL-2, IFN-γ, and TNF-α, while Th2 cells mainly secrete IL-4, IL-5, and IL-10. Interestingly, the cytokine activity of each Th subset downregulates the activity of the other subset. Th1 cells are generally efficient in controlling viral and intracellular pathogens, while Th2 cells better control bacterial and parasitic infections by augmenting humoral immunity. The presence of Th1 and Th2 differences in skin and their involvement in cutaneous disease have been demonstrated [95]. HSV lesions demonstrate a prevailing Th1 pattern in which the induction of MHC-II on epidermal cells and the activation of CD8+ T cells through IL-12 and IFN-γ are particularly important in the control of recurrent infections (Fig. 2.7) [96]. Zhao et al. found that $CD11c^+$ dendritic cells containing viral peptides in the form of MHC-II molecules stimulated HSV-specific CD4+ cells to secrete IFN-γ. Further, they found that only $CD11b^+$ submucosal dendritic cells presented antigens to CD4+ cells and induced IFN-γ secretion. LCs and $CD8\alpha^+$ dendritic cells did not contribute to the Th1 immune response [97].

Thus, the ideal HSV vaccine would induce both neutralizing antibodies and a Th1 immune response. HSV virions consist of a core containing viral DNA, surrounding tegument proteins, and an outer envelope containing numerous glycoproteins (Fig. 2.8). Glycoproteins D (gD) and B (gB) have been used with some success in vaccine studies [96]. Administration to mice of HSV-2 plasmid vaccines encoding the gD protein, as well as the Th1 cytokines: IL-1, IL-12, IL-15, and IL-18, resulted in immunity to subsequent challenge with HSV-2. However, mice inoculated with plasmids encoding the same HSV-2 gD protein, but with Th2 cytokines, IL-4 and IL-10, had increased morbidity and mortality [37]. If the Th2 cytokines downregulate the Th1 response,

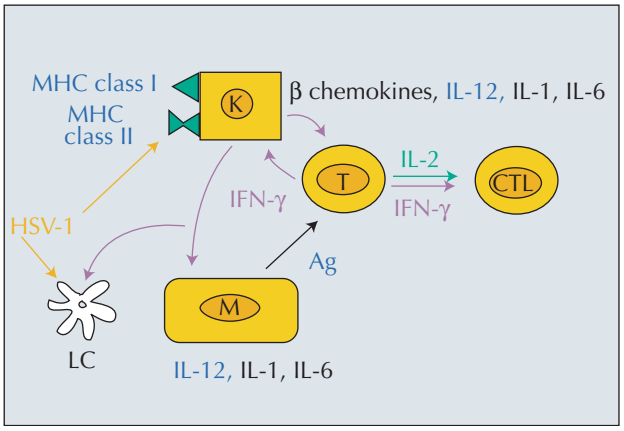


Figure 2.7 Immune processes in the recurrent HSV lesion: in vivo secretion of cytokines and chemokines in herpetic lesions. Ag, antigen; CTL, cytotoxic T lymphocytes; IFN, interferon; IL, interleukin; K, keratinocytes; LC, Langerhans cell; M, macrophage; MHC, major histocompatability complex. (Reprinted from AL Cunningham, Z Mikloska. The holy grail: immune control of human herpes simplex virus infection and disease. Herpes 8 (Suppl 1): 7A, 2001.)

decreased cellular immunity, the primary defense against cutaneous herpes infection is experienced. Stanberry et al. found that a HSV-2 gD subunit vaccine was 73–74% effective in preventing HSV-2 in women who were seronegative for both HSV-1 and -2. They proposed that the vaccine was ineffective in men because men have decreased Th1 immune responses compared to women [98]. Other vaccine-based studies have shown that vaccination with HSV-2 DNA plasmid vaccines favors a Th1 response, whereas induction of immunity with recombinant protein gD induced a Th2 response. While both were protective from lethal challenge, only the plasmid DNA vaccine induced a response that was protective against subsequent herpetic lesions and HSV-induced morbidity [99]. While CMI is most relevant to cutaneous manifestations, the humoral response offers protection from HSV encephalitis and HSV-induced mortality [36,99].

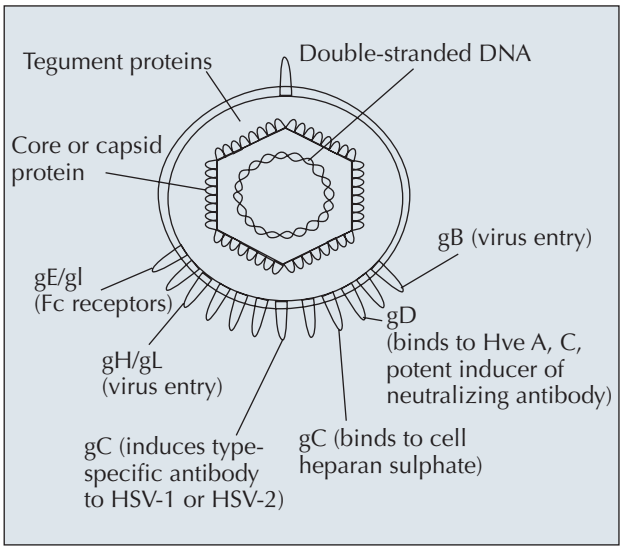


Figure 2.8 Structure of HSV virions: g, glycoprotein; HSV, herpes simplex virus; Hve, herpes virus entry mediator. (Reprinted from AL Cunningham, Z Mikloska. The holy grail: immune control of human herpes simplex virus infection and disease. Herpes 8 (Suppl 1): 8A, 2001.)

Table 2.3 Alterations in T Cells Following Viral Interaction

Virally-induced changes in T cell structure and function
Increased IL-10 in HSV
Increased activation of p38 in HSV
Increased IFN-γ following antigen presentation by dendritic cells
Increased Eta-1 in cell-mediated immune response to HSV
Decreased γδ + T cells in HIV

Eta-1 or osteopontin, a newly described cytokine, further supports the role of CMI in HSV-1 infection. Eta-1 is a necessary component of CMI [100]. Without this cytokine, IFN-γ and IL-12 do not increase appropriately and IL-10 rises inappropriately. Eta-1 −/− mice infected with HSV-1 were unable to mount a delayed-type hypersensitivity (DTH) reaction when further inoculated in the foot pad with HSV-1. Eta-1 +/+, HSV-1 infected mice displayed a strong DTH response in the foot pad when inoculated with HSV-1 (Table 2.3). Use of the antibody against Eta-1 results in similar findings. Although this study does not deny a role for Th2 and the humoral response for HSV protection, it emphasizes the overwhelming significance of CMI.

Endothelial Cells

The endothelium in many respects is the gate keeper of the skin, only allowing certain cells and components through. Adhesion molecules expressed by endothelial cells play a significant role in leukocyte entry into skin. E-selectin, P-selectin, ELAM-1, ICAM-1, ICAM-2, and VCAM-1 are the predominant adhesion molecules of endothelial cells used for interaction with leukocytes. The first part of this interaction involves the slowing of blood flow and the margination of cells towards the periphery of the vasculature near the endothelium. Selectins mediate the next step known as rolling, which consists of loose and transient associations between the white cells and the endothelium. This is followed by the firm and stable adhesions, formed by integrins such as ICAM-1, ICAM-2, and VCAM-1. The final step is diapedesis, mediated in part by ICAM-1 [101]. Through this process, endothelial cells are an important element in the eradication of pathogens. However, certain pathogens show tropism for endothelial cells and can infect them. Cytomegalovirus (CMV) is a virus well documented to have endothelial involvement (Fig. 2.9). Wang and Shenk determined that CMV tropism for endothelial cells is the result of a complex of viral glycoproteins, gH and gL, which are known to be involved in viral entry and fusion, with CMV genes pUL128, pUL130, and possibly pUL131A [102,103]. Although CMV has numerous mucocutaneous manifestations, especially in immunocompromised patients, the majority of research on endothelial involvement of CMV has been carried out on extracutaneous tissues.

CMV infection of endothelial cells directly affects transendothelial migration of white cells and further dissemination of the CMV virus. Studies with human umbilical vein endothelial cells (HUVEC) have shown that CMV infection upregulates endothelial expression of E-selectin, ELAM-1, ICAM-1, and VCAM-1 [104,105]. ELAM-1 and ICAM-1 caused increased adhesion of polymorphonuclear (PMN) cells and T-lymphocytes, while VCAM-1 resulted in increased adhesion of monocytes and T-lymphocytes to

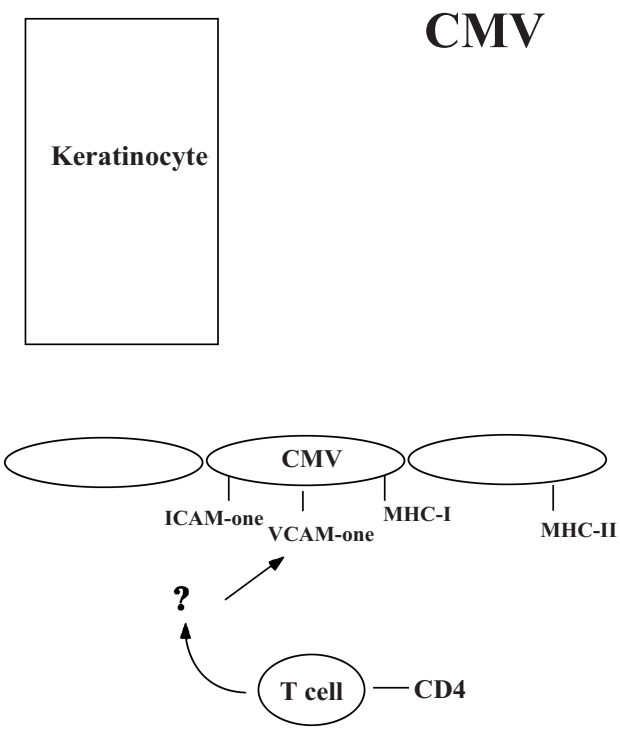


Figure 2.9 CMV is disseminated to healthy tissue through endothelial infection. (1) CMV causes endothelial upregulation of vascular adhesion molecules by a paracrine mechanism; (2) transendothelial migration by white cells results in infection from adjacent endothelial cells; (3) infected white cells disseminate CMV into healthy tissue.

endothelial cells [104]. IL-1β may mediate the increased expression of these endothelial surface antigens. CMV infection of endothelial cells results in increased secretion of IL-1β, which by a paracrine route affects adjacent non-infected endothelial cells. Significantly, studies have shown that certain white cells, such as neutrophils, can become infected during transmigration across infected endothelial cells and subsequently disperse this infection to other cells [106,107]. This can tremendously increase the dissemination of the virus and the inflammatory response throughout the body.

Endothelial cells also express MHC class I and II antigens, subsequent to IFN-γ [108]. In the past few years, a host of other escape mechanisms for CMV have been proposed and many of these involve CMV's influence on MHC class I and II expression by the endothelium. In one study, it was shown that CMV disrupts the signal transduction pathway that normally results in expression of IFN-α [109]. Specifically, CMV decreases the expression of Janus Kinus 1 and p48, important signal transducers involved in the expression of IFN-α. Decreased IFN-α, a key antiviral cytokine, secondarily results in MHC-I, IFN regulatory factor-1, MxA, and 2',5-oligoadenylate synthetase gene expression in fibroblasts and endothelial cells infected with CMV. Similarly, another group showed that CMV-infected arterial and venous endothelial cells are refractory to upregulation of MHC-II by IFN-γ [110]. CMV has the ability to interrupt signal transduction of the JAK/STAT pathway, which is induced by IFN-γ and normally upregulates MHC-II [111]. The combination of these two findings results in decreased expression of both class I and II antigens by the endothelium. The result is an impaired ability to induce an immune response and clear CMV infection. Only with

a competent immune system can important molecules be sufficiently upregulated allowing for effective antigen presentation and immunoresponsiveness.

In a later study, Kas-Deelen et al. determined that CMV leads to enhanced expression and activity of the ecto-ATPase and ecto-5'-nucleotidase enzymes on endothelial cells, which in turn leads to increased adenosine production. They hypothesized that these enzymes are upregulated to offset the procoagulatory effects of CMV. They also found that production of oxygen radicals by PMN cells was decreased in the presence of CMV-infected endothelial cells, which they suggest is a result of increased adenosine production [112]. A related CMV escape mechanism was elucidated by Zandberg et al. They found that the expression of P2 purinergic receptors on endothelial cells was upregulated in CMV-infected cells, but not in uninfected cells or HSV-infected cells. They proposed that these receptors may facilitate rapid hydrolysis of adenosine triphosphate and adenosine diphosphate leading to anti-inflammatory and anti-aggregatory conditions, which may allow CMV to enter endothelial cells [113].

HIV infection also affects the endothelial component of SALT. HIV-infected cells release many different cytokines with TNF-α being the most common [114]. TNF-α contributes to endothelial leakiness by: (1) induction of cytokine release; (2) expression of adhesion molecules; and (3) direct enhancement of endothelial permeability. Furthermore, the HIV-derived transactivator (tat) protein, which is secreted into extravascular tissue, directly stimulates endothelial cells to express E-selectin, ICAM-1, VCAM-1, and ELAM-1 [115–117]. The molecules are necessary for endothelial trapping of leukocytes in the vasculature. IL-6 synthesis, enhanced by tat, increases endothelial permeability, which facilitates leukocyte passage out of the vasculature [118]. This aids in the dissemination of infected cells into virus-free tissue. This may also be deleterious to epithelial homing of leukocytes and contribute to epidermal depletion of LCs.

Interactions between the HIV tat protein and the endothelium may be responsible for the highly aggressive behavior of AIDS malignancies. As mentioned earlier, increased expression of VCAM-1, ICAM-1, ELAM-1, and $\alpha V\beta 3$ integrin, as well as other vascular adhesion molecules is thought to be a direct consequence of the tat protein. These proteins increase cellular motility and transendothelial migration. It has been shown that the tat protein increases the motility of cells from the AIDS-related Burkitt's lymphoma cell lines and AIDS primary effusion lymphoma (PEL) cell lines. Tat not only enhances the migration of lymphoma cells, but increases their adhesion to endothelial cells. This study gives one explanation for the malignant behavior of non-Hodgkin's lymphoma (NHL) in patients with AIDS. Interestingly, antibodies against VCAM-1 inhibited this increased motility. Other actions of tat have also been studied and described.

Human herpes virus-8 (HHV-8), discovered by Chang in 1994, is the causative agent of Kaposi's sarcoma (KS). However, the increased incidence of KS in AIDS patients may be partially related to the HIV tat protein. One mechanism by which the tat protein has been shown to act is mobilization of b-fibroblast growth factor (b-FGF) [116]. Heparin sulfate proteoglycans normally provide binding sites for b-FGF. Tat competes for these sites and increases the concentration of free b-FGF. b-FGF, a well-known angiogenic factor, may act synergistically with the tat protein and HHV-8 in the development of KS [118]. Another study found that tat protected three KS cell lines and HUVECs from apoptosis induced by the chemotherapeutic agent vincristine and serum starvation, respectively. Tat upregulated Bcl-X_L expression, leading to a decrease in caspase-3-mediated apoptotic activity in the vincristine-treated KS cells [119]. Sivakumar et al. discovered that HHV-8 induced vascular endothelial growth factors (VEGF) A and C within 30 minutes of infection of human microvascular dermal endothelial cells (HMVEC-d). They suggest that VEGF A and C may subsequently cause angiogenesis and lymphangiogenesis, respectively, thereby facilitating growth of KS lesions [120]. In a later study, they found that HHV-8 causes the formation of a complex of integrins, including $\alpha V\beta 5$, $\alpha V\beta 3$, and $\alpha 3\beta 1$, with amino acid transporter protein xCT and glycoprotein CD98, which may facilitate viral entry into HMVEC-d (Table 2.4). Further, they determined that the CD98-xCT complex may mediate viral gene expression in the post-entry stage of infection [121].

Table 2.4 Alterations in Endothelial Cells Following Viral Interaction

Virally-induced changes in endothelial cell structure and function
Increased E-selectin in HIV and CMV
Increased ELAM-1 in HIV and CMV
Increased ICAM-1 in HIV and CMV
Increased VCAM-1 in HIV and CMV
Increased cellular motility and transendothelial migration
Increased IL-1β in CMV
Decreased IFN-α in CMV
Decreased MHC-I and -II in CMV
Increased adenosine production in CMV
Increased expression of P2 purinergic receptors in CMV
Increased IL-6 in HIV
Increased $\alpha V\beta 3$, $\alpha V\beta 5$, and $\alpha 3\beta 1$ integrins
Increased b-FGF in HIV/HHV-8 co-infection
Increased VEGF A and C in HHV-8

Conclusion

SALT is comprised of keratinocytes, LCs, skin tropic T cells, and lymphatic endothelial cells of the skin. The epidermis, which is involved in many viral infections, contains all of the components needed for an effective immune response: antigen-presenting LCs, T cells, and cytokines from leukocytes and keratinocytes. There have been some recent advances in the study of the cutaneous immunology involved in infections with HIV, HPV, HSV (Fig. 2.10), and CMV. In general, viral diseases with cutaneous manifestations lead to a decline in epidermal LC numbers, which is probably a reflection of the LCs emigration out of the epidermis and entry into regional lymph nodes. These events lead to LCs activation and antigen presentation to T cells. In HSV, there is subsequent T-cell infiltration of the epidermis, comprised of CD4+ cells that have both immune modulatory action and direct cytotoxic action. In HIV, where there is a systemic depletion of CD4+ cells, the epidermis is left with reduced numbers of T cells. Intradermal injection of IL-2, however, leads to an epidermal cellular infiltration in HIV-positive individuals. In HPV-induced condyloma, intralesional IFN increases LCs, CD4+, CD8+ cells in the skin, as well as TGF-β1, TNF-α, pRB, and p53. Therefore, viral infections

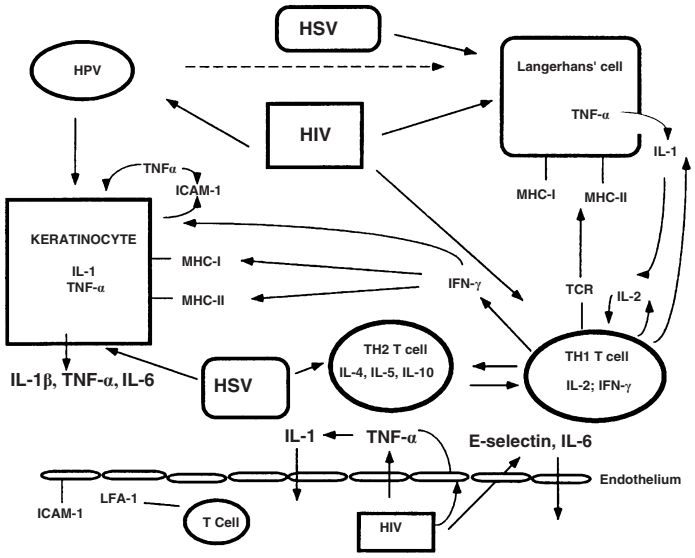


Figure 2.10 The presumed role of SALT in cutaneous viral infections.

involving the epidermal immune system have certain similar characteristics, while other parameters are unique to the infecting virus. The immune system resident in the epidermis is significantly affected by infections with CMV, HIV, HPV, and HSV. SALT is able to eradicate a cutaneous viral infection and retain memory of the infection to ward off future infections. In certain instances, SALT does the opposite and enhances the pathology of a cutaneous viral infection. One common feature in HIV, HPV, and HSV infections is reduction in epidermal LC counts, but this does not indicate a common mechanism. For example, HIV is known to infect LCs and have cytopathic effects, while this has not been shown for HPV or HSV. Possibly, viral infections of the epidermis require the presence of LCs only in extra-epidermal sites (e.g., lymph nodes), where antigen processing takes place. The above-mentioned viruses affect epidermal T-cell counts and subset proportions differently and may indicate the differential cytokine levels or patterns of expression that might exist in different viral infections. Although much has been learned about cutaneous viral immunology during the past few years, further studies are needed to enhance our understanding of SALT in viral infections.

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3 Poxviruses

Jessica Clark and Dayna Diven

INTRODUCTION TO POXVIRIDAE

The poxvirus family affects both humans and animals. The poxviruses are the largest of all animal viruses and are easily visualized on light microscopy. When seen under the electron microscope, the poxviruses are brick-shaped or oval 200–400 nm structures. The nucleosome contains double-stranded DNA surrounded by a membrane. The outer surface of the lipoprotein bi-layer has randomly arranged surface tubules, which give the virion its characteristic textured appearance. The lipid composition of the membrane is different from that of the host cell membrane [1]. The nucleoprotein core, lateral bodies, and membrane constitute an infectious collective unit. The virus may also acquire an envelope (Fig. 3.1).

Replication occurs autonomously in the cytoplasm of cells. After uncoating, the virion produces early enzymes and early virion proteins and late enzymes and late virion proteins [1]. These replication "factories" are independent of the host nucleus and are discernable on light microscopy as basophilic staining B-type inclusion bodies. The genome undergoes spontaneous recombination.

Numerous strategies are used by the poxviruses to evade the host immune system. These include production of homologues of mammalian tumor necrosis factor receptor, interleukin-1 beta-receptor, interleukin-18 binding protein, interferon-alpha/beta receptor, and interferon-gamma receptor, as well as a complement-binding protein and a caspase inhibitor. These proteins are thought to inhibit the function of cytokines and complement proteins, neutralizing the host's antiviral response [2].

The toxic effect of poxviruses causes cell rounding and clumping, degeneration of cell architecture, and the production of cytoplasmic vacuoles. Depending on the poxvirus, clinical presentations can include a localized, self-limited infection by inoculation to the skin (e.g., ORF) or a fulminant systemic disease

Table 3.1 Hosts and Portal of Entry for Selected Poxvirus Species

Genus	Species	Hosts	Portal of entry (for Humans)
Orthopoxvirus	Vaccinia virus	Humans	Skin
	Cowpox virus	Humans, cats, cattle	Skin
	Variola virus	Rodents, humans	Respiratory tract
	Monkeypox virus	Humans, monkeys, rodents	Skin
Parapoxvirus	Orf virus	Goats, sheep, camels, humans	Skin
	Bovine papular stomatitis virus	Cattle, humans	Skin
	Pseudocowpox virus	Cattle, humans	Skin
	Red deer poxvirus	Red deer	
Avipoxvirus	FowlPox virus	Birds	
Capripoxvirus	Sheep-Pox virus	Sheep, goats, cattle	
Leporipoxvirus	Myxoma virus	Squirrels, rodents, rabbits	
Suipoxvirus	Swinepox virus	Swine	
Molluscipoxvirus	Molluscum contagiosum virus	Humans (chimpanzees)	Skin
Yatapoxvirus	Tanapox virus	Humans, monkeys	Mosquitoes suspected
	Yabapox	Humans, monkeys	Skin

*Adapted from Buller and Palumbo [1], 1991, Tables 1 and 3, p. 82 and 98.

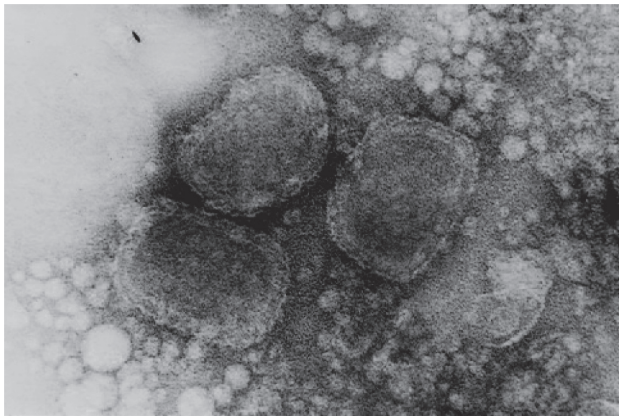


Figure 3.1 Poxvirus (vaccinia) brick-shaped to oval virus particles with electron-dense DNA core and visible outer membrane are seen in the vacuolated keratinocyte cytoplasm (× 20, 160). (Photograph courtesy of Harvey Blank, M.D., Department of Dermatology, University of Miami School of Medicine, Miami, FL.)

TAXONOMY OF VIRUSES

Poxviridae family
Chordopoxvirinae subfamily
Orthopoxvirus genus (vaccinia, cowpox, variola, monkeypox)
Parapoxvirus genus (orf, bovine papular stomatitis, pseudocowpox)
Yatapoxvirus genus (tanapox)
Molluscipoxvirus genus (molluscum contagiosum)

WORLDWIDE GEOGRAPHICAL INCIDENCE

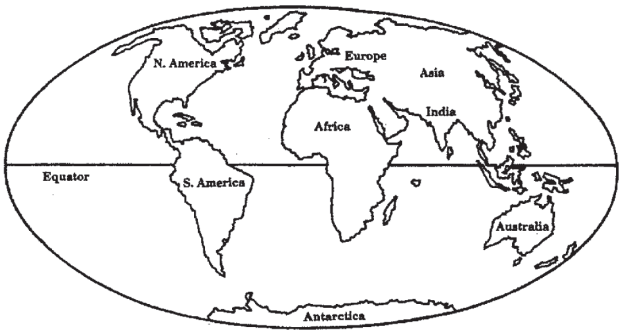


Figure 3.2 Taxonomy and incidence of poxviruses.

(e.g., variola). Different species can demonstrate a wide range of signs and symptoms from the same virus. Other poxviruses, like molluscum contagiosum, cause localized cell proliferation. Variola virus, the causative agent of smallpox, and molluscum contagiosum virus (MCV) are the only two known poxviruses to cause disease exclusively in humans [2] (Table 3.1).

Poxviruses that are not known to infect humans, including camelpox and sheep and goat lumpy skin disease complex, may result in great economic hardship in dependent farming communities. Our review includes only those poxviruses that infect humans (Fig. 3.2).

ORTHOPOXVIRUS INFECTIONS

Smallpox

Definition

An infection caused by the variola virus that affects only humans.

History

The history of the rise and fall of the smallpox virus is both fascinating and unique. The saga includes centuries of death and disfigurement followed by scientific triumph, although the fate of the virus remains undecided. For generations, the interaction of smallpox and humans has been characterized by unparalleled persistence and diffusion [5]. Smallpox is thought to have originated in Africa with subsequent spread to India and China thousands of years before Christ. The first recorded smallpox epidemic was in 1350 BC during the Egyptian-Hittie war [5]. Spread to Europe was evident between the 5th and 7th centuries. Smallpox was documented in the West Indies in 1507 and followed the Spanish conquest into the New World [6]. The immunity of the Spanish troops and the susceptibility of the peoples of Mexico and Peru to smallpox may have been a factor in the outcome of that conquest. During the 17th and 18th centuries, epidemics occurred in the North American colonies [6]. At one time, smallpox was endemic throughout the world, except in Australia and other small islands [6]. Large-scale epidemics caused millions of deaths in Europe and Mexico [5].

In the 1700s, the observation that smallpox survivors were immune to future outbreaks led to the practice of variolation in China, India, and Turkey. Variolation is the deliberate inoculation of an uninfected person with the smallpox virus by contact with the pustular lesion as a prophylaxis against a more severe form of smallpox. Lady Mary Wortley Montague, herself a smallpox survivor, is credited with advancing the smallpox variolation in England [7,8]. In the late 18th century, Edward Jenner, acting on reports of smallpox immunity by milkmaids who had developed cowpox, developed the first smallpox vaccine. The Council of the Royal Society rejected his idea. Jenner ended up self-financing the publication, and the vaccine has been used for over 200 years [5].

The decline of smallpox during the 20th century is correlated with a rise in smallpox vaccination. In the latter half of the 20th century, other countries including Africa and Asia continued to suffer major disease outbreaks, whereas most of North America, Western Europe, Australia, and New Zealand were free of the disease. In 1967, the World Health Organization (WHO) set forth a worldwide campaign to eradicate smallpox. By 1976, only Ethiopia and surrounding areas were still affected by the disease. On May 8, 1980, the World Health Assembly declared the world free of smallpox [8]. The spread of smallpox evolved over thousands of years, the global spread occurred for hundreds of years, and its eradication was sealed 13 years after the WHO program was initiated.

Incidence

In the USA, the last outbreak of smallpox occurred in Texas in 1949 (eight cases, one death) [9]. The last endemic case of smallpox occurred in Somalia in October 1977 [9]. A laboratory-associated outbreak was reported at a university in England in 1978 [9,10]. The infected person worked on a floor above the laboratory and died 1 month after infection [10]. By 1984, all countries had discontinued vaccination of the general population and they did not require travelers to certify vaccination [11] (Fig. 3.3).

Routine vaccination in the USA continued until 1971. The vaccine was given sporadically after this until 1983, when vaccine producers were urged to reserve the vaccine for military personnel only [12]. In 1986, it was recommended that military personnel no longer be vaccinated [13]. Smallpox vaccination was officially discontinued in US military recruits, except for special units, in 1990. In 2000, however, fears of biological

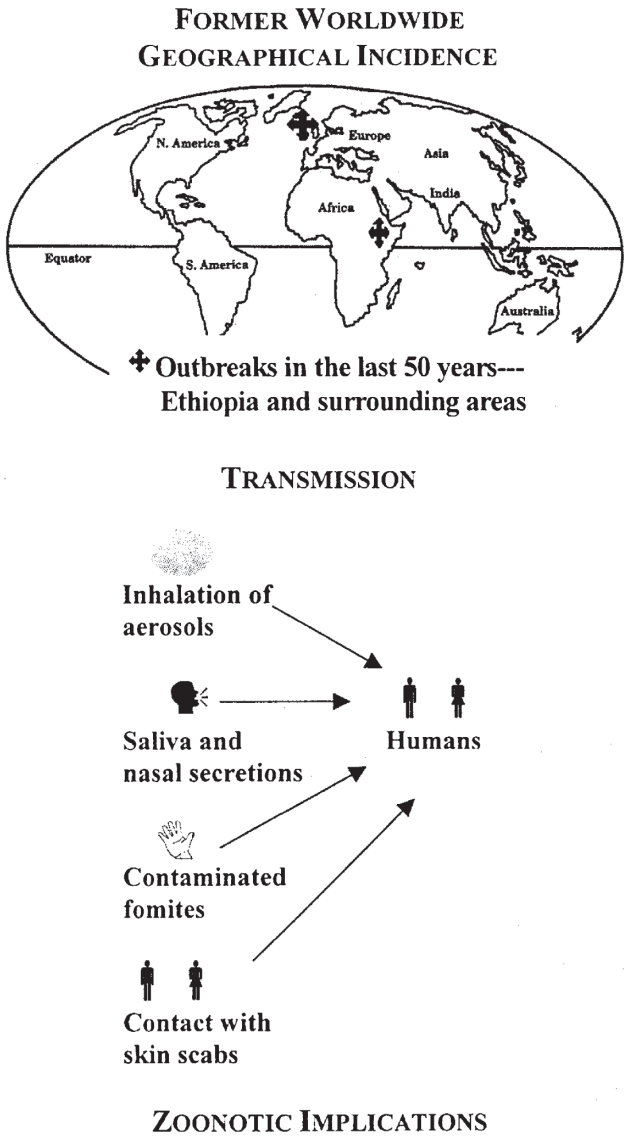


Figure 3.3 Incidence and transmission of smallpox.

warfare led to renewal of vaccine production for use by the military. In January 2003, the Department of Defense initiated vaccination of selected military forces and essential deployed civilians and contractors [14]. A 2007 Department of Defense release reports that over 1,200,000 operational forces and healthcare workers have been vaccinated against smallpox with adverse event rates below historically reported rates [14].

The WHO has investigated rumors of smallpox, all of which turned out to be misdiagnosed varicella or other skin disease. The CDC and the Russian State Center for Research on Virology and Biotechnology in Koltsovo are the only laboratories known to house the smallpox virus [15]. In this post-eradication era, it still remains a possibility that unsanctioned laboratories are storing variola viruses. Due to increased threats of bioterrorism, physicians should familiarize themselves with the signs and symptoms of this infection.

Pathogenesis/Epidemiology

The spread of smallpox usually occurs through intimate contact via the respiratory route [1]. Infection can develop from inhalation of aerosolized virus, contact with saliva or nasal secretions, contact with skin crusts, or through contaminated fomites, such as bedding [17].

On the third to fourth day after infection, an asymptomatic viremia develops with continued viral production in the spleen, bone marrow, and lymph nodes. Fever and toxemia follow on day 8. The virus goes on to infect adjacent cells of the dermis and oral mucosa. Death most likely results from the toxemia produced by circulating immune complexes and soluble variola antigens [18].

Infected people are contagious from the onset of illness until the last crusts of the lesions are gone, although infectivity is greatest in the earlier stages of disease. The rate of infectivity for susceptible contacts is 30% [19]. Population density and immunity affect the extent of spread. Eradication was obtainable because there are no known animal reservoirs for smallpox. Also, no significant subclinical carrier state exists [6]. Generally, environmental conditions do not affect the virility of the virus.

Infection is observed only in humans. However, current research has elicited infection in macaques. This development is exciting as the macaques may be a source to learn more about the virus [20].

Clinical Manifestations

Currently, the clinical diagnosis of smallpox is based on several criteria. The major criteria are (1) a febrile prodrome 1–4 days before rash onset; (2) the classic smallpox lesions (i.e., deep-seated, firm, round, well-circumscribed vesicles); and (3) lesions that are at the same stage of development (Figs. 3.4 and 3.5). The minor criteria include (1) a centrifugal distribution of lesions, with the first lesions on the oral mucosa or palate, face, or forearms; (2) a toxic or moribund appearance; (3) the slow evolution of lesions of 1–2 days per stage; and (4) lesions that appear on the palms and soles [21] (Table 3.2).

Variola major, the severe form of smallpox infection, can cause pulmonary edema from heart failure, leading to death. The case fatality rate for variola major ranges from 30–40% [22]. Variola minor (alastrim) is a milder form of the illness and results in few fatalities. Although the pathogenicity varies tremendously, the two different strains of variola only differ by 2% of their genome [22].



Figure 3.4 Smallpox in a Chinese soldier. (Photograph courtesy of Harvey Blank, M.D., Department of Dermatology, University of Miami School of Medicine, Miami, FL.)

The four types of variola major presentations include (1) ordinary, (2) modified (by previous vaccination), (3) flat (also known as malignant), and (4) hemorrhagic, with the latter two having the highest fatality rates. The majority of cases in unvaccinated individuals were of the ordinary or classic type. Case reports of modified smallpox in previously vaccinated individuals were mild and did not result in mortality. The malignant and hemorrhagic forms of smallpox were attributed to host factors, such as a deficient cellular immune response to the virus. The malignant or flat form of variola was more common in children, progressed more slowly than the classic presentation, and did not produce pustules. The mortality rate for this form approached 100%. The hemorrhagic variety of variola is characterized by mucosal and skin hemorrhage. It was reported more commonly in pregnant women and carries a high mortality rate of 90–100% regardless of vaccination status. Of note, pregnant women who contracted smallpox had a 3–4 times higher case fatality with any form of smallpox compared to men and non-pregnant women of the same age, possibly linked to a T-helper type 2 immune response associated with pregnancy [22].

The incubation period for the variola virus is 12–13 days. Those who survive often have significant scarring from pustules and granulation tissue formation. Corneal infection frequently results in blindness (Table 3.3).



Figure 3.5 Smallpox in an Indian baby. (Photograph courtesy of the World Health Organization, Geneva, Switzerland.)

Dermatopathology

Ballooning degeneration and cytoplasmic inclusion bodies (Guarnieri bodies) within keratinocytes are observed. Reticular degeneration and dermal hemorrhage ensue, with massive polymorphonuclear cell infiltrates. This is followed by crusting and new epithelial formation [23].

Laboratory Findings

Laboratory confirmation may be obtained from silver impregnation or fluorescent antibody staining of smears taken from skin lesions [6]. However, a negative smear does not exclude the disease. A laboratory designed to handle the virus uses chick embryo or tissue culture for identification. A fourfold or greater rise in antibody titer is diagnostic. Electron microscopy can also be used to identify the virus.

Treatment/Prophylaxis

If the diagnosis of smallpox is considered, immediate isolation of the patient is in order, after which the Centers for Disease Control (CDC) should be contacted. All patient contacts should be identified. Supportive care and treatment of bacterial infections are the mainstays of treatment (Table 3.4). The current population of the USA is considered immuno-naive to the variola virus with over half of the population never vaccinated and the remainder with unknown titers of waning immunity [20].

Future Considerations

The smallpox virus is a potentially dangerous agent of biological terrorism. Infection may be caused by only a few virions [18]. The fear is significant because a large portion of the world's population is not immune to smallpox, no effective treatment exists, and the secondary attack rate is 25–40% with a case fatality rate of 30% [16].

There is ongoing debate regarding whether all stocks of the variola virus should be destroyed. Opponents of destruction argue that more scientific inquiry requiring the whole virus could be done to identify the virulence segment of the genome [24–27]. Opponents also believe that variola's unique host specificity makes it valuable for future research and that completely destroying the virus would set a bad precedent. Additionally, they argue that specimens collected during epidemics could still be in

Table 3.2 Clinical Manifestations of Smallpox Infection

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
12–13 days	Prodrome of fever, malaise and backache—lasts 3–4 days ↓ Exanthem appears and quickly evolves:	Silver impregnation or fluorescent antibody stain of skin lesion smears;* electron microscopy; chick embryo or tissue culture (reserved for specialized laboratories); fourfold increase in antibody titer	Portal of entry—respiratory tract Infectivity is maximal during the first week of rash
14–16 days	↓ macules ↓ papules ↓ Vesicles		Initial eruption on palms of hands and soles of feet; distribution is centrifugal and on extensor surfaces All lesions are in a similar stage at any one time
19–20 days	↓ Pustules		Overall mortality rate is 30%
25–27 days	↓ Crusts (see Fig. 3.5), new epithelial formation		Scarring may occur; corneal infections may result in blindness Scarring may be severe

*A negative smear does not exclude disease.

Table 3.3 Differential Diagnoses of Smallpox

Varicella (chickenpox): Small delicate vesicles, concentrated on trunk, face, and flexor extremities, with rare deep scarring. Lesions are generally in various states of development
Syphilis: Resembles early smallpox but does not progress as smallpox does
Monkeypox: Has a greater tendency to produce both lymphadenopathy and skin lesions in "crops"

existence and that similar viruses, such as monkeypox, could mutate [24–27].

Those who want the virus destroyed argue that the genomes of reference strains have been cloned and sequenced. Also, monkeypox virus DNA is easier to study than variola virus in that it is similar to variola, has an animal host, and requires less stringent laboratory precautions [16]. In mid-1999, the World Health Assembly recommended a delay in the destruction of known smallpox reserves. The WHO was directed to appoint a new group of experts to establish what research, if any, had to be carried out to reach a global consensus on the timing for the destruction of existing variola virus stocks. This action permits further research into antiviral agents, improved vaccines, genetic structure analysis, and pathogenesis of smallpox. The World Health Assembly authorized continued postponement of destruction of the virus in 2002 [28]. By mid-2002, the USA ordered 209 million doses of smallpox vaccine [29]. In 2005, the World Health Assembly continued to work on increasing global smallpox vaccine reserves [28].

Conclusion

For centuries, smallpox terrorized the civilized world and affected millions of people [5]. Worldwide eradication of this virus is a unique event in history. Controversy still exists regarding the fate of the remaining stores of virus [26,27,30].

Vaccinia

Definition

An orthopox virus that affects a wide range of vertebrate hosts. Vaccinia virus is the constituent of the smallpox vaccine.

History

Vaccinia virus is the best studied poxvirus. Edward Jenner first used cowpox in 1796 [4]. It has been used for over 200 years as a vaccine for smallpox. The virus was originally thought to be isolated from infected cows and, later, horses [31–33]. However, it is now considered to be a laboratory virus with no natural reservoir [4]. In 1972, routine vaccination in childhood was discontinued in the USA. In early 2003, smallpox vaccination of selected US military forces and emergency healthcare civilian personnel was initiated [14]. The vaccine is currently given to select military recruits and civilian first responders [34].

Table 3.4 Symptomatic Treatment of Smallpox

Secondary symptoms	Treatment
Fever	Antipyretics
Secondary bacterial infection of open lesions	Systemic antibiotics
Pulmonary edema	Morphine, oxygen, intravenous loop diuretics, afterload reduction, inotropic support, aminophylline

Incidence

Infection with vaccinia virus occurs only in laboratory workers and after smallpox vaccinations in patients with atopic dermatitis (eczema herpeticum) who are either vaccinated themselves or exposed to family members getting smallpox vaccinations. The vaccine strain is considered to be a relatively safe virus because it does not cause serious disease in immunocompetent humans or animals [35] (Fig. 3.6).

Pathogenesis

The vaccinia virus is introduced into the outer layers of skin. Fifteen punctures are performed with a bifurcated needle in the deltoid region [36]. A localized infection occurs owing to the host immune response. Although immunity is induced through antibody and cell-mediated responses, the T-cell response appears to be necessary for full protection. This has been noted with observation of total immunity in children with agammaglobulinemia. New evidence suggests that relevant immunity may last for up to

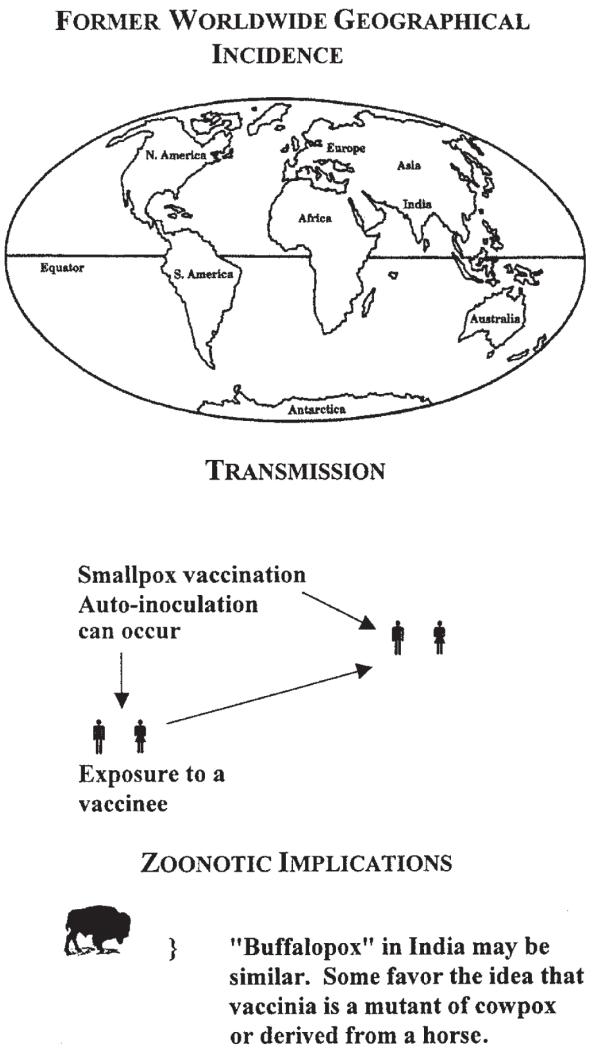


Figure 3.6 Incidence and transmission of vaccinia.

75 years after vaccinia vaccination, instead of only 3–5 years as previously thought [37].

The vaccinia vaccine induces neutralizing antibodies that are also protective for other orthopox viruses (monkeypox, cowpox, and variola). Symptoms and severity of smallpox disease may be decreased with administration of vaccinia vaccine within the first days after initial exposure [36]. Laboratory employees do not require routine vaccination if working with highly attenuated strains of vaccinia [36].

Clinical Manifestations

The vaccine causes a local reaction by multiplying in the basilar epithelium. A papule occurs 2–3 days after vaccination with a bifurcated needle multiple puncture technique. A successful primary vaccination produces a major reaction characterized by the appearance of a Jennerian pustule on day 7 [18] (Figs. 3.7 and 3.8). In the past, vaccination scars were used with considerable accuracy to assess the vaccination status of the individual or of populations [38] (Table 3.5).

Swelling and tenderness of regional lymph nodes can occur 3–10 days after vaccination and can persist up to 4 weeks after healing of the vaccination site. Other common reactions include local satellite lesions, local edema, and intense inflammation similar in appearance to bacterial cellulitis (Figs. 3.9–3.15). Systemic symptoms can also occur in healthy individuals. Thirty-six percent of adults reported feeling malaise enough to miss work, school, or recreational activities, or to have sleeping difficulties [39] (Table 3.6).

Complications of Vaccination

Rarely, healthy patients can experience a generalized vaccinia, where lesions similar to the primary inoculation site appear all over the body. The virus multiplies in epidermal cells after spreading hematogenously. Full recovery is expected without treatment.

Autoinoculation or inoculation of another person from the inoculation site is possible. The nose and the eyelid are the most common sites of inadvertent spread from the vaccination site. Permanent corneal damage is possible. Secondary transmission



Figure 3.7 Vaccinia vesicopustule—a sign of successful vaccination. (Photograph courtesy of Harvey Blank, M.D., Department of Dermatology, University of Miami School of Medicine, Miami, FL.)

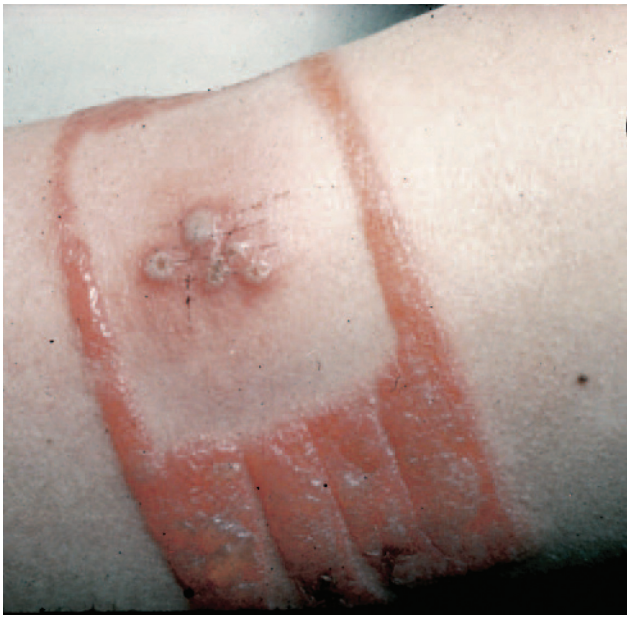


Figure 3.8 Vaccination site with contact dermatitis from tape.

may be increased in patients with other skin conditions, such as scabies, burns, impetigo, seborrheic dermatitis, pemphigus foliaceus, acne, and abrasions [40]. As the vaccinia virus is not attenuated, it can cause serious complications in some patients. Thymic aplasia, thymic dysplasia, acquired immune defects, and other impaired cell-mediated immunities contribute to progressive vaccinia, which is a very serious disease.

Adverse reactions involving the skin and the central nervous system (CNS) do occur. Increased mortality rates are reported in immunocompromised patients. Eczema vaccinatum, or extensive lesions in eczematous patients or eczematous family contacts of vaccines, is an occasional but serious problem. Complications such as eczema vaccinatum and vaccinia necrosum demonstrate a 10% and nearly 100% mortality rate, respectively, without treatment. Fortunately, mortality rates have decreased dramatically with the availability of vaccinia immune globulin (VIG) [18].

Nervous system complications are not responsive to VIG. Encephalopathy is most common in children between 6 months and 2 years of age and carries a mortality rate of 15–25%. An additional 25% are left with permanent neurological sequelae [36]. A demyelinating process has been described in adults. Adverse risks to the CNS may vary depending on the strain of the vaccinia virus. Cardiovascular complications such as ischemic heart disease, dilated cardiomyopathy, myocarditis, and pericarditis can occur in those with underlying heart disease [41]. Research findings reported in 2007 identified eight common genetic variations linked to fever susceptibility following smallpox vaccination. The study raises the possibility of identifying patient populations susceptible to more serious complications [42].

Dermatologists will be on the front line in the case of a smallpox outbreak. A study published in 2006 assessed dermatologist's knowledge of smallpox vaccination. Although most identified some contraindications to vaccination, such as immunosuppression and eczema, few identified myocardial infarction, angina, congestive heart failure, use of steroid eye drops, and non-emergency vaccination of patients under the age of 18 [43].

Table 3.5 Clinical Manifestations of Vaccinia

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
2–3 days	Papule appears ↓ (loculated and umbilicated) jennerian vesicle ↓	Laboratory analysis is usually not indicated since the source of infection is known	Lesion formation confirms successful vaccination Generalized vaccinia can occur at 6–9 days. Reaction may be more severe (see Figs. 3.9, 3.10, 3.11)
10 days	Pustule with surrounding erythema and induration (Fig. 3.7) ↓		Inoculation into eczema may occur. Infants and the elderly are at risk of spread, as are those with immune deficits (see Figs. 3.13, 3.14, 3.15)
12–13 days	Maximum erythema; lymphadenopathy; fever and malaise ↓		
22–24 days	Scab falls off		Pitted scar remains as evidence of vaccination

Vaccinees should be instructed to avoid high-risk individuals, including young children, pregnant women, immunocompromised individuals, and those with eczema, for 10–14 days after vaccination. Occlusive dressings and careful disposal of bandages can help prevent exposure to others [40]. Since the US military reinstated a program for smallpox vaccination in 2002, increased reports of cutaneous and systemic reactions in vaccinees and close contacts have been reported. In May 2007, a case of vulvar vaccinia was reported after intimate contact with a recently vaccinated member of the military. According to the US Department of Defense, 61 cases of contact vaccinia have been reported from 2002 to 2007 [44]. The CDC reports the risk of serious side effects from vaccination to be 1 in 1000. Life-threatening reactions such as eczema vaccinatum, progressive vaccinia, and post-vaccinal encephalitis occur in 14–52 in 1,000,000 vaccinees, with 1–2 in 1,000,000 dying as a result [43].

At this time, exposure is uncommon due to limited vaccination. However, with the threat of bioterrorism, large-scale vaccination is a possible future scenario. Hospitals may provide a unique environment for transmissibility and increased safety concerns. Large numbers of hospital employees would be vaccinated for the first time in an area concentrated with immunocompromised patients [40].

Future Applications

The vaccinia virus genome is large and can accept as much as 25 kb of foreign DNA, allowing it to be used to treat other disease processes as a live recombinant vaccine [50]. Its broad host range, including humans, laboratory animals, and common tissue culture cells allows for many potential applications [47,48]. Because vaccinia virus replicates in the cytoplasm, problems with host cell DNA integration and nuclear transcription errors do not occur [35].



Figure 3.9 Local dissemination of vaccinia from vaccine site.



Figure 3.10 "Vaccinial roseola," a transient erythematous eruption following vaccination. (Photograph courtesy of Harvey Blank, M.D., Department of Dermatology, University of Miami School of Medicine, Miami, FL.)



Figure 3.11 Autoinoculation of vaccinia to the lower eyelid produced a pustule. (Photograph courtesy of Roberto Arenas, M.D., Mexico City, Mexico.)

Recombinant vaccinia virus strains that express influenza hemagglutinin, hepatitis B surface antigen, and *Plasmodium falciparum* antigens have been produced [35]. An oral wild-life rabies vaccine has been developed [49]. The vaccinia virus is also currently under investigation for use as a HIV vaccine and for the treatment of various malignancies [50]. Potential laboratory applications include the insertion of virtually any coding sequence for a protein into the vaccinia virus genome, but its clinical use depends upon improving the safety of live vaccines and achieving high immune responses to recombinant protein [49,50].

Scientists are currently working on a recombinant interleukin-15 vaccine, which provides >1000 fold reduction in lethality of vaccinated athymic mice [51]. The vaccine also induces several-fold higher cellular and humoral immune responses that persist longer than that induced by the current vaccine. Recent research also supports using a higher dilution of the currently used vaccine. In 2007, results demonstrated reduced morbidity without loss of effectiveness. Furthermore, in case of a smallpox outbreak, dilution would allow for production of many more doses of vaccine [52].

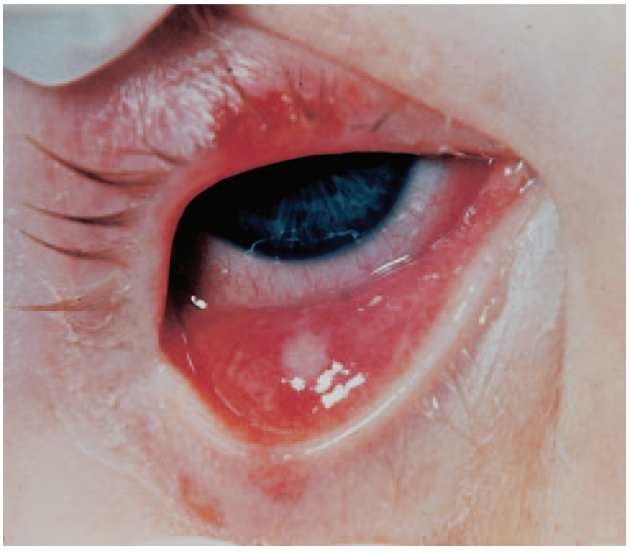


Figure 3.12 Conjunctival autoinoculation of vaccinia.



Figure 3.13 Eczema vaccinatum.

In the event of a terrorist attack, many subpopulations such as immunocompromised patients and pregnant women are contraindicated to receive vaccination. Cidofovir has been increasingly used as an antiviral drug in treating poxviruses. Historically, two drawbacks made this treatment difficult to use. Originally, cidofovir was only available in IV form. Also, renal side effects can be a problem with the large doses required to achieve appropriate intracellular concentrations. A new compound, which contains cidofovir in a partially degraded fat molecule, may prove viable as an oral treatment in the future [53].

Conclusion

The incidence of vaccinia decreased when routine smallpox vaccination with vaccinia was discontinued. In the future, the incidence of vaccinia may increase if the general public is vaccinated with potential exposure to our increasingly prevalent immunocompromised population.

Monkeypox

Definition

Monkeypox is an orthopox virus that occasionally infects humans. Monkeypox has been monitored closely in the post-smallpox eradication era.



Figure 3.14 Eczema vaccinatum.



Figure 3.15 Early vesicopustules of eczema vaccinatum.

History

Monkeypox is the most serious orthopoxvirus infection in human beings since the eradication of smallpox in the 1970s. In 1958, monkeypox was discovered in laboratory monkeys [54]. Human monkeypox infection was identified in 1970. Residents and visitors of western and central Africa are most likely to be infected. Squirrels and monkeys in the rain forests of this area have been identified as reservoirs. However, rats, mice, and rabbits are also know to be infected with monkeypox [55].

Until 2003, monkeypox was isolated to the rain forests of central and western Africa. The first reports of monkeypox in the midwestern USA were in the spring of 2003, affecting people exposed to infected prairie dogs [56]. No fatalities were reported in the US outbreak. It is unknown if monkeypox has established an enzootic reservoir in the USA.

Pathogenesis/Epidemiology

Previous smallpox vaccination confers 85% protection against monkeypox [54]. Unvaccinated children are mostly affected, and deaths have been reported [4,8]. Preliminary DNA studies indicate only minor genetic variation among animal strains collected from 1970 through 1979 [57]. In 1986, the committee on orthopoxvirus infections identified human monkeypox as an insignificant worldwide health problem because of its low incidence in humans and their belief that inter-human transmission did not occur [12].

Surveillance reports from 1981 to 1986 documented 338 cases in the Democratic Republic of Congo (DRC; out of a 1982 estimated population of 5 million). In the 1996–1997 DRC outbreak, the attack rate was 22 cases per 1,000 population [58]. A review of 282 cases of monkeypox reported 50% of cases involved children aged 4 years or younger, and an additional 40% occurred in children from 4 to 14 years old [60]. The case fatality rate is generally 10% [61].

The first report of human monkeypox outside of Africa occurred in the USA in April 2003 [62]. Eight hundred small animals shipped from Ghana were implicated. An infected Gambian giant-pouched rat was housed with native prairie dogs in Illinois. The prairie dogs were subsequently sold as pets. Other animals from the shipment, including dormice and rope squirrels, also tested positive for monkeypox virus [63]. Seventy-two cases of human monkeypox were identified in six midwestern states in 2003. The risk of symptomatic infection correlated with the time and intensity of animal exposure [56].

Monkeypox virus has two different forms of transmission. Primary transmission occurs after skinning, handling, or consuming the meat of wild monkeys. Acquisition of the virus is from

Table 3.6 Differential Diagnoses of Vaccinia

Smallpox: Similar to generalized vaccinia but history of exposure to vaccinia via research or vaccination would differentiate

small lesions on the skin or mucous membranes of the animal. Secondary transmission involves close contact with infected humans. Not much is known about human to human transmission. The report from the 1996–1997 outbreak in the DRC suggests an 8–15% risk of secondary transmission to human contacts. However, investigation into past outbreaks and the recent US outbreak suggests that the predominant route of transmission is animal to animal and animal to human [54]. Reports from the 2003 US outbreak investigated 40 healthcare workers who had at least one unprotected exposure to a patient infected with monkeypox [64]. No signs or symptoms of monkeypox virus were reported in any of the exposed employees.

Some clinical differences were apparent in the US patients infected with monkeypox. Overall, the US infections demonstrated a decreased total number of lesions, a less predictable disease course, and no scarring. The morphology, evolution, and absolute number of lesions were more variable than those identified in African populations infected with monkeypox. Appearance and number of lesions seemed to vary in US individuals, including members of the same family with similar exposures. Also, healing of lesions with hemorrhagic crusts was distinctive of US cases. The differences may be attributed to mode of transmission, strain virulence, and the prevalence of prior smallpox vaccinations [63]. The route of exposure may also play a role in disease presentation and severity. Patients who sustained an invasive bite or scratch from an infected prairie dog were more likely to have a shorter incubation period without a febrile prodrome. This group also experienced pronounced signs of systemic illness and were more likely to be hospitalized [62] (Fig. 3.16).

Clinical Manifestations

The incubation period ranges from 10–14 days [54]. Viral spread resembles that of smallpox. Monkeypox and variola virus are unique in their capacity to cause severe systemic disease accompanied by a generalized vesiculopustular rash [62]. A febrile illness including severe headache, pharyngitis, and productive cough is often followed by lymphadenopathy within 2–3 days [54]. Lymphadenopathy is common and was noted in 47% of patients in the US outbreak. The submental, submandibular, cervical, and inguinal nodes are often involved and can be a reliable clinical sign to differentiate monkeypox from smallpox and chickenpox.

Lesions usually develop 1–10 days after the febrile illness and occur in crops, which progress from macules to papules to vesicles and pustules. Umbilication and desquamation may follow. The face, trunk, extremities, and scalp are typically involved. Lesions may be seen on the palms and soles as well (Fig. 3.17 and Table 3.7). Resolution generally occurs within 2–4 weeks. Children may demonstrate a more severe course and require ICU care [65]. Those who have been vaccinated against smallpox may demonstrate a milder form of disease with non-specific erythematous papules that resemble an arthropod bite [54] (Table 3.8). Mortality rates of 1–10% are reported in Africa. Factors such as amount of exposure to the virus, host immune status, vaccination status, present complications, and overall baseline health contribute to the prognosis.

Complications

Complications reported from African outbreaks include deforming scars, secondary bacterial infection, bronchopneumonia, respiratory distress, keratitis, corneal ulceration, blindness, septicemia, and encephalitis [54,65].

Treatment/Prophylaxis

Prior smallpox vaccination confers 85% protection from monkeypox, leading the CDC to recommend smallpox vaccination to those exposed in the recent US outbreak [66]. Recommendation

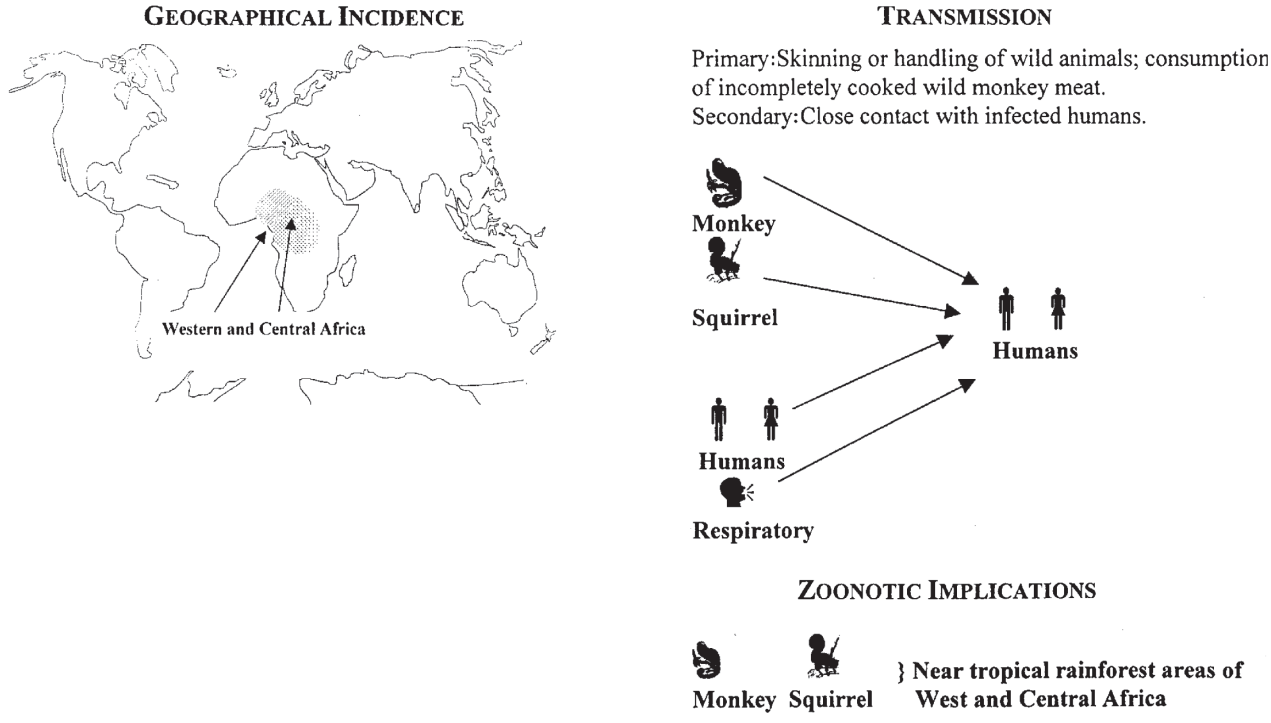


Figure 3.16 Incidence and transmission of monkeypox.



Figure 3.17 Monkey pox: Crop of pustules on fingers (Photograph courtesy of Dr. John Melski, Marshfield Clinic, Marshfield, WI).

of vaccination within 4 days of exposure is ideal, with some possible benefit up to two weeks after exposure. VIG is not efficacious for the treatment of monkeypox. In severe cases, cidofovir may be a treatment option.

Conclusion

Monkeypox produces a clinical disease in humans that is indistinguishable from smallpox, except for the more pronounced enlargement of cervical and sometimes inguinal lymph nodes, and a tendency for lesions to occur in crops. The incidence of this viral disease is increasing in frequency. Those without smallpox vaccination have increased susceptibility to monkeypox and increased severity of the illness.

Cowpox

Definition

An orthopox virus that infects cats, cows, rodents, and occasionally humans.

History

Cowpox is thought to be the original isolate used by Edward Jenner in the 18th century for development of his vaccine. This signaled the beginning of the age of vaccination [67].

Incidence

Cowpox has never been reported in the USA. Cowpox now appears to occur primarily in Europe and the former USSR [32,68]. Despite its name, cows are not the reservoir for infection. Infection in humans is primarily due to exposure to infected cats. Outbreaks in cattle are actually rare and of unknown origin. Infection in humans is relatively rare, but can be severe. Fewer than 150 cases of human cowpox have been reported. Exposure is more common in late summer and fall [69] (Fig. 3.18).

Pathogenesis

Cowpox virus is transmitted to humans primarily through contact with infected cats [69,70]. Typically, a broken area of skin, such as a minor abrasion, comes into contact with ulcers or lesions on an infected animal. Case reports have also noted contact through mucosa of the eye or nose. The natural reservoir of cowpox virus is believed to be small woodland animals, such as bank voles, wood mice, and short-tailed field voles [71]. It is important to note that this zoonosis is rarely contracted directly from a primary natural reservoir such as rodents, and not only accidental hosts commonly thought of such as cats. Although this is the exception rather than the rule, it became clearly evident after the report of a 14-year-old girl who contracted cowpox after caring for a sick wild rat [72].

Clinical Manifestations

After a week-long incubation period, infected humans develop a painless papule or papules at the site of inoculation that quickly evolve to a vesicular phase. Umbilicated pustules, which may become hemorrhagic, soon develop with surrounding erythema and edema. Transformation into a crust, eschar, or ulcer is often observed (Figs. 3.19 and 3.20). Lymphadenopathy is common, and fever or influenza-like illness may occur. Severe, but rarely fatal infections have been reported in atopic patients. In one fatal case, an 18-year-old eczematous patient on corticosteroids for asthma developed a smallpox-like eruption [68,73].

Only six cases of severe generalized skin infection have been reported, with atopic dermatitis as the main risk factor. The hands

Table 3.7 Clinical Manifestations of Monkeypox

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
1 day	Local inflammation	Isolation of virus from vesicular fluid or scabs	Transmission from animals was the most common form until 1996, when human-to-human transmission became more prominent
2–10 days	↓		
	Febrile response, with lymphadenopathy lasting 1–3 days, particularly in submandibular, cervical, and inguinal locations	(PCR) or hemagglutination	Infection is most common in children and the unvaccinated
	↓		Mucous membrane involvement is common
11 days	Severe headache, backache, and malaise		Monkeypox is a milder illness in those who received the vaccinia vaccine for smallpox
	↓		
	Papule		Severe generalized infection has approximately 10% mortality
	↓		
	Vesicle		
	↓		
Up to 4 weeks	Pustule		
	↓		
	Crust		

Table 3.8 Differential Diagnoses of Monkeypox

Smallpox: Clinically similar to smallpox, but monkeypox has a greater tendency to produce both lymphadenopathy and skin lesions that occur in "crops"
Varicella: Scabs and vesicles are not simultaneously present in monkeypox as they are in varicella

and face are most commonly affected. Ocular findings can include conjunctivitis, periorbital edema, and corneal involvement. Enlarged painful local lymph nodes are common with few reports of necrotizing lymphadenitis [74] (Table 3.9).

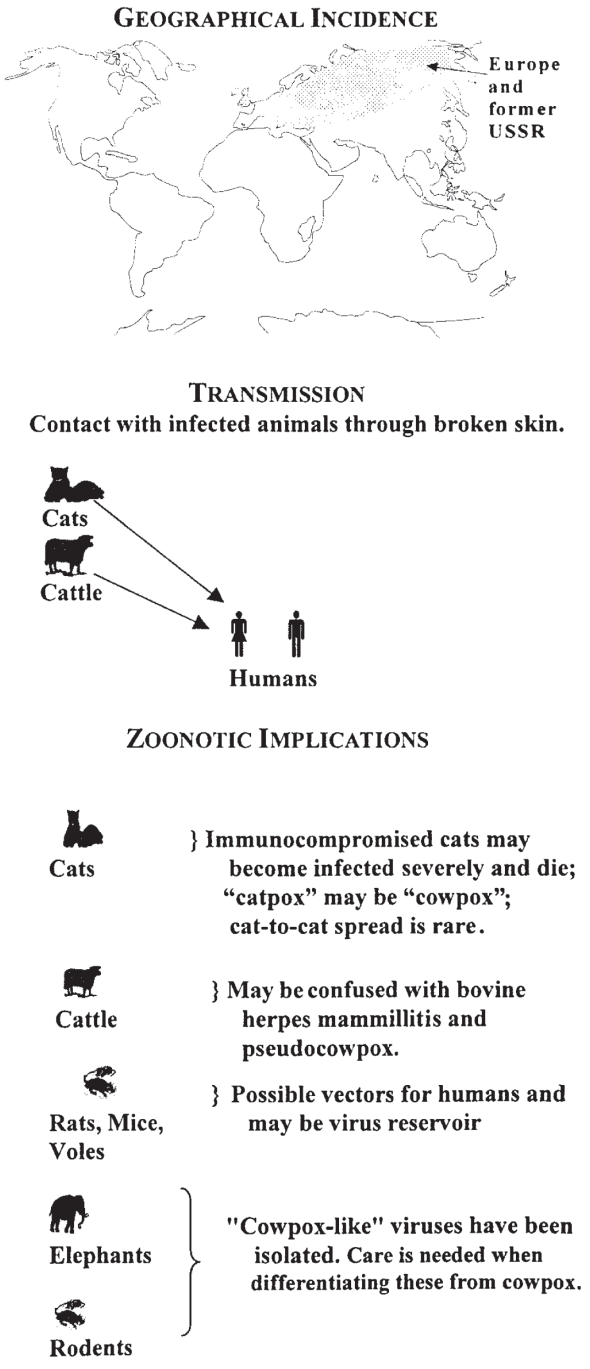


Figure 3.18 Incidence and transmission of cowpox.



(a)



(b)

Figure 3.19 (a) Facial appearance of cowpox, showing marked left-sided swelling and periorbital edema and four crusted lesions. (b) Close view of crusted lesion on the chin. (Photographs from Lewis-Jones et al., Br J Dermatol 129:625–627, 1993, used with permission, and courtesy of M. S. Lewis-Jones, M.D., Department of Dermatology, Ninewells Hospital and Medical School, Dundee, Scotland.)



Figure 3.20 Eschar of the finger resulting from cowpox. (Photograph from Vestey et al., Int J Dermatol 30:696–698, 1991, used with permission, and courtesy of James Vestey, M.D., Department of Dermatology, University of Edinburgh, Edinburgh, Scotland.)

Dermatopathology

The histological appearance of cowpox is similar to that of vaccinia, but with less necrosis and more hemorrhage [32]. Cytoplasmic inclusions are larger than the Guarnieri bodies of vaccinia and smallpox [76].

Diagnosis

Painless, orf-like lesions that may be located on the skin or mucosa of a patient with a relevant history should raise the possibility of a cowpox infection. The appearance of the inoculation site can be hemorrhagic with local edema and regional lymphadenopathy. Most cases do have mild systemic symptoms that can aid in distinguishing cowpox from orf (Table 3.10).

Treatment/Prophylaxis

No known treatment for cowpox exists. Healing is spontaneous. In a severe case, homologous vaccinia antiserum was given [73]. The prediction has been that orthopoxvirus infections would provide protection against cowpox infection [67]. This may not be true because infection has occurred in a recently vaccinated adult [69].

Conclusion

Cowpox infection usually affects humans by contact with an infected cat or other animal [73,75–79]. The infection is usually localized, but can be severe. Geographical locations of infections thus far are limited to Europe and the former USSR. The virus appears to have low infectivity for humans [68].

PARAPOXVIRUS INFECTIONS

Parapox viruses are distinguished from other poxviruses by a unique spiral coat. Erythema multiforme and Gianotti-Crosti syndrome may be temporally related to infection with a parapox virus [79].

Orf

Definition

Orf is a parapoxvirus that infects sheep, goats, and humans. It is also referred to as ecthyma contagiosum, scabby mouth, sore mouth, contagious pustular dermatosis, and infectious pustular dermatitis.

History

In 1937, George Peterkin reported the occurrence of orf in humans from contagious pustular dermatitis of sheep [80,81]. The word orf is derived from the Anglo-Saxon name for cattle [82]. In 1520, Pope Leo X referred to Martin Luther, the founder of the Reformation, as a "scabby sheep" infecting "the flock," a reference to orf [82].

Incidence

The economic impact of this parapoxvirus is important. Infected lambs may fail to grow properly and lesions can become secondarily infected [83]. Although the infection is relatively trivial in humans, the disease has a worldwide distribution (Fig. 3.21).

According to the US Department of Agriculture Animal and Plant Health Inspection Service's National Animal Health Monitoring System 2001 Sheep Survey, 40% of US operations reported sore mouth affecting their flocks in the previous 3 years. Some suggest vaccine use only for previously infected flocks due to the possible contamination of the entire flock after exposure to a vaccine-induced lesion. Primary lesions of orf in sheep can be severe and

Table 3.9 Clinical Manifestations of Cowpox

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
7 days	Painful papule(s); most patients have only 1 lesion	Electron microscopy of skin lesions to view virions [39,45]; screen samples to determine epidemiology by DNA restriction endonuclease analysis of viral isolates; tissue culture of virions	Agent may be from exposure to domestic cats [2, 37, 38]. Most common in July-October [37] and in young girls. Infection in humans rare but severe
	↓		
11–12 days	Vesicles		Pustules are usually hemorrhagic. Lesions most commonly on hands or face [22, 37]
	↓		
	Umbilicated pustules with surrounding edema and erythema		Lymphadenitis and general flulike symptoms are common
	↓		
	Crust, eschar, or ulcer	Serum samples for antibody detection are useful later in the course of the disease [37]	The draining lymph node may become enlarged and swollen. One third of patients are hospitalized. Severe cases may take as long as 12 weeks to heal
	↓		
6–8 weeks	Cutaneous healing of lesions begins (with probable scarring)	Orthopoxvirus antibodies in paired sera may be used but are not definitive [43]	Atopic patients (e.g., on corticosteroids) may have lesions that resemble those of smallpox

Table 3.10 Differential Diagnoses of Cowpox

Vaccinia: Has more necrosis and less hemorrhage; has smaller cytoplasmic inclusions (Guarnieri bodies)
Smallpox: Multiple lesions with more generalized spread
Orf/Milker's nodules: More granulomatous lesions, which are not usually painful
Anthrax: Relatively painless and progresses more rapidly to an eschar in 5–6 days
Herpesvirus infection: Usually not hemorrhagic or as erythematous as cow pox. Lesions are more superficial than in cowpox. Patients often have a history of recurrent lesions

take 4–6 weeks to resolve. However, reinfection is less severe and generally resolves within 2 weeks [84]. The live virus vaccine for farm animals can cause infection in exposed humans [85].

Pathogenesis

Transmission to humans occurs from infected lesions on animals or from fomites, such as wire fencing, barn doors, feeding troughs, or shears [83]. The virus remains infective on fomites for years at room temperature. It is able to survive heating and drying, but is sensitive to ether [83]. The saliva of affected animals is highly infectious. Person-to-person transmission under natural conditions has not been demonstrated, although a nurse who changed the dressing of an infected patient contracted the disease [86].

Clinical Manifestations

Orf is characterized by six stages lasting approximately 6 days each. Infected individuals usually develop a small, sometimes painful papule about 1 week following exposure. This stage is followed by a target stage (raised lesion with erythematous center), an acute stage (inflamed weeping nodule), a regenerative stage (early crusting), a papillomatous stage (late crusting), and finally regression [87] (Figs. 3.22–3.26). Secondary bacterial infection is rare, but can occur during disease progression. Possible secondary complications include lymphadenopathy and lymphangitis [84], fever [82], erythema multiforme, vesicular eruption [88,89], and secondary spread of lesions to face and hands associated with active atopic dermatitis [90]. A "giant orf" lesion measuring 6 cm failed to regress in a patient with chronic lymphocytic leukemia [91]. Fortunately, one report of orf virus contracted during late pregnancy demonstrated no appreciable effects on the infant or placenta [92] Table 3.11.

Dermatopathology

Routine histopathologic studies can be helpful in the diagnosis. Cells in the upper third of the epidermis are vacuolated and have intracytoplasmic inclusions. In the weeping and regenerative stages, the following signs are seen: multilocular vesicles, lymphohistiocytic dermal infiltrates with plasma cells, reticular degeneration of the epidermis, and dilated hair follicles [82]. Papillomatous and regressive stages of orf have finger-like downward projections that produce acanthosis and papillomatosis. Electron microscopic examination of lesional skin shows the characteristic brick-shaped viral particles that are 200–380 nm long. Intranuclear inclusions are occasionally seen [93].

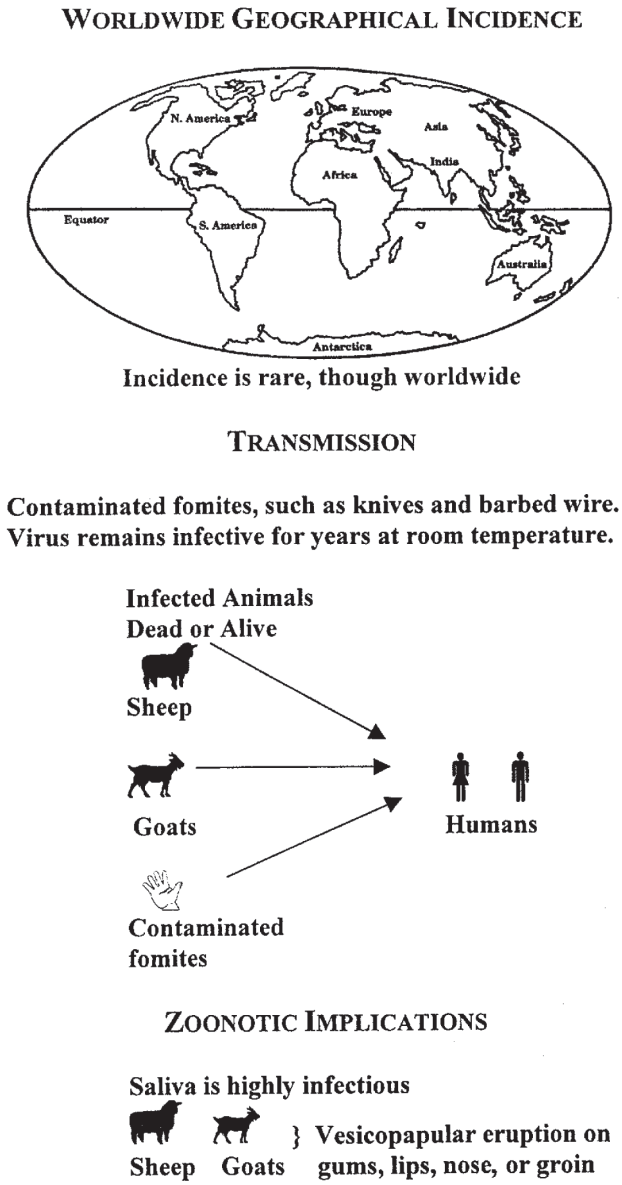


Figure 3.21 Incidence and transmission of orf.



Figure 3.22 Acute stages in orf infection.



Figure 3.23 Acute weeping nodule stage in orf on hand of a Mexican shepherd.

Laboratory Findings

The immune response of humans to the orf virus has been studied in a series of patients [94], although this method is not commonly employed for clinical diagnosis. Soon after infection, subjects developed a vigorous lymphoproliferative immune response including peripheral blood mononuclear cells. Western blot analysis and enzyme-linked immunosorbent assay (ELISA) demonstrate a rise in orf virus antibody levels as early as 2 weeks after infection. With serial sampling, the majority of patients have a fourfold or greater rise in orf virus antibody titers.

Diagnosis

The diagnosis of orf infection can be made by patient history and physical examination. If necessary, this may be confirmed by using cell culture, complement fixation, fluorescent antibody testing, or by biopsy of a lesion for examination by routine histologic study or electron microscopy [93] (Table 3.12).



Figure 3.24 Acute weeping nodule stage of orf on jaw of woman who rested her chin on the head of her pet sheep. (Photograph courtesy of Dearl Dodson, M.D., Department of Dermatology, University of Texas Medical Branch at Galveston, Galveston, TX.)



Figure 3.25 Early regenerative dry stage of orf.

Treatment

There is no specific antiviral treatment for orf, however, a recent report documented rapid regression of lesions in four patients with imiquimod [87]. Lesions will regress spontaneously without treatment. Antibiotics are warranted only if secondary infection is present. A live vaccine is available for animals [95]. Prevention includes vaccinating animals every 6–8 months. Isolation of infected animals helps limit the spread of disease. Infection confers lasting immunity in humans.

Conclusion

Orf is a self-limited viral infection of humans. Cross-immunity for variola or other orthopoxviruses does not result from infection [94,96].

Pseudocowpox

Definition

Pseudocowpox, or paravaccinia, is a parapox virus that infects the teats of cattle. In humans, it is called milker's nodules, milker's node, or paravaccinia. The DNA of ovine (orf), bovine (pseudocowpox, paravaccinia), and papular stomatitis strains is distinct



Figure 3.26 Papillomatous stage of orf.

Table 3.11 Clinical Manifestations of Orf

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–7 days	One to four papules on hand (typically only one lesion); begins as a red maculopapular lesion ↓ Vesicle ↓	Can confirm by histologic study, viral culture, increase in serologic titers, or complement fixation. Electron microscopy of lesional skin shows brick-shaped viral particles (200–380 nm in length) (Fig. 3.1); intranuclear inclusions are occasionally seen	Systemic symptoms are rare but may include lymphadenopathy and lymphangitis, fever, rigors, drenching sweats, malaise, and urticaria
10–14 days	Target lesion with red center, white middle ring, and red halo ↓		
			Lesions are relatively painless
14–21 days	Acute weeping stage (Figs. 3.23, 3.24) ↓		
21–28 days	Regenerative dry stage with black dots (Fig. 3.25) ↓		
28–35 days	Papillomatous stage (Fig. 3.26) ↓		
35 days	Regressive stage with dry crust and eventual shedding of the scab		Typically no scarring occurs

[97,98]. Infection in the bovine mouth is called bovine papular stomatitis. The viruses responsible for pseudocowpox and bovine papular stomatitis are designated as separate species by most investigators [97,98]; however, some contend that only one virus may be involved [99].

History

William Jenner grouped milker's nodules or pseudocowpox under the heading of "spurious cowpox" because it did not immunize against smallpox [100]. In 1957, Wheeler and Cawley suspected a viral etiology for milker's nodules and a relationship to vaccinia [100]. In 1963, Friedman-Kien et al. isolated a poxvirus from a case of milker's nodule [101].

Incidence

New milkers (young people, vacation milkers) have been infected worldwide [100]. Veterinary students who have contact with the mouths of cows during feeding or endotracheal tube placement are susceptible to milker's nodules from bovine papular stomatitis [102] (Fig. 3.27).

Table 3.12 Differential Diagnoses of Orf

Milker's nodules: Clinically identical; source of infection is cattle
Cowpox: Early lesions of cowpox are similar
Anthrax: More hemorrhagic and lesions progresses more rapidly to an eschar
Tularemia: Typically, tularemia has systemic symptoms, with high fever, headache, malaise, and myalgias. The skin ulcer is more chancrelike
Tuberculosis (primary inoculated): Most lesions occur in children. A painless shallow ulcer develops and heals poorly
Mycobacterial infection (atypical): Lesions often last 1 to 2 years before healing
Syphilitic chancre: Lesions typically occur on the genitalia rather than on the hand
Sporotrichosis: Begins as a single necrotic nodule, but multiple nodules arise in a linear fashion along the lymphatics
Pyogenic granuloma: Juicy red papule that bleeds easily, often with an epidermal collarette at the base
Keratoacanthoma: Appears as a dome-shaped papule or plaque with a central crater filled with keratin
Giant molluscum contagiosum: Lesions do not weep or become necrotic and often appear in clusters

Pathogenesis

The virus can be isolated from mucosal fluids of animals, even without obvious infection. Most commonly, human exposure is secondary to direct contact with affected farm animals, but the environmentally resistant virus may also be present on fences, feeding troughs, barn beams, and equipment. Although the majority of visible lesions are found on the teat, up to 10% of cows may have infection on the skin of udders as well [103]. Human-to-human spread has not been reported.

Clinical Manifestations

Pseudocowpox infection of the teats of cattle produce lesions similar to those produced in humans. Bovine papular stomatitis, a mild disease, is difficult to diagnose because papules in the oral cavity and muzzle area are difficult to see. When humans are infected with either pseudocowpox or bovine papular stomatitis virus, the lesions are identical to those of orf. Milker's nodules associated with burn wounds have been reported in which the source of inoculation was assumed to be contaminated water or grass [104] (Figs. 3.28–3.30 and Table 3.13).

Complications

See section on Orf.

Dermatopathology

See section on Orf.

Laboratory Findings, Differential Diagnosis, and Treatment

See section on Orf.

Conclusion

Paravaccinia viruses affect cattle, causing oral or cutaneous teat infections. When either type of infection is transmitted to humans, the result is a self-limited disease identical to orf (Table 3.14).

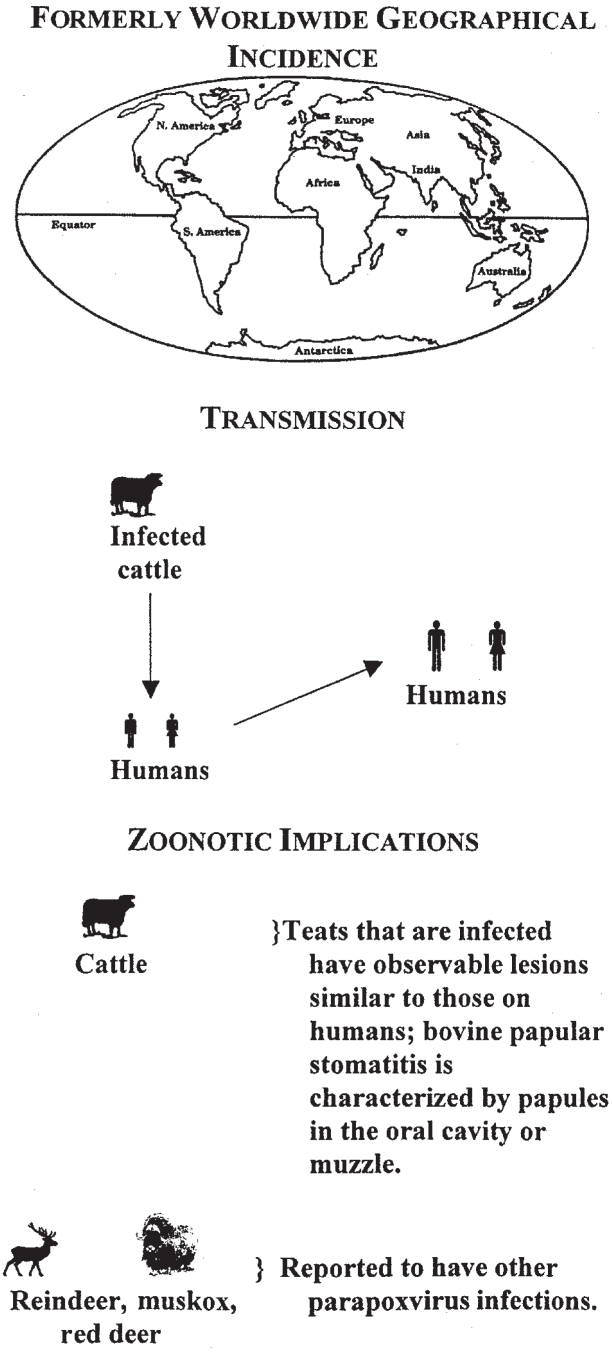


Figure 3.27 Incidence and transmission of pseudocowpox.



Figure 3.28 Milker's nodules of the hands. (Photograph courtesy of Roberto Arenas, M.D., Mexico City, Mexico.)



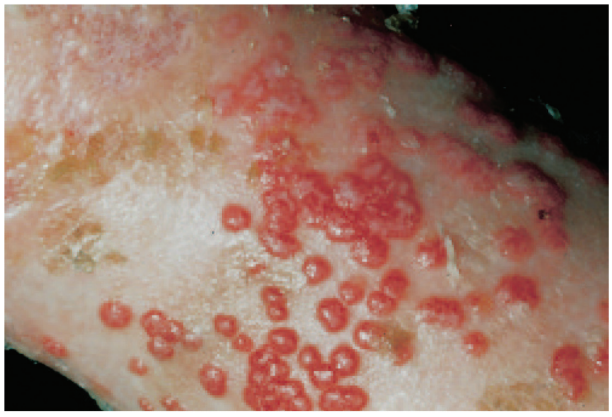
Figure 3.29 This milker's nodule was identical to the nodules of orf.

OTHER PARAPOXVIRUS INFECTIONS

Cutaneous infections can occur in humans from contact with a reindeer or a musk ox with a parapoxvirus infection [78,105]. In 1997, Mercer stated that the parapoxvirus of red deer in New Zealand (PNVZ) had not yet infected humans [106]. Tentative



(a)



(b)

Figure 3.30 (a) Milker's nodules within a burn scar. (b) Closer view of milker's nodules. (Photographs from Schuler et al., JAAD, 334–339, 1982, used with permission, and courtesy of Klaus Wolff, M.D., Department of Dermatology, University of Vienna School of Medicine, Vienna, Austria.)

Table 3.13 Clinical Manifestations of Pseudocowpox/Paravaccinia (Milker's Nodules)

Time after exposure	Clinical manifestations	Laboratory analysis	Other notes
5–7 days	Papular stage with hemispherical, extremely vascular papule(s); Generally only one lesion but can be up to four	Electron microscopy; viral culture; complement fixation; routine histopathology	Usually infects new or recent milkers, veterinary students
	↓		
12–14 days	Target stage—large purple nodule up to 2 cm in diameter with a red center surrounded by a white ring and a red halo		Infection generally induces longlasting immunity Lesions are painless but may have pruritus. No frank ulceration occurs
	↓		
19–21 days	Weeping and erosion		
	↓		
26–28 days	Firm, crusted nodule		Occasionally there is mild swelling of draining lymph nodes
	↓		
4–6 weeks	Regressive stage; granulation tissue is absorbed and the crust sloughs off		

members of the genus are camel contagious ecthyma, chamois contagious ecthyma, and sealpox viruses [98].

Tanapox

Definition

This "unclassified" poxvirus affecting humans and monkeys [107] is usually placed in the genus *Yatapox* [1,108].

History

The virus was first isolated in 1962 after causing epidemics in 1957 and 1962 near the Tana River Valley in Kenya [107,109]. Now central Africa is affected [79].

Incidence

Local children in the village of Ngau in the Tana River Valley of Kenya were the first documented cases in 1957. In 1962, several hundred cases were reported in the Wapakomo tribe, affecting sexes and age groups equally. Massive flooding of the area was reported simultaneously during both epidemics and proved to be an ideal breeding ground for the *Mansonia* mosquito [109]. Under these conditions, the evening mosquito bite rate was reported to be more than 700 per hour.

Four cases have been reported in the USA. One paper from 2002 reports infection of a 21-year-old female college student, who cared for orphaned chimpanzees in Africa for 8 weeks. Contact with laboratory animals accounted for the other three [110] (Fig. 3.31).

Table 3.14 Differential Diagnoses of Pseudocowpox/Bovine Papular Stomatitis Virus/Milker's Nodules

Orf: Lesions are identical but source of infection is sheep
Bovine papular stomatitis: Similar to milker's nodules, but bovine papular stomatitis rarely occurs
Anthrax: Lesions are hemorrhagic and progress to an eschar more rapidly
Herpetic whitlow: Characterized as more vesicular, not as nodular and elevated, and more painful
Pyogenic granuloma: Vascular papule, often with collarette of epidermis at the base

Dermatopathology

Microscope examination of tissue stained with hematoxylin and eosin revealed acanthosis, reticular degeneration of the epidermis, eosinophilic intracytoplasmic inclusions in keratinocytes, and papillary dermal edema [110]. Histology is comparable to swinepox, with pronounced epithelial hyperplasia. Irregular inclusion bodies and vacuolated nuclei are noted [109].

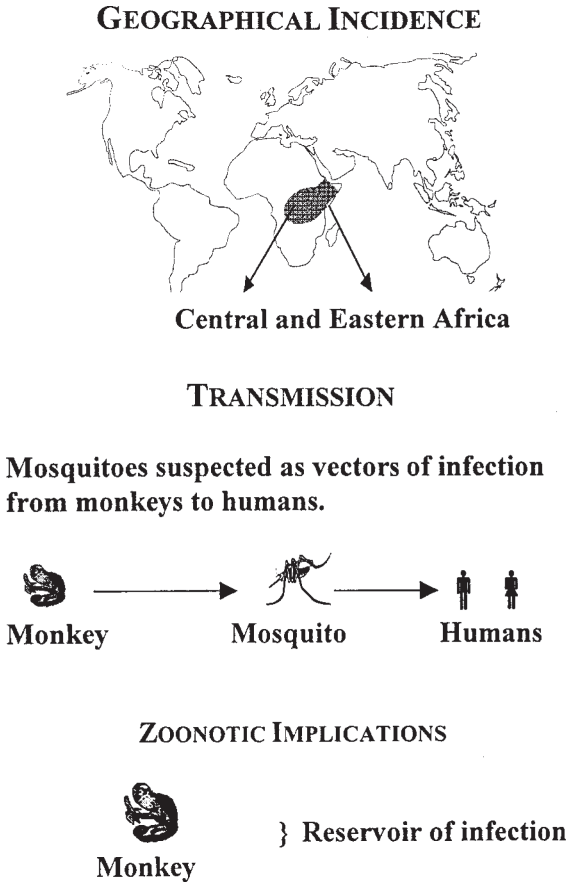


Figure 3.31 Incidence and transmission of tanapox.

Pathogenesis

The mode of transmission of tanapox is not completely known. Direct contact transmission occurs when animal handlers are scratched by monkeys. However, many individuals have acquired the disease with no known exposure to monkeys or their carcasses. Mosquitos have been suspected as vectors of infection from monkeys to humans [79,107,109,111].Most infected patients can recall repeated bites from blood-sucking insects prior to developing the disease, and most lesions have occurred on exposed body parts [107]. In addition, the seasonal increase in tanapox during the 5-month period from November to March corresponds with a similar increase in blood-sucking insects, such as mosquitoes [107].

A species of monkey in the Tana River Valley is suspected as a reservoir due to the observation that the virus could only be grown in monkey and human cells and direct inoculation of the virus has only produced disease in monkey and man. Growth of tanapox virus is not inhibited by antisera to other poxviruses and suggests tanapox as separate from other poxviruses [109].

Clinical Manifestations

The incubation period for tanapox is unknown. Infection begins with a febrile illness that lasts 3–4 days. Associated symptoms can include severe headache and backache. During the febrile period, a single lesion appears first as a papule, then as a vesicle that progresses to umbilication. No pustule stage is observed [109]. The vesicle can also form a necrotic crust, ulcerate, or form a nodule (Fig. 3.32). The vesicles can be pruritic and tender and have a maximum diameter of 2 cm. Resolution of the lesion typically takes about 6 weeks. Lymphadenopathy is common [107]. Lifelong immunity occurs with infection, but protection is not conferred with vaccination or infection with other poxviruses [110] (Table 3.15).



Figure 3.32 Umbilicated vesicle of Tanapox (Photograph courtesy of Dr. Sidney Klaus, Dartmouth-Hitchcock Medical Center, Lebanon, NH).

Treatment/Prophylaxis

This is usually a benign illness that resolves within 6 weeks. Smallpox vaccination does not protect an individual from tanapox infection [107].

Conclusion

Tanapox is generally a mild disease with a limited geographic distribution. Further studies of the natural history of viruses such

Table 3.15 Clinical Manifestations of Tanapox

Time since exposure	Clinical manifestations	Laboratory analysis	Other
3–5 days	Short febrile illiness, at times with headache, backache, and lymphadenopathy, lasting 3–4 days	Electron microscopy of skin samples or necrotic tissue	Incubation and clinical features not fully known Generally a benign illness
	↓		
Commonly appear during febrile stage	1–10 skin lesions, about 1.5 cm in diameter, usually on exposed body parts, especially the torso [66]. The face is often spared. Most patients have only 1 lesion		Human-to-human spread is extremely rare Lesions consist of pruritic, indurated, and sometimes umbilicated papules that become necrotic and are surrounded by edematous skin; lymphadenopathy is common
	↓		
Rapid growth	Pruritic papule with induration		
	↓		
	Papule becomes poxlike with little or no fluid but with a significant amount of necrotic tissue		Scarring occurs
	↓		
	Raised nodule, often firm and deepseated		High probability of lifelong immunity
	↓		
Slow process of healing	Frequent ulceration, with a base of soft necrotic tissue and slightly raised border; pain and pruritus		
	↓		
6 weeks	Complete healing		

Table 3.16 Differential Diagnoses of Tanapox

Monkeypox: Rapidly develops into vesicles and pustules, with no ulceration. Lesions are smaller (≤5 mm) than those of tanapox
Tropical ulcers: Tropical ulcers are characterized by larger lesions than occur in tanapox. Most have a foulsmelling, grey-green membranous covering and purulent discharge

as tanapox could provide clues about the human immune system and, perhaps, a better understanding of viral evolution [112] (Table 3.16).

Molluscum Contagiosum

Definition

Molluscum contagiosum is a virus of the *Molluscipox* genus that produces multiple umbilicated skin lesions. Only humans are known to be affected, except for one report each of molluscum contagiosum occurring in chimpanzees and a horse [113,114].

History

In 1817, Bateman described the lesions characteristic of this infection and assigned its name [115]. In 1841, Henderson and Paterson described the intracytoplasmic inclusion bodies, now known as "molluscum bodies" [116]. In the first decade of the 20th century, Juliusberg showed transmissibility of molluscum papules by a filterable agent [117], and Lipshutz granules within the molluscum bodies were described [118].

Incidence

MCV has a worldwide distribution, but is more prevalent in tropical areas. It mainly affects children, sexually active adults, and individuals with impaired cellular immunity. Its incidence in the USA has been increasing since the 1960s, mainly as a sexually transmitted disease [120]. Less than 5% of children in the USA are believed to be infected with molluscum virus. However, infected children without clinical manifestations may go undiagnosed [121]. In one study, the incidence of molluscum contagiosum was found to be twice as high in children who went to public swimming pools than in children who did not [123] (Fig. 3.33).

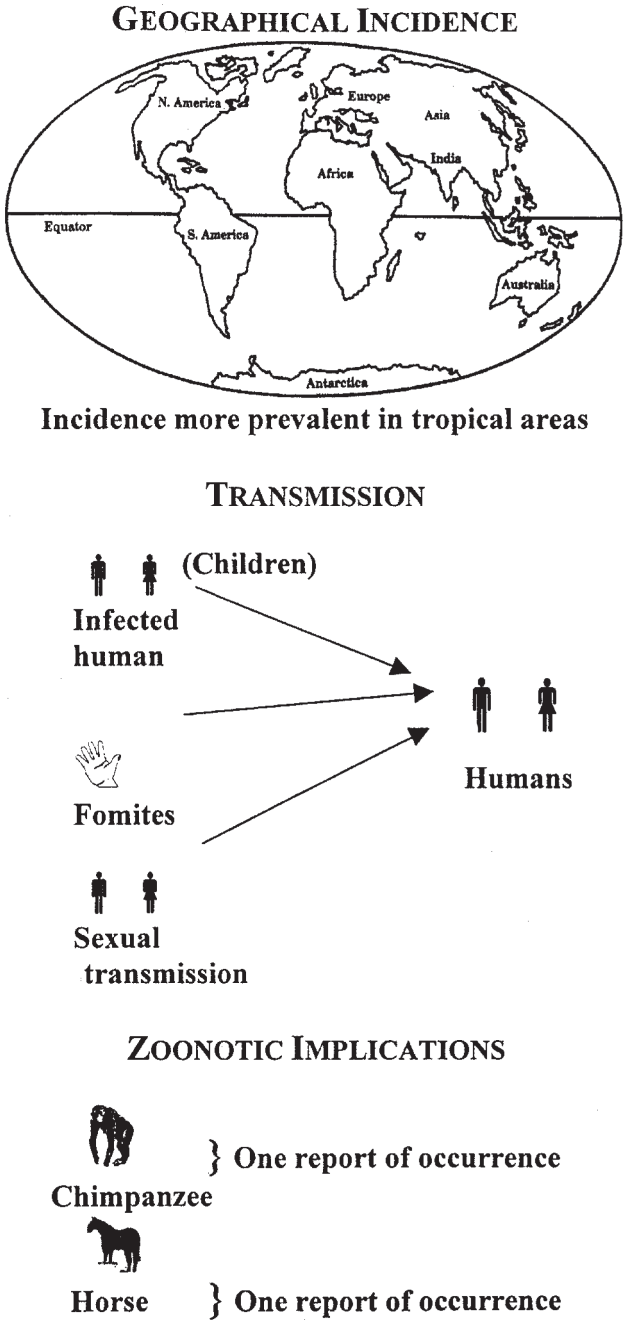


Figure 3.33 Incidence and transmission of molluscum contagiosum.

Pathogenesis

Transmission of this virus is primarily through direct skin contact with an infected individual. Sexual transmission also occurs. Fomites have been suggested to be another source of infection, with molluscum contagiosum reportedly acquired from bath towels, tattoo shops, beauty parlors, and Turkish baths [126].

The virus has not been grown reproducibly in cell cultures, which has hindered studies of infection and immune detection. The pathogenesis of skin lesions involves hyperplasia and hypertrophy of the keratinocytes [127]. Free virus cores have been identified in all layers of the epidermis. "Viral factories" are located in the malpighian and granular cell layers [127]. The molluscum bodies contain large numbers of maturing virions. These are contained intracellularly in a collagen- and lipid-rich sac-like structure that is thought to deter immunological recognition by the host [128]. Rupture and discharge of the infectious virus-packed cells occur in the crater of the lesion. Notably, MCV induces a benign tumor instead of the usual necrotic "pox" lesion associated with other poxviruses.

Clinical Manifestations

There are four main subtypes of molluscum contagiosum, with type I being the most prevalent in the general population. Type II is associated with HIV+ patients, which suggests that it is not simply a re-emergence of a latent childhood disease [129] (Table 3.17).

Any cutaneous surface may be involved, but favored sites include the axillae, the anticubital and popliteal fossae, and the crural folds [130,131]. Autoinoculation is common. Rarely,

Table 3.17 Clinical Manifestations of Molluscum Contagiosum (MCV)

Time since exposure	Clinical manifestations	Laboratory analysis	Other
1 week to several months	Small, firm, umbilicated papule with smooth, wavy, or pearly surface (1 mm to 1 cm in diameter) (Fig. 3.37)	Virus does not grow reproducibly in cell cultures Use of PCR to detect MCV in skin lesions	10–20 lesions are most common; autoinoculation (Koebner's reaction) may occur. MCV produces benign tumors rather than the usual necrotic pox lesion
Months to years	Span of individual papule is 2 months Spontaneous resolution		
Subsequent months to years	Remission Relapse and reappearance of lesion	Histologic examination—cells of lesions demonstrate inclusion bodies Electron microscopy shows characteristic poxvirus structure (Fig. 3.1) Polyclonal antibody recognizes MCV in fixed tissue In situ hybridization for MCV DNA	Immunocompromised hosts show widespread eruption, especially on the face (Fig. 3.41) Solitary lesion can resemble a furuncle or a pyogenic granuloma MCV can infect the conjunctiva or cause unilateral chronic conjunctivitis when the eyelid is involved

molluscum contagiosum lesions occur in the mouth [132], or conjunctivae [133,134]. The lesions produced by MCV I and II are clinically indistinguishable. Molluscum contagiosum in adults is often acquired sexually and affects the groin, genital area, thighs, and lower abdomen. Children usually acquire molluscum through direct skin contact on the face, trunk, and extremities. They may have genital lesions, but this is in addition to lesions in extragenital areas (Figs. 3.34 and 3.35).

Molluscum dermatitis, or an eczematous reaction around a molluscum papule, occurs occasionally. Resolution of the papule is presumably as a result of the host immune response to viral antigens [138,139]. Occasionally, molluscum lesions can become inflamed and resemble a pyoderma [139,140]. Immunocompromised patients, those on steroid therapy, and patients affected by atopic dermatitis and lymphoproliferative disorders have increased rates of molluscum contagiosum. This population may also progress with widespread persistent lesions that can be disfiguring. Patients with atopic dermatitis are more likely to autoinoculate because of underlying pruritus and a compromised skin barrier [141] (Fig. 3.36).

Atypical presentations, especially in the HIV+ population, may resemble furuncle-like lesions, comedones, abscesses, condylomas, syringomas, keratoacanthomas, basal cell carcinomas, ecthymas, sebaceous nevi of Jadassohn, and cutaneous horns. Diagnosis is frequently dependent on biopsy in these patients. Lesions on the eyelid may be the initial manifestation of AIDS [129]. Widespread facial mollusca, in particular, has been associated with low CD4 counts and HIV disease [141]. AIDS patients have been reported to have lesions greater than 15 mm (Figs. 3.37–3.41).

Viral skin infections can erupt with the use of topical immunosuppressants and molluscum contagiosum is no exception. In 2007, an adult patient with extensive atopic dermatitis developed a large eruption of molluscum contagiosum after local application of tacrolimus [142]. Other unique complications have been noted in the HIV+ population. During the initial phase of therapy with highly active antiretroviral therapy (HAART), CD4 lymphocyte counts rise and viral load decreases. With increasing numbers of HIV+ patients on HAART, a syndrome of inflammatory reactions has been recognized. Immune reconstitution inflammatory syndrome (IRIS) has been identified 1 week to 1 year after initiation of HAART. Reports of extensive molluscum infections surfacing with the induction of HAART are increasing in number and physicians need to be aware of this entity. Fortunately, spontaneous healing usually occurs after the initial phase of reconstitution of the immune system [143]. This is in contrast to the chronic facial infection seen in HIV disease before HAART.

Lesions of molluscum usually resolve spontaneously in 6–12 months in immunocompetent patients, but may take up to 4 years. Smallpox vaccination is not protective [141].

Dermatopathology

Histologically, molluscum contagiosum exhibits intraepidermal lobules with central cellular and viral debris. In the basal layer, enlarged basophilic nuclei and mitotic figures are seen. Progressing upward, the cells show cytoplasmic vacuolization and



Figure 3.34 Umbilicated shiny papules of molluscum contagiosum acquired by casual contact in a child.



Figure 3.35 Sexually transmitted papules of molluscum contagiosum of the right labia majora.

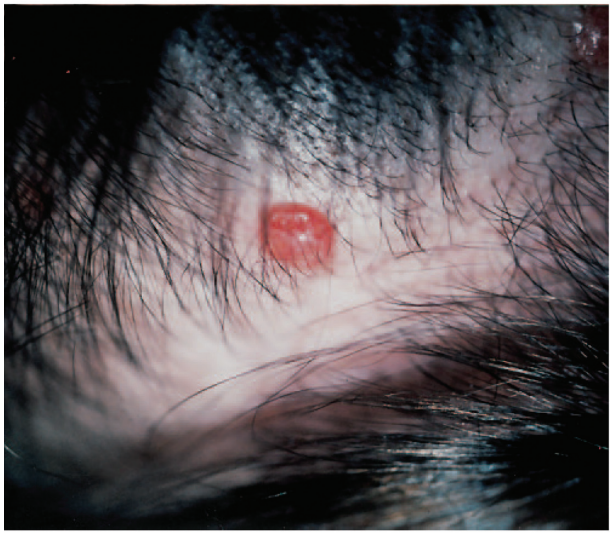
eosinophilic granules. The nucleus becomes compressed at the periphery of the cell and at the level of the granular cell layer. The molluscum bodies lose their internal structural markings. Undisrupted lesions show an absence of inflammation, but dermal changes can include an infiltrate that is lymphohistiocytic, neutrophilic, or granulomatous. The granulomatous form has been found in solitary lesions [131]. Acanthosis is present and the epidermis may be several times the normal thickness (Fig. 3.42).



Figure 3.36 Disseminated molluscum contagiosum in a patient with atopic dermatitis.



(a)



(b)

Figure 3.37 (a) Large molluscum contagiosum lesions in a patient with AIDS. (b) The umbilication is seen in this close-up photograph of another AIDS patient.

Laboratory Findings

Antibody to MCV by indirect immunofluorescence has been found in 69% of patients with visible lesions [144]. Polymerase chain reaction (PCR) can detect MCV in skin lesions [146,147]. Currently, there is no in vitro or animal model for MCV. MCV can undergo an abortive infection in some cell lines, which can cause confusion with herpes simplex virus by laboratories [148]. Investigators have infected human skin with molluscum contagiosum and grafted it onto athymic mice. No continued viral replication was observed [149,150].

Diagnosis

The diagnosis of molluscum contagiosum is a clinical one (Table 3.18). When necessary, histological examination of a curetted or biopsied lesion is diagnostic. The curetted material can be crushed on a slide and left unstained or one can use Wright's, Giemsa, Gram, or Papanicolaou stains to demonstrate the inclusion bodies. Electron microscopy shows characteristic poxvirus



Figure 3.38 Molluscum contagiosum of the toe in an AIDS patient. (Photograph courtesy of Mario Marini, M.D., Department of Dermatology, University of Buenos Aires School of Medicine, Buenos Aires, Argentina.)



Figure 3.40 Molluscum contagiosum of the penis in an AIDS patient. (Photograph courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

structures. Penneys and coworkers generated a polyclonal antibody that recognizes molluscum contagiosum in fixed tissue using immunohistochemical methods [151]. In situ hybridization for MCV DNA has also been used [152].

Treatment/Prophylaxis

Molluscum contagiosum may be left untreated, as most papules will eventually resolve. Many patients seek medical attention to rid themselves of the papules. Various methods have been used including curettage, liquid nitrogen, cantharidin, podophyllin, podophyllotoxin, salicylic acid/lactic acid, phenol, tincture of iodine, tretinoin cream or gel, silver nitrate, trichloracetic acid, oral cimetidine, repeated application and removal of tape (tape stripping), squeezing with blunt forceps, and diathermy. Alternative treatments include the use of a carbon dioxide or pulsed-dye laser or topical photodynamic therapy [153,154]. Lesions that are clinically undetectable at the time of examination may appear later and necessitate multiple treatments. Although oral cimetidine is a



Figure 3.39 Molluscum contagiosum of the eyelid in an AIDS patient. (Photograph courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)



Figure 3.41 Molluscum contagiosum of the face of a 13-year old girl with AIDS in Romania. (Photograph courtesy of Mark Klein, M.D., Department of Pediatrics, Baylor College of Medicine, Houston, TX.)

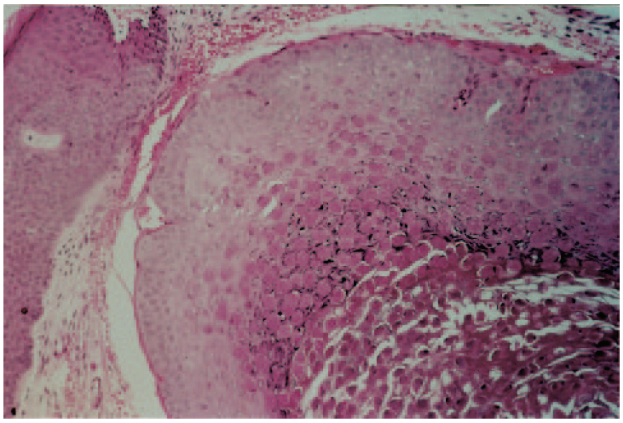


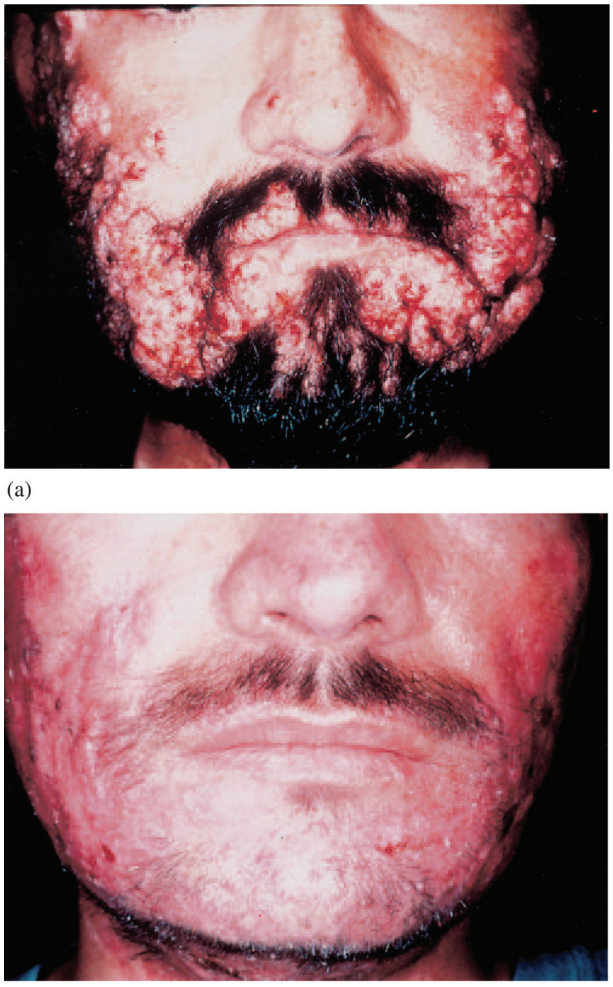
Figure 3.42 Molluscum contagiosum. Intraepidermal lobule containing cellular and viral debris. Large eosinopilic globules within keratinocytes are termed "molluscum bodies" (H & E × 100).

painless treatment alternative for children, the results have been inconsistent [141].

Treatment of facial molluscum lesions in HIV patients poses a great challenge. Treatment with antiviral medications, especially protease inhibitors in combination with nucleoside analogs that inhibit reverse transcriptase, is helpful. Improvement has also been noted with imiquimod, ritonavir, intravenous and topical cidofovir, zidovudine, and intralesional interferon alpha [156–160] (Fig. 3.43 and Table 3.19).

Conclusion

MCV causes a benign cutaneous infection in humans with normal immunological responses. It differs from other poxviruses in that it does not cause a "pox-like" vesicular lesion, but does cause spontaneously regressing tumors of the skin.



(a)

(b)

Figure 3.43 Molluscum contagiosum of the face of an AIDS patient before (a) and after (b) cidofovir therapy. (Photographs from Meadows et al., Arch Dermatol 133: 987–990, 1997, used with permission, and courtesy of Kappa Meadows, M.D., Department of Dermatology, University of Utah School of Medicine, Salt Lake City, UT.)

Table 3.18 Differential Diagnoses of Molluscum Contagiosum

Herpes simplex virus: HSV lesions are vesicular and often are accompained by burning pain. Lesions progress and heal more rapidly
Verruca vulgaris: Hyperkeratotic and verrucous without central umbilication of MC
Syringoma or other adnexal tumors: Usually occurs as dermal papules that do not resolve
Pyodermas: Pyoderma is crusty or purulent and may spread
Papular granuloma annulare: Diffuse papules, usually widespread
Condyloma acuminata: Verrucous papules and plaques in genital region
Cutaneous cryptococcosis: May be found in immunocompromised hosts (requires biopsy)
Histoplasmosis: May be found in immunocompromised hosts (requires biopsy)
Keratoacanthoma: May be confused with a single molluscum lesion and require biopsy confirmation
Epidermal inclusion cyst: A dermal cyst, often with overlying pore
Basal cell carcinoma: May be confused with a single molluscum lesion and require biopsy confirmation
Neurilemmoma: Firm nodule usually located along nerve trunks
Pyogenic granuloma: May be confused with a single molluscum lesion and require biopsy for confirmation. It is usually more vascular in appearance

Table 3.19 Treatment of Molluscum Contagiosum

Symptoms	Treatment
Shiny umbilicated papules seen in children and young adults	Can be handled with "benign neglect," but many destructive methods are available. Antiretroviral therapy has benefited the cause of facial molluscum in the immunocompromised patient Immunotherapy: imiquimod Antiviral therapy: cidofovir

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4 Herpes Simplex Viruses

Richard J Whitley and John W Gnann Jr

Introduction

Our knowledge of human herpes simplex virus (HSV) infections has increased dramatically since the initial historical descriptions of the clinical manifestations and the histopathology of HSV lesions. Advances in our understanding of the natural history and pathogenesis of HSV infections have been paralleled by the development of both sensitive and specific serologic tests, which distinguish HSV-1 from HSV-2 infections and antiviral drugs that are selective inhibitors of viral replication. Type-specific serologic markers of infection have allowed for a detailed evaluation of the epidemiology of both HSV-1 and HSV-2 infections. The establishment of the unequivocal value of antiviral therapy has permitted clinicians to alter the spectrum of human disease and has implications for long-range control of HSV infections. This chapter will summarize the current status of our knowledge of the epidemiology, clinical manifestations, and treatment of HSV infections. Photographic illustrations of the clinical manifestations will reinforce the descriptions.

History

Human HSV infections have been recognized since ancient times. Records of human HSV infections began with descriptions of cutaneous spreading lesions thought to be of herpetic etiology, as described by Hippocrates [1]. Scholars of Greek civilization define the word "herpes" as "to creep or crawl," in reference to the spreading nature of the skin lesions [2,3]. The Roman scholar, Herodotus, associated mouth ulcers and lip vesicles with fever, calling it "herpes febralis" [3,4]. Galen deduced that the appearance of such lesions was an attempt by the body to rid itself of evil humors and perhaps led to the name of "herpes excretins" [1]. However, some of these original descriptions of skin lesions bear little resemblance to later reports of HSV infections from the 19th and 20th centuries [4].

During the 18th century, Astruc, physician to the King of France, drew a correlation between herpetic lesions and genital infection [5]. By the early 19th century, the vesicular nature of lesions associated with herpetic infections was well characterized [3]. However, only in 1893, Vidal recognized human-to-human transmission of HSV infections [1,3].

Observations at the beginning of the 20th century advanced our knowledge of HSV infections beyond simple descriptions. First, histopathologic studies identified the multinucleated giant cells associated with HSV infections [6]. Second, the infectivity of HSV was recognized by Lowenstein in 1919, whereby virus retrieved from the lesions of humans with HSV keratitis or the vesicles of HSV labialis produced lesions on the rabbit cornea [7]. Furthermore, vesicle fluid from patients with herpes zoster failed to reproduce similar dendritic lesions in the rabbit eye model. In fact, these observations were originally made by Gruter, who performed virtually identical experiments around 1910, but did not report them until much later [8].

Investigations reported between 1920 and the early 1960s focused on the biologic manifestations of HSV infections and the natural history of human disease, as reviewed [9–12]. In the early 1930s, Andrews and Carmichael identified H5 neutralizing antibodies in the sera of previously infected adults [13]. Subsequently, some of these individuals developed recurrent labial lesions, albeit less severe than those associated with the initial episode. This observation defines a unique biologic property of HSV, namely its ability to recur in the presence of humoral immunity, a characteristic known as reactivation of latent infection. By the late 1930s, infants with severe stomatitis, who shed a virus thought to be HSV, subsequently developed neutralizing antibodies during the convalescent period [14,15]. Later in life, some of these children developed recurrent lesions of the lip, as had been reported for adults.

The medical literature of the 1940s and 1950s was replete with papers describing specific disease entities, such as primary and recurrent infections of mucous membranes (e.g., gingivostomatitis, herpes labialis, and genital HSV infections), the skin manifestations of herpetic whitlow or eczema herpeticum [16], keratoconjunctivitis [17], neonatal HSV infection, visceral HSV infections of the immunocompromised host, and herpes simplex encephalitis (HSE) [18]. Furthermore, the clinical spectrum of HSV infection was expanded to include Kaposi's varicella-like eruption and recurrent infections of the immunocompromised host.

Antigenic differences between HSV types were first suggested by Lipschitz [19] on clinical grounds and by others from laboratory observations [20,21], but it was not until 1968 that these differences were demonstrated between HSV type 1 and HSV type 2 [22]. HSV type 1 was more frequently associated with nongenital infection, while HSV type 2 was associated with genital disease, although this distinction has changed over the past decade. This observation was seminal for many of the clinical, serologic, immunologic, and epidemiologic studies that have followed.

Several other critical advances have aided our understanding of the natural history and pathogenesis of HSV infections. First, successful antiviral therapy was established for HSE [23] and, subsequently, for virtually all HSV infections [24–30], as recently reviewed [24]. Second, differences between strains of HSV were demonstrated by restriction endonuclease analyses of viral DNA, allowing for molecular epidemiologic studies [31]. Third, the use of type-specific antigens for serologic studies has advanced our understanding of the epidemiology of infection [32]. Fourth, the elucidation of the molecular events of viral replication and the resultant gene products aids in the development of vaccines and antiviral drugs. Fifth, the engineering of HSV and the expression of specific genes will provide technology for new vaccines and gene therapy [10]. Finally, the recent advances in our knowledge of the molecular basis of latency and the definition of a gene responsible for neurovirulence are leading to clues regarding

the molecular pathogenesis of infection [33,34]. Many of these advances have been summarized [10]. This chapter will focus exclusively on the pathogenesis, epidemiology, clinical manifestations, and treatment of HSV infections with particular emphasis on dermatologic manifestations (Fig. 4.1).

Pathology of Infection

The pathologic changes induced by HSV replication are similar for both primary and recurrent infection, but vary in the extent of cytopathology. The histopathologic characteristics of a skin lesion are shown in Fig. 4.2a. These changes represent a combination of virus-mediated cellular death and an associated inflammatory response. Changes of the parabasal and intermediate cells of the epithelium include ballooning of infected cells and the appearance of chromatin within nuclei, followed by degeneration of the cellular nuclei. Cells lose intact plasma membranes and multinucleated giant cells form, as demonstrated on a Tzanck smear (Fig. 4.2b). With cell lysis, clear fluid containing large quantities of virus accumulates between the epidermis and dermal layer, forming a vesicle. The vesicular fluid also contains cell debris, inflammatory cells, and multinucleated giant cells. There is an intense inflammatory response in deeper dermal structures, usually in the corium of the skin, and more so with primary infection than with recurrent infection. With healing, the vesicular fluid becomes pustular with the recruitment of inflammatory cells and forms a scab. Scarring is uncommon, but has been noted in patients with frequently recurrent lesions.

These histopathologic findings become more prominent when organs other than skin are involved, as with HSE or disseminated neonatal HSV infection. Vascular changes associated with infection include perivascular cuffing and areas of hemorrhagic necrosis, as shown in Fig. 4.3. With HSE, oligodendrocytosis and gliosis are common, as well as astrocytosis developing late in the disease course. Local lymphatics can show evidence of infection with intrusion of inflammatory cells, since the lymphatic channels allow for the drainage of infected fluid from the area of viral replication. The intensity of the inflammatory response is significantly less

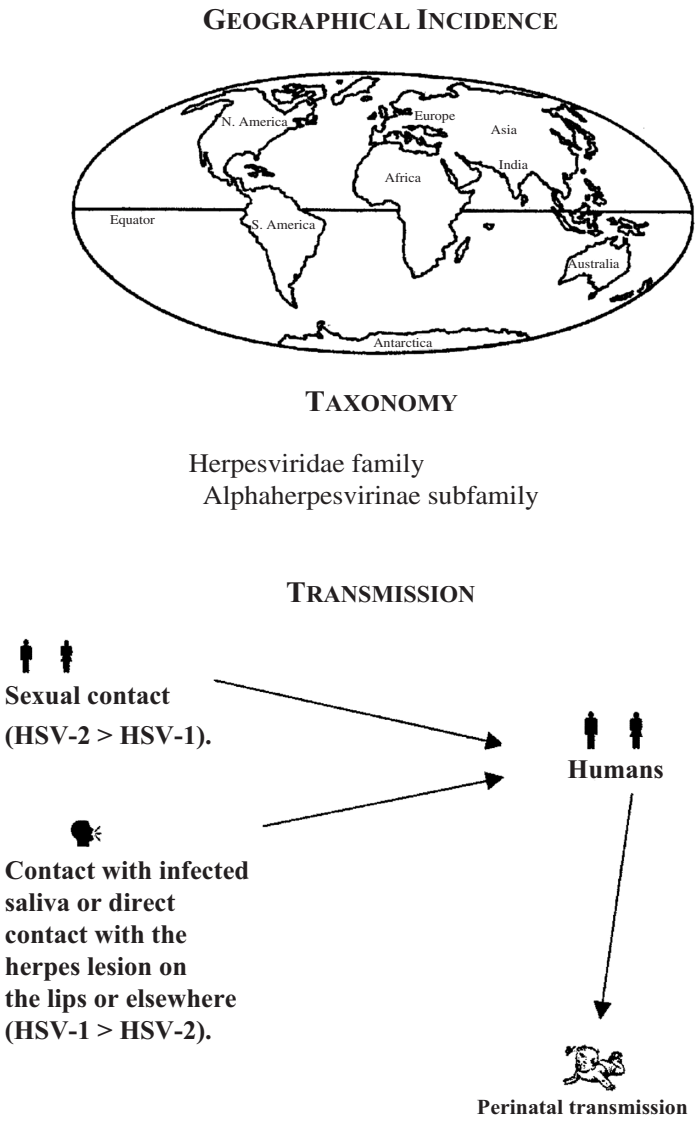


Figure 4.1 Incidence and transmission of HSV.

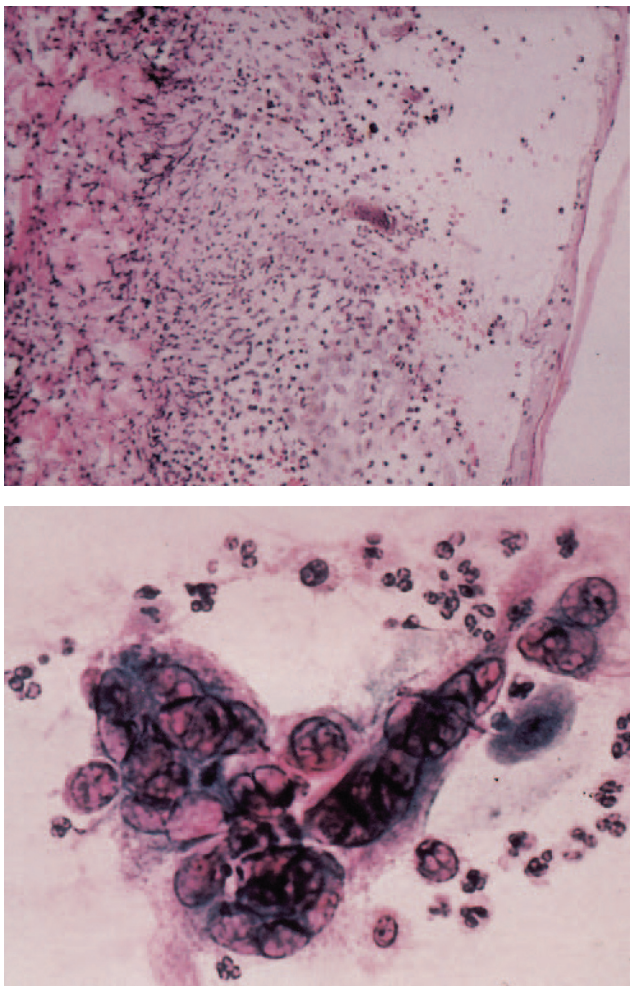


Figure 4.2 (a) Histopathologic findings of cutaneous HSV infection with multinucleate giant cells and lymphocytic infiltration; (b) Tzanck smear.

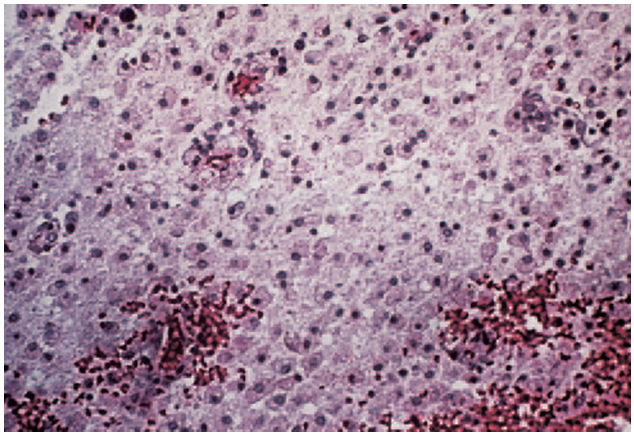


Figure 4.3 Hemorrhagic necrosis and perivascular cuffing from H&E stain of brain tissue.

with recurrent disease. As host defenses are mounted, an influx of mononuclear cells can be detected in infected tissue.

Pathogenesis of Human Infection

The transmission of HSV infection is dependent upon intimate, personal contact between a susceptible seronegative individual and someone excreting HSV. Virus must come in contact with mucosal surfaces or abraded skin for infection to be initiated. Following viral replication at the site of primary infection, either an intact virion or, more simply, the capsid is transported by neurons to the dorsal root ganglia where, after another round of viral replication, latency is established. These events have been demonstrated in a variety of animal models, as reviewed [35]. Transport of the virion is by retrograde axonal flow [36]. The fundamental principles of disease pathogenesis are the propensity of virus to replicate at mucosal surfaces, to be transported to dorsal root ganglia, and to become latent. While, in some instances, replication can lead to disease and, infrequently, life-threatening infections, usually, the host-virus interaction leading to latency predominates. After latency is established, with a proper provocative stimulus, reactivation occurs and virus again becomes detectable at mucocutaneous sites, appearing as skin vesicles or mucosal ulcers or, frequently, being shed in the absence of any symptoms or signs. During primary infection, systemic symptoms can occasionally develop. Such circumstances include disseminated neonatal HSV infection with multi-organ involvement, multi-organ disease of pregnancy and, infrequently, dissemination in patients who are immunocompromised (e.g., organ transplant recipients). Presumably, widespread organ involvement is the consequence of viremia in a host not capable of limiting replication at mucosal surfaces.

Primary infection with HSV-1 or HSV-2 results in viral replication at the mucosal point of contact (i.e., the mouth, the genital tract, or both) as the consequence of oral-oral, oral-genital, or genital-genital contact. Oral infection leads to the establishment of latent virus in the trigeminal ganglion, while latency is established in the sacral ganglia with genital infection.

Operative definitions regarding the type of infection are relevant. For individuals susceptible to HSV infections, namely those without pre-existing antibodies, first infection with either HSV-1 or HSV-2 is defined as "primary infection." After the establishment of latency, a recurrence of HSV is known as "reactivated" or "recurrent infection." This form of infection results in recurrent vesicular skin lesions, such as HSV labialis or recurrent HSV genitalis. An individual with pre-existing antibodies to only one type of HSV (type 1 or type 2) can experience a first infection with the other virus type, defined as a "non-primary initial infection." An example of a nonprimary initial infection would be an individual who has pre-existing HSV-1 antibodies acquired after HSV gingivostomatitis, who then acquires a genital HSV-2 infection. Reinfection with a different strain of either HSV type can occur. This circumstance is defined as "exogenous reinfection."

Latency allows HSV to persist in an apparently inactive state and then be reactivated by a provocative stimulus [37–43]. The molecular basis of latency has been reviewed extensively [38–40]. The biologic phenomenon of latency has been recognized since the beginning of the 20th century [37,43–50]. In 1905, Cushing noted that patients treated for trigeminal neuralgia by sectioning a branch of the trigeminal nerve developed herpetic lesions along the areas innervated by that branch [51–56]. Similarly, surgery of the lower back with manipulation of sacral ganglia reactivated genital HSV infections [57,58].

Viral replication can be induced by axonal injury. The sectioning of a peripheral nerve results in the appearance of virus within the ganglia 3–5 days later [59]. Not surprisingly, if an attempt is made to excise the lesions induced by HSV, vesicles will still recur adjacent to the site of excision [59,60]. Fig. 4.4 illustrates a patient with recurrent genital HSV infection in whom a surgeon attempted to excise the lesion. Recurrences appear in the presence of both cell-mediated and humoral immunity. Virus can be isolated from patients during interim periods with asymptomatic shedding at or near the usual site of recurrent lesions. Recurrences are spontaneous, but there are associations with physical or emotional stress, fever, exposure to ultraviolet light, tissue damage, and immune suppression [45,61–65]. Latent virus has been retrieved from the trigeminal, sacral, and vagal ganglia of humans [37–43,49,50,66].



Figure 4.4 Genital herpes simplex virus (type 2) infection in an immunocompromised host. Note: physician attempted surgical excision of lesions.

Demonstration of exogenous reinfection became possible with restriction endonuclease analysis of viral DNA [67]. Analyses of numerous HSV-1 and HSV-2 isolates from a variety of clinical situations and widely divergent geographic areas demonstrated that epidemiologically unrelated strains yielded distinct HSV DNA fragment patterns. By contrast, HSV DNA derived from the same individual obtained years apart or from epidemiologically related sources (such as mothers and their newborns, monogamous sexual partners, or following short and long passages in vitro) had identical cleavage patterns. When this technique was applied to HSV genital isolates, analyses of endonuclease digestion patterns of HSV DNA fragments revealed that isolates from the same patients or their respective sexual partners could be either the same or different [31,68]. Stated differently, a given patient might have nonidentical isolates obtained from lesions at adjacent sites. This finding indicates that an individual can be infected with different strains. The frequency of this occurrence has been evaluated in two reasonably large studies and appears to be uncommon in the immunocompetent host [69,70].

Reinfection with the same strain of HSV can occur by autoinoculation at a distant site. Thus, HSV-1 could be mechanically transmitted from one site to either an adjacent site or a distal one. These instances have been reported in cases of mouth to genital transmission via scratching [71] or intentional inoculation of vesicle fluid to "bolster immunity" [72–75]. Autoinoculation, however, is unlikely to occur after high levels of circulating immunoglobulin G (IgG) develop, i.e., approximately 1 month following primary infection.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS OF DISEASE

Mucocutaneous Herpes Simplex Virus Infections

HSVs are distributed worldwide and occur in both developed and underdeveloped societies, including remote Brazilian tribes [76]. Animal vectors for human HSV infections have not been described, and man remains the sole reservoir. Virus is transmitted from infected to susceptible individuals during close personal contact. There is no seasonal variation in the incidence of infection. Because infection is rarely fatal and because these viruses become latent, it is estimated that over one-half of the world's population has been infected by HSV and, therefore, has the capability of transmitting HSV during episodes of productive infection.

Oropharyngeal Infections

Epidemiologic Considerations

Mucosal and skin surfaces are the usual sites of primary or initial infection. The mouth and lips are clearly the most common sites of HSV-1 infections. Primary HSV-1 infections usually occur in young children and are most often asymptomatic. Cross-sectional seroprevalence studies in developing countries have shown that infection is influenced by age (occurring early in life) and socioeconomic status. Predictably, middle-class individuals of industrialized societies acquire antibodies to HSV significantly later in life. The most common manifestation of oropharyngeal infection is gingivostomatitis. Primary infection in young adults has also been associated with pharyngitis and a mononucleosis-like syndrome [77].

Utilizing type specific serologic assays, by age 5, over 35% of black versus 18% of Caucasian children have been infected by HSV-1 [78–80]. Through adolescence, blacks had an approximately two-fold higher prevalence of antibodies to HSV-1 as compared to Caucasian counterparts. Females had a slightly higher prevalence of HSV-1 antibodies than males. By the age of 40, both blacks and Caucasians had high prevalence of antibodies. Similar analyses performed worldwide in individuals 20–40 years of age have detected antibody prevalence in excess of 95% in Spain, Italy, Rwanda, Zaire, Senegal, China, Taiwan, Haiti, Jamaica, and Costa Rica.

The largest reservoir of HSV infections in the community is that associated with recurrent herpes labialis. A history of recurrent herpes labialis was noted in 38% of 1800 students attending the University of Pennsylvania [81,82]. The frequency of recurrence is relatively constant among studies, being approximately 33% [83–85]. Viral shedding may occur in the absence of clinical symptoms. The prevalence of asymptomatic excretion of HSV in children is approximately 1% [86,87] and varies in adults from 1 to 5% [77,88–91].

Clinical Disease

Great variability exists in the clinical manifestations of primary HSV-1 infections, ranging from a total absence of symptoms to combinations of fever, sore throat, ulcerative and vesicular lesions, gingivostomatitis, edema, localized lymphadenopathy, anorexia, fever, and malaise (Table 4.1). Asymptomatic infection is the rule rather than the exception. The incubation period ranges from 2 to 12 days with a mean of approximately 4 days. Symptomatic disease in children is characterized by involvement of the buccal and gingival mucosa, as shown in Fig. 4.5a,b. The duration of clinical illness may extend from 2 to 3 weeks with fever ranging between 101 and 104°F. It is not at all uncommon for children with symptomatic primary infection to be unable to swallow liquids because of the significant edema and ulcerations of the oropharynx and the associated pain. Mouth lesions evolve from vesicles to shallow ulcerations on an erythematous base, which then slowly heal. Submandibular lymphadenopathy is commonly associated with primary HSV gingivostomatitis, but rarely with recurrent infection. With primary HSV infections later in life, a common presentation is pharyngitis with a mononucleosis syndrome. Under such circumstances, ulcerative tonsilar lesions on an erythematous base with associated submandibular lymphadenopathy are common [77].

The differential diagnosis of both primary HSV gingivostomatitis and pharyngitis focuses on other mucosal lesions of the oropharynx (Table 4.2). These would include herpangina (caused by coxsackieviruses), candida infections of the mouth, Epstein-Barr virus (EBV)-induced mononucleosis, lesions induced by chemotherapy or radiation therapy, and Stevens-Johnson syndrome.

The onset of recurrent orolabial lesions is heralded by a prodrome of pain, burning, tingling, or itching, which generally lasts for less than 6 hours, followed within 24–48 hours by vesicles [72,92–94]. Vesicles appear most commonly at the vermillion border of the lip and persist in most patients for 48 hours or less, as shown in Fig. 4.6. Vesicles generally number three to five. The total area of involvement is usually less than 100 mm^2 and lesions progress to the pustular or ulcerative and crusting stage within

Table 4.1 Clinical Manifestations of Herpes Labialis

Time After Laboratory Exposure	Clinical Manifestations	Laboratory Analyses	Other Notes
2–12 days, average of 4 days	Onset of fever, soreness of mouth and throat, and development of painful vesicles on the lips, anterior tongue or hard palate, gingiva, or buccal mucosa. The lesions are typically on an erythematous base	Viral culture (specific) Tzanck smear (not specific)	Fever may range between l0lF and 104 F
18–25 days	↓ Progression to ulcerations	Direct fluorescent antigen (specific)	Submandibular lymphadenopathy is commonly associated with primary HSV gingivostomatitis but rarely with recurrent infections
	↓ Resolution of symptoms and lesions, usually within 2–3 weeks	Type-specific serology	
Time varies greatly	↓ ↓ Prodrome of burning pain, tingling, or itching for several hours or days prior to recurrence		Precipitating factors, such as stress, sunlight, local trauma, or infection may precede the onset of recurrences
	↓ One or more papules arise in the localized area		
	↓ Lesions evolve into vesicles. With healing, the vesicular fluid may become pustular with the recruitment of more inflammatory cells		
	↓ Ulceration of each vesicle typically occurs		
Within 7-9 days of onset of recurrent lesions	Lesions crust and resolve. Scarring uncommon but has been noted in patients with frequently recurrent lesions		Frequency of recurrences varies among individuals

72–96 hours. Pain is most severe at the outset and resolves quickly over 96–120 hours. Healing is rapid and is generally complete in 8–10 days. The frequency of recurrences varies among individuals [72].

Genital Herpes Simplex Virus Infections

Epidemiologic Considerations

Because infections with HSV-2 are usually acquired through sexual contact, antibodies to this virus are rarely found before the age of onset of sexual activity [95–104]. While most recurrent episodes of genital HSV infections are caused by HSV-2, an ever-increasing percentage of primary infections are attributable to HSV-1 [95–98,105,106]. Predicated upon newer serologic methods for detection of prior HSV-2 infection, the prevalence of infection is probably 60 million individuals in the USA [107].

Women have higher rates of infection than men, particularly prostitutes and others with multiple sex partners. While the detection of HSV-2 antibodies correlates with the onset of sexual activity [108–110], crowded living conditions may indirectly contribute to prevalence [111]. Historically, if HSV-2 antibodies are sought in healthy women, there is a wide discrepancy in prevalence, ranging from 20% in Americans to 77%



(a) (b)

Figure 4.5 (a) An example of primary gingivostomatitis secondary to HSV type 1 in a child; (b) primary HSV gingivostomatitis in an adult.



Figure 4.6 Herpes simplex labialis (type 1).

in Ugandans [112]. As many as 50–60% of lower socioeconomic women in the USA and elsewhere develop HSV-2 infection by adulthood [42]. The overall seroprevalence of HSV-2 in the USA is 17.0% (years 1999–2004). The seroprevalence of HSV-2 increases from 10.6% at 20–29 years of age to 26% by the age of 40–49. Importantly, if the populations were analyzed according to race, 13.7% of Caucasians, 40.3% of non-Hispanic, and 11.9% of Hispanic Americans are infected with HSV-2, overall [113]. These data indicate a decrease in the HSV-2 infection from a prior National Health and Nutrition Examination Survey (NHANES) study. Factors found to influence acquisition of HSV type 2 include: sex (women greater than men), race (blacks more than whites), marital status (divorced versus single or married), and place of residence (city greater than suburb). In addition, the number of sexual partners also influences acquisition of infection [78,113,114]. Because HSV-2 infection causes ulcerative disease, its occurrence correlates with acquisition of both HIV-1 and human T-lymphotropic virus type 1 (HTLV-1), resulting in increased risk of at least two-fold [115–121].

Table 4.2 Differential Diagnosis of Herpes Labialis

Herpangina: Herpes infection typically affects the anterior portion of the mouth, while enteroviral infection involves the posterior oropharynx and may have an associated eruption on the distal extremities (hand-foot-and-mouth disease)

Aphthous stomatitis: This condition typically presents as a solitary ulcer, usually on the buccal mucosa, with no associated vesicles

Stevens-Johnson syndrome: While this condition affects the mucosal surfaces, it is also characteristically associated with erythema multiforme skin lesions

Epstein-Barr virus–induced mononucleosis: Diffuse hyperemia and hyperplasia of oropharyngeal lymphoid tissue; gelatinous greyish-white exudative tonsillitis; small petechiae at the border of the hard and soft palates

Oral candidiasis: A white coating containing yeast is seen on the tongue, buccal mucosa, and pharynx

Recurrent genital infection is the largest reservoir of HSV-2. Recurrent HSV-2 infection can be either symptomatic or asymptomatic, as with HSV-1; however, recurrence is usually associated with a shorter duration of viral shedding and fewer lesions. The frequency of recurrences varies somewhat between males and females with calculations of 2.7 and 1.9 recurrences per 100 patient days, respectively [95]. Overall, several studies have implicated a frequency of recurrence as high as 60% in individuals with a symptomatic primary infection [108,111]. The type of genital infection, HSV-1 versus HSV-2, is predictive of the frequency of recurrence [99]. HSV-1 infections recur less frequently than those caused by HSV-2.

Clinical Disease

The most severe clinical disease is encountered with primary genital herpetic infection (Table 4.3). Following acquisition of HSV infection at an abraded site, macules and papules, followed by vesicles, pustules, and ulcers will appear. Duration of lesions averages 3 weeks. There are both similarities and differences in the clinical symptomatology of men and women with genital herpes [122]. Primary infection is associated with larger quantities of virus replicating in the genital tract (>10^6 viral particles per 0.2 ml of inoculum) and a period of viral excretion that may persist for 3 weeks. Systemic complications in the male are relatively uncommon; however, aseptic meningitis can occur. Furthermore, paresthesias and dysesthesias can result as a consequence of genital herpetic infection, particularly with recurrence.

Primary infections occurring in either sex can be associated with fever, dysuria, localized inguinal adenopathy, and malaise. As reviewed, the severity of primary infection and frequency of complications are statistically higher in women than men for unknown reasons [95]. Systemic complaints are common in both sexes, occurring in 70% of all cases. The most common complications include aseptic meningitis (approximately 10%) and extragenital lesions (approximately 20%) [122].

In women with primary infection, lesions usually appear on the vulva bilaterally (Fig. 4.7), with the cervix invariably involved (Fig. 4.8). Lesions are usually excruciatingly painful, associated with inguinal adenopathy and dysuria and may involve the vulva, perineum, buttocks, cervix, and/or vagina. A urinary retention syndrome may be encountered in 10–15% of women patients and as many as 25% of women will develop a clinical picture of aseptic meningitis [95].

In males, primary genital HSV infections are most often associated with vesicular lesions superimposed upon an erythematous base, usually appearing on the glans penis or the penile shaft, as shown in Fig. 4.9a–d. The total number of lesions can vary significantly from six to ten to many more. Extragenital lesions can occur on the thigh (Fig. 4.9e), buttocks, and perineum. The differential diagnosis of herpes genitalis is given in Table 4.4.

Complications following primary genital herpetic infection have included sacral radioculomyelitis, which can lead to urinary retention, neuralgias, and meningoencephalitis [123–127]. Primary perianal and anal HSV-2 infections, as well as associated proctitis, are common in male homosexuals, as shown in Fig. 4.10 [128]. As with HSV-1, many primary HSV-2 infections are subclinical, involving the mouth or the uterine cervix [101,102,129,130].

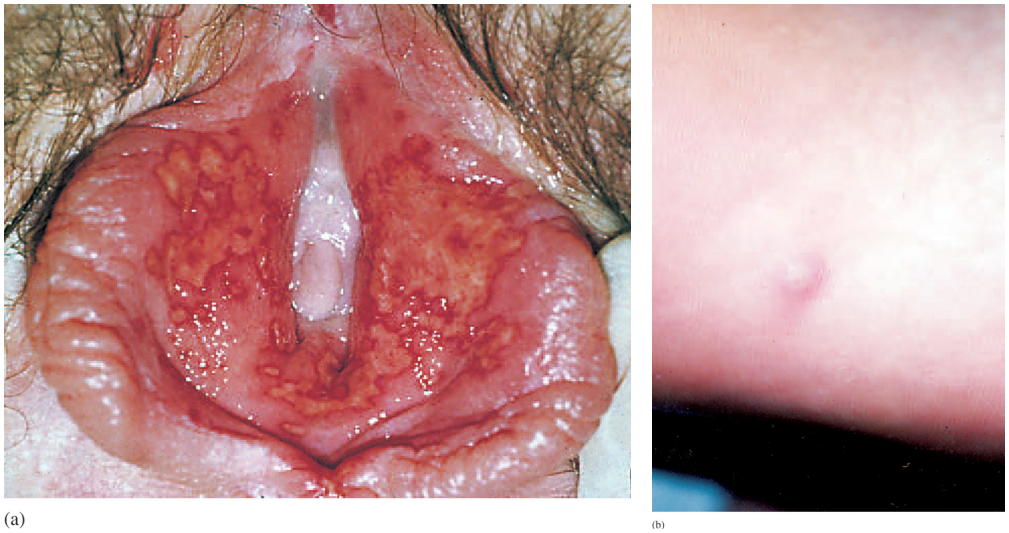
Table 4.3 Clinical Manifestations of Herpes Genitalis

Time After Exposure	Clinical Manifestations	Laboratory Analyses	Other Notes
2–12 days, average of 4days	Onset of painful grouped vesicles or papules (either painful or painless) that become vesicles, typically with an erythematous base ↓ Lesions become ulcerated ↓	Viral culture (specific) Tzanck smear (not specific) Direct fluorescent antigen (specific) Type-specific serology	Associated signs and symptoms include fever, malaise, dysuria, polyuria, headache, and tender inguinal lymphadenopathy. Other symptoms may include urethral and vaginal discharge, vulvar irritation, and scrotal, vulvar, or perianal fissures Precipitating factors, such as stress, sunlight, local trauma, or infection may precede onset of recurrences. Recurrent genital herpetic infection in both men and women is characterized by a prodrome and localized irritation. With healing, the vesicular fluid becomes pustular with recruitment of more inflammatory cells
18–25 days Time course varies greatly	Resolution of symptoms and lesions, typically after 2–3 weeks ↓ ↓ Recurrent papules or vesicles appear in the localized area, progressing to ulcerations ↓ Crusting and resolution of lesions, typically after 7–10 days. Scarring is uncommon but has been noted in patients with frequently recurrent lesions		

Non-primary but initial genital infection (i.e., occurring in an individual with pre-existing heterologous antibody) is less severe symptomatically and heals more quickly. Under such circumstances, the actual duration of disease is closer to 2 weeks. The number of lesions, severity of pain, and likelihood of complications are significantly decreased.

The mildest form of genital herpetic infection is that associated with recurrent disease. With recurrent genital herpetic infection, a limited number of vesicles, usually three to five, will appear on the shaft of the penis of the male or as simply a vulvar irritation in the female [131]. The duration of disease paralleling that encountered with recurrent HSV labialis, is approximately 7–10 days. Neurologic or systemic complications are uncommon with recurrent disease. Virus is shed for only 2–5 days (average of 3) and at lower concentrations (approximately 10^2–10^3 per 0.2 ml of inoculum in tissue culture systems) in women with recurrent genital infection. Recurrent genital herpetic infection in both men and women is characterized by a prodrome (which is a useful marker for therapeutic trials) and localized irritation. Events of healing in the presence of an asymptomatic infection are not well defined.

The major problem with genital HSV infection is the frequency of recurrences, which varies from one individual to the next. Approximately one-third of patients have in excess of eight or nine recurrences per year, one-third of patients will have less than three per year, and the remaining one-third of patients between four and seven [95]. Obviously, with recurrences, either



(a) (b)

Figure 4.7 (a) Primary genital herpes in a female (type 2); (b) occasionally vesicles can be observed as far away as the plantar surface of the foot.



Figure 4.8 Recurrent cervical lesions secondary to HSV-2.

symptomatic or asymptomatic, the patient can transmit infection to sexual partners.

As knowledge about genital HSV-2 infection has increased by using polymerase chain reaction (PCR) detection of viral DNA in the genital tract, viral excretion can occur up to 20% of days [131] and be as short as a few hours [132]. Interestingly, following serial biopsy of lesion sites, inflammation can persist for months in the absence of either shedding or lesions [133].

A particularly serious, but fortunately uncommon, problem encountered with HSV infections during pregnancy is that of widely disseminated disease. As first reported by Flewett [134], infection was demonstrated to involve multiple visceral sites, in addition to cutaneous dissemination. In a limited number of cases, dissemination after primary oropharyngeal or genital infection has led to such severe manifestations of disease as necrotizing hepatitis with or without thrombocytopenia, leukopenia, disseminated intravascular coagulopathy, and encephalitis. The mortality among these pregnant women is reported to be greater than 50% in the absence of therapy. Fetal deaths occurred in more than 50% of cases, although mortality did not necessarily correlate with the death of the mother. Surviving fetuses were delivered by Cesarean section either during the acute illness or at term and none had evidence of neonatal HSV infection. The cumulative experience, then, suggests that factors associated with pregnancy may place both mother and fetus (for those succumbing) at increased risk for severe infection, possibly because of decreased cell-mediated immunity.

Miscellaneous Cutaneous Herpes Simplex Virus Infections

Skin infections caused by HSV manifest in a variety of fashions, including eczema herpeticum in patients with underlying atopic dermatitis, as illustrated in Fig. 4.11a–c [135–137]. The lesions can either be dermatomal, resembling herpes zoster, or disseminated. The latter occurs commonly in Kaposi's varicellaform eruption [138]. An example of periocular Kaposi's



(a) (c) (b)

Figure 4.9 (a–c) Primary genital herpes in a male.





Figure 4.9 (d) recurrent genital herpes in a male; (e) recurrent herpes simplex of the upper thigh.

varicellaform eruption appears in Fig. 4.12. More recently, recurrent cutaneous HSV infections have been associated with erythema multiforme (Fig. 4.13). HSV infections of the digits, known as herpetic Whitlow, was especially common among dental and medical personnel [139,140] before the use of examination gloves became standard, with an estimated occurrence rate of 2.4 cases per 100,000 population per year. An increasing incidence of HSV-2 Whitlow has been recognized due to digital/genital contact (Fig. 4.14a,b,c) [139]. Herpetic Whitlow can be characterized by cutaneous HSV infection of the hand and secondary lymphadenitis (Fig. 4.15). Toxic epidermal necrolysis can occur in association with recurrent HSV infection (Fig. 4.16). Additional common presentations of HSV infections include facial, ear, neck, arm, and trunk HSV infection (Fig. 4.17) and HSV folliculitis (Fig. 4.18).

Table 4.4. Differential Diagnosis of Herpes Genitalis

Syphilis: Chancre, usually not painful, not preceded by vesicles or pustules, and not recurrent
Chancroid: Ulcers are usually tender and multiple; the base is usually covered by a yellowish-grey exudate over granulation tissue; not recurrent
Granuloma inguinale: Nodular ulcerovegetative, hypertrophic, and cicatricial varieties
Lymphogranuloma venereum: Painless erosion in minority of patients, followed by secondary inguinal lymphadenopathy with "groove sign"
Behçet's disease: Genital and/or oral aphthosis, can be recurrent and may be associated with any of the following: synovitis, posterior uveitis, cutaneous pustular vasculitis
Crohn's disease: Sinuses and fistules may develop around the anus and vulva but are deeper than ulcers of herpes and are not associated with vesicles
Candidiasis: Associated with white discharge and occasionally with superficial erosions but not often with discrete ulcers

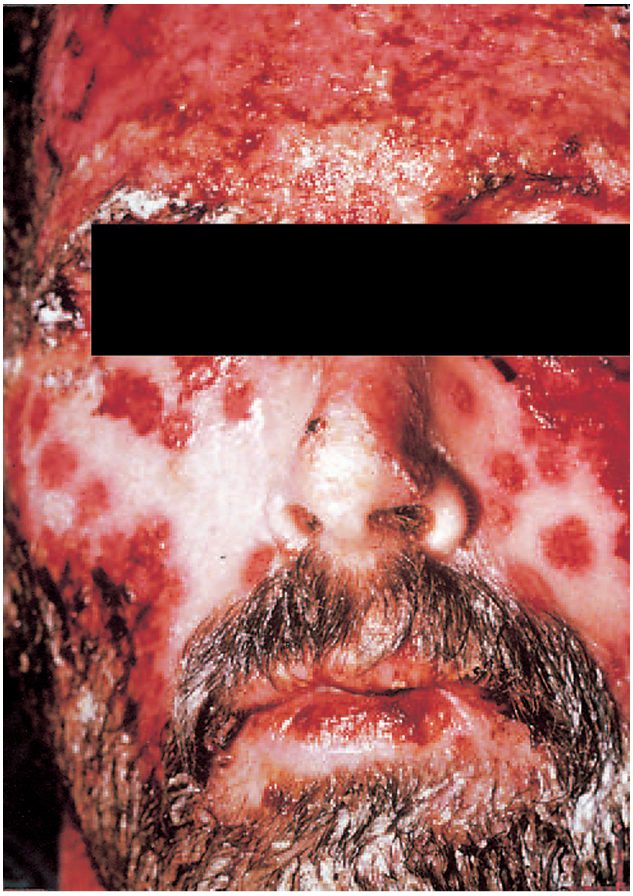


Figure 4.10 Perianal HSV-2 lesions in an HIV-infected individual

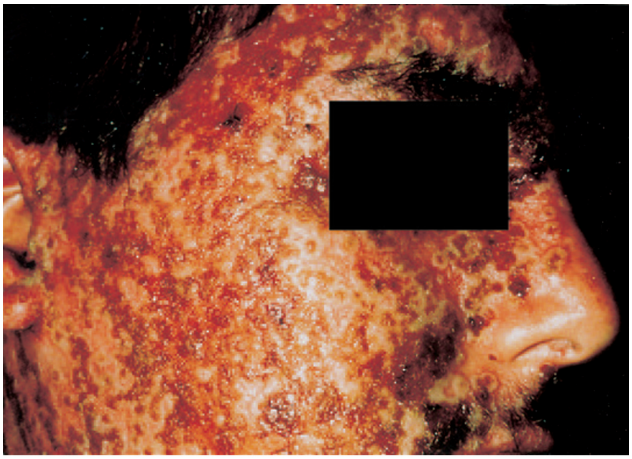
Overall, studies performed in dermatology clinics identify about 2% of men and 1.5% of women who present with herpetic skin infections [141]. In addition to individuals with atopic disease, patients with skin abrasions or burns appear particularly susceptible to HSV-1 or HSV-2 infections and some may develop disseminated infection (Fig. 4.19) [142]. Disseminated cutaneous HSV infections have also been reported among wrestlers, being referred to as herpes gladitorium [143], as summarized [144]. Other skin disorders associated with extensive cutaneous HSV lesions include Darier's disease and Sezary's syndrome (Fig. 4.20) [145,146].

Herpes Simplex Keratoconjunctivitis

Viral infections of the eye occurring beyond the newborn age are usually caused by HSV-1 [147–150]. Approximately 300,000 cases of HSV infections of the eye are diagnosed yearly. These infections are second only to trauma as a cause of corneal blindness in the USA. Primary herpetic keratoconjunctivitis may result in either unilateral or bilateral conjunctivitis (which can be follicular



(a)



(b)



(c)

Figure 4.11 (a) Herpes simplex virus type 1 lesions in patient with eczema herpeticum; (b) eczema herpeticum in a patient with atopic dermatitis before therapy; (c) same patient following 7 days of intravenous acyclovir therapy.



(a)



(b)

Figure 4.12 (a) Periocular HSV-1 lesions in a patient with eczema herpeticum; (b) periocular HSV-1 in an immunocompetent person.



(a) (b) (c) (d)

Figure 4.13 (a) Herpes simplex virus type 1 lesions associated with erythema multiforme; (b) target lesions of erythema multiforme of the palms; (c) target lesions of erythema multiforme of the heel; (d) patch of erythema multiforme of the head of the penis associated with herpes labialis.

in nature), followed soon after by preauricular adenopathy. Symptoms include photophobia, tearing, eyelid edema, and chemosis with the pathognomonic sign of branching dendritic lesions (Fig. 4.21). Less commonly, advanced disease can result in a geographic ulcer of the cornea (Fig. 4.22). As disease advances, uveitis can be a complication (Fig. 4.23). Healing of the cornea can take as long as 1 month, even with appropriate antiviral therapy.

Recurrent HSV infections of the eye are common and usually unilateral. Characteristically, either dendritic ulcerations or stromal involvement appears. Visual acuity is decreased in the presence of the ulcers and, with progressive stromal involvement, opacification of the cornea may occur. Repeated individual attacks may last for weeks or even months following appropriate antiviral therapy. Progressive disease can result in visual loss and even rupture of the globe.

Herpes Simplex Virus Infections in the Immunocompromised Host

Patients compromised by immunosuppressive therapy, underlying disease, or malnutrition are at increased risk for severe HSV infections. Transplant recipients are at particular risk for increased frequency and severity of HSV infection [151–156]. An example of cutaneous dissemination following shaving in a renal transplant recipient is shown in Fig. 4.24. Virus was probably autoinoculated to multiple skin sites by the razor blade. The presence and quantity of HSV antibodies to HSV before transplantation predicts the individual at greatest risk for recurrence. These patients may develop progressive disease involving the respiratory tract, esophagus (Fig. 4.25), or even the gastrointestinal tract [153,154]. Severity of disease is directly related to the degree of immunosuppressive therapy employed [153]. Reactivation of latent HSV infections can occur at multiple sites and healing in these patients occurs over an average of 6 weeks [157]. An example of progressive cutaneous dissemination of HSV-2 at sacral sites is shown in Fig. 4.26a,b. Since the first reports of acquired immune deficiency syndrome (AIDS), the severity of HSV clinical disease in these severely immunocompromised hosts has become apparent [151]. Examples of perioral and intraoral HSV-1 in AIDS patients are shown in Fig. 4.27a,b. Exophytic, verrucous lesions of HSV-2 have been reported in AIDS patients with very high viral loads and low CD4 counts (Fig. 4.27c,d).



(a)



(b)



(c)

Figure 4.14 (a, b) HSV-1 Whitlow; (c) HSV-2 Whitlow.

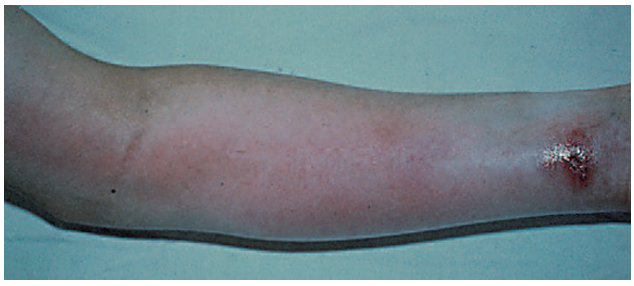


Figure 4.15 Cutaneous HSV lesions with secondary lymphangitis.

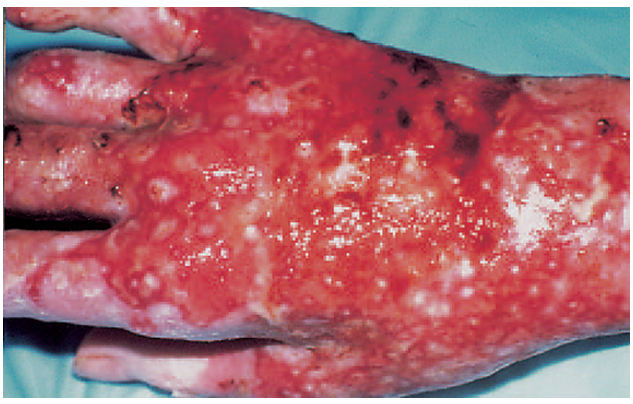
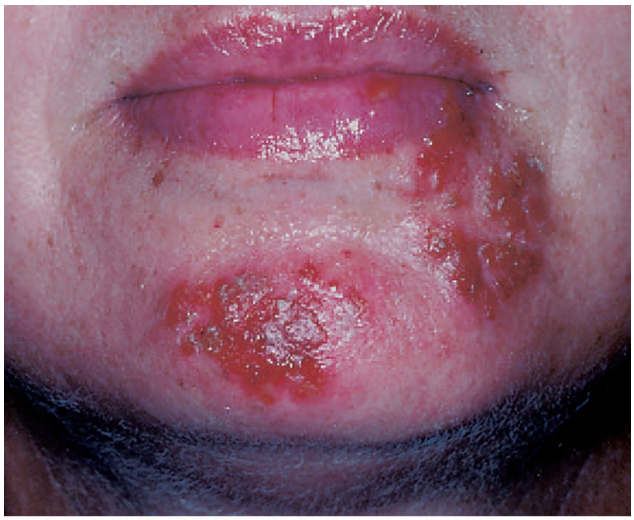


Figure 4.16 Toxic epidermonecrolysis secondary to HSV infection.



(a)



(b)



(c)



(d)



(e)

Figure 4.17 (a, b) Facial HSV infection; (c) HSV infection of the ear; (d, e) HSV infection of the neck.



(f)



(g)

Figure 4.17 (f) HSV infection of the arm; (g) HSV infection of the nipple.



Figure 4.18 HSV facial folliculitis.



Figure 4.19 Disseminated herpes simplex in a patient with thermal burns.

LIFE-THREATENING HERPES SIMPLEX VIRUS INFECTIONS

Neonatal Herpes Simplex Virus Infections

Background

The estimated incidence is approximately one in 2000 to one in 5000 deliveries [12]. At least four factors appear to have the greatest effect on disease transmission. First, the type of maternal genital infection (primary versus recurrent) at delivery influences the duration and quantity of virus excreted and the time to total healing [122]. The incidence of neonatal herpes in babies born to women with primary or initial genital HSV infection is approximately 33% as compared to 3% for recurrent infection [158]. Second, transplacental maternal neutralizing and antibody-dependent cell-mediated cytotoxicity (ADCC) antibodies decrease the probability of infection for babies exposed to virus [159–161].

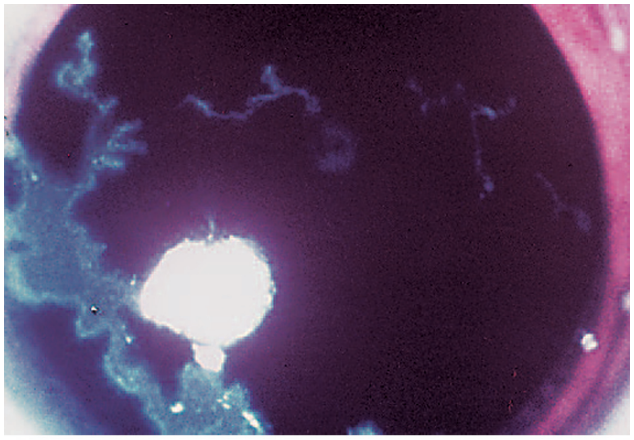


(a)

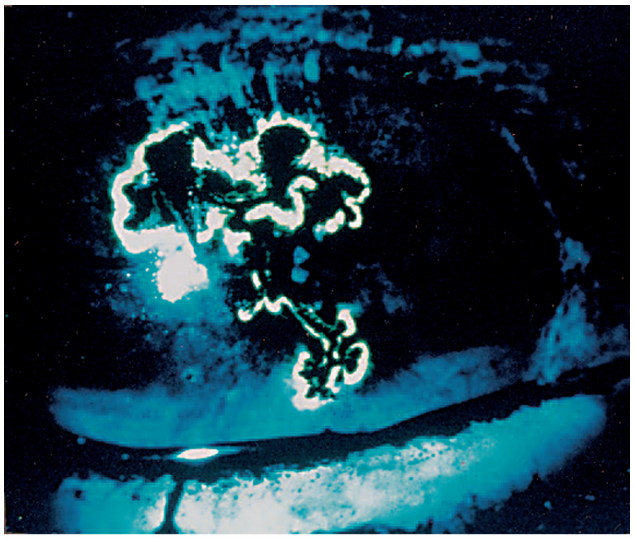


(b)

Figure 4.20 (a, b) Disseminated herpes simplex in patients with cutaneous T-cell lymphoma (photographs courtesy of Margretta A. O'Reilly, MD, University of Utah, Salt Lake City, UT).



(a)



(b)

Figure 4.21 (a, b) Dendritic lesions secondary to HSV-1 keratoconjunctivitis.

Third, the duration of ruptured membranes is an important indicator of risk for acquisition of neonatal infection. Women with active genital lesions at the time of onset of labor are usually delivered by Cesarean section. Infection of the newborn has occurred in spite of delivery by Cesarean section [162]. Fourth, fetal scalp monitors can create a site of inoculation of virus [163,164].

HSV infection of the newborn can be acquired at one of three times: in utero, intrapartum, and postnatal. The mother is the most common source of infection for the first two of these routes of transmission of infection to the newborn. While intrapartum transmission accounts for 75–80% of all cases, the other two routes must be considered in a child with suspected disease for both public health and prognostic purposes.

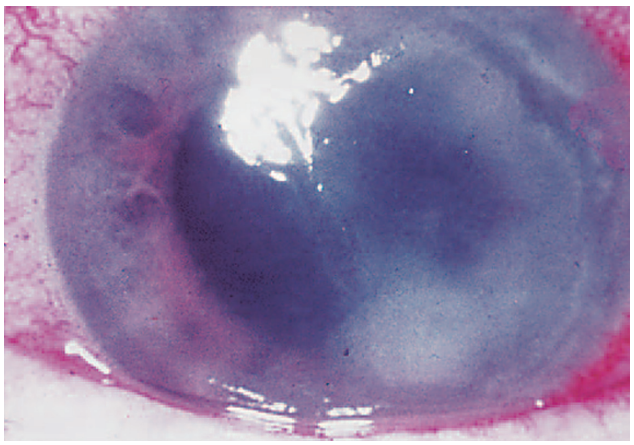


Figure 4.22 Geographic ulcer as a complication of herpes simplex keratoconjunctivitis.

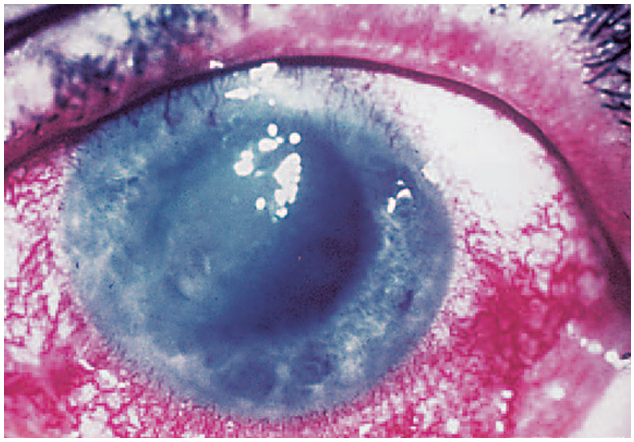


Figure 4.23 HSV uveitis.



Figure 4.24 Disseminated facial HSV-1 infection in an organ transplant recipient.

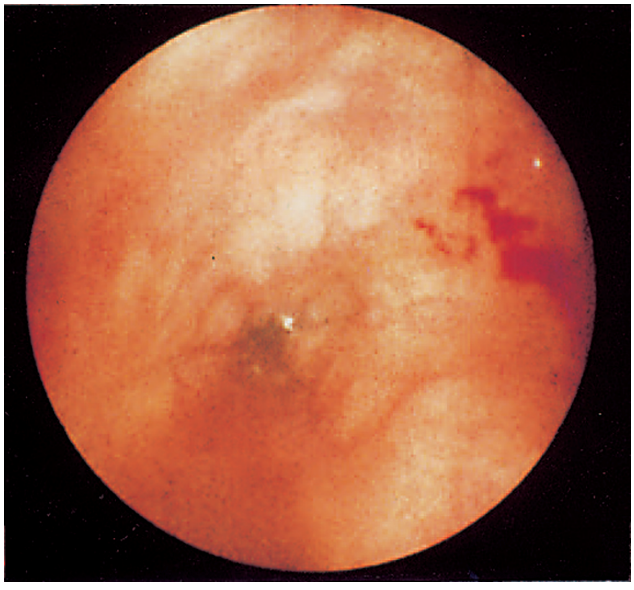
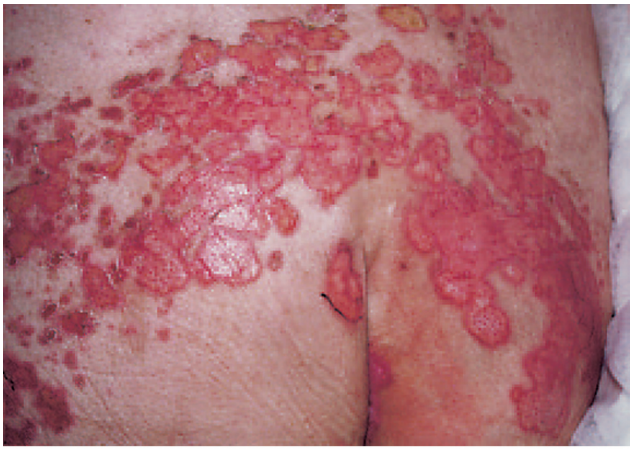


Figure 4.25 HSV esophagitis in an immunocompromised host.



(a)



(b)

Figure 4.26 (a) Disseminated sacral HSV-2 infection in an immunocompromised host; (b) sacral ulcer resulting from herpes simplex in an AIDS patient.

Clinical Presentation

The clinical presentation of babies with neonatal HSV infection reflects the site and extent of viral replication. Neonatal HSV infection is almost invariably symptomatic and frequently lethal. Congenital intrauterine infection is usually identified within the first 48 hours following birth. Babies infected intrapartum or postnatally with HSV infection can be divided into three categories, namely those with: (1) disease localized to the skin, eye, and/or mouth, (2) encephalitis with or without skin, eye, and/or mouth involvement, and (3) disseminated infection, which involves multiple organs, including the central nervous system (CNS), lung, liver, adrenals, skin, eye, and/or mouth [165].

Intrauterine infection is characterized by the triad of skin vesicles or skin scarring, eye disease, and the far more severe manifestations of microcephaly or hydranencephaly [166]. Often chorioretinitis, alone or in combination with other eye findings such as keratoconjunctivitis, is a component of the clinical presentation [167]. An example of a child with bullous skin lesions secondary to intrauterine infection is shown in Fig. 4.28.



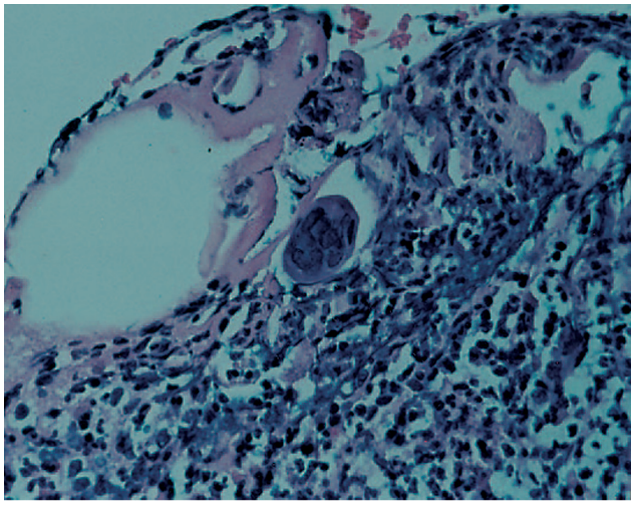
(a)



(c)



(b)



(d)

Figure 4.27 (a) Ulcerative oropharyngeal HSV-1 lesion in an HIV-infected individual; (b) facial herpes simplex in an AIDS patient (photograph courtesy of Jeffery Callen, MD, Department of Dermatology, University of Louisville, Louisville, KY); (c, d) Exophytic, verrucous lesions of herpes simplex of the scrotum in an AIDS patient as confirmed by culture and histology.



Figure 4.28 Intrauterine HSV infection (newborn).

Babies with the worst prognosis both for mortality and morbidity are those with disseminated infection. Children with disseminated infection usually present to tertiary care centers between 9 and 11 days of life. The principal organs involved include the liver and adrenals. However, infection can involve many other organs including the larynx, trachea, lungs, esophagus, stomach, lower gastrointestinal tract, spleen, kidneys, pancreas, and heart. Constitutional signs and symptoms include irritability, seizures, respiratory distress, jaundice, bleeding diatheses, shock, and frequently the characteristic vesicular exanthem, which is often considered pathognomonic for infection. Encephalitis is a common component of this form of infection, occurring in about 60–75% of children. The vesicular rash, as described below, is particularly important in the diagnosis of HSV infection. However, over 20% of children with disseminated infection will not develop skin vesicles during the course of their illness [162,167]. Mortality in the absence of therapy exceeds 80%.

Infection of the CNS alone or in combination with disseminated disease presents with the findings indicative of encephalitis. Brain infection can occur either as a component of multi-organ disseminated infection or as encephalitis alone with or without skin, eye, and mouth involvement. Nearly one-third of all babies with neonatal HSV infection have only the encephalitic component of disease. Clinical manifestations of encephalitis (alone or in association with disseminated disease) include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanelle, and pyramidal tract signs. While babies with disseminated infection often have skin vesicles in association with brain infection, the same is not true for the baby with encephalitis alone. This latter group of children has skin vesicles 60% of the time [162,167].

While cultures of cerebrospinal fluid yield virus in 25–40% of all cases, PCR detection of viral DNA is the diagnostic tool of choice. Anticipated findings on cerebrospinal fluid examination include pleocytosis and proteinosis (as high as 500–1000 mg/dl). Death occurs in 50% of babies with localized CNS disease who are not treated and is usually related to brain stem involvement. With rare exceptions, survivors are left with neurologic impairment [168,169].

Infection localized to the skin, eye, and/or mouth is associated with no mortality, but it is not without significant morbidity.



Figure 4.29 Cutaneous HSV lesions in a newborn. (Courtesy of Dale G. Schaefer, M.D., AustinDermCare, Texas, U.S.A.)

When infection is localized to the skin, the presence of discrete vesicles remains the hallmark of disease, as illustrated in Fig. 4.29. Clusters of vesicles often appear initially on the presenting part of the body that was in direct contact with the virus during birth, such as the scalp (Fig. 4.30). With time, the rash can progress to involve other areas of the body as well. Vesicles occur in 90% of children with skin, eye, or mouth infection. The skin vesicles are usually 1–2 mm in diameter. They can progress to larger bullous lesions greater than 1 cm in diameter. These larger lesions and their progression are illustrated in Fig. 4.31. While discrete vesicles on various parts of the body are usually encountered, crops and clusters of vesicles have also been described. Infections involving the eye may manifest as keratoconjunctivitis in newborns, or later as chorioretinitis. Children with disease localized to the skin, eye, or mouth generally present at about 10–11 days of life. Those babies with skin lesions will invariably suffer from recurrences over the first 6 months (and longer) of life, regardless of whether



Figure 4.30 Scalp lesions caused by HSV infection in a newborn.

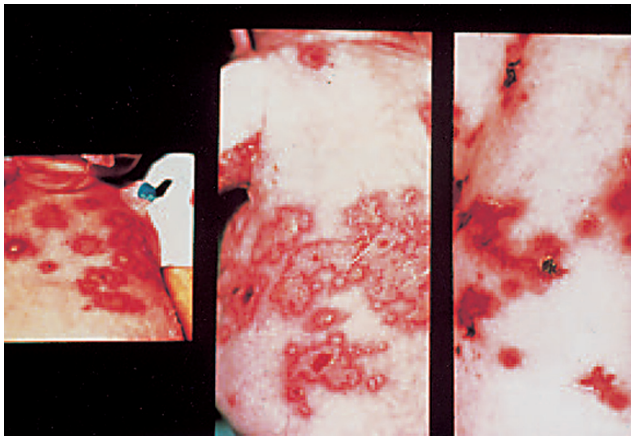


Figure 4.31 Evolution of cutaneous HSV lesions.

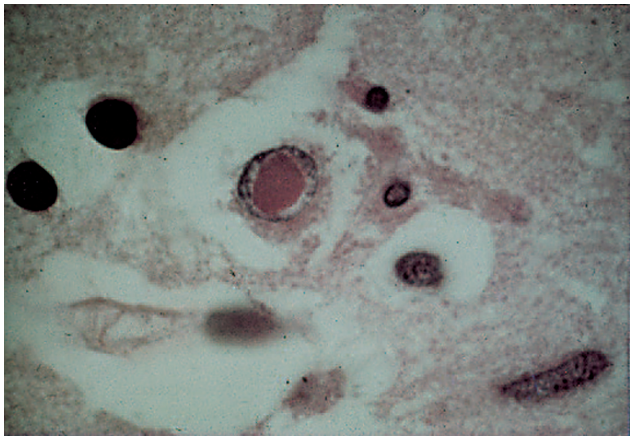


Figure 4.33 Cowdy type A intranuclear inclusion.

therapy is administered or not. Although death is not associated with disease localized to the skin, eye, and/or mouth, approximately 30% of these children eventually develop evidence of neurologic impairment. The reader is referred to more thorough reviews of neonatal HSV infection for more detailed descriptions of the disease and its management [12].

Herpes Simplex Encephalitis

HSE is one of the most devastating of all HSV infections (Fig. 4.32), being the most common cause of sporadic, fatal encephalitis in the USA [170]. The incidence of HSE is approximately 1 in 200,000 individuals per year, for a national annualized rate of approximately 1250 cases. Importantly, the actual incidence remains unknown, as no national reporting system exists for any HSV infection, even for life-threatening diseases such as HSE.

Clinical Manifestations

The manifestations of HSE in the older child and adult reflect the areas of pathology in the brain. Fig. 4.33 indicates the classic Cowdry type A intranuclear inclusion evident on brain biopsy from a patient with HSE. The most common findings include fever, altered consciousness, bizarre behavior, disordered mentation, and focal neurologic findings. These clinical signs and symptoms can often be correlated with localized temporal lobe disease, as demonstrated by neurodiagnostic procedures [23]. There is no characteristic set of findings pathognomonic for HSE; however, progressively deteriorating levels of consciousness, fever, an abnormal cerebrospinal fluid formula, and focal neurologic findings in the absence of other causes should make this disease highly suspect. Other diagnostic evaluations should be initiated immediately, since other treatable diseases may mimic HSE [171]. Mortality in untreated patients is in excess of 70%, and only 2.5% of all patients recover full neurologic function. Factors that influence outcome include age, level of consciousness (Glasgow coma score) at the outset of therapy, and disease duration.

Diagnosis

Standard neurodiagnostic procedures used in the evaluation of patients with suspected HSE include cerebrospinal fluid examination, electroencephalogram, and one or more scanning procedures

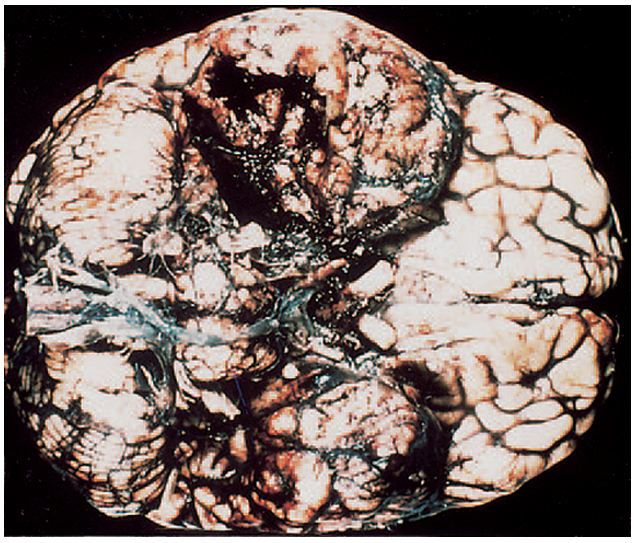


Figure 4.32 Herpes simplex encephalitis.

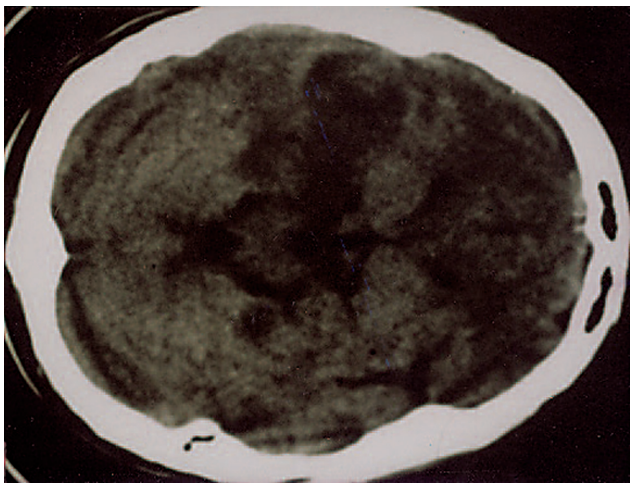


Figure 4.34 Computed tomographic scan from patient with herpes simplex encephalitis.

such as computed tomography (Fig. 4.34) or magnetic resonance imaging. Characteristic abnormalities of the cerebrospinal fluid include pleocytosis (usually mononuclear cells) and elevated protein. Red blood cells are found in most (but not all) cerebrospinal fluid samples obtained from patients with HSE. Upon serial cerebrospinal fluid examination, protein concentration and cell counts almost always increase dramatically. This observation is helpful in distinguishing HSV infection of the CNS from other viral infections. The electroencephalogram generally localizes spike and slow wave activity to the temporal lobe. A burst suppression pattern is considered characteristic. Early after onset, imaging may reveal only evidence of edema. As the disease progresses, this finding is followed by evidence of temporal lobe hemorrhage and midline shift in the cortical structures. From a laboratory perspective, as noted below, the use of PCR for detection of HSV DNA in the cerebrospinal fluid is the diagnostic tool of choice.

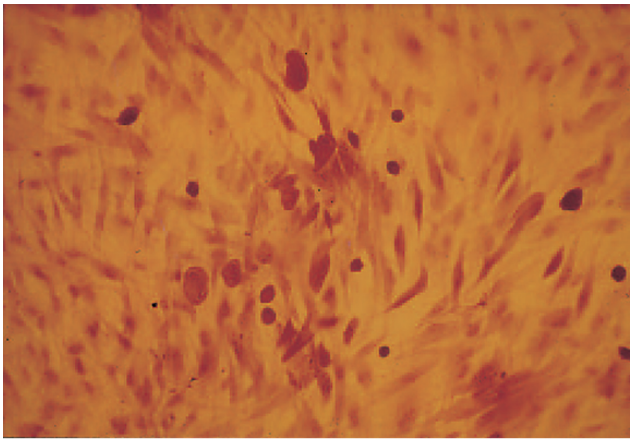
Other Neurological Syndromes

In addition to encephalitis with cortical disease, HSV can involve virtually any anatomic area of the nervous system. HSV has been associated with meningitis, myelitis, radiculitis, and other syndromes. The relationships between HSV infections of the brain and chronic degenerative disease, psychiatric disorders, or Bell's palsy require further definition [172–174].

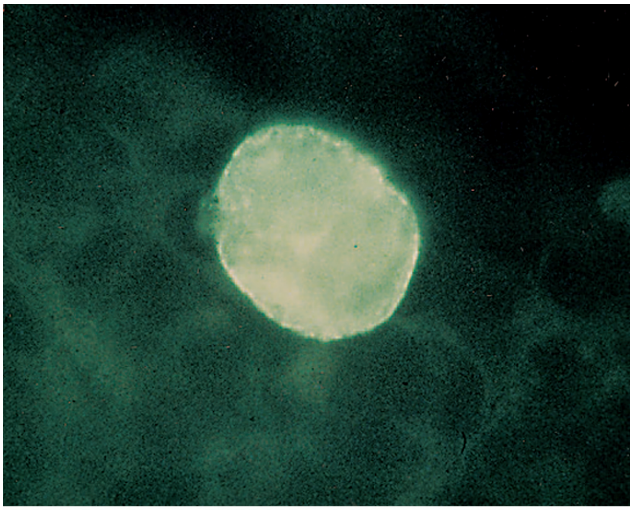
Diagnosis

The appropriate utilization of laboratory techniques is essential if a diagnosis of HSV infection is to be established. Virus isolation remains the definitive diagnostic method. If skin lesions are present, a scraping of skin vesicles should be made and transferred in appropriate virus transport media to a diagnostic virology laboratory. Clinical specimens should be shipped expeditiously on ice for inoculation into cell culture systems that are appropriate for the demonstration of the cytopathic effects characteristic of HSV replication, as illustrated in Fig. 4.35a. In addition to skin vesicles, other sites from which virus may be isolated include the cerebrospinal fluid, stool, urine, throat, nasopharynx, and conjunctivae. In infants with evidence of hepatitis or other gastrointestinal abnormalities, it may also be useful to obtain duodenal aspirates for HSV isolation. Typing is of epidemiologic and pathogenetic importance and is increasingly available.

In the absence of diagnostic virology facilities, cytologic examination of cells from the maternal cervix, or the infant's skin, mouth, conjunctivae, or corneal lesions may be useful in making a presumptive diagnosis of HSV infection. These methods only have a sensitivity of approximately 60–70%, therefore, they should not be the sole diagnostic determinant for infection in the newborn [42]. Alternative methods, such as a direct fluorescent antigen (DFA) assay (Fig. 4.35b) have a slightly higher sensitivity and specificity in adults with genital herpes [175]. Cellular material obtained by scraping the periphery of the base of lesions should be smeared on a glass slide and promptly fixed in cold ethanol. The slide can be stained according to the methods of Papanicolaou, Giemsa, or Wright before examination by a trained cytologist. Tzanck smears (Fig. 4.2b) will probably not demonstrate the presence of intranuclear inclusions. The presence of intranuclear inclusions and multinucleated giant cells are indicative, but not diagnostic, of HSV infection. It is important to recognize that the Tzanck smear cannot differentiate HSV infection from that of other human herpesviruses, such as varicella-zoster virus (VZV). Electron microscopic (EM) assays are continuing to be developed [176]. Fig. 4.36 illustrates a classic EM of HSV.



(a)



(b)

Figure 4.35 (a) Cytopathic effect of HSV in cell culture; (b) positive direct fluorescence antigen assay for HSV-2.

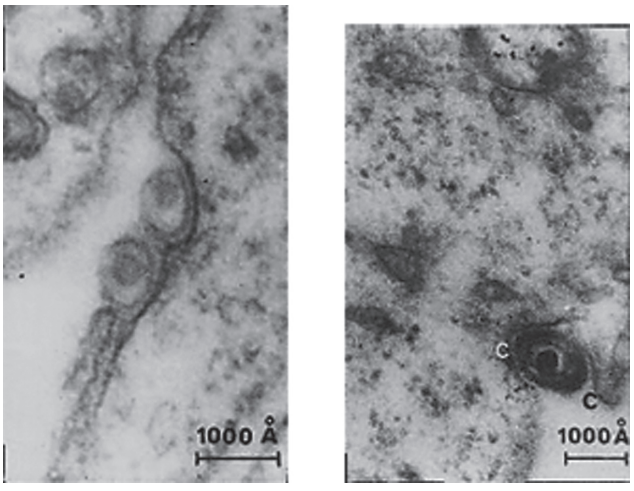


Figure 4.36 Election micrograph of HSV at time of absorption and penetration.

PCR methodology is the diagnostic method of choice for assessing cerebrospinal fluid from patients with suspect CNS HSV infections. It has replaced all other laboratory diagnostics [177–179]. More recently, the use of PCR has been shown more sensitive than culture for detecting evidence of HSV in skin lesions. A note of caution is indicated, namely, the value of PCR is dependent upon the quality of the laboratory that is performing the study.

Therapeutic decisions cannot await the results of serologic studies. However, type-specific serologic assessments are available that allow distinction between prior HSV-1 and HSV-2 infection [180–183]. These serological tests use the enzyme-linked immunosorbent assay (ELISA). The Western blot assay is available for the diagnosis of HSV infection only in research laboratories, but it has high sensitivity and specificity in differentiating between HSV-1 and HSV-2 antibodies.

Treatment

Background. Acyclovir, the prototypic drug for the treatment of HSV infections, has proven its value over nearly three decades of use. Acyclovir was synthesized in 1974 by Drs. Lilia Beauchamp and Howard Schaffer of Burroughs Wellcome Company as part of a program designed to produce anti-cancer drugs. These compounds were screened both for inhibition of cell replication and for antiviral activity [184]. Acyclovir, 9-((2-hydroxy ethoxy)methyl) guanine, demonstrated significant antiviral activity against herpesviruses, especially HSV and VZV [185]. After extensive preclinical studies revealed an extremely favorable toxicity profile, acyclovir began clinical trials for a number of herpesvirus infections in the late 1970s. More recently, the prodrugs valacyclovir (prodrug of acyclovir) and famciclovir (prodrug of penciclovir) have proven of enhanced value as compared to acyclovir (Table 4.5).

Table 4.5 Treatment of Herpesvirus Infections

Symptom	Treatment
Herpes labialis:	Topical application of 1% penciclovir cream every 2 hours while awake for 4 days. (Mucous membrane application is not recommended)
	Topical application of 10% docosanol cream five times daily
	Acyclovir is often used off label for oral treatment of herpes labialis, at 400 mg 5 times daily for 5 days
	Famciclovir is often used off label for oral treatment of herpes labialis, at 125 mg twice daily for 5 days, although a recent study showed that high dosages are more optimal (500 mg three times daily for 5 days) FDA approval is for 1500 mg once
	Valacyclovir is often used off label for oral treatment of herpes labialis, at 500 mg twice daily for 5 days, but current studies suggest higher doses may be more efficacious FDA approval is for 2 g BID for one day
	For chronic suppression, if needed (off label): Acyclovir, 400 mg twice daily, or famciclovir, 250 mg twice daily, or valacyclovir, 500 mg once daily
Herpes genitalis:	Acyclovir, 200 mg five times daily (or 400 mg tid for 10 days initial infection) or 5 days (recurrent attacks). Intravenous acyclovir may be given for severe primary infections, at 5 mg/kg over 1 hour every 8 hours for 7 days, followed by oral therapy. Daily suppressive therapy may be given to prevent frequent attacks, at 400 mg twice daily
	Valacyclovir, 1 g twice daily for 10 days for initial episodes, and 500 mg twice daily for 3 days for recurrent attacks. For chronic suppressive therapy, 1 g daily is given for patients with 10 or more recurrences per year, and 500 mg once daily is given for those with less frequent outbreaks
	Famciclovir, 250 mg tid for 10 days for initial episodes, and 125 mg twice daily for 5 days or 1 g BID for one day for recurrent outbreaks only. For continuous suppressive therapy, 250 mg twice daily is given
Other cutaneous HSV infections (i.e., herpetic whitlow):	Although no controlled studies have evaluated acyclovir for therapy of HSV infections in other cutaneous areas, if disease is severe and recurrent, it would seem prudent to prescribe oral acyclovir (or valacyclovir or famciclovir) initially at dosages utilized to treat primary genital HSV infections. If suppressive therapy is planned those dosages utilized for frequently recurrent genital HSV infection would seem appropriate
Mucocutaneous HSV infections in immunocompromised patients:	Intravenous acyclovir infusion at 5 mg/kg over 1 hour, given every 8 hours for 7 days. For children less than 12 years of age, the dosage is 250 mg/m2 at the same schedule
	For limited disease, topical application of acyclovir 5% ointment every 3 hours (six times daily) for 7 days
Recurrent orolabial or genital HSV infections in HIV-infected patients:	Famciclovir, 500 mg twice daily for 7 days. This same dosage is used off label on a daily basis for chronic suppression of recurrent episodes in HIV-infected persons
	Valacyclovir, 500 mg to 1000 mg bid, can also be used off label for episodic therapy (e.g., 7 days) or on a daily basis for chronic suppression in these patients
Herpes simplex keratoconjunctivitis:	Trifluridine 1% ophthalmic solution for primary keratoconjunctivitis and recurrent epithelial keratitis due to HSV, given as one drop in the affected eye(s) every 2 hours while awake (maximum of 9 drops per day). This is continued until re-epithelialization of the corneal ulcer occurs, followed by one drop every 4 hours while awake for 7 more days
	Vidarabine 3% ophthalmic ointment applied in the lower conjunctival sac five times daily at 3-hour intervals. This is continued until complete re-epithelialization of the ulcer occurs, followed by twice daily application for 7 additional days
	Topical acyclovir for HSV ocular infections is effective but probably not superior to trifluridine [280–282] and is no longer recommended
Herpes simplex encephalitis:	Intravenous acyclovir infusion at 10 mg/kg over 1 hour, given every 8 hours for 14 days. For children ages 6 months to 12 years of age, the dosage is adjusted to 500 mg/m2
Neonatal herpes simplex infection:	Intravenous acyclovir infusion at 20 mg/kg over 1 hour, given every 8 hours for skin, eye, mouth (SEM) disease for 14–21 days (encephalitis or multiorgan disease)
Neonatal HSV:	Intravenous acyclovir infusion at 10 mg/kg every 8 hours for 10 to 14 days
Acyclovir-resistant HSV infections:	Intravenous foscarnet infusion at 40 mg/kg over 1 hour either every 8 or 12 hours, for 2–3 weeks or until all lesions are healed
	Cidofovir 1% cream or gel may be compounded as an alternative therapy

Acyclovir and Valacyclovir: Mechanism of Action and Pharmacology

Acyclovir is a synthetic acyclic purine nucleoside analogue that is a selective inhibitor of HSV types 1 and 2 and VZV replication [184,185]. Acyclovir is converted by virus-encoded thymidine kinase (TK) to its monophosphate derivative, an event that does not occur to any significant extent in uninfected cells [186]. Subsequent di- and tri-phosphorylation is catalyzed by cellular enzymes, resulting in acyclovir-triphosphate concentrations 40–100 times higher in HSV-infected than in uninfected cells. Acyclovir triphosphate inhibits viral DNA synthesis by competing with deoxyguanosine triphosphate as a substrate for viral DNA polymerase [187]. Because acyclovir triphosphate lacks the 3' hydroxyl group required for DNA chain elongation, viral DNA synthesis is terminated. Viral DNA polymerase is tightly associated with the terminated DNA chain and is functionally inactivated [188]. Also, the viral polymerase has greater affinity for acyclovir triphosphate than does cellular DNA polymerase, resulting in little incorporation of acyclovir into cellular DNA [189]. In vitro, acyclovir is most active against HSV-1 (average EC_{50}=0.04 ug/ml), HSV-2 (0.10 ug/ml), and VZV (0.50 ug/ml). EBV requires higher acyclovir concentrations for inhibition [190] and cytomegalovirus (CMV), which lacks a virus-specific TK, is resistant.

Acyclovir was originally released in topical and intravenous formulations and subsequently became the first orally administered therapeutic for herpesvirus infections. The topical preparation is 5% acyclovir in a polyethylene glycol ointment base. Oral formulations include a 200-mg capsule, a 400-mg tablet, an 800-mg tablet, and a suspension (200 mg/5 ml). Absorption of acyclovir after oral administration is slow and incomplete, with oral bioavailability of about 15–30%. After multi-dose oral administration of 200 or 800 mg of acyclovir, the mean steady-state peak levels are about 0.57 and 1.57 μg/ml, respectively. Much higher plasma levels can be achieved with intravenous administration. Steady-state peak acyclovir concentrations following intravenous doses of 5 or 10 mg/kg every 8 hours are about 9.9 and 20.0 μg/ml, respectively. Acyclovir penetrates well into most body tissues, including the brain. The terminal plasma half-life is 2–3 hours in adults with normal renal function. Acyclovir is minimally metabolized and about 85% is excreted unchanged in the urine via renal tubular secretion and glomerular filtration. For patients with severe renal failure (CrCl <10 ml/min), the dose of oral acyclovir should be reduced to 200 mg (for HSV) or 800 mg (for VZV) every 12 hours. Acyclovir is readily removed by hemodialysis, but not by peritoneal dialysis.

Valacyclovir, the L-valine ester of acyclovir, was developed to address the poor oral bioavailability of acyclovir. When administered orally, the L-valine ester is cleaved upon absorption, resulting in plasma concentrations of acyclovir with an equivalent of 70% bioavailability. The only active metabolite is acyclovir, thus the clinical profile is identical to the parent drug. It is available as 500 or 1000 mg tablets.

Penciclovir and Famciclovir: Mechanism of Action and Pharmacology

Like acyclovir, penciclovir is a guanosine analogue that is active against HSV-1, HSV-2, and VZV in vitro. It is similarly phosphorylated by viral TK and subsequently converted to its active form, penciclovir triphosphate. However, its mechanism of action differs from acyclovir in that, while a competitive inhibitor of DNA polymerase, it does not cause chain termination. Penciclovir's clinical utility is limited to topical treatment for herpes labialis due to its minimal bioavailability. Famciclovir is the diacetyl ester prodrug of penciclovir and confers 70% bioavailability [191]. It is indicated for treatment of herpes zoster infections as well as genital herpes, and has similar efficacy to valacyclovir. It is excreted by the kidney and thus requires dose adjustment in patients with renal insufficiency. Famciclovir is well tolerated, resulting in minimal side effects with headache and gastrointestinal upset being most common. The resistance profile is similar to that of acyclovir with mutation of the viral TK being the most common mechanism [192].

Because of improved pharmacokinetics and pharmacodynamics, valacyclovir and famciclovir are the recommended therapies for HSV and VZV infections where oral therapy is indicated. Famciclovir is available as 125, 250, and 500 mg tablets in the USA.

Treatment of Mucocutaneous Herpes Simplex Virus Infections

Genital herpes

Both primary and initial genital HSV infections can be treated with topical, oral, or intravenous acyclovir. While topical application of acyclovir reduces the duration of viral shedding and the time to complete lesion crusting, it is not recommended for treatment since it is less effective than oral or intravenous therapy [27,29]. Intravenous acyclovir is the most effective treatment for first-episode genital herpes, and results in a significant reduction in the median duration of viral shedding, pain, and time to complete healing (8 versus 14 days on average) [28,193]. Since intravenous acyclovir therapy usually requires hospitalization, it is reserved for patients with severe local disease or systemic complications (e.g., meningitis, urinary retention, transverse myelitis, etc.). Oral therapy (200 mg five or 400 mg two times daily) is effective, but not to the extent of valacyclovir or famciclovir, and has become the standard treatment. Unfortunately, none of these treatments of acute HSV infection alter the frequency of subsequent recurrences [30,193–195].

Both valacyclovir (1000 mg bid or 500 mg tid) and famciclovir (250–500 mg tid) can be administered orally to treat primary genital HSV infections. Both drugs provide convenient dosing regimens and fewer pills, increasing compliance.

As previously described, recurrent genital herpes is less severe and resolves more rapidly than primary or initial infection, offering a shorter time interval for successful antiviral chemotherapy. According to current Centers for Disease Control and Prevention guidelines, acyclovir and valacyclovir are effective for the treatment of recurrent genital HSV infections. Short-course treatment with famciclovir (1–2 days) or valacyclovir (1–3 days) appears more efficacious [193,196–202].

Oral acyclovir has been successful in treating herpes labialis in immunocompetent persons [203]. Intravenous acyclovir has been demonstrated to be effective in the therapy of mucocutaneous HSV infections in immunocompromised hosts [204,205].

Oral administration of acyclovir is effective for suppression of frequently recurring oral or genital herpes [206–208]. Daily administration of any of these three drugs reduces the frequency of recurrences by up to 80% (Table 4.6). Emergence of

Table 4.6 Reasons to Consider Suppression versus Episodic Therapy with Acyclovir, Valacyclovir or Famciclovir

Immunocompromised patient?
Frequency of outbreaks?
Time since first outbreak?
Severity of outbreaks?
Presence of prodromes?
Gender of partner?
If susceptible partner is female, is she pregnant?

acyclovir-resistant HSV appears to be an infrequent occurrence in immunologically normal individuals. Importantly, asymptomatic virus shedding can continue despite clinically effective acyclovir suppression, resulting in the possibility of person-to-person transmission.

Valacyclovir has also been shown to decrease the probability of person-to-person transmission. When 500 mg is administered once daily to the infected partner, transmission is decreased by about 50% over 8 months [209].

Herpes labialis

Acyclovir has not been evaluated in children and adults with primary HSV gingivostomatitis in order to avoid hospitalization for rehydration. Therapy should be reserved for those with more severe cases. In the treatment of herpes labialis, all three drugs are efficacious and for short course. Orally administered acyclovir (at a dose of 200 mg five times or 400 mg two times daily for 5 days) reduces the time to loss of crust by approximately 1 day (7 versus 8 days), but does not alter the duration of pain or time to complete healing [203]. Thus, oral acyclovir has modest clinical benefit only if initiated very early after recurrence and cannot be recommended for routine therapy of herpes labialis.

Both valacyclovir and famciclovir have been shown to be effective in the treatment of herpes labialis. Indeed, both valacyclovir and famciclovir can be administered over the period of 1 day and provide the same benefit as longer periods of therapy [210,211]. Under such circumstances, therapy must be initiated at the onset of prodrome, requiring patients to have medication available before symptoms of a recurrence. Combining an oral antiviral and a topical steroid appears to speed healing of herpes labialis lesions faster than antiviral monotherapy [212].

Other Cutaneous Herpes Simplex Virus Diseases

While no controlled studies have evaluated acyclovir, valacyclovir, or famciclovir for therapy of HSV infections associated with erythema multiforme, herpetic Whitlow, or herpes gladitorium, if disease is severe and recurrent, it would seem prudent to prescribe oral therapy with one of these three drugs initially at dosages utilized to treat primary genital HSV infections. These authors favor using either valacyclovir or famciclovir since both have improved pharmacokinetics and are administered less frequently. If suppressive therapy is planned, those dosages utilized for frequently recurrent genital HSV infection would seem appropriate.

Ocular Herpes Simplex Virus Infections

Trifluorothymidine (Viroptic) is the treatment of choice for HSV keratoconjunctivitis and topical idoxuridine is an alternate choice. Topical acyclovir for HSV ocular infections is effective, but probably not superior to trifluorothymidine [216–218]. The use of oral acyclovir for suppression of frequently recurrent ocular HSV infections has been suggested to be quite successful, as with genital HSV infections. Since ocular HSV infections can be sight threatening because of corneal scarring, this approach appears to have both scientific and medical validity.

Mucocutaneous Herpes Simplex Virus Infections in Immunocompromised Patients

Remarkable clinical benefit from intravenous acyclovir was documented in placebo-controlled trials [204]. Acyclovir recipients had a significantly shorter duration of viral shedding and accelerated lesion healing [205]. Both valacyclovir and famciclovir have been shown beneficial in the treatment of HSV infection in this population. Acyclovir, valacyclovir, and famciclovir can be used prophylactically to prevent HSV infections in severely immunocompromised patients, especially those undergoing induction chemotherapy or transplantation. Intravenous or oral acyclovir administration reduces the incidence of symptomatic HSV infection from about 70% to 5–20% [206,207]. A variety of oral dosing regimens for acyclovir (ranging from 200 mg three times daily to 800 mg twice daily), valacyclovir (500 or 1000 mg qd or bid), and famciclovir (250 or 500 mg bid or tid) have been used successfully. Among hematopoietic stem cell transplant recipients, acyclovir-resistant HSV isolates have been identified more frequently following therapeutic acyclovir administration than during prophylaxis [208].

The treatment of HSV infections in HIV/AIDS patients can pose unique problems if the CD4 count is low (<50). Under such circumstances, recurrences are much more likely, often requiring long-term suppressive therapy. Even so, resistance to the available therapies can occur in as many as 10% of patients [213]. Valacyclovir and famciclovir become therapeutic mainstays for physicians treating and suppressing herpesvirus infections in immunocompromised patients, including those with AIDS.

Life-threatening Herpes Simplex Virus Infections

Neonatal Herpes Simplex Virus Infections

Acyclovir is as effective as (but not superior to) vidarabine treatment in a head-to-head comparison [168]. However, when the dose of acyclovir is increased (20 mg/kg/q8h) and the duration of therapy is extended (21 days), outcome appears significantly improved [168,169]. No baby with disease localized to the skin, eye, or mouth died, while 5 and 25% of babies with CNS or disseminated infection died, respectively. For babies with disease localized to the skin, eye, and mouth, all developed normally. However, the initial cerebrospinal fluid must be negative for HSV DNA by PCR, lest these children be misdiagnosed. For babies surviving encephalitis, 50% developed normally. For survivors of disseminated infection, about 60% of acyclovir recipients develop normally. The safety and ease of administration of acyclovir prompts its recommendation as the treatment of choice for neonatal HSV infections. The recommended intravenous dose is 20 mg/kg every 8 hours for 21 days for encephalitis and disseminated disease, but only 14 days for skin, eye, and mouth disease.

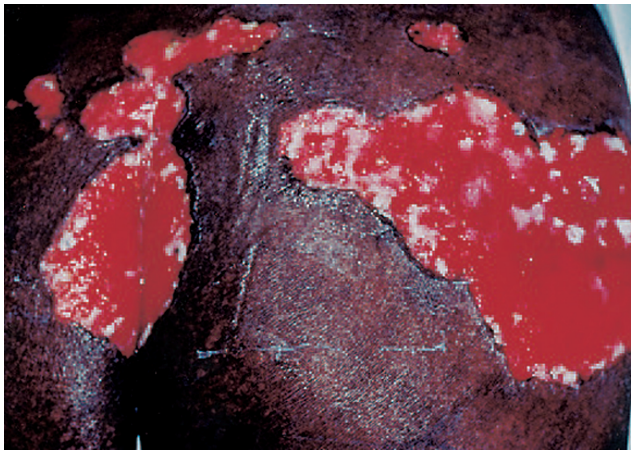
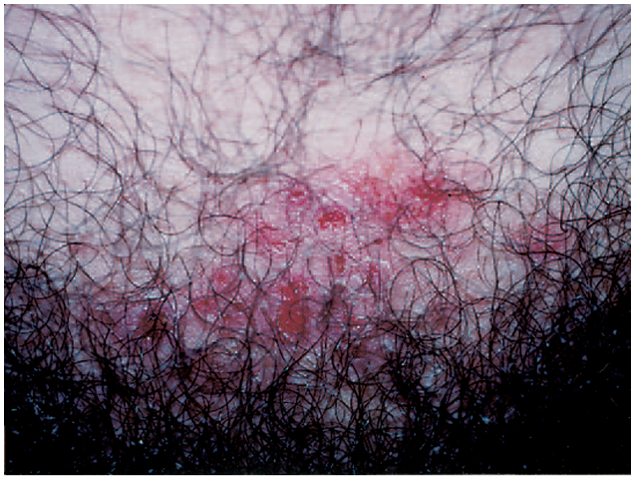


Figure 4.37 Aggressive herpes simplex of the buttocks in an AIDS patient (photograph courtesy of Margaret Muldrow, MD, Aurora, CO).



(a)



(a)

Figure 4.38 Primary herpes simplex in men who gave histories of always wearing condoms during sexual intercourse. (a) Vesicles at the base of the penis; (b) suprapubic erosions from HSV-2.



(a)



(b)



(c)

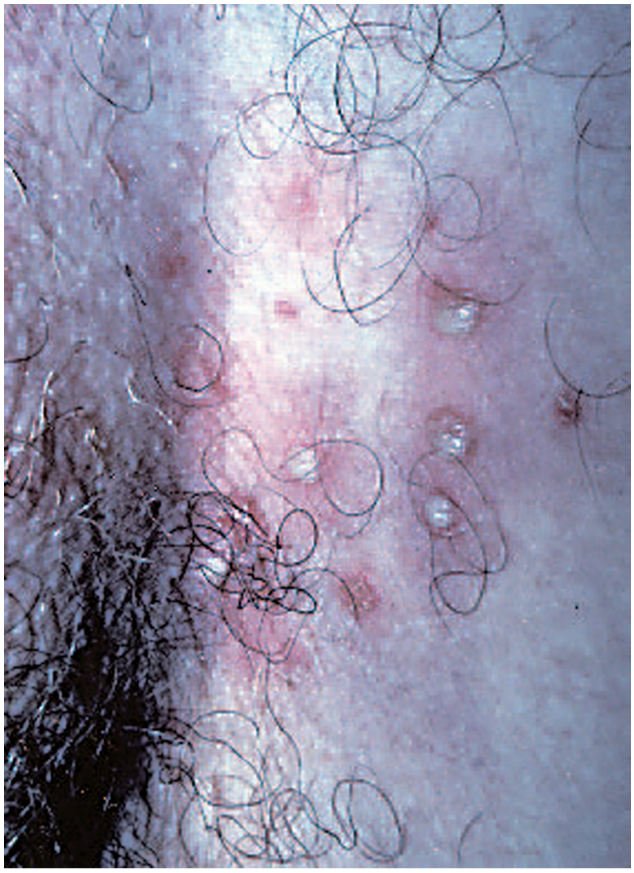
Figure 4.39 Diseases with vesicles or ulcers that may mimic the lesions of herpes simplex. Behcet's disease produces ulcers of the (a) scrotum; (b) lip; and (c) tongue. Primary syphilis may produce ulcers (chancres) of the (d) lips.

Herpes Simplex Encephalitis

Acyclovir therapy at 10 mg/kg every 8 hours for 14 days reduced mortality at 3 months to 19%, as compared with approximately 50% among vidarabine recipients [214]. Over time, mortality directly attributable to HSE increases to approximately 30% overall. Furthermore, 38% of acyclovir recipients returned to normal function. Patients with a Glasgow Coma Score of less than 6, individuals over 30 years of age, and those with encephalitis (any clinical sign or symptom) longer than 4 days had a significantly



(d)



(e)



(f)

Figure 4.39 (e) *Staphylococcus aureus* can produce bullous impetigo of the inguinal folds. (f) Tularemia may present as vesicles. (Fig. 4.39(a–c) courtesy of Meltem Onder, MD, Department of Dermatology, Gazi University School of Medicine, Ankara, Turkey; Fig. 4.39 (f) courtesy of Margretta A. O'Reilly, MD, University of Utah, Salt Lake City, UT).

poorer outcome. For the most favorable outcome, therapy must be instituted before semicoma or coma develops. These data stress the need for improved therapeutic regimens for HSE. Because of the safety of acyclovir therapy, as noted below, acyclovir is often used empirically and in the absence of definitive diagnostic efforts.

Other Herpes Simplex Virus Infections

The spectrum of HSV infections continues to expand. Case reports have described the successful use of antiviral therapy in the treatment of other HSV infections, such as hepatitis, pulmonary infections, herpetic esophagitis, and proctitis.



(a)



(b)



(c)

Figure 4.40 Nonviral diseases sometimes include the word "herpes" in their name, such as the following autoimmune diseases: (a, b) "herpes" gestationis; and (c) dermatitis herpetiformis.

Viral Resistance

HSV resistance to acyclovir can develop through mutations in the viral gene encoding TK via generation of TK-deficient mutants or the selection of mutants possessing a TK that is unable to phosphorylate acyclovir. Clinical isolates resistant to acyclovir are almost uniformly deficient in TK, although DNA polymerase mutants have also been recovered from HSV-infected patients [215]. Drug resistance was considered rare and resistant isolates were thought to be less pathogenic until a series of acyclovir-resistant HSV isolates from patients with AIDS were characterized [216]. These resistant mutants were deficient in TK, but remained sensitive to vidarabine and foscarnet, drugs that do not require viral TK for activation. Lesions tend to be more extensive with significant erosion of the dermis, as illustrated in Fig. 4.37. Acyclovir-resistant HSV isolates have been identified as the cause of pneumonia [169], encephalitis [217], esophagitis [215], and mucocutaneous infections [218], all occurring in immunocompromised patients.

Toxicity

Acyclovir, valacyclovir, and famciclovir therapy are associated with very few adverse effects. Renal dysfunction induced by acyclovir has been reported, but appears to be very uncommon and is usually reversible [219,220]. Such findings appear less common with famciclovir therapy. Creatinine elevations have been noted in patients given large doses of acyclovir by rapid intravenous infusion and have been attributed to crystallization of the drug in the renal tubules and collecting ducts, resulting in a transient nephropathy [221]. The risk of nephrotoxicity can be minimized by administering acyclovir by slow infusion over 1 hour and ensuring adequate hydration. Oral therapy with each of the three drugs has not been associated routinely with renal dysfunction. A few reports have linked intravenous acyclovir use with CNS disturbances, including agitation, hallucinations, disorientation, tremors, and myoclonus [222,223].

An "Acyclovir in Pregnancy Registry" has gathered data on prenatal acyclovir exposures. Though no significant risk to the

mother or fetus has been documented, the total number of monitored pregnancies remains too small to detect any low-frequency events [224]. Since acyclovir crosses the placenta and can concentrate in amniotic fluid, there is valid concern about the potential for fetal nephrotoxicity, though none has been observed [225]. No similar registries exist for either valacyclovir or famciclovir.

Prevention

Currently, there is no licensed vaccine for the prevention of HSV infections. The NIH is completing a clinical trial of a glycoprotein D vaccine with a unique adjuvant in an attempt to prevent both infection and disease in women who lack antibodies to both HSV-1 and HSV-2. This vaccine consists of glycoprotein D with a proprietary adjuvant and was shown to decrease both infection and disease in seronegative women [226]. Another method of reducing transmission is daily use of one of the approved nucleoside analogs by the person with HSV-2 infection who has a partner seronegative for HSV-2 [209].

An important and available method of preventing or reducing HSV transmission is the use of barrier protection with condoms during sexual exposure [227,228]. As expected, protection only occurs over the specific area covered by the condom, and transmission of virus to and from the uncovered skin can still take place (Fig. 4.38). In addition, subclinical viral shedding can occur at any time without apparent lesions [229–231]; condoms can only reduce HSV transmission if used each and every time. Unfortunately, abstinence is the only method to guarantee prevention of genital HSV transmission. Therefore, the most practical method to reduce genital HSV transmission is the combination of daily antiviral suppression and condoms, as well as avoidance of sexual intercourse during the presence of herpetic lesions.

Conclusions

Tremendous progress has been made in our understanding of the molecular biology, natural history, and therapy of HSV infections; however, it is apparent that a great deal remains to be learned. Confusion still originates from many diseases that produce vesicles or ulcers that mimic the lesions of herpes simplex (Fig. 4.39) as well as several nonviral diseases that include the word "herpes" (Fig. 4.40). Understanding of the molecular pathogenesis of these infections and prevention of resultant disease with molecularly derived vaccines remain critical goals for future research efforts. The development of antiviral therapy has increased our knowledge of HSV infections. The synthesis of acyclovir was a true milestone in the development of selective and specific inhibitors of viral replication. Valacyclovir and famciclovir offer improved pharmacokinetics over orally administered acyclovir. However, acyclovir remains the only intravenous drug available to treat life-threatening infections. Perhaps the next generation of drugs directed against HSV will further reduce mortality and morbidity of serious HSV disease, as well as decrease, if not prevent, the establishment of latency and subsequent recurrences.

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5 Varicella-Zoster Virus

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Introduction

Varicella-zoster virus (VZV) is a unique virus, occurring worldwide (Fig. 5.1), which causes two different clinical syndromes: chickenpox (varicella) and shingles (herpes zoster). Primary infection with varicella is typically a self-limited disease of childhood characterized by a pruritic rash. Herpes zoster, predominantly a disease affecting adults, is caused by reactivation of the latent virus. In affected persons, the associated pain during and after zoster infection may lead to significant impairment. Varicella and zoster in immunocompromised individuals can often be severe and cause significant illnesses.

History

Until the 19th century, varicella was frequently confused with smallpox infection. In 1767, Heberden was the first to clearly distinguish the two illnesses [1]. However, in 1892, Osler still saw the need to emphasize the distinction between the two diseases in his book on clinical medicine [2]. The origin of the name chickenpox is not completely known, although there are several theories. It may have been derived from the French word "chiche-pois" used to describe the "chick-pea"-size varicella vesicles [3]. It was also suggested by Thomas Fuller in 1730 that the origin might lay in the similarity of the lesions to what one might imagine if a child had been pecked by a chicken [4]. Alternatively, the word may have been derived from the Old English word "gican," which means "to itch" [5]. It has also been postulated that the word may be derived from "chequeen" – the English translation of a coin used in Venice that came to imply a small amount, which in the context of diseases, is what chickenpox is in comparison to smallpox [4].

Since ancient times, herpes zoster has been recognized as a separate clinical entity [6]. The origin of the word herpes is derived from the Greek word meaning "to creep." Zoster and shingles are derived from the Greek word and Latin word, respectively, for "girdle" or "belt" [7].

In 1892, von Bokay noted that children developed varicella after coming in contact with herpes zoster patients, suggesting that the two disease were related [8]. Kundratiz (1922) and Bruusgarrd (1932) were then able to show that the same agent was the cause of both diseases by successfully inoculating susceptible children with vesicle fluid from patients with zoster [8,9]. These experiments produced localized varicella lesions at the site of inoculation in some recipients and a generalized varicella-like exanthem in others. The etiology of varicella and herpes zoster was proved later to be identical by Weller et al. through isolation and propagation of the viruses in vitro [8,10,11]. Garland and Hope-Simpson were the first to suggest that reactivation of latent varicella led to zoster infection [8].

Incidence

Varicella infection occurs worldwide, though the virus is more transmittable in temperate climates than in tropical environments. This phenomenon results in unique epidemiologic differences among regions [12]. In temperate climates, varicella is typically a disease of childhood, whereas in tropical regions, the infection more commonly occurs in susceptible adults. There is also seasonality to the infection in both temperate and tropical regions. There appears to be a peak in the winter and spring, which may be related to environmental or social factors [13–15]. The CDC reported that in the USA the peak for varicella infection was during April [16].

Prior to the varicella vaccine, approximately 90% of the US population was seropositive for VZV [17,18]. Recent studies have shown up to a 90% decline in the actual incidence of varicella between 1995 and 2005 due to the advent of the vaccine [19].

Of the estimated 1 million cases of herpes zoster that occur each year in the USA, 50% occur in adults 50 years of age or older, although the infection can occur at any age. The availability of the shingles vaccine, however, appears to be causing a decrease in the average age of herpes zoster to below 50 years. Persons with a history of primary varicella infection have a 10–20% lifetime chance of later developing herpes zoster infection. The incidence and duration of zoster infection increase significantly with age. Fifty percent of people aged 85 years and older have had herpes zoster (HZV) [20]. The annual incidence for all ages is about 3.2 per 1000 persons, but increases to 6.9 per 1000 for those aged 60–69 years. It further increases to 10.9 per 1000 for those aged 80 years or older. The incidence is even higher in immunocompromised patients, such as those with HIV, leukemia or lymphoma, bone marrow or solid organ transplantation, systemic lupus erythematosus, or in persons using immunosuppressants. Initiation of highly active antiretroviral therapy (HAART) may also increase the incidence of HZV for the first few months of treatment [21]. In post-allogeneic bone marrow transplant patients, 41% develop VZV reactivation with 88% of cases occurring within the first 24 months [22].

Pathogenesis

Varicella disease is highly contagious. Between 61 and 100% of contacts develop clinical infection after exposure to the infected individual [13,17,23,24]. VZV is transmitted by respiratory droplets from the nasopharynx 1–2 days before the onset of the skin lesions and then can be transmitted from the rash for about 5–7 days after the lesions appear. This contagious period can last for weeks in immunocompromised patients. Once the lesions become crusted, they are no longer infectious [17]. Susceptible persons can develop primary varicella from airborne secretions or from direct contact with patients with either primary varicella or zoster. However, because of the localized nature of herpes zoster, HZV patients are less contagious than those with primary varicella. Herpes zoster does not develop from contact with varicella or zoster patients [8,18].

The virus is a DNA α-herpesvirus surrounded by a capsid and a lipid-containing envelope with glycoproteins. The virus enters the host through the respiratory tract and then adheres to the mucosa via these glycoproteins [17]. The first cycle of viral replication

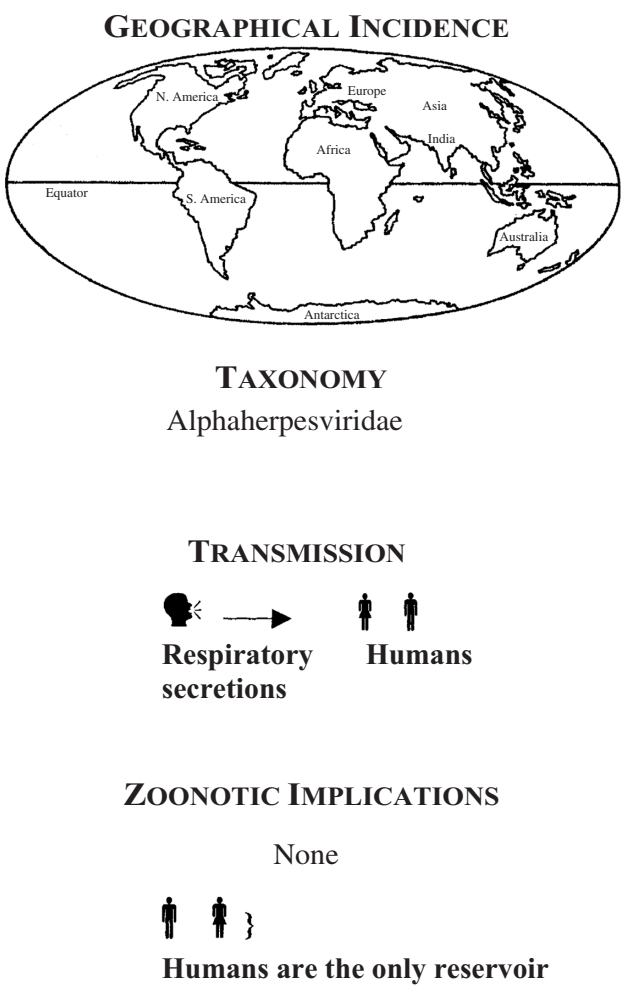


Figure 5.1 Incidence and transmission of varicella-zoster virus (herpes 3).

occurs in the regional lymph nodes 2–4 days after exposure, followed by a primary viremia that develops 4–6 days after exposure. During this viremia, the virus disseminates to the viscera. The virus further replicates in the reticuloendothelial system. A secondary viremia then develops about 14 days after infection, during which the virus spreads to the nasopharynx and skin [17,25]. The mechanism of spread of the virus to the skin is not clear, but it may be due to the virus invading the capillary wall's endothelial cells and subsequently spreading to epithelial cells. It may also be due to the migration of infected peripheral blood mononuclear cells or infected T cells to the skin [8]. Cell-mediated immunity appears to be more important than humoral immunity in responding to the varicella virus [13,17,20,26].

At some point during the primary varicella infection, VZV travels to the dorsal root ganglia and cranial root ganglia, where it becomes latent [20,26–28]. Although there is no definitive mechanism of varicella zoster's travel to the ganglia, it is possible that the virus reaches the ganglia via retrograde axonal transport from the sites of skin infection. It is also possible that during the viremia, before cutaneous evidence of infection occurs, virus-infected T cells may transport the virus to the ganglia and allow the virus to establish latency in that manner as well [27,28]. Unlike the herpes simplex virus, which resides only in neurons, varicella zoster resides in both neurons and satellite cells [20,27].

Reactivation of the zoster virus is likely related to a decline in cell-mediated immunity. With immunosuppressive therapy, immunocompromised states, and progressing age, there is a decline in zoster-specific T cells [13,29]. The memory CD4 cells involved in preventing the reactivation of the zoster virus are of the IFN-γ-producing Th1 subtype, which has been shown to decrease with age [30].

A decline in cell-mediated immunity is typically seen in elderly persons or those with immunocompromised conditions, such as human immunodeficiency virus (HIV) infection, organ transplantation, or treatment with chemotherapy, radiotherapy [31], or long-term corticosteroids [8,20,32]. In the first year following transplantation, 20–40% of bone marrow transplant recipients develop herpes zoster [25,33–35]. Similarly, 20–50% of patients with Hodgkin's disease develop herpes zoster [36–43], usually within 1 month of induction chemotherapy or 7 months of radiotherapy [44]. These immunocompromised patients may also have a more severe rash and even a viremia that can lead to visceral involvement. The development of herpes zoster in a person is not, however, an indication of a potential malignancy [8]. By contrast, varicella zoster reactivation may be the first sign of HIV infection [45,46]. This patient population may present with atypical or recurrent zoster infection [47–53]. With the advent of highly active antiretroviral therapy, herpes zoster has also been seen with the immune reconstitution syndrome in HIV patients [21,54–57].

When the varicella zoster reactivates, it undergoes replication in the affected ganglia, producing inflammation and necrosis of neuronal and non-neuronal cells. This, in turn, causes severe neuralgia. The virus then spreads down the axons of sensory neurons to reach the skin [8,20,58,59]. The severe neuropathic pain associated with shingles is likely due to damage to these afferent neurons as well as altered central nervous system (CNS) signal processing [59,60].

Clinical Manifestations of Varicella

Primary varicella typically manifests itself as a fever and a rash that begins on the head with subsequent spread to the trunk, followed by the extremities. In adolescents and adults, the rash is often preceded by a prodrome of fever, malaise, and headache 24–48 hours prior to the onset of the rash, while in children the rash and fever usually develop simultaneously. A typical immunocompetent child has about 100–300 lesions, although the rash can be more extensive in adolescents and household contacts who get the disease. The lesions start as macules and progress to papules, then vesicles, then pustules, and finally to scabs. Scarring is unusual. Lesions may involve the mucosal surfaces as well [8,61]. Lesions will be in different stages, as new lesions form while old ones begin to crust [26]. Varicella is usually a mild and self-limited disease in immunocompetent children (Figs. 5.2–5.9). Significant morbidity may occur. Prior to the advent of the vaccine, there were approximately 11,000 hospitalizations each year in the USA due to complications of varicella infection in children who were often otherwise healthy. Susceptible adults typically develop more frequent complications, more profuse skin lesions, and more prominent constitutional symptoms, such as prolonged fever (Tables 5.1 and 5.2).

Primary varicella infection may result in multiple complications. The most common complication is bacterial superinfection,



Figure 5.2 Primary varicella in a 16-year-old girl with juvenile rheumatoid arthritis.

usually caused by staphylococcus or streptococcus. The superinfection may manifest as cellulitis, impetigo, erysipelas, furuncles, or bullous lesions resulting from the bacterial production of staphylococcal exfoliative toxin (Fig. 5.10) [62]. Bacterial infection frequently results in scarring, but rarely leads to septicemia [63]. CNS complications occur in less than 1 in 1000 cases and may include Reye's syndrome, acute cerebellar ataxia, encephalitis, meningoencephalitis, polyradiculitis, myelitis, and Guillain-Barré syndrome [64,65]. Reye's syndrome is rare since aspirin is no longer

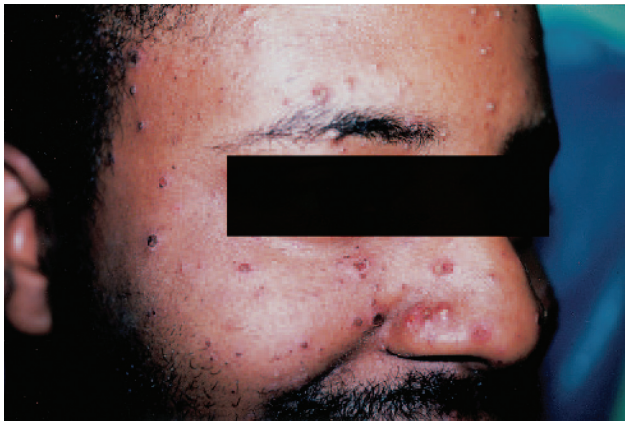


Figure 5.3 Primary varicella in an adult.



Figure 5.4 Primary varicella in an adult.

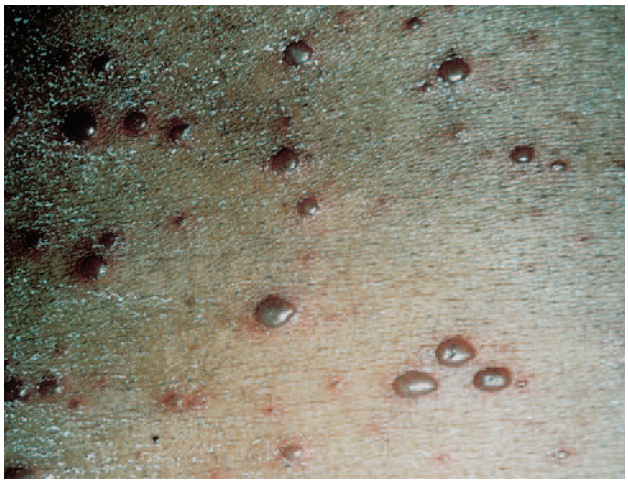


Figure 5.5 Vesicles of primary varicella.



Figure 5.6 Primary varicella in a pregnant woman.

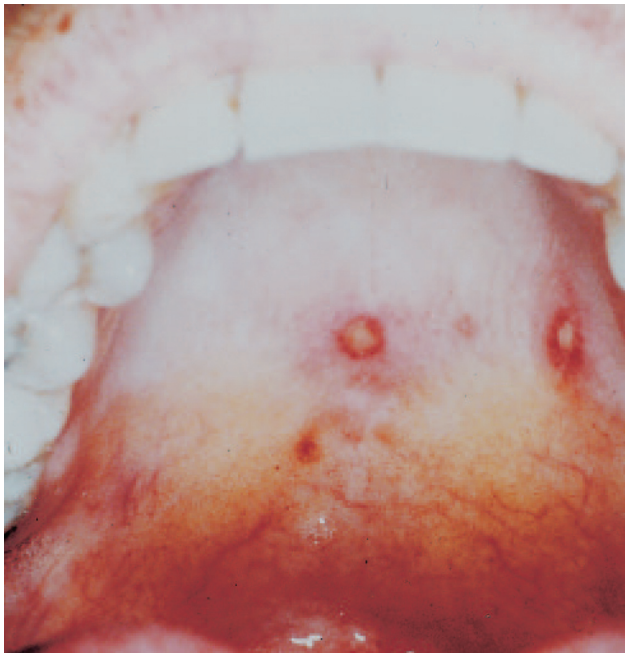


Figure 5.7 Oral vesicles of primary varicella.

recommended for children with varicella or other infections. Varicella pneumonia can be a complication in adults (Fig. 5.11). In a study of otherwise healthy military recruits with varicella, radiographic evidence of pneumonia was found in 16%, but only 4% of subjects had clinical evidence of pulmonary involvement. This complication usually develops within 6 days after the onset of rash. The mortality rate for adults with varicella pneumonia is high, with death occurring in 10% of immunocompetent and 30% of immunocompromised individuals [66]. Pregnant patients have a 10% risk of getting varicella pneumonia, which may be more severe than that seen in other populations [65]. Other complications of varicella that rarely occur include myocarditis, glomerulonephritis, pancreatitis, hepatitis, appendicitis, orchitis, arthritis, Henoch-Schönlein vasculitis, optic neuritis, keratitis, iritis [67], and varicella gangrenosum (Fig. 5.12) [68]. Varicella infection during pregnancy may produce a wide array



Figure 5.8 Primary varicella in an elderly man.



Figure 5.9 Husband and wife with primary varicella. Since both persons were born in the United States and over 90% of adults in this country are varicella-zoster virus seropositive, this is an unusual situation. In this case, the wife acquired primary varicella during her hospital employment. Her husband developed vesicles of primary varicella approximately 2 weeks later.

of fetal complications, ranging from asymptomatic latency to severe congenital defects [69]. Congenital developmental malformations most commonly occur when maternal infection occurs during the first trimester. These defects may include hypoplastic limbs, cortical atrophy, cicatricial skin lesions, ocular abnormalities, psychomotor retardation, and low birth weight. The absolute risk of embryopathy after primary maternal VZV infection in the first 20 weeks of pregnancy is about 2% [70]. Maternal varicella infection occurring after the first 20 weeks of pregnancy is associated with a much lower risk of congenital malformation. The risk of congenital problems after maternal herpes zoster infection at any time during pregnancy is much less than with primary VZV infection. The exposure of a pregnant woman without a history of chickenpox to a person with a clinically active VZV infection is always of concern. It should be noted, however, that about 85% of adults who report that they have not had chickenpox are actually seropositive for antibodies to VZV [70]. With the introduction of the varicella vaccine, it is now recommended that susceptible women be vaccinated prior to pregnancy [65].

Varicella infection can be associated with significant morbidity and mortality in immunocompromised adults or children. The lack of immunity in these populations allows for continued virus replication and dissemination, leading to persistent viremia; prolonged fever; a more extensive rash (often with hemorrhagic and/or purpuric lesions); and involvement of other organs of the body such as the lungs, liver, or CNS [71,72]. Table 5.3 highlights potential complications of varicella.

Clinical Manifestations of Zoster

Reactivation of the herpes zoster virus typically begins with a prodromal phase 1–5 days before the rash appears and may include malaise, headaches, and skin symptoms such as pruritus, paresthesias, or severe pain [73]. Because the pain is present before cutaneous manifestations, it often leads to a wide array of misdiagnoses, such as myocardial infarction, pleurisy, cholecystitis, peptic ulcer, appendicitis, ovarian cyst, prolapsed intervertebral disk, thrombophlebitis, or renal colic [61]. The pain may be constant or intermittent and may be accompanied by pruritus, tingling,

Table 5.1 Clinical Manifestations of Varicella

Time after exposure	Clinical manifestations	Laboratory analysis	Other notes
14–15 days	Occasional prodrome symptoms lasting 2–3 days: low-grade fever, chills, headache malaise, backache, anorexia, myalgia, nausea, or vomiting	Tzanck smear of lesion scraping but does not differentiate from varicella or herpes simplex	Older children and adults may have prodrome symptoms Younger children usually have an abrupt onset of rash with mild fever and malaise
16–17 days	Rash with crops of small red macules, beginning on the face and scalp, and spreading rapidly to the trunk. Relative sparing of the distal upper and lower extremities	Viral culture, serology, and direct immunofluorescense	Pruritus typically occurs with the rash.
16–17 days	Rash progresses over 12–14 hours to 1–3 mm papules, vesicles, and then pustules.		Vesicles are classically described as "dew drops on a rose petal" (clear serous fluid surrounded by a small red halo). Most children have 250–500 lesions, mostly vesicular.
17–19 days	Crust formation		
23–27 days	Healing		Scarring is rare in uncomplicated cases

tenderness, or hyperesthesia [20]. Rarely, a patient with dermatomal pain and serologic or virologic evidence of zoster infection does not develop the cutaneous manifestations of herpes zoster. This condition is known as zoster sine herpete (zoster without rash) [74,75]. This diagnosis is occasionally suspected but rarely confirmed. Laboratory confirmation is, however, possible with paired serology (i.e., acute and chronic) or with polymerase chain reaction (PCR; i.e., to detect VZV DNA) [76]. Herpes zoster has been associated with several neurologic manifestations including meningoencephalitis, vasculopathy, myelitis, cerebellar ataxia, and polyneuritis cranialis [77]. One study even found that 29% of patients with Bell's palsy had zoster sine herpete [78]. In addition, patients with shingles may rarely have skin changes that are zosteriform (e.g., livedo reticularis), but never develop the classic lesions (Fig. 5.13). The clinical manifestations of herpes zoster are listed in Table 5.4, and the differential diagnoses of herpes zoster are presented in Table 5.5.

The rash of herpes zoster is commonly localized to the skin area innervated by a single sensory ganglion (dermatome) and does not typically cross the midline of the body (Figs. 5.14–5.24). However, bilateral zoster has been observed in both immunocompetent (Fig. 5.25) and immunocompromised persons (Fig. 5.26). The dermatomal rash usually occurs at the site that was most severely affected during primary varicella infection [23]. Any dermatome can be affected, but the most common regions of involvement

Table 5.2 Differential Diagnoses of Varicella

Smallpox: Historically, smallpox has been an important differential diagnosis, but no longer occurs.
Herpes simplex virus: Disseminated disease may sometimes mimic varicella, but herpes simplex typically has a predominance of localized vesicle clusters at the primary site of infection.
Hand-foot-and-mouth disease: Lesions are more prominent on the mucous membranes of the mouth and on the distal extremities with hand-foot-and-mouth disease.
Insect bites: Insect bites typically occur on the extremities and have an underlying wheal.
Drug eruption: Fever does not occur; simultaneous appearance of multiple types of lesions is rare.
Scabies: More chronic development of the lesions, which tend to appear in body folds and often have a linear distribution.
Contact dermatitis: Pustules do not tend to form and fever does not occur; lesions are less likely on the trunk than on the extremities.



Figure 5.10 Bullous varicella from *Staphlococcus aureus* secondary infection.

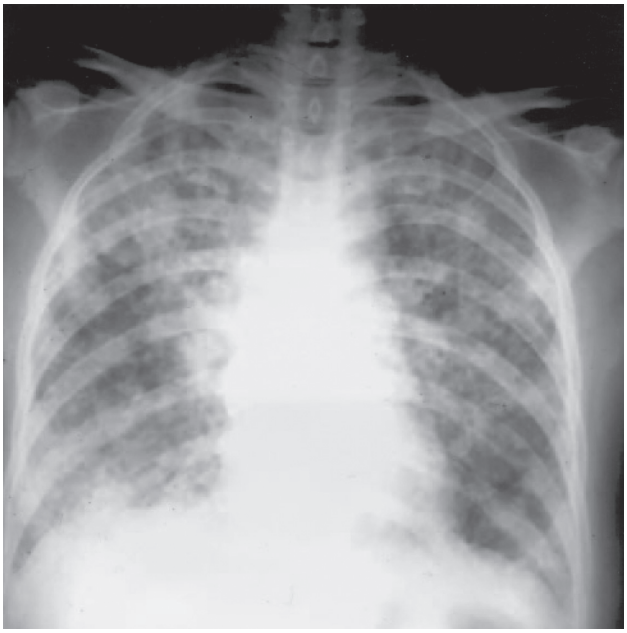


Figure 5.11 Varicella pneumonia. (Courtesy of Siri Chiewchanvit, M.D., Chiang Mai, Thailand.)



(a) (b)

Figure 5.12 (a) Varicella gangreosum of the right eye in a previously healthy man with untreated primary varicella. (b) Enucleation of the necrosed right eye. (From Ref. 47. Used with permission.)

include the ophthalmic (V1) and midthoracic to upper lumbar (T3-L2) dermatomes [79]. The rash starts proximally and spreads distally. New lesions form over 3–7 days. The rash starts as papules, progressing to vesicles within 24 hours. In 3–5 days, they become pustules, and in 7–10 days the lesions become crusted [20].

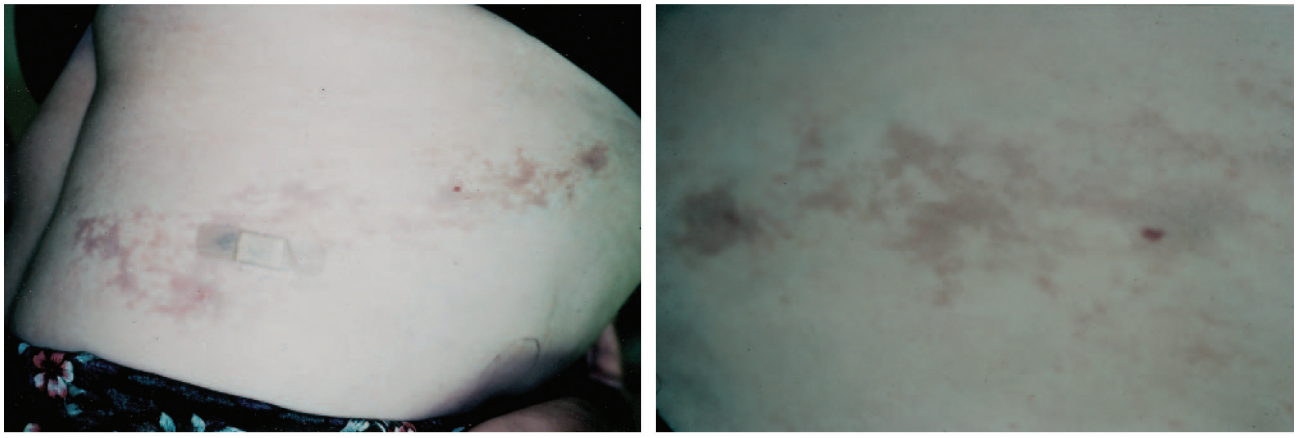
A recent study documents that viremia accompanies the cutaneous zoster outbreak in even immunocompetent patients [80]. VZV DNA has been found in the saliva of zoster patients, independent of the location of the rash [81]. It has also been noted that the presence of VZV DNA and the burden of VZV DNA correlates with the amount of pain a patient has. Because VZV DNA has been detected in the saliva of patients during the prodrome of herpes zoster [81], it is possible that PCR testing may allow the diagnosis of shingles before the first vesicle appears.

Herpes zoster in immunocompetent children or young adults tends to evolve rapidly, with few complications, and resolution of the neuralgia as the lesion crusts fall off. In immunocompromised and elderly individuals, the pain and rash of zoster are usually more severe and complications occur more frequently (Fig. 5.27). Post-herpetic neuralgia (PHN) is a common complication, but it has varying definitions in the medical community. The most commonly accepted definitions have been pain at either 90 or 120 days after the onset of rash [82]. This complication occurs in 10–15% of zoster cases [83,84], but it infrequently affects persons under 40 years of age. On the other hand, more than one third of affected individuals aged 60 years or older develops PHN [79,83,84]. In addition to older age, greater rash severity, greater acute-phase pain, presence of a prodrome, and being female are also risk factors for PHN development [85]. The pain of PHN typically remits or lessens significantly within 1–6 months, although the duration is variable [86]. After crusting of the lesions, other abnormal sensations may occur in patients, such as pruritus, paresthesia, dysesthesia, or anesthesia (Table 5.4).

Table 5.3 Complications of Varicella

Bacterial superinfection of lungs, bones, or skin, rarely with septicemia
Scarring from skin lesions
Pneumonia
Neurologic complications
Transient cerebellar ataxia
Aseptic meningitis
Transverse myelitis
Reye's syndrome
Meningoencephalitis
Guillain-Barré syndrome
Neutropenia
Thrombocytopenia
Renal complications
Glomerulonephritis
Nephrotic syndrome
Hemolytic-uremic syndrome
Optic neuritis, keratitis, or iritis
Arthritis
Myocarditis
Pericarditis
Pancreatitis
Orchitis
Vasculitis

Complications from herpes zoster are summarized in Table 5.6. Scarring with hypopigmentation or hyperpigmentation is occasionally seen, especially if the patient did not receive appropriate antiviral therapy (Figs. 5.28 and 5.29). Herpes zoster ophthalmicus (HZO), or HZV reactivation of the ophthalmic division of the trigeminal nerve (V1), accounts for 10–20% of zoster cases and is associated with a high complication rate. Anywhere from 20 to 70% of cases develop associated ocular disease [84]. Of the three branches of V1, nasociliary, frontal, and lacrimal, the frontal branch is most commonly involved in HZO. Involvement of the nasociliary branch manifests as Hutchinson's sign and presents as vesicles on the side and top of the nose (see Fig. 5.21) [87]. HZO usually develops the same skin rash that would be seen in HZV in any other part of the body, but it is possible to have ocular complications without a rash being present [88,89]. The ophthalmic complications of HZO may include scleritis, acute epithelial keratitis, uveitis, cicatricial lid retraction, oculomotor palsies, paralytic ptosis, glaucoma, chorioretinitis, optic neuritis, or panophthalmitis (due to secondary bacterial infection). All of these complications have the potential to produce visual impairment or blindness. Corneal sensation is frequently impaired with ophthalmic zoster and may result in corneal ulceration or neurotrophic



(a) (b)

Figure 5.13 (a,b) Livedo reticularis as the only cutaneous manifestation of serologically confirmed herpes zoster.

keratitis. PHN is also more commonly associated with ophthalmic zoster [76,90].

Herpes zoster less commonly involves the second and third divisions of the trigeminal nerve or other cranial nerves [91–94]. Involvement of these nerves may result in lesions of the mouth, pharynx, larynx, or ears. Ramsey-Hunt syndrome is due to involvement of the facial or auditory nerves and consists of ipsilateral facial palsy, in addition to zoster lesions of the external ear, tympanic membrane, or anterior two thirds of the tongue. Involvement of these nerves may also result in tinnitus, vertigo, otalgia, loss of taste, or deafness (Fig. 5.30) [91].

Other nervous system complications rarely occur with herpes zoster disease. Meningoencephalitis and myelitis have been reported in 0.2–0.5% of patients. These conditions are associated with fever, headache, photophobia, meningeal irritation, vomiting, altered mentation, or nerve palsies [64,95–99]. Herpes zoster may involve the vagus nerve or its ganglia, resulting in dysphagia, nausea, vomiting, gastric upset, or cardiac irregularities. Other patients may develop motor paralysis resulting from direct extension of the virus from the sensory ganglion to the anterior horn cells. This complication occurs in 1–5% of all zoster cases [38,100–102], and usually develops in the first 2–3 weeks after rash onset. The muscles associated with the involved dermatome are typically affected, and the prognosis for recovery is generally good (Fig. 5.31) [103]. Although mild motor paralysis of the trunk often goes unnoticed, the incidence of motor deficiencies resulting from herpes zoster of the facial nerve or extremities is 10–20% [64].

Granulomatous cerebral angiitis is a delayed CNS complication of zoster, developing weeks to months after the zoster rash. This condition predominantly occurs in the elderly and results in signs and symptoms that resemble those of a cerebrovascular hemorrhage or thrombosis [104]. Patients may present with symptoms of transient ischemic attacks, stroke-in-evolution, or isolated or multiple cerebral infarctions. The most frequent CNS finding is asymptomatic cerebrospinal fluid abnormalities, such as elevated levels of protein and lymphocytes. The mortality rate with this complication is 15%, and autopsy examination reveals vascular inflammation with thrombosis and microinfarcts [105].

Table 5.4 Clinical Manifestations of Herpes Zoster

Time after initial symptoms	Clinical manifestations	Laboratory analysis	Other notes
	Reactivation of the virus may occur up to several decades after initial varicella infection	Tzanck smear of lesion scraping, but does not differentiate from varicella or herpes simplex	5% of patients (particularly children) will have fever, malaise or headache during the prodrome period. Pain is not normally significant in children
	↓		
0 days	Prodrome of localized pain	Viral culture, serology, and direct immunofluorescense	Regional lymphadenopathy is usually present
	↓		
3–7 days or more	Unilateral dermatomal rash with erythematous macules and papules		
	↓		
4–8 days	Vesicles		Skin lesions resemble varicella but are more confluent
	↓		
6–10 days	Pustules		
	↓		
10–14 days	Crusts		Scarring may occur with healing, particularly in dark-skinned individuals
	↓		
2 wk, up to 4–6 wk	Complete healing		Localized hypersensitivity or post herpetic neuralgia may persist for months or years after healing



Figure 5.14 Herpes zoster in a thoracic dermatome in an adult.



Figure 5.15 Herpes zoster in a thoracic dermatome in a two year old child.



Figure 5.16 Herpes zoster in cervical dermatome.



Figure 5.17 Herpes zoster in a sacral dermatome.

Herpes zoster has a high rate of dissemination (up to 40%) in immunosuppressed individuals, while this complication is rare in immunocompetent persons [66]. In immunocompetent patients, 17–35% may have a few vesicles located remotely from the primary dermatomal eruption, likely due to hematogenous spread of the virus. Cutaneous dissemination is defined as more than 20



Figure 5.18 Herpes zoster in a sacral dermatome.



Figure 5.19 Herpes zoster in a lumbar/sacral dermatome in an adult.

vesicles outside the area of the primary and adjacent dermatomes. This is followed by visceral dissemination (i.e., into lungs, liver, or brain) in 10% of immunosuppressed patients. HIV-infected patients with zoster have been observed to have an increased rate of neurologic complications (e.g., aseptic meningitis, radiculitis, and myelitis) and ophthalmic complications (particularly progressive outer retinal necrosis) [106–108]. Retinal necrosis can be related to HZO or HZV reactivation in a distant dermatome and can rapidly progress to retinal detachment [109]. Other manifestations of herpes zoster in immunocompromised patients include: (1) multidermatomal zoster (Fig. 5.32), (2) chronic verrucous nodules (Fig. 5.33), and (3) one very unusual case of post-herpetic hyperhidrosis (Fig. 5.34) [110].

Risk Factors for Herpes Zoster

A history of primary varicella infection is a prerequisite for developing zoster infection, but there are multiple other risk factors for developing zoster infection. Advancing age, immunocompromised states, immunosuppressive drugs, HIV or AIDS, solid organ or bone marrow transplantation, chronic steroid use, stress, and physical trauma are associated with a depression in cell-mediated immunity, increasing the risk of developing zoster disease [20,111,112]. Acquiring primary varicella in utero and at 1 year of age or younger has also been linked to an increased risk of zoster infection later. A genetic component has also been suggested. One study looking at the polymorphisms of the promoter for the IL-10 gene showed that 53% of patients with zoster had the ATA haplotype [113]. This was followed by a case-control study that showed that 39% of zoster patients recalled a blood relative with a history of shingles, whereas 11% of control cases without a history of zoster reported a blood relative with a history of shingles. There was an additional risk for zoster patients who reported multiple family members with a history of zoster [112].



(a) (b)

Figure 5.20 Herpes zoster in a sacral dermatome in a man. (a) The patient was referred for the treatment of primary genital herpes as the referring physician only observed the penile vesicles. (b) The patient, however, also had vesicles of the right buttock, which confirmed the diagnosis of sacral herpes zoster.

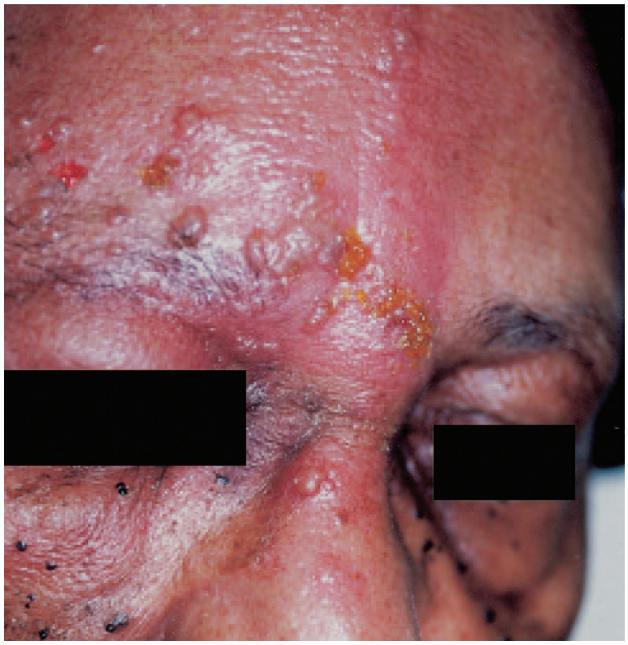


Figure 5.21 Herpes zoster of the first branch of the trigeminal nerve. Vesicles on the nose are termed *Hutchinson's sign*.

Socioeconomic status, population density, and rural versus urban residence have not been associated with HZV. More frequent exposure to varicella patients may increase immunity and decrease the risk of developing zoster [111].

Dermatopathology

The Tzanck smear is often the initial test of choice, performed by scraping the base of an early lesion and staining it with hematoxylin-and-eosin, Papanicolaou, Giemsa, Wright's, or toluidine blue stains. A smear of varicella or zoster lesions will have multinucleated giant cells and epithelial cells that contain acidophilic intranuclear inclusions. However, herpes simplex infections also have identical findings, so these two infections cannot be differentiated by using a Tzanck smear. The same is true of histopathologic findings from lesion biopsies. Varicella, zoster, and herpes simplex have findings of ballooning degeneration, intranuclear inclusion bodies, and multinucleated giant cells. The multinucleated cells are created by the fusion of adjacent infected cells [114]. This process allows direct cell-to-cell spread of the virus and protects the virus from extracellular neutralization by host antibodies [6].



Figure 5.22 Herpes zoster of a cervical dermatome (C3).



Figure 5.23 Herpes zoster of the second branch of the trigeminal nerve.

Laboratory Findings

Most straightforward cases of varicella and herpes zoster are diagnosed based on history and clinical findings [99,115,116]. VZV can be differentiated from herpes simplex virus by several laboratory tests, such as viral culture, serology, direct immunofluorescence, and molecular techniques. Isolation of the virus by culture is the most specific test, but it is not always sensitive, since the VZV is extremely labile [117–119]. Serologic testing for the virus (e.g., complement fixation) is limited by possible cross-reactivity with herpes simplex virus, but a retrospective diagnosis of varicella zoster infection can be made [120,121]. Direct immunofluorescence of cellular material from skin lesions utilizes a monoclonal antibody conjugated to fluorecein (Fig. 5.35). Dot-blot hybridization and PCR have been used to detect the virus in skin lesions, peripheral blood mononuclear cells, and other tissues of infected patients [80,81,117,122–125]. Direct immunofluorescence and PCR have become the preferred methods of diagnosis because of their high



Figure 5.24 Herpes zoster of the second branch of the trigeminal nerve.



(a)



(b)

Figure 5.25 (a,b) Bilateral herpes zoster in an otherwise healthy girl. (Courtesy of Stan Gilbert, M.D., Bellingham, WA.)

sensitivity and rapid results. PCR can be used on skin cells, saliva, blood, vesicular fluid, respiratory secretions, and CSF and can even differentiate between wild-type and vaccine strains of VZV [121].

Treatment of Varicella

Immunocompetent children with varicella are typically treated symptomatically, since varicella infection in this population is usually benign and self-limited. With the development of antiviral drugs, acyclovir has been shown to decrease the duration and severity of varicella in this population if begun within 24 hours of the rash onset [126], although some benefits are still seen if acyclovir is initiated between 24 and 72 hours after rash onset (Table 5.7). In particular, it has been shown to decrease the number of days with fever and the maximum number of lesions in



Figure 5.26 Bilateral herpes zoster in an AIDS patient. (Courtesy of Siri Chiewchanvit, M.D., Chiang Mai, Thailand.)

immunocompetent children [127]. Acyclovir has been approved for the treatment of varicella in children 2 years of age and older and in adults. Several factors have forestalled the wide acceptance of this therapy for children: the high cost of treatment, the delay in rapid institution of therapy, and the concern of possible development of acyclovir resistance. However, this treatment allows the child to resume school or play activities 1–2 days earlier, which is considered cost effective in working families because it allows the caretaker to return to work sooner than if no antiviral therapy were used. Because of the increased risk of severe varicella infection and complications in adults, systemic antiviral treatment is clearly indicated in this population. In a clinical study, oral acyclovir significantly reduced the extent of disease and duration of signs and symptoms [128]. Antiviral treatment of varicella is mandatory in immunocompromised patients [129,130]. Intravenous acyclovir continues to be the drug of choice in this population. Although not FDA approved for primary varicella and not studied in controlled trials, famciclovir and valacyclovir are known to be



Figure 5.27 Herpes zoster in a pregnant woman with AIDS (Courtesy of Edith Garcia-Gonzalez, M.D., Mexico City, Mexico.)

Table 5.5 Differential Diagnoses of Herpes Zoster

Herpes simplex virus: Herpes simplex virus may occasionally simulate zoster, but it is associated with recurrent symptoms and lesions at the same site.
Localized contact dermatitis: Dermatitis is not typically associated with pain, and Tzanck smear is negative.
Localized bacterial skin infection (e.g., bullous impetigo): Tzanck smear is negative.

effective against the virus through herpes zoster studies. Vidarabine and interferon alpha have also proved to be effective in the treatment of varicella in immunocompromised persons, but significant toxicity with these drugs has limited their use [72,131].

Prevention of Varicella

Because the available treatment for varicella is limited, prevention of the disease is imperative. The development of the varicella vaccine has had a significant impact on the incidence of the disease and the associated complications and hospitalizations. Since the live attenuated varicella-zoster vaccine (Oka strain) was developed by M. Takahashi during the 1970s in Japan, the clinical studies of the vaccine also began in Japan. During the 1980s, Merck began testing the vaccine in the USA [132]. The vaccine was shown to be highly efficacious with a 96% seroconversion rate in healthy children, with 99% of children tested at 1 year maintaining their antibody response in one study [133]. Due to the method of preparation, composition, and dose, the short-term efficacy of the vaccine ranged from about 66–96% in clinical studies during the 1980s [134]. In one double-blind, randomized, placebo-controlled trial of the monovalent vaccine, efficacy during the first varicella season was 100%. Efficacy after the second varicella season was 98%, with an efficacy of 95% after 7 years. This suggested long-term efficacy was adequate as well [135]. This study, however, evaluated a vaccine with a much higher concentration of virus than the vaccine that was eventually licensed.

Only mild side effects such as fever, slight varicelliform rash, and pain at the injection site have been reported [136–139]. Evaluations of the safety of the vaccine from 1995 to 2005 have shown that serious adverse events are rare and that overall safety continues to be very good [139]. From 1 to 4% of immunized children develop a mild varicella-like syndrome. Some pregnant women have inadvertently received the vaccine, but no congenital

Table 5.6 Complications of Herpes Zoster

Bacterial superinfection
Cutaneous dissemination of lesions
Scarring of skin lesions
Arthritis
Ocular complications
Cicatricial lid retraction
Optic neuritis
Acute epithelial keratitis
Scleritis
Uveitis
Glaucoma
Oculomotor palsies
Chorioretinitis
Panophthalmitis
Visual impairment
Paralytic ptosis
Blindness
Neurologic complications
Postherpetic neuralgia
Peripheral nerve palsies
Sensory loss
Granulomatous angiitis
Transverse myelitis
Cranial nerve palsies
Deafness
Meningoencephalitis
Motor paralysis
Visceral complications
Pneumonitis
Hepatitis
Pericarditis
Gastritis
Esophagitis



Figure 5.28 Scarring from herpes zoster.



Figure 5.29 Scarring from herpes zoster.



Figure 5.30 Facial palsy resulting from the Ramsey-Hunt syndrome. The suborbital hematoma on the left side was the result of a fall secondary to vertigo (also a manifestation of the Ramsey-Hunt syndrome).

varicella syndromes are known to have resulted from these vaccinations. Moreover, the incidence of zoster in vaccinated children is less than that seen in naturally infected children [140]. The decreased incidence of zoster after vaccination also holds true for children with leukemia [141].

The FDA approved the monovalent vaccine in 1995 with the recommendation to administer the vaccine routinely to children 12–18 months of age. There were also recommendations made for vaccination of susceptible children over 18 months of age and adolescents [142,143]. The quadrivalent vaccine, which includes measles, mumps, rubella, and varicella, was approved in 2005 for children 12 months to 12 years of age [143].

In 1999, the CDC recommended that children attending day care centers or entering elementary schools be required to have varicella vaccination. This was expanded in 2005 to include all grade levels, including college [143]. In 2006, 43 states and the District of Columbia required varicella vaccination for day care and elementary school entry. Overall coverage of children aged 19–35 months increased from 25.8% in 1997 to 87.9% in 2005 [145].



Figure 5.31 Unilateral abdominal distention secondary to motor nerve involvement with herpes zoster.



Figure 5.32 Multidermatomal herpes zoster in an AIDS patient. (Courtesy of Siri Chiewchanvit, M.D., Chiang Mai, Thailand.)

There were approximately 4 million cases of chickenpox annually in the USA before the VZV vaccine was licensed in 1995. Each year about 100 persons died of primary varicella [146]. Between 1988 and 1995, there was an average of 10,632 hospitalizations annually from complications of varicella, such as viral pneumonitis, electrolyte and fluid disturbances, and soft tissue infections [147].

A surveillance of three US communities from 1995 to 2000 showed that the incidence of varicella decreased 71–84%. Although the most significant decline was in children aged 12 months to 4 years, every age group saw a decline [148]. In 2006, the reported overall annual incidence was 48,445, a decrease of 85% [149]. An analysis of data from 1993 to 2001 compared the hospitalization rate before and after the vaccine was approved. Between 1993 and 1995, prior to the advent of the VZV vaccine, varicella-related hospitalization rates were over 0.5 per 10,000 persons. By 2001, the rate had declined to 0.13 per 10,000. The rates declined more among children between 0 and 4 years of age, but decreased in all age groups, including adults. This equates to a decrease from 14,121 hospitalizations in 1993 to 3720 in 2001 [132,150]. In 2004, only 19 deaths due to varicella were reported, an 82% decrease from the pre-vaccine era [149].



Figure 5.33 Chronic verrucous nodules of disseminated herpes zoster in an AIDS patient.

Despite the significant changes in the epidemiology of varicella in the last 10 years, there have been questions about the efficacy of the one-dose approach. Post-licensure studies of the efficacy of a one-dose vaccine regimen demonstrated an overall efficacy around 80–85% with a 97% efficacy in preventing severe disease [151]. However, this is not sufficient to prevent outbreaks in highly immunized populations. Breakthrough disease is defined as varicella occurring more than 42 days after vaccination. Typically, patients have a much milder form of varicella, but they are still highly infectious [152–154]. An investigation of an outbreak at a Connecticut day care showed an overall vaccine efficacy of 45% and an efficacy against moderate to severe disease of 86% [153]. Another outbreak in Minnesota demonstrated a 56% overall efficacy and 90% efficacy against moderate to severe disease [154]. These outbreaks and others have associated breakthrough disease with increased time since vaccination and immunization at a younger age [132,153,154]. From 1995 to 2004, the peak incidence of the disease also shifted from the 3–6 year olds to 9–11 year olds [143,155].

In a randomized control trial comparing a one-dose and a two-dose regimen, the 10-year efficacy was 94.4% for the one-dose regimen and 98.3% for the two-dose regimen. Thus, the risk for developing breakthrough disease was 3.3-fold less for those children administered the two-dose regimen [156]. This led to the ACIP recommendation in June 2006 that children aged 12 months to 12 years be routinely given the two-dose vaccine schedule [151]. The first dose is recommended at 12 months of age, and the second dose at 4–6 years of age. For children 13 years of age and older, the minimum recommendation is that the two doses be given at least 4 weeks apart [143].

The varicella vaccine can also be used in post-exposure prophylaxis. Studies of the single-antigen varicella vaccine in children and adults have shown that vaccination within 3 days of exposure to the rash is ≥90% effective in preventing development of the disease, and vaccination within 5 days of exposure is 70% effective. Vaccination is also effective in modifying the severity of varicella. It is recommended that adults that do not have evidence of immunity be given the vaccine if they are exposed to a varicella patient [143].

For immunocompromised patients who have had recent substantial exposure to varicella, varicella-zoster immune globulin (VZIG) is available. This prophylaxis is indicated also for



(a) (b)

Figure 5.34 Hyperhidrosis following herpes zoster in an AIDS patient. (a) Hemorrhagic vesicles of herpes zoster in cervical dermatome (i.e., C8). (b) Marked sweating in the same dermatome 2 months later.

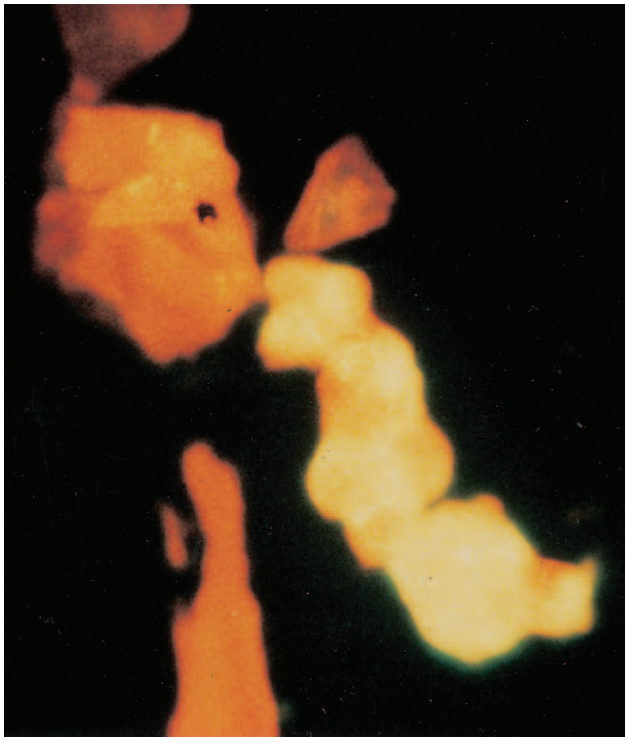


Figure 5.35 Positive direct fluorescence antigen (DFA) staining for VZV.

susceptible pregnant women and neonates whose mothers become infected with varicella up to 7 days prior to delivery or within 28 days after delivery [157]. VZIG should be given within 96 hours of varicella exposure, and the duration of protection lasts at least 3 weeks [143]. Unfortunately, one third to one half of individuals still develop clinical infection after VZIG administration [144].

Treatment of Zoster

Several antiviral agents are used to effectively treat the acute phase of herpes zoster, although no medication has been shown to completely prevent the development of PHN. However, early therapy with antiviral agents has demonstrated reduction in the duration of PHN. Topical idoxuridine was the first agent to be evaluated for the treatment of herpes zoster. Its use has not been recommended because of the high potential for toxicity and the lack of effect on PHN [158]. Vidarabine is a systemic antiviral agent that was given intravenously, and was shown to decrease the duration of viral shedding, new vesicle formation, healing time, cutaneous dissemination, time to cessation of pain, and complications [70,159]. However, this agent was no more effective than acyclovir [160], and the significant side effects and difficulty of administration of vidarabine limited its use. This led to the replacement of vidaribine with acyclovir, valacyclovir, and famciclovir in the treatment of herpes zoster disease (Table 5.9).

Acyclovir was the standard of treatment for acute herpes zoster infection until valacyclovir and famciclovir were developed. Early studies showed that intravenous acyclovir effectively decreased the pain and duration of the acute phase of zoster disease in both immunocompromised and immunocompetent patients [161–164]. For immunocompetent patients, the oral route of antiviral therapy is the standard. The oral route is also acceptable in immunocompromised patients if the zoster infection is uncomplicated or if the antiviral is used as prophylaxis after solid organ or bone marrow transplantation. In patients who develop disseminated or severe zoster infection, intravenous acyclovir is still the standard of care [123,165–170]. Adverse effects with acyclovir are rare and include headache, nausea, diarrhea, and renal toxicity. CNS toxicity is also rare and may result in disorientation, delirium, tremor, seizures, or slurred speech. Treatment of PHN is outlined in Table 5.10.

Valacyclovir is the prodrug of acyclovir. Bioavailability is three to five times that of oral acyclovir, which allows valacyclovir to be dosed orally three times daily as compared to the five times daily necessary with oral acyclovir. Valacyclovir also has better efficacy than acyclovir, demonstrates a faster resolution of the zoster-related pain, and reduces the duration of PHN [58,171–173].

Table 5.7 Treatment of Varicella

Symptom	Treatment
Fever	Antipyretics (although aspirin should be avoided in children, due to its association with Reye's syndrome [105, 106])
Pruritus	Oral antihistamines, calamine lotion, and tepid baths with baking soda (1/4 cup per bath). Trimming of nails to discourage scratching.
	Systemic Antiviral Treatment
Otherwise healthy children: oral acyclovir (20 mg/kg) 4 times a day for 5 days	
Immunocompetent adults (and children over 40 kg): oral acyclovir 800 mg 5 times a day for 7 days; valacyclovir 1 g tid or famciclovir 500 tid for 7 days are commonly used but not specifically FDA approved for primary varicella in adults.	
Immunocompromised persons: intravenous acyclovir: 10mg/kg (500 mg/m [2]) every 8 h for 7–10 days	

Table 5.8 Prophylaxis of Varicella and Herpes Zoster

Varicella-zoster immune globulin (VZIG)	125 U/10 kg (up to 625 U) within 96 h of exposure for immunosuppressed patients with substantial varicella exposure.
Live attenuated varicella vaccine (Oka strain)	Routine vaccination at 12–18 mo of age, followed by second dose at 4–6 yrs;
Varivax (prevention of primary varicella)	Susceptible persons ages 13 yrs and above require 2 doses, 4–8 wk apart.
Zostavax (prevention of herpes zoster)	non-immunocompromised persons ages 60 yrs and above, 1 dose

Table 5.9 Treatment of Zoster

Symptoms	Treatment
Local pain and pruritus	Analgesics, oral antipruritics, calamine lotion, cool compresses
	Systemic Antiviral Treatment
Immunocompetent patients (oral therapy):	
acyclovir 800 mg 5 times daily for 7 days	
valacyclovir 1 g tid for 7 days	
famciclovir 500 mg tid for 7 days	
Immunocompromised patients: intravenous acyclovir: 10 mg/kg (500 mg/m [2]) every 8 h for 7 days	

Table 5.10 Treatment of Postherpetic Neuralgia

Treatment	Notes on efficacy
Non-narcotic analgesics	Frequently not effective
Narcotic analgesics	Temporary benefit
Capsaicin cream	Applied topically every 4 h for pain relief, but usually with local burning sensation.
Topical lidocaine gel or patch	For topical pain relief (patch is FDA approved), first-line therapy
Tricyclic antidepressants (amitriptyline, maprotiline, and desipramine)	Doses needed are much less than that used for depression treatment
Anticonvulsants (Gabapentin, or pregabalin)	First-line therapy
Sympathetic nerve blockade	Some reports of success
Steroids	Intrathecal methylprednisolone appears effective
Transcutaneous electrical stimulation	Some reports of success

At 6 months, 19% of patients who took valacyclovir had pain compared with 26% of acyclovir recipients [171]. In uncomplicated herpes zoster in immunocompromised patients, valacyclovir was documented to be safe and effective [174]. Valacyclovir has a similar side effect profile as acyclovir, but with no reports of nephropathy or neurotoxicity [175].

Famciclovir, the oral prodrug of penciclovir, also has a bioavailability superior to that of acyclovir, allowing for three times daily dosing as well [58,176]. Famciclovir is equally as effective as acyclovir in the healing of skin lesions and resolution of acute pain, but has a better adverse effects profile [58,176–178]. In comparison with placebo, famciclovir also reduces the duration and prevalence of PHN [179,180]. As with all antiviral agents, treatment should be initiated as soon as possible after the zoster rash onset, preferably within 72 hours. It has been reported recently, however, that patients may also benefit if antiviral therapy is started after 72 hours of rash onset, but the upper limit of time for initiation of antiviral therapy has not been established [181].

In controlled studies, famciclovir has been demonstrated to be equally as safe, convenient, and effective as valacyclovir in reducing the duration of PHN in immunocompetent patients over 50 years of age [182]. Famciclovir has also been shown to be as safe and effective, but more convenient, than acyclovir for the therapy of herpes zoster in immunocompromised patients [183], as well as for the treatment of ophthalmic zoster in immunocompetent patients [177].

Many practitioners have tried corticosteroids to decrease inflammation and subsequently decrease the progression of the nerve damage that leads to PHN. This treatment has been used both alone and in combination with antiviral agents. Some clinical trials have shown a reduction in persistent pain [184] or accelerated healing [185], though several studies have shown that although steroids may have some short-term benefits, they have little influence on PHN [186–188]. A study of 349 patients demonstrated that the combination of steroids and acyclovir allowed for a more rapid resolution of the rash and a decrease in acute pain, but had no effect on PHN relative to acyclovir monotherapy. In addition, adverse effects were more frequent with the addition of corticosteroids [187]. A second study yielded similar results with patients showing no difference in pain at 6 months when comparing a combination of acyclovir and prednisone with acyclovir alone, prednisone alone, and double placebo, although they initially demonstrated improvement in sleep, acute neuritis, time to return to routine daily activity, and analgesic usage [188]. In a small study of patients with Bell's palsy, a combination of prednisone plus acyclovir was more effective than prednisone monotherapy for those who presented with zoster sine herpete and had VZV DNA in their saliva [189].

Treatment of Post-herpetic Neuralgia

No single antiviral agent has been consistently effective in the treatment of PHN. However, the duration and severity of this complication can generally be reduced by early treatment of herpes zoster with the appropriate antiviral agents. The majority of clinical trials have studied and recommended treatment within 72 hours of the first vesicle. However, patients frequently present after the 72-hour window of treatment. It appears reasonable to initiate treatment after 72 hours in specific situations if the lesions are not completely crusted and the individual is older than 50 years of age, immunocompromised, and/or has trigeminal zoster [181].

The lidocaine 5% patch and gabapentin have become popular first-line treatments of PHN. In an 8-week randomized, double-blind, multicenter trial of gabapentin, 229 patients were treated with either placebo or gabapentin. For the first 4 weeks, the gabapentin was titrated to a maximum dose of 3600 mg/d. Patients were then maintained at the maximum dose for the next 4 weeks. This agent was found to be effective in the treatment of pain and sleep interference associated with PHN. Those persons who received gabapentin had a statistically significant reduction in average daily pain scores from 6.3 to 4.2 points compared with placebo recipients whose change was from 6.5 to 6.0 points ($P<0.001$). Sleep rating scores, Short-Form McGill Pain Questionnaire, and Profile of Mood States were also improved. Adverse events that were observed more frequently in gabapentin recipients included somnolence, dizziness, ataxia, peripheral edema, and infection [190]. Another double-blind, placebo-controlled, randomized study of 334 patients with PHN showed that dosages of 1800 or 2400 mg/d were also effective. Even from week 1, patients had improved pain scores. Final results showed an 18.8% improvement of pain scores in the 2400 mg/d arm and an 18.7% improvement in the 1800 mg/d arm. Sleep scores and global scores were also greatly improved in the gabapentin-treated arms. The most common adverse effects were dizziness and somnolence, which were observed primarily during the titration of the dose of gabepentin [191].

The efficacy of gabapentin and nortriptyline was compared in another randomized, double-blind, clinical trial of 70 patients with PHN. Both medicines were efficacious in improving pain and sleep scores, but gabapentin had less adverse effects. Fifty-eight percent of patients in the nortriptyline group had adverse effects related to the anticholinergic effects of the drug [192].

The combination of gabapentin and opiates has also been shown to have greater efficacy in diabetic neuropathy and PHN than either drug alone. Additionally, this can be obtained at lower doses of each medicine [193].

Clinical trials have also shown that pregabalin is effective in the treatment of neuropathic pain related to diabetes neuropathy and PHN [194–196]. In a double-blind, placebo-controlled trial of 173

patients with PHN, pregabalin was effective in improving sleep and relieving pain. There was a greater incidence of adverse effects in the pregabalin arm than in the placebo arm, but the adverse effects were mild to moderate in severity [194].

Several other modalities have been employed in the treatment of PHN, such as analgesics, narcotics, tricyclic antidepressants (TCAs), capsaicin, biofeedback, nerve blocks, and cutaneous stimulation. Systemic analgesics are not usually effective against PHN. However, a double-blind crossover study of controlled-release oxycodone showed improvement in PHN-related pain and allodynia [197]. In another double-blind crossover trial comparing nortriptyline or desipramine to controlled-release morphine or methadone for the treatment of PHN, there was no significant difference in efficacy. Side effects of the opioids included constipation, sedation, and nausea. There is some concern that opioids may affect cognitive function, particularly in an older population, although one study of opioids versus TCAs did not find evidence to support this belief [198]. There is also concern that long-term narcotic use may lead to tolerance, physical dependence, and substance abuse, but in most cases this should not prohibit clinicians from considering opioids in the treatment of PHN. However, these agents may be more beneficial for short-term treatment of acute pain with herpes zoster (Table 5.10).

TCAs have shown considerable efficacy in the treatment of PHN, although the mechanism of action appears to be independent of the antidepressant effects. However, because of their adverse effects, TCAs have become a second-line therapy. Common side effects include dry mouth, constipation, sweating, dizziness, vision changes, and drowsiness. Additionally, caution must be used if TCAs are given to patients with cardiac disease, glaucoma, urinary retention, and autonomic neuropathy. Patients over 40 years of age should also have a baseline electrocardiogram to screen for any conduction abnormalities. The comorbidities that older patients with PHN often have make TCAs a less desirable choice in the treatment of PHN. If a TCA is to be used, there are several options within the class. TCAs should also be started at lower doses (10–25 mg once daily) and titrated to 75–150 mg over weeks [199].

In a comparison of amitriptyline and maprotiline, amitriptyline had better analgesic effects with less adverse effects [200]. Desipramine may be more preferable with its lower anticholinergic and sedative effects [201]. A randomized, double-blind, crossover study of amitriptyline and its metabolite, nortriptyline, demonstrated equivalent analgesic effects with less adverse effects in the nortriptyline patients [202]. All of these TCAs appear to work in PHN because of the noradrenergic effects of the class [201].

Antipsychotics (chlorprothixene, fluphenazine, and haloperidol) have also been tried for the treatment of PHN, often in combination with antidepressants. However, results have been unimpressive so far. One placebo-controlled study of chlorprothixene demonstrated only marginal efficacy [203]. Another double-blind, placebo-controlled study of amitriptyline showed that fluphenazine was not effective by itself, nor did it provide any advantage when combined with amitriptyline [204].

Topical treatments have also been beneficial in the treatment of PHN. Topical lidocaine is available as a cream, a gel, and a patch and is FDA approved for the treatment of PHN [205–208]. The lidocaine patch has been shown to improve both pain and allodynia. It is favored because of its lack of systemic side effects or drug interactions [199]. This may be particularly beneficial in the elderly, who may already be taking multiple medications and are at an increased risk of drug interactions [208]. Up to three patches a day may be applied to the painful area for a maximum of 12 hours. Typically, it takes about 2 weeks for patients to determine if the drug will give them enough relief [199].

Capsaicin cream acts by enhancing the release or inhibiting the reaccumulation of substance P from cell bodies and nerve terminals. This leads to an initial burning sensation that is followed by an anesthetic effect. In a clinical trial, nearly 80% of patients treated with capsaicin experienced some pain relief [209]. However, some patients cannot tolerate the burning sensation associated with capsaicin treatment. Some authors recommend pre-treatment with topical anesthetics (lidocaine) to alleviate this problem [210]. Patients should be cautioned against applying capsaicin to any unhealed skin lesions. Other local treatments such as EMLA cream, injections of bupivacaine, cryoanalgesia, and sympathetic and epidural nerve blockade have led to pain relief in some patients [5,123,211–215]. Transcutaneous electrical stimulation has also been tried with some success for the treatment of PHN [216].

Steroids have been used in various preparations, doses, and schedules for the treatment of PHN, but generally with limited success. Kotani et al. demonstrated that intrathecal administration of methylprednisolone with lidocaine produced excellent or good pain relief at 4 weeks and at 1 and 2 years in over 90% of persons who had suffered intractable PHN for at least 1 year. By contrast, relief was reported in only 6% of those who received only lidocaine and 4% of those who received no treatment. Moreover, allodynia was reduced by more than 70% in the methylprednisolone-lidocaine group and less than 25% in the lidocaine-only group. Importantly, no serious adverse events were observed in any of the patients [217].

The literature reveals that, while a decrease in PHN severity has been reported with a variety of therapies, there is no clear expectation of what that reduction might be if such therapies were used acutely in combination with an antiviral drug.

Prevention of Post-herpetic Neuralgia by Prophylaxis of Herpes Zoster

The hypothesis that decreased cell-mediated immunity is associated with the development of herpes zoster led to the initiation of the Shingles Prevention Study in 1998. To elicit the cell-mediated immunity necessary to prevent zoster reactivation, the zoster vaccine is 14 times more concentrated than the varicella vaccine administered to children [218]. In the Shingles Prevention Study, over 38,000 subjects, aged 60 and over, were enrolled in the study designed to test if the VZV vaccine would decrease the severity and incidence of both zoster and PHN. The zoster vaccine decreased the incidence of zoster disease by 51.3% and decreased the severity and duration of the disease in those who did develop zoster reactivation. It also decreased the incidence of PHN by 66.5% [219]. This led to the FDA approval of the zoster vaccine for people aged 60 years and older in 2006 (Table 5.8). Since the vaccine appears to be more effective in subjects who are between 60 and 69 years of age than in those aged 70 years and older, the vaccine may also have significant benefit in the 50–59 age range as well [218]. Cost-benefit analysis has shown that the benefit of

the vaccine is greater for those aged 60–64 years than in those aged 80 years or older. This has also led to the suggestion that the benefit may be even more for those in their fifties, although this is dependent on the duration of the vaccine, which at this point, is still unknown [220]. Further studies will show whether this is the next step in the prevention of herpes zoster and PHN.

Conclusion

Although primary varicella is generally considered a mild, self-limited disease of children, the large population of immunosuppressed patients in our society will likely continue to have significant morbidity with this illness. The potential morbidity of herpes zoster, particularly in the elderly and



Figure 5.36 Zosteriform herpes simplex.



Figure 5.37 Zosteriform allergic contact dermatitis to surgical tape.



Figure 5.38 Zosteriform echovirus 6 eruption. (From Ref 221. Used with permission.)



Figure 5.39 Zosteriform vesicular insect bite reactions.

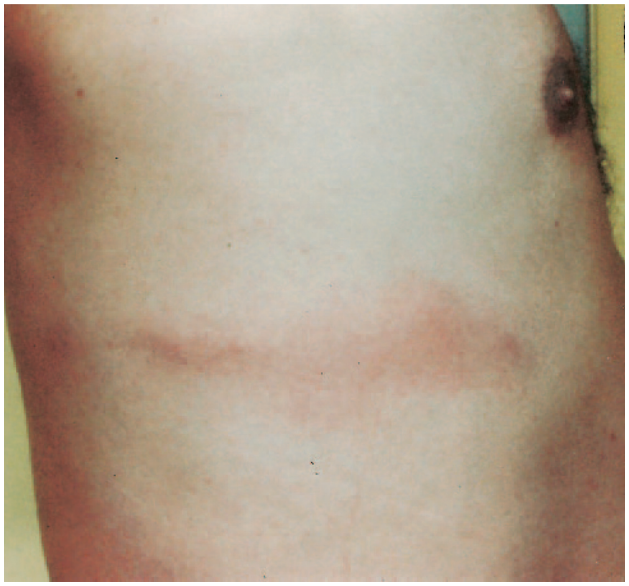


Figure 5.40 Zosteriform eruption due to gnathostomiasis. The patient became infected with the responsible organism, *Gnathostoma spinigerum*, by eating ceviche (raw fish). (Courtesy of Francisco Bravo, M.D., Universidad Peruana Cayetano Heredia, Lima, Peru.)



Figure 5.41 Zosteriform paederus dermatitis ("latigazo"). The pustules resulted from contact of the skin with an insect, which is a member of the order Coleoptera, the paederus. (Courtesy of Francisco Bravo, M.D., Universidad Peruana Cayetano Heredia, Lima, Peru.)

immunosuppressed persons, can also be quite devastating. Considering that 20% of otherwise healthy individuals and approximately 50% of markedly immunocompromised persons will eventually develop herpes zoster, the clinician's level of suspicion for this condition should remain high. This fact is especially important as initiation of antiviral therapy early in the course of the disease can reduce or eliminate complications. Therefore, it is important to differentiate herpes zoster from the many other conditions that may have zosteriform cutaneous presentations (Figs. 5.36–5.41) [221]. It is expected that the epidemiology of both of these diseases will continue to change significantly as vaccination against primary varicella and zoster infection becomes more widespread. Although the available treatment for these illnesses has advanced dramatically in recent years, there is a continued need for more effective medications, particularly for PHN.

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6 Epstein-Barr Virus

S David Hudnall and Angela Yen Moore

Introduction

The Epstein-Barr virus (EBV) is a human gammaherpesvirus that is related to the lymphocryptoviruses of the old world primates [1]. EBV consists of a 170–180 kb double-stranded DNA genome that encodes 80–100 genes. EBV isolates can be classified on the basis of levels of genome complexity. There are two distinct types of EBV, type 1 and type 2. Within each EBV type, distinct strains can be identified based on nucleotide substitution patterns within specific genes. Viral variants are created through genetic recombination within or between different types and strains. The infectious particle of EBV consists of linear viral DNA packaged within a hexagonal protein nucleocapsid and surrounded by a lipid envelope.

EBV routinely infects human mucosal epithelial cells and B lymphocytes, and is capable of infecting other cell types, including T cells, under certain conditions [1]. As with all human herpesviruses (HHV), EBV infection persists for the life of the host. The state of EBV infection may be productive or latent. In productive infection, the viral genome is repeatedly replicated by viral DNA polymerase. This high level of replication ultimately results in the production and release of infectious virions from the host cell. In the latent state of infection, no infectious virions are produced. Each latent viral genome within a host cell is replicated only once by the host cell DNA polymerase as the cell divides. Over the life of the host, EBV may transit between latent and productive infection many times.

History

In 1964, an African Burkitt lymphoma was found to contain a herpesvirus that was subsequently named Epstein-Barr virus after two of its discoverers [2]. In 1968, an association was made between EBV and the previously described infectious mononucleosis syndrome [3]. Since that time, EBV has been associated with a variety of different diseases and syndromes that can be classified by the infected cell type and the predominant state of viral infection (Table 6.1). Worldwide (Fig. 6.1), the most common and clinically important EBV-associated diseases include the infectious mononucleosis syndrome, Hodgkin lymphoma, African Burkitt lymphoma, and nasopharyngeal carcinoma. In the USA, the infectious mononucleosis syndrome, Hodgkin lymphoma, and the lymphoproliferative diseases of immunocompromised patients account for most of the EBV-associated morbidity and mortality. EBV is now recognized as an oncogenic virus based on its association with a variety of cancers and its ability to immortalize B lymphocytes in vitro [1].

Primary Infection and the Infectious Mononucleosis Syndrome

Epidemiology

The prevalence of EBV infection approaches 95% by early adulthood [4]. However, in developing countries and in the lower socioeconomic population in the USA, EBV seropositivity rates reach 60–80% during childhood. The rate in the higher socioeconomic population does not reach this level until late adolescence (Fig. 6.2) [5]. In preadolescent children, primary infection with EBV is asymptomatic or occasionally results in a mild, nonspecific, febrile illness. After adolescence, approximately 50% of primary EBV infections result in the syndrome of infectious mononucleosis. Thus, with the majority of primary EBV infections in the USA occurring later in life, the incidence of infectious mononucleosis in the USA is 45.2 cases per 100,000 population per year [6]. Consequently, infectious mononucleosis has its largest public health impact on young college student and military recruit populations, but may occur at any age.

Pathogenesis

EBV is transmitted person-to-person by infectious virions that are produced at mucosal surfaces and shed into body fluids [7]. Oral mucosal contact with infectious saliva is the most common route of transmission. The presence of EBV in breast milk [8] and in genital secretions [9,10] suggests additional modes of transmission. Congenital EBV infection has been documented [11–13]. EBV may also be transmitted via organ transplantation or blood transfusion if these tissues contain EBV-infected lymphocytes [14].

Primary EBV infection usually occurs at the oropharyngeal epithelium (Fig. 6.3). The mechanism by which EBV enters epithelial cells is not known, but may involve a cell surface receptor. In epithelial cells, EBV infection typically results in productive viral replication in a cell differentiation-dependent manner. The EBV genome is replicated and packaged into protein nucleocapsids with lipid envelopes generated by the nuclear membrane. After processing through the Golgi apparatus, secretory vesicles fuse with the cell membrane and release mature infectious virions to the environment to transmit the infection (Fig. 6.3).

At least two EBV genes may be important to the pathogenesis of productive infection. The EBV gene *BCRF1* encodes a viral homologue of human interleukin 10. Expression of *BCRF1* may down-regulate the TH1 immune response of the host, thereby prolonging the duration of productive replication [15]. The EBV gene *BHRF1* encodes a viral homologue of human *Bcl-2*, an inhibitor of apoptosis or programmed cell death [16]. Expression of *BHRF1* and inhibition of apoptosis may preserve the cellular machinery necessary to support productive viral replication as the squamous epithelial cell differentiates.

Eventually, the host immune response succeeds in terminating EBV replication in the oropharynx. Although it is uncertain if EBV establishes latent infection in oropharyngeal epithelial cells [17], circulating B lymphocytes do become latently infected with EBV (Fig. 6.3).

Table 6.1 Epstein-Barr Virus (EBV)–Associated Diseases and Syndromes

I. EBV in lymphocytes
  A. Latent Infection
    1. Infectious mononucleosis
    2. African Burkitt's lymphoma
    3. Hodgkin's lymphoma
    4. Lymphoproliferative diseases of immunocompromised patients
      a) Polyclonal nonmalignant lymphoproliferations
      b) Monoclonal malignant lymphomas of various histologic types
    5. T-cell lymphomas
      a) Angioimmunoblastic lymphadenopathy type
      b) Nodal T-cell immunoblastic lymphoma
      c) Peripheral T-cell lymphoma with hemophagocytosis
    6. Kikuchi's histiocytic necrotizing lymphadenitis
II. EBV in smooth muscle cells
  A. Latent infection
    1. Leiomyomas of immunocompromised patients
    2. Leiomyosarcomas of immunocompromised patients
III. EBV in epithelial cells
  A. Latent infection
    1. Lymphoepithelial carcinoma
      a) Nasopharynx
      b) Salivary glands
      c) Gastric mucosa
      d) Thymus
      e) Lung
    2. Squamous cell carcinoma of the oropharynx
  B. Productive infection
    1. Oral hairy leukoplakia

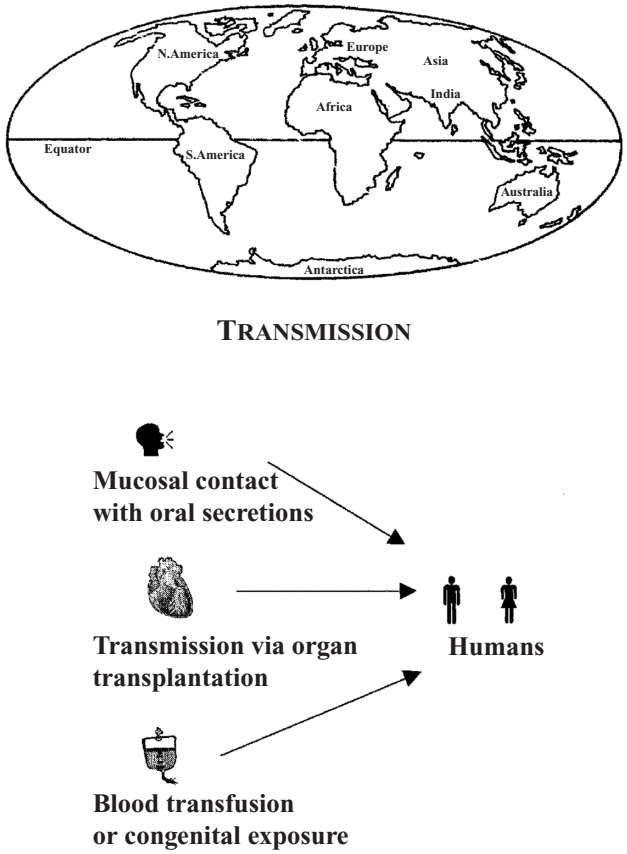


Figure 6.1 Incidence and transmission of Epstein-Barr virus (EBV; human herpes virus 4.)

EBV enters the B lymphocyte by specific binding to the cell surface complement receptor CR2 or CD21 [18]. The EBV genome circularizes, briefly replicates, and is maintained in the cell nucleus as multiple episomes (Fig. 6.3).

Expression of the EBV *EBNA-1* gene product is required to replicate and partition the EBV genomes as the B lymphocyte divides [19]. The *EBNA-1* protein also contains elements that inhibit antigen processing and major histocompatibility complex (MHC) class I-restricted antigen presentation. Thus, cytotoxic T-lymphocyte responses are not generated against this critical EBV protein [20]. Expression of the viral *LMP-2* gene also aids in the maintenance of EBV latency [21]. With restricted gene expression and evasion of the cellular immune system, latent infection of B lymphocytes may explain how EBV maintains a persistent infection [22].

Cytotoxic T lymphocytes and natural killer (NK) cells constitute the primary form of host defense against EBV (Fig. 6.3) [23]. MHC class I-restricted cytotoxic T lymphocytes are largely directed toward antigens involved in the regulation of cell growth of viral proteins (*EBNA-2*, *EBNA-3*, *EBNA-4*, *EBNA-5*, *EBNA-6*, *LMP-1*, and *LMP-2*). Thus, in the presence of a normal immune response, EBV-induced growth and transformation of B lymphocytes is severely limited (Fig. 6.3). In the infectious mononucleosis syndrome, numerous atypical CD8-positive T lymphocytes are formed in response to the lytic EBV-infected B-cell lymphocytes (Fig. 6.3). In some cases, direct EBV infection of T lymphocytes results in T-cell lymphoproliferative disorders [24]. This may trigger the autoimmune neurological manifestations of infectious mononucleosis or the EBV-associated hemophagocytic syndrome [25].

The humoral response to EBV infection generates antibodies against a variety of EBV antigens. However, the role of these antibodies in the pathogenesis of, and recovery from, disease is not clear. EBV-specific antibodies are not protective against EBV superinfection, and multiple EBV types and strains may be found in the oropharynx and peripheral blood lymphocytes of some individuals. Immunoglobulin A (IgA) anti-EBV antibody may actually facilitate virion entry into mucosal epithelial cells [26]. During the infectious mononucleosis syndrome, autoreactive antibodies against erythrocytes and platelets may contribute to the pathogenesis of complications such as autoimmune hemolytic anemia and thrombocytopenia [27,28].

Finally, long after the resolution of infectious mononucleosis, EBV reactivation from latent-infected B cells results in viral reinfection of the oropharyngeal epithelium (Fig. 6.3). Subsequent productive replication and shedding of infectious virions into saliva occurs completely asymptomatically [29]. Whereas latency

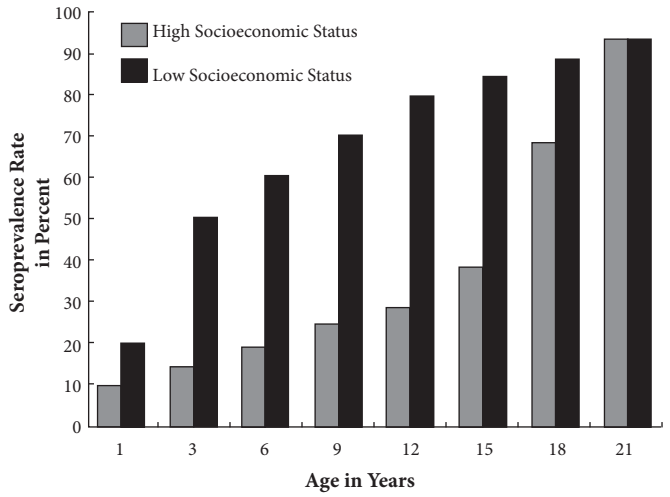


Figure 6.2 EBV seroprevalence rate as a function of age and socioeconomic status.

is a strategy for EBV persistence for the life of the host, periodic reactivation allows the virus to be transmitted to new human hosts via the oral route.

Clinical Manifestations

After an incubation period of 3–7 weeks, the EBV-associated infectious mononucleosis syndrome presents with a triad of fever, pharyngitis, and cervical lymphadenopathy [30]. In some cases, one or more of these signs may be absent. The most frequent manifestations of infectious mononucleosis are listed in Table 6.2.

Serious complications may occur with infectious mononucleosis. Severe edema of the oropharyngeal lymphoid tissue may lead to encroachment of the airway, with stridor and breathing difficulties. Splenic rupture occurs in 0.2% of affected adults. This complication most frequently occurs during the second week of the illness and typically results from trauma. Other potential complications of the infectious mononucleosis syndrome are listed in Table 6.3.

Although most childhood EBV infections are asymptomatic or mild, infants and children who develop the infectious mononucleosis syndrome may present with signs and symptoms similar to those in adults. However, they are more likely to exhibit HSM and

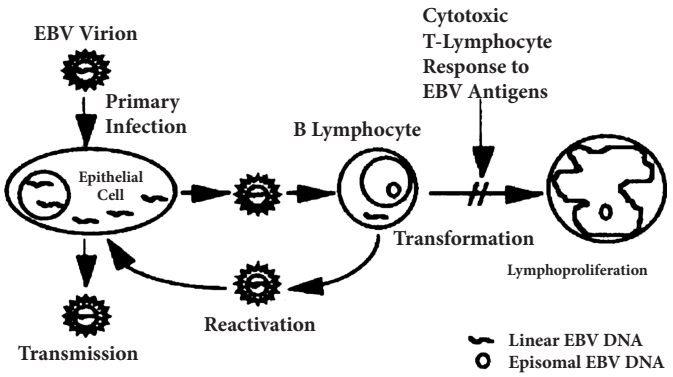


Figure 6.3 A simplified model of EBV infection and pathogenesis.

Table 6.2 Signs and Symptoms of Infectious Mononucleosis

Present in >50% of patients	Present in 10–50% of patients	Present in <10% of patients
Fever	Anorexia	Palatal enanthem
Pharyngitis and sore throat	Nausea	Cutaneous exanthems
Lymphadenopathy	Abdominal discomfort	Jaundice
Malaise and fatigue	Hepatomegaly	Vomiting
Headache	Hepatic tenderness	Cough
Splenomegaly	Myalgias	Arthralgias
	Chills	

respiratory tract infections [31]. Other clinical presentations in this age group may include otitis media, recurrent tonsillitis and pharyngitis, and failure to thrive.

Dermatological Manifestations

A wide range of mucocutaneous findings have been associated with primary EBV infection (Table 6.4). A faint, nonspecific erythematous exanthem may be seen in 10% of all patients with infectious mononucleosis [32], but a 70% incidence has been reported in a series of hospitalized patients [33]. In children with infectious mononucleosis, exanthems may occur in 15–30% of patients [34]. The exanthem usually develops during the first week of the illness and may persist from 1 to 7 days. It usually involves the trunk and upper arms with occasional extension to the face and forearms. Several manifestations of the exanthem have been described, including macular, urticarial, vesicular, morbilliform, petechial, and purpuric forms [34,35]. In approximately 25% of infectious mononucleosis cases, an enanthem occurs consisting of 5–20 clustered, 1- to 2-mm petechiae at the border between the hard and soft palates. Appearing between the 5th and the 17th day of illness, the petechiae fade within 3 or 4 days. Periorbital edema also occurs during the first week of illness in about 30–40% of patients. Upper eyelid edema may be markedly out of proportion to the overall severity of the disease [32].

Nearly all patients with the infectious mononucleosis syndrome who are administered ampicillin, amoxicillin, or another semisynthetic penicillin antibiotic will develop an acute hypersensitivity

Table 6.3 Potential Complications of Infectious Mononucleosis

Neurological	Hematological
Encephalitis and seizures	Neutropenia
Meningoencephalitis	Thrombocytopenia
Transverse myelitis	Aplastic anemia
Cranial neuritis	Hemolytic anemia
Optic neuritis	Hemophagocytic syndrome
Peripheral neuropathy	Splenic rupture
Mononeuritis multiplex	Lymphoproliferative disease
Guillain-Barré acute syndrome	Hepatic
Reye's syndrome	Hepatitis
Respiratory	Hepatic necrosis
Airway obstruction	Reye's syndrome
Pneumonitis	Renal
Cardiac	Glomerulonephritis
Myocarditis	Interstitial nephritis
Pericarditis	
Hematological	

Table 6.4 Dermatological Manifestations Associated with Primary EBV Infection

I. Infectious mononucleosis syndrome
A. Exanthem
1. Macular
2. Urticarial
3. Vesicular
4. Bullous
5. Morbilliform
6. Petechial
7. Purpuric
B. Enanthem
1. Palatal petechiae
C. Periorbital edema
D. Ampicillin-associated scarlatinaform rash
E. Erythema multiforme
F. Erythema nodosum
G. Acute urticaria or cold urticaria
H. Acrocyanosis
I. Erythema annulare centrifugum
J. Pityriasis lichenoides
K. Palmar dermatitis
L. Granuloma annulare–like eruption
M. Papular-purpuric gloves and socks syndrome
N. Genital ulcers
O. Cutaneous amyloidosis
II. Asymptomatic primary EBV infection
A. Gianotti-Crosti syndrome (infantile papular acrodermatitis).

skin eruption. Seven to ten days after taking the drug, a scarlatinaform rash, which consists of pruritic copper-colored macules (Fig. 6.4), appears. The rash first occurs over pressure points and extensor surfaces and becomes confluent as it generalizes over the trunk, extremities, palms, and soles. Desquamation ensues approximately 1 week later. The rash is believed to result from EBV-induced IgM and IgG antibodies to the penicillin-like drug, rather than from a true IgE-mediated penicillin hypersensitivity. Penicillin drug-associated rashes do not recur after the resolution of the infectious mononucleosis syndrome, and these patients should not necessarily be labeled as penicillin allergic [36–38].

Gianotti-Crosti syndrome, or infantile papular acrodermatitis, is sometimes seen with primary EBV infection in children, often in conjunction with recent immunizations [33,39–41]. Manifesting as symmetrical, nonpruritic, lichenoid papules on the distal extremities, face, and buttocks, EBV-associated Gianotti-Crosti lesions may be indistinguishable from those arising from other viral etiologies, such as hepatitis B virus or coxsackievirus. The skin lesions resolve spontaneously after approximately 1 month.

Erythema multiforme may occur with infectious mononucleosis and may persist for greater than 1 month [42,43]. Erythema nodosum may also occur with prolonged courses of infectious mononucleosis [44]. Acute urticaria of prolonged duration has been reported both alone and in association with an exanthem [45]. Cold urticaria associated with cold agglutinins in serum



(a) (b)

Figure 6.4 (a,b) Macular eruption in a patient with infectious mononucleosis who had taken ampicillin.

Table 6.5 Clinical Manifestations of Infectious Mononucleosis

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–7 wk	3–5 day prodromal period of fatigue, malaise, and headache ↓	Screening with heterophile antibody test (negative in 10% of patients).	Infection in younger children is often asymptomatic or causes a mild, nonspecific febrile illness.
3½–7½ wk	Classical triad of fever, pharyngitis, and tender lymphadenopathy (80% of cases). Other common symptoms listed in Table 6–2. A variety of mucocutaneous manifestations may occur in a minority of patients (see text). ↓	Definitive diagnosis by specific EBV serologies.	Pharyngitis typically consists of moderate to severe sore throat with tonsillar enlargement and occasional exudate. Tonsillar crypt abscesses are not uncommon. Lymphadenopathy most often involves the posterior cervical nodes, followed in frequency by the anterior cervical and submandibular nodes. Axillary and inguinal lymphadenopathy may also occur. Splenomegaly and hepatomegaly may be present.
5½–10½ wk	Resolution of illness after 2–3 wk. Fatigue and malaise may last longer. Chronic mononucleosis is extremely rare.		

may also occur [46]. Other rarely reported cutaneous manifestations of primary EBV infection include acrocyanosis [47], erythema annulare centrifugum [48], pityriasis lichenoides [49], palmar dermatitis [50], granuloma annulare-like eruption [51], papular-purpuric gloves-and-socks syndrome [52], genital ulcers [53], chronic bullous disease of childhood [54], and primary cutaneous amyloidosis [55]. Chronic nonpruritic, erythematous and purpuric, maculopapular lesions containing EBV have also been described in an immunocompromised patient with past persistent EBV infection. These lesions demonstrated an unusual histopathology resembling graft-versus-host disease [56]. A variety of other clinical manifestations are seen with infectious mononucleosis (Table 6.5).

Hydroa vacciniforme (HV) is a chronic photosensitivity disorder associated with chronic latent EBV infection. HV and HV-like (on non-sun-exposed skin) skin lesions contain Epstein-Barr encoded RNA (EBER)-positive cytotoxic T cells. Patients with HV and HV-like skin disease may develop cutaneous T-cell lymphoma. Skin biopsy reveals a deep superficial and deep dermal infiltrate of CD4+ T cells and EBER+ cytotoxic T cells [57–59]. Other inflammatory diseases associated with EBV reactivation include hypersensitivity to mosquito bites [60,61], anticonvulsant hypersensitivity syndrome [62], and Gianotti-Crosti syndrome [63]. Hypersensitivity to mosquito bites is an EBV-associated NK cell lymphoproliferative disorder characterized by high fever, localized skin lesions, lymphadenopathy, and hepatosplenomegaly (HSM) [64]. The role of EBV in these disorders is unclear, and the presence of EBV+ lymphoid cells may be a secondary phenomenon related to immune disturbance.

Unilateral laterothoracic exanthema (ULE) is a benign self-limited condition seen most often in young children that is marked by coalescing erythematous papules predominantly on one side of the body, and often preceded by a viral prodrome. Biopsy reveals a dense perivascular lymphoid infiltrate. While often associated with parvovirus B19 infection, cases associated with EBV serologic reactivation have also been described [65]. To date, however, there has been no direct demonstration of EBV within the skin lesions.

Dermatopathology

There are no pathognomonic histopathological findings that characterize the mucocutaneous lesions associated with primary EBV infection. Nonspecific exanthems demonstrate nonspecific pathologies. Specific cutaneous manifestations may be identified by their characteristic pathologies, but none is specific for EBV infection as the etiology. Although the subject has not been well studied, most EBV-associated cutaneous manifestations likely arise through immune-mediated events. However, direct EBV infection of cutaneous epithelial or vascular endothelial cells may account for some manifestations [42,53,55,56].

Laboratory Findings

Hepatic transaminase levels are frequently mild-to-moderately elevated in patients with infectious mononucleosis, but significant hyperbilirubinemia and clinically detectable jaundice occur in only 5% of cases [30]. The white blood cell count commonly demonstrates a lymphocytosis of greater than 50% with at least 10% atypical lymphocytes (Fig. 6.5). The atypical lymphocytes have been shown to be mostly CD8-positive cytotoxic T cells [66]. However, the absence of atypical lymphocytes does not exclude the diagnosis of infectious mononucleosis. Importantly, atypical lymphocytosis is not pathognomonic for EBV infection and may also be seen during infections with cytomegalovirus (CMV), HHV-6, toxoplasmosis, acute viral hepatitis, rubella, mumps, and with drug hypersensitivity reactions. Mild thrombocytopenia may occur in up to one half of patients with infectious mononucleosis [67], but platelet counts below 20,000/mm^3 are rare and are associated with potentially life-threatening hemorrhages [68].

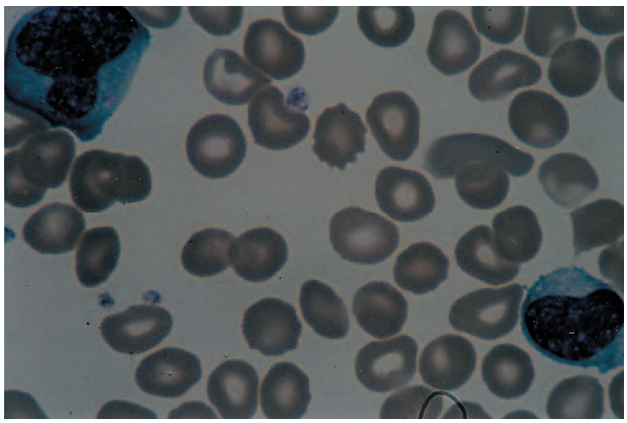


Figure 6.5 Atypical lymphocytes (1000×)—Wright-stained peripheral blood smear showing infectious mononucleosis.

Diagnosis

The diagnosis of primary EBV infection must be differentiated (Table 6.6) from a variety of other conditions of infectious and noninfectious etiologies, and is best made by serological testing. Heterophile antibodies capable of agglutinating sheep, horse, or bovine erythrocytes are present at titers of greater than 1:40 in approximately 90% of adolescent and adult patients with the infectious mononucleosis syndrome [69]. They may also be positive in patients with mild or asymptomatic primary EBV infection. False-positive tests are rare. Heterophile antibodies may persist after the onset of illness for 3–6 months and up to 18 months in some cases. However, in young children, heterophile antibodies are positive in only a small minority with primary EBV infection [70]. The greatest utility of the heterophile antibody test is as a rapid screen for primary EBV infection in young adults with a compatible clinical presentation. Several commercially produced rapid spot or slide tests for the presence of heterophile antibodies are currently available.

Specific EBV serologies are required to make a definitive diagnosis of EBV infection, especially when the heterophile antibody test is negative [30]. Titers of three different antibodies are needed to determine the stage of EBV infection (Fig. 6.6). IgG and IgM against EBV viral capsid antigen (VCA) appear concurrently, at or before the onset of clinical symptoms in primary EBV infection. VCA IgG remains positive for life. VCA IgM reverts to negative within 2 or 3 months, usually after the clinical symptoms have resolved. Between 1 and 6 months after the onset of symptoms, IgG against EBV nuclear antigens (EBNA) appear and then remain positive for life. Antibodies to EBV early antigens (EA) lack sensitivity and specificity for primary EBV infection and are rarely helpful in determining the stage of EBV infection. Thus, primary EBV infection is diagnosed by the presence of VCA IgG and VCA IgM antibodies in the absence of EBNA IgG antibodies (Table 6.7). The presence of antibodies to EBNA indicates that primary EBV infection occurred 1 or more months in the past and usually suggests that a patient's present clinical syndrome is unrelated to primary EBV infection. Thus, EBV serological tests are most useful to differentiate between acute primary infection and the chronic state of past, persistent infection.

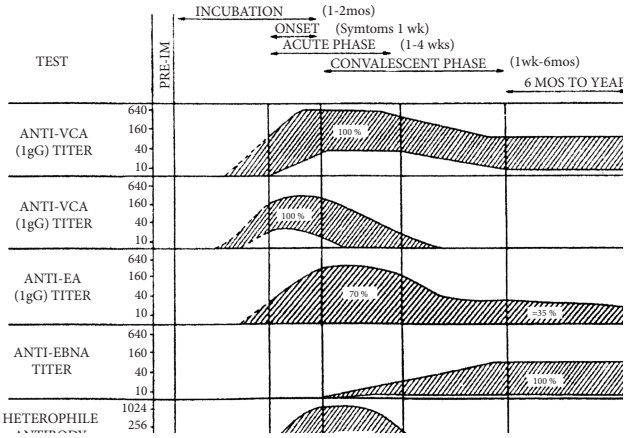


Figure 6.6 Characteristic EBV-specific antibody responses observed in young adults with acute infectious mononucleosis.(Adapted from Ref.5 with permission.)

Treatment

In the majority of cases, infectious mononucleosis is a self-limited disease, and patients need only supportive medical care (Table 6.8). Antiviral agents, such as acyclovir, inhibit EBV replication, but they do not influence the clinical course of infectious mononucleosis [71]. Acyclovir therapy does not eliminate the latent form of EBV infection and does not reduce the number of EBV-infected lymphocytes in the peripheral blood [72]. Combination therapy with oral acyclovir and oral corticosteroids provided no significant benefit over placebo in one large, randomized, prospective clinical trial [73].

Corticosteroids do not negatively influence the clinical outcome of infectious mononucleosis, but the associated risks of corticosteroid therapy cannot justify their routine use in uncomplicated cases. There are three clear indications for the use of corticosteroids in infectious mononucleosis: (1) lymphadenopathy and edema of the neck and throat causing respiratory compromise or airway obstruction, (2) hemolytic anemia, and (3) severe thrombocytopenia [30]. The role is less clear for corticosteroids in the neurological complications of EBV infection, but some experts advocate their use in more serious cases.

Table 6.6 Differential Diagnoses of Infectious Mononucleosis

Group A streptococcal infection: Infection is similar with pharyngitis, fever, and submandibular adenopathy, but is not associated with hepatosplenomegaly.

Acute viral hepatitis (hepatitis A, B or C virus): Infection may be similar with fever, hepatomegaly and elevated hepatic enzymes, but negative heterophile antibody test and specific serologies.

Primary cytomegalovirus infection: Fever, lymphadenopathy, and malaise, but negative heterophile antibody test and specific serologies.

Primary human herpesvirus-6 infection: Fever, lymphadenopathy, and malaise, but negative heterophile antibody test and specific serologies.

Human immunodeficiency virus (HIV): May sometimes appear clinically similar, with fever, lymphadenopathy, and malaise, but negative heterophile antibody test and specific serologies.

Toxoplasmosis: Fever, lymphadenopathy, and malaise, but negative heterophile antibody test and specific serologies.

Lymphoma: May have a similar presentation, but negative heterophile antibody test and specific serologies.

Rubella: May rarely present with fever, malaise, adenopathy, maculopapular skin rash, and palatal petechiae, but negative heterophile antibody test and specific serologies.

Phenytoin hypersensitivity reaction: This reaction may present with fever, lymphadenopathy, hepatitis, and skin rash. The patient may develop leukocytosis with atypical lymphocytes. Unlike infectious mononucleosis, facial and periorbital edema are common and there is a history of phenytoin use (or other aromatic anticonvulsants), often begun in the previous 2–6 wk.

Table 6.7 Serological Diagnoses of EBV Infection

Antibody	Viral capsid antigen immunoglobulin G (VCA IgG)	VCA IgM	EBV nuclear antigens (EBNA) IgG
Acute primary infection	Positive	Positive	Negative
Past persistent infection	Positive	Negative	Positive

Table 6.8 Treatment of Infectious Mononucleosis

Symptom	Treatment
General	Rest, proper nutrition, and adequate hydration
Fever	Antipyretics (aspirin should be avoided in children)
Headache	Analgesics (acetaminophen or nonsteroidal antiinflammatory drugs)
Myalgias	Analgesics
Sore throat	Analgesics and salt water gargle
Cutaneous manifestations	Topical steroids for exanthems and oral antihistamines as needed for pruritus
Splenomegaly	Patients should be cautioned against physical activities that may traumatize the abdomen and cause splenic rupture.
Major complications:airway encroachment, hemolytic anemia, or severe thrombocytopenia	Prednisone 0.5 mg/kg per dose twice daily (maximum of 60 mg/24 hr tapered over a 1–2 wk period if clinical response is prompt)

Table 6.9 Immunocompromised Patients at Risk for EBV-associated Lymphoproliferative Disease

I. Acquired immunodeficiency
  A. Acquired immunodeficiency syndrome (AIDS) secondary to human immunodeficiency virus (HIV) infection
  B. Iatrogenic immunosuppressive therapy
    1. Organ transplant recipients
      a) Anti–T-lymphocyte antibodies
      b) Multiple high-dose steroid pulses
      c) Cyclosporine
      d) Azothiaprine
    2. Autoimmune disease patients
      a) Cyclosporine
      b) Methotrexate
      c) Azothiaprine
II. Congenital immunodeficiency
  A. Wiskott-Aldrich syndrome
  B. Ataxia-telangiectasia syndrome
  C. Common variable immunodeficiency syndrome
  D. Severe combined immunodeficiency syndrome
  E. X-linked lymphoproliferative syndrome (Duncan's syndrome)

It is believed that the majority of the signs and symptoms of infectious mononucleosis result from the host immune response to the EBV infection, especially against the transformation-associated EBV antigens expressed in B lymphocytes. Thus, persistent cell-mediated immunity to EBV is protective against developing the symptoms of the infectious mononucleosis syndrome with EBV superinfection later in life. A vaccine to prevent primary EBV infection is not yet available.

Lymphoproliferative Disease and Malignancy

Epidemiology

EBV-associated lymphoproliferative diseases occur in immunocompromised patients, such as those with human immunodeficiency virus (HIV) infection, those receiving iatrogenic immunosuppression, or those with certain congenital immunodeficiency syndromes (Table 6.9). In the USA, the incidence of lymphoproliferative disease is between 2 and 10% for organ transplant recipients and between 10 and 30% for patients with acquired immunodeficiency syndrome (AIDS) [74–76]. Hodgkin lymphoma, endemic African Burkitt lymphoma, certain T-cell lymphomas, and nasopharyngeal carcinoma are EBV-associated malignancies that typically occur in otherwise nonimmunocompromised patients (Table 6.1).

A prior history of infectious mononucleosis is a risk factor for developing Hodgkin lymphoma [77]. African Burkitt lymphoma is epidemiologically associated with malarial infection in sub-Saharan Africa. Nasopharyngeal carcinoma commonly occurs in certain ethnic groups and geographical regions, including southern China, southeast Asia, Mediterranean Africa, and populations indigenous to Alaska. The epidemiology is still unclear for the recently recognized EBV-associated T-cell lymphomas, but most reports originate from east Asia [78]. Other EBV-associated malignancies are rare or contain EBV in only a small percentage of lesions (Table 6.1).

Primary cutaneous lymphomas of B, T, and NK cell-type have been associated with EBV infection. Extranodal NK/T-cell lymphoma, typically a high-grade EBV-associated lymphoma that involves the nasal region, is also rarely seen as a primary cutaneous disease. In one case of an 11-year-old boy, disease was confined to the skin of the face and hands for 4 years [79]. Intravascular large T/NK-cell lymphoma, a rare EBV+ non-B-cell variant of intravascular large cell lymphoma, often presents as primary cutaneous disease [80].

Primary cutaneous diffuse large B-cell lymphoma with LMP1+ tumor cells has been described in an elderly female who presented with high fever, and skin lesions of the face, limbs, and palms [81]. Primary cutaneous EBV+ post-transplant lymphoproliferative disorders (PTLD) have been described. In one case, a 63-year-old male presented 5 years post-lung transplant with an asymptomatic solitary indurated plaque on the face [82]. Biopsy revealed a dense granulomatous lymphohistiocytic infiltrate in the dermis with scattered large EBV+ B cells. Reduction in post-transplant immunosuppression was followed by a complete remission. A primary post-transplant cutaneous plasmacytoma (solitary dermal nodule) with EBER+ cells has been described [83].

Pathogenesis

In patients with deficient cytotoxic T-lymphocyte activity against EBV, the number of EBV-infected lymphocytes in the peripheral blood rises dramatically, heralding the risk of lymphoproliferative disease [84]. Expression of the EBV proteins *EBNA-2*, *EBNA-3*, *EBNA-4*, *EBNA-5*, *EBNA-6*, and *LMP-1* is associated with the transformation and immortalization of B lymphocytes in vitro and in vivo [85]. As a group, these viral proteins transactivate the expression of cellular genes and interact with cellular proteins involved in the regulation of cell growth. The viral proto-oncogene *LMP-1* is especially important to the process of B-lymphocyte transformation, influencing cell surface receptor signaling pathways, interacting with cellular transcription factors, and inhibiting cell apoptosis. Several different patterns of expression of these latent, transformation-associated EBV genes have been described for different EBV-associated malignancies. Although the biology of EBV latency and transformation is complex, it is believed that these EBV genes are important to the oncogenic process of all EBV-associated neoplasia [85,86]. Clearly, multiple other factors are involved as well, including host genetic

susceptibility, host immune status, host age and route of infection, dietary and environmental influences, and EBV genetic variation. The exact role of EBV in the process of oncogenesis remains an important area of active investigation.

Clinical and Dermatological Manifestations

EBV-associated lymphoproliferative diseases and malignancies may involve any organ system of the body and may present with an enormous range of clinical findings. The most common cutaneous manifestation of EBV-associated lymphoproliferation or malignancy is subcutaneous lymphadenopathy secondary to invasion of, or metastases to, pre-existing lymph nodes. Less commonly, EBV-associated lymphoproliferation may involve the skin and subcutaneous tissues directly. The dermatological manifestations of EBV-associated lymphoproliferative disease and malignancy are listed in Table 6.10.

The primary tumor of nasopharyngeal carcinoma is often asymptomatic, and the disease frequently presents with metastases to lymph nodes in the head and neck (Fig. 6.7). Hodgkin lymphoma may present primarily with palpable lymphadenopathy, including the cervical and submandibular lymph nodes. African Burkitt's lymphoma typically arises in lymphoid tissue associated with the oropharyngeal mucosa or gastrointestinal tract and may present in salivary glands or submandibular lymph nodes (Fig. 6.8). Lymphoproliferative diseases and malignant lymphomas occurring in immunocompromised patients may involve any of the groups of subcutaneous lymph nodes.



Figure 6.7 Nasopharyngeal carcinoma with marked cervical lymphadenopathy.

Primary cutaneous B-cell lymphomas containing EBV may occur in iatrogenically immunosuppressed patients after solid organ transplantation [87]. These cases presented clinically with multiple ulcerative cutaneous nodules in the absence of peripheral lymphadenopathy or internal organ involvement. In HIV-infected patients with AIDS, EBV-associated B-cell and T-cell lymphomas may occur in the oral cavity with manifestations including swelling (Fig. 6.9) and ulcerations of the gingivae, hard palate, or tongue [88–91].

Table 6.10 Dermatologic Manifestations of EBV-associated Lymphoproliferative Disease and Malignancy

I. Solid tumors
  A. Nasopharyngeal carcinoma
    1. Cervical lymphadenopathy from metastases
II. B-cell lymphoproliferative disorders
  A. Hodgkin lymphoma
    1. Cervical and submandibular lymphadenopathy
  B. Burkitt's lymphoma
    1. Submandibular lymphadenopathy
    2. Parotid salivary gland enlargement
  C. Lymphoproliferative diseases of immunocompromised patients
    1. Diffuse subcutaneous lymphadenopathy
    2. Primary cutaneous lymphoma
      a) Nodules and ulceration
    3. Oral lymphoma in HIV-infected patients
      a) Swelling, ulceration, and necrosis
III. T-cell lymphoproliferative disorders
  A. Oral lymphoma in HIV-infected patients
    1. Swelling, ulceration, and necrosis
  B. Angiocentric cutaneous lymphoma
    1. Violaceous plaques
    2. Papules
    3. Nodules
    4. Bullae
    5. Chronic ulcers
    6. Subcutaneous tumors
  C. Subcutaneous lymphoma
    1. Panniculitis
  D. Histiocytoid cutaneous lymphoma
    1. Papules with necrosis
  E. Vesiculopapular lesions of the face
    1. Vesiculopapular eruptions
    2. Subcutaneous nodules



Figure 6.8 African Burkitt's lymphoma with marked cervical lymphadenopathy. (Courtesy of Barbara Lepard, M.D., Moshi, Tanzania.)



Figure 6.9 Lymphoma of the palate in an HIV-seropositive patient.(Courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

Recently, cutaneous T-cell lymphomas in otherwise immunocompetent patients have been found to contain EBV in some cases [92–97]. In these reports, the dermatological manifestations included multiple violaceous plaques, papules, nodules, bullae, chronic ulcers (Fig. 6.10), and subcutaneous tumors on the trunk and extremities. Interestingly, a history of hypersensitivity to mosquito bites (intense erythematous swelling and skin ulceration, fever, and hepatitis) was noted for some patients with cutaneous EBV-associated lymphoproliferative disease. Notably, EBV is not associated with classical mycosis fungoides or with human T-cell lymphotropic virus (HTLV)-I-associated cutaneous adult T-cell lymphoma.

Laboratory Findings

There are no laboratory findings specific for, or even characteristic of, EBV-associated lymphoproliferative diseases or malignancies.

Dermatopathology

Histologically, nasopharyngeal carcinoma is a lymphoepithelial carcinoma characterized by either squamous, nonkeratinizing, or undifferentiated epithelial cells, and a prominent desmoplastic lymphoid infiltration [98]. In nasopharyngeal carcinoma, EBV is present in the malignant epithelial cells, but not the infiltrating lymphocytes. Hodgkin lymphoma manifests a variety of histologic subtypes, but the mixed cellularity and nodular lymphocyte predominance subtypes are most likely to be EBV-associated [99]. In Hodgkin lymphoma, EBV is detected only within the Reed-Sternberg cells [100]. Hodgkin lymphoma rarely if ever involves the skin. Cutaneous B-cell lymphomas associated with EBV



(a)



(b)

Figure 6.10 (a,b) Cutaneous facial and edematous T-cell lymphoma of childhood. The classic findings include a recurrent facial edema, along with the presence of papules and nodules that ulcerate and scar. It is associated with a fatal outcome, despite therapy. (Courtesy of Francisco Bravo Puccio, M.D., Instituto Dermatologico, Lima, Peru.)

demonstrate a dense infiltrate of abnormal lymphocytes of varying morphology, including immunoblasts, plasmacytoid cells, and reactive lymphocytes. In some cases, the abnormal lymphocytes may maintain an angiocentric distribution.

A review from Japan has described four distinct EBV-associated cutaneous lymphoproliferative disorders involving T cells and/or NK cells [101].

(1) Angiocentric cutaneous lymphoma is characterized by angiocentric infiltration of atypical lymphoid cells and has similar histopathology to peripheral T-cell lymphomas arising within the nasal cavity (lethal midline granuloma).

(2) Subcutaneous lymphoma is characterized by atypical lymphocyte infiltration into subcutaneous tissue, including fat lobules. Phagocytizing cells, called "beanbag cells," are described. This disorder presents as a panniculitis and is associated with hemophagocytosis.

(3) Histiocytoid lymphoma is described as a diffuse infiltration of the skin of phagocytizing histiocytoid cells and atypical lymphoid cells. This disorder is also associated with hemophagocytosis.

(4) Vesiculopapular eruptions on the face, mimicking HV, have been described only in children. Histologically, this disorder is characterized by dermal angiocentric infiltration of atypical lymphoid cells with dermal necrosis. Although not initially malignant, this disorder may eventually evolve into malignancy.

Diagnosis

EBV serological tests have a very limited role in the diagnosis of EBV-associated lymphoproliferations and malignancies. Antibody titers may be difficult to interpret in immunocompromised patients with EBV reactivation [102–104]. VCA IgG titers may be quite high, but the titer level itself has no clinical utility. VCA IgM titers may intermittently return to positive, and the EBNA titer may revert to negative. This phenomenon confounds the differentiation between acute and past EBV infection. Except in cases of primary EBV infection and seroconversion, EBV antibody titers have no role in the diagnosis of EBV-associated lymphoproliferative diseases in immunocompromised patients.

The utility of EBV serological tests is limited to two clinical situations. In the case of nasopharyngeal carcinoma, high titers of IgA to EBV VCA and EA often indicate the presence of the tumor before it becomes clinically apparent [105]. In the southern Chinese and southeast Asian populations at risk for nasopharyngeal carcinoma, EBV serology is often used as a screening test. In the case of infectious mononucleosis, EBV serology is useful in identifying EBV as the causative agent, particularly in those cases that are heterophile antibody negative. EBV-associated mononucleosis can usually be confirmed by demonstration of either an elevated titer of EBV VCA IgM or a rising titer of EBV VCA IgG (from acute and convalescent serum samples).

For all EBV-associated lymphoproliferative disorders and malignancies, the definitive diagnosis is best made by biopsy histopathology supplemented with EBV in situ hybridization and/or immunohistochemistry. The diagnosis of EBV infection within pathological tissues may be accomplished by a variety of methods. In situ techniques can identify the specific cells infected and even the subcellular location of the viral genome or gene products. There are several excellent commercially available kits for in situ hybridization to the EBV-encoded RNA transcripts EBER-1 and

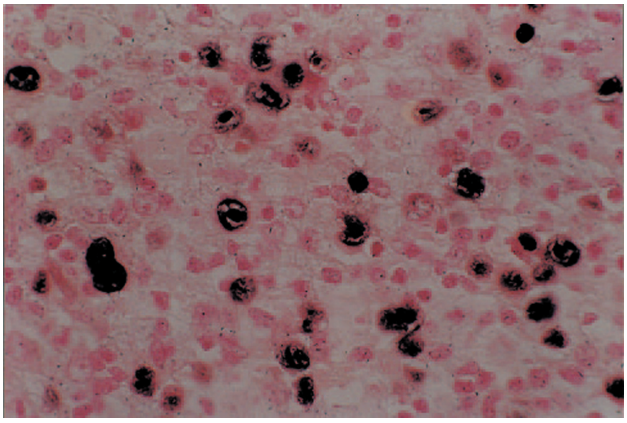


Figure 6.11 EBV-encoded RNA transcript–1 (EBER-1) in situ hybridization (600×) of a lymph node that contained EBV-positive B lymphocytes of posttransplant lymphoma.

EBER-2, which are expressed in latent EBV infection (Fig. 6.11) [106]. Monoclonal antibodies (MAb) against EBV proteins are also commercially available, including a MAb against ZEBRA (BZLF1), an EBV immediate-early gene product of productively infected cells; a MAb against EA-D, an early gene product of productively infected cells; and a cocktail of MAbs against LMP-1, an EBV protein expressed in a variety of EBV-associated lesions, most notably Hodgkin lymphoma (Fig. 6.12) [17]. Of these EBV-specific antibodies, only the LMP-1 and BZLF1 antibodies work on formalin-fixed paraffin-embedded tissues. Electron microscopy (EM) may demonstrate intracellular virions with characteristic herpesvirus morphology, but EBV cannot be specifically identified by EM [107]. EM for detection of virus in tissues has largely been relegated to a research tool.

Extraction and purification of DNA from tissue specimens permits the identification of EBV DNA by blot nucleic acid hybridization. This assay is useful to quantitate the number of EBV genomes present and to determine the clonality and state of infection of the EBV present in the tissue [108]. Amplification of EBV DNA by polymerase chain reaction is an extremely rapid and sensitive method of detecting the virus [109]. Direct viral culture of EBV is technically difficult, low in sensitivity, and available in only a few research laboratories. EBV culture has no role in routine clinical practice. With any method of detecting EBV in clinical

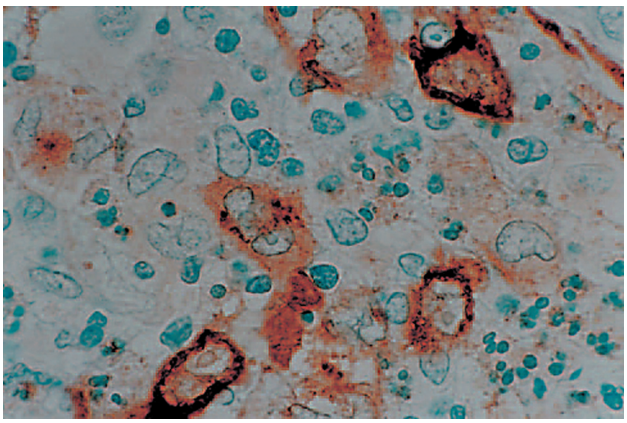


Figure 6.12 LMP-1 immunoperoxidase (1000×) of a lymph node that contained EBV-positive Reed-Sternberg cells characteristic of Hodgkin disease.

tissue, caution must be used in interpreting the results. As with all persistent viruses, the presence of EBV in a pathological tissue does not necessarily imply causality of disease.

Treatment

Nearly all EBV-associated malignancies are latently infected, usually in a monoclonal manner with respect to the EBV genome. Therefore, antiviral drugs that inhibit EBV productive replication have no role in the therapy of EBV-associated lymphoproliferations and malignancies. Specific therapies vary with the type and stage of the disease and may include cytotoxic chemotherapy, radiation therapy, and surgical excision. The prognosis of many forms of EBV-associated malignancy is poor, especially for metastatic nasopharyngeal carcinoma and malignant non-Hodgkin lymphomas of immunocompromised patients. Hodgkin lymphoma in a nonimmunocompromised patient is an exception to this rule and often has a good prognosis with appropriate therapy.

In many cases, lymphoproliferative disorders in iatrogenically immunosuppressed patients are not malignant. They occur by the polyclonal proliferation of EBV-transformed B lymphocytes in the absence of an effective cytotoxic T-lymphocyte immune response [110]. In these cases, the EBV latency and transforming genes are expressed at high levels [111]. Successful therapy of these lymphoproliferative disorders requires at least partial restoration of cytotoxic T-lymphocyte immune function by a reduction in the immunosuppressive chemotherapy. In organ transplant recipients, the degree of reduction must be balanced against the increased risk of graft rejection. In some cases, a subset of the proliferating lymphocytes also exhibits productive EBV replication [112]. Although controlled data are lacking, high-dose parenteral acyclovir is often used as adjunctive therapy for these lymphoproliferative disorders [113]. Alpha interferon and intravenous immunoglobulin have also been used for their antiviral and immunomodulatory properties. Perhaps the most promising new therapeutic approach to lymphoproliferative disorders in iatrogenically immunosuppressed patients involves the ex vivo expansion of host cytotoxic T lymphocytes against EBV-infected host target cells, followed by reinfusion of the activated cytotoxic T cells back into the patient. Preliminary data are encouraging from bone marrow transplant patients with EBV-associated lymphoproliferations for this still experimental therapy [114].

Kikuchi's Histiocytic Necrotizing Lymphadenitis

Epidemiology

Kikuchi's histiocytic necrotizing lymphadenitis (Kikuchi's disease) is a rare disorder of unknown origin, although an association with primary EBV infection as well as other infectious etiologies has been suggested. Kikuchi's disease most frequently affects females aged 20–30 years, but may affect any individual. First reported in Japan in 1972 [115,116], Kikuchi's disease has subsequently been recognized worldwide.

Pathogenesis

The etiology of Kikuchi's disease is not known, but the clinical and pathological features of the disease are suggestive of a hyperimmune reaction to an infectious agent. Several infectious agents including EBV [117,118], *Yersinia enterocolitica* [119], HIV [120,121], parvovirus B19 [122], HHV-6 [123], and *Toxoplasma gondii* [124] have been proposed as potential etiologic agents. Other studies have found no association between Kikuchi's disease and specific infections [125,126]. The fact remains that a consistent etiological factor has yet to be discovered, and the hyperimmune pattern of Kikuchi's disease may be a reaction to a wide variety of etiological factors, possibly infectious, physical, chemical, or neoplastic.

Clinical Manifestations

The characteristic symptoms of Kikuchi's disease include regional lymph node enlargement with associated symptoms (Table 6.11). Lymphadenopathy of the cervical chain is most common, particularly the posterior cervical chain [127]. Other nodal regions may be involved, such as the supraclavicular, axillary, or inguinal nodes, and generalized lymphadenopathy occasionally occurs [128]. Splenomegaly develops in less than 10% of cases, and hepatomegaly is even more uncommon. Cutaneous lesions are present in up to 40% of patients and may include facial erythema, erythematous papules, plaques, nodules, cutaneous ulcers, and oral mucosal ulcers (Figs. 6.13 and 6.14) [129,130]. The signs and symptoms of Kikuchi's disease resolve spontaneously within 1–6 months of onset, and often rapidly after excisional lymph node biopsy. The differential diagnosis of Kikuchi's disease is listed in Table 6.12.

Table 6.11 Clinical Manifestations of Kikuchi's Histiocytic Necrotizing Lymphadenitis

Time course of disease	Clinical manifestations	Laboratory analyses	Other notes
Incubation period unknown	Prodrome of upper respiratory symptoms may occasionally occur ↓	Positive serologies for primary EBV infection are supportive of a diagnosis.	The lymphadenopathy is typically painless, but may be tender in some cases
Over the course of weeks	Slow-growing, localized lymphadenopathy, sometimes with fever, chills, night sweats, fatigue, malaise, headache, sore throat, nausea, vomiting, weight loss, or arthralgias ↓	Definitive diagnosis is made only by lymph node biopsy and histological interpretation	
1–6 mo	Benign, self limited-course ↓		In some cases, the disease may recur and then spontaneously resolve again
	Resolution of all symptoms		

Dermatopathology

The histological findings of the skin lesions and the affected lymph nodes in Kikuchi's disease may mimic those of malignant lymphoma, causing occasional misdiagnosis. Characteristically, there is a dense dermal lymphohistiocytic infiltrate with histiocytic aggregates, atypical lymphoid cells, karyorrhectic debris, and patchy necrosis. These features may extend into the outer root sheaths of hair follicles and deep into the reticular dermis. In affected lymph nodes, pathological foci appear as pale, wedge-shaped areas with atypical lymphoid cells, phagocytic histiocytes, and karyorrhectic debris. A characteristic histological feature of Kikuchi's disease is the absence of neutrophils despite the presence of necrosis.

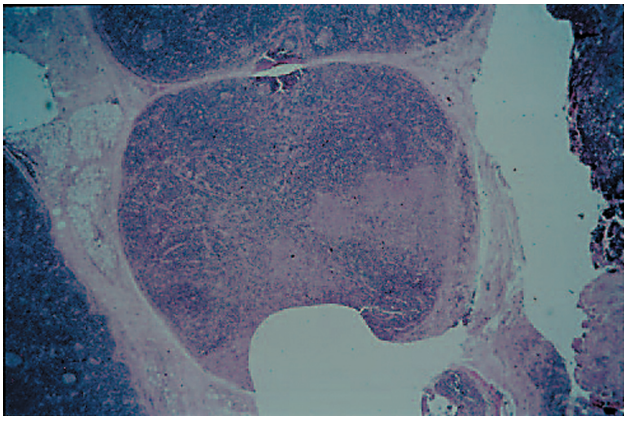


Figure 6.14 Lymph nodes of a patient with Kikuchi's disease. (From Ref. 101. Used with permission.)

Histopathologically, Kikuchi's disease may be difficult to differentiate from malignancy. Immunohistochemical demonstration of a predominance of B lymphocytes suggests lymphoma cutis, and chloroacetate esterase staining suggests leukemia cutis. Other diagnostic considerations include regressing atypical histiocytosis, malignant histiocytosis, anaplastic large cell lymphoma, lymphomatoid papulosis, and lymphomatoid granulomatosis.

Diagnosis

Serological evidence of primary EBV infection (Table 6.7) is supportive of the diagnosis of Kikuchi's disease. As described in the section on EBV-associated lymphoproliferative disorders and malignancies, in situ histopathological techniques to detect EBV within the pathological tissue would be highly suggestive of the diagnosis of Kikuchi's disease. EBV has been demonstrated within the atypical immunoblasts by immunohistochemical staining for



(a)



(b)



(c)

Figure 6.13 (a,b,c) Erythematous papules and plaques of Kikuchi's disease. (From Ref. 101. Used with permission.)

Table 6.12 Differential Diagnoses of Kikuchi's Histiocytic Necrotizing Lymphadenitis

Atopic dermatitis: The skin manifestations may occasionally mimic this condition, but atopic dermatitis lacks the associated constitutional symptoms or lymphadenopathy.
Systemic lupus erythematosus: May also cause regional lymphadenopathy, but is normally associated with other autoimmune signs and symptoms (e.g., butterfly rash, photosensitivity). Can be differentiated by positive ANA titers and histology.
Scrofula (chronic tuberculous adenitis): Causes cervical lymphadenopathy, with nodes becoming harder and matted during the course of disease. Can be differentiated by histology.
Cat-scratch disease: May appear similar and require histological differentiation. History of recent cat exposure.
Malignant lymphoma: May have an identical presentation, but can be differentiated by histology.
Sarcoidosis: May also cause lymphadenopathy, but respiratory symptoms (e.g., cough, dyspnea, or chest discomfort) are typical.
Toxoplasmosis: Also causes lymphadenopathy and fatigue, but associated fever is uncommon. Can be differentiated by histology.
Kawasaki's disease: May also cause lymphadenopathy, but has other symptoms of conjunctival injection, oral mucosal findings, edema and erythema of the distal hands and feet, fine desquamation of the skin, etc.

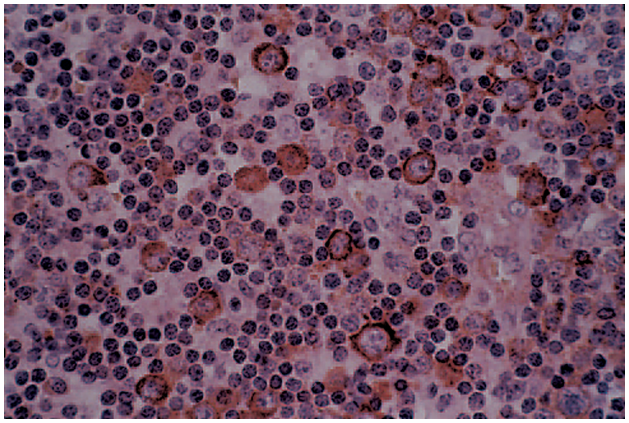


Figure 6.15 LMP-1 immunoperoxidase (600×) of a lymph node showing EBV-positive B immunoblasts in Kikuchi's disease.(From Ref. 101. Used with permission.)

the EBV latent membrane protein (LMP-1) and by in situ nucleic acid hybridization to the EBV latency-associated transcript EBER-1 (Fig. 6.15) [117]. Definitive diagnosis of Kikuchi's disease can be made by histological examination of an excisional lymph node biopsy.

Treatment

Kikuchi's disease is a benign clinical entity that resolves without specific therapy (Table 6.13). It does not respond to chemotherapy or radiation therapy. The presence of latent EBV infection within B lymphocytes suggests that antiviral therapy is not indicated.

Oral Hairy Leukoplakia

Epidemiology

Oral hairy leukoplakia is an oral mucosal lesion common in EBV-seropositive patients who are infected with HIV [107]. The point prevalence may be as high as 25% in HIV-infected patients, and the lesion often appears early in the clinical course prior to the onset of AIDS [132,133]. Antiretroviral and/or antiherpesviral therapy reduces the prevalence of HIV-associated oral hairy leukoplakia [134]. In HIV-infected patients, oral hairy leukoplakia is more common in men [135,136] and in patients who smoke cigarettes [137,138]. Although the reasons are not clear, oral hairy leukoplakia is rarely reported in children who are infected with HIV [139–141]. Oral hairy leukoplakia is also relatively common in patients receiving immunosuppressive therapy, such as organ transplant recipients, especially patients receiving the drug cyclosporine [142]. Oral hairy leukoplakia has also been described in several HIV-seronegative individuals who appeared to be otherwise immunocompetent [143–145].

Table 6.13 Treatment of Kikuchi's Histiocytic Necrotizing Lymphadenitis

Symptom	Treatment
General	Rest, good nutrition, and symptomatic treatment, as needed. Nonsteroidal anti-inflammatory agents have been helpful in many cases.
Fever	Antipyretics

Pathogenesis

Oral hairy leukoplakia is the only EBV-associated pathology characterized by high-level productive viral replication and is the only nonmalignant lesion of epithelial cell infection [107]. Inhibition of viral replication results in resolution of the lesion [146]. However, in all patients, the prevalence of EBV replication in the oropharyngeal epithelium far exceeds the incidence of oral hairy leukoplakia [147,148]. Thus, EBV replication itself is insufficient for the pathogenesis of oral hairy leukoplakia. The presence of oral hairy leukoplakia in otherwise healthy individuals suggests that severe immunodeficiency is not required for the pathogenesis of the lesion. Contrary to early reports, human papillomavirus is not routinely found in oral hairy leukoplakia and plays no apparent role in its pathogenesis.

Oral hairy leukoplakia is a unique form of EBV infection for the frequent presence of multiple co-infecting EBV types, strains, and recombinant variants within the lesion [149–152]. Intrastrain recombination results in juxtaposition, duplication, or deletion of specific gene sequences. Interstrain recombination between two or more strains coinfecting within the same cell may create new hybrid EBV genotypes. Genetic variation may contribute to EBV pathogenesis if critical viral protein functions are altered or if specific viral epitopes are mutated to permit evasion of cytotoxic T-lymphocyte immune surveillance. Oral hairy leukoplakia is also characterized by the expression of EBV gene products involved in the regulation of cell growth and apoptosis, including BHRF1, EBNA-2 and LMP-1 [151,153,154]. Thus, a convergence of factors may be necessary for the pathogenesis of oral hairy leukoplakia. These factors include EBV coinfection, replication, recombination, and expression of specific EBV gene products in tongue epithelium in the setting of an ineffective cytotoxic T-lymphocyte immune response to EBV.

Clinical Manifestations

The gross appearance of the oral hairy leukoplakia lesion may be variable (Table 6.14), and the lesion may easily be misdiagnosed (Table 6.15) [155]. Although oral hairy leukoplakia most often presents on the lateral borders of the tongue, it may spread to the ventral surface of the tongue where it can become flat and lack the characteristic "hairy" appearance (Figs. 6.16–6.18). Rarely, the lesion may occur on the dorsal surface of the tongue (Fig. 6.19) or the buccal mucosa (Fig. 6.20) [156]. Oral hairy leukoplakia often presents with bilateral involvement of the tongue, although the size of the corresponding plaques is not usually equal. The lesions are adherent and only the superficial layers can be scraped and removed from the mucosal surface. There is no associated erythema or edema of the surrounding tissue. Oral hairy leukoplakia does not appear to be a premalignant lesion, but some patients are disturbed by the cosmetic appearance of this condition.

Laboratory Findings

There are no laboratory findings specific or even characteristic of oral hairy leukoplakia. EBV serologies are usually indicative of past persistent infection and do not differ from those of individuals without oral hairy leukoplakia [157]. Oral hairy leukoplakia associated with primary EBV infection has not been described.

Table 6.14 Clinical Manifestations of Oral Hairy Leukoplakia

Time course of disease	Clinical manifestations	Laboratory analyses	Other notes
"Incubation" period unknown	Superficial white, raised plaque with corrugated or "hairy" appearance presents on the oral mucosa, most commonly on the lateral borders of the tongue	EBV-specific serologies and cultures are not helpful	The lesions are typically asymptomatic, but some patients describe mild pain, discomfort, or alteration in taste
	↓		
Weeks to months	Self-limited course, with resolution within weeks in immunocompetent persons and within months in immunocompromised persons	Definitive diagnosis, if needed, by combination of histological examination and demonstration of EBV DNA or EBV gene products in epithelial cells	
	↓		
Weeks to months	Lesions may sometimes recur and remit repeatedly in immunocompromised persons		The natural history of oral hairy leukoplakia is variable in immunocompromised persons

Dermatopathology

Histologically, oral hairy leukoplakia demonstrates a hyperplastic and irregular tongue epithelium resulting from parakeratosis and hyperkeratosis of the upper epithelial layers (Fig. 6.21) [158]. The hyperkeratosis is largely responsible for the characteristic gross appearance of the lesion. Superficial infections of the hyperkeratinized epithelium with bacteria or fungal hyphae may also be seen (Fig. 6.22). The prickle cell layer in the midzone of the epithelium demonstrates acanthosis with foci or layers of cells resembling koilocytes (Fig. 6.23). These ballooning cells have a homogenous "ground-glass" appearance to the nuclei. Some authors have reported the presence of Cowdry type A intranuclear inclusions in these cells, but this is not a consistent or even common finding. The basal layer of the epithelium is histologically normal. Characteristically, there is a minimum or complete absence of inflammatory infiltrate associated with oral hairy leukoplakia. In HIV-infected patients, Langerhans cells are reported to be absent from oral hairy leukoplakia, but the pathogenic implications of this finding are not clear [159].

Diagnosis

Although the major histopathological features of oral hairy leukoplakia are highly suggestive of the diagnosis, none is unique to the lesion. Depending on the plane of tissue sectioning, hyperplasia, parakeratosis, and acanthosis appear in autopsy specimens of grossly normal tongues [160]. In both immunocompromised and immunocompetent patients, pseudo-hairy leukoplakia lesions may have the gross appearance and the histological features of oral hairy leukoplakia without the presence of EBV [161–163]. Therefore, the definitive diagnosis of oral hairy leukoplakia requires both an appropriate histopathological appearance and the demonstration of EBV DNA or EBV gene products within the epithelial cells of the lesion. EBV may be demonstrated using the detection techniques described in the section on EBV-associated lymphoproliferative disorders and malignancies. In oral hairy leukoplakia, EBV is detected within ballooned and nonballooned cells of the prickle cell layer, as well as the keratinized cells of the superficial epithelium (Fig. 6.24). EBV has not been convincingly demonstrated within the basal epithelial layer. In an HIV-infected

Table 6.15 Differential Diagnoses of Oral hairy Leukoplakia

Oral candidiasis: Oral hairy leukoplakia is most often confused with candida (thrush) in HIV-infected patients. Candida typically occurs as a plaque-like lesion that is easily removed by scraping with a blunt instrument, revealing an erythematous base. Resolution of lesions after topical antifungal therapy also suggests candidiasis, whereas failure of the lesions to resolve suggests hairy leukoplakia. However, these clinical maneuvers are unreliable, and oral hairy leukoplakia lesions are commonly superinfected with candida.

Frictional keratosis: When located on the lateral borders of the tongue, this lesion may mimic oral hairy leukoplakia. There may be an obvious source of irritation, and the lesion typically resolves after removal of the provoking stimulus.

Tobacco-induced leukoplakias: Frequently seen in smokers and in individuals who chew smokeless tobacco. These lesions are often premalignant and should be carefully evaluated.

Lichen planus or lichenoid reactions: This condition of the oral mucosa may resemble oral hairy leukoplakia, but most commonly has a reticulated pattern and may be associated with the characteristic cutaneous lesions.

Syphilis: Oral manifestations of secondary syphilis usually present as atrophic patches on the tongue but elevated variations mimicking oral hairy leukoplakia have been described. Syphilis serology can be used to distinguish those entities.



Figure 6.16 Oral hairy leukoplakia on the lateral border of the tongue demonstrating a discontinuous, patchy distribution of the lesion. (Courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)

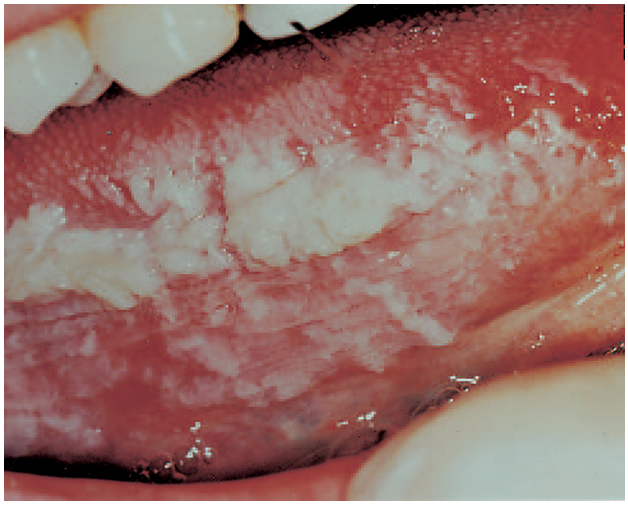


Figure 6.17 Oral hairy leukoplakia on the lateral border and ventral surface of the tongue demonstrating marked hyperkeratinization on the lateral border and a flatter, less keratinized appearance on the ventral surface.(Courtesy of Catherine M.Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)

patient with typical-appearing oral hairy leukoplakia, cytological examination of exfoliated cells from the lesion may support the diagnosis of oral hairy leukoplakia, and the demonstration of EBV in these cells is sufficient to make the diagnosis without a biopsy [164].

Treatment

Several therapeutic options exist for oral hairy leukoplakia, but treatment is usually not necessary. Some patients with oral hairy leukoplakia describe mild pain, discomfort, paresthesias, or alteration in the sensation of taste, but many patients are unaware of the presence of their lesions. Although it has not been well studied, treatment of the lesion usually brings resolution of the symptoms as well. Treatment of oral hairy leukoplakia for cosmetic indications must be decided between the patient and the health care provider on an individual basis. The variable natural history of the lesion and its tendency toward spontaneous resolution should be considered in that decision (Table 6.16).

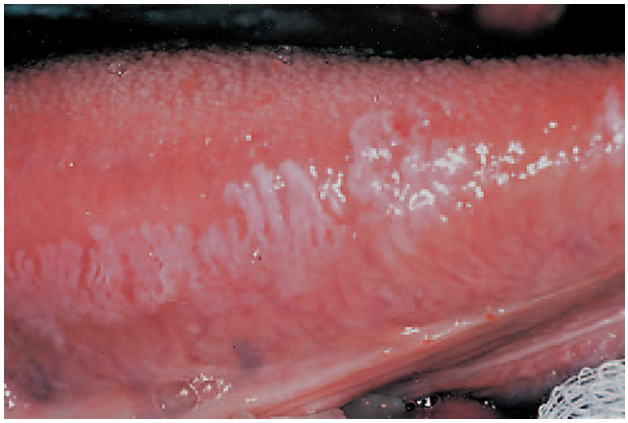


Figure 6.18 Oral hairy leukoplakia on the ventral surface of the tongue demonstrating a finer, more subtle appearance of the lesion. (Courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)



(a)



(b)

Figure 6.19 (a,b) Oral hairy leukoplakia involving the dorsal surface of the tongue with marked hyperkeratinization.(a, courtesy of Karen Wiss, M.D., Department of Dermatology, University of Massachusetts School of Medicine, Worcester, MA; b, courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)

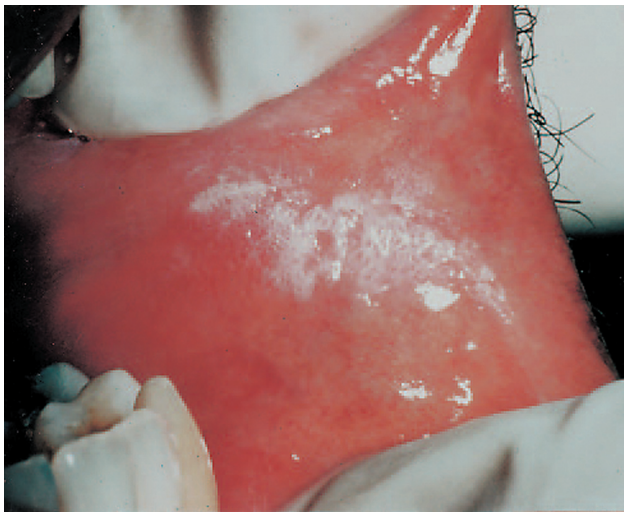


Figure 6.20 Oral hairy leukoplakia involving the buccal mucosa. (Courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)

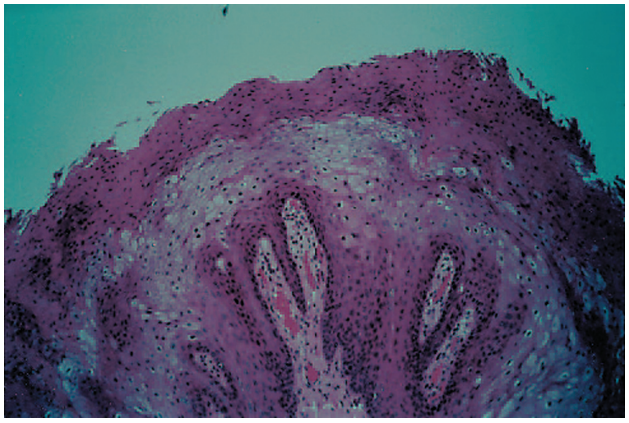


Figure 6.21 Oral hairy leukoplakia biopsy from tongue demonstrating epithelial hyperplasia with hyperkeratosis and parakeratosis of the superficial layer of the epithelium.Hematoxylin and eosin stain at 20× magnification.(Courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)

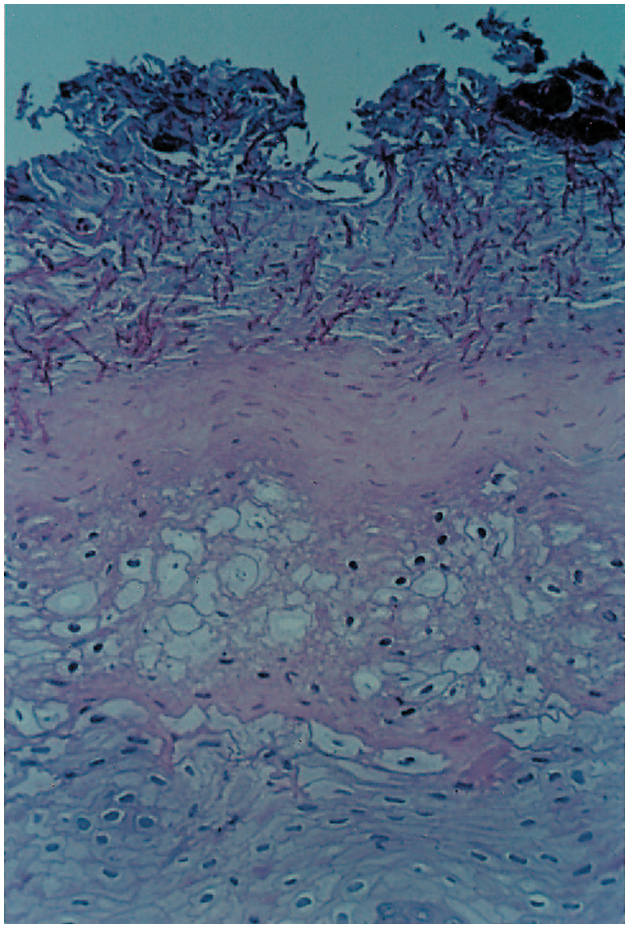


Figure 6.22 Oral hairy leukoplakia biopsy from tongue demonstrating fungal superinfection of the lesion.Magenta-staining fungal hyphae are abundant within the superficial, hyperkeratinized epithelium of the lesion. The epithelial midzone of the lesion demonstrates acanthosis. Periodic acid–Schiff stain at 40× magnification. (Courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)

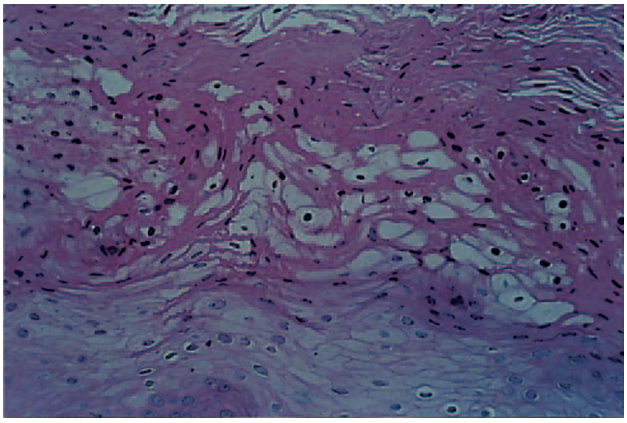


Figure 6.23 Oral hairy leukoplakia biopsy from tongue demonstrating marked acanthosis of the prickle-cell layer. The epithelial midzone contains palisades of ballooning cells with perinuclear cytoplasmic clearing and a homogeneous "ground-glass" appearance of the nuclei. Hematoxylin and eosin stain at 80× magnification. (Courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, TX.)

Systemic antiviral therapy with oral or parenteral agents active against EBV usually results in resolution of the lesion after 1–2 weeks of therapy. The response of oral hairy leukoplakia to acyclovir is well documented [133], but oral therapy with acyclovir requires high doses (800 mg five times/day) to achieve therapeutic levels. Valacyclovir (an acyclovir prodrug) and famciclovir are newer antiviral drugs with higher oral bioavailability than acyclovir and can be dosed less often. In many HIV-infected patients receiving parenteral ganciclovir, foscarnet, or cidofovir for CMV disease, oral hairy leukoplakia will resolve as well. All of these antiviral drugs inhibit EBV productive replication, but do not eliminate the latent state of infection. Therefore, in immunocompromised patients, oral hairy leukoplakia often recurs after the cessation of antiviral therapy [133].

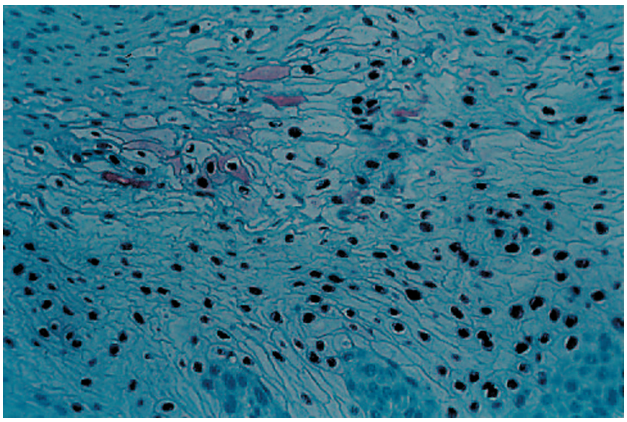


Figure 6.24 Oral hairy leukoplakia biopsy from tongue demonstrating the presence of EBV within the lesion using an immunohistochemical stain for the EBV early gene product EA-D. Hematoxylin counterstain at 80× magnification.(Courtesy of Catherine M. Flaitz, D.D.S., M.S., University of Texas–Houston Dental Branch, Houston, Texas.)

Table 6.16 Treatment of Oral Hairy Leukoplakia

Symptoms	Treatment
Pain	**Topical therapy**
Paresthesias	Podophyllin resin 25% solution: applied to lesion for 5 min.
Altered taste	Treatment may need to be repeated once, and the lesions typically recur after treatment.
Unsightly appearance	Topical retinoids (reported by some authors)
	Cryotherapy with liquid nitrogen (reported by some authors)
	Systemic therapy
	Antiviral therapy with oral acyclovir, valacyclovir, or famciclovir. The lesion usually resolves in 1–2 wk. (Intravenous ganciclovir, foscarnet, or cidofovir given for CMV infection has led to resolution of oral hairy leukoplakia.)
	Surgical therapy
	Complete excision is rarely performed, but has been reported by some authors

Topical therapy for oral hairy leukoplakia with podophyllin resin 25% solution is effective in achieving partial or total resolution in most patients after only one or two treatment applications [165]. The treatments may temporarily cause local pain, discomfort, and alteration of taste. In one study, 17% of patients treated had recurrence of oral hairy leukoplakia with a mean interval to recurrence of 17 weeks [166]. Cases have also been reported of lesions resolving following topical application of retinoids [167] or following liquid nitrogen cryotherapy [168]. Surgical excision of oral hairy leukoplakia eliminates the lesion and resolves the associated pain [169]. Interestingly, the lesion does not recur at the excision site, but may reappear at adjacent sites on the lateral tongue. Therapeutic surgical excision is more invasive than other treatments, but provides the opportunity to also make a histopathological diagnosis of oral hairy leukoplakia.

Conclusion

EBV is a ubiquitous HHV that is responsible for a significant amount of morbidity and mortality worldwide. The biology and pathogenesis of EBV infections are complex and not completely understood. Antiviral drugs inhibit EBV productive replication, but many EBV-associated diseases result from EBV latency and the expression of EBV genes with the ability to transform cells. Important clinical manifestations of EBV infection include the infectious mononucleosis syndrome, lymphoproliferative disorders, oral hairy leukoplakia, and a variety of malignancies. The cutaneous manifestations of EBV infection may arise through various immunological mechanisms or from direct EBV involvement of mucocutaneous and subcutaneous tissues. Cutaneous manifestations of EBV infection are common, especially in certain patient populations.

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7 Cytomegalovirus

Istvan Boldogh, Janak A Patel, Stephen K Tyring, and Tasnee Chonmaitree

Cytomegalovirus (CMV), otherwise known as human herpesvirus 5, belongs to the subfamily of Betaherpesvirinae that is characterized by a narrow host range and a long replicative cycle. Human CMV is a ubiquitous virus that, for the most part, causes asymptomatic infection. This human pathogen silently infects an overwhelming majority of humans (60–100%). However, clinical disease in certain groups, such as neonates and immunocompromised individuals, can lead to significant morbidity and mortality. The range of clinical manifestations in these populations is broad and may impact nearly every medical subspecialty. As is characteristic of all herpesviruses, CMV persists in the host following primary infection and remains latent in infected individuals for life (Fig. 7.1).

History

In 1881, Ribbert first histologically observed "protozoanlike cells" in the organs of a stillborn with presumed congenital syphilis [1]. In 1921, Goodpasture and Talbot suggested that the enlarged cells, or "cytomegalia," could be due to injury by a viral agent [2]. This disease became known as "cytomegalic inclusion disease" before a viral etiology was ever discovered, based on the characteristic large cells and intranuclear inclusions [3]. In 1956, Rowe et al. [4], Smith [5,6], and Weller et al. [7] each independently isolated human CMV strains in tissue culture. The virus was initially known as "salivary gland virus" or "salivary inclusion disease virus." In 1960, Weller and colleagues proposed the term "cytomegalovirus" [8].

Virion Structure and Organization of the Viral Genome

The overall structure of the CMV particle is similar to that of other herpesviruses. The outermost layer is the lipid bilayer envelope that contains cellular and virally encoded glycoproteins. At the core of the particle is the viral DNA that is surrounded by an icosahedral capsid. Between the capsid and the envelope is an amorphous layer referred to as the tegument [9]. The CMV virion tegument also contains many proteins, including DNA polymerase, protein kinase and a cellular topoisomerase II enzyme, serine/threonine protein phosphatase PP1, and the host cell-derived phosphatase PP2A [10,11]. An Fc receptor for human immunoglobulin G and viral gene products UL82, UL69, and UL83 is located within the tegument [12]. These proteins are released into the cytoplasm after viral infection and are required for viral replication [13].

Recent studies showed that the CMV virion contains not only DNA, but also four species of mRNA, indicating that this virus is more complex than previously believed [13,14]. The genome of CMV is extremely large and is more complex than that of any other DNA virus. This genome can be divided into two segments, referred to as long (L) and short (S) components, which are flanked by terminal repetitive sequences (Fig. 7.2). The junction between the L and S component is composed of internal repeat (IR) sequences (designated TRL, 11 kb and IRS, 2 kb), which are flanked by terminal repetitive sequences (designated TR_L and TR_S) (see Fig. 7.2). The sequences between the repeat regions are unique (U) and are referred to as unique long (UL, 175 kb) and unique short (US, 38 kb) regions [15].

The various clinical isolates of CMV may differ in both size and number of terminal additions. The junction between the UL and L repeat is a major site of inter-strain sequence variation. Oligonucleotide probes designed for this region can be used to differentiate one strain of CMV from another. The restriction endonuclease profiles of the DNA in various strains of CMV have many similarities, but no two profiles are identical. Because of genomic variation, CMV may gain the ability to avoid neutralization; thus, some individuals may become reinfected with an epidemiologically (genotypically) unrelated isolate [16] that is resistant to one or more antiviral drugs [17]. However, the genomic polymorphism has not yet been linked to pathological differences among the CMV strains.

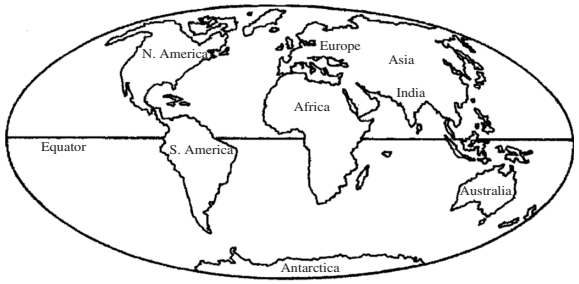
Incidence

CMV infection is endemic in all parts of the world, and the prevalence of CMV-infected individuals is related to the socioeconomic status of the population. For instance, 60–70% of the population is seropositive for CMV in Central and Western Europe and the USA compared with 80–100% of the African population. The acquisition of CMV in developing countries also occurs at a younger age than in industrialized countries. This earlier and increased seroprevalence in lower socioeconomic environments has been attributed to crowded and communal living conditions, poor hygienic standards, and greater numbers of people (extended family) caring for an infant [18,19]. In the USA, age-related CMV prevalence studies have demonstrated that there is an increased risk of acquisition during early childhood, adolescence, and the reproductive years [20–22].

Pathogenesis

CMV is transmitted primarily by intimate person-to-person contact. Potential sources of infectious virus include oral secretions, urine, breast milk, semen, cervical and vaginal secretions, blood, and transplanted organs. Indirect transmission via contaminated fomites, such as toys, is also possible. CMV infection can occur as primary infection in those with no prior exposure to the virus or as a recurrent infection in those with previous exposure. In those with immunosuppression, reactivation of latent virus may also occur. Following primary or recurrent CMV infection in a pregnant woman, the virus may be transmitted to the fetus in utero in 40–50% of primary cases, but in less than 1% of recurrent cases [23]. The rate of congenital CMV infection ranges from 0.2 to 2.5% of newborns [24,25], although most cases are asymptomatic. Pregnant women with primary infection frequently excrete CMV in cervical and vaginal secretions during the last trimester of pregnancy, which significantly increases the risk of perinatal

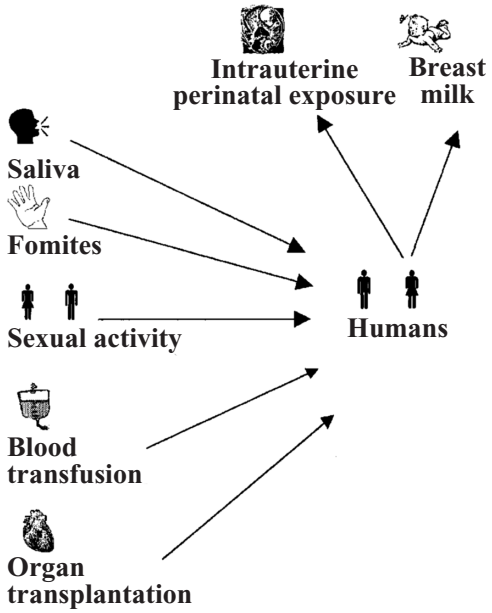
WORLDWIDE GEOGRAPHICAL INCIDENCE



TAXONOMY

Herpesviridae family
Betaherpesvirinae subfamily
(Human herpes virus 5)

TRANSMISSION



ZOONOTIC IMPLICATIONS

None
No known animal reservoirs for human cytomegalovirus

Figure 7.1 Incidence and transmission of cytomegalovirus.

transmission during delivery [15]. Infected mothers who breast-feed may also transmit the virus to their offspring.

CMV infection during early childhood often occurs as a result of horizontal spread among children, usually through exposure to infected saliva or urine. The incidence of CMV seropositivity in day-care centers is high, particularly among children aged 1–3 years [26,27]. Beyond childhood, CMV is most frequently acquired through intimate physical contact and sexual transmission. The risk of CMV infection after transfusion of one unit of blood is approximately 3–4% [28,29]. Since CMV is transported in the bloodstream via leukocytes, leukocyte-depleted or cryopreserved blood carries less risk of transmission. CMV is not transmitted through fresh frozen plasma transfusions.

The incubation period for CMV is not exactly known, but is estimated to be 4–8 weeks from study of cases acquired through perinatal transmission and blood transfusions [18,30]. Upon entering the human host, CMV disseminates throughout the body via the bloodstream and utilizes the blood leukocytes as transport media. CMV is rarely found free in plasma, but can be isolated from the cellular fraction, particularly the polymorphonuclear cells. During the acute phase of CMV invasion, viral DNA and proteins can be demonstrated in both polymorphonuclear cells and monocytes. Although most infections with CMV remain latent and asymptomatic, the virus can also cause productive and symptomatic infection through cell lysis. During viremia, the virus may spread and infect various organs. The target organs involved with lytic infection vary with the age and immune status of the host. CMV infection in the fetus or neonate typically involves the salivary glands (submandibular, sublingual) and neurons, among other organs [6]. Infection in otherwise healthy individuals most commonly affects the lymphoid tissues [31], whereas the lungs and other organs are frequently involved in immunocompromised persons [32].

CMV is a cytotoxic virus that alters the metabolic biochemical cascade of cells, resulting in cell enlargement (cytomegaly) and condensation of nuclear mass (nuclear inclusion). Consequently, CMV can produce cell injury and tissue destruction during productive, symptomatic infection [33]. In organ disease, an inflammatory response ensues. Numbers of lymphocytes and plasma cells in the infected tissue may vary in degree and distribution. This inflammatory response, along with alteration of cellular biochemical cascade events and/or cytotoxic effects of CMV replication, contributes to organ dysfunction [34].

Viremic spread of CMV often results in renal involvement and excretion of infectious CMV particles in urine (viruria). In immunocompetent individuals, CMV exposure of the kidneys is seldom associated with renal dysfunction. In immunocompromised patients (e.g., renal transplant recipients), hypertrophy and necrosis of endothelial cells may produce an accumulation of fibrillar material in the glomerular capillaries. Cytomegalic cells with nuclear inclusions are seen in the convoluted proximal tubules and occasionally in the glomeruli. CMV-specific macromolecules (DNA, RNA, IE, E and L proteins) can be detected by in situ nucleic acid hybridization or by immunochemistry in the inflammatory mononuclear cells of the interstitial spaces of kidney biopsies. During glomerulopathy, there are deposits of immune complexes (IgG, IgM) on the basal membranes of glomeruli and mesangial areas, which may result in immune complex-associated diseases [34,35].

As stated previously, the lungs are frequently affected by CMV infection in immunosuppressed individuals, particularly after bone marrow transplantation. In the lungs, enlarged cells with late nuclear inclusion bodies and associated mononuclear cell inflammation are found primarily in the alveolar and bronchial epithelia [36]. These findings are rarely seen in the mucous membranes of the tracheobronchial region.

Histological studies of cutaneous ulcerations have often documented nuclear inclusions in capillary endothelial cells during CMV infection. When kidney, gastrointestinal tract, lung, and brain ulcerations are examined, endothelial cells also show

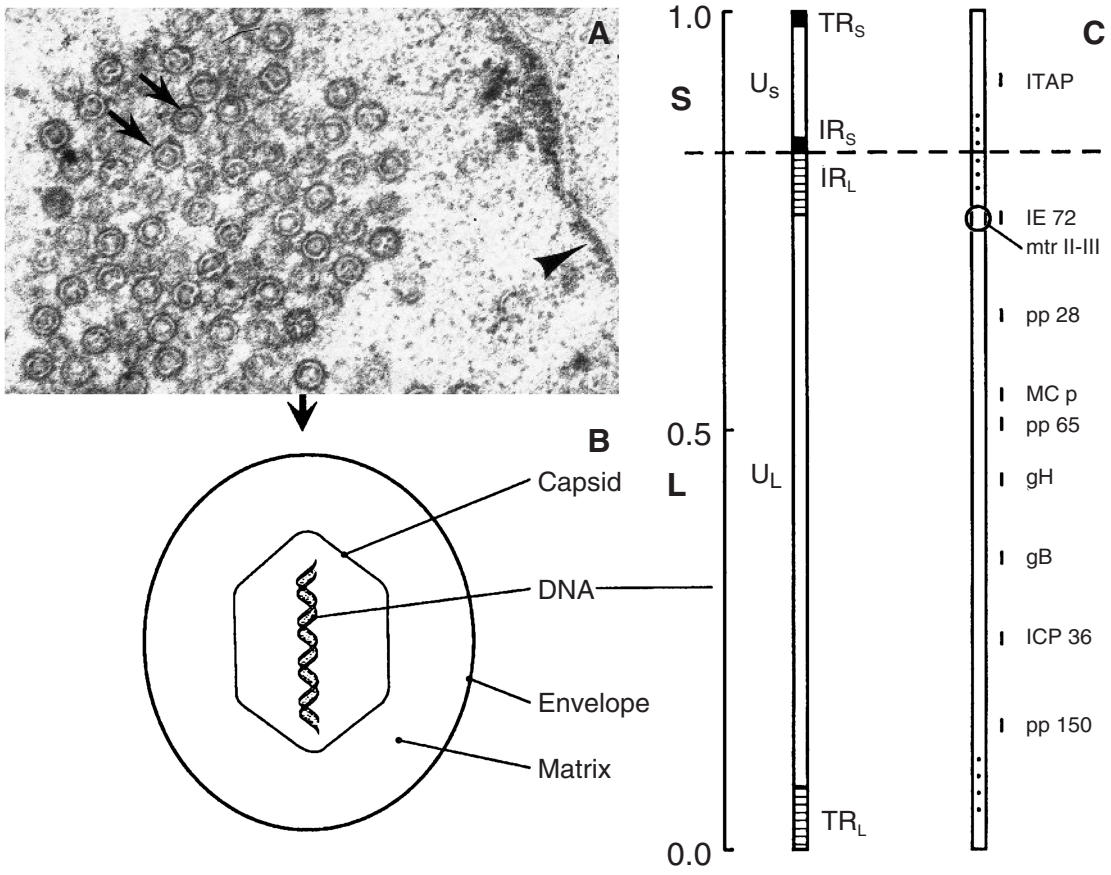


Figure 7.2 Electron micrographic and schematic demonstration of the CMV particle and structural arrangement of the CMV genome. (A) Section of a CMV-infected cell containing CMV particles (arrows) and nuclear membrane (arrowhead) (×23,000); (B) main components of CMV virion; (C) physical organization of CMV DNA. U, unique region; TR, terminal repeats; IR, internal repeats; S, L, short and long region, respectively. Positions of open reading frames in the CMV genome encoding for proteins that are most important in human infections. ITAP, inhibitors or transporter-associated antigen processing; IE 72, regulatory phosphoprotein; pp28, pp65, pp150, structural components; MCp, major capsid protein; gH and gB, glycoprotein components of the envelope; ICP36, DNA-binding protein. Mtr (morphological transforming region) II–III found in various human malignancies. Dotted region of the DNA found to be most variable among CMV isolates.

cytomegaly and contain nuclear inclusions. Infectious CMV and CMV-specific macromolecules have been detected in the walls of blood vessels of patients afflicted with atherosclerosis [37].

Gastrointestinal involvement of CMV is commonly reported in human immunodeficiency virus (HIV)-infected individuals, infected neonates, and other immunosuppressed persons. An important complication is gastrointestinal hemorrhage, with occasional perforation and development of pneumatosis intestinalis. The colon, particularly the cecum, is the usual site of these lesions. However, the esophagus, stomach, pancreas, and proximal small bowel may also be affected. The induced lesions may vary from punctate superficial ulcerations to deep ulcerations. In untreated cases, perforation of the gut may occur. CMV-associated gastrointestinal lesions can appear in the absence of other manifestations of CMV disease.

Abnormal liver function is a common finding in CMV infection, with mild to moderately severe hepatitis occurring in 30–50% of organ transplant patients. By using in situ cytohybridization or immunofluorescent staining, the presence of CMV can be demonstrated in liver biopsies of these patients. Biopsy studies of immunocompetent individuals with CMV mononucleosis syndrome have also demonstrated histological abnormalities, such as increased hepatocellular mitotic activity, mild hepatocellular necrosis, granuloma formation, and bile duct epithelial damage. In addition, mononuclear portal/sinusoidal infiltrates can be seen in the absence of typical cytomegalic cells (Fig. 7.3). In the livers of infected newborns, cytomegalic cells are commonly seen in the bile duct epithelium, less frequently in capillary endothelium, and rarely in the parenchymal cells. In adults, however, hepatocytes may contain nuclear inclusions [38].

CMV infections often disseminate in neonates with congenital infection as well as in burned and immunocompromised adults. The physical findings include granulated tissues, localized ulcers, vesiculobullous lesions, hyperpigmentation, and induration. Despite the clinical variability, the histopathologic appearance of CMV skin lesions is similar – dilated dermal vessels with irregularly shaped periendothelial and endothelial cells containing large hyperchromatic, basophilic intranuclear inclusions [39,40].

Congenital CMV infection often adversely affects the central nervous system of the fetus and causes microcephaly, periventricular calcification, hydrocephaly, chorioretinitis, and optic atrophy [41,42]. Glial and neural cells may be productively and abortively infected. Pathologic manifestations may include microglial nodules, focal parenchymal necrosis, necrotizing ventriculitis, hemorrhages, astrocytic proliferation, perivascular inflammation, and ependymal granulation. Sensorineural hearing loss is a common feature of both clinical and subclinical congenital CMV infections. In the inner ear, enlarged cells with nuclear inclusions

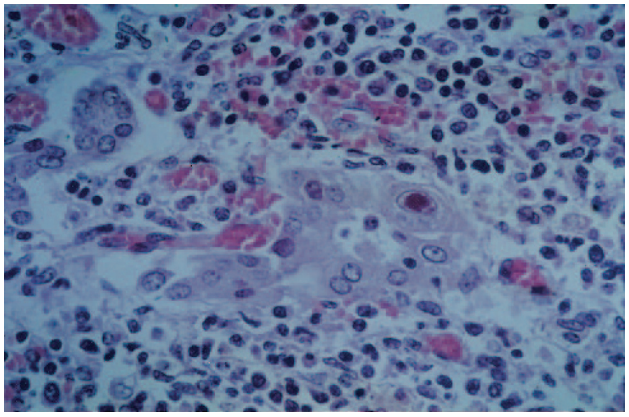


Figure 7.3 Cholangiole (bile duct) with CMV cytopathic effect in one cell and prominent portal infiltration with lymphocytes, plasma cells, macrophages, and eosinophils. (H & E stain.) (Photograph courtesy of Jerome H. Smith, M.D., Department of Pathology, University of Texas Medical Branch at Galveston, Galveston, TX.)

are often detected in epithelial cells of the cochlea, stria vascularis, limbus spiralis, Reissner's membrane, saccule, and utricle. Congenital CMV infections with diffuse inflammation, villitis, plasma cell infiltration, focal necrosis, and hemorrhage, with or without detectable cytomegalic cells in the placenta, have also been observed [42].

CMV may be immunosuppressive; primary CMV infection produces a decrease in the ratio of helper to suppressor lymphocytes. The decrease in this ratio is caused by an increase in the circulating suppressor cells. Immunocompetent adults with CMV mononucleosis also have impaired immunoproliferative responses of lymphocytes to mitogens [43]. CMV infection may lead to other transient immunological aberrations, such as the presence of immune complexes, cold agglutinins, rheumatoid factor, a positive Coombs' test result, or monoclonal gammopathies [44–46].

Similar to oncogenic viruses, CMV has been demonstrated to promote host DNA and RNA synthesis in infected cells. Both CMV particles (live or inactivated) and viral DNA (e.g., morphological transforming regions mtrI, mtrII, and mtrIII; see Fig. 7.2) can transform animal and human cells in culture and these cells are tumorigenic in animal models [47,48]. In addition, CMV or its macromolecules have been found in various human tumors, including prostatic carcinoma, adenocarcinoma of the colon, cervical carcinoma, and Kaposi's sarcoma [48]. The significance of these associations and the etiological role of CMV in malignancy are yet to be determined [49,50].

Cellular Pathology and Immune Avoidance in Cytomegalovirus Infections

A large number of cell types have receptors for CMV, but only a few permit productive virus replication. After entry into the cells, the CMV genome may either remain in a quiescent (latent) state or progress to a productive state. In productive infection, there is a temporally regulated sequential expression of the viral genome. The synthesized viral proteins can be classified into three broad categories: (1) immediate early (IE, alpha) proteins specified by viral mRNA whose synthesis does not require prior viral protein synthesis; (2) early (E, beta) proteins translated from mRNAs transcribed prior to the onset of viral DNA synthesis; and (3) late (L, gamma) proteins directed by mRNAs transcribed predominantly after synthesis of viral DNA. CMV infection results in changes in cell shape and size (Fig. 7.4) and a high production of progeny in fibroblast cells of human origin. CMV replication is a slow process, and more cell-associated virus than extracellular virus is produced. The ratio of infectious to defective particles is usually in the range of 1:500 to 1:5000. Cultured epithelial cell types, endothelial cells, or cells of lymphoid origin permit low CMV levels of replication only when treated with chemical agent, such as phorbol-12-myristate-13-acetate, 5-azacytosine, iododeoxyuridine, or interleukin-2 (IL-2). In various organs, however, CMV replicates productively in a broad range of cells (mainly epithelial) and the virus can be isolated from saliva, urine, tears, semen, vaginal secretions, milk, and other specimens [51].

The restricted expression of one or more of the gene classes results in an abortive infection [52]. Restricted virus gene expression appears to be associated with the development and maintenance of persistent or latent infection in vivo. For example, evidence suggests that cultured T and B lymphocytes are semipermissive for CMV, and gene expression is limited to the IE proteins. In contrast, monocytes of peripheral blood permit IE, E, and L gene expression and production of infectious virus at a low level. The restriction of CMV replication in monocytes and lymphocytes may be eliminated by immunosuppression (e.g., HIV infection), which allows productive infection of these cells [53].

As noted above, CMV persists in the host for life following primary infection and remains latently associated with infected individuals [53]. The precise sites and mechanism of CMV latency remain unknown, although latent virus appears to have a broad tissue distribution as indicated by the transmission of CMV following organ transplantation. Salivary glands, blood cells, spleen, uterus, and kidneys are often observed to harbor CMV. To date, very little is known about the molecular events directed by the virus and/or cell that control persistence and/or latency. CMV has mechanisms whereby the infected cells or the released CMV can protect itself from immune surveillance and can produce a productive infection in the presence of functional humoral and cellular immunity [54]. Spread of virus within tissues occurs mainly via the intercellular transmission of CMV particles from one cell into adjacent cells. This avoidance of the extracellular milieu may be one of the important mechanisms of the virus for escaping neutralization by antibody. Virus shedding in many body fluids, such as saliva, urine, cervical secretions, and breast milk, may persist for months, which suggests that anti-CMV antibodies neutralize CMV in plasma, but not in other body fluids.

An important mechanism by which CMV avoids host defenses is by the induction of receptors for the Fc portion of IgG antibody in the cytoplasmic membrane of infected cells (Fig. 7.5). These molecules could provide a protective coat for the infected cells, preventing lysis by specific cytolytic antibody or lysis by cytotoxic T cells. The Fc receptors on the CMV-infected cells may bind antibody-coated bacteria or immune complexes and may cause secondary inflammation in a CMV-infected organ [55].

Beta-2 microglobulin (β_2-microglobulin; light chain of class I HLA molecules) has a high binding affinity to CMV and provides another unique mechanism that may be important in avoiding neutralization by blocking the attachment of antibody to extracellular

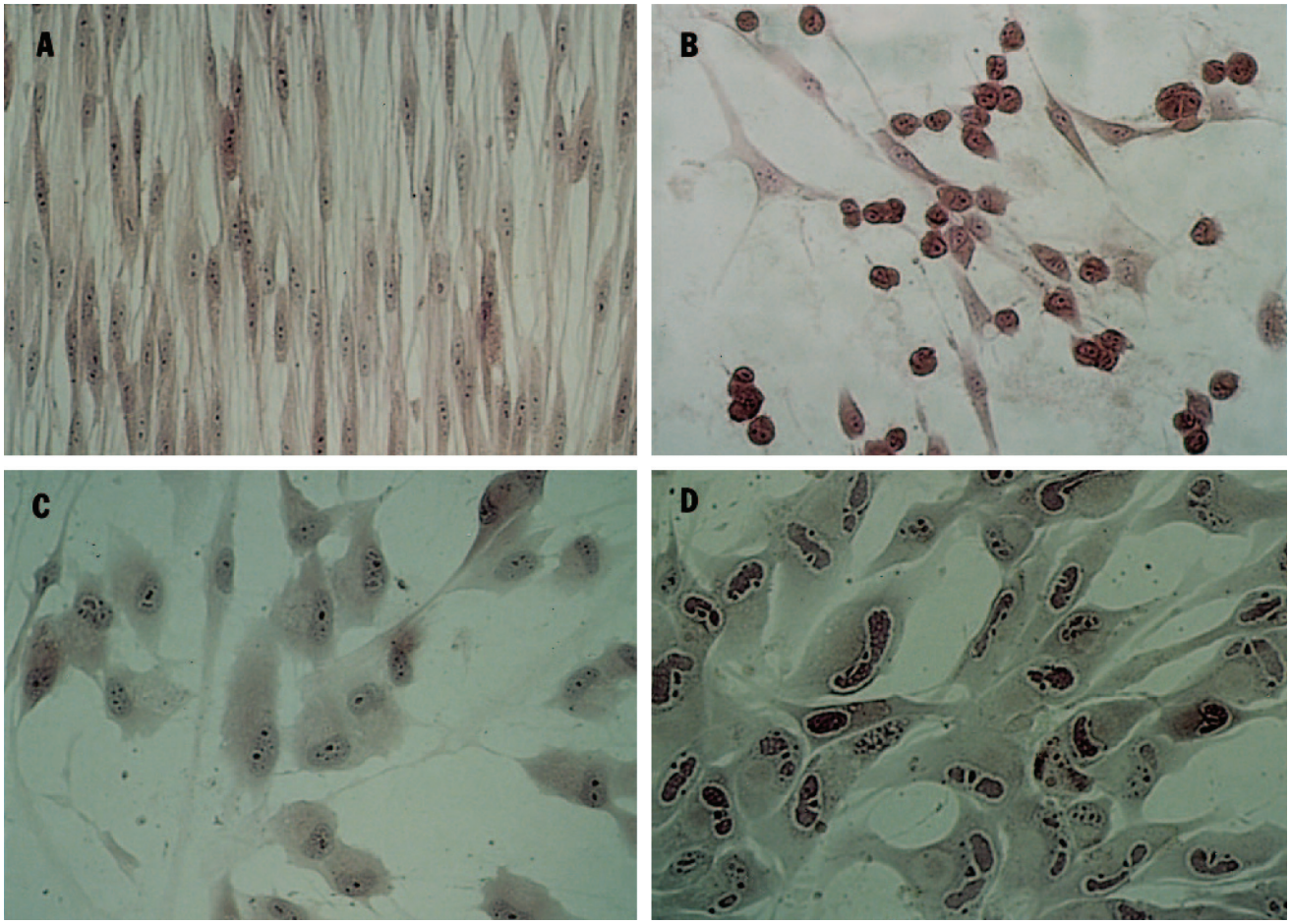


Figure 7.4 Morphological changes of CMV-infected permissive cells in vitro. (A) Non-infected human embryonic lung cells. Cell cultures in panels (B–D) are infected with a multiplicity of infection (MOI) of 5 plaque-forming units (PFU) per cell. (B) Cells are rounded and smaller in size at about 6 hours. (C) Cells demonstrate early nuclear inclusions between 24 and 36 hours. (D) Nuclei of enlarged (cytomegaly) cells show late type A nuclear inclusions from 72 hours on, after infection.

virions. On the other hand, β_2-microglobulin may mask CMV proteins, preventing efficient neutralization antibody production. Since β_2-microglobulin-free virus suspension demonstrates decreased infectivity in comparison to virus with β_2-microglobulin bound to its surface [56], β_2-microglobulin may also be a component in the process of binding of CMV to the cell membrane.

Clinical Manifestations

Infection in Normal Children and Adults

The most commonly acquired CMV disease in immunocompetent individuals is CMV-induced mononucleosis. CMV causes fewer than 10% of all cases of mononucleosis [57] and is clinically indistinguishable from Epstein-Barr virus (EBV)-induced mononucleosis (Tables 7.1–7.3). In addition to the characteristic fever and malaise with this illness, atypical lymphocytosis (Fig. 7.6) and mild elevation of liver enzymes usually occur [58,59]. A small percentage of patients develop a rubelliform or maculopapular cutaneous eruption. However, when ampicillin is administered during this illness, 80–100% of cases develop a maculopapular, morbilliform rash within a week or so (Fig. 7.7).

The disease course of CMV-induced mononucleosis is typically self-limited and benign, with only occasional complications. These may include interstitial pneumonia, hemolytic anemia, splenic infarction, thrombocytopenia, hepatitis, Guillain-Barré syndrome, meningoencephalitis, myocarditis, arthritis, pleuritis, and gastrointestinal and genitourinary syndromes. A mononucleosis syndrome caused by CMV has also been observed in immunocompetent individuals after blood transfusion. The symptoms of this postperfusion syndrome are similar to those described above and manifest several weeks to several months after the contaminated transfusion.

Congenital Infections

Congenital CMV infection occurs in approximately 1% of all newborn infants in the USA as a result of transplacental transmission of CMV. Most of the infected newborns are asymptomatic at birth. However, 5–17% demonstrate unilateral or bilateral deafness and/or other neurodevelopmental sequelae [60–63].

Symptomatic congenital CMV infection occurs in up to 10% of infected infants (see Table 7.1). The syndrome is characterized by intrauterine growth retardation, hepatosplenomegaly, pneumonitis, jaundice, thrombocytopenia with petechiae, and central nervous system involvement, such as microcephaly, intracerebral calcifications (Fig. 7.8A, B), chorioretinitis, other ocular defects, and sensorineural hearing loss. Other less common manifestations include long bone osteitis, cutaneous vasculitis, hemolytic anemia, ascites, and chronic hepatitis [64]. Symptomatic congenital CMV infection is distinct from other congenitally transmitted

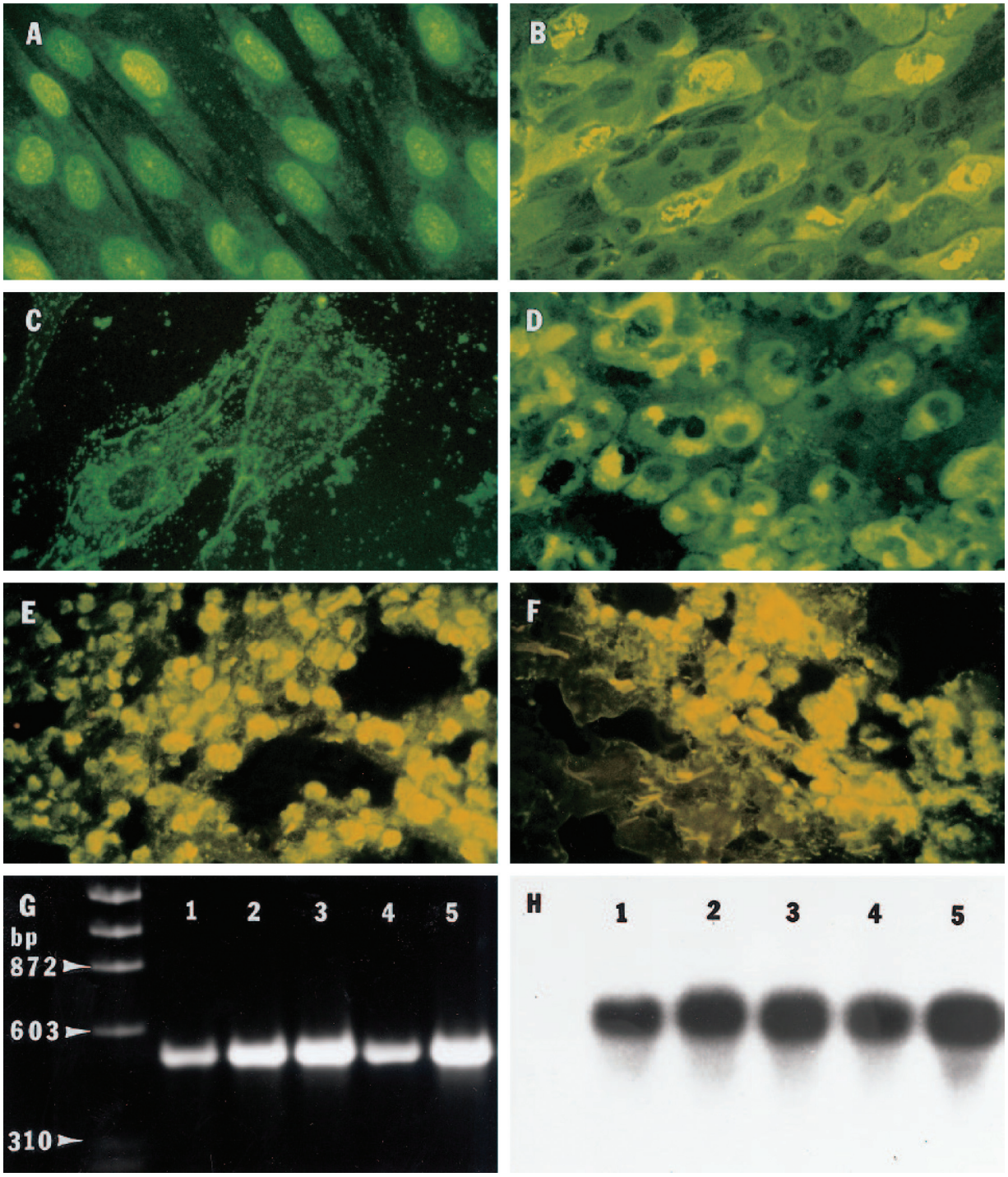


Figure 7.5 Detection of CMV-specific macromolecules at cellular and molecular levels. Immediate early (A) and late antigens (B) demonstrated in CMV-infected cells by indirect immunofluorescent assay. CMV-induced cellular Fc-binding receptors on the (C) membrane and in the (D) cytoplasm of the infected cells. (E, F) CMV-specific proteins in sections of CMV-induced skin lesions by immunohistochemistry. (G) Amplification of a 541 base pair segment of CMV immediate early 2 region of CMV DNA by polymerase chain reaction. (H) Autoradiogram demonstrates hybridization of ^{32}P-labeled oligonucleotide probe to polymerase chain reaction-amplified sequences shown in panel (G) (lanes 1 and 2, skin biopsies from HIV-infected patients; lanes 3 and 4, HIV-associated Kaposi's sarcoma; lane 5, Kaposi's sarcoma unrelated to HIV infection).

infections, such as rubella, herpes simplex, enteroviral infection, congenital toxoplasmosis, and congenital syphilis [65].

Perinatal Infections

Perinatal CMV infection may be acquired from exposure of the newborn to virus in the maternal genital tract at delivery, from breast milk, or through multiple blood transfusions. The disease may manifest between 4 and 16 weeks of age, but most infections are asymptomatic. In a small percentage of infants, there may be signs and symptoms of self-limited lymphadenopathy, hepatosplenomegaly, or pneumonitis. CMV pneumonitis is generally associated with an afebrile course. It is clinically and radiographically

Table 7.1 Diseases and Complications Associated with Cytomegalovirus Infections

Congenital (transplacental), perinatal infection
Symptomatic
Intrauterine growth retardation
Prematurity
Hepatosplenomegaly
Jaundice
Thrombocytopenia with petechiae
Microcephaly with or without cerebral calcification
Chorioretinitis
Asymptomatic disease with neurological impairments
Hearing loss
Disorders of hearing, language, and learning
Mental retardation with or without seizures
Blindness
Paraparesis
Diplegia
Infection in children and adults
Mononucleosis (fever, malaise, splenomegaly, hepatitis, peripheral and atypical lymphocytosis)
Hemolytic anemia, thrombocytopenia
Immunological abnormalities such as production of autoantibodies, cold agglutinins, rheumatoid factor, cryoglobulins
Interstitial pneumonia
Myocarditis
Postperfusion syndrome
Granulomatous hepatitis
Guillain–Barré syndrome
Meningoencephalitis (rare)
Myocarditis
Gastrointestinal syndromes (colitis, esophagitis)
Genitourinary syndromes (cervicitis, urethral syndromes)
Proliferative diseases associated with CMV infection*
Colon carcinoma
Cervical carcinoma
Prostate carcinoma
Kaposi's sarcoma
Atherosclerosis

*A causal relationship has not been definitively established.

indistinguishable from other types of afebrile pneumonia caused by agents such as *Chlamydia trachomatis*, *Pneumocystis carinii*, or respiratory viruses [61,62]. Occasionally, severe protracted pneumonitis occurs in premature infants with bronchopulmonary dysplasia [62].

Infection in the Immunocompromised Host

The population of immunocompromised hosts has increased, largely due to the increase in HIV infection and the use of immunosuppressive chemotherapy for malignancies or solid organ and hematologic transplantation. Thus, the incidence of disseminated CMV infection with significant morbidity and mortality has also increased [66,67].

The typical susceptible individual may have an underlying defect in the cellular (T cell) and humoral (B cell) immune responses. The CMV-infected host may remain asymptomatic, with prolonged viral shedding from mucosal sites, or may experience illnesses characterized by fever and mononucleosis syndrome, as seen in the normal host. However, these patients are at risk for persistent viremia with systemic dissemination to distant organs, where continued viral replication results in tissue injury. The brain, lungs, eyes (Figs. 7.8–7.11), intestines, bone marrow, and blood vessels are the target tissues most frequently involved. The various disease manifestations are listed in Table 7.4.

Synergistic Interactions between Cytomegalovirus and Human Immunodeficiency Virus

CMV is considered to be one of the most important viral infections among HIV-infected patients, as there are high morbidity and mortality rates in this population [68,69]. For example, in the HIV-infected patient, the following may occur: (1) CMV may produce a number of clinical syndromes, including retinitis, pneumonitis, encephalitis, and gastroenteritis; (2) CMV may potentiate cellular immunodeficiency, either directly or in association with enhanced HIV replication; and (3) after primary infection, CMV alone may depress T-lymphocyte helper/suppressor ratios and predispose the patient to opportunistic infections.

The synergistic and cofactorial roles of CMV in AIDS can be assessed by the following in vitro and in vivo observations. Transactivation of the HIV genome by IE proteins of CMV occurs through enhancer-promoter sequences located within the HIV long terminal repeat. Transactivation by IE proteins is mediated either directly or by the induction of cellular transcription factors, such as NFκB and Spl. CMV IE genes are expressed during both productive and latent infection. Thus, transactivation could occur in the absence of active virus replication at any time during the course of HIV disease. Recent molecular studies suggest that CMV and HIV act in synergy within the same cell. Indeed, infection of semipermissive cell types (e.g., lymphoblastoid, neural, endothelial) by HIV allows productive CMV replication, providing evidence for a bidirectional interaction between CMV and HIV. Moreover, this synergism could provide a mechanism for the observed increase in the degree of viremia for both of these viruses in AIDS patients [70].

CMV infection can enhance expression of cell membrane molecules that are involved in HIV binding to the cell surface and introduction of HIV particles into cells [71]. Entry of immunoglobulin-coated HIV into CD4-negative cells (neural cells and endothelial cells) has been shown to occur via receptors for the Fc portion of IgG molecules expressed on the cell membrane of CMV-infected cells. CMV infections induce the expression of Fc receptors on the plasmalemma of cells that normally do not

Table 7.2 Clinical Manifestations of CMV-induced Mononucleosis

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
4–8 weeks	Syndrome of fever (=/− chills) and severe malaise. Some patients may have headache, myalgias, sore throat, rash, abdominal pain, splenomegaly, or, rarely, hepatomegaly	Viral culture of body secretions; CMV-specific serologies with seroconversion or significant rise in antibody titers	This illness most often affects persons aged 20–40 years, but can also be seen in children and adolescents

Table 7.3 Differential Diagnosis of Cytomegalovirus Mononucleosis

Epstein-Barr virus-induced mononucleosis: Generally, CMV-induced mononucleosis produces less severe and less frequent pharyngitis, lymphoadenopathy, and splenomegaly. Exudative pharyngitis is rare with CMV disease. Heterophil antibody test and specific serologies can differentiate the two etiologies
Toxoplasmosis: This illness most frequently manifests with posterior cervical lymphadenopathy and fatigue without fever or pharyngitis
Viral hepatitis: Patients typically have jaundice and tender hepatomegaly, but may also have low-grade fever, fatigue, atypical lymphocytosis, and occasional lymphadenopathy
Lymphoma: Non-tender fixed adenopathy is most characteristic

display this molecule. As a result of these CMV-induced cellular changes, HIV can coinfect a broad range of cell types in vivo, possibly explaining the wide variety of clinical syndromes described in acquired immunodeficiency syndrome (AIDS) patients.

CMV infection stimulates production of cellular factors that support HIV replication [70]. For example, CMV-infected cells (e.g., monocytes, macrophages) express enhanced quantities of tumor necrosis factor alpha, transforming growth factor beta, IL-1 beta, colony-stimulating factor-1, monocyte-derived neutrophil chemotactic factor, and neutrophil-activating factor. These cytokines, in turn, induce HIV gene expression and replication in chronically infected cells and so release the HIV from latency.

Cutaneous Manifestations of Cytomegalovirus Infection

Cutaneous manifestations of CMV in the normal host are uncommon but well described (Table 7.5). Those seen in congenital CMV infection include blueberry muffin lesions (Fig. 7.12), which represent dermal erythropoiesis [72]; also seen are petechiae (Fig. 7.13) and purpura [73], cutaneous vesicles [74], and ichthyosis of the skin found in conjunction with keratitis and deafness [75]. Reports of rashes associated with CMV mononucleosis syndrome include the maculopapular rubelliform rash, the ampicillin-induced rash (Fig. 7.7), erythema nodosum [76], and erythema multiforme [77]. Cutaneous vasculitis, vasculopathy, and scleroderma sans inclusion bodies has also been reported as a presenting symptom of acute CMV infection [78,79]. Primary

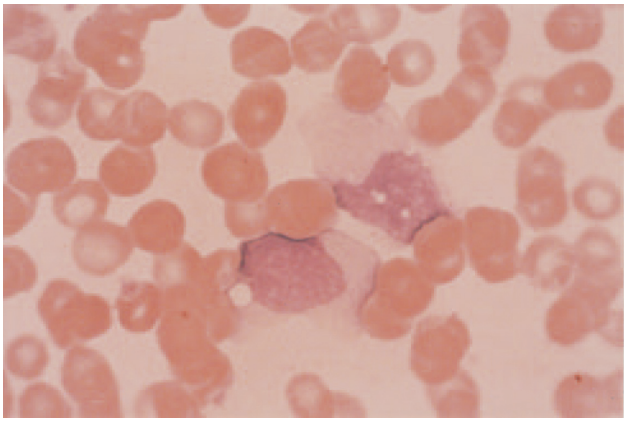


Figure 7.6 Atypical lymphocytes seen in peripheral blood smear in CMV mononucleosis.



Figure 7.7 Ampicillin-induced morbilliform rash during the course of CMV mononucleosis.

and reactivated CMV infections were associated with a syndrome complex mimicking and/or triggering a primary immune-based cutaneous microvascular injury syndrome [79]. CMV has been found in ulcerations of the genital area, oral biopsy specimens, hyperpigmented and indurated areas of the thighs, granulating areas of burned patients, cutaneous ulcerations of the chest, verrucous plaques of the heel, crusted papules of the face, ulcerated nodules of patients with systemic lupus erythematosus, and ulcerations of the oral mucosa [80–84]. CMV was also found in skin lesions of patients with vitiligo, and it has been reported that viral infections in select patients might trigger vitiligo [79,85]. Genetic, environmental, and infectious agents have been identified as possible triggering factors of systemic sclerosis [86–88]. Among these, CMV infection plays a major role in the pathogenesis of the systemic sclerosis owing to its ability to infect both endothelial and monocyte-macrophage cells [86,88,89].

CMV-associated skin lesions in the immunocompromised host (Figs. 7.14 and 7.15) are rare compared with the prevalence of CMV infection of other organs. Although several case reports have been published, the true incidence of cutaneous CMV is unknown. Various forms of cutaneous CMV have been described (Table 7.5). Ulcers are the predominant lesions and occur most frequently over the perianal area and buttocks (30% of reported cases) [73,90,91]. These lesions frequently contain other microorganisms, such as herpes simplex virus or *Staphylococcus aureus.* Other less commonly reported cutaneous lesions include purpura, petechiae, morbilliform and maculopapular rash, vesicles, and verrucous or indurated plaques and nodules. Although CMV does not appear to play a direct role in the pathogenesis of bacillary angiomatosis and Kaposi's sarcoma, CMV nucleic acid sequences and antigens have been detected in these tissues [92].

CMV-associated ulcers and nodules seem to arise from infection of the endothelium of cutaneous blood vessels during the viremic phase of illness. These lesions may progress to vasculitis [71], with the appearance of purpuric nodules that may undergo infarction and sloughing of the overlying epidermis. However,

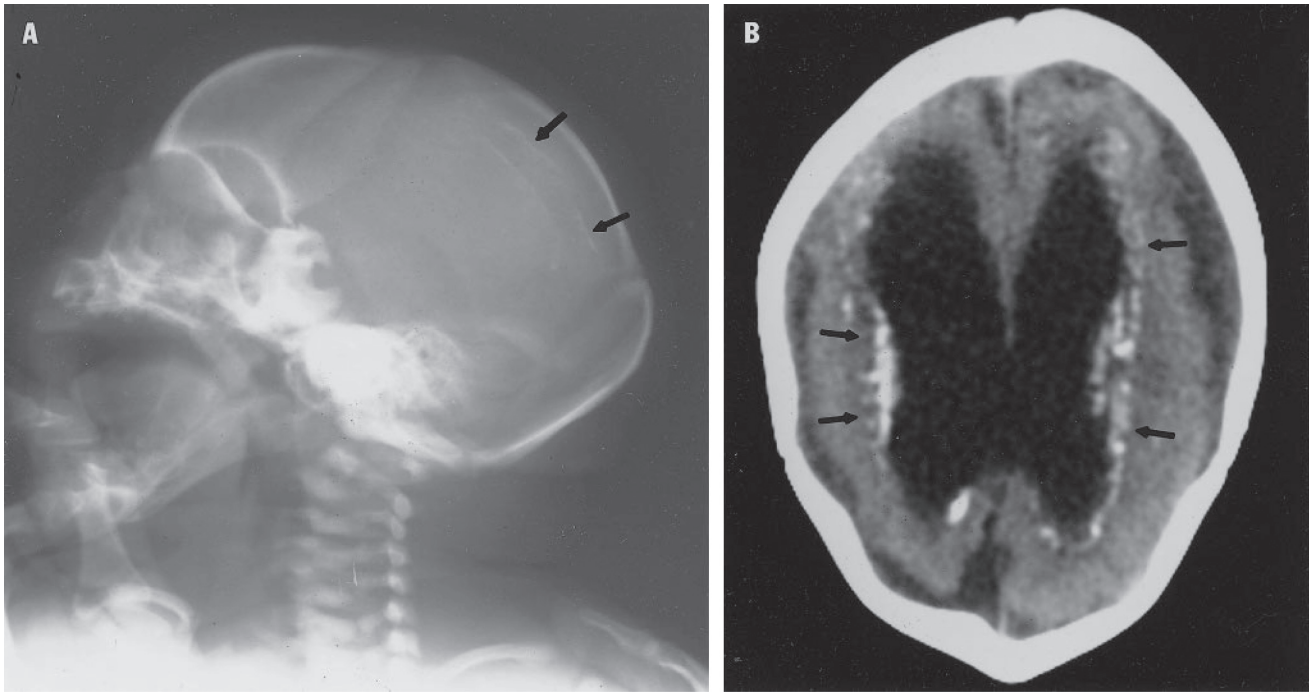


Figure 7.8 Neurodevelopment sequelae associated with CMV infection. (A) Lateral view demonstrates microcephaly and curvilinear paraventricular calcification (arrows). (B) An axial computed tomographic scan of microcephaly, brain atrophy, enlargement of the ventricles, and a classic distribution of periventricular calcifications (arrows). (Radiograph courtesy of Susan D. John, M.D., and Leonard E. Swischuk, M.D., Department of Radiology, University of Texas Medical Branch at Galveston, Galveston, TX.)

there is also evidence that the endothelial infection may not necessarily progress to skin lesions [73,92].

The immunocompromised host with cutaneous CMV usually has concurrent systemic CMV disease [78,90]. Therefore, prognosis with cutaneous CMV is poor, and the mortality rate is approximately 85% [37]. Nonetheless, the skin lesions of patients may show a beneficial response to CMV-specific antiviral chemotherapy [93]. Burn patients are known to be immunocompromised [94]. It has been shown that thermally injured patients who are seronegative are at risk of acquiring CMV infection, while CMV antibody-positive patients often reactivate. CMV infection in burn patients can lead to a broad spectrum of infection and disease, ranging from mild febrile illness to extensive viral dissemination and organ manifestation [94]. While the burn injury alone can cause immunosuppression [94], CMV infection itself is immunosuppressive by impairing or evading cell-mediated immunity [95].



Figure 7.9 Chest radiograph of CMV pneumonitis. Note the bilateral reticulonodular infiltrates with mild overaeration of the lungs. (Radiograph courtesy of Susan D. John, M.D., and Leonard E. Swischuk, M.D., Department of Radiology, University of Texas Medical Branch at Galveston, Galveston, TX.)

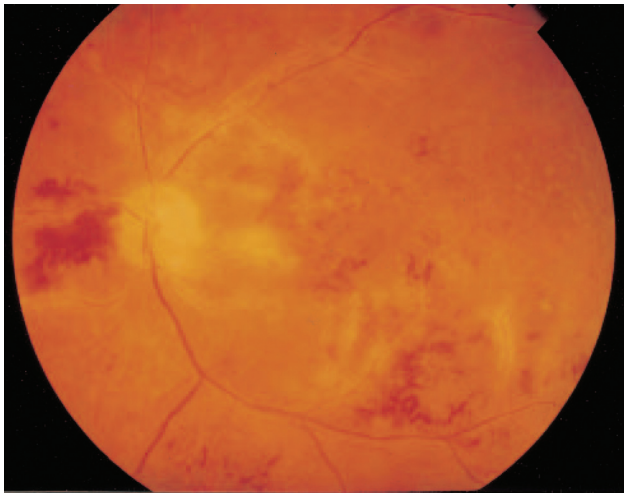


Figure 7.10 CMV-induced chorioretinitis in an HIV-infected patient. (Photograph courtesy of Helen Li, M.D., Department of Ophthalmology, University of Texas Medical Branch at Galveston, Galveston, TX.)

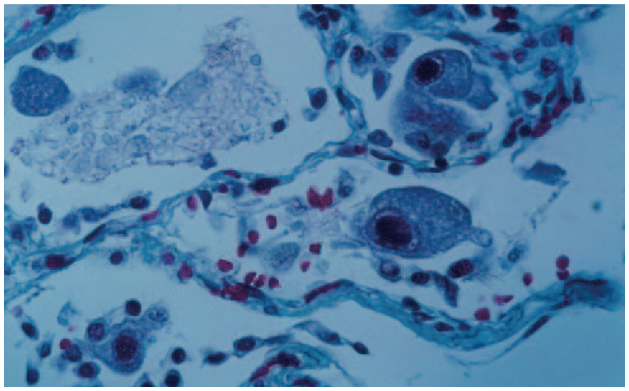


Figure 7.11 Photomicrograph of pneumocytes demonstrating CMV-induced cytopathic effect (cytomegaly and Cowdry type A nuclear inclusion) (Mallory's trichrome stain). (Photograph courtesy of Jerome H. Smith, M.D., Department of Pathology, University of Texas Medical Branch at Galveston, Galveston, TX.)

Diagnosis of Cytomegalovirus Infections

The possibility of effective therapy has heightened the need for accurate and rapid laboratory methods for diagnosis of CMV infection. Histological diagnosis of CMV has a high specificity, but its sensitivity can be 2–6 times less than that of viral isolation [96]. The characteristic histological feature of CMV infection is the "owl's eye" appearance, owing to viral inclusion bodies found in infected endothelial cells (Fig. 7.16) [97]. These cells are typically enlarged one to threefold and have large intranuclear inclusions with a surrounding clear halo. The cytoplasm also contains purplish, granular inclusions. The intranuclear inclusions seen in CMV infection appear identical to, but slightly larger than, those of herpes simplex virus and varicella-zoster virus infection,

Table 7.4 Manifestations of CMV Infections in Immunocompromised Patients

Bone marrow
Leucopenia
Anemia
Thrombocytopenia
Atypical lymphocytosis
Endocrine
Adrenalitis
Pancreatitis
Renal
Glomerulonephritis
Rejection of kidney graft
Skin
Ulcers
Papules
Plaques
Purpura
Morbilliform rash
Maculopapular rash
Gastrointestinal tract
Stomatitis
Esophagitis
Gastritis
Duodenitis
Ileitis/colitis
Bowel ulcers
Choleocystitis
Cholangitis
Papillary stenosis
Central nervous system and eye
Encephalitis
Transverse myelitis
Guillain-Barré Syndrome
Chorioretinitis
Lung
Interstitial pneumonitis

Table 7.5 Cutaneous Manifestations of CMV Infections

Normal host
Congenital infections
Blueberry-muffin lesions (dermal erythropoiesis)
Petechiae and purpura
Cutaneous vesicles
Ichthyosis
Mononucleosis-associated
Ampicillin-induced rash
Erythema nodosum
Urticaria
Cutaneous vasculitis
Immunocompromised host
Ulcer
Purpura
Petechiae
Morbilliform and maculopapular rash
Vesicles
Verrucous or indurated plaques
Nodules



Figure 7.12 Blueberry-muffin lesions (from dermal erythropoiesis) in congenital CMV infection.

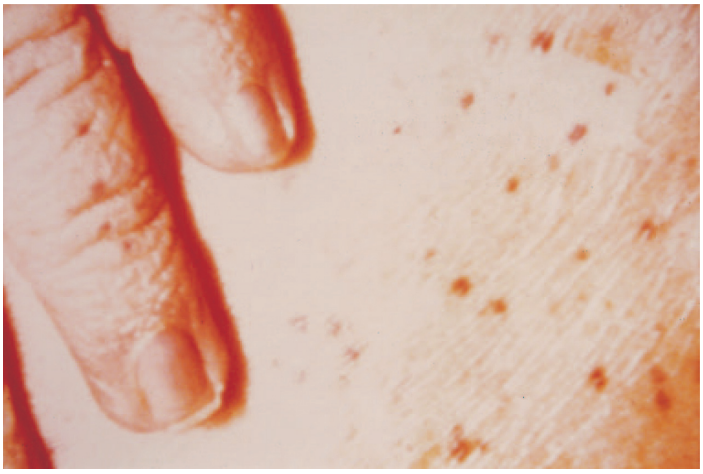


Figure 7.13 Petechial lesions in congenital CMV infection.

which may at times cause confusion in diagnosis [98]. A sparse perivascular lymphocytic infiltrate in the upper dermis, along with spongiosis, is also seen with CMV infection. Involvement of the vascular endothelium with vasculitis may be evident in some cases and is indicative of disseminated infection.

Current non-histological diagnostic tools include virus isolation in tissue culture (shell vial culture/immunochemistry/nucleic acid hybridization), histological-cytological detection of typical CMV cytopathology, immunological methods to detect seroconversion, and the detection of CMV antigens and/or nucleic acids within cells of infected organs and tissues [99–101]. The usual clinical specimens used for culture diagnosis of CMV are urine and saliva. The virus can also be isolated from stool, breast milk, semen, cervical secretions, and peripheral blood cells. Although culture of CMV in human fibroblasts is still considered the diagnostic gold standard, isolation of infectious virus may take a few days to several weeks. Use of the shell vial culture, in conjunction with staining with monoclonal antibodies directed at IE CMV antigens, has made it possible to detect CMV in culture within 24–48 hours [102,103]. For direct demonstration of the virus or inclusion-containing cells (Fig. 7.17), a urine sample is the most appropriate specimen. Patients with CMV infection excrete the virus consistently and in high quantity in the urine.



Figure 7.14 Cutaneous nodules associated with CMV in an HIV-infected patient.

Immunofluorescence using monoclonal antibodies is a frequently used method to detect CMV-specific antigens in clinical specimens, such as peripheral blood cells, biopsies, autopsies, and amniotic cells. Radio- or biotin-labeled DNA or RNA probes are also used to detect CMV nucleic acid sequences (using in situ cytohybridization, Southern-, slot/dot-blot hybridization) directly in cells of clinical specimens. DNA amplification using polymerase chain reaction (PCR) achieves a high level of sensitivity in CMV nucleic acid detection in single cells (in situ PCR), body fluids, and tissue sections [104,105].

Transmission of CMV via blood transfusions and donor organs has created a continuing need for serological methods that are suitable for screening donors and recipients, in an effort to avoid adverse clinical outcomes of CMV infection in immunocompromised recipients. Numerous modalities for serological diagnosis are available and include (1) complement fixation; (2) enzyme-linked immunosorbent assay (ELISA); (3) immunofluorescence assay; (4) hemagglutination inhibition; (5) neutralization tests; and (6) latex agglutination assay. The presence of CMV-specific IgG antibody indicates past or present infection, but has no diagnostic significance for acute infection unless a recent seroconversion can be documented. A fourfold or greater rise in CMV-specific IgG antibody titers is indicative of current active infection, but this does not differentiate between a primary or recurrent process. To document a rise in IgG antibodies, a blood sample should be drawn as soon as possible during the acute phase and a second sample drawn 4 weeks later during the convalescent period. CMV-specific IgM antibody levels can also be useful in the diagnosis of illness. If the test is performed properly, the presence of this antibody indicates recent or current CMV infection. In immunocompetent adults, IgM antibody usually persists for 6 weeks, but may remain detectable for 3–6 months after primary infection [106]. The antibody may persist for 1 year or more in immunosuppressed individuals. False-positive reactions occur in the presence of rheumatoid factor, so this factor should be removed from the serum specimen prior to IgM testing [107].

Unfortunately, for various reasons, the variety of diagnostic methods available may still frequently fail to definitely establish CMV as the etiology of clinical problems. For instance, diagnosis of acute infection may be distorted because patients may shed CMV in urine, saliva, blood, and genital secretions for months to years following primary infection or virus reactivation.

Control of Cytomegalovirus Infection

Approaches that could ultimately control CMV infection include prevention, immunoprophylaxis, and therapy with antiviral drugs (Tables 7.6 and 7.7). Preventive therapy is practical for immunocompromised individuals who are not yet infected, but are at risk for infection from a defined exposure, such as blood transfusion or organ transplantation. The best preventive measure is to use tissues and blood from CMV antibody-negative donors for this specific population. Currently, there are five drugs approved for treatment of CMV infections: ganciclovir and its prodrug valganciclovir, foscarnet, cidofovir, and fomivirsen (reviewed in

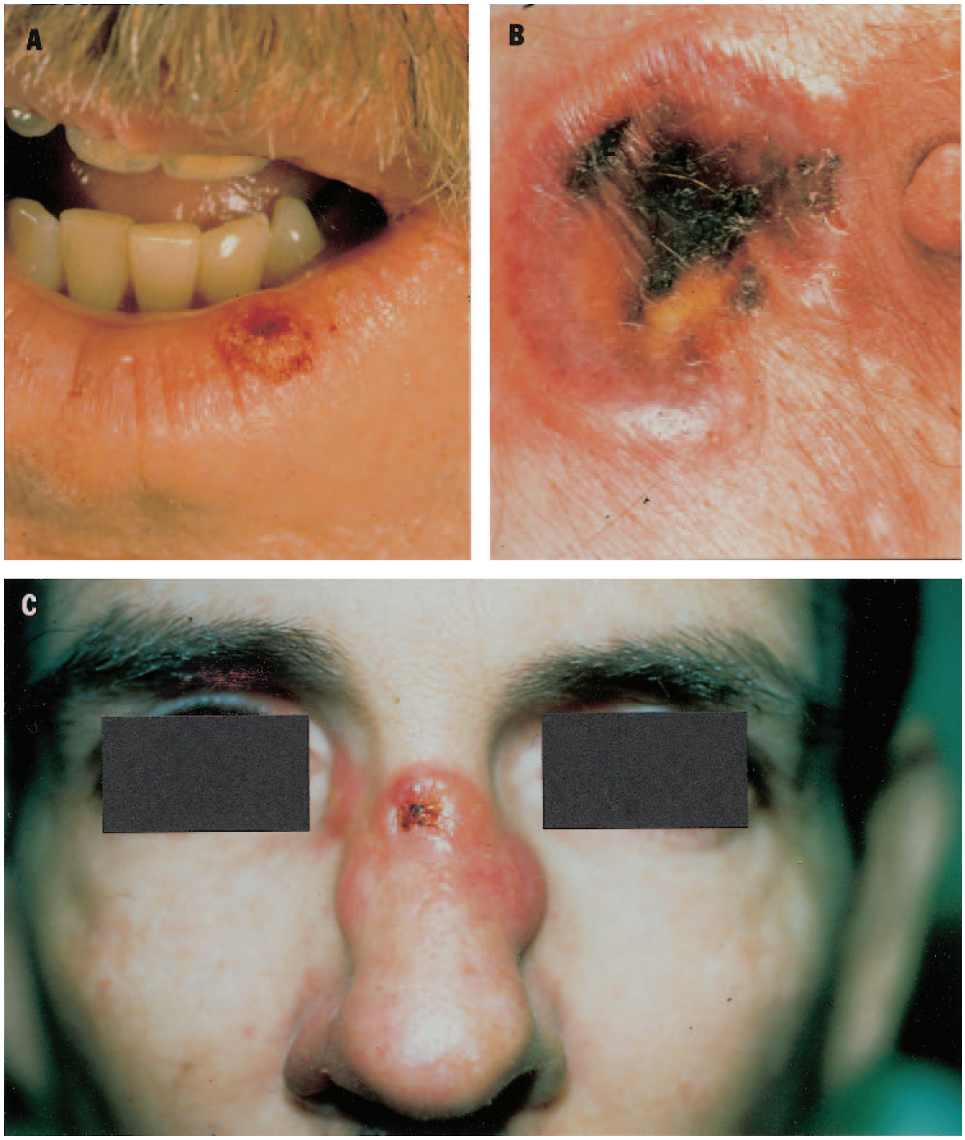


Figure 7.15 Cutaneous ulcerations (A) lip; (B) chest; (C) nose;

[37,108–111]). These drugs have provided a major advance in proactive approaches of CMV disease management; however, they have low bioavailability, significant toxicity, modest effectiveness, and development of drug resistance. Other pre and postinfection treatment modalities include interferon [112], as well as use of intravenous immunoglobulins, particularly high titer CMV immunoglobulins [113]. For the treatment of CMV infection in immunocompromised persons, antiviral agents (Table 7.7) have been used with limited success. All of the currently available drugs are virustatic and not virucidal, and long-term administration is required to suppress the effects of the disease [109–111].

Ganciclovir

Ganciclovir was the first antiviral agent licensed and remains the first-line treatment for life-threatening and sight-threatening CMV infections [114]. It is a synthetic acyclic nucleoside analogue of guanine (acyclic nucleoside analogue of 2′-deoxyguanosine). Cellular enzymes generate the triphosphate form. Ganciclovir triphosphate inhibits DNA synthesis catalyzed by the viral DNA polymerase, resulting in slow DNA elongation by incorporating in place of dGTP into the viral DNA. It can be administered intravenously, orally, or by intravitreal implant. Ganciclovir is virustatic, providing suppression of active CMV infection, but not complete cure. The disease process of CMV continues to progress after discontinuation of the medication. Ganciclovir is recommended for the treatment of CMV retinitis in immunocompromised patients [115] and for CMV prophylaxis in transplant recipients [116,117]. It may also be effective in CMV colitis, esophagitis, hepatitis, meningoencephalitis, and pneumonitis [118]. Neither ganciclovir nor any other antiviral agent is currently recommended for the treatment of symptomatic congenital CMV. This subject remains controversial. Several case reports describe the benefit of ganciclovir treatment in children with urgent life-threatening complications of this illness [119,120].

Because of poor oral bioavailability (8–9%), ganciclovir is usually given intravenously, particularly for initiation of treatment. Oral ganciclovir is more convenient for long-term maintenance, but is not as effective as intravenous ganciclovir. Recently, the

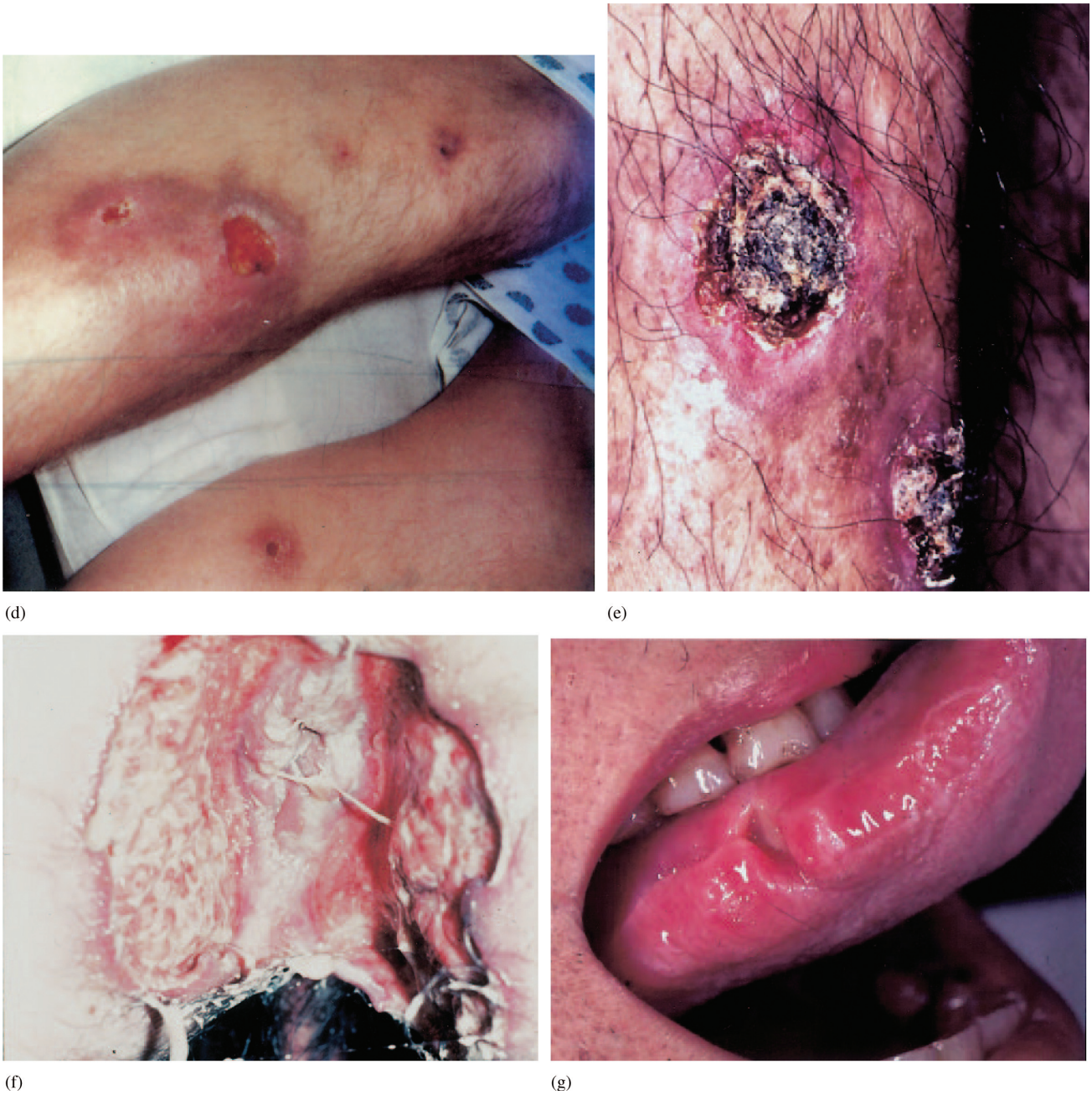


Figure 7.15 (Continued.)(D) CMV-induced ulceration on legs in HIV-positive patients; (E) CMV ulcers may be verrucous; (F) may become large in the perianal area; (G) or may appear on the tongue. [(D) Courtesy of James C. Shaw, M.D., Section of Dermatology, University of Chicago, Chicago, IL; (E, G) courtesy of Siri Chiewchanvit, M.D., Chiang Mia, Thailand; (C) courtesy of Rocio Orozco-Scholtes, M.D., Department of Dermatology, National Institute of Nutrition, Tlalpan, Mexico.]

oral prodrug of ganciclovir, valganciclovir (the l-valyl ester of ganciclovir), became the first orally administered CMV therapy approved for both induction and maintenance therapy of CMV. Valganciclovir is rapidly metabolized to the active form (ganciclovir) in the intestinal wall and liver. Valganciclovir has an oral bioavailability of around 60%. The intravitreous implant is useful for localized CMV retinitis. However, this modality provides no protection against CMV for the remaining eye or other organs, and it requires surgical insertion every 6 months. A recent study combining treatment with the intraocular implant and oral ganciclovir demonstrated further delay in the progression of retinitis and decrease in the incidence of new CMV disease [121]. Adverse effects of ganciclovir include reversible neutropenia, thrombocytopenia, azoospermia, renal insufficiency, and central nervous system symptoms [122]. Resistance to ganciclovir and subsequent progression of the disease may develop in some strains of CMV through mutations in the viral DNA polymerase [17,123].

Foscarnet

Foscarnet (Foscavir®, AstraZeneca) became the second drug approved in 1991, for treatment of CMV retinitis in AIDS patients. Foscarnet is the trisodium salt of phosphormophonic acid (a pyrophosphonate analogue). Foscarnet inhibits activity of the viral DNA polymerase by binding to the pyrophosphate binding site and blocking cleavage of pyrophosphate from the terminal nucleoside triphosphate added to the growing DNA chain [108].

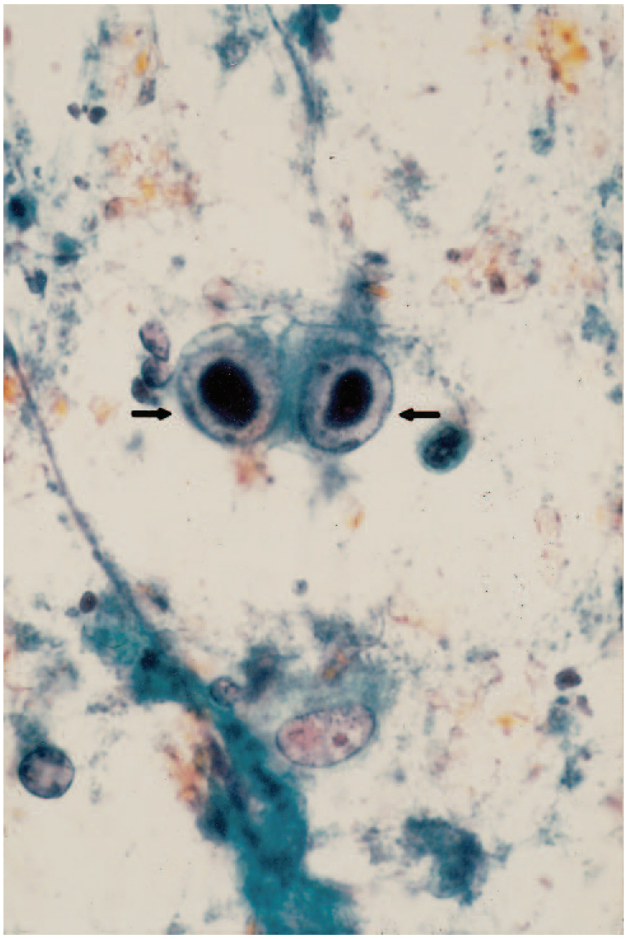


Figure 7.16 CMV-infected cells with prominent nuclear inclusions producing the typical "owl's eye" appearance.

This virustatic drug has a consistent impact on virus shedding, and its effectiveness appears to be related to the time of initiation of therapy and particularly to the extent of tissue involvement [124]. Foscarnet has been successfully used for the treatment of CMV retinitis in AIDS patients and with some success in transplant recipients with life-threatening CMV infection [125,126]. This antiviral agent has two attributes that make it an attractive alternative to ganciclovir: it is not toxic to the bone marrow, and it is effective against ganciclovir-resistant CMV strains [127]. Due to its poor oral bioavailability, foscarnet must be given intravenously, and its common side effect, renal dysfunction, is often dose limiting. Other adverse effects include electrolyte imbalances, genital ulceration (Fig. 7.18), nausea and vomiting, central nervous system disturbances, and deposits of the drug in bone, teeth, and cartilage. Results from studies using cell cultures [128] suggest synergistic action between lower doses of ganciclovir and foscarnet, which may help to reduce toxicities and the development of drug resistance [101].

Cidofovir

Cidofovir (Vistide®, Gilead) is an acyclic nucleoside phosphonate. Its chemical name is 1-[(*S*)-3-hydroxy-2-(phosphonomethoxy) propyl]cytosine dehydrate. Cidofovir is a broad-spectrum antiviral agent and potentially effective against herpes and other DNA viruses. Cidofovir has been approved (in 1996, USA) for the treatment of CMV retinitis in HIV-infected patients who are unable to tolerate ganciclovir or foscarnet therapy. The drug must be given intravenously, but it has a more convenient dosing regimen of once every 2 weeks after the initial induction regimen of once every week (for 2 weeks). One HIV-infected patient with CMV retinitis, encephalitis, and esophagitis responded well to this therapy after becoming resistant to ganciclovir and foscarnet [129]. Adverse effects, including nephrotoxicity, neutropenia, metabolic acidosis, and ocular hypotonia, require treatment discontinuation in approximately 25% of patients. The major route of drug elimination occurs via the kidneys. The major limitation of cidofovir therapy is its renal toxicity. Its toxicity is due to accumulation of drug in the renal cortex via an anion transporter located in the convoluted proximal tubules [130] Cidofovir must be given together with probenecid to protect against kidney failure. Neutropenia is another toxicity associated with cidofovir, in addition to its carcinogenic and teratogenic potential. Recent reports describe a promising series of cidofovir alkoxyalkyl ester derivatives that overcome renal toxicity. Further, these derivatives showed improved uptake and absorption, and oral bioavailabilities (88–97%) in animal models [131].

Fomivirsen

Fomivirsen (Vitravene®; Novartis Ophthalmics) is a 21-base long oligo-nucleotide (5′-GCG TTT GCT CTT CTT CTT GCG-3′), targeted against the major IE mRNA of the virus [108,109]. It is recommended as an intravitreal (intraocular) injection for CMV retinitis in HIV-infected patients who are unable to receive more conventional therapies because of intolerance or insufficient response. The drug is administered by monthly in-office injections, and the most common side effects include ocular inflammation and increased intraocular pressure [132].

Anti-Cytomegalovirus Drugs in Clinical Development

The currently used drugs have significant acute and long-term toxicities, and due to their similar mechanism of action (viral DNA polymerase), development of viral resistance and cross-resistance is a potential problem.

Maribavir (1-(β-l-ribofuranosyl)-2-isopropylamino-5,6-dichlorobenzimidazole) is one of the most promising anti-CMV drugs in clinical trials [108,133,134]. Maribavir is a potent and selective, orally bioavailable drug active against only CMV and EBV. Although it has not been fully elucidated, maribavir appears to inhibit the replication by interfering with viral DNA synthesis and nucleocapsid egress from the nucleus, thereby effectively reducing the yield of infectious CMV [133,134]. Based on preclinical trials, it shows advantages over existing anti-CMV drugs in its potency, bioavailability, safety, and the lack of development of resistance.

BAY 38-4766 (3-hydroxy-2,2-dimethyl-*N*-[4([[5-(dimethylamino)-1-naphthyl] sulfonyl]amino)-phenyl]propanamide) is a non-nucleoside inhibitor, which interferes with DNA maturation during CMV replication [135]. In animal models, it shows activity against human CMV, has a favorable safety and efficacy profile, and measurable amounts of drug were detected in fetal blood [136]. BAY 38-4766 entered clinical development and showed a favorable safety profile; however, no recent reports have revealed the current status of clinical development.

Table 7.6 Treatment of CMV-induced Mononucleosis

Symptom	Treatment
Fever	Antipyretics (e.g., acetaminophen); increase fluid intake to prevent dehydration
Malaise	Bed rest
Sore throat	Warm saltwater gargle 3–4 times a day
Splenomegaly	Avoid strenuous activity or contact sports for 4–6 weeks to lessen the risk of splenic injury
Elevated liver enzymes	Avoid alcohol consumption for 4–6 weeks to lessen the work of the liver

GW275175X (2-bromo-5,6-dichloro-1-β-d-ribopyranosyl-1*H*-benzimidazole) inhibits the maturational cleavage of CMV DNA by interaction with two subunits of the viral terminase complex [137]. GW275175X was advanced through a Phase I trial of safety, tolerability, and pharmacokinetics; however, its clinical potential is yet to be determined.

Cytomegalovirus Immune Globulin

Cytomegalovirus immune globulin (CMVIG) may be used for the prevention of CMV disease in certain immunocompromised patients, particularly transplant recipients. Prophylactic treatment with CMVIG in at-risk renal transplant recipients significantly reduces the rate and severity of CMV disease, as well as the risk of complications from fungal superinfection [113]. However, although CMVIG greatly impacts clinically evident disease, it has no effect on the rates of viral isolation or seroconversion [138]. More recently, application of pooled monoclonal antibodies to the major epitopes of CMV surface glycoproteins has been shown to prevent clinical disease.

Data from several studies indicate that regimens consisting of high-dose CMVIG combined with ganciclovir, acyclovir, foscarnet, or interferon are more effective than monotherapy of CMV-induced syndromes in transplant patients [139]. A combination of ganciclovir and CMV-specific or polyvalent immune globulin has been reported to improve survival significantly in CMV pneumonitis in recipients of allogeneic bone marrow transplants [140]. Combination therapy may also have a role in bone marrow transplant recipients with gastrointestinal CMV disease [118], as well as in renal transplant patients with fulminant CMV disease.

Cytomegalovirus Vaccines

Currently, there are two CMV vaccines in Phase II clinical trials [141]. One is the CMV gB/MF59 subunit vaccine, which is a disulfide-linked glycoprotein complex (major component of the envelope glycoprotein of human CMV) with 130 and 55 kDa components; human convalescent sera antibodies to the glycoprotein complex are abundant due to the seven neutralizing epitopes. Accordingly, when administered with the adjuvant MF/59, the glycoprotein complex induces high levels of neutralizing antibodies in animals and humans. The glycoprotein complex also contains epitopes that stimulate T-lymphocytes cytotoxic for CMV [142–144].

Another vaccine is a live, attenuated, high passage Towne strain of CMV [144,145]. When administered, it does not reactivate in either healthy volunteers or immunocompromised patients. This vaccine strain does not produce viral latency, induce alterations of the CD4/CD8 ratio, or affect other T-lymphocyte subsets. The vaccine is given subcutaneously, appears to be safe, and induces neutralizing antibodies comparable to those induced by wild-type virus [144,145]. Vaccination has been shown to protect against the severity of symptomatic illness, but not against infection in transplanted individuals with CMV-bearing organs [144,146]. However, the efficacy of the vaccine in preventing child-to-mother transmission of CMV acquired in day-care centers was poor. The rate of acute CMV infection of vaccinated mothers was not different than that for the placebo, whereas naturally seropositive mothers were protected from infection [147–149]. Finally, data presently available indicate that CMV immunity is substantial but not sufficient and that reinfection of naturally seropositive individuals depends on the dose and exposure frequency. Therefore, the best CMV vaccine is unlikely to be 100% effective [141,146].

Conclusion

CMV is the most common cause of intrauterine and perinatal infection in humans. It is also of increasing importance in the

Table 7.7 Drugs Effective in Treatment and Prophylaxis of CMV Infection

Drug	Mechanism of action	Therapeutic effect
Idoxuridine Vidarabine Trifluridine	Inhibition of viral DNA synthesis	Poor
Ribavirin	Inhibition of inosine monophosphate dehydrogenase; depletion of guanosine 5'-triphosphate (GTP) pool; alteration of mRNA capping	Moderate
Interferons	Inhibition of viral protein synthesis through degradation of viral RNA; inactivation of the initiating factor eIF2alpha	Moderate
Foscarnet*	Inhibition of pyrophosphate receptor site of the viral DNA polymerase	Good
Cidofovir*	Inhibition of CMV DNA polymerase	Good
Ganciclovir*	Selective inhibition of CMV DNA polymerase; termination of CMV DNA elongation	Good
Valganciclovir*	Selective inhibition of CMV DNA polymerase; termination of CMV DNA elongation	Good
Fomivirsen*	Inhibition of viral protein synthesis and thus of replication through binding with specific viral mRNA	Good

*FDA approved for use in treatment of CMV infections.

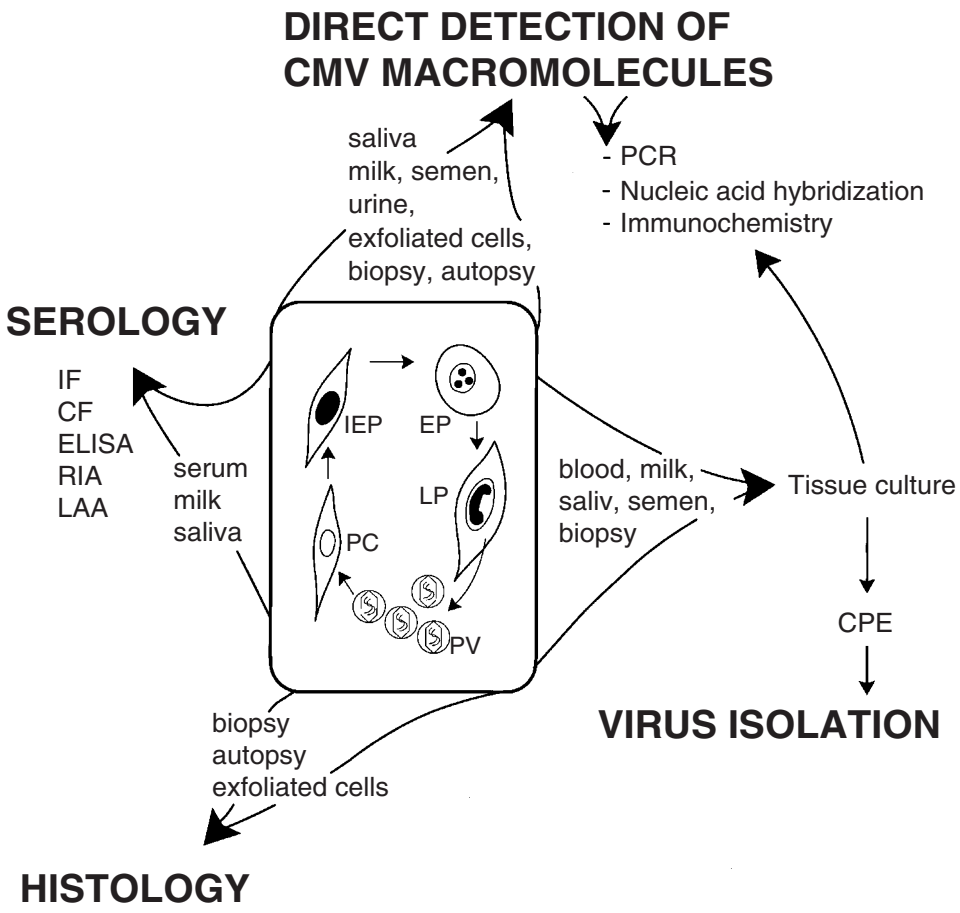


Figure 7.17 Diagnostic approach to detect primary or reactivated CMV infection. The central area demonstrates the phasing of CMV replication in the infected host (PC, permissive cell; IEP, immediate early; EP, early and LP, late proteins; PV, progeny virus). Main arrows: examples for clinical specimens most frequently used to detect CMV infection. PCR, polymerase chain reaction; IF, immunofluorescence; CF, complement fixation assay; RIA, radioimmunoassay; ELISA, enzyme-linked immunoabsorbent assay; LAA agglutination assay; CPE, cytopathic effect.

immunocompromised host, although a rare cause of symptomatic infection in the normal host. Up to 10% of infants with congenital CMV infection have severe symptoms at birth, and 5–17% of infants born with asymptomatic congenital infection suffer late sequelae, mostly deafness and other neurological problems. CMV infection in the immunocompromised host has a broad range of clinical manifestations, including a variety of mucocutaneous manifestations. Drug therapy for CMV has improved dramatically in the last few years, but remains far from optimal. Several drugs are effective in controlling CMV disease in most patients, but relapse is common and is expected after discontinuation of long-term therapy. In addition, adverse effects associated with these drugs are not benign. Prevention of CMV infection may be achieved by serological screening of blood and organ donors, as well as the use of leukocyte-free blood in transfusions. Immunoglobulin prophylaxis may also be effective in ameliorating disease in renal allograft patients. Use of combinations of therapy, including antivirals, immunoglobulins, and cytokines, has been reported to decrease the morbidity and mortality associated with CMV disease; however, these therapeutic regimens require further study.



Figure 7.18 Penile erosion resulting from excretion of foscarnet in the urine.

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8 Human Herpesvirus 6

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Human herpesvirus 6 (HHV-6) is a β-herpesvirus, first isolated in 1986 from peripheral blood mononuclear cells of patients with lymphoproliferative diseases [1]. It is a 160–200 nm, enveloped, double-stranded DNA virus with a genome of more than 110,000 base pairs, and molecular and morphological characteristics distinct from other members of the Herpesviridae family [2–4]. In vitro, HHV-6 can infect B and T lymphocytes, megakaryocytes, fibroblasts, and glial cells [4]. In vivo, the host range of HHV-6 broadens to include salivary glands, kidney endothelial cells, lymph nodes, and central nervous system tissue (neurons and oligodendrocytes) [5]. HHV-6 has been shown to be an etiological agent of exanthem subitum, a common childhood exanthem characterized by several days of high fever followed by the abrupt onset of a diffuse rash coinciding with defervescence [6]. It has also been associated with a variety of disorders in both healthy adults and immunocompromised persons (see Table 8.1 and Fig. 8.1 for more details).

History

Through the years, exanthem subitum has been known by several different names, such as roseola infantum, exanthem criticum, 3-day fever, pseudorubella, rose-rash, sixth disease, Filatov-Dukes disease, and Dukes' syndrome. This disease process may have been described as early as 1870 [7]. However, early reports probably represent descriptions of a variety of exanthems, and credit for the first description of exanthem subitum is given to Zahorsky, who separated this disease from other exanthems in 1910 [8]. In 1941, Breese unsuccessfully attempted to culture a viral agent from three children with exanthem subitum [9]. In 1950, Kempe observed that the peak age of infection coincided with the ebb of passive maternal antibodies, and he predicted that a ubiquitous virus carried by healthy individuals was responsible for the infections [10]. He postulated that infection occurred through contact with nasal and pharyngeal secretions and suggested that a member of the Herpesviridae family would be an ideal candidate. In 1986, Salahuddin isolated a new virus from the peripheral blood leukocytes of six patients with lymphoproliferative disorders [1]. The infected cells were enlarged and balloonlike. The identified virus had unique host range, in vitro biological effects, and antigenic features. It also lacked cross-hybridization with other known human herpesviruses; thus, it was named human B-lymphotropic virus (HBLV) [2]. The following year, experiments demonstrated that the cellular tropism of HBLV extended beyond B lymphocytes, and the taxonomic designation of human herpesvirus-6 (HHV-6) was proposed [11].

In 1988, Yamanishi isolated and cultured HHV-6 from the peripheral blood leukocytes of four patients with exanthem subitum, and he confirmed by serological testing that HHV-6 was the cause of exanthem subitum [6]. Besides the viral finding in children with exanthema subitum, more than 100 strains of HHV-6 have been isolated to date in both healthy and immunocompromised adults and children [18–28,36].

Subsequent restriction enzyme analysis of DNA obtained from patients has demonstrated that all the HHV-6 strains known to date can be separated into two main variants [12], classified as A (HHV-6A) and B (HHV-6B). Both variants are closest in homology to HHV-7 and cytomegalovirus (CMV) [152]. These two variants differ in biological, immunological, and molecular characteristics in that they exhibit differences in cell tropism, transcription regulation, and splicing patterns; although current serologic tests cannot easily distinguish between them. Variant B is known to be the etiological agent of exanthem subitum, whereas variant A has not as yet been found to cause any specific disease process [5]. With DNA analysis of peripheral blood lymphocytes in healthy donors, variant B has been demonstrated to be three times more common than variant A [13]. Variant A appears to be more common in samples of uninvolved skin [5], in Kaposi's sarcoma [14], and in human immunodeficiency virus-1 (HIV-1)-infected individuals (both symptomatic and asymptomatic) [15,16].

Incidence

HHV-6 is one of the most ubiquitous viral agents infecting humans [17] and has been reported in patients worldwide [18–28]. Seroprevalence studies have shown that antibody to HHV-6 is present in 60–95% of the general population [29–37]. Exceptions are found in countries where the seroprevalence is much lower (e.g., Morocco) [161]. The majority of infections occur in the first 3 years of life [36,38]. It has been shown that between 0 and 4 weeks of age, immunoglobulin G (IgG) antibody to HHV-6 is present in 72–97% of infants tested because of transfer of maternal antibodies. By 6 months of age, seroprevalence decreases to 21–60% as a result of the waning of maternal antibodies. By 1 year of age, the seroprevalence again rises to 70–90%. Seroprevalence peaks at 80–100% in children aged 3–5 years and then declines to 66–94% in the adult population [37,39]. Many clinical studies demonstrate a decline in HHV-6 antibodies with advancing age [32,39–41].

Exanthem subitum (roseola infantum) is one of the most common exanthems encountered in young children [42]. It is rarely seen before 3 months or after 4 years of age, and 95% of cases occur between the ages of 6 months and 3 years. Fifty-five percent of cases occur within the first year of life and 90% occur within the first two years of life [43]. The sex ratio of affected individuals is equal in most large studies. In a prospective study of 70 newborn babies, approximately 16% developed classic clinical signs of exanthem subitum during the first year of life [9]. According to an age distribution curve, the author concluded that approximately 30% of all children eventually develop the disease. One particular study found that HHV-6 could be cultured from the peripheral blood of 14% of children aged 2 years or less who were brought to the emergency room with a febrile illness [42]. Of those patients, 85% had at least a fourfold increase in IgG antibody titers against HHV-6, and an exanthem was noted at some time during the disease in 35% of children with positive cultures. The characteristic clinical feature of

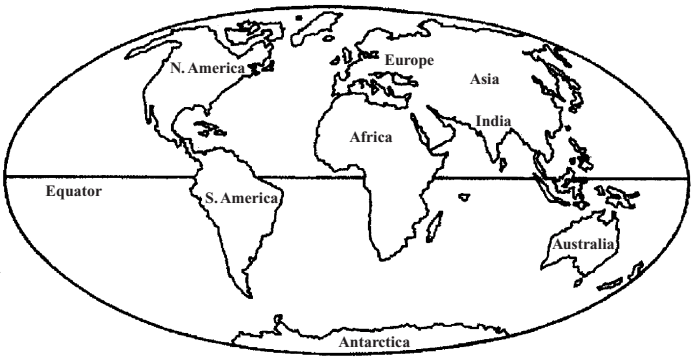
Table 8.1 Disorders Possibly or DefinitelyAttributed to HHV-6

Childhood illness
Exanthem subitum
Fever
Lymphadenopathy
Encephalitis
Meningitis
Hepatitis
Intussusception
Interstitial pneumonitis
Immune thrombocytopenic purpura
Adult illness
Mononucleosis
Lymphadenopathy
Encephalitis
Multiple sclerosis
Chronic fatigue syndrome
Autoimmune diseases
Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman syndrome)
Post-transplantation disorders
Bone marrow suppression
Skin eruptions
Interstitial pneumonitis
Encephalitis
Malignancy
Leukemia
Lymphoma
Oral carcinoma

TAXONOMY

Herpesviridae family
Betaherpesvirinae subfamily

GEOGRAPHIC WORLDWIDE INCIDENCE



TRANSMISSION



ZOONOTIC IMPLICATIONS

None

Figure 8.1 Incidence and transmission of human herpesvirus 6.

exanthem subitum, a rash that appears as the fever subsides, was noted in only 9% of these cases. The apparent discrepancy between a seroprevalence rate of 90–100% at 3 years of age and a clinical incidence rate of 30% is explained by the fact that the infection is associated with varied clinical manifestations, including subclinical infection. The infection has been described as having seasonal variation with the highest incidence in spring, summer, and fall [8,9,42,44,45]. In one study, 55% of cases occurred in February, March, and April [44]. Epidemics of exanthem subitum have been reported [46–49].

Pathogenesis

In 1950, Kempe proposed that the route of transmission was probably nasopharyngeal viral shedding from healthy adults [10]. This hypothesis was supported by the fact that case-to-case transmission was extremely rare and that infection occurred in infants who were carefully protected against exposure to sick children or adults [10,36]. In 1988, HHV-6 was isolated from the saliva of nine out of nine healthy individuals [20]. Subsequently, 63–95% of people tested were shown to have HHV-6 in their saliva [36,50,51]. Serial collections of saliva in healthy adults showed that viral shedding was intermittent and was not associated with specific antibody titer changes [36]. HHV-6 DNA and proteins have been demonstrated in submandibular, parotid, bronchial, and labial gland biopsies [52,53]. It is assumed that transfer of infected saliva from mother to infant is the most common source of HHV-6 transmission. Other tissues may serve as viral reservoirs as well. Okuno et al. [54] detected HHV-6 antigen in the tubular epithelium of rejected renal transplants. However, viral shedding in the urine is rare, both during the acute phase of exanthem subitum and after disease resolution [55,56]. There is also serological evidence that HHV-6 can be transmitted to transplant patients in their grafted tissues [57,58]. In utero transmission is rare, but can be a potential source of HHV-6 infection. One retrospective study of 799 cord-blood specimens demonstrated HHV-6-specific IgM antibodies in 0.28% of newborns [59]. A separate study of 305 newborns demonstrated HHV-6-specific DNA in uncultured cord blood mononuclear cells in 1.6% of cases [60]. Spontaneous abortions associated with HHV-6-positive placental or fetal tissue [61,62] and symptomatic congenital infection [63] have also been described. The possibility of perinatal transmission has been suggested after HHV-6 DNA was isolated from cervical tissue and secretions in women [64–66]. However, children born to mothers with positive cervical swabs did not acquire early HHV-6 infection in these studies. Viral secretion of HHV-6 in breast milk is doubtful, since HHV-6 DNA has not been found in breast milk [67], and 10 out of 11 babies withheld from breast milk seroconverted at the same age range as their breast-fed counterparts [68].

Like other members of the Herpesviridae family, HHV-6 is suspected to establish a latent infection in lymphocytes and monocytes, persist in many tissues, and may be reactivated at a later time, particularly in immunosuppressed patients [57,69]. Another

possible form of latency is via integration of the HHV-6 genome in the host chromosomes [162,163]. Moreover, in one report, early bone marrow progenitor cells were found to be infected [164].

Most reactivations in immunocompetent adults occur in the salivary glands; rarely does it result in systemic illnesses. In 1991, Kusuhara et al. [70] reviewed 23 otherwise healthy patients with previous exanthem subitum who developed a second episode of this disease. IgM and paired IgG serological examination revealed that 30% of the cases involved primary HHV-6 infection; therefore, the initial episode of the so-called exanthem subitum must have been caused by another virus. Fifty-seven percent of the cases had no evidence of current HHV-6 infection, and these second episodes were probably due to another cause. Seventeen percent of the cases were suggestive of reinfection or reactivation of HHV-6.

Transplant patients may undergo viral reactivation of HHV-6 as a result of immunosuppression [54,57,81–86]. Significant increases in HHV-6 IgG titers associated with clinical findings have been reported in recipients of cardiac, bone marrow, liver, and renal transplants [54,57,82,83,85]. Overall, 40–50% of transplant recipients have HHV-6 infection. Almost half of these patients have symptomatic disease, accounting for the most serious manifestations of HHV-6 infection, most commonly manifesting as bone marrow suppression [87]. HHV-6 infection or reactivation in this population can lead to serious illness, including hepatitis [85], fever and rash [83], pneumonitis [84,88], encephalitis [89,90], bone marrow suppression [91,92], and graft dysfunction or rejection [95]. HHV-6 is also known to have a synergistic deleterious effect with CMV in transplant recipients, since simultaneous detection of both HHV-6 and CMV DNAs in urine and serum was shown to be the strongest predictor of disease severity [94,95]. HHV-6 antigens have also been demonstrated in kidney biopsies of renal transplant patients who have CMV infection [173]. Additionally, a recent study found HHV-6 reactivation to be a common event in stem cell transplant patients in Beijing, and a correlation was shown between HHV-6B infection and CMV reactivation, early rash, and possibly increased incidence of hemorrhagic cystitis [174]. Both variant A and B have been known to cause disease in the transplant population [165].

Interestingly, several studies have suggested a potential causal relationship between HHV-6 reactivation and the development of graft-versus-host disease (GVHD) based on viral isolation, polymerase chain reaction (PCR), or serological testing [175–178], while others have failed to demonstrate a relationship [179,180]. Kitamura et al. studied 10 patients with GVHD, demonstrating that HHV-6 DNA levels correlated with the onset of skin rash; moreover, IL-10 levels increased, suggesting that the engrafted T cells were perhaps activated by HHV-6 reactivation [181]. The exact mechanism of this relation is unclear.

The role of HHV-6 in HIV-l-infected patients is not completely clear. It has been suggested that HHV-6 may play a role in HIV-1-related disease, since both viruses are tropic for CD4+ cells [96,97]. Studies of HHV-6 seroprevalence in HIV-1-positive individuals have yielded conflicting results, showing increased seroprevalence [15,71], decreased seroprevalence [98,99], or seroprevalence similar to that of the general population [36,39,98,100,101]. In vitro studies have produced equally conflicting data. One group found that the replication of HIV-1 increased when cells were coinfected with HHV-6 [96,102], while another group found that HIV replication was inhibited by HHV-6 [20,103,104]. More specifically, HHV-6 has been found to transactivate HIV [105–107], upregulate the expression of CD4 cells [102], and induce particular cytokines that can switch HIV from a latent to a replicative state [108,109]. It has been proposed that coinfection with HIV and HHV-6 may lead to further immunosuppression in the AIDS patient [15]. However, in HIV-positive children, AIDS progression seemed unaffected by the onset of HHV-6 infection; in fact, those whose disease progressed more rapidly, developed HHV-6 infection later [166]. More research is needed to further dissect this intriguing relationship. With highly active anti-retroviral therapy, the incidence of clinical HHV-6 disease in this population has significantly decreased. However, this virus may lead to widespread organ dissemination of the disease, pneumonitis, retinitis, and central nervous system involvement in patients with AIDS [110–112].

HHV-6 has been implicated in the pathogenesis of several other diseases (Table 8.1). Patients with systemic lupus erythematosus, Sjögrens syndrome, sarcoidosis, multiple sclerosis (MS), chronic fatigue syndrome, drug-induced hypersensitivity syndrome, and facial palsy have elevated seroprevalence and/or antibody titers to HHV-6 [71–76,172,182,184].

Active HHV-6 and HHV-7 infections have also been associated with pityriasis rosea, with mounting evidence in recent years [188–190]. Pityriasis rosea is a common, mild, papulosquamous skin eruption characterized by rose-colored patches that often have a collarette of scale and a herald patch, being the largest and earliest lesion, usually found on the back. The distribution of the lesions is said to be in a "Christmas tree" pattern on the back, parallel to the lines of cleavage of the body. This eruption is generally self-limited, although women who developed pityriasis rosea during pregnancy were associated with an increased risk of premature delivery and miscarriage [191]. Evidence suggests that pityriasis rosea may be secondary to reactivation of HHV-6 and HHV-7 leading to viremia [189].

The role of HHV-6 in causing MS is controversial. Both variants of HHV-6 are highly neurotropic; HHV-6 viral DNA sequences can be found in two thirds of brain specimens, and its viral antigen expression has been found in brain cells, including astrocytes of MS patients as well as adults without MS [167,172]. In studies involving MS patients, increased IgG titers were seen against HHV-6, and increased HHV-6B antigen expression was shown specifically in MS plaques and in oligodendrocytes [75,167]. There also appears to be an association between anti-HHV-6 IgM antibodies and early MS compared with healthy controls and late/progressive MS patients [168]. A recent study found that HHV-6 sequences are more prevalent in the cerebrospinal fluid (CSF) of MS patients than in patients with other neurological diseases [171]. The proposed mechanism of viral infection is thought to be molecular mimicry; possibly via cross-reactivity between myelin basic protein and HHV-6 [169,170]. Whether HHV-6 is the causal agent or the elevated titers represent an epiphenomenon or host response remains to be elucidated. Further research is needed to clearly define the role of HHV-6 in MS.

Patients with Hodgkin's, non-Hodgkin's, Burkitt's, and follicular large cell lymphoma, as well as those with angioimmunoblastic lymphadenopathy and acute myelogenous leukemia, have higher anti-HHV-6 antibody titers than normal [77–80]. A causal relationship between HHV-6 and any of these disorders remains

unproven; however, it has been hypothesized that HHV-6 may induce polyclonal B-cell activation, alter the immune system, and lower the body's threshold for oncogenesis.

Clinical Manifestations

Although HHV-6 has been implicated in a number of human illnesses, it has been proven to be the etiological agent of only one disease, exanthem subitum. The incubation period for this condition ranges from 5 to 15 days, with an average of 10 days [46–49]. The fever that heralds the abrupt onset of exanthem subitum is often as high as 38.4–40.6°C (102–105°F), may be constant or intermittent, and typically peaks in the early evening. Oropharyngeal lesions may precede the onset of the viral exanthem. Pharyngeal injection, round to linear erythematous macules, lymphoid hyperplasia, and tonsillar exudate have been described [8,10,42,44]. Mild injection of the tympanic membranes is frequently observed and conjunctival injection may be seen. Rare signs and symptoms include splenomegaly, abdominal pain, nausea, vomiting, and headache. Just before the onset of the exanthem, the patient may show a "sleepy" or "droopy" appearance resulting from localized palpebral edema [113]. This physical sign typically appears on the first to third day of fever and remits 24 hours after the onset of rash (see Table 8.2).

Table 8.2 Clinical Features of Exanthem Subitum

	%
High fever	98
Maculopapular rash	30–98
Mild diarrhea	68
Nagayama's spots (erythematous papules on the soft palate)	65
Cough	50
Cervical lymphadenopathy	31
Edematous eyelids	30
Bulging anterior fontanelle	26
Seizures	8

The appearance of the rash usually coincides with defervescence, although it has been noted to occur before the patient's temperature has returned to normal or up to 2 days after subsidence of the fever. The rash usually lasts 24–48 hours, but has been reported to be as fleeting as 2–4 hours or as persistent as 9 days. The lesions are described as discrete, circular or elliptical, erythematous, 2–5 mm, "rose-red" macules or maculopapules that are occasionally surrounded by a white halo (Figs. 8.2–8.7). The eruption may look very similar to that seen in rubella or rubeola [114]. The classic form of exanthem subitum occurs in approximately 30% of HHV-



(a) (b)

Figure 8.2 (a,b) Diffuse truncal eruption consisting of blanching erythematous macules appearing shortly after defervescence in an asymptomatic infant. (Photograph courtesy of Karen Wiss, M.D., Department of Dermatology, University of Massachusetts School of Medicine, Worcester, MA.)

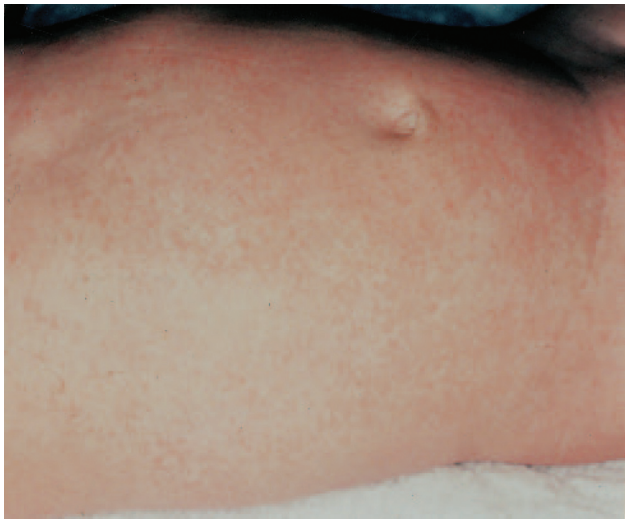


Figure 8.3 Rose-red macules on the abdomen of a young child. (Photograph courtesy of Susan Boiko, M.D., San Marcos, CA.)

6-infected individuals. HHV-6 infection may also appear as fever alone, exanthem alone, or asymptomatic infection [115,116]. An atypical eruption with oral and perineal lesions in a 13-month-old immunocompetent patient has also been described [117] (Table 8.3).



Figure 8.4 Discrete 1–3 mm erythematous oval macules and maculopapules on the lower abdomen.Some of the lesions are surrounded by a white halo. (Courtesy of Susan Boiko, M.D., San Marcos, CA.)



Figure 8.5 Discrete 1–3 mm erythematous oval macules and maculopapules on the lower abdomen. Some of the lesions are surrounded by a white halo. (Courtesy of Karen Wiss, M.D., Department of Dermatology, University of Massachusetts School of Medicine, Worcester, MA.)

Exanthem subitum is generally a benign disease and complications are infrequent. Neurological complications may include convulsions, which accompany the abrupt rise of fever [7,10,42,118–121]. There have been occasional descriptions of increased CSF pressure, as well as bulging of the anterior fontanelle [120,122,123]. Encephalitis has also been reported with prolonged convulsions followed by coma and hemiparesis [124–129]. Several infants have died as a result of HHV-6 pneumonitis [130–132]. Thrombocytopenic purpura has been reported in association with primary HHV-6 infection on several occasions [133–136]. In addition, the virus has been shown to cause hepatitis, sometimes with fatal outcomes [23,137–140]. A mononucleosis-like syndrome not attributable to CMV or Epstein-Barr virus has been linked to increased titers or seroconversion to HHV-6 in both children and adults [141–146].

Dermatopathology

Ultrastructural features of HHV-6 in lymphocytes from an infant with exanthem subitum have been described. The most characteristic ultrastructural feature is the coating of intracytoplasmic and extracellular nucleocapsids by a thick tegument, similar to human CMV. However, the two viruses can be differentiated by the lack of beaded viral cores and lack of formation of dense bodies in cells infected by HHV-6 [147]. Histological features of a skin biopsy taken from one exanthem subitum patient with an atypical eruption included interface dermatitis with scattered necrotic keratinocytes, epidermal hyperplasia, and a lichenoid infiltrate composed of lymphocytes and histiocytes [117].

Laboratory Findings

Common laboratory examinations are generally not helpful in making the diagnosis of exanthem subitum. The only consistent abnormality seen is in the white blood cell count (WBC) [10,38,49]. In the majority of cases, the total WBC count is low, although higher counts have been recorded early in the febrile period. The counts usually reach their nadir (as low as 3000 cells/mm^3) between days 3 and 6 of the illness and gradually normalize over a period of days. Concomitantly, the percentage of

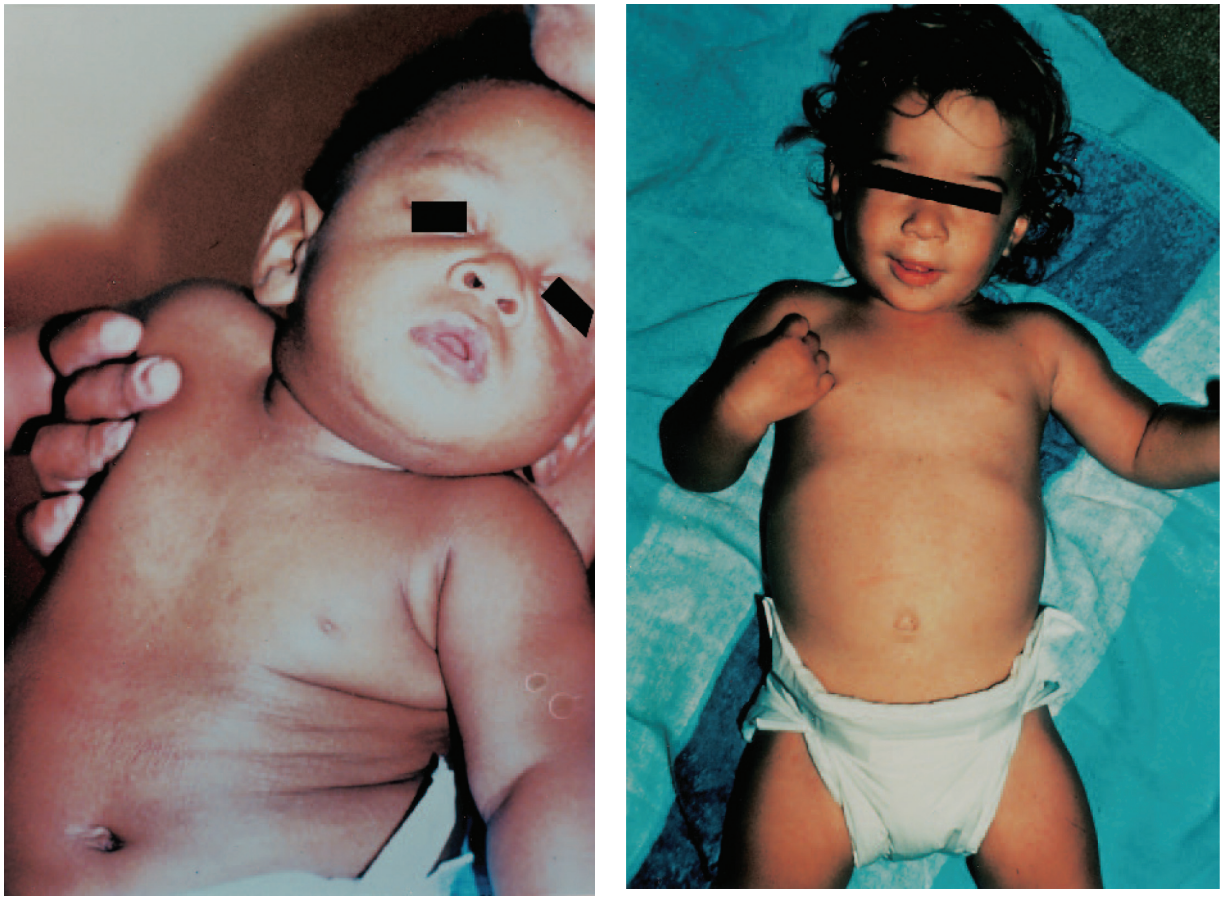


Figure 8.6, 8.7 Widespread exanthem consisting of discrete erythematous papules. Note relative sparing of the face and extremities.

lymphocytes increases from 50–60% to 80–90%. In a study that compared emergency room visits of children with acute febrile illnesses, the HHV-6-positive group had a significantly lower WBC count than that of the HHV-6-negative group (8.9×10^3/mm^3 versus 13.2×10^3/mm^3), but no difference was seen between the two groups in the percentage of lymphocytes [38]. Another study of 25 patients with exanthem subitum found that the majority of cases showed no leukopenia or leukocytosis [121]. These results suggest that even WBC counts may be variable.

Diagnosis

Exanthem subitum is a benign, self-limited disease with rare long-term sequelae. In the majority of cases, the diagnosis of exanthem subitum is based on the clinical findings of an otherwise asymptomatic young infant or child with abrupt onset of high fever followed by the appearance of a rash and defervescence. It has been shown that these clinical findings correlate with a positive virological result in 86% of cases. It must be remembered, however, that only approximately 30% of children with HHV-6 infection have classic exanthem subitum. In cases that are equivocal or atypical, serological studies may prove useful. Differential diagnoses are listed in Table 8.4.

Serological assays for HHV-6 antibody are available. They can be useful in primary infection with detection of IgM titers, a fourfold increase in IgG titers among acute and convalescent serum samples, or a 1.6-fold increase in antibody by enzyme immunoassay (EIA). Although the presence of IgM in infants and children is a reliable marker for primary infection, its detection

Table 8.3 Clinical Manifestations of Exanthem Subitum

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
10 days	Abrupt onset of high fever lasting 3–5 days	Serology: IgM or fourfold increase in IgG; PCR detection of HHV-6 DNA in cell-free serum or plasma; viral culture; electron microscopy	Child is typically asymptomatic during the febrile stage
13–15 days	Appearance of a rose-pink maculopapular or macular eruption on neck and trunk lasting 1–2 days. May sometimes spread to face and proximal extremities		Slight irritability and malaise may be associated with higher elevations of temperature
14–17 days	Blanching and then fading of rash		Rash is not pruritic and does not desquamate

Table 8.4 Differential Diagnosis of Human Herpesvirus 6

Measles: Begins as fever accompanied by upper respiratory symptoms, such as cough, coryza, and palpebral conjunctivitis. Koplik's spots are also characteristic. The skin eruption in measles develops as the fever rises, not as it remits, and the lesions are dark red macules and papules. In addition, discrete papules become more numerous and merge to form large, irregular blotchy patches or plaques

Enteroviruses (e.g, Coxsackie, ECHO): These viruses infect infants and young children, particularly during the summer. Associated exanthems may be rubelliform, morbilliform, scarlatiniform, vesicular, urticarial, petechial, or pustular. Boston exanthem, caused by Echo 16, has a similar presentation to that of exanthem subitum in that the exanthem may appear with or shortly after defervescence. However, associated signs and symptoms such as upper respiratory tract symptoms, conjunctivitis, vomiting, diarrhea, and aseptic meningitis frequently occur with this disease

Adenovirus: The viral infections typically affect children ages 6 months to 5 years and most commonly occur during the winter and spring months. In addition to fever and upper respiratory symptoms, maculopapular,morbilliform, rubelliform, or petechial eruptions have been described

Epstein-Barr virus This virus can cause exanthems in up to one third of infected children. Maculopapular, petechial, papulovesicular, scarlatiniform, urticarial, and erythema multiforme-like exanthems have all been described. Fever, upper respiratory tract symptoms, hepatosplenomegaly, and adenopathy are often present at the time of the skin eruption.

Rubella: Begins with general malaise and a skin eruption that may vary from morbilliform on the chest to scarlatiniform over the abdomen and nodular on the extensor surfaces. Occipital adenopathy is prominent. Arthritis, encephalitis, and fetal damage may occur

Fifth disease (erythema infectiosum): Generally affects children older than 5 years of age. The infection begins with general malaise and low-grade fever, which is followed by malar erythema, or a "slapped-cheek" appearance. Subsequently, a reticular erythema develops over the extensor surfaces of the extremities. Arthralgias may be prominent in adults. Aplastic crisis may occur in individuals with hemoglobinopathies

Scarlet fever: Patients typically have fever, headache, malaise, marked pharyngitis, and adenopathy. While the patient is febrile, a "sandpaper-like" maculopapular eruption will appear, often accentuated in the skin folds. Circumoral pallor is common. Linear petechial lesions in the antecubital fossae and axillary folds, known as Pastia's lines, as well as subsequent acral desquamation, are helpful in making the diagnosis

Rocky Mountain Spotted Fever (and other rickettsial infections): Begins with an abrupt onset of fever, headache, and malaise with subsequent development of distal blanching macules that progress to involve the proximal extremities and trunk. The eruption ranges from blanching erythema to petechial and purpuric lesions. A history of tick bite is helpful but often not available.

Kawasaki's disease: Five of six criteria must be met for the diagnosis of this disease: fever persisting for 5 days or more, polymorphous eruption, conjunctival injection, oral mucosal changes, acral changes, and cervical lymphadenopathy. The major complication is coronary artery vasculitis

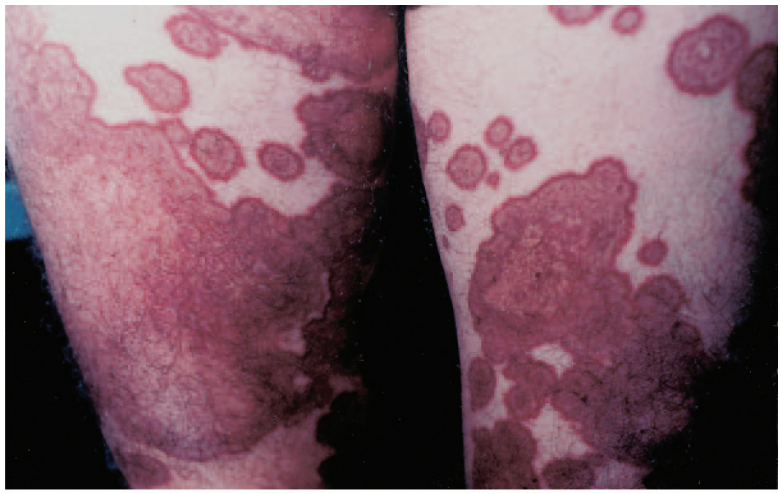
in adults can also appear during reactivation of HHV-6 [148]. Of note, the dzetection of IgG titer increases in paired serum samples can only provide retrospective information, and elevation can be seen in other herpesvirus infections.

HHV-6 in formalin-fixed, paraffin-embedded tissue biopsy specimens can be detected via immunohistochemical stains. However, only cells that are actively infected demonstrate positivity with this technique. Latent infections will stain negatively with these antibodies [183].

Other laboratory investigations include viral culture, electron microscopic studies, detection of viral DNA using Southern blot techniques, in situ hybridization, and PCR [18]. Viral culture, PCR, and electron microscopy are highly accurate and can be used reliably during the febrile phase of the



(a)



(b)

Figure 8.8 (a,b) Sinus histocytosis with massive lymphadenopathy (Rosai-Dorfman syndrome). Multiple discrete plaques with erythematosus pigmented borders and central clearing were observed on the face, neck, trunk, arms, and legs. Virological confirmation of DNA from HHV-6 variant B in these plaques was obtained by using PCR. (Photographs courtesy of Amit Pandya, M.D., Department of Dermatology, University of Texas Southwestern School of Medicine, Dallas, TX.)

disease when detectable viremia can reach 100%. Viral culture is not routinely feasible because it is technically demanding and may take over 1 week for results. Detection of HHV-6 DNA in cell-free plasma, CSF, or serum by PCR is a definitive marker of active HHV-6 replication [149,150]. It must be remembered, however, that detectable virus decreases to 20% by day 4 of the illness and to 7% by days 5–7. Since the infection is permanent and intermittent shedding of viral particles may occur, there are doubts about the usefulness of these tests beyond the identification of primary infection. One study found that rapid microbiological diagnosis of acute HHV-6 infection is best performed with a combination of IgM serological methods and PCR detection of DNA in serum [151]. Quantitation of HHV-6 may prove useful and an investigational technique is underway. This method may then afford the opportunity to confirm the association of HHV-6 with various other disease syndromes.

Treatment and Prophylaxis

Although HHV-6 infection is usually a benign disease that requires no treatment, the potential for serious infections in both immunocompetent and immunocompromised hosts raises the need for antiviral therapy. HHV-6 lacks thymidine kinase, as does CMV, and the antiviral susceptibilities of these two human herpesviruses are similar [152]. In vitro studies show that HHV-6 is susceptible to inhibition by pyrophosphate analogues, phosphonoacetic acid, foscarnet, and ganciclovir [153–155]. From a comparative study of the in vitro activity of acyclovir, ganciclovir, cidofovir, and foscarnet against HHV-6A in lymphocytes, cidofovir appears to be the most selective, most potent agent [187]. HHV-6 is relatively resistant to acyclovir [156]. HHV-6A appears to be relatively resistant to ganciclovir, while HHV-6B is susceptible [130,157]. Few clinical trials have been undertaken to explore the therapeutic options for HHV-6. Ganciclovir has been used successfully to prevent HHV-6 reactivation in patients who have had stem cell transplantation [185]. A few case reports have described the successful treatment of serious HHV-6 infection with foscarnet and/or ganciclovir, but the appropriate dosage is not known [90,158]. Several authors recommend the use of antiviral therapy for the treatment of serious HHV-6 infections, such as meningoencephalitis [90,159], or for the treatment of actively infected transplant recipients with bone marrow suppression, encephalitis, or pneumonitis [87]. Currently, research is under way for novel drugs such as nucleoside and nonnucleoside analogues, as well as protein kinase inhibitors, which may demonstrate potent and selective activity against HHV-6 [186]. Further studies are needed before appropriate treatment of significant disease or prophylaxis for high-risk individuals can be recommended.

Conclusion

HHV-6 was first isolated in 1986 and was identified as the etiological agent for exanthem subitum in 1988. Since that time, the virus has been shown to be ubiquitous, infecting 90–95% of the worldwide population. Although associations with many different syndromes have been noted, the only disease for which HHV-6 has been proven as the etiological agent is exanthem subitum. This disease, previously thought to infect about 30% of children, has now been shown to have several forms, including the classic presentation of fever followed by rash, fever alone, rash alone, or a subclinical syndrome defined only by isolation of the virus or detection of antibodies to the virus. By 3 years of age, 95% of children have contracted the virus. The virus appears to remain in the salivary glands of infected patients for life and has been reported to reactivate if the patient becomes immunosuppressed. Additional reports of the occurrence of hepatitis, pneumonitis, and transplant graft rejection, among others, are commonly associated with these patients.

Elevated titers of HHV-6 have also been associated with several other disorders, including pityriasis rosea, lymphoproliferative disorders, HIV infection, sinus histocytosis with massive lymphadenopathy (Fig. 8.8) [160], drug hypersensitivity syndromes, neurologic diseases, GVHD, systemic lupus erythematosus, Sjögrens syndrome, sarcoidosis, MS, chronic fatigue syndrome, drug-induced hypersensitivity syndrome, and facial palsy. Whether a definite association is found, and to what extent the role of HHV-6 plays in the pathogenesis of these other syndromes, remains to be elucidated after careful study.

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9 Human Herpesvirus 7

Jing Feng Gill and Angela Yen Moore

Human herpesvirus 7 (HHV-7) is a recently discovered lymphotropic herpesvirus that is ubiquitous across the globe (Fig. 9.1). No clinical disease has yet been definitely linked to HHV-7, although several different conditions, such as exanthem subitum and pityriasis rosea (PR), have been attributed to the virus by some investigators.

History

In 1990, Frenkel et al. first isolated what is now known as HHV-7 from cultured and activated CD4+ T-lymphocytes in peripheral blood of a healthy young adult [1]. DNA analysis revealed this virus to resemble HHV-6 and cytomegalovirus (HCMV). HHV-7 belongs to the beta herpesvirus subfamily [2,3].

Incidence

The epidemiology of HHV-7 appears similar to that of HHV-6. The majority of adults have serological evidence of previous HHV-7 infection [4–6], with a seroprevalence rate of more than 85% in the USA [7]. Primary infection occurs slightly later than that for HHV-6, although most infections develop in the first 5 years of life [8]. While the highest period for primary HHV-6 infection is 6–12 months of age, that for HHV-7 infection is 1–2 years of age [9]. An American study of 164 children by Lanphear et al. revealed that low income and black race were risk factors for the early acquisition of HHV-7 [10]. An increased rate of infection in November, when compared with those of September and October, indicates seasonal variability.

Pathogenesis

Little is known about the pathogenesis of HHV-7 infection. The portal of entry, site of primary infection, and mechanism of latency are yet to be determined [7]. The human salivary glands are the only host cells known to persistently produce infectious HHV-7 virions. Several investigators have shown that HHV-7 can be readily isolated from the saliva of adults and children over the age of 12 months [11–14]. Although not definitively proven, transmission of HHV-7 likely occurs through saliva. The epidemiological patterns of transmission suggest intimate family contact and exchange of the salivary excretions [9]. The possibility of perinatal transmission of HHV-7 is also a consideration, since HHV-7 DNA has been detected in cervical swabs of pregnant women [15].

While little is known of its pathogenesis, HHV-7 is trophic for T cells, and CD4 has been identified as the cellular receptor for this virus [16]. The host-cell range for HHV-7 is significantly narrower than that of HHV-6, and its infectivity is shown to be limited to cultured CD4+ T cells, specifically the SupT1 cell line [48]. Like HIV-1, additional surface protein and/or co-receptor interactions besides CD4 are needed for HHV-7 infection, since HHV-7 is unable to penetrate many other CD4+ cell lines in vitro [16]. These may include the presence of specific cell surface sulfated proteoglycans [49]. Cellular infection is evidenced by significant decreased expression of CD4 within 1 week after infection, as well as the presence of cellular syncytia and cell membrane blebbing [1,4,17,50].

It has been suggested that HHV-7 may have an immunosuppressive effect, since CD4+ T-lymphocytes play a crucial role in the development of immunity and HHV-7 down-modulates the expression of the CD4 receptor [17]. This has led researchers to speculate whether HHV-7 can be used as an immunotherapeutic agent to down-regulate autoimmune processes involving CD4+ T-cell clones [51]. Further, since human immunodeficiency virus (HIV) and HHV-7 viruses compete for the same cell receptor, investigation is under way on whether binding of HHV-7 decreases the infectivity of HIV on CD4+ T-lymphocytes [16]. Another application of HHV-7 in the treatment of HIV may be the development of novel pharmaceutical compounds that competitively bind to HIV co-receptor gp120, so that CD4 binding does not occur [51]. Finally, T-lymphotropic vectors are in development from HHV-7 for potential use in gene therapy for diseases affecting CD4+ T-lymphocytes, such as acquired immunodeficiency virus (AIDS), autoimmune diseases, and T-cell lymphomas [18].

HHV-7 typically remains latent in the infected human host [19]. This virus has been shown to establish latency in peripheral blood mononuclear cells and may be propagated in vitro in activated cord blood lymphocytes. The range of tissue hosts of HHV-7 has been considered more limited than that for HHV-6, although Kempf et al. demonstrated the persistence of HHV-7 antigen in human lungs, skin, and mammary glands [20]. The infected cells were distinctly different from lymphocytes, and HHV-7 was not detected in brain, spleen, or large intestine tissues. These authors also suggest from their results that HHV-7 causes a persistent rather than a true latent infection. Compared with HHV-6, HHV-7 is more cell-associated, less cytopathic, and has a slower growth rate in culture [21]. The two viruses are serologically distinct, and prior infection with HHV-6 provides no protection against HHV-7 infection [2].

Little information is known regarding the effects of HHV-7 infection in immunocompromised individuals [22,23]. It has been shown that HHV-7 has been reactivated from latency in transplant recipients (kidney and bone marrow) [24,25]. One Japanese study of HHV-7 in bone marrow transplantation found no associated clinical symptoms that could be attributed to the virus [26]. Although the role of HHV-7 in transplantation is yet to be determined, this virus has been suspected as a cofactor for the development of other infections (CMV) or the delay of engraftment [24]. In HIV+ adults, one report found that the expression of HHV-7 is increased compared to the general population [52]. This apparent paradoxical result does not appear to be clinically significant. As mentioned previously, HHV-7 infection leads to down-regulation of CD4 expression, which may be potentially beneficial in HIV+ patients. Further studies are necessary to investigate these interesting findings.

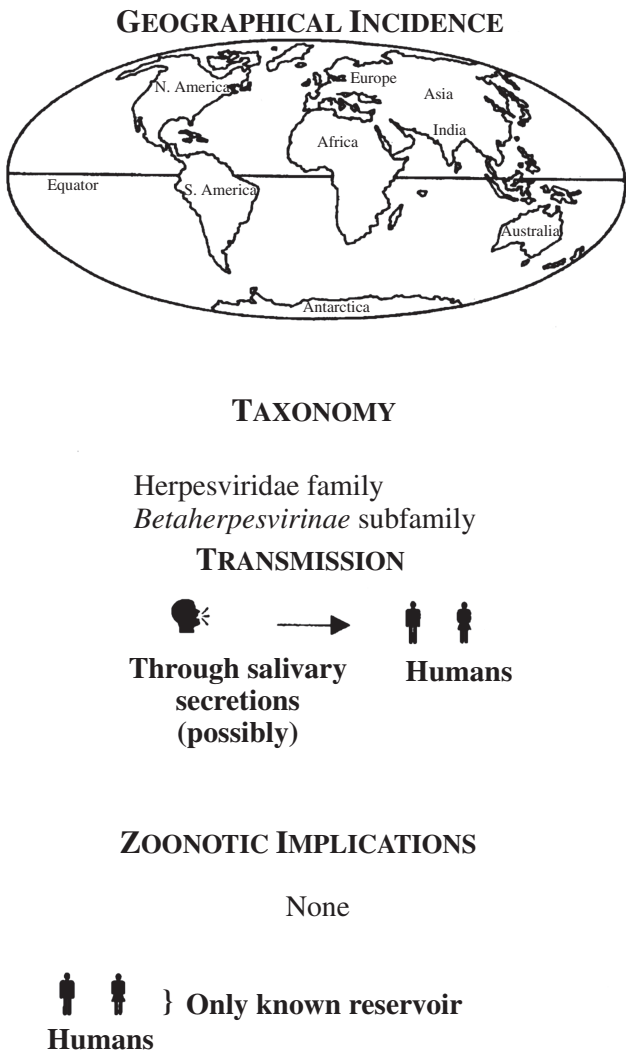


Figure 9.1 Incidence and transmission of human herpesvirus 7.

Limited antigenic cross-reactivity has been reported between HHV-6 and HHV-7 [8,11], due to the significant genetic homology between the two viruses. A study by Huang et al. revealed that almost 36% of positive anti-HHV-7 serological tests came from cross reactions with HHV-6 [9]. These authors noted that primary HHV-6 infection can induce reactive HHV-7 antibodies, although the titer is lower than that of primary HHV-7 infection. This reaction has also been observed by other authors [8,27]. However, a separate study has suggested that HHV-7 infection can induce HHV-6 antibodies, but not the reverse [28]. In this investigation, several patients with documented HHV-7 seroconversion developed a simultaneous elevation of HHV-6 antibody titers, which resembled a booster effect. This HHV-6 antibody response has been seen in other studies of primary HHV-7 infections [27,29]. An in vitro study has demonstrated that HHV-7 has the potential to reactivate latent HHV-6 in activated peripheral blood mononuclear cells [30]. Although not proven, these authors hypothesize that in vivo primary infection with HHV-7 could be linked to the reactivation of HHV-6, which subsequently causes the clinical manifestations of exanthem subitum.

Clinical Manifestations

As previously stated, HHV-7 has not been definitively linked to any clinical disease (Table 9.1). Early on, HHV-7 was isolated from a patient with chronic fatigue syndrome [2], but no association was found in seroepidemiologic studies. HHV-7 has been isolated from one child with a chronic Epstein-Barr virus-like clinical infection [31]. Although no other viruses could be isolated in this patient, the definitive role of HHV-7 cannot be established from this one case report. Two children with minor upper respiratory tract infections were documented to have HHV-7 seroconversion, suggesting HHV-7 as the etiology [28]. Several authors have also linked HHV-7 infection with childhood febrile illnesses, sometimes complicated by seizures [29,32–34]. One study demonstrated that children with primary HHV-7 infection were more likely to have seizures (75%) when compared with children with primary HHV-6 infection (17%) [32].

Much controversy exists regarding the role of HHV-7 in PR. This association was first proposed by Drago et al. in 1997, when they isolated HHV-7 DNA in lesional skin biopsy specimens, peripheral blood mononuclear cells, and plasma specimens of 12 patients with this disease [35,36,53,54]. Watanabe and colleagues later confirmed these findings [40,55]. However, these results have not been established by other studies of HHV-7 DNA by polymerase chain reaction (PCR) and antigen detection in skin lesion specimens or HHV-7 serological tests in patients with PR [37–39,56–59]. A systemic review published by Chuh et al. analyzed the above published data for a causal association according to the Fredericks and Relman criteria of viral infection, and deemed that the positive findings of the causation were unsubstantiated [61]. These studies are limited in that the techniques used (i.e., nested PCR) are too sensitive for a ubiquitous virus, and therefore cannot provide definite causal evidence. A recent article by Broccolo et al. used a different method of

Table 9.1 Clinical Manifestations of Exanthem Subitum

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
10 days	Abrupt onset of high fever, lasting 3–5 days	Serology: IgM or 4-fold increase in IgG; PCR detection of HHV-6 or HHV-7 DNA in cell-free serum or plasma	Child is typically asymptomatic during the febrile stage
13–15 days	Appearance of a rose-pink maculopapular or macular eruption on neck and trunk, lasting 1–2 days. May sometimes spread to face and proximal extremities.	Viral culture	Slight irritability and malaise may be associated with higher elevations of temperature
14–17 days	Blanching and then fading of the rash	Electron microscopy	Rash is not pruritic and does not desquamate

Table 9.2 Differential Diagnoses of Exanthem Subitum

Measles: Begins as fever accompanied by upper respiratory symptoms, such as cough, coryza, and palpebral conjunctivitis. Koplik's spots are also characteristic. The skin eruption in measles develops as the fever rises, not as it remits, and the lesions are dark red macules and papules. In addition, discrete papules become more numerous and merge to form large, irregular blotchy patches or plaques with measles

Enteroviruses (e.g, Coxsackie, ECHO): These viruses infect infants and young children, particularly during the summer. Associated exanthems may be rubelliform, morbilliform, scarlatiniform, vesicular, urticarial, petechial, or pustular. Boston exanthem, caused by ECHO 16, has a similar presentation to that of exanthem subitum in that the exanthem may appear with or shortly after defervescene. However, associated signs and symptoms such as upper respiratory tract symptoms, conjunctivitis, vomiting, diarrhea, and aseptic meningitis frequently occur with this disease

Adenovirus: These viral infections typically affect children ages 6 months to 5 years and most commonly occur during the winter and spring months. In addition to fever and upper respiratory symptoms, maculopapular, morbilliform, rubelliform, or petechial eruptions have been described

Epstein-Barr virus: This virus can cause exanthems in up to one third of infected children. Maculopapular, petechial, papulovesicular, scarlatiniform, urticarial, and erythema multiforme-like exanthems have all been described. Fever, upper respiratory tract symptoms, hepatosplenomegaly, and adenopathy are often present at the time of the skin eruption

Rubella: Begins with general malaise and a skin eruption that may vary from morbilliform on the chest to scarlatiniform over the abdomen and nodular on the extensor surfaces. Occipital adenopathy is prominent. Arthritis, encephalitis, and fetal damage may occur

Fifth disease (erythema infectiosum): Generally affects children older than 5 years of age. The infection begins with general malaise and low-grade fever, which is followed by malar erythema, or a "slapped-cheek" appearance. Subsequently, a reticular erythema develops over the extensor surfaces of the extremities. Arthralgias may be prominent in adults. Aplastic crisis may occur in individuals with hemoglobinopathies

Scarlet fever: Patients typically present with fever, headache, malaise, marked pharyngitis, and adenopathy. While the patient is febrile, a "sandpaper-like" maculopapular eruption will appear, often accentuated in the skin folds. Circumoral pallor is common. Linear petechial lesions in the antecubital fossae and axillary folds, known as Pastia's lines, as well as subsequent acral desquamation, are helpful in making the diagnosis

Rocky Mountain Spotted Fever (and other rickettsial infections): Begins with an abrupt onset of fever, headache, and malaise with subsequent development of distal blanching macules that progress to involve the proximal extremities and trunk. The eruption ranges from blanching erythema to petechial and purpuric lesions. A history of tick bite is helpful but often not available

Kawasaki's disease: Five of six criteria must be met for the diagnosis of this disease: fever persisting for 5 days or more, polymorphous eruption, conjunctival injection, oral mucosal changes, acral changes, and cervical lymphadenopathy. The major complication is coronary artery vasculitis

calibrated quantitative real-time (CQ)-PCR to compare the HHV-7 viral load in PR, which was purported to distinguish between active and latent viral-infected cells. They showed that HHV-7 (more than HHV-6) was active during early PR, and that the plasma viral load is associated with PR symptoms [62]. PR is a common, mild, papulosquamous skin eruption characterized by rose-colored patches with a collarette of scale on the trunk and proximal extremities which are distributed along the Blashko's lines in a "Christmas tree" pattern on the back, parallel to the lines of cleavage of the body. Lesions often begin with a herald patch, which is the largest and earliest lesion, usually found on the back (Fig. 9.2). PR is self-limited, and lasts an average of 6 weeks, although PR may persist up to a year if lesions are treated with systemic steroids or phototherapy.

Exanthem subitum is the most convincing clinical disease thought to be caused by HHV-7. While this illness is known to be caused by HHV-6, several studies have implicated HHV-7 as an etiological factor in a percentage of cases [27,28,41–44]. One specific study evaluated paired serological tests to both HHV-6 and HHV-7 from 49 patients with clinically diagnosed exanthem subitum [28]. Based on evidence of seroconversion, HHV-6 caused 73.5% of cases, while HHV-7 led to 10.2% of cases. While investigating the association of HHV-7 and exanthem subitum, Tanaka et al [27]. have noted that the rash associated with HHV-7 infection is lighter in appearance and occurs slightly later during the course of disease than that of HHV-6 infection. They also observed that incomplete clinical features of exanthem subitum may occur with both viruses, producing only high fever and no rash. Neurological complications of HHV-7-induced exanthem subitum have been reported, such as acute hemiplegia and febrile convulsions [41]. Cerebrospinal fluid analyses from two of these cases were suggestive of encephalitis. Chapter 8 provides an overview of the clinical features of exanthem subitum.



Figure 9.2 Close-up of herald patch with collarette of scale seen in pityriasis rosea as well as rose-colored patches distributed along the Blashko's lines.

Table 9.3 Treatment of Exanthem Subitum

Symptom	Treatment
Fever	Acetaminophen or nonsteroidal anti-inflammatory drugs
Cough	Antitussives
Exanthem	Reassurance. No treatment is needed
Neurologic complications	Anticonvulsants for seizures. Control of intracranial pressure and frequent neurological monitoring are indicated for meningitis

Diagnosis

HHV-7 infection can be detected by several methods. Serological diagnosis is made with immunofluorescence assays, enzyme immunoassays, or immunoblot assays, each using HHV-7 infected cells as the antigen source [2,8]. To decrease the rate of cross-reactivity with HHV-6 and to increase the specificity, absorption steps are essential with these tests. One longitudinal serological study noted that anti-HHV-7 titers, which were falsely elevated because of HHV-6 cross-reactivity, remained at a level less than 20 [9]. They concluded that a titer of at least 20 is appropriate for the serological diagnosis of HHV-7 infection.

HHV-7 DNA can be detected in specimens with PCR, most commonly from throat swabs or peripheral blood samples. Antigens to HHV-7 can be detected by flow cytometry and immunohistochemical tests. The virus can also be isolated and cultured from saliva or peripheral blood of infected patients. After preparation, the samples are inoculated onto mitogen-stimulated human cord blood lymphocytes. Cytopathic effects are typically seen in the culture within 2–4 weeks of cultivation, and the virus can be confirmed with an immunofluorescence assay. A variety of diseases may mimic exanthem subitum, as shown in Table 9.2.

Treatment

No treatment is currently available or recommended specifically for HHV-7 infection (Table 9.3). Treatment of PR is symptomatic, with topical steroids and antihistamines, since the exanthem is self-limited and usually resolves after an average of 6 weeks. Phototherapy and systemic steroids are not recommended since they may prolong the duration of PR for up to a year. The susceptibility of the virus to antiviral agents is unknown. One in vivo small-scale study suggested that HHV-7 activity is suppressed with full therapeutic doses of both acyclovir and ganciclovir [24]. However, prophylactic or suppressive doses of these drugs had no noticeable impact on HHV-7 in this study. A handful of in vitro studies have demonstrated the inhibition of HHV-7 by various agents, such as ganciclovir, foscarnet, cidofovir, lobucavir, and others [45–47]. However, more research will be necessary to characterize the optimal treatment for HHV-7 and when or if such treatment would be indicated.

Conclusion

HHV-7 is a recently discovered virus with many unsolved puzzles. Medicine continues to search for a clinical disease to which it may be attributed. Our understanding of the pathogenesis, transmission, and development of latency of this virus remains limited. With further knowledge acquired through painstaking research, we may one day discover that HHV-7 has a much more important role in clinical medicine, especially in the treatment of HIV and autoimmune diseases, as well as its role in exanthem subitum, PR, and other disorders.

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10 Human Herpesvirus 8

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Kaposi's Sarcoma

Human herpesvirus 8 (HHV-8), previously called Kaposi's sarcoma-associated herpes virus (KSHV), was first detected in 1994 in Kaposi's sarcoma (KS) from patients with acquired immunodeficiency syndrome (AIDS). Using a modified form of polymerase chain reaction (PCR), all four types of KS have been associated with HHV-8: (1) the classic form that typically occurs in elderly Mediterranean men, (2) the endemic form that affects persons of all ages in tropical Africa, (3) the immunosuppressive form that occurs in organ transplant recipients, and (4) the AIDS-associated form (Fig. 10.1) [1–4].

History

In 1872, Moriz Kaposi first described a rare cutaneous neoplasm that predominantly affected elderly men of Jewish and/or Mediterranean descent [5]. Intense medical interest did not develop until the AIDS epidemic, when clusters of young homosexual men began to develop KS [6]. For many years, the cause of KS was suspected to be an infectious agent [7], but it was not until 1994 that Chang et al. [8] identified herpes-like DNA sequences isolated from KS lesions of a patient with AIDS. This newly discovered virus was found to be closely related to the gammaherpesviruses, Epstein-Barr virus (EBV), and *Herpesvirus saimiri*, all of which infect lymphocytes and cause cell immortalization and transformation [9]. HHV-8 has also been associated with other cancers, such as Castleman's disease (an angiofollicular hyperplasia) [10–12] and body-cavity-based lymphomas (BCBL) [13–15] in patients with AIDS.

Incidence

Classic KS occurs mainly in individuals of Mediterranean or Ashkenazi Jewish descent and is uncommon in countries with a small proportion of these ethnic groups. The average age of onset for classic KS is 65 years of age. Approximately 0.6% of organ transplant recipients (e.g., kidney, heart, and liver) develop KS, typically within 5 years of transplantation [16,17]. These tumors most frequently involve transplant recipients of Mediterranean, Jewish, Arabic, or African ancestry [18]. Human immunodeficiency virus (HIV)-positive homosexual men develop KS at a rate that is 20,000-fold higher than that of the general population [19]. African endemic KS is the cause of up to 10% of all histopathologically proven malignancies in southern equatorial Africa with a predominance in males of all ages.

HHV-8 has been found in the vast majority of all types of KS lesions across the globe and seroprevalence varies by geographic location. HHV-8 seropositivity is uncommon prior to puberty in the USA, as prevalence rates of antibodies to lytic and latent HHV-8 antigens vary from 0 to 5% in this population [20,21]. The prevalence of antibodies to lytic and latent HHV-8 antigens in otherwise healthy adults without KS in the USA has been reported as high as 25–27% [20,21]. Overall, the seroprevalence rates range from less than 5% in North America, the UK, and northern Europe, to approximately 10% for southern Europe [22–24]. In African countries, the HHV-8 seroprevalence rates range from 30 to 100% [22,25–28]. Approximately 30% of HIV-1-infected homosexual men in North America and Europe have evidence of HHV-8 infection [22,29–31]. The seroprevalence rates for HHV-8 closely correspond with the incidence rates for KS, as non-AIDS-related KS occurs more commonly in southern Europe and most frequently in Africa [19,32–34].

Pathogenesis

Several studies have evaluated the spread of HHV-8 infection, although our knowledge of this aspect is far from complete. The studies suggest that HHV-8 is spread mainly through sexual transmission among homosexual men in the USA [3,35], whereas mother-to-child transmission occurs most commonly in African countries [26,36,37]. In a study of perinatal transmission, approximately one third of HHV-8-infected mothers transmit the virus to their offspring [36]. Anal receptive intercourse appears to be a major mode of sexual transmission, since the incidence of HHV-8 is higher in homosexual men than in HIV-infected women [20]. One study found HHV-8 seropositivity to be strongly associated with the number of homosexual male partners and the presence of HIV infection [35]. Infectious HHV-8 was recovered from the donated blood of one individual, indicating that HHV-8 could possibly be transmitted by blood transfusion [38]. Despite the relatively high seroprevalence reported in some non-KS endemic regions of the USA (23%), no HHV-8 virus was detected in blood from healthy adult donors in the same region (39,40). In Uganda, HHV-8 occurrence among prepubertal children suggests a horizontal pattern of transmission, perhaps similar to that of EBV [27].

In addition to KS skin lesions, the virus has been isolated in normal skin [41,42], peripheral blood mononuclear cells [41,43–48], seminal fluid [41,43,49–52], and saliva [41,53–55] from HHV-8-infected persons. Presence of HHV-8 in the blood is strongly predictive of later development of KS, with 75% of these patients developing KS within 5 years [44].

Nucleotide sequence analysis at five distinct loci across the 14-kb genome of more than 60 HHV-8 samples from KS and lymphoma from North America, Africa, Middle East, Asia, and the Pacific have revealed that they cluster into four major subtypes (A–D). These can be further differentiated into 13 distinctive variants or clades, with B subtypes, found in Africa, being the original. Interestingly, it is hypothesized that the evolution of four distinct strains, each concentrated in different locales, correlates with models describing human migration out of Africa in three distinct waves [56]. The strong association between locales and subtype also indicate that HHV-8 is much more cryptic and much more difficult to transmit than other herpes viruses [57,58]. This and other epidemiological data thus far strongly suggest that HHV-8 is less ubiquitous than other human herpesviruses [59].

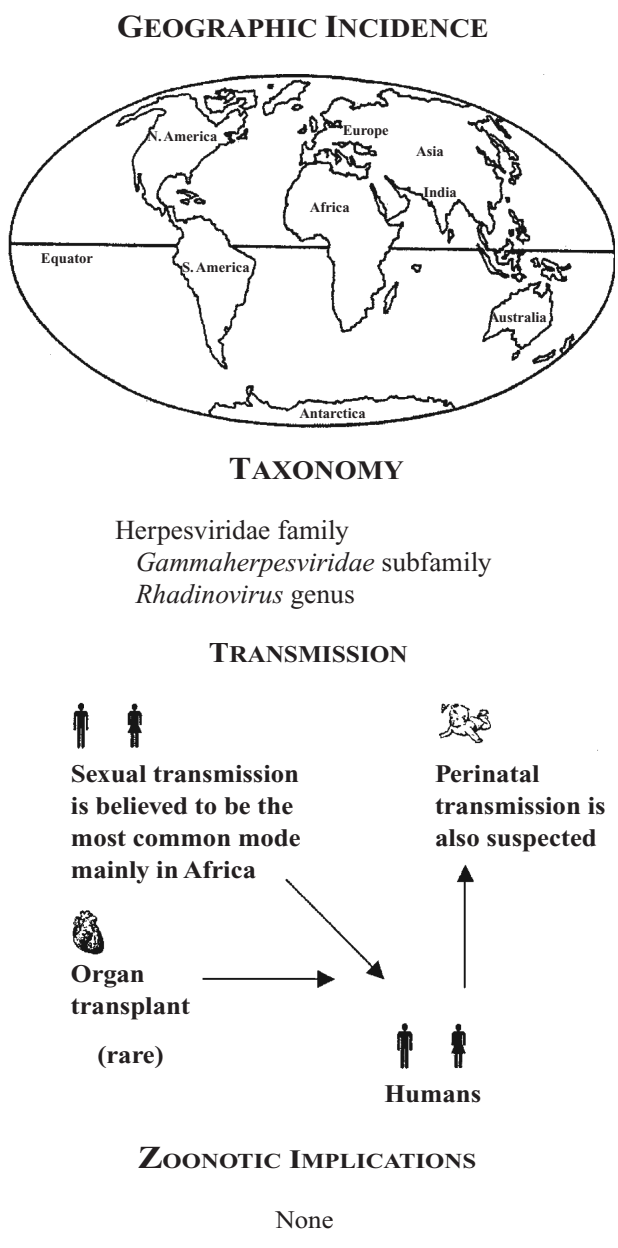


Figure 10.1 Incidence and transmission of human herpesvirus 8.

KS is considered to be a lymphatic endothelial malignancy, although the origin of this tumor is not completely known [60]. Whether this tumor is a true malignancy or a reactive cellular proliferation caused by angiogenic factors is not clear. The function of HHV-8 in the development of KS is not yet understood. The virus likely plays a causative role in KS, but this remains uncertain [35,61,62].

The role of HIV-1 infection in the promotion of HHV-8 replication has been assumed to be due to immunosuppression of the host. Yet, HIV-2 infection is significantly less often associated than HIV-1 with KS despite a high prevalence of HHV-8 [28,63]. In addition, the risk of KS is much higher in those with HIV-1 infection when compared with organ transplant recipients receiving pharmacologic immunosuppression [19]. The promotion of aberrant cytokine production by the HIV-1 tat protein may play a causal role in the development of KS [64,65]. HIV-1 tat stimulates the activation and growth of endothelial cells as well as the expression and production of adhesion molecules and angiogenic factors such as basic fibroblast growth factor (b-FGF).

The 14-kb genome of HHV-8 is flanked by GC-rich terminal repeat units. This HHV-8 genome has been sequenced in its entirety except for a 3-kb sequence near the right end of the genome. Of the 95 genes of HHV-8, 25 are unique to the Herpesviridae [60]. Molecular studies have revealed a number of viral oncogenes within the HHV-8 genome, most of which are not expressed in the latent state of infection [61].

Several of the genes believed to be most important in oncogenicity of the HHV-8, including ORF 71, ORF 72, and ORF 73, will be selectively discussed because they are consistently expressed in the latent state of HHV-8 infection [62]. The potential relevance of viral IL-6 (vIL-6) will also be discussed. Although this gene is expressed in the lytic cycle, investigators believe it may be significant in a paracrine fashion [66–69].

ORF 71 encodes the viral homologue to cellular Fas-ligand-interleukin-2-converting enzyme inhibitor protein (FLIP), which can inhibit Fas-mediated apoptosis. Normally, when the CD95 or Fas ligand is activated by natural killer and other effector cells, signal transduction is mediated through the Fas-associated death domain protein (FADD). This protein subsequently activates death effector domains (DED) of the protease, also known as caspase-8. This activates cysteine proteases, which are responsible for activating the apoptosis cascade. Excessive expression of ORF 71 could be an obvious contributing factor to cell transformation.

ORF 72 is a viral-encoded homologue of cellular cyclins that shares the greatest degree of homology with cyclin D2 [61]. Normally, cyclin D2 associates with cyclin-dependent kinase 6 (CDK6) and has weaker associations with other CDKs. The cyclin D2–CDK6 complex has the responsibility of phosphorylating retinoblastoma protein (RB) and releasing E2F, which activates the S-phase genes. The complex formed between ORF 72 and CDK6 is immune to the CDK inhibitors, p16, p21, and p27, which normally inhibit the cyclin D2–CDK6 complex [70]. This could also lead to unregulated progression of the cell cycle and cell transformation.

ORF 73 is the latency-associated nuclear antigen (LANA), which may contribute to HHV-8-induced cell transformation by two distinct mechanisms. Through fluorescence in situ hybridization and immunofluorescence studies, LANA, as well as HHV-8 DNA, has been localized to the metaphase chromosome. It has been hypothesized that LANA tethers the HHV-8 DNA to the metaphase chromosome and maintains the latent state [71]. LANA also has the potential to inhibit the ability of P53 to induce cell death and to repress the transcriptional activity of the P53 gene [72].

Unlike the other genes described above, vIL-6 is primarily expressed during lytic infection and has not been found to be expressed in the latent state [67]. This, however, does not exclude its capability to contribute in a paracrine fashion, since KS lesions contain primarily latently infected cells, interspersed with a few lytically infected cells [62]. Despite expression of IL-6 during lytic infection, KS lesions do not seem to express IL-6 receptor-alpha [61,67]. This is one of the two subunits that form the IL-6 receptor, with the other one being gp 130. Osborne et al. have suggested that vIL-6, unlike human IL-6, does not require the IL-6 receptor-alpha subunit, but is capable of activating the JAK1 and STAT

1/3 pathways with gp 130 alone [67]. Activation of the JAK1 and STAT 1/3 pathways would lead to increased cell division.

Variance in the expression of vIL-6 may also be one of the key factors explaining the production of different pathological states from a single etiological agent. One important question, unanswered in HHV-8 research is, "How is it possible that three distinct disease entities could arise from a single virus?" These diseases include KS, primary effusion lymphoma (PEL), and multicentric Castleman's disease (MCD). Infection of different cell types and expression of a different genetic program is one theory. Many investigators have reported on differential expression of vIL-6 as a significant factor [68,69]. For example, it has been determined that vIL-6 is expressed in both PEL and MCD cells, but not in KS [66]. The explanation for this differential expression has not yet been determined. However, it has been shown that in both KS and PEL, HHV-8 infection is primarily of the latent type.



Figure 10.3 Both plaque and nodule stages of Kaposi's sarcoma are seen in this patient with acquired immunodeficiency syndrome.

Clinical Manifestations

AIDS-related KS typically presents as small macules or patches and/or plaques (Figs. 10.2–10.5) (Table 10.1). KS spreads to the oral or perioral areas in more than 50% of AIDS-related mucocutaneous KS and may sometimes be the presenting manifestation of HIV infection [70] (Fig. 10.6). Involvement of the oral mucosa causes significant discomfort, and problems with speech and eating may occur. Genital mucosa is also a common location for KS (Fig. 10.7). Approximately 80% of patients with AIDS-related KS have gastrointestinal involvement, particularly in the stomach and duodenum. Gastrointestinal involvement may lead to such clinical symptoms as nausea, vomiting, gastrointestinal bleeding or ulceration, perforation, and ileus. Pulmonary involvement may result in persistent cough, bronchospasm, or dyspnea with respiratory insufficiency and is associated with a poor prognosis. Overall, AIDS-related KS has a variable course, often with progressive deterioration after significant declines in CD4+ cell counts.

With the advent of highly active antiretroviral therapy (HAART), the incidence of AIDS-associated KS has markedly decreased, although, rarely, lesions of KS have been reported to persist in patients despite otherwise successful HAART therapy. In a subset of subjects who are HIV seropositive, however, KS may recrudesce early following the introduction of HAART as immune reconstitution inflammatory syndrome (IRIS). IRIS-associated HIV-KS is not a disease, but rather a temporary paradoxical



Figure 10.2 Plaques of Kaposi's sarcoma in a patient with acquired immunodeficiency syndrome.



Figure 10.4 Extensive Kaposi's sarcoma in a patient with acquired immunodeficiency syndrome (Photograph courtesy of Axel Hoke, M.D., Novato, CA).

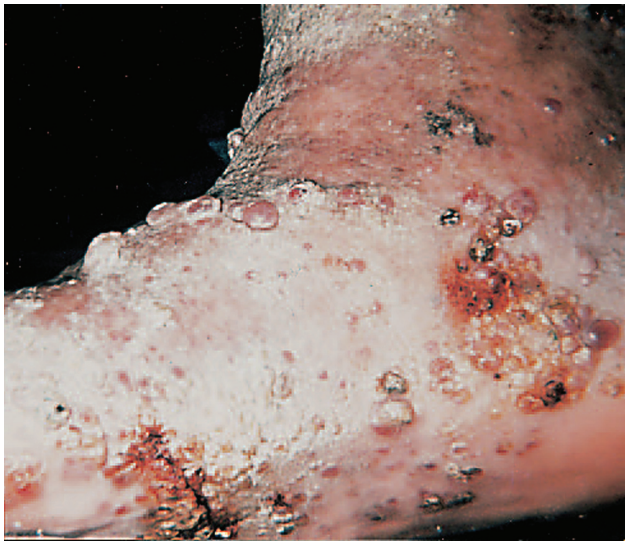


Figure 10.5 Kaposi's sarcoma may be very extensive and become verrucous as in this patient with acquired immunodeficiency syndrome. (Photograph courtesy of Axel Hoke, M.D., Novato, CA.)

immunoinflammatory reaction brought about by improvement in immune status following HAART [71].

Classic KS typically has a slow progression and a benign and protracted course of disease. The early lesions have a spongy feel, but with time, they become firm. This variant classically involves the lower legs of elderly Mediterranean males, but it rarely develops on the oral mucous membranes and gastrointestinal tract [72] (Figs. 10.8 and 10.9).

KS associated with immunosuppression has a clinical course similar to classic or AIDS-related KS. This iatrogenic form of KS may have an aggressive course with rampant progression and dissemination unless the immunosuppressive agents are discontinued [73]. The lesions may improve or completely resolve with a reduction or withdrawal of immunosuppressive agents [74], and they may recur with resumption of immunosuppressive therapy [75].

The African endemic variant of KS has four subtypes: nodular, lymphadenopathic, florid, and infiltrative. The nodular form is most similar to classic KS and typically has a benign course lasting 5–8 years. A limited number of cutaneous, well-circumscribed nodules are present with this form. The lymphadenopathic variant more commonly affects children and young adults and involves lymph nodes more often than skin. The florid type is more aggressive than the nodular form and may spread deeply to involve the dermis, subcutaneous tissue, muscle, and bone. The infiltrative form is even more aggressive. These two latter forms typically have extensive cutaneous lesions on one or more extremities.

KS is a highly vascular tumor, with some resemblance to angiosarcomas. A case of multinodular anaplastic KS presenting in a 50-year-old female with a lymphedematous arm postmastectomy has been described [76]. The lesions mimicked a classical Stewart-Treves syndrome (cutaneous angiosarcoma). Despite several case reports that indicate the presence of HHV-8 in angiosarcoma [77], most studies with large patient numbers have shown a low prevalence of 0–18% of HHV-8 in vascular tumors [78]. Lasota and Mittienem found a prevalence of 18% for HHV-8 in 33 cases of angiosarcoma [79]. Total regression of the lesion was obtained by elastic contention and intradermic liposomal doxorubicin. Similar results have been found in other vascular tumors, including angiokeratomas, papillary hemangiomas, pyogenic granulomas, cavernous hemangiomas, arteriovenous hemangiomas, circumscribed lymphangioma, and hemangiopericytoma. In contrast to these vascular tumors, preliminary evidence supports a role for HHV-8 in angiolymphoid hyperplasia with eosinophilia (AHLE), which is an uncommon disorder characterized by soft angiomatous tumors on the face, ear, and scalp [80]. Subsequent studies confirming or disputing this evidence are needed.

Table 10.1 Clinical Manifestations of Kaposi's Sarcoma

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
Incubation varies and is unknown	Development of small red to pink violaceous or brown macules (often elliptical), particularly in cleavage lines on the trunk. AIDS-related KS most commonly affects the face and trunk. Size varies from several millimeters to several centimeters. Classic KS more often presents as blue-red nodules on the lower legs	Histopathologic examination of lesional skin biopsy	AIDS lesions may become plaque like and exophytic, sometimes with skin ulceration
	These lesions may progress to form large plaques		Classic lesions may become more brown, hyperkeratotic, eczematous, or ulcerated. Associated edema is often present is all types
	All types of KS lesions typically evolve through stages as patches, plaques, and nodules		Multiple KS lesions of varying stages may be present
	↓		
Several years	AIDS-related KS may slowly progress, often disseminating to lymph nodes, intestinal mucosa, and lungs. Patients with classic KS survive for at least 10–15 y		AIDS-related KS often spreads to the oral mucosa, particularly the palate
	Immunosuppressive KS may be either rapidly progressive or chronic and slow. In the African endemic form, children usually survive 2–3 yr, while young adults survive several years longer		KS lesions may bleed easily. Pain may develop with large, edematous lesions

AIDS, acquired immunodeficiency syndrome.

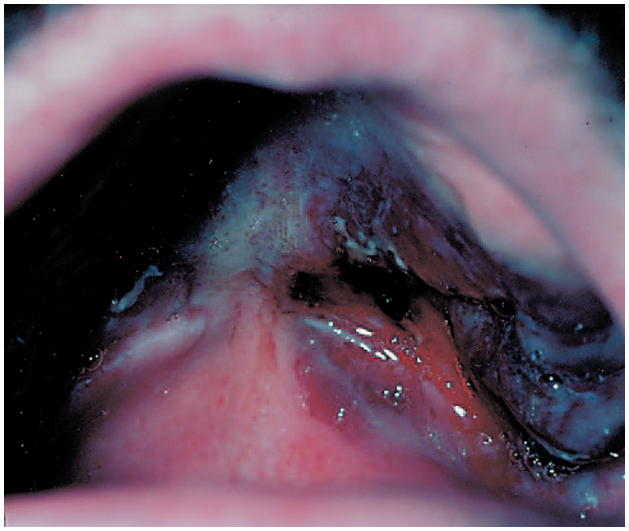


Figure 10.6 More than 50% of AIDS patients with acquired immunodeficiency syndrome with Kaposi's sarcoma will have oral lesions. (Photograph courtesy of Axel Hoke, M.D., Novato, CA.)

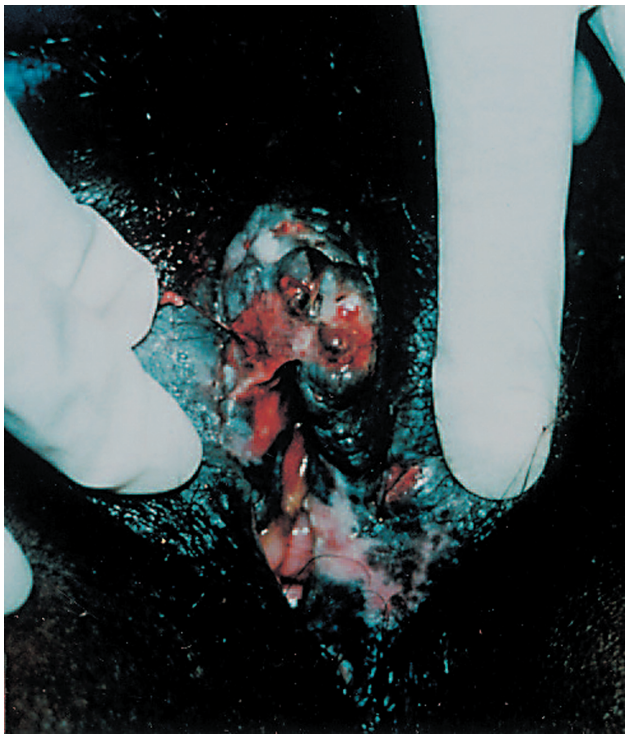


Figure 10.7 Mucosal lesions of Kaposi's sarcoma may also be observed in the vaginal canal in a patient with acquired immunodeficiency syndrome. (Photograph courtesy of Concepcion Arrastia, M.D., Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, TX.)



Figure 10.8 Classic Kaposi's sarcoma lesions most often affect the lower legs and feet as seen in this elderly man.



Figure 10.9 Nodular lesions of classic Kaposi's sarcoma made walking very difficult this elderly man, especially because of ulceration of some plantar lesions.

With the discovery of HHV-8 in KS, researchers were quick to determine whether HHV-8 had a role in other more common epithelial lesions. KS is occasionally detected by PCR in squamous cell carcinoma (SCC), actinic keratosis (AK), seborrheic keratosis (SK), basal cell carcinoma (BCC), leukoplakia, and Bowen's disease, leading some to believe that HHV-8 is much more ubiquitous than previously believed [81,82]. Furthermore, the virus becomes active and hence detectable in the immunocompromised, contributing to the development of the lesions described above. Most experts, however, feel that HHV-8 has little to do with the pathophysiology of these lesions [83]. In fact, extensive studies have been done on these and other epithelial lesions, including verruca vulgaris (VV), atypical squamous proliferation (ASP), Paget's disease, malignant melanoma, neurofibroma, sarcomas, histiocytofibroma, nevi, and chronic dermatitides. The presence of HHV-8 in these lesions was comparable to normal skin and consistently showed a lack of correlation between HHV-8 and all of the aforementioned lesions [83–88].



Figure 10.10 This angioma on the palm of a woman with POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome and multicentric Castleman's disease contained human herpesvirus 8. (Photograph Courtesy of Tiffany Angel, M.D., Department of Dermatology, Baylor College of Medicine, Houston, TX.)

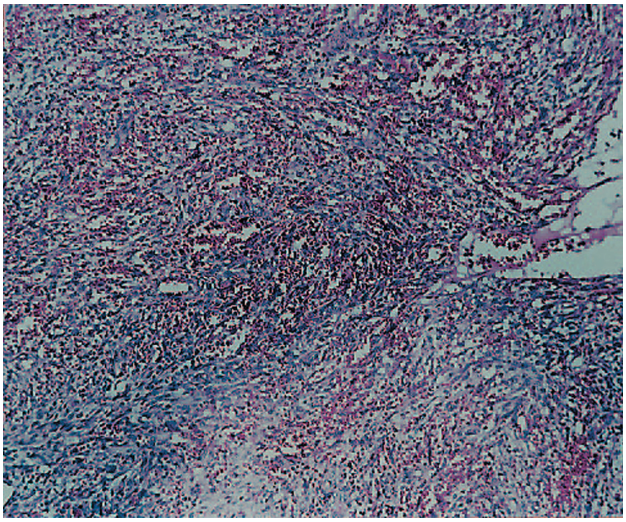
The reported presence of HHV-8 in four of six patients with pemphigus vulgaris and six of six patients with pemphigus foliaceus in 1997 was the first study to associate HHV-8 and pemphigus [89,90]. Since then, further studies regarding the prevalence of HHV-8 in paraneoplastic pemphigus, pemphigus vulgaris, and pemphigus foliaceus have been done using in situ hybridization, PCR, and serology. Most investigators have been unable to detect the presence of HHV-8 in pemphigus and doubt the existence of a causal relationship [91–94]. Other than KS, the malignancy most often associated with KS is Castleman's disease. Polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes (POEMS) syndrome is commonly coexistent with MCD. HHV-8 has been reported in POEMS syndrome coexisting with MCD (Fig. 10.10) [95].

Dermatopathology

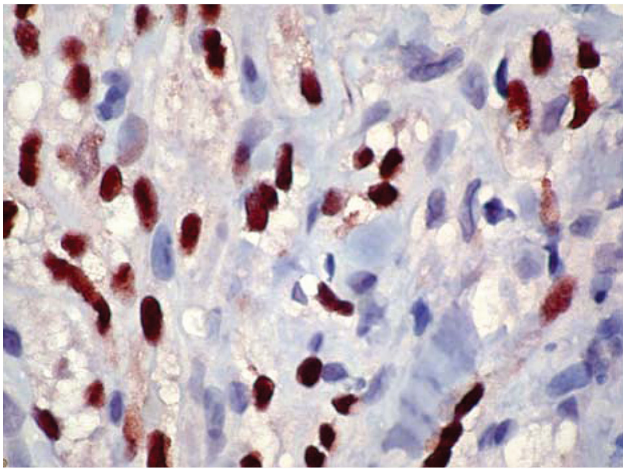
The histology of the different variants of KS generally is identical. Histopathological examination reveals jagged vascular channels lined by atypical vascular endothelial cells (Fig. 10.11a). These vessels are surrounded by a proliferation of spindle-shaped cells. KS lesions often progress through a series of three stages, each with characteristic histological changes. During the patch stage, the presence of a predominantly lymphocytic perivascular infiltrate (+/− plasma cells) may be minimal. Early changes are limited typically to the reticular dermis, but progress to involve the entire dermis. A subtle proliferation of irregular, jagged, endothelial-lined spaces around normal blood vessels may be seen microscopically.

During the plaque stage, there is a proliferation of spindle cells among dermal collagen bundles and vessels. Hemosiderin deposits and hyaline globules become prominent. The predominant lymphocytic perivascular infiltrate is still evident and remains throughout the course of disease. The neoplastic process begins to involve the superficial subcutaneous tissue.

The nodular stage of KS consists of a well-circumscribed intradermal nodule of cuboidal vascular endothelial cells arranged in fascicles and sheets, with slit-like vascular spaces between them. Single erythrocytes can be seen trapped within the vascular slits. Cytological atypia, ranging from mild to moderate, is present in the spindle cells. Mitotic figures may be scant or numerous.



(a)



(b)

Figure 10.11 (a) Histopathologic examination of Kaposi's sarcoma reveals jagged vascular channels lined by atypical vascular endothelial cells. These vessels are surrounded by a proliferation of spindle-shaped cells. (b) Kaposi's sarcoma showing HHV-8 LANA(+) immunohistochemistry.

Immunohistochemistry for HHV is usually positive in Kaposi's sarcoma (Fig. 10.11b).

Diagnosis

Diagnosis of KS is confirmed by examination of a skin biopsy from the suspected lesion. Serology for HHV-8 is not indicated and is typically limited to the research environment. Table 10.2 lists possible differential diagnoses.

Treatment and Prevention

Currently, a complete cure for KS is not available, and treatment is aimed at palliation and control of disease (Table 10.3). For iatrogenic KS, reduction or cessation of immunosuppressive therapy generally leads to regression or resolution of disease, although the KS lesions often recur with reinstitution of immunosuppressive agents. With all forms of KS, inconspicuous, small, slow-growing

Table 10.2 Differential Diagnoses of Kaposi's Sarcoma (KS)

Insect bite: Lesions of KS are more violaceous than insect bites
Dermatofibroma: Lesions of KS are more violaceous than dermatofibromas
Ecchymosis: Lesions of KS may feel firm on palpation, whereas ecchymotic lesions tend to be flat and involve larger areas
Hemangioma: Lesions of KS are more violaceous than hemangiomas
Bacillary angiomatosis: Lesions of KS are generally less raised and less discrete than bacillary angiomatosis
Pyogenic granuloma: Lesions of KS are generally more violaceous than pyogenic granulomas
Melanocytic nevus: Lesions of KS are generally more erythematous: violaceous than melanocytic nevi
Verruga peruana: Lesions of KS are generally less raised and less discrete than those of verruga peruana, which is usually found only among people living in high elevations in Peru

cutaneous lesions may be monitored without treatment. Treatment is indicated if the lesions become cosmetically disturbing to the patient or if complications such as bleeding, lymphedema, or interference with functional activity develop. Classic KS lesions usually respond well to radiotherapy, and AIDS-associated KS lesions are extremely sensitive to this modality. Clinical studies have reported complete response with radiotherapy of KS lesions in 32–85% of patients [96,97]. Higher doses of radiation typically lead to higher response rates, and early lesions tend to respond more than mature lesions [98]. Surgery is generally not considered to be an effective therapy (Fig. 10.12). Intralesional vinblastine in localized lesions has a 60–90% response rate, which lasts for several months [99]. This modality is most effective for small, early lesions. Side effects may include pain, alterations in skin pigmentation, and transient alopecia when vinblastine is injected in hair-bearing areas. Other intralesional agents may also be used (see Table 10.3). Intralesional interferon-α and tumor necrosis factor-α have high rates of complete response, although results are slow and side effects may include pain, local inflammation, and systemic symptoms [99,100]. The first topical at-home therapy for limited KS disease was approved for use in the USA [101,102]. Alitretinoin 0.1% gel is a 9-*cis*-retinoic acid that has a 35% response rate, typically seen within 12–16 weeks of therapy. Side effects include rash, pain, and paresthesia. This agent should not be applied to mucosal lesions.

Prior to the AIDS epidemic, systemic chemotherapeutic agents were traditionally administered for extensive classic and endemic KS disease [103]. With combination therapy, response rates are improved, although survival is not prolonged [99,104]. The liposomal encapsulated forms of doxorubicin and daunorubicin have shown more promising results in the treatment of classic and AIDS-related KS. These agents are more effective and significantly less toxic than their older counterparts [104–106].

With the advent of HAART, the incidence of AIDS-associated Kaposi's sarcoma has been decreasing steadily [107]. This may be due to the suppressive effect of HAART on KS via decreased HIV-related cytokines (rapid effect) on the immune system, the suppression of the HIV tat protein, which stimulates KS spindle-cell production [108,109], or other mechanisms. With the recent knowledge that KS is associated with HHV-8 infection, newer therapies have focused on the antiviral agents. In vitro susceptibility testing has shown HHV-8 to be insensitive to acyclovir, but sensitive to ganciclovir and foscarnet [110]. In vivo case reports and

Table 10.3 Treatment of Kaposi's Sarcoma

Symptom	Treatment
Inconspicuous lesions	May be monitored without treatment
Limited disease	Cryotherapy for flat or superficial lesions, with two freeze thaw cycles
	Laser therapy (pulsed-dye laser) for small superficial lesions only
	Surgical excision for selected small solitary lesions only
	Radiotherapy is particularly good for facial lesions, lymphedema, or painful or bulky local lesions. Also indicated for confluent lesions involving a large surface area, large extremity lesions, or large oropharyngeal lesions
	Intralesional chemotherapy, with interferon-α, tumor necrosis factor-α, vinblastine, bleomycin, or the sclerosing agent, sodium tetradecyl sulfate (for oral lesions)
	Vinblastine is administered as 0.1 mg injected per square centimeter, which may be repeated in 3 weeks for recalcitrant lesions. Persistent lesions may be given incremental injections at doses of up to 0.2 mg per square centimeter
	Topical alitretinoin 0.1% gel, applied twice daily, and gradually increased to 3 to 4 applications daily, as tolerated
	Electrodessication
	Hyperthermia
Extensive disease	Systemic interferon-α, given at 30 million IU/m^2 3 times a wk until no further evidence of tumor, unless contraindications prevent continuation of therapy
Note: Single best treatment for HIV(+) KS is HAART	Systemic interferon-α with zidovudine but zidovudine is no longer used for monotherapy of HIV except where it is the only treatment available
	Systemic chemotherapy is most commonly performed with paclitaxel or with liposomal doxorubicin or daunorubicin
	Alternative chemotherapeutic agents include vinblastine, adriamycin, bleomycin, doxorubicin, daunorubicin, etoposide, retinoic acid, and teniposide. These agents may be used in combination or alone.

HIV, human immunodeficiency virus.

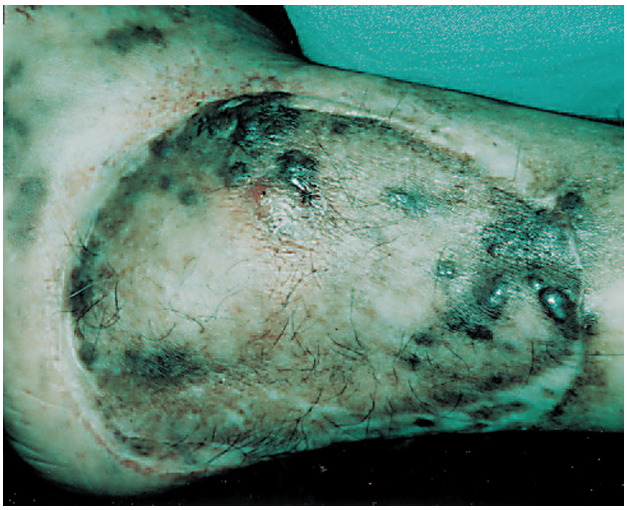


Figure 10.12 Nodules of Kaposi's sarcoma (KS) are seen appearing in this graft that was used in the repair of the surgical site of a previous KS lesion. (Photograph courtesy of Luke Lewis, M.D., and Robert Purvis, M.D., Department of Dermatology, Texas Technological University Health Science Center, Lubbock, TX.)



Figure 10.13 A pyogenic granuloma may have a clinical appearance very similar to that of nodular Kaposi's sarcoma.

clinical trials have shown differing results in some cases. Improvement, remission, or prevention of KS lesions has been reported with foscarnet [111–114], ganciclovir [113,114], and cidofovir treatment [115], often administered for cytomegalovirus retinitis. However, reports of no improvement of KS or HHV-8 with cidofovir [116], foscarnet [45], and ganciclovir therapy [45,111] have been described.

Systemic interferon-α therapy has been studied more thoroughly than other antiviral agents for the treatment of KS. This modality is most successful for the treatment of extensive mucocutaneous disease or asymptomatic visceral involvement in patients who have an intact immune system. In clinical trials, overall response rates, including partial response, range from 30 to 46% [117–119]. In general, higher doses of interferon are more effective than lower doses in inducing tumor regression [118–120]. Patients who respond to interferon-α treatment have prolonged survival compared with nonresponders [118,119]. Many months of therapy are required before tumor response becomes evident, and patients must often discontinue therapy prior to improvement because of severe adverse effects. These side effects may include fever, chills, fatigue, malaise, nausea, vomiting, mental status changes, myalgias, anorexia, weight loss, diarrhea, hypotension, hepatotoxicity, and neutropenia [117–121]. Neutropenia and extreme fatigue are the most common dose-limiting factors. In patients with AIDS-associated KS, a combination of systemic interferon-α and zidovudine has been shown to be effective [122–126]. Zidovudine is no longer used for monotherapy of HIV except when it is the only treatment available.

With the need for more effective treatment of KS, many novel therapies are currently under evaluation. Oral retinoic acid therapy, with either *trans*-retinoic acid [127] or 9-*cis*-retinoic acid [128], has demonstrated some promising results in clinical trials. Intralesional human chorionic gonadotropin (HCG) has been shown to induce regression of KS lesions in a dose-dependent manner [129,130]. Thalidomide [131] and intravenous immunoglobulin [132] have also produced regression of KS lesions in anecdotal reports.



(a)



(b)

Figure 10.14 (a) A solitary lesion of bacillary angiomatosis may mimic a progenic granuloma or nodular Kaposi's sarcoma (KS). (b) Rarely, bacillary angiomatosis lesions may be multiple and verrucous, thus mimicking KS (as seen in Fig. 10–5). (Photograph a courtesy of Timothy Berger, M.D., Department of Dermatology, University of California San Francisco School of Medicine, San Francisco, CA); photograph b courtesy of Axel Hoke, M.D., Novato, CA.)

Because the transmission of HHV-8 is not well understood, methods of prevention have not been determined. If HHV-8 acquisition is associated with high-risk sexual behaviors, it is assumed, but not proved, that the practice of safe sex may decrease the risk of infection. Further studies are needed to expand our knowledge of this and other areas concerning KS and HHV-8.



(a) (b)

Figure 10.15 (a,b) Although rarely observed in persons living in locations other than the high elevations of Peru, verruga peruana may mimic nodular lesions of Kaposi's sarcoma, but it often may appear identical to bacillary angiomatosis. (Photographs courtesy of Francisco Bravo, M.D., Universidad Peruana Cayetano Heredia, Lima, Peru.)

Cutaneous Lymphoma

Plasmablastic lymphoma most often arises in the oral cavity of HIV-positive individuals. However, other sites of involvement have been described, including skin. While EBV has been detected in most cases of plasmablastic lymphoma (76%), HHV-8 has been found, ranging from 17 to 37% [131–133]. There have been a few reports of cutaneous HHV-8 positive plasmablastic lymphoma in AIDS patients who also suffered from MCD and KS [136,137]. In one case, the lesions were described as tender subcutaneous lesions on the arm. In some cases, these cutaneous lesions may be recurrent and self-healing [138].

MCD preceded by a diffuse rash with HHV-8 positive plasmablasts has been described in an HIV-positive male. An elderly HIV-positive male presented with a recurrent diffuse maculopapular rash on the upper extremities and trunk with a perivascular lymphoid infiltrate containing mostly T cells with admixed HHV-8 LANA and vIL-6 positive plasmablasts. This was followed by development of lymphadenopathy due to MCD [137].

In contrast to cutaneous plasmablastic lymphoma, cutaneous plasmacytosis is a rare disorder that typically affects middle-aged to older individuals of Asian descent. Clinically, it is characterized by multiple asymptomatic red-brown plaques and nodules on the trunk. In a recent study, HHV-8 LANA immunohistochemistry was negative in all cases [139].

There have been a few reports of an association between HHV-8 and both large-plaque parapsoriasis (LPP) and mycosis fungoides (MF). In one study, while small amounts of HHV-8 DNA were detected in both LPP (87%) and MF (70%), LANA immunohistochemistry was negative in all cases [140]. These results were considered inconclusive. In another study, a highly significant association between HHV-8 seropositivity and LPP was found (100%) as compared with MF (25%) [141]. The presence of HHV-8-infected cells was confirmed by immunohistochemistry performed on paraffin-embedded tissues in 40% of the LPP cases. The positive cell types included endothelial cells and infiltrating dermal lymphocytes.

Conclusion

HHV-8 is a recently discovered human herpesvirus with significant clinical implications because of its association with KS, MCD, PEL, and plasmablastic lymphoma. The AIDS epidemic and its resulting dramatic increase in KS tumors have brought HHV-8 to the forefront of medicine. Although the various clinical stages are usually easily recognized, KS may be mimicked by a variety of other conditions, such as angiosarcoma, pyogenic granuloma (Fig. 10.13), bacillary angiomatosis (Fig. 10.14), and verruca peruana (Fig. 10.15). While our understanding of HHV-8 continues to grow, it is incomplete. Further studies are necessary

to expand our knowledge of HHV-8 transmission, pathogenesis, prevention, and treatment of HHV-8-related disorders.

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11 Cercopithecine Herpesvirus 1 (Herpes B)

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Cercopithecine herpesvirus 1 is the only one of the 35 herpesviruses identified in non-human primates that can cause definite disease in humans. The name Cercopithecine herpesvirus 1 from the Herpesviridae, subfamily *Alphaherpesvirinae*, and genus *Simplexvirus*, has been designated by the Herpes Study Group for the International Committee on Taxonomy of Viruses [1]. The virus is most commonly referred to as "B virus," which was the name given by the original researchers. Several other terms have been associated with this virus, including monkey B virus, *Herpes simiae*, *Herpesvirus simiae*, and herpes B. This virus is endemic among monkeys of the macaque genus, which includes rhesus macaques, pig-tailed macaques and cynomolgus monkeys (Fig. 11.1). Infected monkeys may appear asymptomatic, have mild systemic symptoms, or develop oral and genital lesions. Infected primates may harbor the virus latently in sensory ganglia. The virus may reactivate under stress or other conditions and shed infectious virus from mucosa, even in the absence of symptoms or vesicles.

Infection in humans is rare and may result from exposure to macaques and their secretions or tissues. Human infection may manifest with local symptoms such as vesicles or erythema around the exposure site, a flu-like illness, and/or peripheral nervous system (PNS) and central nervous system (CNS) manifestations ranging from paresthesias to rapidly ascending encephalomyelitis. When humans are infected, untreated mortality rates approach 80% [2]. While there has been some improvement in morbidity and mortality since the use of post-exposure prophylaxis and treatment with antiviral medications, rapid diagnosis and initiation of therapy are essential in reducing neurological sequelae or death. Despite these advances, B virus is considered an extremely dangerous, potential occupational hazard for those who work with macaques or their tissue.

History

In 1932, a physician (W.B.) was bitten by a clinically asymptomatic rhesus monkey. Local inflammation ensued with rapid development of lymphangitis, lymphadenitis, encephalomyelitis, respiratory paralysis, and death. Autopsy specimens were analyzed and a filterable agent was isolated from W.B.'s spinal cord and brain in 1933 [2,3]. A lethal disease similar to that observed in W.B. was seen in rabbits injected via multiple routes with the filtrate. However, a rhesus macaque injected with the filterable agent demonstrated no signs or symptoms of disease. Neutralization testing of the agent revealed that it was related to herpes simplex virus (HSV). Sabin and Wright also discovered an infectious agent in the ultrafiltrate from tissue of W.B. They demonstrated this agent to be distinct from HSV and termed it B virus after the patient's last initial [4].

In 1955, B virus was isolated from an asymptomatic rhesus monkey [5]. Suspension of neurological tissue from this monkey produced disease after inoculation of several other animals including rabbits. The rabbit has become the infectious animal model of choice for this virus, since intradermal injection of B virus into rabbits results in rapidly ascending myelitis and fatality.

Shortly after its discovery, B virus resulted in multiple human fatalities with few exposed survivors. Since then, there has been some variation in reports of virulence and infectivity, however, neurologic infection and fatality have been repeatedly demonstrated. To date, there have been approximately 40 cases of human B virus infections, allowing for limited evaluation of this disease in humans.

Despite this, understanding of the virus has significantly improved since its discovery, with molecular and genetic characterization, and improved diagnostic methods for recognizing and differentiating B virus from other types of herpes viruses.

Epidemiology

Seropositive macaques are the natural host reservoir for transmission of B virus. Every species of macaque tested has demonstrated some prevalence of seropositivity to B virus. Evidence of virus exposure is very common in adult monkeys, both in the laboratory and wild habitat setting, particularly in environments where there is close exposure to other macaques [6,7]. In these more densely populated groups, seropositive rates range from approximately 80 to 100%. However, a wide variation in seropositivity has been reported [2,6,8] and groups have also been identified where seroprevalence is zero.

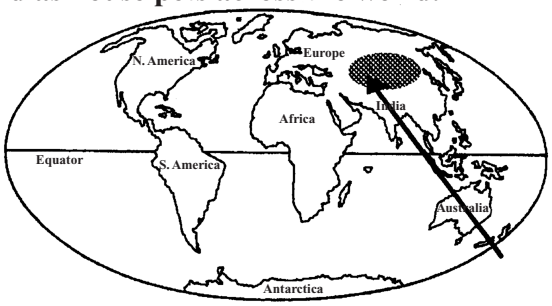
B virus is transmitted from the host via viral shedding from herpetic lesions or mucosal sites. This transmission can occur between macaques, from macaques to humans, via fomites containing virus, and in one case from human to human [2,9,10]. Macaque vertical transmission is rare. As with other herpes viruses, B virus can establish latency in the sensory ganglion of infected macaques, and intermittent shedding of the virus occurs upon symptomatic and asymptomatic reactivation. In macaques, viral shedding has been demonstrated from the conjunctiva, oropharyngeal mucosa, and urogenital region during primary infection and reactivation. Viremia has been reported in macaques, but is rare [11–13]. The overall frequency of B virus excretion in infected monkeys is less than 5%, which yields a low risk of human infection after contact with seropositive monkeys [14].

It has been postulated that antibodies against HSV can cross-react with B virus, contributing to low rates of infection. While hundreds of monkey bites and scratches occur in the USA each year, B virus infection in humans is rare. In a study of 321 primate workers, 166 of these workers reported prior macaque bites or scratches, yet none were evaluated as being seropositive to B virus [15]. Despite the antibody cross-reactivity, prior exposure to HSV does not appear to affect the clinical course of human B virus infection [16].

Nearly all reported cases have resulted from exposure to the virus in the research laboratory setting [16–30]. The majority of

GEOGRAPHICAL INCIDENCE

The *Macaca* genus primates are enzootic in Asia, but the incidence is likely worldwide, since these macaques are commonly used for laboratory research and as house pets across the world.



***Macaca* genus primates are enzootic in Asia**

TAXONOMY

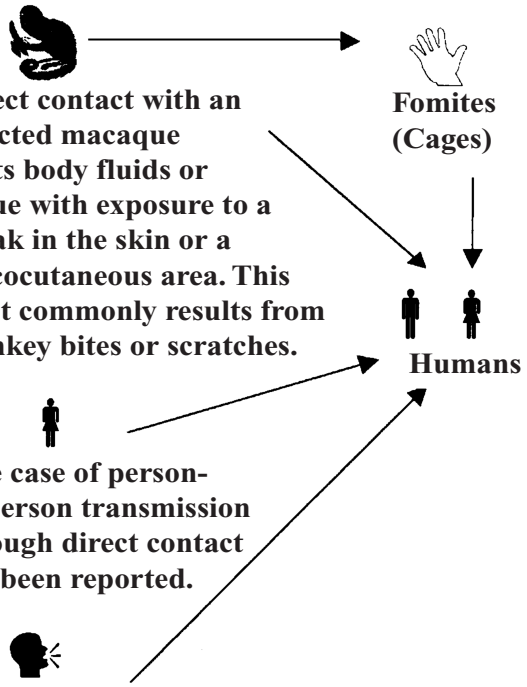
Herpesviridae family

Alphaherpesvirinae subfamily

Simplex virus

Cercopithecine herpesvirus 1
(B virus)

TRANSMISSION



ZOONOTIC IMPLICATIONS



Monkeys } **Indigenous to Old World primates of the *Macaca* genus, particularly rhesus and cynomolgus monkeys.**

Figure 11.1 Incidence and transmission of herpes B.

cases have occurred in the USA. Herpes B is enzootic in Asian macaques, but no cases have been reported in Asia. A study performed in Nepal at a monkey temple, where there is frequent contact between macaque species and humans, found that nearly 70% of the macaques tested were seropositive for B virus [31]. Another study of workers in a wildlife refuge and tourist attraction in Bali demonstrated that there was sufficient contact between seropositive macaques and humans to transmit B virus on a frequent basis [32,33]. The unexpectedly low amount of reported cases in enzootic regions is likely, in part, due to the limited availability of medical care or diagnostic methods for identifying B virus in these areas [19].

Despite the lack of macaque to human infection cases outside the laboratory setting, there was a case reported in 2008 of a woman bitten by a vervet monkey (*Cercopithecus aethiops*) in Garamba National Park in the Democratic Republic of the Congo [34]. This is the first report of a case occurring via macaques in a wild habitat.

A car accident in Puerto Rico in which a macaque was hit and subsequently found to be B virus seropositive, resulted in exposure of over 20 people to seropositive macaque body fluids [35]. B virus does not typically reside in the blood and no human infections resulted from these exposures. As a result of this and a concern for increasing macaque populations in Puerto Rico with more potential for human exposure to B virus, education programs regarding B virus and macaques have ensued. The cases of potential exposures involving these wild macaques in Africa and Puerto Rico may hold implications for the future understanding and management of infections. As the possibilities for human contact with wild macaques escalates due to increasing world travel and greater human population densities near these animals' natural habitats, it remains to be seen if additional suspected or confirmed cases of B virus are reported in the non-laboratory setting.

Pathogenesis

Herpes B, like all herpesviruses, is a double-stranded DNA virus. B virus belongs to a subset of herpesviruses, the alphaherpesviruses, which are neurotropic and not typically found in the blood. Studies of sequence analysis and secondary structure of the virus have also demonstrated that B virus, HSV-1, and HSV-2 probably

diverged from a common ancestor. B virus is most closely related to herpesvirus papio 2, and recent studies have reported improved methods of differentiating B virus from HSV-1 and HSV-2 [36,37]. It has been suggested that the virulence of B virus to non-macaque hosts varies with distinct B viral genotypes. In addition, it has been proposed that differences in microRNAs between these herpesviruses, which are important regulators of viral gene expression, may be a factor in the poor outcomes of B virus infection in humans versus macaques [38].

Several modes of transmission of human B virus infection have been reported, but infection usually results from direct inoculation of contaminated macaque fluids or tissue, usually from a bite or scratch from the monkey or from contact with its cage [2,16,19,20]. Infection via mucous membranes is also possible, including nasal, pulmonary, and conjunctival. In macaques, genital mucous membrane transmission is also known to occur. The route of infection affects the clinical time course, spread of the virus, and which organs are affected. This may also be useful in understanding the best sites of virus retrieval for diagnostic purposes.

In most cases, the incubation period of B virus is 5–21 days after exposure, but has ranged from 2 days to months. At the site of inoculation of the infectious material, B virus attaches to host epithelial surface receptors and penetrates through the plasma membrane. Viral DNA reaches the nucleus and viral replication occurs. Subsequent lysis of infected cells releases large numbers of virus and facilitates viral spread. This may manifest with erythema, edema, vesicles, and necrosis of the involved area. Virus can be found at the epidermal site of replication for several weeks after infection [7].

B virus can spread via lymphatics, however, the virus is neurotropic and is typically not seen in the blood. Infection of neurons and subsequent axonal ascension of the virus to the CNS leads to acute neurologic findings [39]. Human B virus infection frequently causes pontine and medullary lesions, but virtually any region of the CNS can be affected. On histopathology, this manifests as edema, neural degeneration, gliosis, and astrocytosis [19].

The virus may also enter directly into neurons and establish latency. During latency of the virus in the nerve ganglia there is limited viral transcription. Reactivation occurs under stress or illness, and facilitates the delivery to, replication in, and release of virus from mucosal epithelial cells.

Lymphatic infection may spread disease to local and more distal drainage sites, a mode that may result in abdominal organ involvement. Autopsy data has demonstrated B virus in the liver and lungs, with occasional involvement in the heart, spleen, kidneys, and adrenals. Focal hemorrhagic necrosis is the identifying pathological feature of parenchymal involvement.

Clinical Manifestations

Humans exposed to B virus have varying clinical manifestations. Incubation prior to clinical disease onset is typically days to weeks, however, it can range up to months or longer. Somewhat varied clinical manifestations occur most likely as a result of the route of inoculation. Infection course is also influenced by several factors, such as patient age, immunological status, site of viral entry, and the quantity of virus inoculated.

Direct cutaneous inoculation with infectious fluids or tissue is the most common presentation. This results in local signs including vesicles, erythema, and edema at inoculation site (Figs. 11.2–11.4). Subsequent regional lymphadenitis and lymphadenopathy occurs usually days to weeks after viral inoculation (Table 11.1). The involved local lymph nodes may become hemorrhagic and focally necrotic. Influenza-like symptoms may ensue, including fever, fatigue, and myalgias. This is usually followed by symptoms of PNS involvement, such as sensory abnormalities including dysesthesias, hyperesthesias, and paresthesias. Neuronal spread of B virus to

Table 11.1 Clinical Manifestations of B Virus

Time after exposure	Clinical manifestations	Laboratory analysis	Other notes
3–5 days or more	Regional lymphadenopathy and lymphadenitis,/herpetic vesicular lesions at the site of inoculation, with erythema and edema	Viral culture of vesicular fluid, tissue, or specimens (urine, CSF, stool)	Incubation may last for 2–5 weeks in some patients Some patients may develop fever, myalgia, cramping, and cranial nerve abnormalities during the lymphatic spread of disease
	↓		
10–12 days	Sensorimotor abnormalities: dysesthesia, hyperesthesia, paresthesia	Identification of the virus in specimens, with polymerase chain reaction or in situ hybridization	
	↓		
13–19 days	Progressive ascending paralysis, beginning as weakness and hyporeflexia	Virus-specific serologies, although false positives may occur	
	↓		
	Flaccid paralysis and areflexia		
	↓		
Rapid progression	Decreased consciousness, altered mentation, seizures, and respiratory depression		
	↓		
May occur within 2 weeks of symptom onset, or much later	Respiratory arrest and death		Late disease is often avoidable with antiviral treatment

CSF, cerebrospinal fluid.

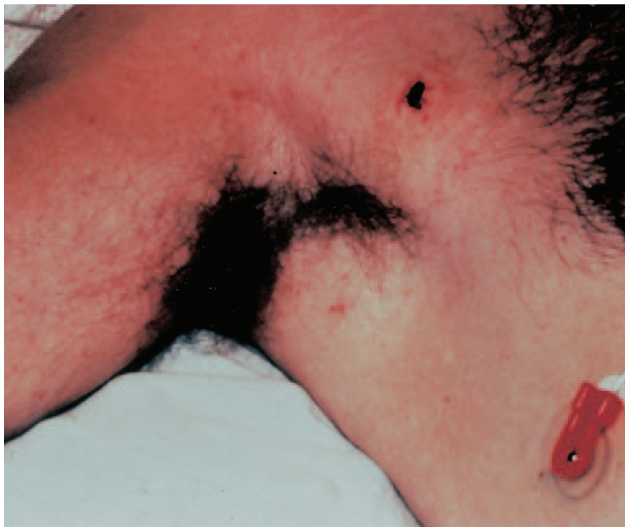
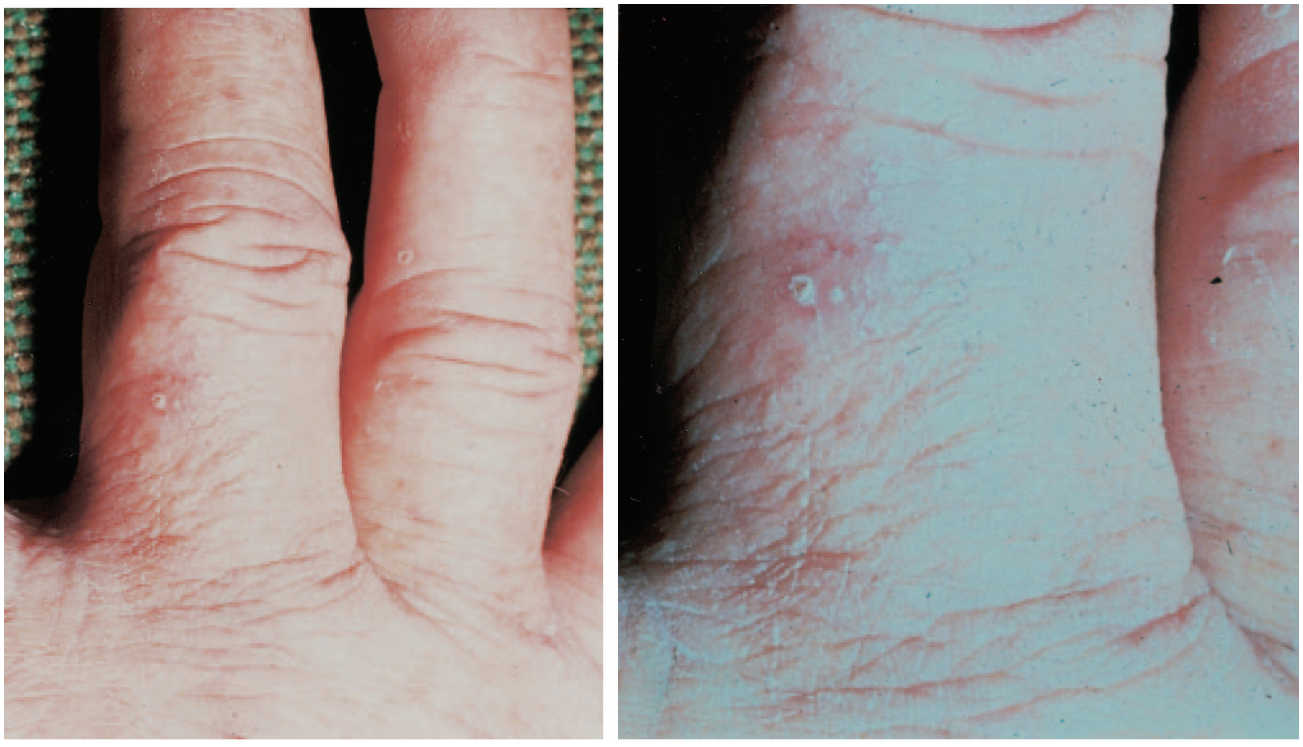


Figure 11.2 Site of chest bite of rhesus macaque monkey from which B virus was recovered. (Photographs courtesy of Julia Hilliard, Ph.D., SW Foundation for Biomedical Research, San Antonio, TX.)



Figure 11.3 Finger bite site from rhesus macaque monkey originally suspected of being site to which B virus was transmitted. No virus was recovered. (Photographs courtesy of Julia Hilliard, Ph.D., SW Foundation for Biomedical Research, San Antonio, TX.)



(a) (b)

Figure 11.4 Inoculation site of scratch of finger on cage housing infected rhesus macaque. (a) Multiple sites appear in scratch areas. (b) Close-up of (a). (Photographs courtesy of Julia Hilliard, PhD, SW Foundation for Biomedical Research, San Antonio, TX.)

the CNS leads to an ascending transverse myelitis with paralysis manifesting in late stages. Brainstem involvement results in cranial nerve signs, such as paresthesias, diplopia, nystagmus, ptosis, and dysphagia. Signs of meningeal irritation, such as headache, photophobia, nausea, vomiting, and nuchal rigidity may also be observed. In most patients, this is followed by meningoencephalomyelitis with involvement of the respiratory center, leading to death.

Aerosol inhalation of infectious airborne droplets can occur less frequently and results in infection through contact of the virus with mucous membranes. Upper respiratory tract flu-like symptoms including low-grade fever, rhinorrhea, coryza, cough

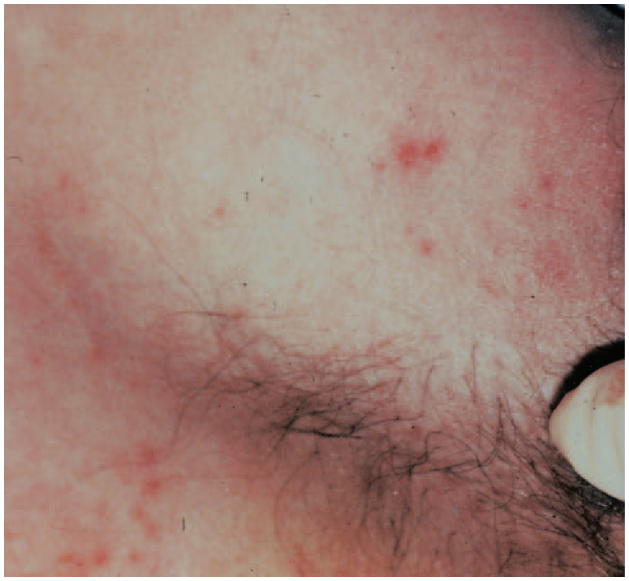


Figure 11.5 Secondary vesicular/papular eruption from B virus infection. (Photographs courtesy of Julia Hilliard, PhD, SW Foundation for Biomedical Research, San Antonio, TX.)

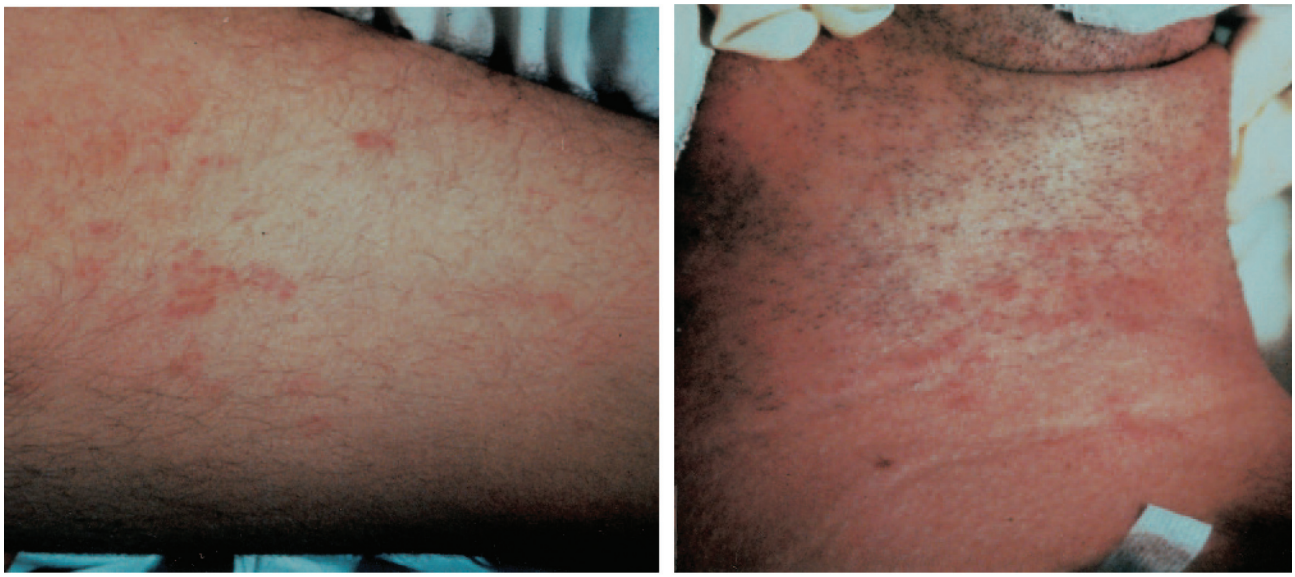
pharyngitis, and laryngitis can ensue. Spread of infection to the lower respiratory tract can also occur and result in additional symptoms of respiratory distress due to interstitial pneumonitis. While it may be more difficult for the virus to gain access distally into the respiratory mucosa, the lungs are a more ideal setting for viral replication than nasal and upper respiratory mucosa [9,21,40–42]. Inoculation via aerosol inhalation has been reported in two patients, one of whom died after CNS involvement [21].

Recurrent vesicular eruptions have been reported in two human cases (Figs. 11.5 and 11.6). The source in one case was identified as being transmitted by a human from a herpetiform lesion, which has been the only reported case of human-to-human transmission [20]. A zoster-like eruption with isolation of B virus was the other case involving recurrent vesicles [18]. B virus latency and reactivation has been well studied in macaques and animal models. These recurrent forms of infection indicate that B virus shares with other herpesviruses the potential for latent infection and subsequent reactivation.

An asymptomatic infection has also been reported in an animal handler stuck with a needle used to inject a seropositive macaque [22,43]. Physical examination and laboratory tests were unremarkable; however, B virus was cultured from the puncture site of the patient. The patient was placed on empiric treatment with intravenous acyclovir followed by oral therapy, which may have prevented the expected manifestations of disease. While it is possible that this form of infection occurs more frequently but is under-reported due to minor or complete lack of symptoms, caution should be used when evaluating and interpreting data from cases of suspected asymptomatic infection. Some tests, as discussed further in the diagnostic section, have cross reactivity with other herpes viruses and are therefore not 100% specific for B virus. These types of results must be carefully evaluated with the whole clinical picture and risk of exposure when analyzing B virus infections and success of treatment.

Diagnosis

Rapid diagnosis is critical for reducing potential morbidity and mortality. Animal handlers exposed to contaminated monkey secretions and tissues, or any patient with a recent history of a bite, scratch, or needle stick injury associated with monkeys should be evaluated by a physician familiar with B virus. Inflammation and vesicles at the inoculation site are indicative of B virus in this clinical setting and should be treated accordingly. Lymphatic spread and lymphadenopathy, as well as neuronal dissemination leading to PNS and CNS abnormalities, are additional diagnostic indicators of B virus infection. However, not all cases have these manifestations. See Table 11.2 for differential diagnosis.



(a) (b)

Figure 11.6 Secondary papular eruptions in patients with B virus infection. (a) Arm. (b) Neck. (Photographs courtesy of Julia Hilliard, Ph.D., SW Foundation for Biomedical Research, San Antonio, TX.)

Table 11.2 Differential Diagnosis of B Virus

Herpes simplex virus: The early finding of herpetiform lesions of B virus infection may appear similar to this common infection. Encephalitis with herpes simplex virus may also present with neurological findings. Herpes simplex infection often has a history of recurrent lesions, particularly in the orolabial and genital areas, while B virus infection usually has a history of monkey exposure associated with the area of inoculation. Tzanck smear of B virus vesicles may also show giant cells with viral inclusions.
Herpes zoster infection: B virus may present with herpetiform lesions that spread in a region of the body and are not localized to the site of inoculation. The associated dyesthesias may also mimic the clinical picture of herpes zoster. The history of exposure to a macaque and the development of neurological manifestations strongly points to B virus infection.

B virus is most frequently recovered from skin lesions or inoculated sites. Viral DNA can also be recovered from the CNS, including cerebrospinal fluid (CSF), once symptoms of CNS involvement occur. Other less frequent sites of virus recovery in humans include the oropharynx, conjunctiva, and from urine and stool of infected persons.

Laboratory confirmation of B virus infection can be challenging because few facilities having biosafety level 4 laboratory capabilities and licensing necessary for the preparation of B virus antigen [44]. The gold standard in laboratory diagnosis is tissue culture utilizing vesicular fluid or tissue homogenates from skin and mucous membranes of rabbit or monkey cell lines. Other virological or serological techniques are often used that yield faster and more sensitive results than tissue culture and may be less hazardous.

Isolated B virus can be identified by a variety of virological techniques. Molecular methods, such as in situ hybridization and polymerase chain reaction (PCR), can directly detect B-virus DNA and are not subject to these limitations [45,46]. PCR is one of the virological techniques now available that can directly identify the presence of B-virus DNA [47]. In addition, probes have been identified that are very specific for amplification of B virus and not HSV, eliminating much of the problem with cross reactivity to HSV that is seen with some serological techniques [48]. However, viral DNA detection by PCR does not necessarily indicate that complete viruses capable of replicating are present in a wound. However, a positive PCR result from a specimen obtained from another site not directly inoculated, or in a patient with symptoms, is compatible with infection. Positive PCR results from a site with signs of infection, such as vesicles or hemorrhagic necrosis, are also diagnostic of infection. Positive PCR results should be confirmed with other molecular methods that can detect viral components [49,50].

A rise in B virus antibodies over a few days signifies infection. Serologic testing can be complicated, especially when the patient has antibodies to HSV from prior infection, since there is cross reactivity between these viral antibodies. The high prevalence of HSV antibodies among humans further contributes to the potential of obtaining false-positive serologies to human B virus infection. B virus serologic cross reactivity to HSV-1, more so than with HSV-2, has been demonstrated. This, in part, may account for detection of B virus antibodies in asymptomatic individuals [51,52] and reduces the specificity of serological tests. Competitive enzyme and monoclonal antibody assays have better sensitivity, while immunoblot and dot-immunobinding assays have greater specificity [53–55]. Pre-absorption of human sera with HSV antigens can greatly decrease false-positive serological results [28,56]. Interpretation of serological results in combination with the clinical data is necessary [44,57]. It is recommended that serological diagnosis be confirmed with an immunoblot (Western blot) or competition ELISA test [57].

Dermatopathology

Due to the small number of cases and the biological hazards associated with B virus, dermatopathologic information of the associated lesions is somewhat limited. Biopsy of wounds or inoculation sites is not routinely recommended. The existing reports indicate that a Tzanck smear of the herpetiform vesicles may show Cowdry A type intranuclear inclusion bodies and giant cells, although this is a rare feature. Viral replication leading to syncitium formation has been well identified in animal models. Hemorrhagic necrosis is known to occur especially in lymph nodes and organ parenchyma. Specific safety precautions are required if a skin biopsy is performed and analyzed.

Control and Prevention

Vaccination attempts have failed to demonstrate a protective benefit in humans [58]. Testing of gamma globulin in conjunction with B virus challenge also produced minimal and non-specific protective effects in rabbits [27]. Prevention of B virus infection is, therefore, crucial and is currently addressed via education of laboratory workers who could potentially be exposed to B virus. Handling techniques, laboratory safety, and animal colony management are preventative strategies utilized.

Recommendations for work involving rhesus and macaque monkeys are available and aimed to limit risks of exposure [18,59,60]. Virus-free colonies have been established and funded by the NIH National Center for Research to help eliminate the use of B virus-infected macaques in biomedical research. Guidelines aimed at maintaining virus-free colonies should be utilized. Macaque monkeys should only be used in research when clearly indicated.

Direct handling of monkeys should be minimized and accomplished using physical restraints, such as squeeze-back cages, tunnels, or chutes, and use of protective gear by handlers. In addition to education, infection control measures include obtaining annual serologies from handlers in the event of a suspected B virus infection [44].

Treatment

Cleansing the wound or exposure site is the first and probably most important step after a potential exposure. All wounds incurred by animal handlers that might be contaminated or that result in bleeding should be immediately and thoroughly scrubbed for 15 minutes, cleansed with soap and water, and treated with 10% iodine in alcohol or another concentrated detergent. Exposed mucosal surfaces of the eyes, mouth, and nose should be irrigated for at least 15 minutes with sterile saline solution or copious amounts of water.

After initial culture specimens and serology samples have been obtained from the patient and monkey, the degree of risk for B virus infection should be determined. In the relatively few patients who have received antiviral therapy for B virus

Table 11.3 Management of B Virus Infection in Humans

Clinical presentation	Management
Low risk of infection	
• Exposure with skin intact	• No treatment recommended
• Exposure from non-macaque species	• Monitor for 2 weeks with follow-up >2 months to ensure no signs or symptoms of disease develop
Moderate risk of infection	
• Mucosal exposure splash that has been adequately cleaned	• Consider valacyclovir 1 g PO TID ≥2 weeks (consider IV acyclovir for high-risk exposures)
• Laceration or mucosal exposure that has been adequately cleaned	• If no infectious symptoms at 2 weeks, discontinue medication and monitor 2–3 times/week with follow-up for ≥2 months. Check serologies at 3–6 weeks
• Needle stick involving blood from a macaque	• If infectious symptoms occur at any time during prophylaxis or follow-up, start treatment (see below)
High risk of infection	
• Deep puncture wound	• Discontinue at 2 weeks if patient asymptomatic with negative cultures and serology. Patient should be followed for ≥2 months, to ensure no signs or symptoms of disease develop
• Needle stick with fluid/tissue from macaque nervous system, eyelids, mucosa, or vesicles	• Consider re-culture of oropharynx, conjunctiva, or unhealed lesions 1–2 weeks after stopping treatment
• Inoculation of head, neck, or torso	• If signs or symptoms of infection develop, start IV treatment below
• Wound or mucosal exposure from macaque that appears ill, has vesicles, or is known to be shedding virus	
• Inadequately cleaned site of exposure	
• Infection site is culture-positive post-cleaning	
Signs or symptoms of B virus infection (including CNS infection)	
	• IV acyclovir 5 mg/kg every 8 hours
	• Continue until symptoms improve and cultures are negative for at least 10–14 days
	• Treatment may then be changed to PO valacyclovir

infection, the patients' neurological condition at the start of therapy correlates well with outcomes [61]. Frequently, patients started on treatment after symptoms of CNS involvement developed had fatal outcomes despite initiation of high dose intravenous therapy [16,17,20,24,25]. Early administration of acyclovir is thought to slow the progression of disease and may decrease the clinical severity and improve clinical outcomes. These findings, combined with the low toxicity of acyclovir and the high mortality associated with untreated B virus infection, favor use of prophylactic oral acyclovir immediately after exposure to B virus. If subsequent signs or symptoms of B virus develop or a positive culture result occurs, then intravenous (IV) acyclovir treatment should begin. Updated guidelines for the evaluation, including risk stratification for infection, and management of this disease are listed in Table 11.3 [57].

Several factors should be considered when evaluating for post-exposure prophylactic therapy. The four major factors to consider



Figure 11.7 Healing arm bite in a subsequently fatal case. (Photographs courtesy of Julia Hilliard, Ph.D., SW Foundation for Biomedical Research, San Antonio, TX.)

are: (1) did the infective source come from a macaque species; (2) was first aid administered as per recommendations, and if so, how adequate was this; (3) the wound type, depth, and location; (4) site or tissue where the infective source originated.

Inadequate cleansing of the wound or exposed area in a timely manner should initiate consideration for prophylactic antiviral therapy. Indications for immediate initiation of antiviral therapy include the identification of herpetic lesions in the source animal, injuries involving the head, neck, or torso, and mucosal exposure to macaque fluid. Asymptomatic B-virus shedding occurs in macaques, so an asymptomatic monkey may be infectious.

The efficacy of both acyclovir and ganciclovir against B virus have been demonstrated in vitro and in vivo studies [62–64]. In vitro studies have shown ganciclovir to have a slightly greater efficacy than acyclovir against B virus [54], but the associated toxicity of ganciclovir is greater. In reviews of case reports, ganciclovir appears to be a less effective treatment. It is notable, however, that in these cases, ganciclovir was initiated after failing acyclovir treatment, so this data is difficult to interpret. In addition, the few clinical reviews performed in humans favor oral acyclovir for post-exposure prophylaxis [16,20,22,23,43,44,47].

Clinical scenarios and prophylaxis treatment recommendations are listed in Table 11.3. Prophylaxis should consist of oral acyclovir for at least 2 weeks [54]. Close monitoring and follow-up with the patient for two or more months is necessary as antiviral prophylactic therapies may delay the onset of clinical disease [55].

If symptoms of disease ensue or results are positive for B virus infection, treatment should be initiated with IV acyclovir, and should be continued for at least 2 weeks. B virus is not as susceptible to acyclovir and ganciclovir as HSV is, therefore, higher doses are utilized for treatment of B virus. Treatment may be discontinued when symptoms have improved and when cultures of genital, oropharyngeal, and conjunctival specimens are negative for at least 2 weeks after beginning antiviral therapy. This process should be carefully monitored, with follow-up two to three times a week for 2 or more months. The initial wound may heal, even in fatal cases (Fig. 11.7). B virus serologies are recommended when

treatment is stopped, as well as 3 and 6 weeks later [16,18]. A significant increase in antibody titers requires close monitoring for disease symptoms or viral shedding.

Some experts recommend post-treatment regimens consisting of long-term suppressive oral acyclovir therapy after a confirmed B virus infection, but its utility and indicated duration are debated [16]. For the complete recommendations regarding post-exposure prophylaxis and treatment see:

- B Virus Working Group Guidelines [49]
- National B Virus Resource Center (http://www2.gsu.edu/~wwwvir/)
- CDC (http://www.cdc.gov/ncidod/diseases/bvirus.htm)

Conclusion

B virus infection in human hosts is rare, with most cases occurring from laboratory exposure to macaque species. The opportunities to study the pathogenesis, clinical manifestations, treatment, and prognosis of human B virus infection are limited. Mortality due to encephalomyelitis is approximately 80% in untreated cases. Improvements in laboratory testing have increased the specificity and sensitivity of diagnosing B virus. Antiviral treatment initiated early has shown some effectiveness in improving outcomes. Since vaccination has not been shown to be effective, prevention strategies are aimed at decreasing risk of exposure via laboratory safety and propagation of B virus-negative macaque colonies for research laboratories. Consideration of B virus infection should be given for any patient with macaque exposure who presents with suspicious dermatological or neurological complaints, since early diagnosis and intervention are important for improved morbidity and mortality.

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12 Human Papillomaviruses

Anita Satyaprakash and Claire Mansur

The papillomaviruses (PVs) are a family of small DNA tumor viruses with a worldwide distribution (Fig. 12.1) that infect a number of species ranging from humans to fish. Historically, the bovine (BPV) and cottontail rabbit (CRPV) PVs have been important models for the genetic analysis of PV gene functions. PVs were previously considered a part of the Papovavirus family, but are now recognized as a separate family, Papillomaviridae. Approximately 100 types of human papillomavirus (HPV) have been identified by differences in their nucleotide sequence (Table 12.1) [1]. Many of these types have a predilection to cause disease in distinct anatomical regions and clinical lesions with specific morphologies. However, the anatomic distribution and physical appearance of a papilloma do not always correlate with the HPV type. In the vast majority of cases, viral infection causes benign epithelial proliferations called warts or verrucae. Although these infections are benign, they cause significant morbidity; as the most common sexually transmitted infection (STI), HPV causes warts of the penis, vulva, rectum, and cervix [2]. The medical cost of treatment of these benign lesions is enormous, as approximately 1% of sexually active adults in the USA and Europe are affected, with more than 1 million new cases of external anogenital warts diagnosed every year [3]. Recently, certain types of HPV have been shown to be the causative factor of a number of epithelial malignancies. These cancer-associated HPV subtypes have been associated with over 99% of all cervical cancers, 85% of anal cancers, 50% of vulvar, vaginal, and penile cancers, 20% of oropharyngeal cancers, and 10% of laryngeal and esophageal cancers [2]. Cervical cancer is the second most common cancer among women worldwide, and one of the most common causes of cancer death, especially in developing countries [4]. HPV is also associated with a percentage of skin cancers and disease of the respiratory tract.

History

Warts were documented in the writings of the ancient Greeks and Romans, and for centuries were thought to be a form of syphilis or gonorrhea. The viral etiology was first demonstrated in 1907 through experimental human inoculation of a cell-free extract of wart tissue from infected individuals [5]. The pathogenic virus was later confirmed in the 1940s by the visualization of viral particles in skin warts with electron microscopy. At first, it was assumed that there was only one type of HPV and that the morphological variation among lesions was due to the differences in epithelium at particular body sites [6]. However, molecular biology techniques that first became available in the 1970s demonstrated several types of HPV [7,8]. The preferential finding of particular types in specific anatomic locations and clinical lesions evidenced that each of the various clinical diseases is a result of infection with specific HPV types.

Virology

These spherical viruses are approximately 55 nm in diameter and, unlike many other viruses, lack an outer lipoprotein envelope. Due to the lack of this coat, PVs are quite stable in the environment and resistant to freezing or desiccation. These viruses show strict cellular tropism, infecting only the epithelial cells of their hosts. Molecular biological techniques have made it possible to clone complete viral genomes from the lesions of humans and animals and determine their nucleotide sequences.

The viral genome is small, comprised of double-stranded DNA, has approximately 8000 base pairs, and contains 10 open reading frames (ORFs), or gene coding sequences (Fig. 12.2). The basic structure of the genome is the same for the different genotypes of PVs and consists of an upstream regulatory region (URR) that contains the origin of replication and many of the control elements for transcription and replication, an "early gene" (E) region, which encodes proteins that regulate viral function, and a "late gene" (L) region, which encodes the structural capsid proteins (Table 12.2). The viral capsid proteins encoded by the two L genes encode antigenic domains that are responsible for group-specific antisera to PVs. The viruses lack the full complement of genes required for DNA replication and so must recruit a number of host cellular proteins for vegetative replication to occur. The regulation of viral gene expression is complex and incompletely understood, but evidence indicates regulation by both cellular and viral transcription factors. Cellular regulation of viral gene transcription is cell type-specific, and this may explain the marked epithelial tropism of the PVs [9–11].

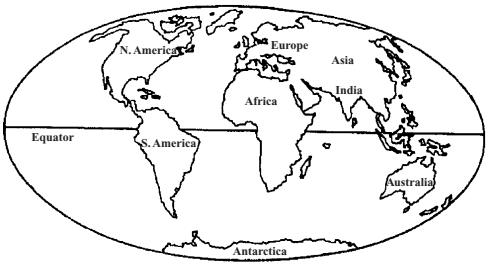
PVs also show a strict species specificity, which means that they do not infect and undergo vegetative replication in cells of species other than their normal host. Thus, mature HPV virions cannot be produced in an animal model. Animal models of PV infection have been developed using specific animal PVs, in particular those using BPV and CRPV [12,13]. These animal models have taught us about the life cycle of these viruses. Although there are many similarities in the pathogenesis of the different PV genotypes, there are also distinct and important differences in the cellular functioning of their gene products, making extrapolation from animal models to HPV difficult. Because of these difficulties, it has been primarily through the application of molecular techniques that we have gained a better understanding of the functions of the HPVs.

With the cloning of a number of different PVs, the heterogeneity of these viruses, particularly the HPVs, became increasingly apparent, as well as the need for formal recognition of the different types. The requirement for identification of a PV type is a difference of 10% in nucleotide sequence in the late gene L1 ORF from all other existing types. Currently, 96 HPV types have been identified and fully sequenced, while data from sequencing polymerase chain reaction (PCR) amplicons suggests that almost 200 types exist [1,14,15]. A HPV subtype is required to differ by 2–10% in its L1 sequence from any known type; HPV 46, 55, and 64, previously classified as types, are now identified as subtypes of HPV 20, 44, and 34, respectively, and are the only currently known

Taxonomy

Papillomaviridae family
Papillomavirus genus

Geographical Incidence

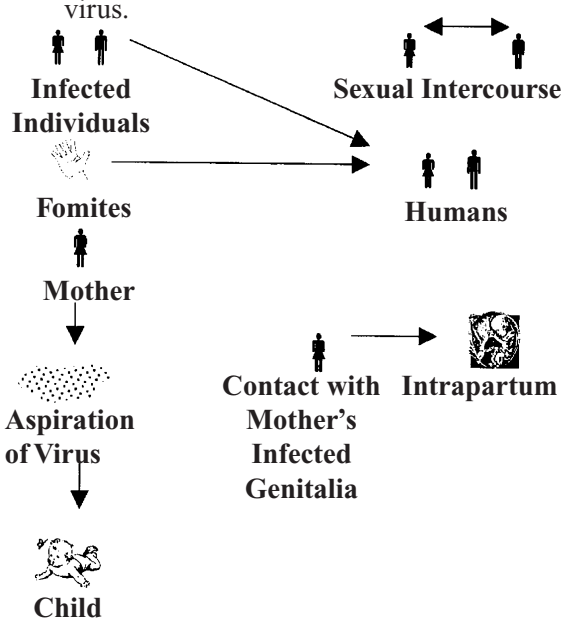


Transmission

Common warts, plantar warts, etc.: direct contact with infected individual or fomites.

Condyloma acuminata: direct genital contact, such as through sexual intercourse. Children may also acquire virus through intrapartum contact with mother's infected genitalia.

Respiratory papillomatosis: Intrapartum transmission from mother to child, likely with aspiration of the virus.



Zoonotic Implications

None for human papillomavirus infection.

Figure 12.1 Incidence and transmission of human papillomaviruses (HPVs).

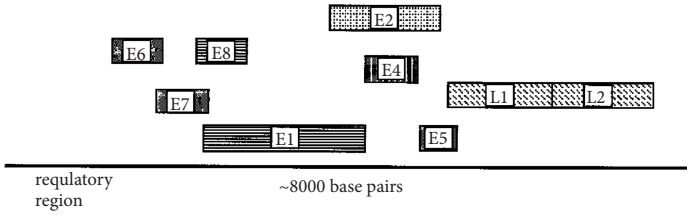


Figure 12.2 Schematic representation of the arrangement of the papillomavirus genome. The genome normally exists as a circular, double-stranded episome. E3 and E8 are not found in humans.

subtypes. HPV variants of known types differ in their L1 sequence by less than 2%. Some preliminary indications exist that suggest that HPV variants differ biologically, which may explain the worldwide disparities in disease associated with specific HPV types, such as cervical cancer [16].

HPV types were previously grouped into one of three categories, also known as "supergroups" or "major branches," based on their anatomic distribution. These groups consisted of genital-mucosal types, types affecting keratinized skin outside of the genital area, and EV-associated types. A few types, such as HPV 63 and 41, did not fit clearly into any of these categories. Often, types that are closely related by nucleotide sequence cause very different phenotypic disease, and highly unrelated types cause similar phenotypic disease, which evidenced a need for change in the classification system. Current taxonomic classification reconciles the PV "type" with the accepted taxonomic terms "species" and "genus," in order to standardize the classification of PVs with that of other biological organisms. Comparison of the L1 ORF of the 118 fully sequenced PVs (22 of which are animal PVs) led to the new classifications. Members of a PV genus share greater than 60% nucleotide sequence identity in the L1 ORF. Within a genus, members of a species share between 60 and 70% nucleotide identity. Within a species, the traditional PV types share between 71 and 89% nucleotide identity. Members of a species generally share biological and pathological behavior, causing a specific severity of disease in a particular anatomic location. Multiple species may cause disease in the same anatomical location, however; for example, HPV 18 is in a different species than HPV 16 and 31 and both cause high-risk mucosal lesions. Although this system is accepted, it is not yet widely used, with most current authors still classifying HPV types as "genital" or "nongenital" [1].

Under this classification system, there are 5 identified genera that cause human disease – alpha-, beta-, gamma-, mu-, and nu-PVs. The alpha-PVs consist of the majority of HPV types that cause disease in humans, including HPV 16 (species 9), 18 (species 7), 6 and 11 (species 10), and 2 and 3 (species 4 and 2, respectively). Beta-PVs consist mostly of HPV types that cause disease in EV or immunosuppressed individuals. Gamma-PVs cause cutaneous lesions that exhibit histologically distinct homogenous intracytoplasmic inclusion bodies. Mu-PVs, including type 1, exhibit histologically distinct heterogenous intracytoplasmic inclusion bodies, while nu-PVs have not yet been linked to any specific human disease [1].

Another commonly accepted way to characterize HPV viruses is based on potential oncogenicity. Certain species of HPV have more oncogenic potential than others, and some members of those species are more prevalent than others. HPV-16 and HPV-18 are the types most commonly isolated from cervical cancers, although types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 have also been established as high risk for genital carcinogenesis. Probable high-risk types include 26, 53, 66, 68, 73, and 82. Types established

Table 12.1 Disease Association of Human Papillomavirus (HPV) Genotypes

Characteristic HPV lesion	Associated HPV type
Palmoplantar warts	1
Common warts	2 (*4, 26, 27, 65, 78)
Flat warts	3, 10 (27, 28, 49)
Butcher's warts	7
Condylomata acuminata	6,11 (70, 83)
Bowenoid papulomatosis	16
Cervical intraepithelial neoplasia and cancers, anogenital cancers	16 & 18 most common; also 31, 33, 35, 39, 45, 51, 52, 58, 66, 69 (30, 34, 40, 42–44, 53–57, 59, 61, 62, 64, 67, 68, 71–74, 82)
Oral papillomas	6, 11
Oral focal epithelial hyperplasia	13, 32
Recurrent laryngeal papillomatosis	6,11
Cutaneous squamous cell carcinoma	41, 48 (29)
Laryngeal carcinoma	16,18
Verrucous carcinoma	16, 6, 11
Epidermodysplasia verruciformis (EV)	3, 5, 8, 9, 10, 12, 14, 15, 17, 19, 20, 21, 22,23, 24, 25, 36, 46, 47, 50 (37, 38)
Most EV-associated cancers	5, 8
Common warts in immunocompromised patients	EV types and 75, 76, 77
Epidermal cyst	60
Myrmecia wart	63

* less frequent associations

Note: HPV types 79 and 81 have been designated but not reported; HPV type 80 has been found in histologically normal skin.

Table 12.2 HPV Proteins and Their Putative Functions

Viral protein	Proposed functions
E1	Forms a heterodimer with E2 and binds to the viral upstream regulatory region (URR) to function in viral DNA replication
E2	Participation with E1 in viral DNA replication Transcriptional regulation via binding sites in the URR, specifically transcriptional repression of E6 and E7
E3	Only in bovine papillomavirus
E4	Binds to and collapses the cellular cytokeratin network, allowing release of mature virions
E5	Enhances epidermal growth factor (EGF) nd platelet-derived growth factor (PDGF) signaling via inhibition of turnover of the growth factor receptors Uncertain role in malignant transformation in HPV-related cancers
E6	High–cancer-risk E6 binds and mediates the rapid degradation of p53, inhibiting its cell cycle arrest and apoptotic responses to cellular DNA damage With high-risk E7, immortalizes primary keratinocytes and induces malignant transformation of cell lines
E7	High–cancer-risk E7 binds to the Rb family of growth regulatory proteins, inhibiting their negative regulation of the cell cycle Binds to and enhances the activity of AP-1 transcription factors Participates with E6 in cellular transformation
L1	Major capsid protein, alone or in combination with L2, can assemble into virus-like particles that have the antigenic epitopes that can stimulate the host's humoral response
L2	Minor capsid protein

as low risk for genital carcinogenesis include HPV-6 and HPV-11, the most common causes of benign genital warts, along with types 40, 42, 43, 44, 54, 61, 70, 72, and 81. Patients afflicted with EV very commonly develop squamous cell cancer (SCC) in warts located on sun-exposed skin. Within the beta-PVs, which most frequently cause lesions in individuals with EV, there are also types that are high risk and low risk for malignancy. Although approximately 20 HPV types have been associated with EV, the vast majority of the skin cancers in these patients are associated with HPV-5 and HPV-8. The mechanisms by which high-risk HPVs participate in malignant transformation of cells is discussed in more detail later.

Epidemiology

HPV infection, either mucosal or cutaneous, is very common, although the lack of reliable serological assays for detection of infection has prevented precise definition of lifetime cumulative incidence. Transmission of HPV is thought to occur through contact with individuals who have clinical or subclinical infection or through contact with infectious virus present in the environment. The likelihood of developing a clinical infection is dependent on several factors including the quantity of virus, the nature of the contact, and the immunologic state of the exposed individual. Warts are particularly common in patients with impairments in cell-mediated immunity (CMI) and occur in the majority of patients on immunosuppressive therapy following renal transplantation [17].

Cutaneous warts are uncommon in infancy, but the incidence in children and young adults may approach 10% [18]. Anogenital

warts are uncommon in children, but are frequently seen in young adults. Anogenital warts are usually sexually transmitted, and they now represent the most common sexually transmitted disease. Anogenital warts do occur infrequently in infants and children and may be sexually transmitted, although infection may also occur from viral contact at birth from an infected mother or through autoinoculation from cutaneous warts. Although the presence of genital warts in children always raises concerns of sexual abuse, evidence indicates that a large proportion of these warts contain HPV types not usually associated with genital lesions. This suggests that transmission may occur via autoinoculation in children with cutaneous warts or contact with infected caretakers [19]. Similarly, laryngeal papillomas contain the same HPV types as genital warts, and approximately half of the cases occur in infants and children. In these cases, it is believed that infection occurs through aspiration of the virus during birth.

In adults, genital HPV infections are usually transmitted sexually. The peak incidence of genital HPV infection in the USA occurs at 15–25 years of age, and the incidence increases with increasing numbers of sexual partners. After this age, the incidence of infection declines sharply. Depending on the assay used to detect HPV, the peak incidence of genital infection has been estimated to exceed 20% in sexually active women in this age group; indeed, more than 50% of sexually active women have been infected at some point with one of the more than 40 HPV types that infect the anogenital tract [20]. The low-risk types, HPV-6 and HPV-11, are more likely to be isolated from genital warts of the external genital epithelium and are less frequently isolated from cervical or vaginal lesions. These types are rarely isolated from genital cancers. The high-risk types, HPV-16 and HPV-18, are most frequently isolated from cervical and vaginal lesions. Asymptomatic genital infections and infections causing mild cervical dysplasia are very common, but the estimated prevalence rates vary substantially according to the assays used and the population studied. The incidence of both asymptomatic genital infection and mild dysplasia decreases dramatically after the ages of 20–25 years, suggesting that spontaneous clearing of infection is a common event. The incidence of HPV-associated cancer is much lower than the incidence of low-grade dysplasia, and the peak incidence of cancer occurs approximately 20 years later. This supports the concept that many infections clear spontaneously, and although infection with high-risk HPV is a necessary condition for the development of cervical cancer, it is not by itself sufficient for development of the disease. A worldwide study of the prevalence of HPV types found that over 99% of invasive cervical cancers contain HPV. Of these, 54.3% of the cancers contained HPV-16 and 12.6% contained HPV-18. HPV 31, 33, 45, 52, and 58 each made up less than 5% of invasive cervical cancers, with other high-risk HPV types comprising less than 1% [21]. Host factors that may increase the likelihood of progression from low-grade cervical lesions to carcinoma include endogenous hormones, genetic factors, and the immune response or its suppression [22]. Environmental cofactors for the development of cervical cancer include tobacco smoking, long-term use of hormonal contraceptives, high parity, dietary deficiencies, and concurrent infection with other sexually transmitted agents, such as *Chlamydia trachomatis* (CT), herpes simplex virus 2 (HSV-2), and human immunodeficiency virus (HIV). The association of tobacco use may be related to the reduction of local immune response in the cervix, free-radical generation, and direct genetic damage by tobacco-related carcinogens. Hormone-related mechanisms may promote integration of HPV DNA into the host genome, resulting in deregulation of E6 and E7 expression; data from some studies demonstrate a synergistic mechanism between long-term estrogen exposure and HPV-16 oncogenes that modulate squamous carcinogenesis in the female genital tract. High parity is thought to increase the risk of cervical carcinogenesis through the maintenance of the transformation zone on the exocervix for many years, which may facilitate HPV exposure. Short-term studies have shown an inverse relationship of increased dietary lutein, lycopene, carotenoids, and retinols and decreased oncogenic HPV persistence, Concurrent STIs, such as CT and HSV-2, may increase risk through the inflammatory response, which has been associated with free radical generation and subsequent development of genetic instability; HIV results in an immunocompromised state, facilitating both infection and malignant transformation [22–24]. Obesity in women has been linked to increased cervical cancer mortality, likely due to decreased rates of cytologic screening in this population [25–27]. The incidence of high-risk HPV infection in men is more difficult to estimate, but as it is a sexually transmitted disease, the incidence in men is likely to be similar to the incidence in women. High-risk HPV infections have been linked to 83–95% of anal cancers and 40–50% of penile cancers [28–31].

Pathogenesis

Infection with HPV is thought to be acquired initially through inoculation of virus into the epidermis through epithelial defects. These may be microdefects, because infection often occurs in the absence of any history of injury to the skin, but skin maceration is probably an important predisposing factor. The HPVs infect only surface epithelial cells of the skin and mucous membranes. After infection, new warts may develop within the same region or more distantly. Spread of infection can occur through direct infection of the skin or autoinoculation from other infected skin cells, but not by blood-borne spread. It is common to see autoinoculation of virus on opposing body sites, such as adjacent digits or in the anogenital region. In general, HPVs induce benign, self-limited proliferation in the skin. Although clinical morphology varies among HPV types, they share a similar histology, showing localized epithelial hyperplasia above an intact basement membrane.

Specific HPV types are much more likely to infect specific body sites and, in particular, to show a preference for cutaneous versus mucosal sites. This is not invariably the case, however, because nongenital types have infrequently been isolated from genital lesions [19]. The clinical appearance of warts varies based on anatomical location, but infection is thought to proceed similarly in all sites. Little is known about the mechanisms of viral attachment and entry into the cell, but it has been demonstrated that PVs can attach to a number of nonepithelial cell types. Thus, it is not via attachment to an epithelial-specific receptor that PV cellular tropism is determined. It has been shown that attachment is mediated via the L1 protein, and it is believed that the receptor is likely to be a widely expressed and highly conserved cell surface protein [32]. Following infection of the basal cell compartment of the epidermis, the viral DNA exists as one or two copies of circular, episomal, double-stranded DNA. Through unknown mechanisms,

the virus stimulates proliferation of basal cells, and the viral DNA is replicated and carried along with the epithelial cells as they stratify and differentiate. The lesion becomes acanthotic, presumably because of the stimulation of unscheduled cellular division. While infecting the basal cells, the virus does not undergo productive synthesis of virions, but rather viral early gene transcription and DNA replication are maintained at very low levels until higher strata of the epithelium are reached.

Following experimental inoculation of PVs in the skin, there is a long latency before clinical lesions develop, on the average of 6–9 months. This long period before the detection of clinical lesions implies that the viral genome may persist within the basal layer as an extrachromosomal genome without stimulating cell proliferation or production of mature virus particles. In support of this, it has been shown that HPV DNA can be detected in normal mucosa of patients with laryngeal papillomatosis while the disease is in remission [33]. In epidemiological studies of genital HPV infection, HPV DNA is often detected in patients with no cytological or clinical abnormalities [34]. It is not clear whether this is a state of viral persistence with a low level of viral DNA replication or true viral latency (defined as nonreplicating, transcriptionally inactive virus). This restriction of viral gene expression in the basal layers makes it difficult for the immune system to detect the virus. Thus, it has been hypothesized that this may be a mechanism by which PVs evade the immune surveillance of the host [35].

Only in the terminally differentiating epithelial cells, presumably in response to differentiation-specific signals, do viral gene transcription and DNA synthesis accelerate and virions assemble. The viral capsid proteins assemble in the nucleus of the infected cell as differentiation moves toward the stratum corneum. Evidence indicates that the viral gene, E4 (which is probably more appropriately termed a *late gene*), attaches to and collapses the cytoplasmic keratin framework, presumably to allow release of infectious virions into the environment [36]. It is likely that in these outer levels of the epidermis, the virus is more protected from the immunological defenses of the host. The level of production of viral particles varies with the different types of warts, with levels being highest in patients with EV; in normal hosts, they are more plentiful in plantar warts and much lower in genital lesions (Fig. 12.3). In HPV-associated dysplasia and cancer, although the viral DNA is retained and genes are expressed, mature virion production is markedly decreased.

It is particularly important to note that it is within this progressively differentiating cellular environment that the virus must recruit the many cellular factors necessary for its own replication. The virus presumably does this by deregulating cell growth in the basal layer of the epithelium so it can utilize the cellular replicative machinery for its own replication. Thus, even in benign infections, the viruses have some ability to stimulate cellular growth [37,38], and it is likely that acquisition of transforming function in the high-risk viruses may have come in part from a loss of regulation of this growth-promoting activity. Production of mature viral particles is seen only in the outer layers of the epidermis where the cells are terminally differentiated and no longer competent for cell division. Another important point is that the viruses require a differentiated environment for growth and it has not been possible to develop a simple means to culture HPVs in vitro. Very limited production of HPV virions has been achieved in vitro using infected human cells in an organotypic culture system [39,40]. However, introduction of cloned viral DNA into cultured cells has not led to synthesis of infectious viral particles.

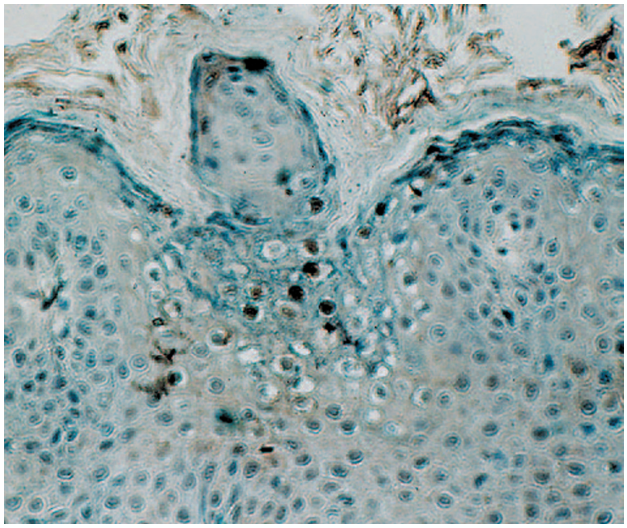


Figure 12.3 Immunoperoxidase staining of a lesion from a patient with epidermodysplasia verruciformis. The black dots represent clusters of mature HPV virions. (Photograph courtesy of Elliot Androphy, M.D., Department of Dermatology, Tufts/New England Medical Center, Boston, MA.)

Whereas there appear to be mechanisms by which PVs evade the host's immune response, there is also indirect evidence that the immune system plays an important role in controlling HPV infection [41,42]. Cutaneous warts frequently undergo spontaneous regression. Infrequently, treatment of a small number of warts may lead to resolution of many or all of the warts in a patient. The prevalence of genital HPV infections peaks in young adulthood and declines thereafter, implying spontaneous clearing of infection presumably by immune mechanisms. There is increased incidence and prolonged persistence of squamous intraepithelial lesions (SIL) in immunosuppressed women [43,44]. All of these phenomena suggest a role for the immune system in controlling HPV infection, but the precise mechanisms remain poorly understood. No consistent defect in the immune system in patients with warts has been demonstrated, but a number of lines of evidence point to the importance of CMI in the course of HPV infection. Patients with defects in CMI have a high incidence of warts, which occur in larger numbers and are more resistant to treatment. Furthermore, these warts frequently resolve spontaneously with correction of the immune defect. There is evidence for T-helper cell involvement in lesion regression, as well as a concomitant humoral and cellular immune response against HPV antigens during regression [44–46]. There is a higher incidence of HPV-associated cancers in renal transplant patients [47]. In immunocompetent patients, flat warts have been reported to undergo spontaneous resolution, and histologically, this is accompanied by a monocellular infiltrate of the skin.

Although there is evidence that the humoral immune system plays an unclear role in HPV infection, patients with humoral defects have not been found to be predisposed to HPV infection. In general, in benign infections the antibody response to early viral proteins is weak and declines over time. The incidence of type-specific reactions to HPV E6 and E7 proteins is somewhat

higher in patients with cervical cancer, being detected in approximately half of these patients [47–49]. It is thought that this may be due to the increase in expression of E6 and E7 in progressively more dysplastic lesions (see Viral Oncogenesis). Improved detection of antibodies to viral capsid antigens has come with the synthesis of virus-like particles (VLPs). When the viral L1 or L1 and L2 proteins are expressed in eukaryotic cell lines, the proteins self-assemble into VLPs that are morphologically indistinguishable from native viral capsids [50]. Using VLPs, anticapsid antibodies are detected in over half of patients with low grade or asymptomatic genital HPV-16 infections and in the majority of patients with HPV-16-associated cervical intraepithelial neoplasia (CIN) and invasive cancer, a somewhat surprising result given the rarity of mature virion production in these lesions. There is no evidence that these antibodies influence the course of the disease. Because these antigens are only produced in the outer layers of the epidermis, it has been hypothesized that these antibodies may be important in limiting reinfection rather than in inducing regression of active infection.

Viral Oncogenesis

Historically, PV infection was first linked to the development of cancer in studies that demonstrated the oncogenic potential of the BPV and CRPV. The first evidence for a link between HPV infection and cancer in humans came from patients with EV in whom SCCs frequently develop in sun-exposed warty lesions. It is clear that among the over 100 different HPV genotypes, only a small subset of these are high risk for malignant transformation. For example, whereas over 20 different HPV types have been associated with the lesions of EV, only HPV-5 and HPV-8 are associated with the majority of HPV-linked SCCs. Similarly, over 25 HPV types have been isolated from mucosal HPV lesions in normal hosts, but only HPV types 16, 18, 31, and 45 are detected at high frequency in cervical cancers. The association of this group of high-risk viruses with cervical cancers is well established, but recent evidence indicates that these viruses may be associated with even more cancers than previously suspected. The cancer-associated EV types have been isolated from skin cancers in immunocompromised patients, particularly renal transplant patients [47,51,52]. The high-risk types have been associated with other epithelial tumors, including those of the penis, vulva, vagina, anus, and oropharynx [4,29,30,53–58]. Now that sensitive methods for detecting a broad range of HPV subtypes have been developed, it has been reported that HPV DNA is detected in up to 30% of nonmelanoma skin cancers, even in immunocompetent hosts [51,59]. These surprising results suggest that the oncogenic potential of HPVs is greater than first imagined.

As noted previously, although the vast majority of cervical cancers are associated with HPV infection, most HPV infections, even with the high-risk HPVs, do not lead to the development of cancer. In addition, there is a long latency between the initial infection and progression toward malignancy (on the order of decades), suggesting that the high-risk viruses predispose to malignancy, but other events, such as mutations or oncogene activation, are required for full malignant transformation. HPV-containing cervical carcinoma cell lines and cancer specimens exhibit changes in the behavior of the viruses in these cells from what is seen in benign lesions. In benign infections, HPV DNA exists as a circular episome, whereas in cervical carcinoma cells, the viral DNA usually becomes integrated into the host DNA [60]. Importantly, with integration, there is frequently a loss of the viral regulatory gene, E2, and sometimes E1, with subsequent dysregulation of E6 and E7 gene expression and increased levels of their protein products [61,62]. Integration may also disrupt host cellular genes. Although integration does not consistently occur at the same sites in the cellular genome, integration near to cellular oncogenes has been reported [63]. As noted previously, production of mature virus particles is dependent upon a differentiated state of the cell, and in the poorly differentiated cells of CIN or frank malignancy, mature viral particles are infrequently detected.

Early evidence for a link between HPV infection and the development of cervical cancer came from identification of HPV-6 and HPV-11 DNA in benign genital warts and HPV-16 and HPV-18 DNA in cervical cancers and the precursor lesions of cervical dysplasia and carcinoma in situ. The detection of HPV DNA in human cancers did not prove that the viruses played an etiological role in the development of cancer, and evidence for this came from several lines of investigation. Several established HPV-positive cervical carcinoma cell lines, such as HeLa and SiHa, were found to continue to synthesize HPV proteins despite maintenance in culture for decades [64,65]. Specifically, these cervical carcinoma cell lines were found to selectively retain and express the early viral genes E6 and E7 [66–68]. In addition, it was demonstrated that repression of HPV protein expression in cervical carcinoma cell lines led to decreased cell growth and loss of the transformed phenotype [69,70].

With the ability to clone the HPV genomes, much work has been done to examine the effect of HPV gene expression using in vitro cellular transformation assays. By introducing HPV genomes or specific viral genes into cells grown in culture, various parameters of malignant transformation that are thought to mirror the in vivo transformation process have been measured [71]. It is now understood that malignant transformation is a multistep process with cellular dysplasia developing first, followed by carcinoma in situ, and finally development of invasive carcinoma. Using classic transformation assays, immortalization of cells corresponds to the early changes seen in carcinoma in situ, whereas measures of anchorage independent growth and tumorigenicity in mice correspond to a more fully transformed phenotype. With numerous such assays, it was demonstrated that the high-risk HPV genotypes could induce immortalization of primary cells [72,73] and malignant progression of immortalized cell lines [61,70,71]. The morphological appearance of the immortalized cells closely mimics that which is seen in CIN. These cells are not tumorigenic but, when maintained for sustained periods in culture, will evolve a fully transformed phenotype. These effects can be achieved with expression of only the E6 and E7 genes, thus identifying these gene products as the major transforming proteins of the HPVs [72,74–76]. The E6 and E7 proteins from the low-risk HPVs show little or no activity in these transformation assays [37,77]. Studies with BPVs showed BPV E5 to be one of the major transforming proteins for BPV, but studies with HPV E5 indicate that it is only weakly transforming [78–80]; rather, it plays a role in early viral infection. The fact that the high-risk HPVs, or the high-risk E6 and E7 gene products alone, induce immortalization of cells, but a

not fully transformed phenotype suggests that this HPV-mediated extension of lifespan allows time for additional genetic or epigenetic alterations that must accumulate for a fully malignant phenotype to manifest. Better understanding of the functions of the individual HPV proteins has shown this to be the case.

As has been demonstrated for other viral oncogenes, the high-risk HPV E6 and E7 oncoproteins exert their transforming effects, at least in part, through interaction with cellular tumor suppressor genes. E6 interacts with and degrades the pro-apoptotic protein Bak, resulting in resistance to apoptosis and an increase in chromosomal instability [44,81]. E6 also contributes to growth stimulation of infected cells through activation of telomerase and inhibition of degradation of the Src-family of kinases [82,83]. Perhaps of most importance, E6 binds to and mediates the rapid degradation of p53 via the cellular ubiquitin proteolysis pathway (Fig. 12.4). The high-risk E6 proteins bind to p53 in complex with a cellular factor called E6-AP, for E6-associated protein [84]. The low-risk E6 proteins do not induce degradation of p53 [85–87]. It has been reported that p53 is normally targeted and degraded through the ubiquitin pathway independent of E6 [88,89]. Thus, it appears that E6 stimulates accelerated turnover of p53 or perhaps stimulates degradation of p53 in the face of signals that would normally induce p53 stabilization. p53 mediates cellular growth arrest and apoptosis of cells particularly in response to DNA damage [90–94]. A critical mechanism by which p53 exerts its effects is through transcriptional activation [95–97]. Under conditions of cell stress and/or DNA damage, cellular levels of p53 rise primarily through a decrease in its degradation and p53-dependent transcriptional activation increases [98–101]. An important transcriptional target of p53 is p21/WAF1, which is an inhibitor of cyclin-dependent kinases (CDKs) [98,101,102]. Through inhibition of CDKs, expression of genes necessary for progression through the cell cycle is inhibited, and there is a G1-mediated growth arrest that allows the cell time to repair damaged DNA. In other cases, presumably in response to more extensive damage to DNA, p53 signals cellular apoptosis, which is a programmed cell death [103]. Without the p53-mediated DNA damage response, the cell would be allowed to continue to divide, thereby perpetuating DNA mutations. Support for this theory has come from the demonstration of genomic instability and gene amplification in cells that lack p53 function [84,85]. Another mechanism by which p53 participates in the response to DNA damage is through binding to proteins such as RPA, TFIIH, and CSB, which have functions in both DNA replication and repair. Although the pathways are not completely worked out, it is thought that p53 may inhibit the DNA replication functions of these proteins, but localize them to sites of DNA damage and perhaps participate directly in facilitating the DNA repair process [104–106]. The functional activities of p53 that are disrupted by interaction with the high-risk E6 proteins are depicted in Fig. 12.5.

Like the high-risk E6 proteins, the high-risk E7 proteins interact with a cellular tumor suppressor. E7 binds to the retinoblastoma protein (Rb) and related proteins, p107 and p130, that, in cooperation with p53, also mediate cellular growth arrest [107–109]. Rb is a cellular growth regulator whose phosphorylation status is regulated through the cell cycle. It is activated in its hypophosphorylated state in G0 and G1 phases of the cell cycle. In this active, hypophosphorylated state, pRb binds to the cellular transcription

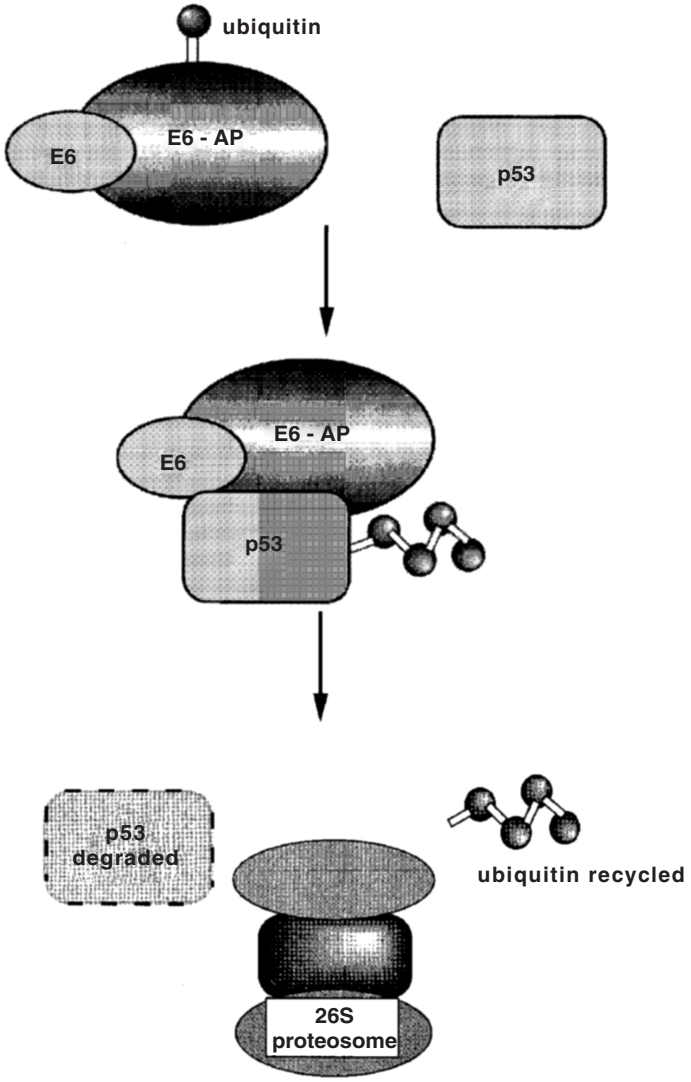


Figure 12.4 The high-risk E6 proteins bind to a cellular protein, E6-AP, and this complex binds to p53, which catalyzes the attachment of a chain of ubiquitin molecules to p53, resulting in its degradation via the cellular 26S proteosome.

factor E2F, inhibiting the transcription of genes necessary for cell cycle progression [110]. In the S and G2 phases, CDKs act to phosphorylate Rb, causing release of E2F and cell cycle progression. Thus, the p53 and Rb pathways converge: p53 increases levels of p21 that inhibits CDKs; with inhibition of CDKs, pRb is maintained in an active hypophosphorylated state. The high-risk E7 proteins bind preferentially to the hypophosphorylated form of Rb and induce the release of E2F [111], thereby providing another pathway to cell cycle progression and unscheduled DNA synthesis (Fig. 12.6). Again as seen with E6, the low-risk E7 proteins bind to Rb with much lower affinity than those of the high-risk HPVs [112,113]. Similarly, the related proteins, p107 and p130, complex with regulators of the cell cycle, including other members of the E2F family, cyclin A and cyclin E [114,115], and participate in the regulation of both G1 and G2 cell cycle blocks. The interaction of high-risk E7 with these other Rb family members, as well as other mediators of cell cycle regulation, is thought to overcome inhibition of cell cycle arrest perhaps at both the G1 and the G2 phases of the cell cycle [109,116,117].

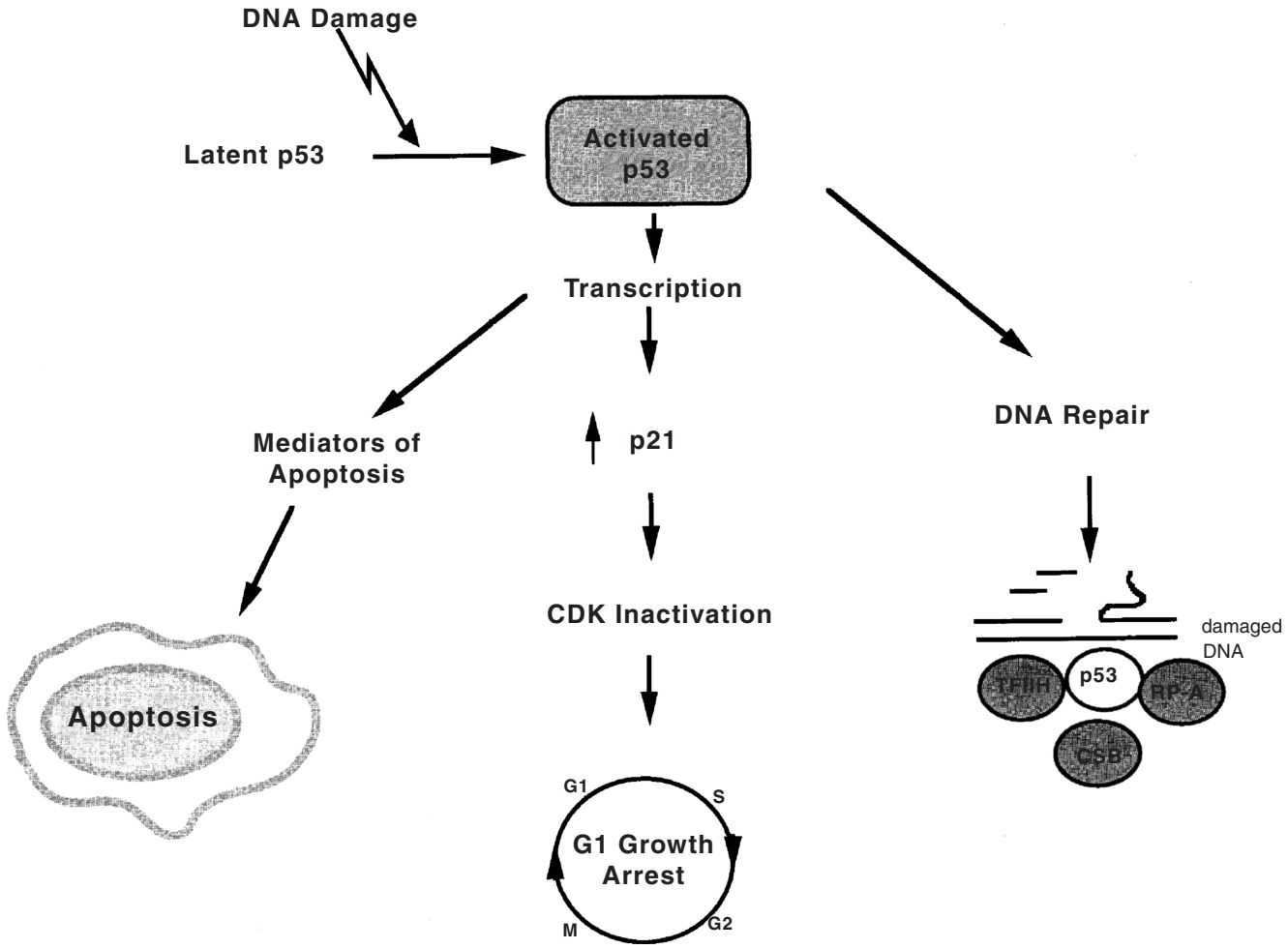


Figure 12.5 Mechanisms of the p53 DNA damage response. With damage to DNA or cellular stress, p53 levels rise and p53-mediated transcriptional activation increases. Through regulation of transcription, p53 mediates a G1 growth arrest. Through transcriptional-dependent and -independent mechanisms, under other conditions, p53 can signal cellular apoptosis. In addition, p53 can bind to proteins that function in DNA repair and through nonspecific DNA binding, localize them to sites of DNA damage.

Independently, E6 and E7 can both immortalize human cells, but at reduced efficiency; working together, however, they have a synergistic effect that leads to a marked increase in transformation ability [44,118,119]. Inhibition of tumor suppressors by E6 and E7 proteins alone is not sufficient for malignant transformation, but does lead to genetic instability, unregulated cellular growth, and the acquisition of additional mutations that presumably allow malignant progression [120]. Evidence indicates that there are other mechanisms by which E6 and E7 exert their transforming effects, such as through binding and/or mediating the degradation of other cellular proteins [121,122] and altering the function of other transcription factors [123], but these functions are at present less well defined. The HPV E2 protein also has an important role in regulating the transforming activity of the HPVs. As mentioned previously, the E2 proteins are regulators of viral gene transcription. Expression of E2 in cells that contain HPV-18 DNA has been shown to down-regulate the expression of E6 and E7 [124]. Disruption of the E2 gene leads to increased expression of the E6 and E7 proteins [61,62] and increases the immortalization capacity of HPV-16 [125]. Thus, the integration of the viral DNA into the host genome and frequent loss of expression of E2 in cervical neoplasias is likely to be an important mechanism by which expression of the viral transforming genes is deregulated. Evidence indicates that viral DNA integration and disruption of the E2 gene are neither necessary nor sufficient for malignant transformation because a number of cervical cancers with episomal viral DNA have been identified, and conversely, cells with integrated viral DNA and active viral gene expression do not always display a malignant phenotype [126,127]. Nonetheless, it is likely that loss of E2's regulatory function serves to enhance the transforming capability of these viruses.

The E5 protein has been shown to be important early in the course of infection by stimulating cell growth through formation of a complex with the epidermal growth factor receptor, the platelet-derived growth factor-β receptor, and the colony-stimulating factor-1 receptor. E5 has also been shown to prevent apoptosis after DNA damage. High levels of HPV E5 have been detected in lesions of CIN [128], but in cervical carcinoma, the E5 gene is often deleted [61]. This is now known to be due to viral DNA integration into host DNA and subsequent deletion of portions of the genome, including the E5 gene, as lesions progress to cervical cancer [44,61,129,130].

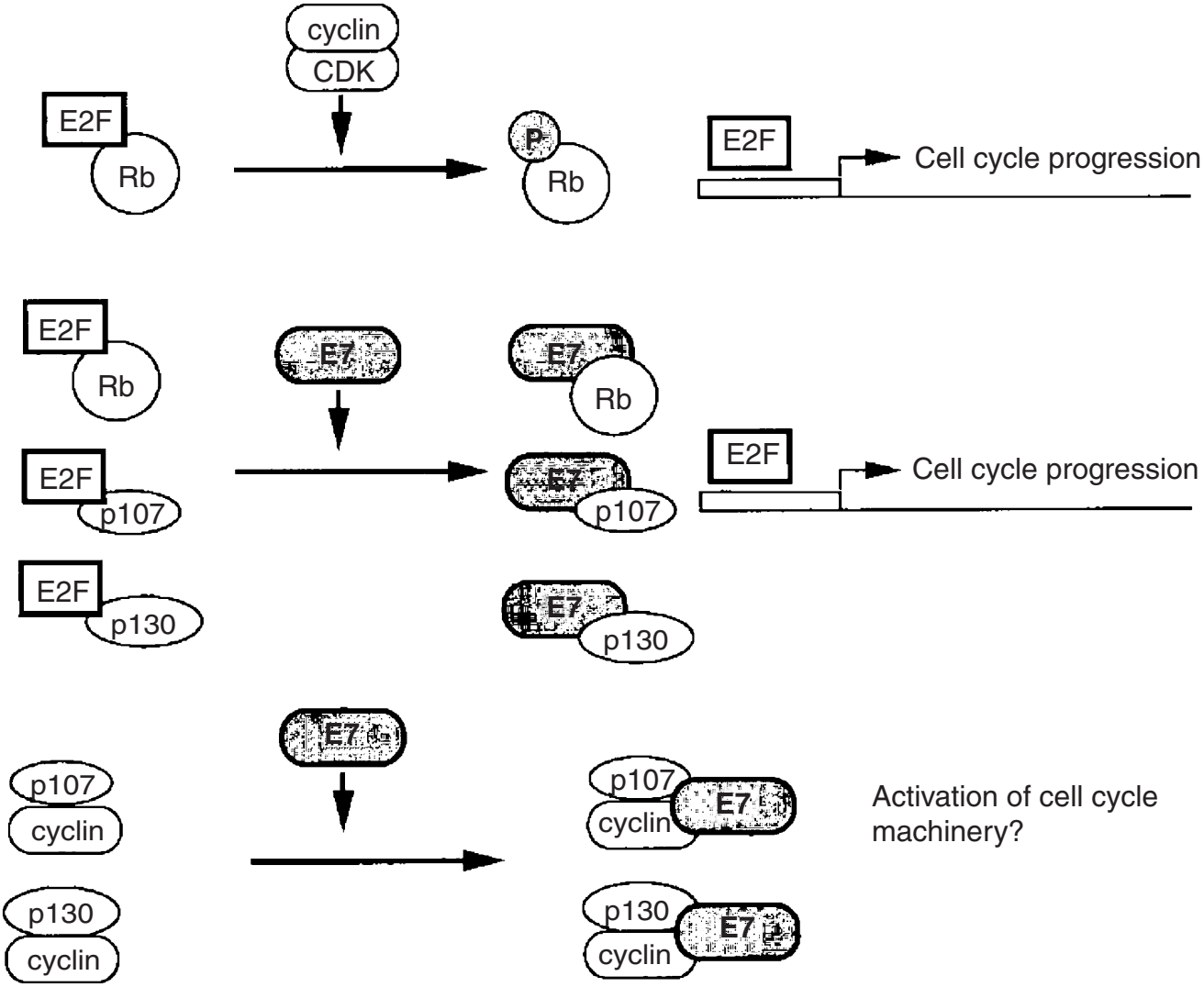


Figure 12.6 The high-risk E7 proteins bind to and inhibit the growth inhibitory functions of the Rb family of proteins.

There is evidence that the cell has other defense mechanisms that protect against malignant transformation in addition to p53 and Rb. The majority of high-risk HPV infections never result in malignant transformation; when such transformation occurs, it is only after a long latent period. This implies the existence of important cellular, immune, and/or viral modulators of HPV-transforming activities. During somatic cell hybridization studies, cells that have been immortalized by E6 and E7 and are hybridized with primary cells have their malignant phenotype suppressed, and they frequently undergo senescence. This modulating effect is likely to be due to down-regulation of E6 and E7 gene expression, but there is some evidence that this effect can be seen even with continued expression of the viral oncogenes [131,132]. When fully transformed cervical cells are grafted onto nude mice, they show no change in the expression of E6 and E7 genes. When immortalized, but not fully transformed, cells are grafted onto mice, expression of E6 and E7 genes is down-regulated [133]. These results suggest that the cell has mechanisms by which it can interfere with the function of the viral oncogenes and/or act to down-regulate their expression, mechanisms that the fully transformed cells have escaped. In order for malignant progression to occur, these cellular growth suppressive functions must be inactivated, and thus, other genetic or epigenetic events would be expected to have occurred. It is clear that the viral oncogenes do induce genetic instability, most profoundly through the interaction between high-risk E6 proteins and p53, but the exact mutations that occur to allow malignant progression have not been identified. In order to identify other likely mechanisms by which inhibition of cell growth is overcome, investigators have searched for genetic alterations that may be found in HPV-transformed cells and potential cofactors that may contribute to malignant progression. When cervical cancer cells have been subjected to cytogenetic analysis, a variety of chromosomal abnormalities at a number of different sites were found [134,135], although no one mutation has been consistently identified.

Despite this, a few candidate genes that may affect HPV function have been identified. It has been postulated that a tumor suppressor that may function in suppression of HPV-mediated transformation resides on the short arm of chromosome 11. Introduction of chromosome 11 into HPV-containing HeLa or SiHa cells suppresses the tumorigenic phenotype of these cells [136,137].

A locus on the short arm of chromosome 11 functions through down-regulation of viral gene transcription acting at the promoter of the viral URR [138,139]. Deletion of this region of chromosome 11 leads to overexpression of an inhibitory subunit of protein phosphatase 2A (PP2A) [140]. Through alteration of protein phosphorylation status, PP2A regulates the activity of a number of important cellular growth regulators and transcription factors (such as Rb, p53, and AP-1), and thus inhibition of PP2A may be a likely mechanism by which viral gene transcription is enhanced. Another candidate gene that has been proposed to be involved in malignant progression encodes the CDK inhibitor, $p16^{INK4}$. The function of $p16^{INK4}$ is not well understood, but it has been shown to up-regulate with inactivation of Rb and participate in the suppression of immortalization of cells. Spontaneous immortalization of Li Fraumeni fibroblasts (which have one mutant p53 allele) is associated with loss or mutation of the second p53 allele and loss of expression of $p16^{INK4}$ [141]. A subsequent study reported that loss of $p16^{INK4}$ may be necessary for immortalization of epithelial cells by HPV-16 E6 alone [142]. Further studies will be needed to clarify the relationship of $p16^{INK4}$ to HPV-induced transformation of cells.

Others have searched for paracrine effectors of HPV function. It has been reported that tumor necrosis factor (TNF)-α, interleukin-1, and transforming growth factor (TGF)-β can all induce down-regulation of viral early gene expression [143,144]. In other reports, it has been shown that HPV-transformed cells have evolved resistance to the growth suppressive effects of TGF-β [145], suggesting that with malignant progression, additional mutational events allow escape from this paracrine regulation. A cellular cofactor that may act in a positive way to stimulate HPV-transforming capability is glucocorticoids. The high-risk HPVs have glucocorticoid-responsive elements within the regulatory region of their genome, and addition of glucocorticoids to transformation assays is reported to enhance the immortalizing effects of HPV-16 [146]. Further, it was shown that HPV-16-mediated transformation is inhibited by exposure of cells to a glucocorticoid antagonist [147]. Clearly, the interaction between the host and high-risk HPVs is complex and incompletely understood. Evidence indicates that there are a number of lines of defense against the progression to malignancy and that these defenses are often successful in preventing the progression from infection to the development of cancer. A better understanding of these mechanisms and how they may fail is needed for the development of specific antiviral therapies for prevention and treatment of these common diseases.

Clinical Manifestations

Warts may occur on any cutaneous or mucosal surface and are generally classified by their morphology and clinical location. As discussed previously, specific HPV subtypes have a predilection to cause warts in specific anatomical locations (Tables 12.1 and 12.3). Common warts are most commonly associated with HPV-2, whereas flat warts are usually caused by HPV-3 or HPV-10 (Figs. 12.7–12.13). Palmar and plantar warts are most frequently due to infection with HPV-1 (Fig. 12.14), whereas butcher's warts are associated with HPV-7. The predilection for butcher's warts is believed to be due to associated trauma to the hands and not to transmission of an animal virus. Warts usually appear as hyperkeratotic papillomas that may occur on all cutaneous surfaces, and the appearance of warts may vary in different body sites. Close inspection of the papules, particularly after paring off the keratotic surface, often reveals "black dots," which represent thrombosed capillaries within the wart (Fig. 12.15).

Anogenital warts, or condyloma acuminata, may occur on the perineum, genitalia, crural folds, and anus and may also extend to involve the vagina, cervix, urethra, and rectum (Figs. 12.16–12.20). HPV-6 and HPV-11 are frequently isolated from anogenital warts, although over 25 different HPV types can cause mucosal lesions. On the cervix, condylomas may appear exophytic, endophytic, papillomatous, or flat or may be visible only by colposcopy. Condylomas are usually asymptomatic, but occasionally cause itching or mild burning. During pregnancy, condylomas may enlarge and have been reported to obstruct vaginal delivery [148]. The detection of small condylomas can be enhanced by the application of a 5% acetic acid soak applied to the skin for a few minutes, after which small or previously undetectable lesions may appear as whitish plaques. This method, however, is associated with high rates of both false positivity and false negativity.

Warts may present in locations other than the typical cutaneous and anogenital surfaces. For example, warts may produce major problems when they grow in the conjunctiva (Fig. 12.21). Another unusual location is around ostomy sites (Fig. 12.22).

Bowenoid papulosis is an unusual manifestation of HPV infection that involves the external male and female genitalia (Fig. 12.23). Histologically, these lesions reveal cellular dysplasia resembling squamous cell carcinoma in situ. Bowenoid papulosis is usually caused by the high-risk HPV-16, which would suggest that this is a precursor lesion to vulvar or penile cancer, but clinically these lesions usually behave in a benign manner. Nonetheless, these lesions need to be followed closely, because they are a potential source of HPV-16 and thus present an increased risk of cervical carcinoma to the patient or his or her sexual partners. In addition, cautious management is warranted because the actual incidence of malignant progression of these lesions, although low, is unknown (Fig. 12.24).

Bowen's disease refers to squamous cell carcinoma in situ (Figs. 12.25 and 12.26). When it presents on the penis, it is sometimes referred to as erythroplasia of Queyrat (Fig. 12.27). Bowen's disease is usually associated with oncogenic HPV (e.g., HPV-16), especially when it presents in the anogenital area.

More than 50% of all external anogenital malignancies are associated with oncogenic HPV. Cervical cancer is the second leading cause of cancer death in women worldwide, with approximately 500,000 cases and 290,000 deaths each year. Recent studies suggest that at least 99% of cervical cancers are associated with oncogenic HPV. Whereas HPV-16 appears most prevalent and is best studied, over 20 HPV types have malignant potential. The primary reason that cervical cancer is not even more prevalent is the use of the Pap smear in industrialized countries. If the Pap smear detects marked cellular atypia and dysplasia is confirmed (Fig. 12.28), treatment would be initiated (especially for high-grade dysplasia) that may help prevent progression to malignancy. Because cervical dysplasia is of viral etiology and standard therapy is usually not antiviral, recurrences are common.

A variety of other anogenital SCCs, such as vulvar, vaginal, penile, and anal cancer are also linked to oncogenic HPV (e.g., HPV-16) (Figs. 12.29–12.35), but as with cervical cancer, HPV alone is not thought to be sufficient for cancer to result. Other cofactors such as cigarette smoking, specific concomitant infections, parity, diet, and

Table 12.3 Clinical Manifestations of HPV

Common warts (verruca vulgaris)	Present with single or grouped scaly, rough papules or nodules, especially on the hands. These commonly occur in children and young adults
Paronychial (periungual) warts	May occur at any age, with single or multiple confluent, keratotic lesions on the proximal periphery of the nails. These lesions are often painful, and may spread beneath the nail plate, causing separation of the nail plate and nail bed
Filiform warts	Consist of a tiny thin base with several keratotic thread-like projections. These occur most commonly on the face, neck, and genitalia. Warts may also take on the appearance of cutaneous horns
Flat warts (verruca plana)	Appear as grouped, minimally raised, flat-topped, skin-colored papules that are usually 2–4 mm in diameter. No papillomatosis or hyperkeratosis occurs with these lesions, so minimal scale is present. They occur most commonly on the face and hands of children, although they are also found in the beard area of men and the legs of women, where they are often spread by shaving. Multiple lesions may occur along a line of cutaneous trauma
Palmar and plantar warts	In the thick skin of the palms and soles, warts may have a number of clinical appearances. Simple palmar and plantar warts appear as minute punctate depressions. When they coalesce into large, thin, endophytic confluent plaques, they are referred to as mosaic warts. When they present as thick confluent plaques, they are known as myrmecia warts. The thickened, hyperkeratotic form is often painful with pressure. The borders are sharply demarcated, often with a surrounding border of thick callus
Butcher's warts	Present as verrucous papules, often multiple, on the hands and fingers of meat cutters
Anogenital warts (condyloma acuminata)	The appearance can vary from small verrucous papules, to discrete, sessile, smooth-topped papules or nodules, to large exophytic masses. These lesions are moist and fleshy and may become friable. Confluence into keratotic plaques is also seen. Their size usually varies from a few millimeters to a few centimeters, but they may reach several centimeters if they coalesce. Their color ranges from skin-colored to reddish-brown
Bowenoid papulosis	Usually presents as groups of 2–3 mm smooth-to-slightly verrucous papules on the external male or female genitalia. The lesions may be slightly reddish in color or hyperpigmented, and are often multiple in number
Respiratory papillomatosis	Consists of multiple benign verruca of the larynx, with possible extensions into the oropharynx or bronchopulmonary epithelium. Patients present with hoarseness or stridor, and in extreme cases, may have blockage of the airways
Oral papillomas	Appear as small, pink to white papules on the oral mucosa and hard palate. When found on the palate, they may become verrucous. Variants include oral florid papillomatosis and focal epithelial hyperplasia (Heck's disease). Oral condylomas may occur from orogenital sexual exposure
Verrucous carcinoma	Appear as large, exophytic tumors that range in size from a few to several centimeters. May develop on the genitals, oral mucosa, or soles of the feet [134]
Epidermodysplasia verruciformis	Present as widespread warts of the face, scalp, trunk, and extremities. These may appear either as flat warts or as red-brown macules resembling tinea versicolor or pityriasis rosea. These lesions usually appear in the first decade of life and may become very extensive and confluent. When present on the trunk, they may be fainter in color and more difficult to detect. Warty "seborrheic keratosis–like" lesions are often seen on the face, neck, and anogenital area. Mucosal lesions are unusual.

genetic predisposition play a role, but the interactions are not well understood [22–24]. Men who have sex with men (MSM), especially those co-infected with HIV, are at the highest risk of anal carcinoma, due to receptive anal intercourse and a high lifetime number of sexual partners, increasing the possibility of transmission of oncogenic HPV types [149–151]. Less commonly, adenocarcinoma may result from HPV oncogenesis (e.g., HPV-18) (Fig. 12.36).

Non-anogenital cutaneous cancers are sometimes associated with oncogenic HPV (Fig. 12.37). This finding is especially prevalent in subungal SCCs (Fig. 12.38) which is thought to be due to digital-genital contact.

Cancers of the head and neck have recently been found to contain HPV (Fig. 12.39), at a rate of 25.9%; however, oropharyngeal cancers have three times the likelihood of being HPV-positive than other head and neck cancers. HPV has been found in 86.7% of oropharyngeal, 68.2% of oral, and 69.2% of laryngeal SCCs and up to 50% of tonsillar cancers [57,152,153]. Some studies suggest that HPV infection is a favorable prognostic indicator in tonsillar cancer [154–156]. Although HPV is an etiological factor in these cancers, the major synergistic risk factors are the use of tobacco and alcohol, with the highest incidence in regions with high rates of tobacco and alcohol use, such as the Indian subcontinent, Australia, Switzerland, the Netherlands, France, Latin America, and Southern Africa. Oral cancer is the 11th most common cancer in the world, while pharyngeal cancer is the 20th most common worldwide. Of note, women with in situ or invasive cervical



Figure12.7 Periungual verruca vulgaris.



Figure 12.9 Subungual wart.

carcinoma have a two- to four-fold increased risk of oropharyngeal cancers associated with HPV [157].

Respiratory, or laryngeal, papillomatosis is a rare disease in which patients develop multiple verruca of the larynx (Fig. 12.40), which may extend to the oropharynx or bronchopulmonary epithelium. Although respiratory papillomatosis may occur at any age, it has a bimodal distribution, with peaks at less than 5 years of age and 20–30 years of age, reflecting the two main modes of acquisition (vertical transmission at birth and sexual transmission, respectively). These lesions are most commonly caused by HPV types 11 and 16. Transmission at birth is believed to be from seeding of the larynx during birth from mothers with condyloma acuminata; supporting evidence comes from studies that show an epidemiological correlation of condyloma in mothers of infants with the disease. One-third to one-half of children born to mothers with HPV genital infection are positive for HPV DNA by oral and respiratory swabs; however, only 1/400 children is at risk for respiratory papillomatosis [21]. These lesions often spontaneously remit during puberty, although recurrence is common and persistence of the viral DNA during remission has been demonstrated. Occasionally, respiratory papillomatosis may be due to oncogenic HPV types that may lead to cancer of the larynx (Fig. 12.41) [158].



Figure 12.8 Paronychial warts with nail dystrophy.

Oral papillomas are also associated with the HPV types isolated from condyloma acuminata (Fig. 12.42). Such lesions are frequently seen in immunocompromised persons (Fig. 12.43–12.45). Focal epithelial hyperplasia, also called Heck's disease, is an unusual HPV infection found mostly in children and is associated with HPV types 13, 32, and 57. It presents with multiple grouped or coalesced, pink to white, 1- to 5-mm, soft papules of the oropharynx that usually resolve spontaneously. It is seen most commonly on the lower lip, but may occur on the buccal mucosa, tongue, or gums (Fig. 12.46). The palate and other areas of the oropharynx appear not to be involved [159]. Heck's disease is most prevalent in certain ethnic groups that appear to be genetically susceptible to these HPV types. Another variant of oral papillomas is oral florid papillomatosis, in which patients develop multiple verrucous papillomas of the oral cavity, which may progress to verrucous carcinoma (Fig. 12.47).

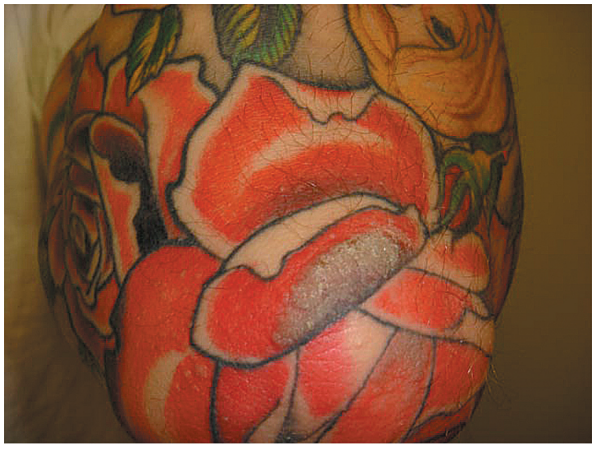
Verrucous carcinoma is a low-grade SCC and is commonly due to infection with HPV-6 and HPV-11, types not usually associated with malignancy [160]. Outside of the anogenital area, HPV-16 has frequently been associated with verrucous carcinoma. It may represent an entity between a benign lesion and a frank malignancy, in that it can be locally invasive and extremely destructive, but rarely metastasizes. When verrucous carcinoma occurs on the genitals, it has been termed a *giant condyloma acuminata of Buschke and Löwenstein* (Figs. 12.48 and 12.49). In the early stages, it resembles a large aggregate of condyloma acuminata; at later stages, a large verrucous tumor develops. It is most frequently located on the glans penis and foreskin of uncircumcised males, but may also occur on the vulva and in the anal area. As



(a)



(b)



(c)

Figure 12.10 (a,b) Extensive verruca vulgaris covering both hands. (Photographs courtesy of Mario Marini, M.D., Department of Dermatology, University of Buenos Aires, Buenos Aires, Argentina.) (c) verruca in a tattoo from contamination of the red ink.



(a)



(b)



(c)

Figure 12.11 (a) Extensive verruca vulgaris in another patient. (Photograph courtesy of Roberto Arenas, M.D., Mexico City, Mexico.) (b,c) extensive HPV 2 in an Indonesian patient. (Photos courtesy of Anthony Gaspari, MD, Department of Dermatology, University of Maryland School of Medicine, Baltimore, MD).



(a)



(b)

Figure 12.12 (a,b) Filiform warts.



(a)



(b)



(c)

Figure 12.13 (a–c) Flat warts. (Photograph 13A courtesy of Axel Hoke, M.D., Novato, CA.)

mentioned previously, verrucous carcinoma may also develop in the lesions of oral florid papillomatosis. Clinically, the lesions evolve from whitish verrucous papules into large cauliflower-like lesions that may coalesce to involve a large area of the oral mucosa. Verrucous carcinoma can also occur on the soles of the feet, where it is termed *epithelioma cuniculatum* (Figs. 12.50–12.52). This lesion, which is thought to arise from a plantar wart, slowly evolves into an exophytic, verrucous, and fungating tumor that can invade deep into the underlying tissues. There is a tendency to form deep fistulae that are filled with horny material.

Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis (EV) is a rare lifelong disease with a worldwide distribution [161]. The patients are susceptible to infection with a specific group of HPV types, and they develop extensive infections with these types. These infections are never entirely cleared, and up to 60% of patients undergo malignant conversion of these warty lesions during their lifetime [162] (Figs. 12.53–12.55). These patients are generally otherwise healthy, although an association with mental retardation has been seen. There are a number of HPV subtypes that are associated with EV (Table 12.1), and the incidence of these specific types is the same throughout the world. HPV-3 and HPV-10 cause flat warts in normal patients and also commonly cause flat warts in EV patients. Otherwise, the HPV types associated with EV are not usually found in the healthy population. Conversely, aside from HPV-3 and HPV-10, EV patients usually do not develop infection with the HPV types found in normal hosts. Of this large group of EV-associated HPV genotypes, those most commonly isolated from these patients are HPV types 5, 8, 17, and 20. HPV-5 and HPV-8 are most commonly associated with the premalignant and malignant lesions found in these patients. Most patients are infected with more than one HPV type [59].



Figure 12.14 Plantar warts.

Genetic mutations are often involved in the pathogenesis of EV – its occurrence is often familial and has been associated with parental consanguinity. Although the pattern of inheritance is mainly autosomal recessive, an X-linked recessive disease pattern has also been reported and EV-like eruptions can occur with acquired immunodeficiency, such as HIV infection [162–168]. Mutations in two adjacent genes, EVER1/TMC6 and EVER2/TMC8 on chromosome 17, are thought to result in the predisposition to HPV infection seen in EV, likely through an induced immune defect [165,169]. Most patients have a decreased number of T cells, especially T-helper cells, a lowered response to mitogens, and anergy to sensitization with dinitrochlorobenzene. The immune defect in EV patients leads to loss of the response of T cells and natural killer cells to EV-specific HPV antigens. The other tests of CMI responses and humoral immunity are normal [170,171]. Further supporting a role for an immune defect in the pathogenesis of EV, HPV-5 and HPV-8 also have been associated with the development of benign lesions and skin cancers in immunocompromised patients, particularly renal transplant patients [51,59,172].

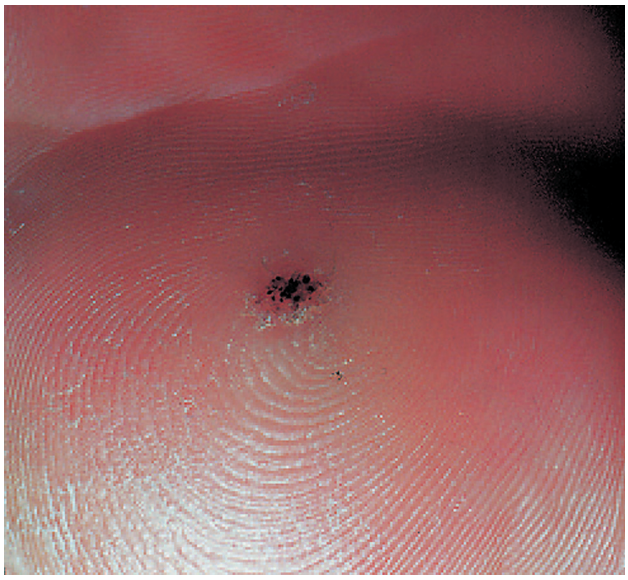


Figure 12.15 Simple punctate plantar wart showing capillary thromboses.

The clinical manifestations of EV fall into two broad categories; those caused by HPV-3 and those associated with the other EV-associated HPV types. HPV-3 causes verruca plana in the normal population and does the same in patients with EV. The main difference is that the flat warts in patients with EV may be more extensive, somewhat larger, more ill defined, and more confluent. Approximately one third to one half of these patients will develop premalignant and malignant change in the warty lesions on sun-exposed skin, beginning about the age of 30 years. These have the appearance of typical lesions of actinic keratosis, Bowen's disease, and SCC arising in the red-brown macules. The high association between the development of these cancers and ultraviolet exposure suggests that this is an important cofactor in the development of these cancers (Fig. 12.56). The rate of degeneration of the premalignant lesions to carcinoma is much higher than in the general population. The number of viral particles is high in the benign lesions of EV; but with malignant degeneration, viral particles are rare or nondetectable. The viral DNA is present in high-copy numbers in the cells of primary and metastatic SCCs, but unlike most cases of cervical carcinoma, the DNA usually remains in an episomal, nonintegrated state [173]. In exceptional cases, however, integration of HPV DNA into the host genome has been demonstrated in SCCs in EV patients [174].

The diagnosis of EV rests on the clinical picture of a lifelong history of extensive, intractable viral warts, usually with a history of familial involvement. On biopsy, the lesions of EV show the same histological changes as seen in the warts, actinic keratoses, and SCCs of normal hosts. The diagnosis can be confirmed by HPV typing by molecular amplification methods, because the EV-associated HPV types are rarely identified other than in patients with EV. The only distinction that must be made is from those patients who have an adult onset of an EV-like syndrome due to immunosuppression. Due to the chronic nature of this condition, important interventions include ensuring protection of the skin from carcinogenic cofactors such as ultraviolet and ionizing radiation (Fig. 12.57) and providing close follow-up to monitor the patient for the development of malignant changes.

Histopathology

The histopathology of verrucae varies with the clinical location and HPV type involved. In general, most lesions show a certain degree of acanthosis, papillomatosis, and hyperkeratosis. A

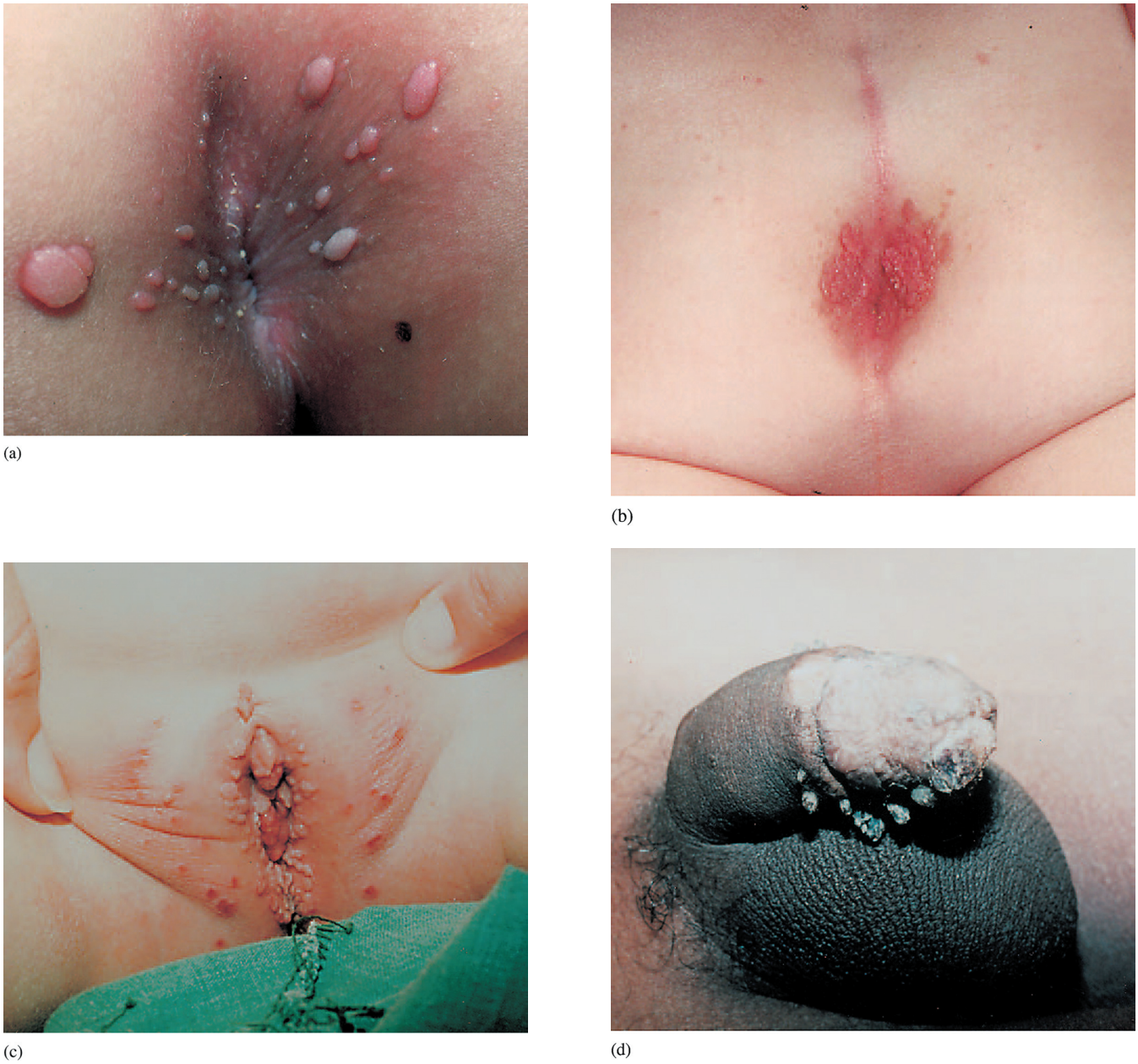


Figure 12.16 (a–d) Condyloma acuminata may be due to sexual abuse or may occur via nonsexual transmission. Perianal condylomata can have a variety of morphologies including (a) sessile smooth topped papules or (b) confluent "cauliflower-like" exophytic masses. It may occur as (c) genital condyloma (in a small girl) or as a (d) penile condyloma (in a 15-yr-old boy with the acquired immunodeficiency syndrome [AIDS]).

characteristic feature that distinguishes most warts is the presence of large vacuolated keratinocytes with pyknotic nuclei surrounded by a narrow clear halo and pale-staining cytoplasm. These are seen in the middle and outer layers of the epidermis and are called koilocytotic cells.

Common warts generally show marked acanthosis and hyperkeratosis. The elongated rete ridges are often bent inward toward the center of the wart. Koilocytes are usually prominent, and there are stacks of parakeratotic cells and foci of clumped basophilic keratohyalin granules. These granules are thought to be composed of or associated with the viral E4 protein. The dermal capillaries are dilated and may be thrombosed (Figs. 12.58 and 12.59). Filiform warts show much more elongated papillae with a thickened horny layer at the tip of the wart. Flat warts also show hyperkeratosis and acanthosis, but lack the papillomatosis and show only slight elongation of the rete ridges. Koilocytes are prominent in a thickened granular layer and the stratum corneum shows a "basket-weave" appearance. The superficial, mosaic-type, palmoplantar warts resemble other verrucae. By contrast, deep myrmecia warts show prominent cytoplasmic eosinophilic inclusion bodies surrounding the vacuolated nuclei of the koilocytes and prominent parakeratosis in the stratum corneum. On involution of verruca vulgaris, flat warts, or palmoplantar warts, the koilocytes and clumped keratohyalin granules become less prominent and there is a mononuclear cell infiltrate.

In condyloma acuminata, there is papillomatosis and marked acanthosis with elongation and branching of the rete ridges that may be extensive enough to resemble pseudocarcinomatous hyperplasia



(a)



(b)

Figure 12.17 Verrucous condylomata on the (a) shaft of the penis and the (b) vulva.



(a)



(b)

Figure 12.18 (a,b) Extensive condyloma of the male genitalia.

(Fig. 12.60). The stratum corneum is only slightly thickened. Large vacuolated keratinocytes with clumped keratohyalin granules are seen and are apt to be spread diffusely through the wart. The dermis is edematous with dilated capillaries, and there is usually a chronic inflammatory infiltrate. The histological appearance is similar in the lesions of oral papillomas.

The lesions of Bowenoid papulosis resemble Bowen's disease histologically. There is again marked acanthosis and elongation and thickening of the rete ridges, but throughout these lesions the epidermal cells lie in marked disorder and have a highly atypical appearance. Cells show large hyperchromatic nuclei, and multinucleated cells are commonly seen. The stratum corneum is parakeratotic with atypical, hyperchromatic nuclei. Dyskeratotic keratinocytes with dense eosinophilic cytoplasm are evident. Despite this resemblance to an SCC, the border between the epidermis and the dermis remains sharp and the basement membrane is intact. In the lesions of verrucous carcinoma, the superficial areas resemble a verruca, and throughout the lesion there is usually little cellular atypia. At the base of the lesion, the tumor has deep downward proliferations extending into the dermis and compressing the collagen bundles (Fig. 12.61).

The lesions associated with EV have a variable histological appearance. The benign verruca associated with HPV-3 are



(a)



(b)

Figure 12.19 (a,b) Extensive perianal condyloma.



Figure 12.20 Condyloma accuminata of the urethral meatus. (Photograph courtesy of Elliot Androphy, M.D., Department of Dermatology, Tufts/New England Medical Center, Boston, MA.)

histologically identical to flat warts. With the lesions associated with HPV-5, there is a somewhat different appearance than is seen with common warts. The epidermal acanthosis is often markedly uneven and varies from very superficial to extremely deep extensions. The cells are swollen and irregular and, unlike typical koilocytes, have been noted to have foamy, pale-blue cytoplasm and lack the clear halo. Dyplastic-appearing keratinocytes with large, round, empty-appearing nuclei are seen. The changes typical of Bowen's disease are seen in more advanced lesions.

On electron microscopy, the various types of HPV-associated lesions all appear similar, but vary in the number of viral particles seen. The large dense intracytoplasmic and intranuclear inclusions are identifiable as keratohyalin granules and are associated with tonofilaments. Viral particles are detected only in the outer layers of the epidermis, first seen in the upper portion of the stratum malpighii. Whereas viral particles are often numerous in common, palmoplantar, and flat warts and the benign lesions of EV, they are very sparse or undetectable in condyloma acuminata and are only rarely detected in dysplastic or malignant lesions.

Diagnosis

The diagnosis of HPV infection is generally straightforward and based on clinical appearance, but can be aided by histological examination (Table 12.4). Genital warts, particularly lesions of the uterine cervix, can be difficult to detect, and detection can be aided by the use of acetowhitening. A 5% acetic acid solution is applied to lesions with gauze or a cotton-tipped swab. A few minutes after application, lesions may appear as whitish patches that were previously undetectable. The use of a magnifying lens or colposcopy further aids in the diagnosis of clinically inapparent lesions. These techniques are also useful for detecting genital warts in males. Acetowhitening, however, is associated with a high rate of both false-positive and false-negative findings. Immunohistochemical and molecular techniques can confirm the presence of HPV within a lesion. The presentation of multiple recalcitrant and recurrent warts with unusual morphology, particularly if familial, must suggest the diagnosis of EV.

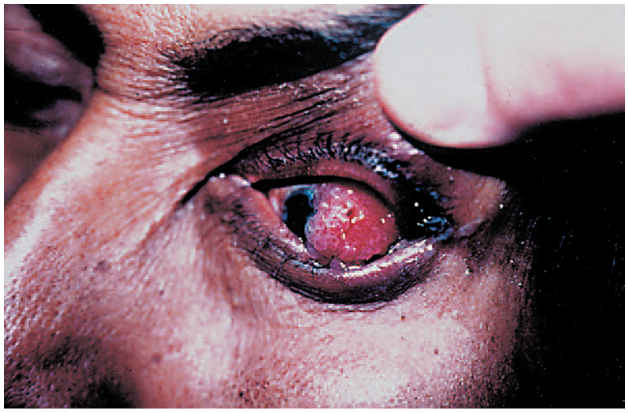
The presence of HPV can be confirmed by detection of viral particles by electron microscopy, although this technique is not apt to be readily available, and more importantly, viral particles are usually very sparse in genital and dysplastic lesions. Immunohistochemical methods can be used to aid in the detection of HPV. The antibodies used are generally directed against viral capsid antigens and are cross-reactive with a broad spectrum of HPV types (Fig. 12.62). This method is again of limited usefulness, however, because mature virions expressing viral capsid antigens are not uniformly present and because these capsid antigens may be absent in HPV-related malignancies. Of emerging importance is the presence of INK4A in HPV-infected tissues, synthesis of



(a)



(b)



(c)

Figure 12.21 (a,b) Conjunctival warts. (c) More extensive warts of the eye in another patient. (Photograph 21a,b courtesy of Robert Brodell, M.D., Warren, Ohio; photograph 21C courtesy of Maria Gabriela Rodriguez, M.D., Mexico City, Mexico.)

which is upregulated by E7 binding and degradation of Rb. Immunohistochemical staining for INK4A allows for the detection of high-risk HPV-infected histological sections or cytologic smears [44]. Serum antibodies to viral early and capsid proteins are detected in only a minority of patients, thus there is no routinely used serological method for detecting HPV infection.

With the development of molecular biological techniques, there are now methods that are highly sensitive for the detection of HPV



Figure 12.22 Warts and molluscum contagiosum surrounding an ostomy site.

DNA and have allowed for the identification of the many different genotypes of PVs. These techniques identify HPV DNA directly and are much more sensitive than standard immunohistochemical methods. The techniques of Southern blot DNA hybridization and dot blot hybridization allow detection of HPV DNA in extracts of lesional tissue via hybridization with labeled complementary strands of known HPV DNA sequence [175]. Southern blot hybridization allows detection of specific HPV types with fairly



Figure 12.23 Perianal Bowenoid papulosis.



(a)



(b)

Figure 12.24 (a) Skin-colored lesions of bowenoid papulosis on the shaft of the penis. (b) The other side of the penis revealed multicentric squamous cell carcinoma. Although this disease usually behaves in a benign manner, in very rare cases Bowenoid papulosis may progress to Bowen's disease or frank malignancy. (Photograph courtesy of Elliot Androphy, M.D., Department of Dermatology, Tufts/New England Medical Center, Boston, MA.)

high specificity and may also provide information on the integration state of the viral genome [176,177]. Another HPV DNA detection method is tissue in situ hybridization [178,179]. Cells or tissue sections mounted on slides are hybridized with labeled DNA or RNA probes to allow direct visualization of the location of the HPV genome within the tissue. When exon-specific probes are used, this test also allows localization of the expression of specific viral genes. The drawback of these tests is that all of these hybridization methods are relatively labor intensive, and with Southern and dot blotting, require more tissue than may be readily available.

The most sensitive and currently preferred method for detection of HPV in the research laboratory makes use of PCR, a technique that allows primer-directed amplification of very small amounts of viral DNA [179–182]. With the most commonly employed PCR methods, the DNA primers are designed in such a way that they will hybridize with and amplify sequences in the L1 gene



Figure 12.25 Bowen's disease of the vulva that was found to contain HPV-16. (Photograph courtesy of Elliot Androphy, M.D., Department of Dermatology, Tufts/New England Medical Center, Boston, Massachusetts.)



Figure 12.26 Perianal Bowen's disease.



Figure 12.27 Erythroplasia of Queyrat (squamous cell carcinoma in situ of the penis).



Figure 12.29 Vulvar squamous cell carcinoma associated with HPV-16. (Photograph courtesy of Concepcion Arrastia, M.D., Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, TX.)

from a large number of HPV types (termed degenerate primers). The amplified product can then be more stringently hybridized with HPV type-specific probes to allow HPV typing. This method is both sensitive and specific. Using PCR methods, it is possible to detect as few as 10–100 copies of the viral genome with very small amounts of tissue, whereas the traditional blotting methods require 10^5–10^6 copies. The increased sensitivity of these methods has been of particular use in epidemiological studies to allow more accurate estimates of HPV incidence. Most recently, the use of the nested PCR method has increased the type-sensitivity of this process, resulting in a higher rate of detection of HPV DNA in positive specimens [183].

Whereas these methods are still mostly used in research laboratories, they are commercially available and are used in certain clinical settings. Clinical use of HPV typing is most commonly used in conjunction with Pap smear for the detection of HPV infection. It has been shown that the histological criteria for HPV infection, such as koilocytosis and dyskeratosis, underestimate the incidence of infection and typing adds to the sensitivity of this screening. A method for detection of HPV DNA with

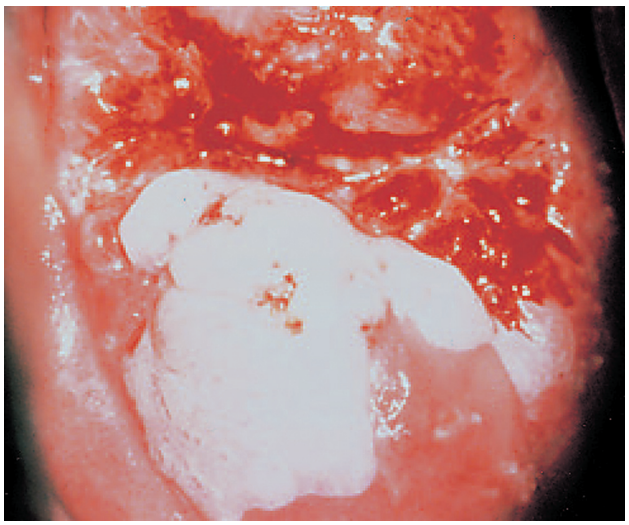


Figure 12.28 Cervical dysplasia. (Photograph courtesy of Kenneth Hatch, M.D., Department of Obstetrics and Gynecology, University of Arizona School of Medicine, Tucson, AZ.)



Figure 12.30 Vulvar squamous cell carcinoma associated with HPV-16. (Photograph courtesy of Kenneth Hatch, M.D., Department of Obstetrics and Gynecology, University of Arizona School of Medicine, Tucson, AZ.)



Figure 12.31 Vulvar squamous cell carcinoma associated with HPV-16. (Photograph courtesy of Concepcion Arrastia, M.D., Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, TX.)

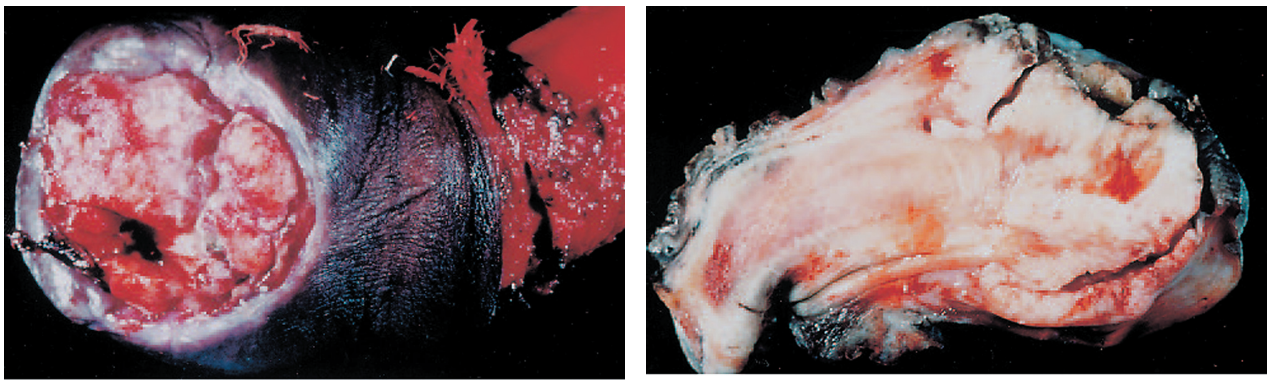


Figure 12.32 Squamous cell carcinoma of the penis associated with HPV-16. The patient was treated with a partial penectomy.

sensitivity and specificity similar to that of PCR is the hybrid capture assay. An improved version of this assay, hybrid capture II (HCII), is generally acceptable for clinical use. Although HPV typing is not routinely performed, except in cases with equivocal histological results, several studies have shown the utility of increasing the clinical use of HPV typing [184–186]. Knowledge of the specific HPV type provides information on patients' risk for development of cervical cancer and can help in planning the frequency of subsequent screening visits. In addition, when used in conjunction with the Pap smear, the HCII assay minimizes the number of missed diagnoses [187]. HPV typing may also be used for the detection of high-risk HPV 5 in EV patients. In addition, epidemiologists have used HPV typing to evaluate the likelihood of child abuse in children with condyloma acuminata. These studies have shown that the incidence of child abuse in these cases may actually be lower than had previously been suspected [19].

Treatment

Unfortunately, there are no specific antiviral treatments for HPV infection (Table 12.5) currently available. Some warts prove very difficult to eradicate, and recurrences are very common. Most current treatment regimens for warts involve physical destruction of the infected tissue. Decisions regarding treatment must take into account the type and location of warts, the age of the patient, and the immunological status of the patient. Because evidence indicates that in healthy children, two thirds of warts will spontaneously remit within 2 years [188], not every wart needs to be treated. If the warts are not physically or psychologically bothersome, a decision to postpone treatment may be made, particularly in younger children, because most of the treatment modalities involve some discomfort. The situation is somewhat different with genital warts because of their sexually transmitted nature and the risk of malignancy. In patients with anogenital warts, the sexual partners should be examined and treated as well, and women should have a Pap smear as well as colposcopic examination of the uterine cervix. If there are anal warts, anoscopy should be considered. Patients need to be counseled regarding the risk of and route of transmission of these warts.



(a) (b)

Figure 12.33 (a) Squamous cell carcinoma of the penis associated with HPV-16. Metastases found in the inguinal lymph nodes also contained HPV-16 integrated into the host DNA. (b) Sagittal section of the penis.



Figure 12.34 Squamous cell carcinoma of the scrotum associated with HPV-16.



Figure 12.36 Vulvar adenocarcinoma associated with HPV- 18. (Photograph courtesy of Concepcion Arrastia, M.D., Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, TX.)

An important consideration, especially regarding genital warts, is that the treatments currently available do not eliminate subclinical or latent infection [189]. HPV DNA has been detected in the clinically normal skin adjacent to treated genital warts, and the presence of HPV correlates with higher rates of wart recurrence [34]. Thus, patients need to be counseled regarding the likelihood of recurrence. Long-term follow-up is recommended for patients with cervical or vaginal lesions. Although the lesions of Bowenoid papulosis will sometimes spontaneously remit,



Figure 12.35 Anal squamous cell carcinoma. (Photograph courtesy of Margaret Muldrew, M.D., Denver, CO.)

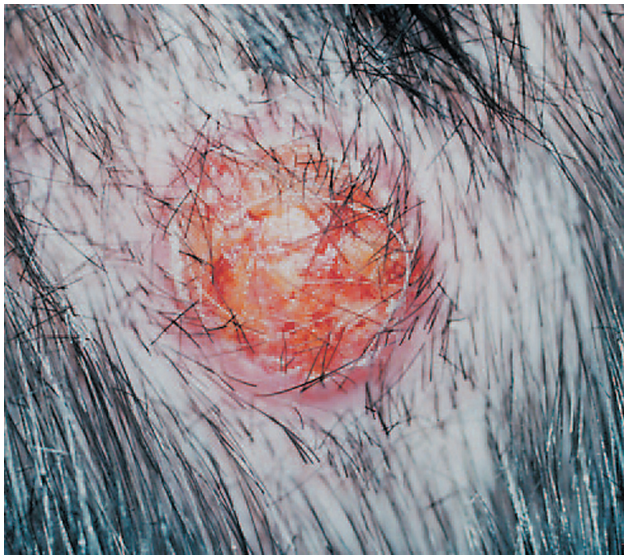


Figure 12.37 Squamous cell carcinoma of the scalp associated with HPV-16 in an AIDS patient.



(a) (b)

Figure 12.38 (a,b) Subungual squamous cell carcinoma associated with HPV-16. (Photograph 38A courtesy of Axel Hoke, M.D., Novato, CA; Photograph 38B courtesy of Roberto Cortez-Franco, M.D., Mexico City, Mexico.)

they represent a potential reservoir of HPV 16 and should be treated.

Topical Therapies

Topical acidic preparations are a commonly used first-line therapy for warts. Most commercial preparations use varying concentrations of salicylic acid in a number of different vehicles. The salicylic acid causes keratolysis of the infected tissue, and the success rate of this method is good with prolonged therapy. When hand warts, simple plantar warts, and mosaic warts are treated for 3 months, resolution has been seen in 45–84% [190]. The main drawback is that this method is time consuming and requires a high degree of patient motivation over a prolonged period of time. Flat warts can be very resistant to therapy, but often respond well to the application of retinoic acid 0.05%, which also presumably acts as a keratolytic agent. Alternating topical or oral retinoids with imiquimod (discussed in further detail later) can have a synergistic effect due to the suppressive effects of retinoids on signal transducer and activator of transcription-3 (STAT-3) and the activating effects of imiquimod on STAT-1. The levels of these two substances modify responses to epidermal growth factors [191–193].

The application of caustic acids, such as 50% trichloroacetic acid, can be used for the destruction of warts in the office setting. These acids cause destruction of cellular proteins and induce inflammation and cell death. Another topical agent is cantharidin, which is a caustic extract from the green blister beetle that causes vesiculation and acantholysis of the skin. The major side effect of this treatment is that it can induce pronounced inflammation and



Figure 12.39 Verrucous carcinoma of the neck associated with HPV-16.

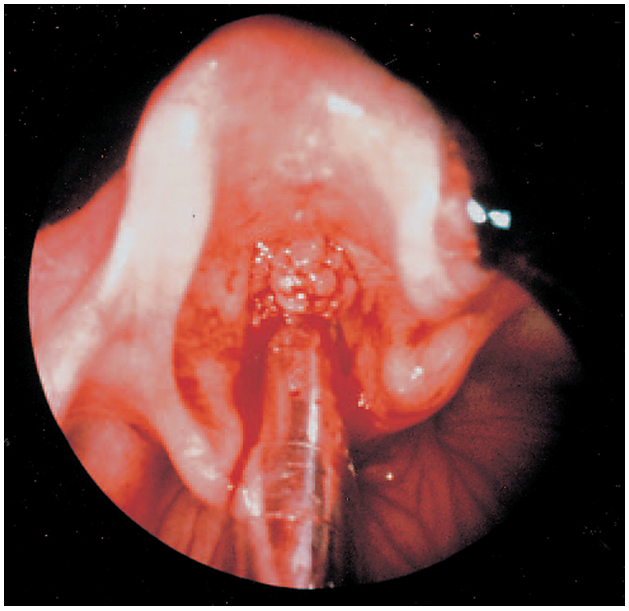


Figure 12.40 Laryngeal papillomatosis. (Photograph courtesy of Christopher Rassekh, M.D., Department of Otolaryngology, University of Texas Medical Branch at Galveston, Galveston, TX.)



Figure 12.41 Squamous cell carcinoma of the larynx that eroded through the skin of the neck. (Photograph courtesy of Christopher Rassekh, M.D., Department of Otolaryngology, University of Texas Medical Branch at Galveston, Galveston, TX.)

discomfort. Both trichloroacetic acid and cantharidin can cause marked epidermal destruction and potential scarring; thus, they are used only in the office setting. Another acid preparation that has been tested as patient-applied therapy and shown to have a beneficial effect on wart clearance is α-lactalbumin-oleic acid, derived from milk [194].

Topical chemotherapeutic agents have also been employed in the treatment of warts. Podophyllin is a complex plant resin that is a potent antimitotic agent. This compound is contraindicated during pregnancy. Podophyllin is not a standardized preparation, and the concentration of its active ingredient, podophyllotoxin, can vary significantly. In addition, podophyllin contains two mutagenic flavenoids, quercetin and kaempherol, that have been epidemiologically implicated as being carcinogens [195,196]. Application of podophyllin should be limited to small areas, applied to intact skin only, and washed off after 30–60 minutes, as systemic absorption and subsequent renal failure, coma, and death have been documented after treatment of large areas [197]. Purified solutions of podophyllotoxin (0.5% solution or gel) are also available that have a much improved safety profile and are approved for treatment of genital warts; local reaction can involve erythema, burning, and superficial erosions. Because podophyllotoxin has no antiviral or immunodulatory activity, recurrences of anogenital warts are common. The antimetabolite 5-fluorouracil (5-FU) in a 5% solution has been used for the treatment of warts, primarily verruca plana and condyloma. Here again, this agent can induce inflammation, erosions, and postinflammatory hyperpigmentation and is teratogenic. 5-FU has also been used in combination with both destructive techniques and other modalities such as interferon-α and imiquimod to decrease the frequency of recurrences [198]. Intralesional therapy with the antimetabolite, bleomycin, is thought to act by inhibiting both cellular and viral DNA synthesis, but may also act by enhancing the host's immune response to the virus. Reported side effects include Raynaud's phenomena with periungual warts and extensive tissue necrosis, and thus this agent must be used cautiously.

Immunotherapy has also been employed in the treatment of warts, as induction of an allergic reaction in the area of a wart may result in clearing. Dinitrochlorobenzene (DNCB) has traditionally been used for this, but concerns over its mutagenicity make its use controversial. Imiquimod, an imidazoquinolin heterocyclic amine, is a topical immunotherapeutic agent that is approved for topical treatment of anogenital condyloma; it has also been used for treatment of cutaneous warts in other locations and in combination therapy [199,200]. In a 5% cream formulation, imiquimod is applied by the patient overnight three times weekly. Although imiquimod has no specific antiviral effects, it is a toll-like receptor 7 (TLR7) agonist, thus functioning as an immunomodulator. It is thought to exert its effect against PV through induction of cytokines including interferon-alpha and TNF-α [201,202]. Clinical



Figure 12.42 Condyloma acuminatum of the lower lip in a human immunodeficiency virus (HIV)–seronegative man.



Figure 12.43 Condyloma acuminatum of the lower lip and tongue in an AIDS patient.



Figure 12.45 Verrucous papules of the lips and oral cavity in an 8-yr-old liver transplant recipient. These papules were found to contain HPV-16.

studies have shown clearance of genital warts in approximately 50% of patients (Fig. 12.63). There are no systemic adverse effects, and local irritation and occasional erosions are the most common side effects. Recurrences following complete clearance of condyloma acuminatum have been very low (e.g., 13% during a 3-month follow-up period in one study) [203]. A course of treatment with imiquimod followed by surgical removal of residual lesions may result in a lower recurrence rate than patients treated with surgery alone [204]. There is potential for other TLR7 agonists to be used in the treatment of warts; these compounds are currently being studied.

Sinecatechin, a topical treatment for external anogenital warts recently approved by the FDA, is a 15% green tea extract ointment that has been shown to have efficacy in the treatment of external anogenital warts. The drug is a standardized extract of green tea leaves from *Camellia sinensis* that contains mainly tea polyphenols, particularly catechins. Catechins have shown antiviral and antioxidant activity, as well as binding to a number of proteins, including inflammatory mediators, proteases promoting tumor invasion, and kinases involved in tumor cell signaling, cell cycle modification, and induction of apoptosis. A multicenter, randomized, double-blind, vehicle-controlled, three-arm parallel-group phase III trial, which was comprised of treatment three times daily, for 16 weeks or until clearance, resulted in 57.2% of patients showing complete clearance with a 15% ointment and 56.3% showing complete clearance with a 10% ointment. In the vehicle group, 33.7% of patients achieved complete clearance. Recurrence rates at 12 weeks were 6.5 and 8.3% in the two treatment groups, respectively [3,205–207].

Another form of immunotherapy for verruca takes advantage of the high prevalence of immunity to mumps and *Candida* in the general population. In several studies, intralesional injections of either of these antigens have resulted in clearing both of the treated warts as well as other anatomically distinct, untreated warts; the results are thought to be due to the inflammation resulting from injection initiating a HPV-directed immunologic reaction [208–210]. The treatment was effective even in warts that were recalcitrant to cryotherapy or topical retinoids and immunomodulators. This modality is especially useful in patients with multiple or large warts or warts located in cosmetically sensitive areas such as the face.

Although garlic has been reputed to have antiviral properties for centuries, investigations are relatively recent into its mode of action, anti-viral activity, and clinical efficacy. In vitro virucidal effects and inhibition of cellular proliferation of virally infected cells have been demonstrated with ajoene and allicin extracts, with thiosulfinates appearing to be the active components [284–285]. In one placebo-controlled trial, the application of chloroform extracts of garlic was reported to result in the complete resolution of cutaneous warts with no recurrence after 3–4 months [286].

A newer immunomodulatory topical treatment for high-grade cervical and anal intraepithelial neoplasia that is currently under evaluation, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-



Figure 12.44 Verruca vulgarus of the lower lip in an AIDS patient.



(a) (b)

Figure 12.46 (a,b) Focal epithelia hyperplasia of the lips and buccal mucosa. (Photograph 46A from Cohen, et al. Pediatr Dermatol 10:245–51, 1993. Used with permission; Photograph a courtesy of Philip Cohen, M.D., Department of Dermatology, University of Texas Health Science Center, Houston, TX; Photograph b courtesy of Mario Marini, M.D., Department of Dermatology, University of Buenos Aires, Buenos Aires, Argentina.)

hydrazone, known as A-007 (Tigris Pharmaceuticals, Inc., Bonita Springs, FL), is an aryl hydrazone derivative with an *m*-dinitrophenyl moiety capable of docking and interacting on the CD45 receptor on T-lymphocytes, resulting in direct up-regulation of CD4 and CD8 cytotoxic T-lymphocyte activation and agglutination. Pilot studies evaluating the efficacy and safety of A-007 showed increased T-lymphocyte infiltration in cervical/vaginal and anal neoplastic areas treated topically, as well as high pathological and HPV response rates. A-007 has previously been studied as a palliative measure for cutaneous metastases of internal malignancies, with promising results [211]. Phase II clinical trials are currently underway to determine the clearance of HPV anogenital infection following use of A-007 [212].

Another new topical treatment under investigation for treatment of anogenital warts is the immunomodulator ammonium trichloro (dioxoethylene-O,O') tellurate, or AS101 (Biomas Ltd., Kefar Saba, Israel). AS101 has previously been shown, in murine and in vitro studies, to have anti-tumor effects when given intravenously [213,214]. Its activity is primarily attributed to direct inhibition of the anti-inflammatory cytokine IL-10; other direct and indirect cellular targets include T cells, macrophages, and granulocytes. AS101 shows a strong modulation response from Th2 to Th1 and has minimal toxicity. An open-label, multicenter trial utilizing a 15% AS101 cream twice daily for up to 16 weeks to treat vulvar and perianal warts resulted in complete clearance for 76% of patients with 4% recurrence rate in a 6-month follow up. Side effects were mild-to-moderate itching, soreness, burning, and erythema [215].

Destructive Procedures

Cryotherapy with liquid nitrogen is a commonly used treatment for warts on any part of the body. It works by destruction of the frozen tissue and induction of an immune response in the area. There is pain during treatment, and patients may note throbbing in



Figure 12.47 Verrucous carcinoma of the tongue. (Photograph courtesy of Mario Marini, M.D., Department of Dermatology, University of Buenos Aires, Buenos Aires, Argentina.)



Figure 12.48 Buschke-Löwenstein tumor of the anus.



Figure 12.49 Buschke-Löwenstein tumor of the penis. (Photograph courtesy of Axel Hoke, M.D., Novato, CA.)

the hours after the procedure. After several hours up to a few days, a clear or hemorrhagic blister develops that generally heals in 1–2 weeks. Occasionally, healing results in a clear area surrounded by a ring of new warts that produces a "halo" or "doughnut" effect (Fig. 12.64). Electrodessication has been used in the treatment of warts resistant to cryotherapy. This procedure is commonly associated with scarring after healing and thus should be avoided on plantar surfaces. The use of surgical excision of warts is usually reserved for debulking a large exophytic wart resistant to therapy



Figure 12.51 Epithelioma cuniculatum. This lesion, which is thought to arise from a plantar wart, slowly evolves into a exophytic, verrucous, and fungating tumor that can invade deep into the underlying tissues. There is a tendency to form deep fistulae that are filled with horny material.

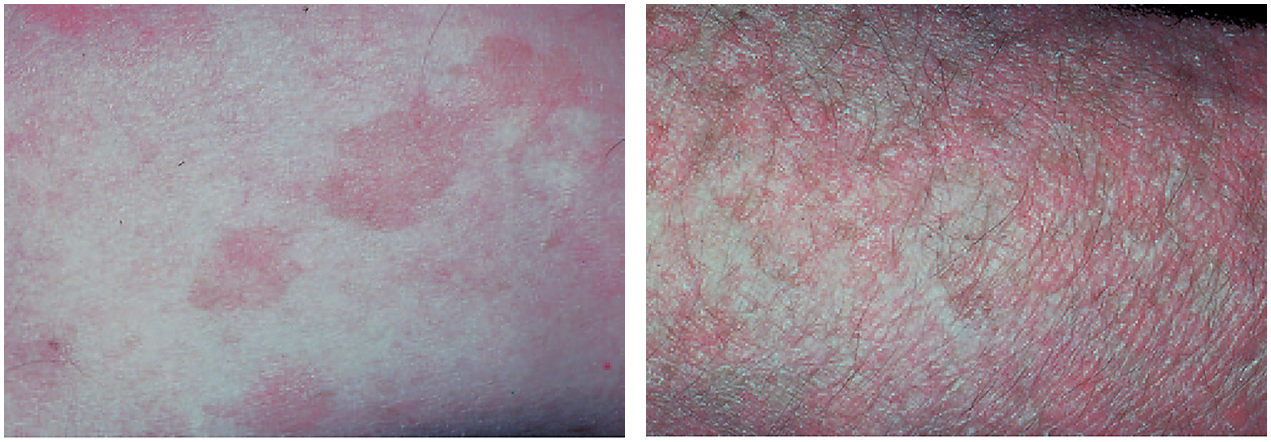
and, because of high recurrence rates, must be used in conjunction with other treatment modalities. Mohs' micrographic surgery has been successfully used in the treatment of verrucous carcinoma. Treatment of verrucous carcinoma with ionizing radiation is strictly contraindicated because it is associated with recurrence of tumors with a greater invasive potential. The CO_2 laser has been used to treat warts, particularly those in which precise control of the extent of destruction of tissue is required and those refractory to other therapies. This is an expensive method of treatment, and reports of success are highly variable. Infectious HPV particles have been identified in the vapor plume with laser therapy, and adequate protection with goggles and surgical mask is important [216].



Figure 12.50 Epithelioma cuniculatum. (Photograph from Ho, et al. Arch Dermatol 136:547–552, 2000. Used with permission; Photograph courtesy of Dayna Diven, M.D., Department of Dermatology, University of Texas Medical Branch at Galveston, Galveston, TX.)



Figure 12.52 Epithelioma cuniculatum. (Photograph from Schell, et al. J Am Acad Dermatol 45:49–55, 2001. Used with permission; courtesy of Theodore Rosen, M.D., Department of Dermatology, Baylor College of Medicine, Houston, TX.)



(a) (b)

Figure 12.53 (a) Pityriasis versicolor–like lesions of the trunk and (b) extremities of a patient with epidermodysplasia verruciformis (EV).

Interferon

The interferons are a large family of proteins that are thought to have antiproliferative, antiviral, and immunomodulatory effects. Intralesional and parenteral interferon has been evaluated in the treatment of refractory genital warts. Intralesional therapy with interferon-α has led to clearing of warts in 36% of patients [217–219], but topical therapy with leukocyte interferon has not been shown to be effective [220]. Parenteral therapy with interferon-α or interferon-β led to clearing of genital warts in the majority of patients [221–223]. Intralesional therapy with interferon has also been investigated in the management of difficult cases of laryngeal and respiratory papillomatosis and EV. Using a number of different treatment regimens, it has generally been shown to reduce warts in these patients, but recurrence is seen when therapy is stopped. In patients with severe respiratory papillomatosis, outcomes may be better if patients are treated with both surgery and interferon [224–226]. The most common side effects are pain at the injection site and flu-like symptoms, including fever, chills, headache, and nausea. In addition, laboratory abnormalities that may be seen include leukopenia, elevation of hepatic enzymes, anemia, and thrombocytopenia. Due to these side effects, as well as the cost, interferon therapy is not widely used for treatment of warts [227].

Cimetidine

Cimetidine, a histamine-2 receptor antagonist, is often used for treatment of warts on the basis of anecdotal evidence of its efficacy. Although one small study showed clearance of extensive condyloma acuminata in children after 3 months of oral treatment with no recurrence after 24 months [228], no randomized, placebo-controlled trials have been performed to assess the efficacy of cimetidine in treatment of anogenital warts [229]. Randomized, controlled trials assessing efficacy of cimetidine in treatment of nongenital warts have failed to show a benefit over placebo [230].



Figure 12.54 Flat warts in a patient with EV. In these patients, flat warts are often quite extensive and somewhat more verrucous than is commonly seen in a normal host. (Photograph courtesy of Elliot Androphy, M.D., Department of Dermatology, Tufts/New England Medical Center, Boston, MA.)



Figure 12.55 Multifocal squamous cell carcinoma in the sunexposed skin of a patient with EV. HPV typing revealed HPV 8. (Photograph courtesy of Elliot Androphy, M.D., Department of Dermatology, Tufts/New England Medical Center, Boston, MA.)

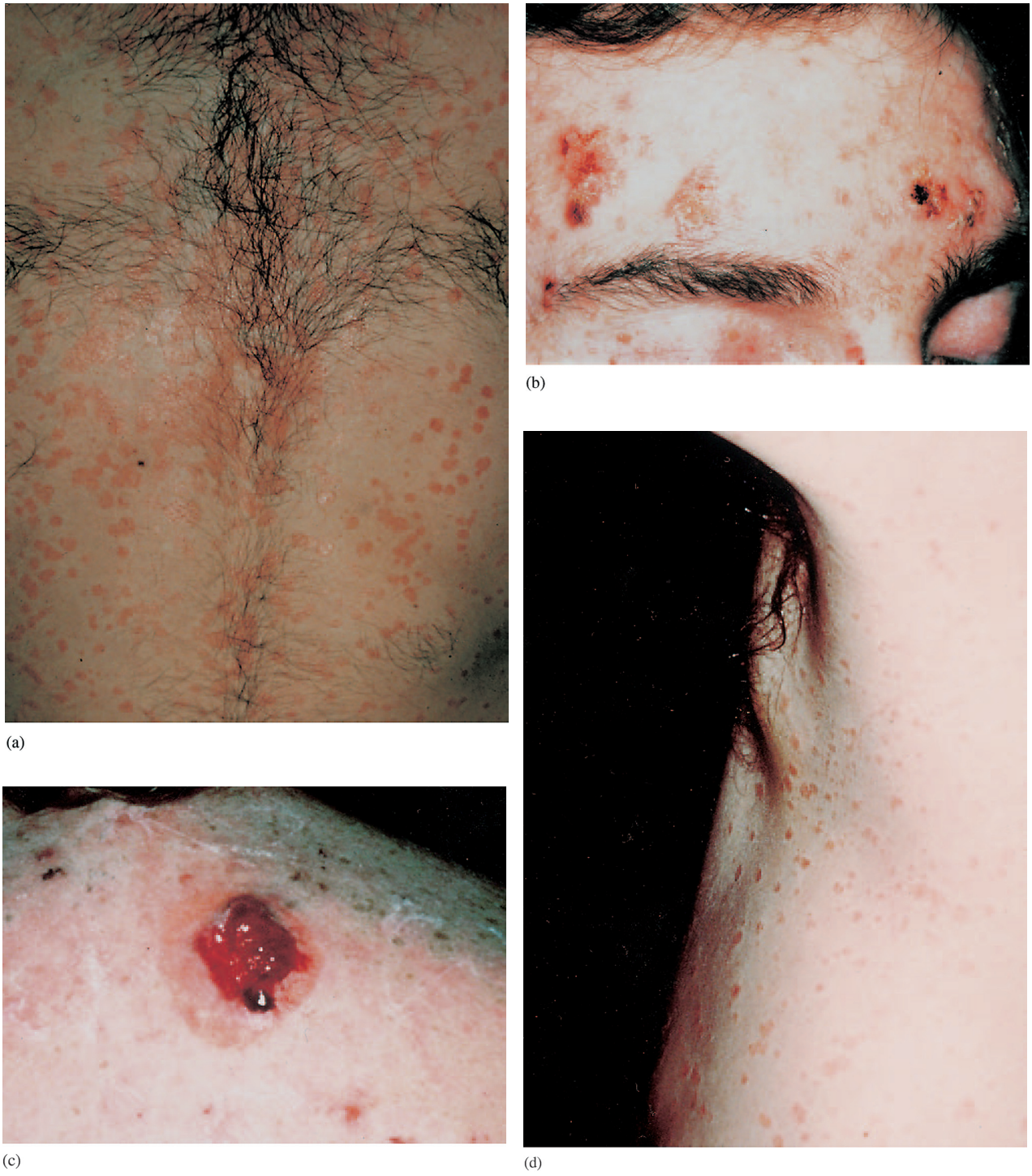


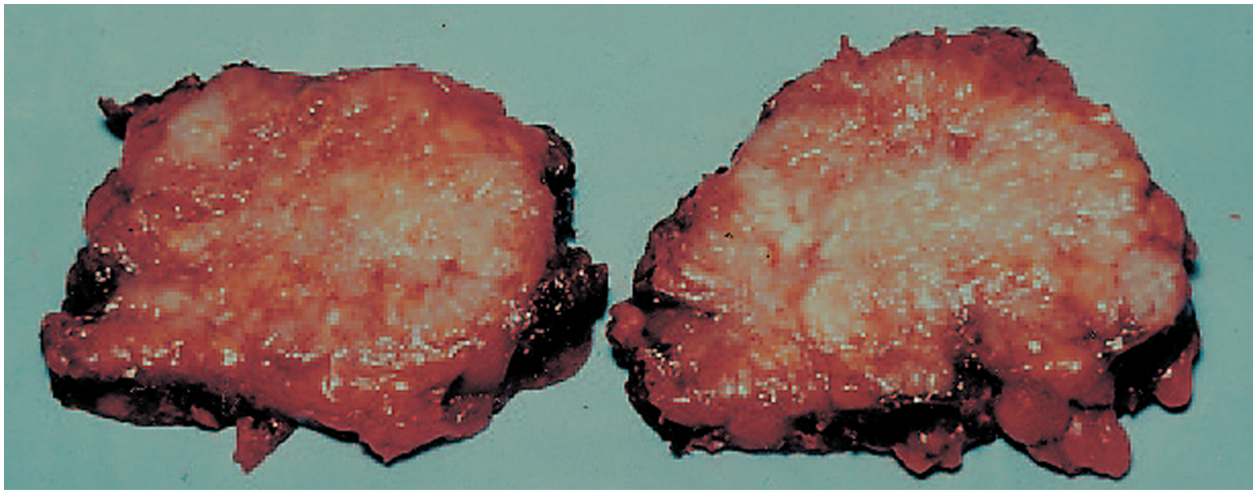
Figure 12.56 EV associated with HPV-8 (a) Erythematous macules containing the episomal form of HPV-8. (b) By age 24 yrs, the patient had developed multitudes of squamous cell carcinomas that contained both the episomal and the integrated forms of HPV-8. He had worked the previous six years in the oil fields of west Texas without sun protection. (c) He continued to develop aggressive squamous cell carcinomas, including this large ulcerated tumor on his back, seen at age 25 yr. (d) During the same clinic visit at which the ulcerated tumor on his back was observed, the patient was found to have marked left axillary lymphoadenopathy.

Retinoids

Oral retinoids, such as isotretinoin, have been shown to have efficacy in treating cervical dysplasia, particularly CIN and recalcitrant condyloma acuminata of the cervix. They have not been tested extensively for efficacy in clearing anogenital warts, but may represent a treatment option for recalcitrant genital warts [229,231–233]. Their efficacy is improved when they are used in conjunction with imiquimod or interferon-α [234–236].

Cidofovir

Cidofovir is an antiviral drug that has been observed to have potential in the treatment of extensive condyloma acuminata [237,238], especially in immunocompromised patients, resulting in a greater than 50% reduction in wart area in 58–60% of HIV patients [239–242]. Topical cidofovir has also been shown to be an effective adjuvant to surgery in the treatment of anogenital warts [241] and can also be used as monotherapy [243]. There are



(e)

Figure 12–56 (continued). (e) The metastatic squamous cell carcinoma from his left axilla is seen in the photograph. The patient died of metastatic squamous cell carcinoma at age 25 yr.



(a)



(b)



(c)

Figure 12.57 EV associated with HPV-5. (a) Squamous cell carcinomas from a patient in Mexico City were found to contain integrated HPV-5. (b) A few weeks after receiving radiation therapy, the patient's tumor became very aggressive. (c) Although the squamous cell carcinoma seen in "b" was removed, the patient continued to form new tumors. He subsequently died of metastatic squamous cell carcinoma. (Photographs courtesy of Roberto Cortez-Franco, M.D., Mexico City, Mexico.)

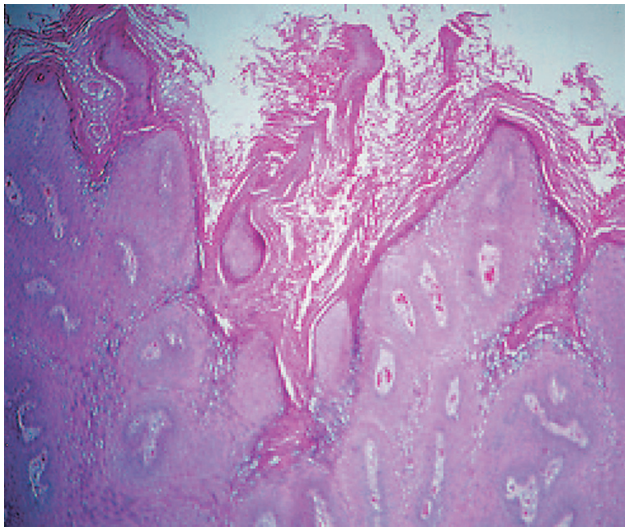


Figure 12.58 Verruca vulgaris showing prominent acanthosis, papillomatosis, and hyperkeratosis.

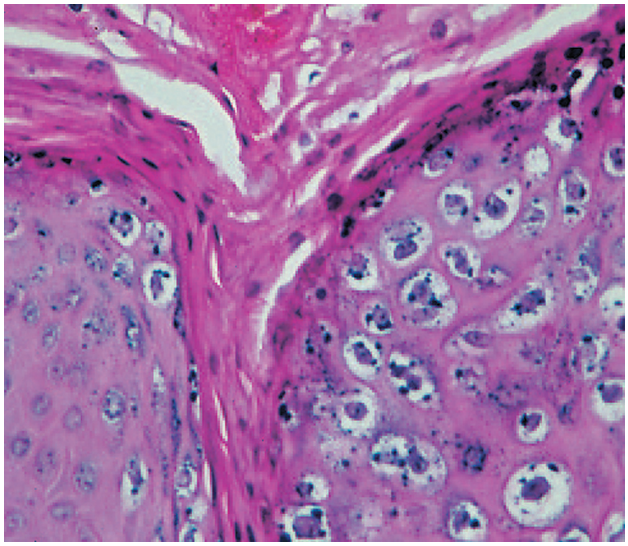


Figure 12.59 Verruca vulgaris with prominent koilocytosis.

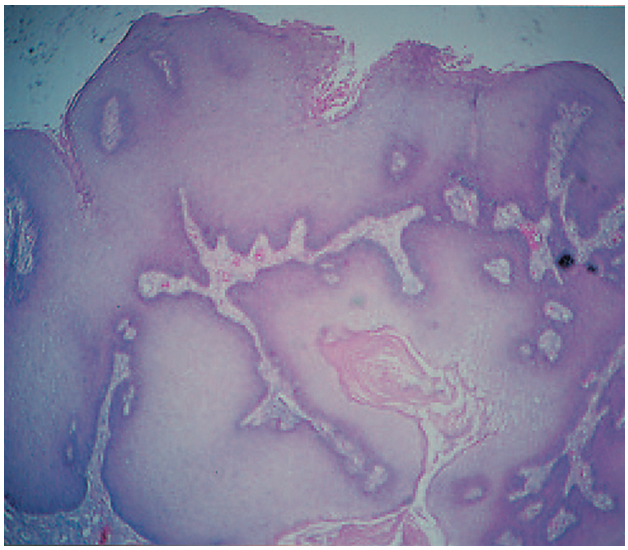


Figure 12.60 Condyloma accuminatum showing extensive acanthosis and large vacuolated keratinocytes and only minimal hyperkeratosis.

reports of successful treatment of respiratory papillomatosis with cidofovir [244,245], but other authors have found no evidence for usage of cidofovir in treatment of this disease [246,247]. A topical formulation of a cidofovir analog, GS-9191, is currently under study for the treatment of genital warts.

Photodynamic Therapy

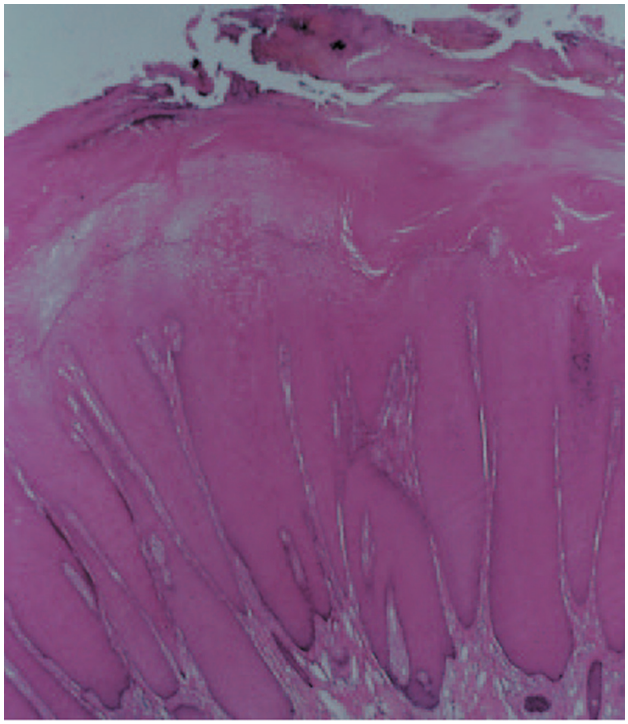
Photodynamic therapy (PDT) uses drugs known as photosensitizers, such as topical 5-aminolevulinic acid, which collect in tumor cells and kill them via generation of reactive oxygen species when they are exposed to specific wavelengths of light. In addition to directly killing cancer cells, PDT can also damage blood vessels in tumors and may activate the immune system to attack tumor cells. A small study has shown not only effectiveness in inducing remission of CIN, but also the possibility of eradicating cervical HPV infection [229,248,249].

Therapy of Epidermodysplasia Verruciformis

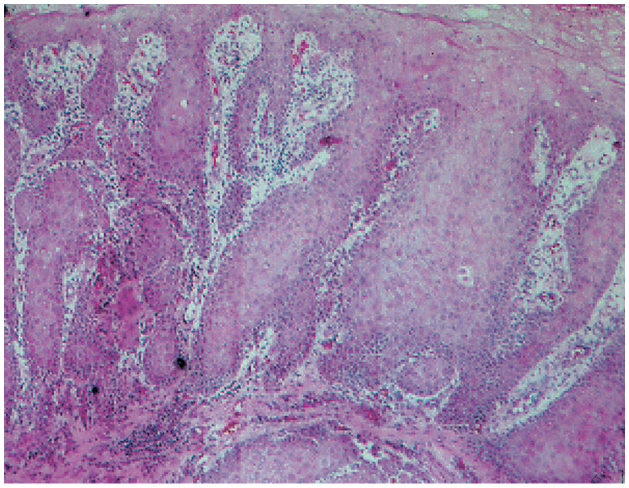
Treatment of EV is a difficult and lifelong process; the locally destructive methods most commonly used for therapy of warts are not effective in EV, and systemic therapy may induce some improvement, but is generally followed by recurrence. The use of systemic retinoids has been explored in EV and the long-term use of isotretinoin or acitretin has been shown to decrease the number of benign lesions and slow the appearance of premalignant and malignant lesions [59]. Interferons have been tried alone and in combination with retinoids, but the resulting improvement was often transient and recurrence was frequently seen with cessation of oral retinoids [225,236,250]. Some success has been seen with imiquimod therapy, both as monotherapy and when used in combination with interferon or oral retinoids [251,252]. PDT has also been shown to be efficacious, but maintenance therapy may be required [253]. Treatment of the premalignant and malignant lesions associated with EV is via the same methods as in the normal host. It is of primary importance to ensure protection of the skin from exposure to ultraviolet radiation and follow patients closely for the development of premalignant and malignant lesions. As with the treatment of verrucous carcinoma, any use of radiation therapy is contraindicated in these patients because ionizing radiation is a potent cocarcinogen for HPV-induced lesions. As with the normal host, treatment of HPV-associated cancers with x-radiation generally induces regression followed by recurrence, with a tumor showing a more malignant and aggressive phenotype.

Papillomavirus Vaccines

A very exciting area of PV research is in the development of potential therapeutic and prophylactic vaccines for HPV infection. Although there are several examples of vaccines that have had spectacular success in the prevention of other viral diseases, there are a number of features of HPV biology that make the development of a vaccine particularly difficult. The first problem is our poor understanding of the immune response to HPV infection. Despite the fact that spontaneous clearing of warts has commonly been seen, we do not understand the mechanism by which this specific immune response is generated and, therefore, cannot particularly target this pathway in the development of a vaccine. Another problem is that because there is no in vitro culture system



(a)



(b)

Figure 12.61 (a,b) Verrucous carcinoma. This lesion shows little cellular atypia but deep downward proliferations of the tumor extending into the dermis cuniculatum. (Photograph a from Ho, et al. Arch Dermatol 136:547–552, 2000. Used with permission; Photograph b courtesy of Dayna Diven, M.D., Department of Dermatology, University of Texas Medical Branch at Galveston, Galveston, TX.)

or an animal culture system for HPV, there is no ready source of live virus that might be exploited for a live attenuated viral vaccine, such as was used with poliovirus. A final problem is that, although most other viruses spend a portion of their life cycle in the systemic circulation where they are vulnerable to neutralizing antibodies, HPVs remain exclusively in the epithelium. Thus, antibodies must transverse the basement membrane and reach the outer layers of the skin or mucosa to be effective in preventing infection. Despite these and other confounding factors, significant progress has been made in the arena of prophylactic vaccines, with two effective vaccines currently on the market. Current research is focusing on identification of new and efficacious targets for prophylactic vaccination and therapeutic vaccination.

Prophylactic Vaccines

Unlike therapeutic vaccines, the goal of a prophylactic vaccine is to generate production of neutralizing antibodies to the viral capsid proteins that will block the virus before it can enter the

Table 12.4 Differential Diagnosis of HPV

Verruca vulgaris

Seborrheic keratosis: "Stuck-on"–appearing papules with verrucous friable surface
Nevi: Typically softer than warts with tan to brown to black pigment
Acrochordons: Typically are fleshy and soft, with no keratosis
Keratoacanthoma: Pink or red papule with central keratotic horn
Cutaneous horn: Conical, dense, hyperkeratotic nodule, often in elderly persons or sun-exposed skin
Squamous cell carcinoma: Indurated papule often with ulcerated or crusted center
Linear epidermal nevi: Linear, verrucous plaques, may have a warty appearance
Acanthosis nigricans: Hyperpigmented plaques may have a warty appearance
Acrokeratosis verruciformis and epidermolytic hyperkeratosis: Both show verrucous papules on the extremities, but can be distinguished by autosomal dominant inheritance in most cases
Molluscum contagiosum: May resemble common warts, but lesions are usually smooth-surfaced, flesh-colored, and often have a central punctum

Flat warts

Lichen planus: May sometimes have a slightly verrucous appearance, but distinguishing features include Wickham's striae, pruritus, and oral involvement

Paronychial warts

Squamous cell carcinoma: In older individuals, this carcinoma must be differentiated from benign warts

Plantar warts

Corns and calluses: Warts are distinguished by the presence of thrombosed capillaries and the disruption in the normal skin markings, features not found in calluses

Condyloma acuminata

Syphilitic condyloma lata: May appear similar, but can be distinguished by serology for syphilis and should be darkfield –positive for spirochetes
Molluscum contagiosum: May resemble genital warts, but lesions are usually smooth-surfaced, flesh-colored, and often have a central punctum
Pearly penile papules: Are 1–2-mm papules evenly distributed circumferentially around the corona of the glans penis

Bowenoid papulosis

Bowen's disease: Bowenoid papulosis can usually be distinguished by its onset at an earlier age, the reddish-brown color, somewhat verrucous surface, and the presence of multiple small lesions

Oral papillomatosis

Oral leukoplakia: Whitish patches usually macular, must be distinguished by biopsy

Epidermodysplasia verruciformis

Erythematous macules of the trunk and verrucous papules of the extremities; malignant transformation is often seen on sun-exposed skin

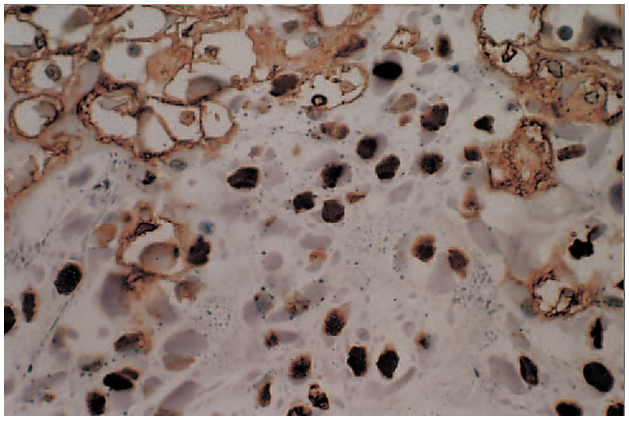


Figure 12.62 Positive immunohistochemical staining for HPV capsid antigens

cell. Because HPV does not enter the systemic circulation, but remains in the epidermis, antibodies that are capable of reaching the skin must be generated. Antibody induction has been demonstrated in the mucus of the vaginal mucosa following systemic immunization, indicating that antibodies can traverse the basement membrane [254]. The preferred immunogens for this type of vaccine are the viral capsid proteins. Following synthesis of the capsid proteins, it is essential that they be folded as seen in the viral capsomere, because when they are synthesized in bacterial or yeast cells, they are denatured and do not induce production of neutralizing antibodies in this form. When the L1 and L2 proteins are generated in eukaryote cells, they self-assemble into the capsid structure, in particles called "virus-like particles", which are indistinguishable from mature virions except they lack the viral DNA (Fig. 12.65). Using animal models, it has been shown that immunization with intact viruses does lead to production of neutralizing antibodies in cows, dogs, and other species. Cottontail rabbits immunized with CRPV VLPs had greatly reduced incidence of papilloma formation after challenge and developed no epithelial cancers [255]. Whereas dogs and rabbits are most commonly used as animal models to study PVs, a wide spectrum of animals is susceptible to the species-specific PVs (Figs. 12.66 and 12.67).

Two prophylactic vaccines against HPV infection are currently available for use in humans. Both vaccines utilize the major capsid protein L1 of specific HPV types, which have the aforementioned ability to self-assemble into VLPs. Infection is prevented by the induction of neutralizing antibodies against L1. Gardasil® (Merck & Co., Inc., Whitehouse Station, NJ), which uses L1 proteins derived from recombinant *Saccharomyces cerevisiae*, is a quadrivalent vaccine, effective against types 6, 11, 16, and 18 [256]. Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium), which uses L1 proteins derived from the baculovirus expression vector in *Trichoplusia ni* cells, is a bivalent vaccine that is effective against types 16 and 18, with the addition of an immune-boosting adjuvant, AS04 [257]. Dosing of both vaccines is achieved through a series of three intramuscular injections at 0, 1–2, and 6 months [256,257].

Partial results have been reported from large phase III clinical trials in both vaccines. The Females United to Unilaterally Reduce Endo/Ecto-Cervical Cancer (FUTURE) I study, a randomized, double-blind, placebo-controlled trial with 3 years of follow-up in 5455 healthy women aged 16–24 years, utilized the quadrivalent vaccine. This study reported 100% efficacy (95% CI=94–100) of the vaccine in preventing external anogenital lesions due to the vaccine genotypes in the protocol analysis and 73% (95% CI=58–83) in the intention-to-treat analysis. Vaccine efficacy in preventing cervical lesions due to the covered genotypes was 100% (95% CI=94–100) in the protocol analysis and 55% (95% CI=40–66) in the intention-to-treat analysis. Some cross-protection against nonvaccine genotypes was also evident, as efficacy was 34% (95% CI=15–49) in preventing external anogenital lesions and 20% (95% CI=8–31) in preventing cervical lesions due to any HPV genotypes [258]. The FUTURE II study, a double-blind, placebo-controlled trial with 3 years of follow-up in 12,167 healthy women aged 15–26 years, utilized the quadrivalent vaccine with an objective of evaluating vaccine efficacy in the prevention of CIN 2/3, in situ adenocarcinoma, or invasive cancer. This study showed 98% (95% CI=86–100) vaccine efficacy in the protocol analysis in preventing any type of high-grade lesion and 44% (95% CI=26–58) in the intention-to-treat analysis. Some degree of cross-protection was again evident, with efficacy in preventing any type of high-grade lesion due to any HPV type of 17% (95% CI=1–31) [58].

The Papilloma Trial against Cancer in Young Adults (PATRICIA), a double-blind study utilizing the bivalent vaccine and the hepatitis A vaccine (Havarix®, SmithKline Beecham) as a control, had an average follow-up of 15 months after the first vaccine dose. A total of 18,664 women aged 15–24 years from 14 countries in Europe, Asia, Latin America, and North America participated, making this the largest HPV vaccine study to date. Vaccine efficacy in preventing high-grade lesions due to HPV types 16 and 18 was 100% (95% CI=74.2–100). Cross-protection was also seen against persistent infection by HPV 45 (59.9%, 95% CI=2.6–85.2), 31 (36.1%, 95% CI=0.5–59.5), and 52 (31.6%, 95% CI=3.5–51.9), and to a lesser degree, 12 other nonvaccine oncogenic types (27.1, 95% CI=0.5–46.8) [20].

Five-year data is available from two phase II studies of these two vaccines. Five years after vaccination, the quadrivalent vaccine was shown to have 95.6% (95% CI=83.3–99.5) efficacy in preventing persistent infection and 100% (95% CI=12.4–100) in preventing disease (cervical dysplasia or genital warts) associated with the vaccine types [259]. Similarly, the bivalent vaccine was shown to have 94.3% (95% CI=53.2–99.9) efficacy against persistent infection and 100% (95% CI=42.4–100) efficacy against any type of CIN 4.5 years after vaccination [260].

Current American recommendations for the quadrivalent vaccination, given by the Centers for Disease Control (CDC) and American Academy of Pediatrics (AAP), are routine vaccination of girls aged 11–12 year (in most cases, prior to the onset of sexual activity) and catch-up vaccination of girls aged 13–26 years [261]. The vaccination series can be started as young as 9 years of age, at the physician's discretion. The vaccine is currently not approved for use in females younger than 9 or older than 26, although studies are ongoing in females over the age of 26 [261]. The quadrivalent vaccine was recently approved for the prevention of vulvar and vaginal cancers as well as vulvar and vaginal intraepithelial neoplasia grades 2 and 3. Although women who are sexually active may have already been infected

Table 12.5 Treatment of Warts

Treatment	Method
Common warts	
Intralesional mumps and candida	For recalcitrant cutaneous warts, intralesional injection with 0.3 cc at 1–3 of the worst lesions with frequent response even in untreated warts. Therapy may be repeated at 2–3 week intervals.
Topical imiquimod 5% cream	For cutaneous warts, application of thin layer nightly with occlusion. May cause irritation of the surrounding skin so apply sparingly and not to sensitive or thin-skinned areas.
Allicin	For cutaneous warts, topical or oral allicin has antiviral activity and inhibition of cellular proliferation of virally infected cells. Oral allicin should be taken with food since it may cause GI upset.
Salicylic acid	Available over the counter, and can be applied at home, once or twice daily, for several months. The wart is soaked in warm water to soften the tissue, followed by removal of the keratotic skin with an emory board or pumice stone. Salicylic acid is then applied to the wart. An adhesive bandage may be applied to enhance penetration. Patches or pads impregnated with salicylic acid are also available.
50% Tricholoacetic acid	Wart is pared down, then acid is applied in the office, either alone or under occlusion. The area should be rinsed off about 2 hr later. Therapy can be repeated at weekly intervals until resolution of the wart.
Cantharidin	This is applied to wart surface with or without occlusion, and left in place for 8–24 hr, after which a blister has usually formed. Therapy may be repeated after healing of the blister, at 1–3 wk intervals.
Cryotherapy with liquid nitrogen	The keratotic material of the wart can be pared off, followed by freezing with liquid nitrogen, usually with two freeze-thaw cycles. The amount of time required for freezing varies with the thickness of the wart. Therapy often has to be repeated to clear the wart completely, usually at 2–3 wk intervals.
Electrodessication	Sometimes used for recalcitrant warts. The area must first be anesthetized, followed by electrodessication of the wart until a white crust appears. This crust is then curretted. Repeated treatments are usually required.
CO_2 laser	Expensive and typically reserved for recalcitrant warts
Bleomycin	Intralesional bleomycin can be used for the treatment of recalcitrant periungual and plantar warts. 0.5–1.0 U/ml concentration is injected directly into the wart tissue
Surgical excision	Reserved for debulking large exophytic warts resistant to therapy
Flat warts	
Retinoic acid 0.05%	Applied daily to warts until desquamation occurs, which is sometimes accompanied by mild local irritation
Condylomata	
Podophyllin	Used primarily in the treatment of genital warts, because it is more effective on mucosal surfaces. (contains mutagens) (not standardized)
Podophyllotoxin 0.5% solution or gel	Applied once or twice daily, stopping if marked irritation occurs (patient applied) (high recurrence rates)
5-Fluorouracil (5%) solution	Primarily used for verruca plana and condyloma; (highly inflammatory) (teratogenic)
Interferon-alpha	Given by injection; flu-like side effects
Cidofovir	Not available in a topical preparation, but can be compounded as a cream or gel (e.g. 1–3%)
Imiquimod 5% cream	Applied (by patient) three times weekly overnight (low recurrence rates)
Sinecatechin 15% ointment	Applied three times daily

with HPV, vaccination confers protection against the remaining genotypes [262]. The vaccine can be given to patients who have abnormal or equivocal Pap smear results, who are breastfeeding, or who are immunocompromised (both acquired and iatrogenic) [261]. Both HPV vaccines have a very high safety profile, although trials with vaccines utilizing highly immunogenic adjuvants such as AS04 reported greater reactogenicity, mainly localized to the injection site [263]. Vaccination of males has been a somewhat controversial topic, but studies regarding the efficacy in males have resulted in approval of the quadrivalent vaccine in men. The vaccine is likely to impact on the incidence of anal cancer in men, especially in the subset of MSM. The importance of universal vaccination is becoming evident as more and more cancers have been linked with HPV infection. It is also evident that these vaccines have the potential to greatly decrease the incidence and transmission of HPV infection and to help prevent its sequelae for both males and females. In addition, as male promiscuity has been associated with a 6.9-fold increase in

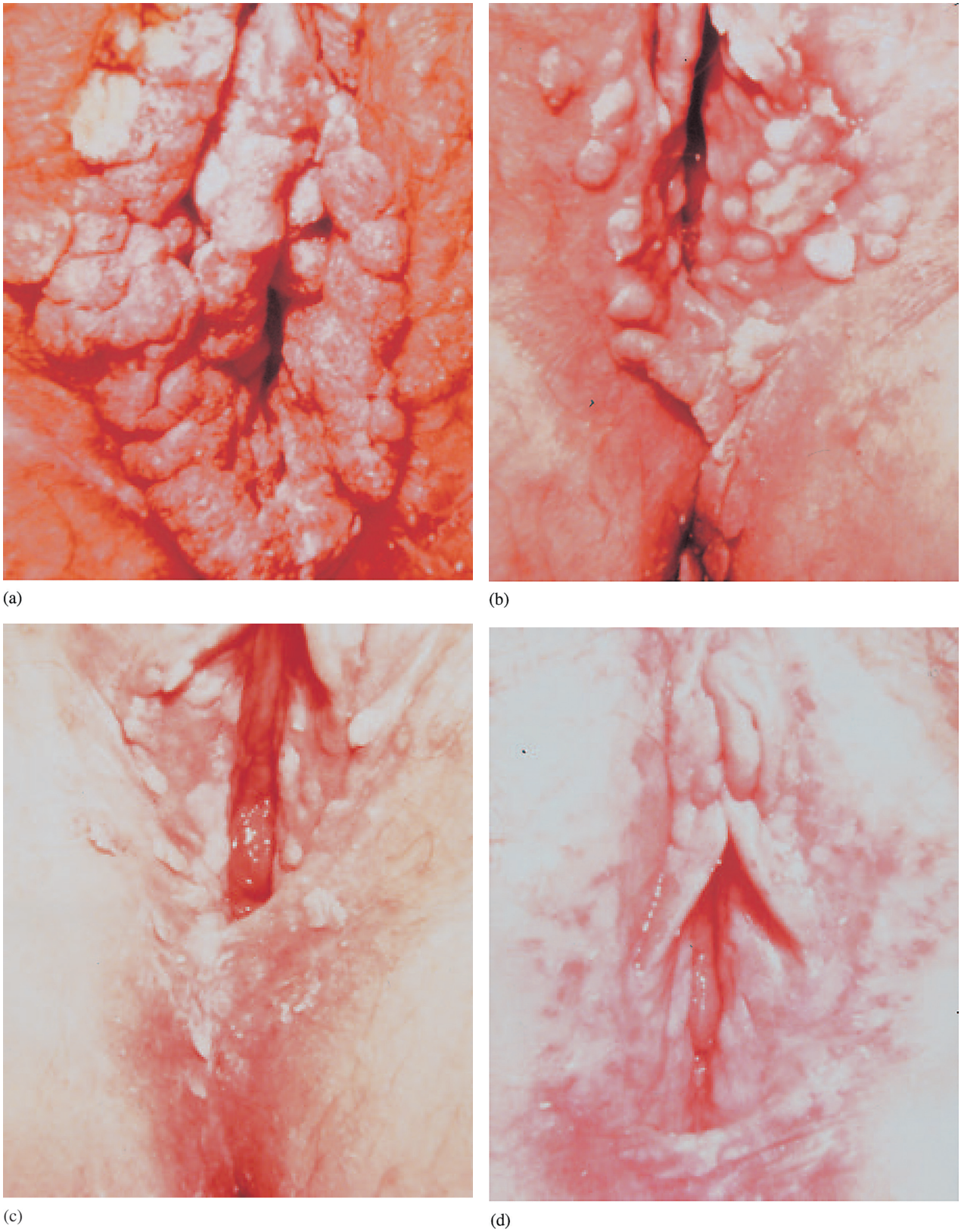


Figure 12.63 (a) Extensive condyloma acuminatum in a patient who had failed several non-antiviral therapies. (b) Four weeks after initiating therapy with 5% imiquimod cream overnight, three times/wk), a 50% decrease in the size and number of lesions was observed. (c) Six weeks after initiating therapy, a 90% reduction in the warts was noted. (d) Eight weeks after starting therapy, complete disappearance of all warts was seen. The patient remains clear six years after imiquimod therapy.

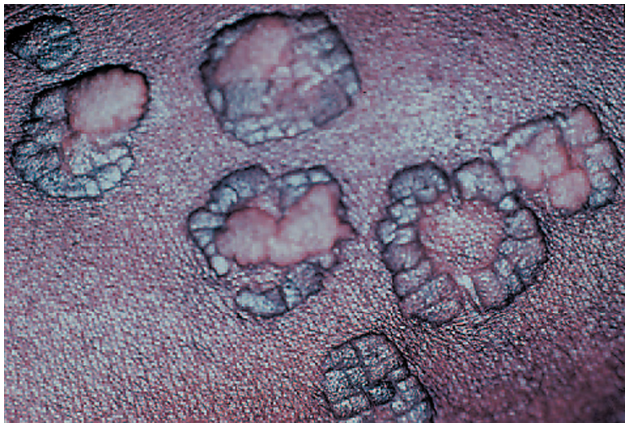


Figure 12.64 A ring of warts appeared around the site of previous warts treated with cryotherapy. (Photograph courtesy of Roberto Arenas, M.D., Mexico City, Mexico.)

cervical cancer in the female partner [264], vaccination of males can prevent not only infection and possibly cancer in the vaccinee, but also in their partners. Long-term efficacy will be revealed as more follow-up data is available from clinical trials.

Future prophylactic vaccines will likely include L1-based vaccines that incorporate a larger number of oncogenic HPV types, with clinical trials currently ongoing for an octavalent vaccine that protects against an additional 4 oncogenic types [265]. The neutralizing antibody response to L1 VLPs is type-restricted [266], requiring type-specific L1 VLPs to be included in vaccines. However, vaccines based on the minor capsid protein L2 have been shown to generate broad spectrum cross-neutralizing antibodies and may possibly reduce the number of VLP types required in the vaccine; an L2-based vaccine is currently in early phase clinical trials [267,268].

Despite the development of effective vaccines against HPV 16 and 18, multiple other oncogenic HPV types have the potential to cause cervical cancer; vaccinated females must continue to have routine Pap smears for early detection of precancerous lesions.

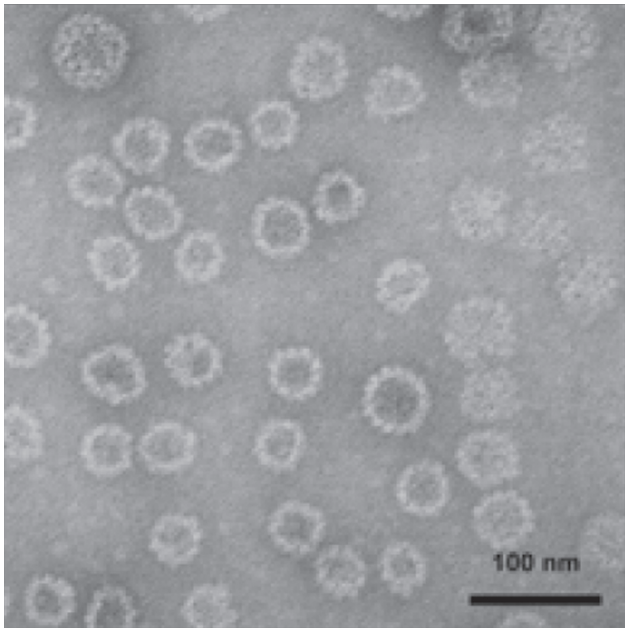


Figure 12.65 HPV 16 Virus Like Particles

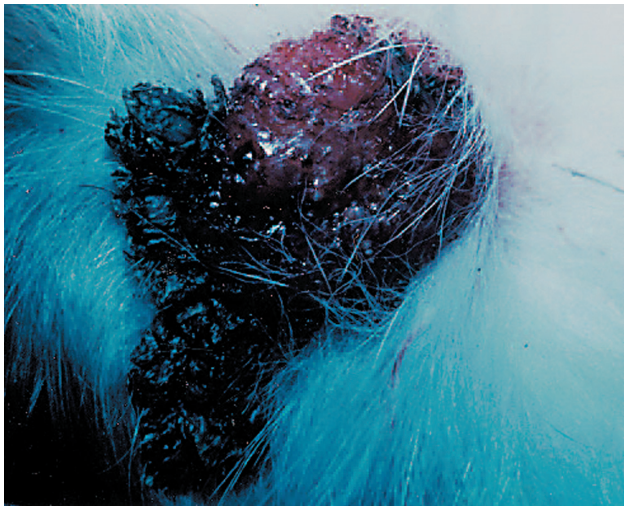


Figure 12.66 This squamous cell carcinoma on the back of a rabbit resulted from infection with the Shope papillomavirus. The rabbit has been used for many decades as an animal model for the study of papillomaviruses.

Therapeutic Vaccines

There are currently no therapeutic vaccines against HPV approved for human use, although many different potential targets are being studied. A therapeutic vaccine is one that will result in clearing



Figure 12.67 Extensive oral papillomatosis in a dog. The oral mucosa of the dog is commonly used for the study of papillomavirus vaccine.

of an already established infection; current prophylactic vaccines have shown no ability to clear existing infections. Because of the significant mortality associated with cervical cancer, and the ability of therapeutic vaccination to have an immediate impact in reducing its incidence, the earliest aims in this field are toward development of a therapeutic vaccine for cervical carcinoma and its precursor lesions. The strategy behind the design of a therapeutic vaccine is to target cells that express a specific viral protein on their cell surface for immune-mediated destruction. These proteins may be viral cell surface proteins or viral proteins that are degraded intracellularly and presented on the cell surface as part of major histocompatibility complex (MHC) class I. The MHC I receptor/viral peptide complexes stimulate a cytotoxic response in CD8+ T cells. L1 and L2 late capsid proteins are not expressed in the infected basal cells in precancerous or cancerous tissues, making them a poor target for therapeutic vaccines [269]. An ideal candidate target for this type of vaccine would be the HPV early genes. Because the viral E6 and E7 genes are selectively retained and expressed in cervical dysplasia and cancer, they are excellent candidates for the development of a therapeutic vaccine [270]. Unfortunately, trials of therapeutic vaccines are often hindered by the fact that most trials have been on limited numbers of patients with end-stage disease only or trials designed so that patients underwent definitive treatment after 3 months due to the ethical and safety issues of leaving lesions untreated when proven methods of treatment such as surgery or cryotherapy are routinely available [248]. Despite this limitation, several different therapeutic vaccine strategies are currently under investigation [152].

Recombinant proteins fused with heat shock proteins (Hsp) have been shown to generate a stronger immune response than immunization with the protein alone [271]. In mice studies, a recombinant E6 and E7 protein fused to Hsp70 of *Mycobacterium tuberculosis* conferred protection against a challenge with HPV 16 E6/E7 transformed tumor cells. A vaccine consisting of Hsp65 from *M. bovis* and HPV 16 E7 fusion protein (HspE7) was evaluated in women with CIN 3 and appeared to provide clinical benefits in some participants, although a randomized controlled trial is needed to determine whether the clinical improvement can be wholly attributed to the vaccine [272].

Some studies have evaluated direct *in vitro* delivery of antigenic proteins to autologous antigen-presenting cells, such as dendritic cells, in a process known as "pulsing," and then re-administering these cells to elicit an immune response. Patients with cervical cancer who showed an immune response when administered dendritic cells pulsed with recombinant HPV 16 or 18 E7 proteins, showed a slower tumor progression [273]. HPV 16 E7 peptide-pulsed autologous dendritic cell therapy in cervical cancer patients was investigated in a recent phase I study; results have yet to be published [274].

Genetic immunization through DNA vaccines is another possible approach; DNA encoding a viral antigen can be delivered via multiple methods to antigen-presenting cells. E6 and E7 have been shown to be poor immunogens by themselves, however; their immunogenicity can be increased by expressing or cross-priming with other immunomodulating and cellular targeting proteins. Care must be taken during production of DNA vaccines to eliminate oncogenic potential. Mouse and rabbit studies have shown the induction of neutralizing antibodies in response to vaccination; these vaccines are currently in phase I trials in humans [275].

Viral vector vaccines function by inducing an immune response in the host and inducing endogenous synthesis of viral and recombinant proteins, producing a strong T-cell response. The vaccinia virus is often used in vaccine studies as vaccination is known to be immunogenic and relatively safe and genetic manipulation is relatively simple, but some researchers have evaluated the use of the adenovirus as another possible vector [276]. E6 and E7 viral vector vaccines are currently in phase II studies in humans [277,278]. E2-based vaccines are also under study [279,280], but as E2 is typically lost from the genome during progression to cancer, this type of vaccine would be unlikely to benefit those with late-stage disease [281].

The possibility also exists for combined prophylactic/therapeutic vaccines that consist of chimeric VLPs incorporating peptides of early proteins fused with L1 or L2; these vaccines are currently in phase I clinical trials [282,283].

Conclusion

The mucocutaneous manifestations of HPV range from benign warts to aggressive SCCs. These HPV-associated lesions often mimic (or are mimicked by) other non-HPV-associated lesions that have far different biological significance and/or therapies. In some cases, even the most well-trained and experienced clinicians cannot always distinguish among these possibilities. In case of doubt, a biopsy (and possibly other diagnostic procedures) should be considered. Owing to a lack of good in vitro culture systems or animal models for HPV, our understanding of the pathophysiology of HPV was very limited until the 1980s. Since that time, however, not only have sensitive molecular tools allowed detection of HPV DNA, they have also led to a markedly greater understanding of HPV viral oncogenesis. Much remains to be understood regarding the role of genetics, immunity, and cofactors in HPV infections (especially oncogenic HPV). Therapy for warts has evolved from surgical and cytodestructive techniques having no antiviral potential, to immunomodulatory agents and the possibility of therapeutic vaccination. A major and recent breakthrough, effective prophylactic vaccination against HPV, will serve to decrease the incidence of cervical cancer and possibly other cancers worldwide. The large volume of ongoing HPV research will surely result in many innovations in the years to come.

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13 Parvovirus B19

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Parvovirus B19 is the only member of the family Parvoviridae known to infect humans. The most characteristic cutaneous manifestation is erythema infectiosum (fifth disease). This illness is distinguished by a "slapped-cheek" appearance of the face and a pink, lacy eruption on the trunk and extremities. The B19 virus may also cause arthritis, aplastic crisis in individuals with hemoglobinopathies, chronic anemia in immunocompromised persons, and fetal hydrops after intrauterine infection. This virus has also been linked to the rare disorder, papular-purpuric gloves-and-socks syndrome (PPGSS). Many of the severe manifestations of B19 viremia relate to the propensity of the virus to infect and lyse erythroid precursor cells in the bone marrow [99].

History

Erythema infectiosum appears to have been a recognized entity throughout the 1800s, but was thought to represent a mild form of rubella or measles [1]. In 1889, Tschamer described an illness suggestive of erythema infectiosum, which he called abortive rubella [2]. The illness was named fifth disease in 1905 during a time when childhood exanthems were designated first through sixth [3].

Interestingly, the virus was discovered a few years before it was associated with any specific illness. The virus was found during routine screening of serum samples from healthy blood donors for hepatitis B surface antigen [4]. Nine samples of blood from these donors were falsely positive for hepatitis by the technique of counter immunoelectrophoresis (CIE), but negative by hemagglutination and radioimmunoassay (RIA), which are more sensitive tests. Immunoelectron microscopy demonstrated viral particles resembling parvovirus, and these were designated B19 after one of the specimen labels [4]. The authors suspected that the virus was an infectious agent because 30% of serum from random adult samples had immunoglobulin G (IgG) antibody to the viral antigen. In 1983, B19 was confirmed to be a parvovirus [5].

The first report of a symptomatic parvovirus B19 infection was of two British soldiers with an acute febrile illness in 1980 [6]. B19 was also found in patients with sickle cell anemia and hypoplastic crisis in 1981 [7]. In 1983, there was an outbreak of fifth disease among London schoolchildren [8]. Serum samples from 31 schoolchildren and 6 adult exposures, all with the clinical signs of the disease, contained parvovirus-specific IgM antibody. No IgM was found in asymptomatic persons who were exposed. This was the first outbreak of erythema infectiosum to be examined for human parvovirus, and the findings of this study suggested B19 as the cause [9] (Fig. 13.1).

Incidence

Although B19 can occur sporadically throughout the year, it tends to occur in epidemics in late winter and early spring [10]. The amount of infection within a community varies from year to year. All ages can be affected and serological studies show increasing prevalence with age [10]. Studies have shown that 15–60% of children aged 5–19 years and 30–60% of adults are seropositive [4,11,12]. The seroprevalence increases to more than 90% in the elderly [12].

Pathogenesis

B19 virus is a member of the family Parvoviridae and the genus *Parvovirus* [13]. The other two genera in this family, the *Dependoviruses* and the *Densoviruses*, infect other vertebrates and insects [14]. Other members of the genus *Parvovirus* include canine parvovirus and feline panleukopenia virus, as well as other animal parvoviruses [15]. The other animal parvoviruses are not thought to infect humans, and B19 is not believed to infect other animals [15].

B19 is the smallest known human pathogenic virus that contains single-stranded DNA encoding for at least two capsid or structural proteins and one nonstructural protein [14]. In contrast to some other parvoviruses and the other two genera, B19 is thought to be capable of autonomous replication (without coinfection of a helper virus) [14]. It replicates in vitro in erythroid progenitor cells derived from human bone marrow, umbilical cord, peripheral blood, or fetal liver sources [99]. There is only one known serotype of parvovirus B19.

Transmission of B19 is primarily via the respiratory route by droplet aerosol [11] during the period of viremia [16]. Once the rash of erythema infectiosum appears, individuals are usually no longer infectious [11]. The rate of transmission among close household contacts is approximately 50% [17,18]. The virus may rarely be spread via blood transfusion [4] and blood products [19], although the risk of transmission with transfusion of one unit of blood is low [20]. Vertical transmission from mother to fetus may also occur [21]. Thirty percent of infected mothers transmit the virus to their offspring, as evidenced by IgM in cord blood or IgG present in the 9- to 12-month-old infant [22].

The pathogenesis of the characteristic rash of fifth disease is not known, but there is speculation that immune complexes play a role [10]. Both the rash and arthralgias are considered to be postinfectious phenomena that are due to immune-mediated defenses of the host. During infection, B19 virus primarily targets the erythroid cell line and is able to infect and lyse erythroid precursor cells [23]. Individuals with chronic hemolytic anemia or anemia associated with acute or chronic blood loss depend on compensatory increases in red cell production to maintain stable red cell indices. In these persons, B19 infection may lead to transient aplastic crisis [10]. Patients with transient aplastic crises have viremia and shed virus, and are therefore highly infectious [99]. In immunodeficient individuals, B19 infection may cause chronic red cell aplasia and associated chronic anemia [24], because they fail to clear B19 viremia [99]. Parvovirus B19 infection in the developing fetus may infect the erythroblasts, leading to hemolysis, anemia, and possibly hydrops and fetal death [25]. The fetus requires a higher level of red cell production than do adults and

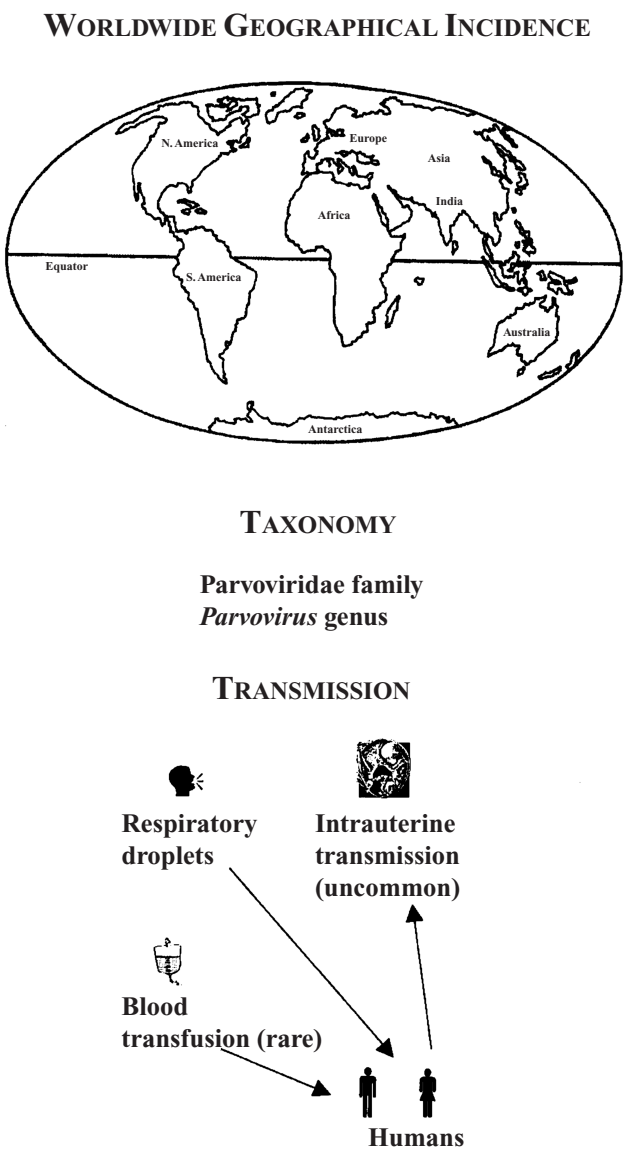


Figure 13.1 Incidence and transmission of parvovirus B19.

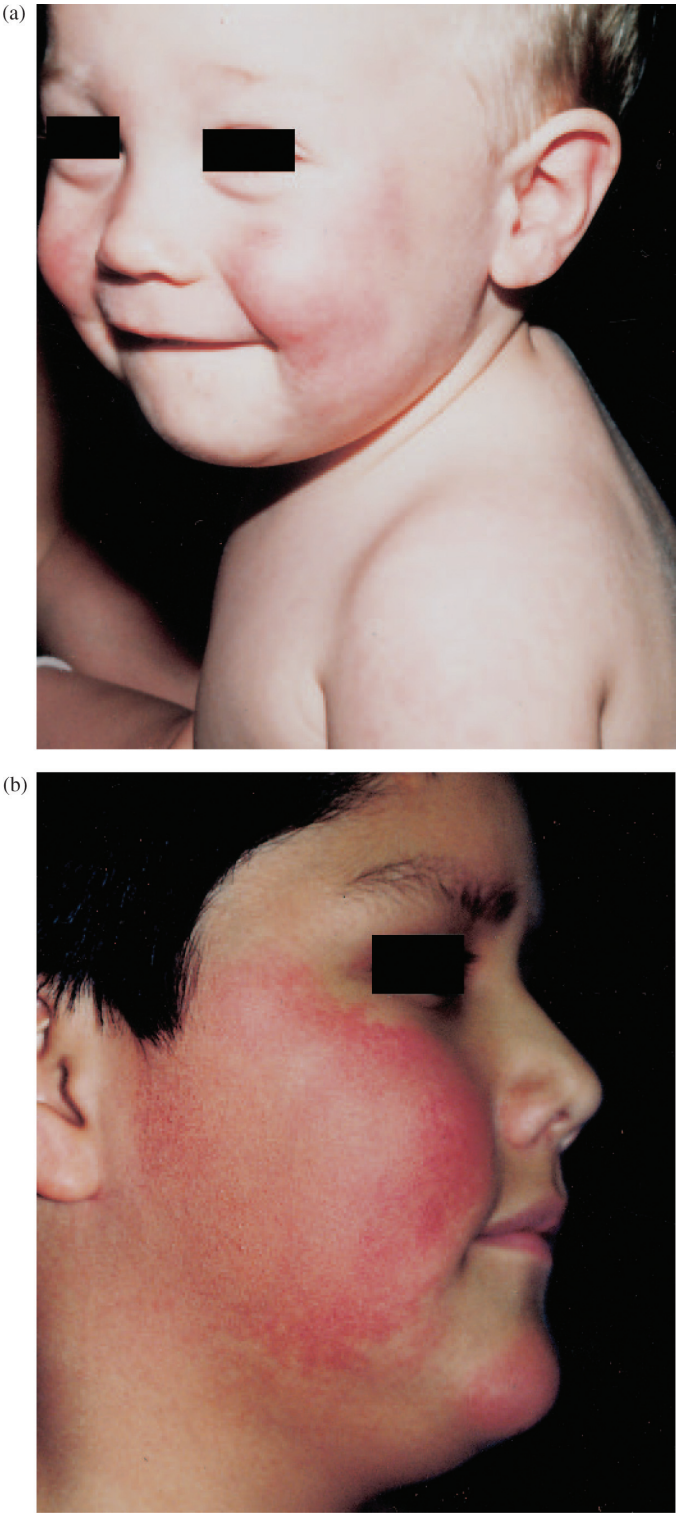


Figure 13.2 (a,b) The characteristic "slapped-cheek" malar rash of erythema infectiosum. (Photograph b courtesy of Edith Garcia-Gonzalez, M.D., Ph.D., and Lourdes Tamayo, M.D., Mexico City, Mexico.)

has an immature immune system; both these factors could explain B19-induced hydrops fetalis [99]. Because recurrent disease with B19 is rarely seen, it is assumed that infection confers long-term immunity [26].

B19 binds specifically to a cellular receptor, erythrocyte P antigen; this specific binding explains the tropism of B19 for erythroid progenitor cells. The few persons who lack P antigen cannot be infected with B19 [99].

Clinical Manifestations

Parvovirus Infection in Children

Whereas most infections due to B19 are asymptomatic and unrecognized, erythema infectiosum (fifth disease) is the most common clinical syndrome associated with the virus (Figs. 13.2–13.6a). This disease is most frequently seen in school-age children, although it may also occur in adults. The clinical manifestations of erythema infectiosum are listed in Table 13.1.

Parvovirus B19 has also been associated with a variety of other clinical syndromes. There have been reports of children with parvovirus infection presenting with symptoms suggestive of juvenile rheumatoid arthritis [27]. Parvovirus B19 infection in children

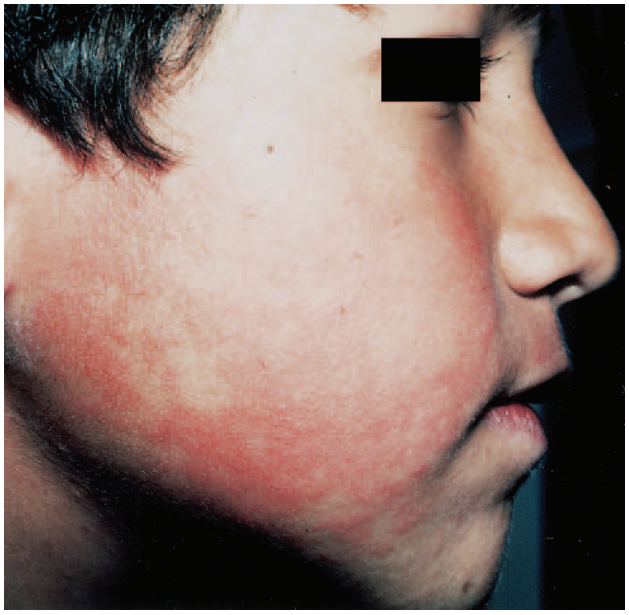


Figure 13.3 Facial erythema in a child with erythema infectiosum.



Figure 13.5 Lacy pink macules on the arms of a patient with parvovirus infection.

has also been associated with vascular purpura [28,29], including Henoch-Schönlein purpura [29]. Some patients develop only an enanthem, which consists of erythema of the tongue and pharynx or red macules on the buccal mucosa, hard palate, or soft palate [30]. Parvovirus B19 has also been responsible for obstructive respiratory disease, such as bronchitis/bronchiolitis, laryngitis, and asthmatic attacks [31]. The differential diagnoses are shown in Table 13.2.



Figure 13.4 Facial eruption and extensive erythematous macules on chest and arms. (Photograph courtesy of Edith Garcia-Gonzalez, M.D., Ph.D., and Lourdes Tamayo, M.D., Mexico City, Mexico.)

Parvovirus Infection in Adults

Adult B19 infection, in contrast to infection in children, is more likely to be asymptomatic, more commonly associated with arthropathy, and usually does not have the characteristic rash [32,33]. The usual course consists of fever, lymphadenopathy, mild arthritis of the hands, wrists, and knees, and no rash [34]. Pruritus can occur in some patients, particularly adults [35]. Infection is often asymptomatic (26% of adults in one study) [36]. Women are likely to have joint complaints and a rash, whereas men tend to have a flu-like illness [36]. Fatigue, malaise, and depression can persist for weeks after acute infection [34].

Acute arthropathy is the primary presentation of B19 infection in adults [35,36]. Women, more so than men, develop the arthropathy with synovitis, clinically manifested by joint swelling, stiffness, and pain [36]. The arthropathy is typically symmetrical and peripheral, involving multiple joints, and is nondestructive, of sudden onset and moderate severity [37]. The joint symptoms are usually brief, but can be persistent or recurrent for more than 2 months in 20% of adults [36,37]. The arthropathy usually involves the small joints of the hands, the feet, and the knees, but can affect almost any joint [36]. It can imitate Lyme arthritis [38], rheumatoid arthritis [39], or lupus arthritis [40]. It is not known whether these individuals have persistent infection or an abnormal immune response to the virus [99].

B19 infection can cause severe pruritus with or without a rash. It has been suggested that parvovirus be considered in any patient with acute arthritis and pruritus [41]. Paresthesias of the fingers have also been described in association with parvovirus infection, with or without other features of the disease [42].

The rash, which is often not present in adults, usually consists of red macules that are occasionally lacy or blotchy, on the extremities (Fig. 13.6b) [36]. The slapped-cheek appearance is rarely present.



Figure 13.6 (a) Reticulated pink macules and papules on the trunk of a child with erythema infectiosum. (Photograph courtesy of Claire Mansur, M.D., Department of Dermatology, Tufts University School of Medicine, Boston, MA.) (b) Erythematous, lacy macules of the axillae of an adult with parvovirus B19 infection.

The rash is frequently pruritic and often severely affects the feet [36]. Other cutaneous presentations in adults include purpura [43], vesiculopustules [44], palmoplantar desquamation [45], polyarteritis nodosa [46], and a malar rash suggestive of lupus erythematosus [40].

Papular-Purpuric Gloves-and-Socks Syndrome

PPGSS is an unusual febrile dermatosis initially described by Harms et al. in 1990 [47]. In 1991, the syndrome was first associated with acute parvovirus B19 infection [48]. Since that time, over 25 cases have been reported [47–62]. Although many possible

Table 13.1 Clinical Manifestations of Erythema Infectiosum

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
7–11 days	Nonspecific symptoms of low-grade fever, mild coryza, and headache, lasting 2–3 days	Serology, particularly immunoglobulin M Detection of Bl9 DNA by polymerase chain reaction, etc	This prodromal stage corresponds with the period of viremia. The constitutional symptoms tend to be more severe in adults
9–13 days	Characteristic rash on the malar eminences, with fiery–red, edematous, confluent plaques that have a "slapped-cheek" appearance (Figs. 13–2 and 13–3). With the rash, some patients may also develop pharyngitis, malaise, myalgias, diarrhea, nausea, cough, and conjunctivitis	Viral isolation (difficult)	Relative circumoral pallor may occur during this stage of disease About 7% of children develop arthralgias following the malar rash, whereas 80% of adults have joint involvement The truncal exanthem can present in a variety of patterns, including morbilliform, confluent, circinate, and annular. Pruritus can occur in some patients, particularly adults
10–17 days	Facial rash fades, while pink macules or papules appear on the trunk, neck, and extensor surfaces (Fig 13–4). The palms and soles are only rarely affected. The rash on the trunk and extremities often develops central clearing, giving it a lacy or reticulate appearance (Figs. 13–5 and 13–6)		
15–26 days	Rash resolves after 5 days. Over the next several weeks, the rash may recur with certain stimuli, such as sunlight, exercise, temperature change, bathing, and emotional stress		

Table 13.2 Differential Diagnosis of Erythema Infectiosum

Rubella: The rash of rubella begins on the face and spreads inferiorly to the trunk and extremities. However, this exanthem progresses rapidly within 1 day, and fades over the next 2 days

Measles: The rash of measles begins on the forehead and spreads inferiorly, although at a slower pace. The rash reaches the feet by the third day, and lasts a total of 4–6 days. The lesions are more discrete papules. The facial exanthem is not limited to the malar eminences

Scarlet fever: Erythema infectiosum usually lacks pharyngitis, although this manifestation may be present. Culture for *Streptococcus pyogenes* can differentiate the two diseases. The rash of scarlet fever tends to be rough and accentuated in body folds

Drug reactions: May sometimes be difficult to differentiate and will require diagnostic testing for parvovirus B19

Erysipelas of the cheeks: This bacterial infection can also have erythematous, edematous, tender plaques involving the cheeks, but the area is typically hot to the touch and unilateral. This disease does not progress to a generalized cutaneous eruption

Collagen vascular disease (including juvenile rheumatoid arthritis and systemic lupus erythematosus): The arthralgias and malar rash of B19 infection can mimic various collagen vascular disorders. With acute B19 infection, the rheumatoid factor test can be positive, but joint destruction does not occur

viruses have been proposed as etiological agents [52,53,60–62], B19 is the only agent that has been sufficiently proved to cause the syndrome [59].

Although few details are known regarding PPGSS, this syndrome most commonly affects young adults and occurs most frequently during spring and summer. The characteristic clinical manifestations (Figs. 13.7 and 13.8) are described in Table 13.3. The disease course is generally self-limited, with no known sequelae. It appears that patients develop the mucocutaneous lesions while still viremic, which implies contagiousness [100]. Differential diagnoses are described in Table 13.4.

Complications

The most widely reported complications of parvovirus B19 infection include transient aplastic crisis in patients with chronic hemolytic anemia, prolonged anemia in immunocompromised persons, and fetal hydrops with intrauterine infection. In addition, cases of aseptic meningitis and encephalitis have been reported with this virus [63–67]. Rare complications that have been attributed to parvovirus B19 infection include hemophagocytic syndrome [68], myocarditis [69], vasculitis [70], and recurrent agranulocytosis [71]. However, these case reports have not yet been substantiated by clinical studies.

Transient aplastic crisis due to B19 infection has been reported in sickle cell anemia [7,72], hereditary spherocytosis [73], pyruvate kinase deficiency [74], heterozygous beta-thalassemia [75], and autoimmune hemolytic anemia [76]. In some patients, the aplasia has been the initial manifestation of the underlying hematological disease [75,76]. Usually after 1 week of fever and constitutional complaints, patients develop pallor, fatigue, and worsening anemia [77]. Hypoplasia or aplasia of the erythroid series is seen with bone marrow examination [77]. Although most patients recover within 1 week, transfusion may be necessary [77]. The aplasia can be fatal if untreated [77]. Although usually asymptomatic, transient aplastic crisis can also occur in healthy individuals [15].

Chronic anemia due to persistent lysis of red cell precursors is another complication of parvovirus infection seen in immunocompromised persons [15]. This prolonged anemia has been described in congenital immunodeficiencies [24], human immunodeficiency virus (HIV)-infected individuals [78], acute leukemia [79], and infancy without immunodeficiency [80]. Chronic anemia may fluctuate in intensity over time [99].

Maternal B19 infections usually do not adversely affect the fetus [99]. The most common complication of intrauterine infection with parvovirus B19 is nonimmune fetal hydrops (hydrops fetalis) [21]. The virus infects erythroid precursors with resultant hemolysis in the fetus leading to anemia, tissue anoxia, and high-output heart failure [21]. The overall risk of fetal death is unknown, but studies have suggested that the risk is less than 10% after maternal infection [21,22]. It has been postulated that infection between the 20th and 28th week of gestation is of the greatest



(a) (b)

Figure 13.7 (a,b) Papular-purpuric gloves-and-socks syndrome. Marked erythema is seen covering the distal hands and feet.



(a) (b)

Figure 13.8 (a,b) Papular-purpuric gloves-and-socks syndrome. Marked erythema is seen covering the distal hands and feet. (Photographs courtesy of Soni Carlton, M.D., Department of Dermatology, University of Texas Medical Branch at Galveston, Galveston, TX.)

threat to the fetus [81]. In a woman with unknown serological status, the risk of fetal death is thought to be less than 2.5% after a household exposure and less than 1.5% after a work exposure [21]. There is no evidence that the rate of congenital anomalies is greater in B19-infected fetuses compared with background rates [21].

Dermatopathology

The histopathological changes in the skin of patients with fifth disease have not been well described and are not considered diagnostic [82]. Histological examination of various other tissues has shown homogeneous intranuclear inclusions in erythroid precursor cells [25,83]. These inclusions demonstrate parvovirus-like particles with electron microscopy [82].

Laboratory Findings

In most persons with erythema infectiosum, all laboratory results are normal [30,33]. Some healthy individuals do develop reticulocytopenia, anemia, lymphopenia, neutropenia, and thrombocytopenia, usually without clinical symptoms [16]. Immunocompromised patients with transient aplastic crisis have reticulocytopenia and anemia, the severity of which depends on the degree of the underlying anemia [11]. Rheumatoid factor can be positive in some patients with parvovirus-associated arthritis

Table 13.3 Clinical Manifestations of Papular-Purpuric Gloves-and-Socks Syndrome

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
Overall time course of illness unknown	Mild transient prodromal symptoms in some patients, with low-grade fever, and less commonly fatigue, myalgias, anorexia, lymphadenopathy, and arthralgias Rapidly progressive symmetrical swelling and erythema of distal hands and feet, which is painful and significantly pruritic Confluent papular-purpuric lesions involving the dorsal and ventral aspects of the distal extremities. The eruption has distinct margins ending at the wrists and ankles Polymorphous enanthem of the hard and soft palate, buccal mucosa, and lips	Serology, particularly immunoglobulin Detection of B19 DNA by polymerase chain reaction, etc Viral isolation (difficult)	Less frequently involved areas include cheeks, elbows, knees, inner thighs, inguinal creases, buttocks, and glans penis Over 50% of patients also have diffuse erythema and edema of the lips, palatal vesicles, ulcerations, and/or petechiae, all of which are painful and pruritic
1–2 wk after onset of rash	Spontaneous resolution of entire syndrome		

[37,39], and the erythrocyte sedimentation rate is occasionally elevated [27].

Diagnosis

The diagnosis of fifth disease is usually based on the clinical findings of a slapped-cheek eruption and a lacy rash on the extremities. In difficult cases, the detection of B19 IgM has been the mainstay for diagnosis. Antibody testing is usually performed with RIA or enzyme-linked immunosorbent (ELISA) techniques. IgM antibody can be detected within a few days after the onset of illness up to 6 months [84–86]. IgG antibody can usually be found by the 7th day of infection and lasts for years, and is most useful to confirm past infection [84,85]. It is often difficult to find antibody to parvovirus in immunodeficient individuals [78], and these cases will require other diagnostic methods. Table 13.2 highlights possible differential diagnoses.

Viral isolation is limited to a few research laboratories because there is no animal model and no easy tissue culture system for the virus. Testing can be arranged through state health departments when parvovirus is suspected in patients with aplastic crisis, immunodeficiency, pregnancy, or fetal hydrops [10].

Antibodies to B19 virus can be found in the serum during viremia with RIA, CIE, or ELISA. Dot-blot hybridization and polymerase chain reaction (PCR) are the most specific techniques to enable identification of B19 DNA in serum, urine, respiratory secretions, and other tissues [87,88]. B19 DNA can be found with PCR for 2–4 months after the onset of illness and can be a complement to specific antibody testing [86,89].

Pregnant women with known exposure to B19 should have their serum monitored for IgM antibodies to the virus and for elevated levels of α-fetoprotein and human chorionic gonadotropin. Ultrasonic examinations of the fetus for hydrops should also be conducted [99].

Treatment and Prophylaxis

Erythema infectiosum usually does not require any treatment, and no specific therapy is available. Supportive treatment, if needed, is the only therapy indicated for most cases. Currently, no vaccine is available to prevent parvovirus B19 infection, although potential candidates are currently in development and clinical trials [90,91]. The B19 virus is easily spread in circumstances of close contact, such as day care facilities, schools, workplaces, and homes. Control measures directed toward individuals with erythema infectiosum are not effective, because persons are no longer infectious by the time they develop the clinical illness [11]. Patients with chronic anemia or aplastic crisis can be infectious for longer periods, and appropriate respiratory and contact isolation should be performed when these individuals are hospitalized [92]. Table 13.5 highlights symptomatic treatment of B19.

In immunodeficient anemic patients, B19 infections should be treated with commercial intravenous immunoglobulin, which is known to contain IgG antibodies to B19 [99,101,102].

Table 13.4 Differential Diagnosis of Papular-Purpuric Gloves and Socks Syndrome

Rocky Mountain spotted fever (and other rickettsial diseases): Rocky Mountain spotted fever is usually a more severe illness, with sudden onset of fever, significant headache, and myalgia. The characteristic exanthem begins on the wrists, forearms, and ankles, and later spreads to the palms and soles. The rash then progresses to involve the extremities, trunk, and face

Atypical measles: In atypical measles, the rash may appear first on the distal arms and legs rather than the face. However, the prodromal symptoms of measles are typically more prominent, and the exanthem of measles lasts only 4–6 days

Hand-foot-and-mouth disease: Low-grade fever, malaise and painful mucosal lesions occur with both diseases. However, the macules and papules that erupt on the distal extremities quickly progress to vesicles with hand-foot-and-mouth disease

Kawasaki disease: The erythema and edema usually begin on the palms and soles or the diaper area and spread to the trunk and extremities over the next 2 days. Also, this disease typically affects young children, and is uncommon after 8 years of age

Table 13.5 Treatment of Parvovirus B19 Infection

Symptom	Treatment
Malaise and fatigue	Bed rest
Pruritus	Starch baths or antipruritics as needed
Arthralgia and arthritis	Nonsteroidal anti-inflammatory medications
Chronic anemia	Intravenous immunoglobulin: administration of either 400 mg/kg for 5 or 10 days, or 1 g/kg for 3 days has been reportedly successful
Transient aplastic crisis	May require blood transfusion and oxygen therapy, if severe
Hydrops fetalis	Intrauterine blood transfusion has been successful in some cases, although treatment is controversial

Conclusion

Erythema infectiosum, with its distinct slapped-cheek eruption followed by a reticulate rash on the trunk and extremities, is the most characteristic presentation of human parvovirus infection. Whereas the disease has been known for a century, parvovirus B19 has only recently been identified as the etiological agent. B19 has now been associated with an increasing number of disorders including an acute polyarthropathy in adults, PPGSS, a wide spectrum of atypical cutaneous presentations, aplastic crisis, chronic anemia, and fetal hydrops. As techniques in identification and characterization of the virus improve, additional clinical syndromes associated with parvovirus B19 may be identified.

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14 Cutaneous Manifestations of HIV Infection

Melissa C Morgan, Brenda L Bartlett, Clay J Cockerell, and Philip R Cohen

Introduction

The diagnosis and management of human immunodefiency virus (HIV) infection has evolved dramatically since the initial recognition of the acquired immunodeficiency syndrome (AIDS) (Fig. 14.1) [1]. The use of combination drug regimens that include protease inhibitors (PIs) plus nucleoside (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (highly active antiretroviral therapy [HAART]) can profoundly suppress viral replication with associated increases of CD4-positive lymphocyte counts and partial immune reconstitution [2–5]. With use of these new drug regimens, a significant drop in HIV-associated morbidity and mortality has been noted [6].

This trend has also been observed with many of the cutaneous manifestations of HIV infection, which are now less recalcitrant to therapy and have fewer unusual presentations. Nevertheless, strains of HIV have been isolated that are resistant to HAART, and reservoirs of HIV have been found in patients receiving HAART who have undetectable viral titers [7,8]. Thus, HAART profoundly suppresses viral replication, but is not able to eliminate the virus completely. While the use of HAART has decreased the incidence of many opportunistic infections in HIV-positive patients, another dilemma has been introduced. A phenomenon in which a diffuse inflammatory reaction occurs as the immune system is reconstituted, known as immune reconstitution inflammatory syndrome (IRIS), often manifests as cutaneous disease [9].

Cutaneous disorders develop in over 90% of HIV-infected persons at some time during the course of the illness [10]. Table 14.1 lists these cutaneous manifestations and related disorders that may arise with HIV infection.

Pathogenesis of Human Immunodefiency Virus-related Skin Diseases

We have a better understanding of the pathogenesis of skin diseases in patients with HIV infection. It is apparent that the effects of HIV on the immune system are much more complex than simple depletion of CD4 lymphocytes. Subsets of T-helper cells, referred to as Th1 and Th2, have been found to play significant roles in HIV infection and AIDS. Th1 cells predominate in the normal state in immunocompetent individuals. Th1 lymphocytes promote cellular immunity and produce interleukin (IL)-2, IL-12, and interferon gamma to eradicate infection. Th2 lymphocytes promote humoral immunity and produce IL-4, IL-5, IL-10, and allergic responses. Th1 cells suppress Th2 cells, and vice versa.

Patients infected with HIV initially manifest a normal CD4 cell count, a low viral load, and a Th1-dominant immunological milieu. Later, with advanced disease, patients convert to a low CD4 cell count, a high viral load, and a Th2-dominant immune state. Thus, many of the unusual cutaneous manifestations of HIV infection may be a result of conversion to a Th2-predominant setting. The profound alteration of the immune system predisposes HIV-infected patients to opportunistic infections, malignancies, and neurologic disease [11]. Cutaneous manifestations of HIV infection are common and result from bacterial, fungal, viral, and noninfectious etiologies [11]. The dermatologic findings may be the same as those seen in immunocompetent individuals, but at increased prevalence or severity. Conversely, the findings may be otherwise rare due to opportunistic infection or nearly exclusive to HIV-infected individuals, such as oral hairy leukoplakia (OHL) and Kaposi's sarcoma (KS). Certain skin conditions are associated with more advanced HIV disease; the cutaneous manifestations of HIV infection more than double as the CD4 count reaches 100 mm^3 or less [12].

VIRAL INFECTIONS

Acute Exanthem of Human Immunodeficiency Virus Disease

Definition

The acute reaction accompanied by HIV seroconversion refers to an acute viral prodrome consisting of fever, fatigue, headache, lymphadenopathy, myalgia, nausea, vomiting or diarrhea accompanied by a cutaneous eruption [13,14]. Other systemic manifestations include pneumonitis, esophagitis, meningitis, abdominal pain, and melena. This syndrome typically occurs in the first few weeks following initial infection with HIV.

Epidemiology

The acute exanthem occurs in approximately two thirds of patients with acute HIV infection [15].

Pathogenesis

Following transmission, HIV disseminates systemically and massive viral replication occurs. As this occurs, CD4 cells are depleted and the immune system becomes hyperactivated. It has been proposed that systemic exposure to bacterial endotoxin following disruption of intestinal mucosa may be responsible for this state of immune hyperactivation. Enhanced immune activation in acute HIV is one of the strongest predictors of progression to AIDS [15].

Clinical Manifestations

The clinical manifestations of the acute exanthem of HIV disease are listed in Table 14.2. Patients are highly infectious during the symptomatic period due to increased plasma and genital HIV RNA concentrations. The cutaneous eruption appears as a macular or morbilliform rash, usually involving the trunk, and may resemble a drug hypersensitivity reaction or other viral exanthema, such as measles. The condition may also include urticaria, perlèche as well as palatal, esophageal, and anogenital ulcers.

Histopathology

Histological evaluation of skin biopsy samples taken from the morbilliform eruption demonstrates an infiltrate consisting primarily of lymphocytes with occasional plasma cells around

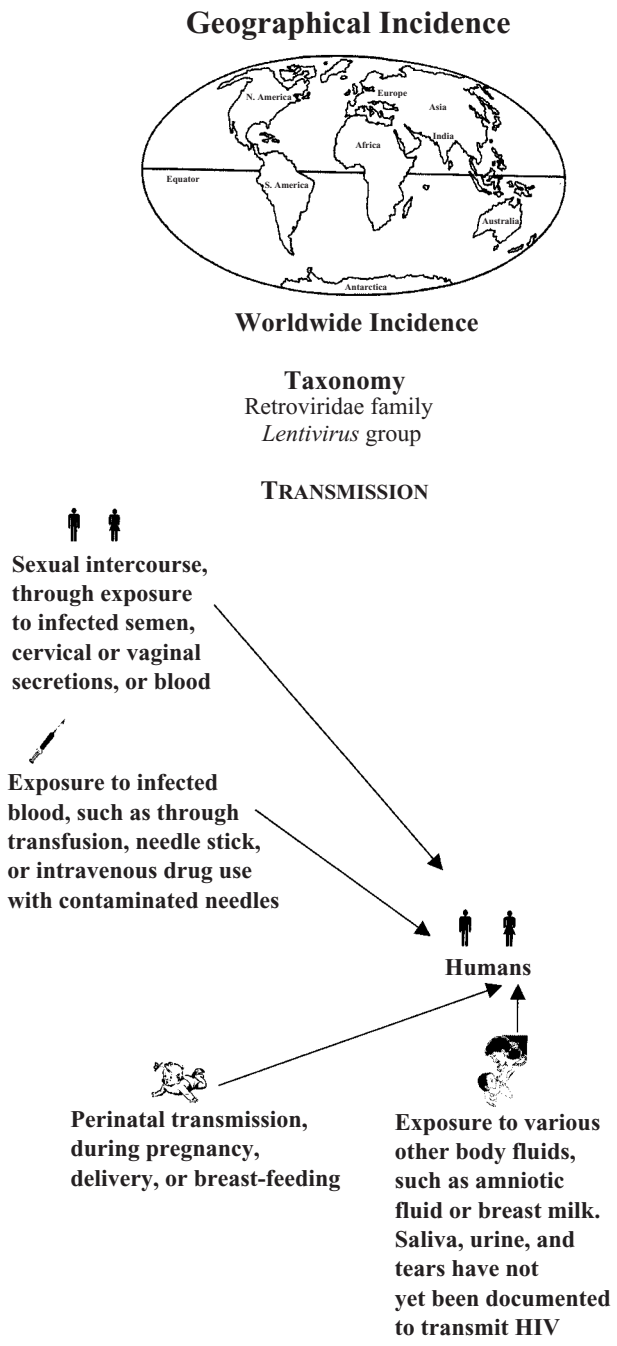


Figure 14.1 Incidence and transmission of HIV-1.

blood vessels of the superficial vascular plexus. There is also slight spongiosis, and occasional individually necrotic keratinocytes may be seen in the epidermis. HIV has not been isolated from the skin findings of primary infection [11].

Laboratory Findings

During acute HIV infection, enzyme immunoassays and Western blots are often negative. Plasma viral load assay has a high sensitivity; however, the p24 antigen assay has fewer false positives and is thus more cost effective in the diagnosis of acute HIV [14]. While viral RNA and CD4 levels are usually highest in the month after seroconversion, these levels are highly variable with acute HIV infection [11]. There is no other specific laboratory finding to demonstrate conclusive evidence of HIV infection.

Table 14.1 Cutaneous Manifestations and Disorders Seen in HIV Infected Individuals

Viral	**Noninfectious Skin Disorders**
Acute exanthem of HIV disease	Seborrheic dermatitis
Herpes simplex virus	Psoriasis
Varicella zoster virus	Reiter's syndrome
Cytomegalovirus	Eosinophilic pustular folliculitis
Oral hairy leukoplakia	Atopic dermatitis
Human papillomavirus	Prurigo nodularis
Molluscum contagiosum	Pityriasis rubra pilaris
Bacterial	Exfoliative erythroderma
Furuncles, abscesses, impetigo	Psoriasiform dermatitis of AIDS
Bacillary angiomatosis	Xerotic dermatitis
Mycobacterial infections	Erythema elevatum diutinum
Syphilis	Multiple dermatofibromas
Other venereal diseases, such as chancroid and granuloma inguinale	Papular urticaria, chronic urticaria
Ectoparasitic Infestations	Vasculitis and vascular-related diseases
Scabies	Chronic actinic dermatitis of HIV
Demodicidosis	Porphyria cutanea tarda
Acanthamebiasis	Actinically aggravated rosacea
Parasitic Diseases	Granuloma annulare
Pneumocystis jiroveci pneumonia	Cutaneous drug eruptions
Leishmaniasis	Hair and nail abnormalities
Toxoplasmosis	Vitiligo
Strongyloidiasis	Acquired ichthyosis
Fungal	**Neoplastic Disorders**
Candidiasis	Basal cell carcinoma
Coccidioidomycosis	Kaposi's sarcoma
Cryptococcosis	Lymphoreticular malignancies
Histoplasmosis	Anal intraepithelial neoplasia
Paracoccidioidomycosis	Cervical carcinoma
Sporotrichosis	Cloacogenic carcinoma
Penicilliosis	Bowenoid papulosis
	Epidermodysplasia verruciformis
	Dysplastic nevi

Diagnosis

The diagnosis of the acute HIV exanthem is based on the presence of a characteristic clinical picture in an individual with risk factors for the development of HIV infection. Screening questions may be used to identify high-risk individuals and determine whether serologic testing is indicated [11]. Blood tests that reveal positive anti-HIV antibody (by the enzyme-linked immunosorbent assay [ELISA] and Western blot assay), circulating p24 antigen, or HIV RNA in plasma (by polymerase chain reaction [PCR]) are confirmatory. Commonly, acute HIV infection is diagnosed by detectable HIV RNA in the setting of a negative or indeterminate HIV antibody test [16].

Treatment

Primary HIV infection generally requires only supportive care as it is usually self-limited. However, current guidelines suggest that antiretroviral agents may be of benefit to persons with recently acquired HIV. Immediate referral to an HIV specialist is recommended [17].

Human Herpesvirus Infections

Definition

Herpesvirus infection refers to infection by any of the eight different viruses of the herpesvirus family. Double-stranded DNA

Table 14.2 Clinical Manifestations of the Acute Exanthem of HIV Disease

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3 to 6 weeks	Malaise, followed by fever as high as 102°F. Within one or more days, night sweats, pharyngitis, fatigue, lymphadenopathy, and a fine morbilliform rash may develop	Demonstration of HIV p24antigen HIV seroconversion typically occurs within 6 weeks of the acute illness. ELISA or Western blot can be used to detect antibodies	The rash generally involves the trunk, chest, back and upper arms Associated mucosal involvement (oropharyngeal, esophageal, or genital) has also been reported
4–8 weeks	↓		
	Entire syndrome usually resolves,with complete recovery		

herpesviruses include: herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus type 8 (HHV-8).

Incidence

Herpesvirus infections are commonly encountered in patients infected with HIV and frequently have cutaneous manifestations. Depending upon the degree of immunodeficiency, the likelihood of a patient developing one of these eruptions can approach 95%, as in the case of CMV infection, when CD4+ counts fall below 100 cells/mm^3 [18]. The prevalence of infection with these viruses ranges from 20 to 40% with HSV to virtually 100% with VZV, CMV, and EBV [19]. While in healthy hosts these infections are usually self-limited, they can cause significant morbidity in immunocompromised persons.

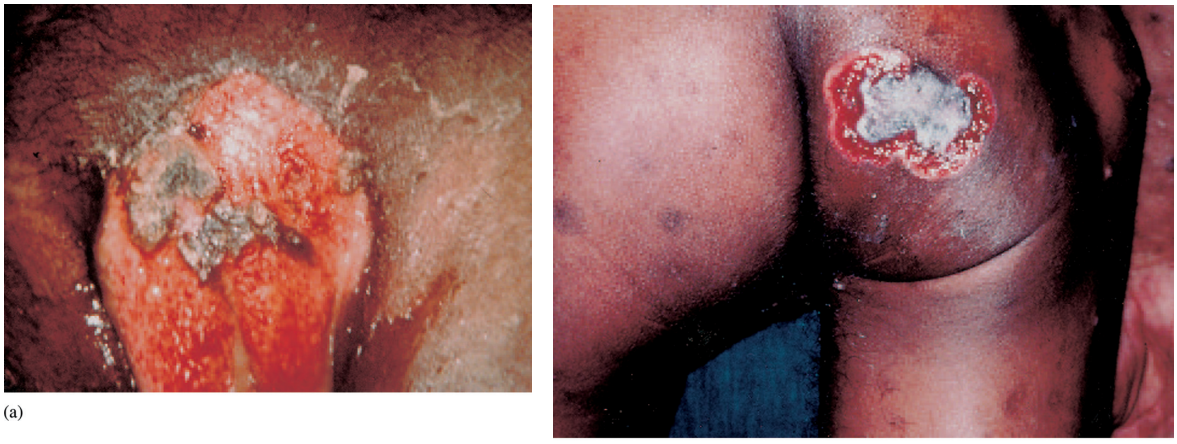
Pathogenesis

HSV-1 is the most common cause of oral herpetic infection, while HSV-2 is the most common etiological agent for anogenital herpes infections. However, crossover infection occurs, likely due to oro-genital sexual exposure [20]. Mucosal membrane contact facilitates transmission. It is well documented that genital ulcerations are risk factors for the acquisition of HIV infection [21]. Given that HSV-2 is the most common cause of genital ulcerations in the USA and Europe, HSV and HIV have important interactions that may have serious implications for patients with HIV infection. The transmission of HIV has been shown to be facilitated by HSV-2 infection [22] and is considered to be a risk factor for HIV infection [23]. HSV infection has been shown to activate latent HIV [24]. In vitro, HSV can potentiate HIV replication independent of HSV replication. This is caused by an early protein produced by HSV that results in enhanced HIV gene expression and replication. This is a result of intracellular transactivation of HIV [25].

Approximately 50% of HIV-1 seropositive patients develop herpes zoster (shingles). Patients treated with HAART whose CD4 lymphocyte counts rise from as low as 1–10 cells/mm^3 to between 200 and 500 cells/m^3 have a high risk of developing herpes zoster. The fact that herpes zoster develops preferentially when the CD4 lymphocyte number reaches a specific level suggests that a certain degree of immunity is required for this process. It may develop either when the CD4 cell number falls from a normal level or when it rises from a lower level [26]. HIV-infected individuals may experience repeated bouts of zoster, involvement of multiple dermatomes, and disseminated zoster in rare cases [12,27].

Clinical Manifestations

Herpes simplex infection. Oral, labial, and genital herpes simplex infections are commonly seen in immunocompetent patients and may be well localized in HIV-infected individuals who are relatively immunocompetent (see Chapter 4) (Figs. 14.2–14.7). Tender, painful ulcerative lesions of the penis, perianal area, and lip are characteristic, although other manifestations include perioral



(a) (b)

Figure 14.2 Vesicles and ulcers of herpes simplex infections in HIV-seropositive patients: (a) chronic perianal ulcer, (b) chronic perianal ulcer.



(c)



(e)



(d)



(f)



(g)

Figure 14.2 (continued). (c) vesicles of the hard and soft palate, and (d) labial eschars. (e) Widespread labial and perioral eschars, (f) zosteriform herpes simplex, (g) aphthae major: Herpetic ulcers should be differentiated from other ulcerative diseases, such as aphthae major. (Photographed and reprinted with permission, Medical Aspects of Human Sexuality, 22:93, 1988; photograph b courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India; photograph g courtesy of Siri Chiewchanvit, M.D., Chiang Mai, Thailand.)



Figure 14.3 This chronic HSV infection had been under treatment with acyclovir at a dosage of 800 mg orally five times a day for 2 months at the time this photograph was taken. The condition responded to treatment with intravenous foscarnet.

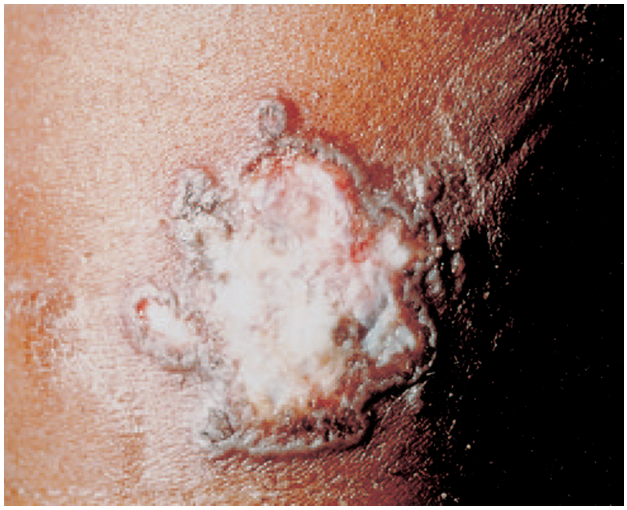


Figure 14.6 Occasionally, HSV infections may manifest as verrucous plaques such as seen here. Usually, numerous virally infected multinucleated epithelial giant cells are seen on microscopic examination of Tzanck preparations. In many cases, the causative virus is shown to be VZV.



Figure 14.4 Nondescript eschars were the manifestation of HSV in this severely immunocompromised host, who died the day after this photograph.

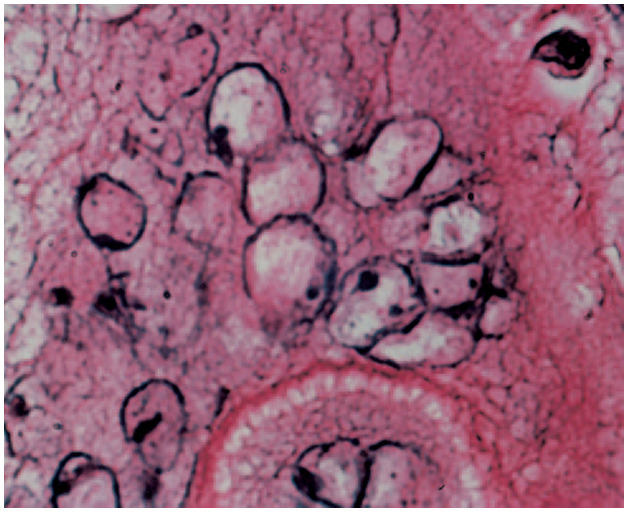


Figure 14.7 Microscopic appearance of multinucleated epithelial giant cells of HSV infection. Identical changes are seen in herpes zoster. (Hematoxylin and eosin, original magnification 800.)

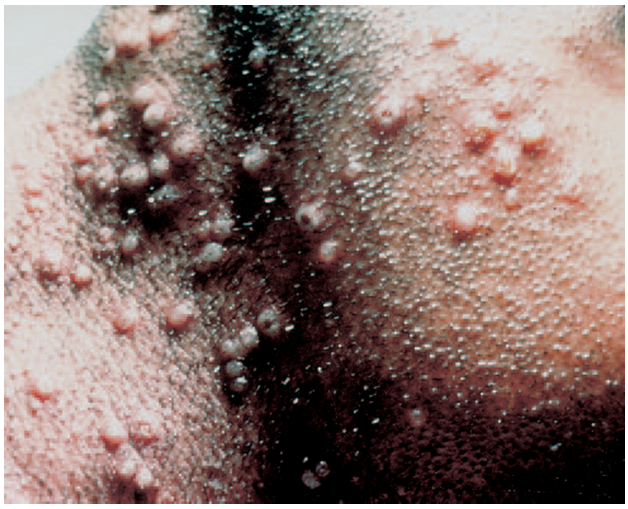
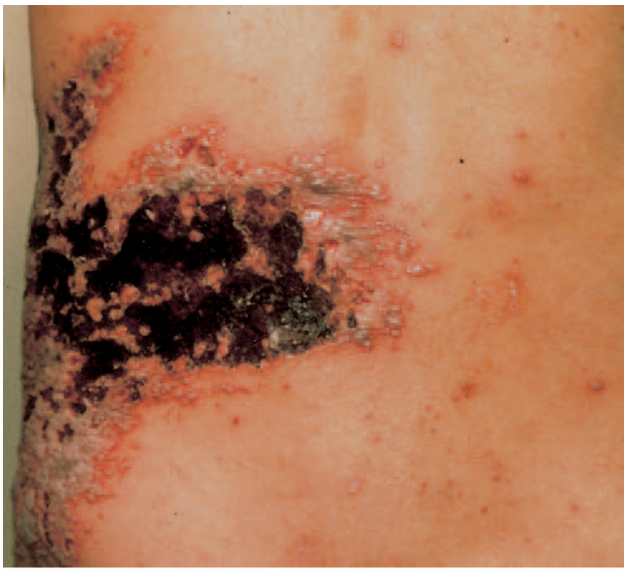


Figure 14.5 Kaposi's varicelliform eruption in an HIV-infected patient. (Reprinted with permission, Arch Int Med 151: 1295–1303, 1991.)

lesions and chronic ulcerative lesions on the glabrous skin such as that of the digits. Lesions that are untreated may continue to enlarge dramatically and become deeply situated and extremely painful. Other lesions may appear verrucous and hyperplastic. Epithelial sites other than mucocutaneous ones may be involved, including the cornea, tracheobronchial tree, and esophagus, as well as visceral sites such as the lung, pericardium, liver, and brain [28].

Varicella zoster virus. Varicella zoster, like other cutaneous infections in HIV-infected hosts, is thought by many to be predictive of progression from HIV infection to AIDS, having been associated with progression in 23% of HIV patients at 2 years, 46% at 4 years, and 73% at 6 years [29]. The virus exists in a dormant state in a dorsal root ganglion that becomes infected during prior varicella infection (see Chapter 5). With activation, the virus progresses down nerves of a solitary dermatome, leading to the characteristic zosteriform distribution of painful tense vesicles in



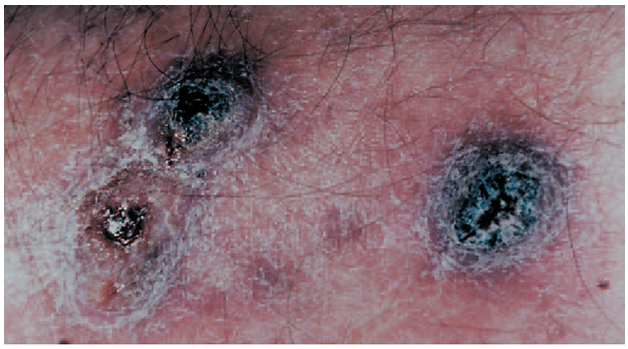
(a)



(b)



(c)



(d)



(e)

Figure 14.8 Herpes zoster may be an early manifestation of HIV infection or it may be seen in advanced AIDS, as depicted in (a). Herpes zoster in HIV-seropositive persons may be very aggressive and result in (b) loss of vision (V-1distribution), or (c) Loss of teeth (V-2 distribution). Herpes zoster may produce (d) verrucous nodules, or (e) multidermatomal distribution, both usually seen only in immunocompromised persons, who have acyclovir-resistant herpes zoster. (Photograph a reprinted with permission, Clin Exp Dermatol 14:273, 1989; photographs b, c, and e courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India; photograph d courtesy of Jeffrey Callen, M.D., Division of Dermatology, Department of Internal Medicine, University of Louisville School of Medicine, Louisville, KY.)

the skin (Figs. 14.8 and 14.9). If an HIV-infected patient is exposed to VZV for the first time, careful consideration should be given to the use of varicella zoster immunoglobulin or the administration of prophylactic acyclovir, valacyclovir, or famciclovir.

Complications, such as a second episode of varicella, repeat zoster infections, and multidermatomal forms, may occur. Varicella zoster may develop in HIV-infected children shortly after a course of primary varicella [30], and recurrent episodes of zoster

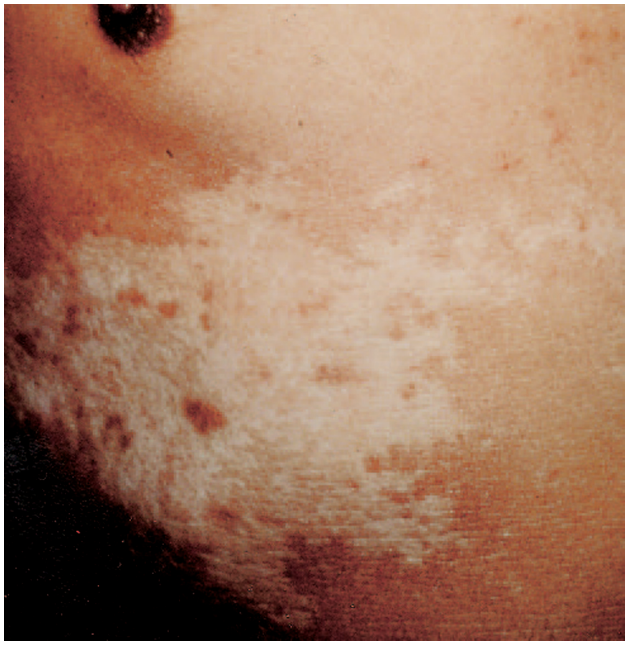


Figure 14.9 Post-inflammatory hypopigmentation, scarring, and pain were complications of a severe episode of zoster in this immunocompromised host.

have been documented in 5–23% of HIV-infected hosts, usually in those with advanced immunodeficiency syndrome. Blisters over large areas of the skin may develop concomitant with the characteristic zosteriform group of vesicles [27]. Crusted, punched-out ulcerations that leave painful atrophic scars may also be associated with postherpetic neuralgia [31]. Generally, these lesions develop a thick overlying eschar and are remarkable for the lack of surrounding erythema. They occur most commonly on the buttocks and lower extremities, but may be disseminated and are often resistant to therapy with acyclovir [32].

Cytomegalovirus. Up to 90% of patients with AIDS may develop acute active CMV infection at some point during their illness. CMV is the most common cause of serious opportunistic viral infection in AIDS [33]. As with other viral infections, HAART diminishes the frequency of this condition. Clinical manifestations may include ulcerations, keratotic verrucous lesions, palpable purpuric papules, and diffuse ulcerations (Fig. 14.10) (see Chapter 7). Vesicular, bullous, and generalized morbilliform eruptions as well as hyperpigmented indurated plaques and a generalized bullous toxic epidermal necrolysis-like eruption may also occur.

Prior to HAART, 50% of all AIDS patients had CMV viremia with clinical manifestations of retinitis and gastroenteritis. Serious CMV retinitis may occur in 5–10% of patients and is found in 30% of AIDS patients at autopsy. Esophagitis and colitis as well as proctocolitis may develop in 5–10%.

Oral hairy leukoplakia (Epstein-Barr virus). EBV selectively infects cells of the B-lymphocyte lineage and certain types of squamous epithelia (see Chapter 6). The majority of adults harbor a latent phase of EBV. Primary EBV infection is manifested as infectious mononucleosis. With advanced immunodeficiency in HIV-infected patients, EBV leads to OHL, Burkitt's lymphoma, or EBV-associated large-cell lymphoma.



(a)



(b)

Figure 14.10 (a, b) Extensive perianal erosions and ulcerations were caused by CMV in these patients. (Photograph b courtesy of Mario Marini, M.D., Department of Dermatology, University of Buenos Aires, Argentina.)

OHL in the immunocompromised patient appears as one or more whitish plaques usually found on the lateral margins of the tongue (Fig. 14.11). OHL has also been correlated with progression from HIV infection to AIDS, as 48% of patients with



Figure 14.11 Whitish verrucous plaques of the sides of the tongue most commonly represent oral hairy leukoplakia, an EBV–induced lesion. (Reprinted with permission, Cutis 40: 406–409, 1987.)

OHL develop AIDS by 16 months and 83% by 31 months [34]. OHL is one of the mucocutaneous disorders that has been noted to regress with HAART.

Histopathology of Herpes Simplex Virus, Varicella Zoster Virus, and Cytomegalovirus

Herpes simplex and VZV infections may manifest as an intraepidermal acantholytic vesicular dermatitis associated with characteristic cytopathic effects in epithelial cells (see Chapters 4 and 5). In severely immunocompromised patients who develop infection with either HSV or VZV, there is extensive cytonecrosis of the epidermis associated with abundant viral infection of keratinocytes [35]. Often, a complete syncytium of infected keratinocytes can be associated with involvement of follicles and adnexal structures. In some lesions, there may be extensive ulceration so that the herpetically infected cells cannot be visualized. In these cases, special immunoperoxidase stains and DNA probes may be useful in detecting viral antigens that may not be visible on routine microscopic examination. Histologically, skin lesions caused by both viruses appear identical.

CMV characteristically infects fibroblasts and endothelial cells in the dermis associated with overlying ulceration (see Chapter 7). Mixed viral infections are not uncommon, and both HSV and CMV may occur within the same section.

OHL is manifest by marked epithelial hyperplasia with a verrucous corrugated appearance [36] (see Chapter 6). Electron microscopy as well as DNA in situ hybridization indicates viral particles in the epithelium, especially in the upper rather than lower portions.

Laboratory Findings

In general, no characteristic laboratory findings are associated with these infections, although patients with primary EBV infection show B-cell proliferation and exaggerated T-cell responses. CD4+ cell counts less than 200 cells/ mm^3 are typical. Zoster and OHL may occur in patients who are more immunocompetent.

Diagnosis

Diagnosis is made on the basis of culture, smears, biopsy, and clinical appearance of lesions (see Chapters 4–7).

Treatment

See Chapters 4–7 for the treatment of human herpesvirus infections. On occasion, patients with seemingly resistant herpes zoster or simplex may be suffering from atrophic gastritis that prevents absorption of acyclovir. A change to intravenous administration of acyclovir or to oral valacyclovir or famciclovir may be effective.

If an HIV-infected patient is exposed to VZV for the first time, either varicella zoster immunoglobulin and/or prophylactic acyclovir, famciclovir, or valacyclovir, should be administered. Administration of the varicella zoster virus vaccine should be considered for HIV-infected individuals who are still relatively immunocompetent and have not had previous infection with this virus.

Human Papillomavirus Infections

Definition

Human papillomavirus (HPV) infection refers to infections with viruses of the family of Papovaviridae (refer to Chapter 12).

Incidence

In HIV-infected individuals, coinfection with HPV is very prevalent. In one study, anogenital warts were demonstrated in 20% of HIV-infected homosexual men and 27% of homosexual men with AIDS. Using more sensitive studies, 48% of HIV-negative homosexual men and 54% of homosexual men with AIDS were shown to have evidence of HPV infection [37]. HPV types 6 and 11 are the most common viral isolates from anogenital condylomata, although oncogenic HPV types such as 16 and 18 are also often found in histologically benign lesions.

Pathogenesis

HPV has a tropism for squamous epithelium and enters the cells of the basal cell layer probably through microscopic abrasions (see Chapter 12).

In addition to causing verrucae and papilloma, HPV infection may cause development of carcinoma, especially in patients with depressed cell-mediated immunity [38,39]. Furthermore, HIV tat protein transactivates HPV, leading to increased HPV expression.

Clinical Manifestations of Human Papillomavirus Infection

Patients with HIV infection, especially those who are most immunocompromised, may have multiple verrucae vulgares, especially in periungual locations (Figs. 14.12 and 14.13). Multiple plantar warts, including mosaic warts, may cause pain on walking. Extensive flat and filiform warts on the bearded area of the face manifest by small verrucous papules are also seen in HIV-infected individuals and may be the first sign of HIV infection.

Epidermodysplasia verruciformis has been reported in patients with HIV infection and consists of a widespread papular eruption of reddish to skin-colored, flat, wart-like lesions mostly involving the sun-exposed areas of the skin (Fig. 14.14) [40].

Verrucous carcinoma, manifest as a large verrucous plaque or tumor, most commonly in the perianal location, has also been reported in patients with HIV infection.



Figure 14.12 Lingual condyloma was an early sign of HIV infection in this patient. (Reprinted with permission, Arch Int Med 151:1295–1303, 1991.)

Histopathology
See Chapter 12.

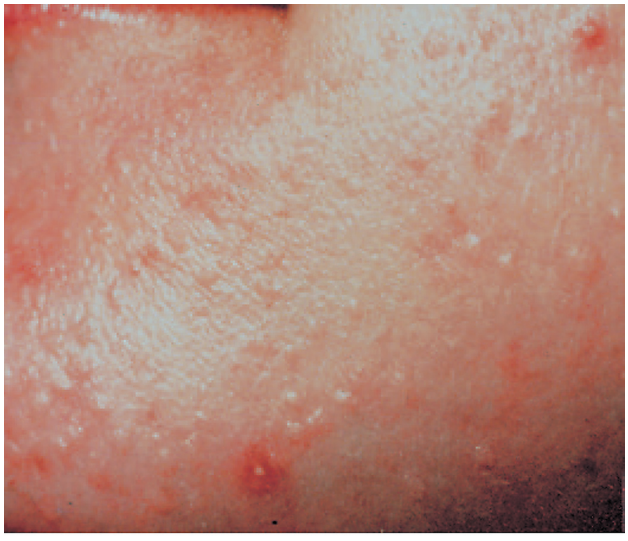
Laboratory Findings
In general, routine laboratory findings are noncontributory in these cases, although patients with extensive disease are often found to have CD4+ cell numbers lower than 500 cells/mm^3 [41].

Diagnosis
The diagnosis of clinical HPV-induced lesions is based on clinical features in the context of histopathological findings. It is important to perform biopsies because any case could conceivably represent manifestations of a malignant HPV-induced condition (see Chapter 12).

Treatment
Treatment of HPV-induced lesions revolves around measures that result in diminution of clinical lesions, destruction of premalignant or malignant lesions, reduction of symptoms, and reduction of transmission to uninfected individuals (see Chapter 12). Successful therapy depends on the ability of the host's immune status to keep viral infection in check. Frequent recurrences are probably a consequence of reactivation of latent HPV infection, and therapy must often be extended to include normal-appearing tissue. Unfortunately, no treatment has been shown to eradicate HPV entirely.

Poxvirus Infections
Definition
Poxviruses are the largest of the animal viruses and, of these, molluscum contagiosum and vaccinia have been reported to infect HIV-seropositive patients. These are complex DNA viruses that replicate in the cytoplasm and are especially adapted to epidermal cells (see Chapter 3) [42,43].

Incidence
Most patients who develop severe molluscum contagiosum have CD4+ cell counts of <200–250 cells/mm^3. Vaccinia virus infection occurs sporadically in patients who have been occupationally exposed or are accidental hosts, such as a military recruit vaccinated for smallpox [42].



(a)



(b)

Figure 14.13 Multiple verrucae planae (a) and extensive perioral and angular HPV infection (b) were signs of immunocompromise in these patients. (Photograph (a) reprinted with permission, Prim Care 16:421–444, 1989.)



Figure 14.14 Epidermodysplasia verruciformis in a patient with HIV infection. This was severely pruritic and initially thought to represent a drug eruption.



Figure 14.15 Extensive giant molluscum contagiosum of the face in patients with severe immunocompromise.

Pathogenesis

Molluscum contagiosum is spread by direct contact with epidermal epithelium. The virus replicates in the cytoplasm and produces molluscum or Henderson-Paterson bodies that fill the cytoplasm. The pathogenesis of molluscum contagiosum infection is thought to be related to an epidermal growth factor-polypeptide induced by infection with the virus [44] (see Chapter 3).

Vaccinia causes a similar infection, but rather than the nucleus being filled with molluscum bodies, prominent vacuolar or ballooning degeneration develops within cells. There is prominent inflammation and scarring.

Clinical Manifestations

Molluscum contagiosum infection is characterized by dome-shaped, umbilicated, translucent 2–4-mm papules that develop on any part of the body, but preferentially affect the genital areas and the face in AIDS patients, especially around the eyes (Figs. 14.15 and 14.16). Lesions are numerous and may become quite large in immunocompromised individuals. Individual lesions have a tendency to affect follicles and are therefore umbilicated with a central keratinous plug. In some cases, molluscum dermatitis occurs [43]. In HIV-infected patients, however, lesions may develop rapidly, i.e., over 2–4 weeks, and may persist for months to years. When HAART therapy is initiated and the CD4 lymphocyte count rises, lesions may undergo regression. Furthermore, the number of patients with multiple giant lesions is decreasing.

Vaccinia lesions are characterized by tense umbilicated vesicles and pustules that are similar to those described in other patients with widespread disseminated vaccinia infection (Fig. 14.17). Patients are usually clinically ill with fever and acute toxic symptoms associated with viremia.

Histopathology

See Chapter 3.

Laboratory Findings

Patients with HIV infection generally have CD4+ counts below 250 cells/mm^3.

Diagnosis

Application of a small amount of liquid nitrogen or ethyl chloride will highlight the central umbilication of individual lesions, a finding that strongly suggests the diagnosis. In most cases, the diagnosis is readily established on the basis of clinical appearance and/or by histological evaluation of a skin biopsy specimen or a smear of contents of a papule. In AIDS patients, lesions may become very large and resemble cutaneous tumors [45]. Vaccinia is diagnosed on the basis of the clinical appearance of the eruption in the context of a history of exposure to the causative agent.

Treatment

Treatment of molluscum contagiosum generally employs destructive measures (see Chapter 3). Cryotherapy may induce dyspigmentation in dark-skinned individuals. Imiquimod and cidofovir have also been observed to be effective.

Vaccinia infection may respond to treatment with cidofovir. Unfortunately, the condition is associated with a high morbidity rate.

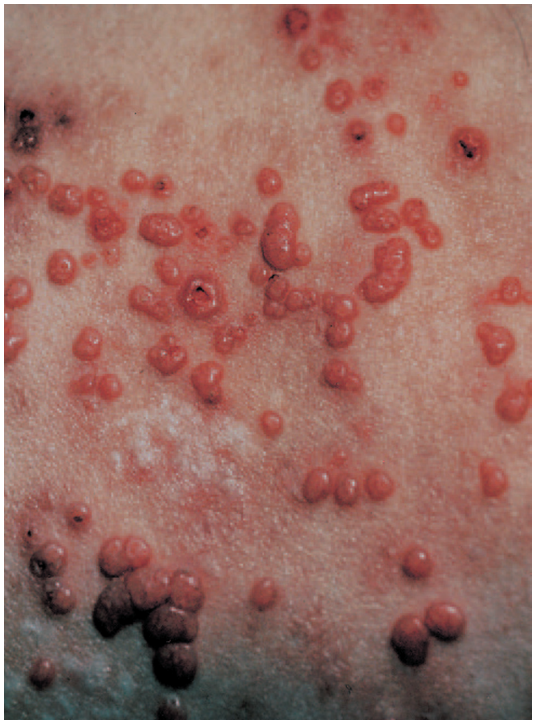


Figure 14.16 Extensive truncal molluscum papules. Lesions such as this must be differentiated from papules of disseminated cryptococcosis.

Other Viral Infections

Several other viral infections have been reported to develop with increased frequency in patients with HIV infection. Parvovirus B19, which is the cause of erythema infectiosum (fifth disease), may cause an exanthem in patients with HIV infection, as well as fatal aplastic anemia [46]. The major target of the human parvovirus is the bone marrow erythroid progenitor cell. The exanthem and polyarthralgia that result in fifth disease are a result of antigen–antibody immune complexes and develop as bone marrow recovery is under way. In patients with immune deficits, however, persistent infection causing severe chronic anemia has been reported. Enteroviruses may also lead to florid morbilliform or vesicular eruptions.



Figure 14.17 Eczema vaccinatum in an immunocompromised patient who received a smallpox vaccine for foreign travel.

Measles has been reported sporadically in patients with HIV infection with a variable course (see Chapter 17). Atypical-appearing exanthems associated with pneumonitis and encephalitis as well as more characteristic-appearing eruptions have been observed. Treatment consists of intravenous ribavirin and gamma globulin [47].

Bacterial Infections

Definition

Bacterial folliculitis, impetigo, bacillary epithelioid angiomatosis, botryomycosis, *Pseudomonas* infections, streptococcal axillary lymphadenitis, mycobacterial infections, syphilis, and other venereal diseases are some of the bacterial infections that may develop in patients with HIV infection. These disorders may be localized or widespread, involving many organs. There may be a number of different clinical morphological findings, many of which may be nondescript. For this reason, it is important that skin biopsies and cultures be performed in any immunocompromised patient in whom a skin lesion develops that could represent a manifestation of a serious bacterial infectious disease.

Epidemiology

Most banal bacterial infections, such as folliculitis and impetigo, are caused by *Staphylococcus* and *Streptococcus*, organisms commonly encountered in immunocompetent hosts. *Staphylococcus aureus* is the most common cutaneous and systemic bacterial pathogen in HIV-infected adults. The initial site of colonization with *S. aureus* is the nares. A nasal carriage rate of approximately 50% has been observed in HIV-infected hosts, twice that of HIV-seronegative homosexual and heterosexual men [48]. Multiple breaks in the skin from needle sticks, dermatoses, and immunodeficiency are risk factors for the development of *S. aureus* infection. Up to 83% of patients with AIDS may suffer from some form of *S. aureus* infection at some point. Infection with *Pseudomonas* sp. is also seen with some frequency in patients who are HIV infected, and up to 8% of all cases of bacteremia in patients with AIDS are caused by these organisms. Aggressive *Haemophilus influenzae* infection of the head and neck has also been observed [49].

Virtually any of the mycobacteria may induce skin lesions in up to 10% of patients with systemic mycobacterial infections. Extrapulmonary disease is commonly found in patients with AIDS. *Mycobacterium avium-intracellulare* occurs in the skin of patients with blood cultures positive for the same organism, and *M. haemophilum* causes skin lesions [50,51]. This is of importance as the latter organism is more difficult to culture than other mycobacteria.

Syphilis is common in patients with HIV infection, and of all reported cases of syphilis, 25% develop in HIV-infected hosts [52]. Lymphogranuloma venereum, chancroid, granuloma inguinale, and *Neisseria gonorrhoeae* infection may develop and be more severe as a consequence of the immunocompromised state.

Pathogenesis

In addition to low CD4 cell counts, dysfunctions in the B-cell arm of the immune response as well as with neutrophils and

macrophages have been described in HIV patients with bacterial infections. HIV-infected patients may be neutropenic because of myelosuppression from medications and bone marrow infections, such as those caused by *M. avium intracellulare*. Furthermore, patients in later stages of HIV infection suffer from defective neutrophil chemotaxis, as well as a decrease in the late stage oxidative burst with consequent diminished killing of *S. aureus*. Indwelling venous catheters that are commonly placed in patients with HIV infection serve as portals of entry and are a risk for systemic infection with bacteria as well as other pathogens. Elevated serum IgE levels are also associated with *S. aureus* infections and may play a role in the alteration of the immune system, leading to defective eradication of organisms.

A predisposition to the development of colonization and infection by bacterial microorganisms also relates to recrudescence or reactivation of latent infections. *Myobacterium tuberculosis* frequently produces infection in HIV-seropositive patients, probably as a result of reinfection or reactivation of pre-existing foci. An increasing number of infections with strains resistant to antituberculous medications have recently been reported, often with devastating consequences. Syphilis, too, has been shown to be associated with reactivation of presumed previously killed organisms in patients having prior disease treated with recommended antibiotic regimens.

Bacillary angiomatosis is a bacterial infection caused by organisms of the genus *Bartonella*, specifically *B. quintana*, *B. henselae*, and *B. elizabethae* [53]. The pathogenesis is not completely known, but it has been postulated that a vasoproliferative factor is either produced by the bacterium itself or is induced to be formed by the host as a consequence of bacterial infection.

Clinical Manifestations

In HIV-seropositive patients, mucocutaneous manifestations of bacterial infections may manifest multiple different morphological features. Pustules, ulcers, cellulitis, nodules, papules, and panniculitis may all be encountered. Clinical appearances may be nondescript and may mimic other disorders. Table 14.3 suggests treatments for bacterial infections associated with HIV infection.

Folliculitis, Abscesses, Furuncles, Impetigo and Related Infections

Folliculitis generally manifests as widely distributed acneiform papules and pustules (Fig. 14.18). Although in most cases infections are confined to the skin, occasionally sepsis may develop. In some cases, the bacterial density may lead to botryomycosis or ecthyma. These disorders appear as nondescript verrucous papules or as necrotizing ulcerations, respectively. Soft-tissue and deep-seated bacterial infections, such as cellulitis, pyomyositis, deep soft-tissue abscesses, and necrotizing fasciitis, may also develop in HIV-infected hosts. These are generally manifest as diffuse, red, warm, tender areas in the skin. Extreme toxemia, associated with deeper infections, requires early recognition. Streptococcal axillary lymphadenitis presents as diffuse, usually bilateral painful swelling of lymph nodes in the axillae (Fig. 14.19) [54]. When the nodes are incised, copious pustular drainage is noted. Impetigo is manifested as localized or widespread edematous crusted areas of the skin associated with yellowish surface crusts. It is seen more often in the axillary, inguinal, and other intertriginous locations in patients with HIV infection. Painful red macules may develop superficial vesicles that rupture and ooze serious and purulent fluid that contains potentially infective HIV. A characteristic honey-colored surface crust usually forms, and satellite lesions may develop. In some cases, intact bullae and pustules may be observed.

Botryomycosis is most commonly caused by *S. aureus* and represents a manifestation of the extension of staphylococcal folliculitis with the formation of bacterial colonies in the dermis. Clinically, this is often manifested as a nondescript papule or plaque in the skin that may be surrounded by pustules on the trunk,

Table 14.3 Treatment of Bacterial Infections

Symptom	Treatment
Pyogenic bacterial infections	Oral dicloxacillin, cephalexin, or ciprofloxacin
	Chlorhexidine gluconate washes daily for 1 week, then every 1–2 weeks for 2–3 months. Application into the nostrils of topical antibiotics (e.g., polymyxin B sulfate, bacitracin, or mupirocin ointment) twice daily for 10–14 days may help to eradicate bacterial colonization
Bacillary angiomatosis	Erythromycin ethyl succinate, orally, 500 mg four times daily for 4 weeks to 6 months
	Doxycycline hydrochloride, 100 mg twice daily, Rifampin, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin, azithromycin, rozithromycin, and norfloxacin
	Trimethoprim-sulfamethoxazole daily can prevent relapse
Atypical mycobacterial infections	Clarithromycin, ansamycin, clofazimine, minocycline, and trimethoprim-sulfamethoxazole
	It is important to culture the organism to determine drug sensitivities for specific antibiotic treatment
Syphilis	Primary syphilis: penicillin G benzathine 2.4 million units injected intramuscularly once each week for up to three doses
	Secondary syphilis (in the absence of neurosyphilis): penicillin G benzathine 2.4 million units injected intramuscularly once each week for 3–4 weeks
	Tertiary syphilis and neurosyphilis: intravenous aqueous penicillin G, 3 million units every 4 hours for 10 days, followed by penicillin G benzathine 2.4 million units intramuscularly once each week for 3 more weeks
Chancroid	Erythromycin (oral), 500 mg four times daily for 7 days, or a single intramuscular injection of ceftriaxone 250 mg
Lymphogranuloma venereum	Doxycycline, 100 mg orally twice daily for 7 days
	Ofloxacin, 300 mg twice daily for 7 days
	Erythromycin, 500 mg 4 times daily for 7 days
Granuloma inguinale	Erythromycin or trimethoprim-sulfamethoxazole
Gonorrhea	Penicillin, spectinomycin, or ceftriaxone



Figure 14.18 Widespread furunculosis and bacterial folliculitis (a, b) may be an early sign of HIV infection (c) ecthyma (a deep-seated infection that may be caused by either S. aureus or P. aeruginosa) may become very aggressive and progress to (d) pyomyositis. (Photographs c, d courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

neck, or extremities. Nonmenstrual toxic shock syndrome, most commonly associated with the use of nasal packing, infected wounds, or surgical sites, has also been reported in patients with advanced HIV disease. Patients have fever, shock, diffuse cutaneous erythema, and conjunctival injection with subsequent desquamation. Recurrent episodes of pyoderma-associated fever, hypotension, and erythroderma may also supervene. This is caused by a toxin-producing variant of *S. aureus*. A similar eruption has been reported caused by *Streptococcus pyogenes*, known as the toxic strep syndrome.



Figure 14.19 Streptococcal axillary lymphadenitis in an HIV infected immunocompromised host.



Figure 14.20 A case of a mixed infection with HSV and Pseudomonas in a patient with AIDS. (Reprinted with permission, Cutis 40:406–409, 1987.)

Folliculitis, otitis externa, and ecthyma gangrenosum (both primary and secondary to septicemia) may be caused by *Pseudomonas aeruginosa* or *P. cepacia* and may be acquired from hot tub use [55]. When caused by *Pseudomonas* sp., the clinical manifestations of these disorders appear similar to those caused by other pyogenic bacteria, namely, firm, erythematous nodules as papulopustules with necrosis; therefore, cultures are essential in making this distinction.

A condition with features similar to Job's syndrome is associated with recurrent staphylococcal abscesses, markedly increased serum IgE levels, and diminished polymorphonuclear leukocyte chemotaxis. Chronic diffuse dermatitis associated with elevated serum IgE levels and eosinophilia associated with recurrent *S. aureus* and *Candida albicans* infection have also been observed [56].

H. influenzae cellulitis manifest as diffuse erythema, and edema, often on the head and neck area, may develop in patients with HIV infection [49]. This infection may be aggressive, with a greater tendency to become disseminated or to involve deeper soft tissues and vital structures. Infections with *Streptomyces*, *Nocardia*, and *Actinomyces* may manifest as thickened verrucous plaques and chronic draining sinuses [57]. Deep-seated abscesses caused by *Rhodococcus equi* have been observed on multiple occasions [58]. *Corynebacterium diphtheriae* may cause bullous lesions that ulcerate and became covered with a greyish pseudomembrane [59]. Infections caused by "diphtheroids" may lead to pustular, folliculitis-like lesions, while salmonellosis may be associated with an eruption of faint pink macules on the skin. Multiple infectious agents may be found within a given skin lesion in patients with HIV infection and AIDS (Fig. 14.20). Mixed infections with pyogenic bacteria and acid-fast bacilli as well as viruses and fungi have been reported.

Bacillary Angiomatosis

Pinpoint reddish to purple papules are the earliest lesions of bacillary angiomatosis (Figs. 14.21 and 14.22). These may assume an appearance similar to that of pyogenic granulomas and are seen in two thirds of patients with cutaneous disease [60]. They range in number from one to several thousand and in size from 1 mm to several centimeters. Lesions may ulcerate and/or be covered by a crust. The second most common skin lesion is the subcutaneous nodule. These may be located deep in the subcutis and involve soft tissue and bone or occur as deep-seated skeletal muscle pyomyositis. When bone is involved, lesions are generally osteolytic in nature. Nondescript crusted ulcerations, plaques, and cellulitis may also be seen.

Viscera may be involved either as disseminated vascular lesions or as bacillary peliosis hepatitis of the liver. Although virtually every organ system may be affected, the liver and spleen are the most common sites of involvement. Liver disease may develop in patients without skin lesions and is usually evidenced by elevated levels of circulating liver enzymes. Fever, weight loss, and night sweats are common. These symptoms usually resolve with institution of antibiotic therapy.

Mycobacterial Infections

Mycobacteria, especially *M. avium-intracellulare* and *M. haemophilum*, may induce skin lesions in up to 10% of patients with systemic mycobacterial infections [50,51]. Other mycobacteria



Figure 14.21 Bacillary angiomatosis, localized "zosteriform" type in an immunocompetent host. (Reprinted with permission, Arch Dermatol 126:787–790, 1990.)



(a) (b) (c)

Figure 14.22 Bacillary angiomatosis, widespread nodules (a), deep dermal and osseous lesions (b), and crusted nodules (c) demonstrate that, in some cases, the characteristic vascular appearance of lesions may not be present. (Photograph b courtesy of Timothy Berger, M.D., Department of Dermatology, UC San Francisco, San Francisco, CA; photograph c courtesy of Walmar Roncalli P. DeOliveira, M.D., São Paulo, Brazil.)

that may induce skin infections in HIV-infected patients include *M. marinum*, *M. chelonae*, *M. bovis* following bacille calmettie guerin (BCG) vaccination, and *M. thermoresistible. M. marinum* may cause classic swimming-pool granulomas that manifest as verrucous nodules in a sporotrichoid distribution. Most reported infections behave in a relatively indolent fashion, demonstrating good response to appropriate antibiotic therapy. *M. haemophilum* is a ubiquitous bacterium that may cause cutaneous infections in AIDS patients. *M. leprae* may be seen in AIDS patients in endemic areas.

Mycobacterial skin lesions may appear as small papules and pustules that resemble folliculitis, atopic dermatitis-like eruptions, localized cutaneous abscesses, suppurative lymphadenitis, nonspecific ulcerations, palmar and plantar hyperkeratoses, and sporotrichoid nodules (Figs. 14.23 and 14.24). Lesions may take the form of painful erythematous papules and nodules on the distal extremities and ears [50]. Tuberculous lymphadenitis, in particular, is a characteristic finding of disseminated tuberculosis (TB) in intravenous drug users with AIDS and is manifested as suppurative draining lymph nodes in the neck, axillae, or groin. *M. leprae* may produce annular lesions (Fig. 14.25). The incidence of mycobacterial infections and related skin lesions has declined with the widespread use of prophylactic antibiotics and HAART.

Syphilis

Syphilis manifestations range from classic papulosquamous forms with involvement of the palms and soles and mucous membranes, to unusual forms that may defy diagnosis (Figs. 14.26 and 14.27). Unusual manifestations of syphilis include rapid progression from the primary chancre to gummatous tertiary lues in a matter of months, lues maligna (syphilis with vasculitis), sclerodermiform lesions, rupial verrucous plaques, extensive oral ulcerations, keratoderma, deep cutaneous nodules, rubeoliform eruptions, and widespread gummas [61]. Central nervous system disease occurs more frequently and with greater severity in patients with HIV infection, and painful meningovascular syphilis may develop after treatment of secondary syphilis.

Other Venereal Diseases

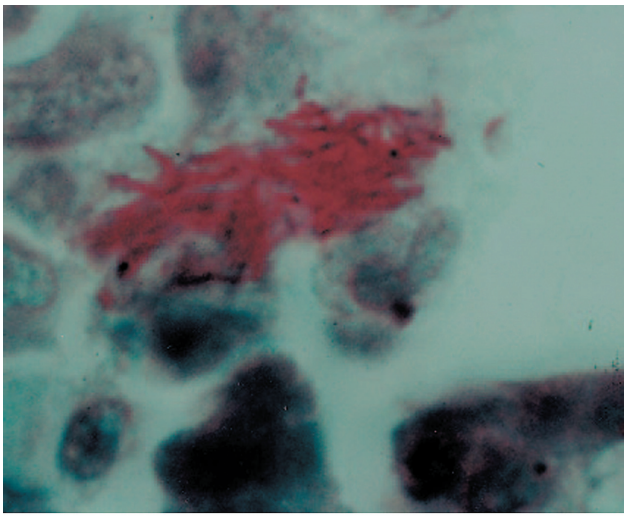
Granuloma inguinale caused by *Calymmatobacterium granulomatis* may develop in HIV-infected individuals as vegetating



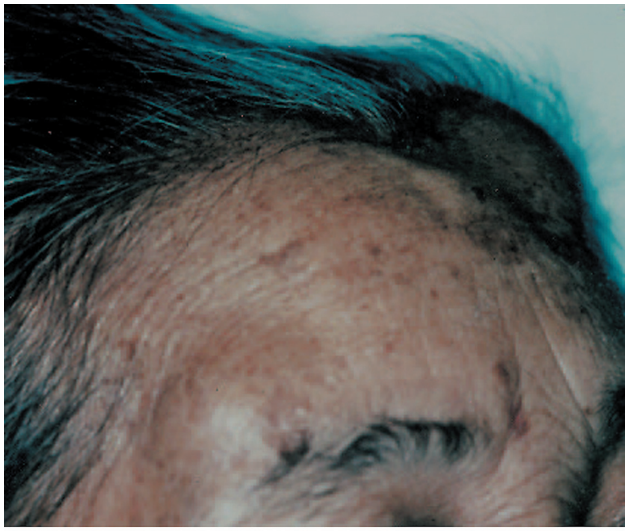
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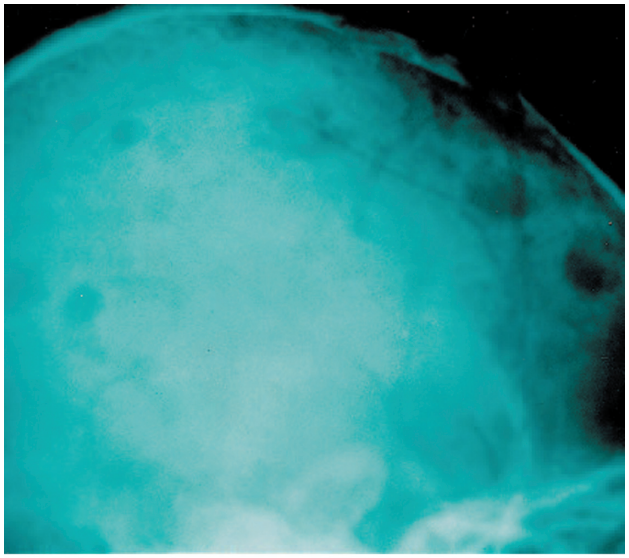
(b)



(c)



(d)



(e)

Figure 14.23 Mycobacterium avium-intracellulare abscesses in AIDS patients (a, b) with systemic mycobacterial infection. These mycobacteria can be found in the (c) bone marrow and can produce (d, e) lytic bone lesions. (Photograph c courtesy of Axel Hoke, M.D., Novato, CA; photographs d, e courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)



(a)



(b)



(c)



(d)

Figure 14.24 Scrofuloderma in HIV infection may be present in many forms (a, b). Mycobacterial infections may also manifest subcutaneously as (c) lymphadenopathy, or (d) cold abscesses. (Photographs b, c, d courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

lesions on the penis or vulva associated with pseudobuboes in the inguinal crease. Lymphogranuloma venereum is manifested by generalized lymphadenopathy accompanied by vulvar or penile edema with ulcerations and erosions. Nonspecific genital ulcerations from which a number of bacteria may be isolated may be observed in which the precise etiology remains unclear. A common sexually transmitted disease in some parts of the world is chancroid, which has been increasing in incidence in the



Figure 14.25 Mycobacterium leprae is observed in HIV-seropositive patients in endemic areas and may produce annular lesions. (Photographs courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

USA. The causative organism is a gram-negative coccobacillus, *H. ducreyi*. Cases have been reported in patients with HIV infection, especially those from Africa. Gonococcoccemia with oligoarticular gonococcal arthritis of the hips and sternoclavicular joints may also develop [62].

Histopathology

Histopathological findings of folliculitis generally include collections of neutrophils within infundibula of hair follicles and a mixed perifollicular inflammatory cell infiltrate. Botryomycosis is characterized by a diffuse inflammatory cell infiltrate in the dermis associated with colonies of gram-positive bacteria forming grains in the skin. Ecthyma is manifested histologically as a deep ulcer that often extends to the subcutaneous fat, with extensive degeneration of dermal collagen. There is a mixed inflammatory cell infiltrate of neutrophils, eosinophils, and histiocytes.

Histopathological findings in bacillary angiomatosis are characterized by a lobular proliferation of capillaries associated with enlarged epithelioid-appearing endothelial cells. The background stroma is usually edematous in superficial lesions and more compact in deeper ones.

The histopathological appearance of cutaneous syphilis is usually similar to that of immunocompetent hosts, demonstrating the characteristic superficial and deep psoriasiform lichenoid pattern of inflammation associated with plasma cells and histiocytes.

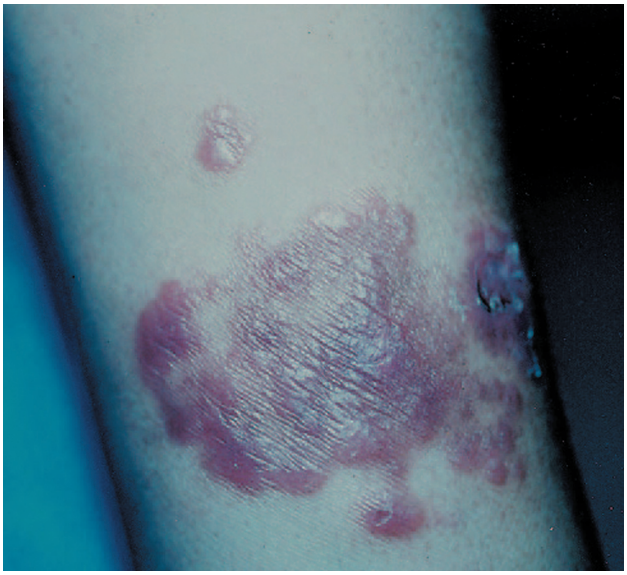


Figure 14.26 An unusual reddish plaque that proved to be syphilis when biopsied from an HIV-infected patient who was seronegative for syphilis.

Laboratory Findings

In pyogenic bacterial infections, laboratory findings may be similar to what would be expected in an immunocompetent host. In the setting of immunocompromise, however, patients may suffer from serious systemic bacterial infections and yet not have significant elevations in white blood cell counts or demonstrate characteristic "left shifts." Patients with syphilis may be truly seronegative for serological tests for syphilis, despite the presence of demonstrable spirochetes in biopsy specimens. Seronegativity may be caused either by a prozone phenomenon, the consequence of improperly diluted very high antibody titers, or as a consequence of true absence of antibody. Patients with bacillary angiomatosis usually have CD4+ cell counts less than 250 cells/mm^3. Serological tests for anti-*Bartonella* antibody are usually positive by the time the clinical diagnosis has been made. *B. henselae* can be isolated from blood, and *B. quintana* can be isolated from cutaneous lesions [63,64].

In attempting to isolate *M. haemophilum*, cultures are often negative unless the culture is kept at low temperatures and supplemental iron is added in the form of hemolyzed red blood cells.

Diagnosis

Diagnosis of these infections is generally made on the basis of clinical findings and the results of smears, biopsies, and cultures. A battery of special stains and, in some cases, immunoperoxidase stains for acid-fast bacilli may increase speed and sensitivity of diagnosis. Use of Gram's stain as well as periodic acid-Schiff and acid-fast stains ensures that more serious infections will not be missed. Cultures, complement fixation studies, and PCR may be used in the rapid diagnosis of these infections. Although serological testing is generally reliable, HIV-infected patients with active syphilis may have negative VDRL (Venereal Disease Research Laboratories) and FTA-ABS (fluorescent treponemal antibody absorption test) results. In such cases, biopsy with special stains for spirochetes may be required. Granuloma inguinale is characteristically diagnosed by crush preparations of a friable skin lesion followed by histological



Figure 14.27 Secondary syphilis may show a wide spectrum of clinical manifestations. (a) This erythematous sclerodermiform eruption was also a manifestation of secondary syphilis in this HIV-infected individual. (b) Mucous patches of secondary syphilis. (c) Annular syphilides with mucosal involvement. (d) Gummas may be produced if syphilis is left untreated. (a, Reprinted with permission, Arch Dermatol 128:530–534, 1992. Photograph d courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

examination. Chancroid is diagnosed by microscopic examination of gram-stained smears of lesions that demonstrate clusters of thin gram-negative rods, the characteristic "schools of fish."

Treatment

Treatment is based on accurate diagnosis and identification of causative microorganisms and their sensitivities to antibiotics. Table 14.3 outlines the recommended treatment for bacterial infections. Unfortunately, recurrence is the rule for pyogenic bacterial infections in immunocompromised hosts.

Cutaneous atypical mycobacterial infections demonstrate variable responses to antibiotics; therefore, it is important to culture the organisms and determine sensitivities. Multiple-drug-resistant TB may not respond to any medication currently available, but regimens employing pyrazinamide, amikacin, olfloxacin, and ciprofloxacin have met with some success [65].

PARASITIC INFESTATIONS

Ectoparasites

Definition

Scabies, both classic and crusted types, demodicidosis, and acanthamebiasis may infect HIV-infected patients. Clinical morphologies may be unusual, and skin biopsies and cultures are often necessary to establish an accurate diagnosis.

Epidemiology

Scabies is one of the most frequent ectoparasitic infections in patients with HIV infection. The causative agent is the mite *Sarcoptes scabiei* var. *humanus*. Papular demodicidosis occurs sporadically in patients with HIV infection.

Pathogenesis

Severe infestation with scabies in patients with HIV infection develops as a consequence of the impaired immunity in these individuals. Patients with altered neurological status may fail to scratch away mites. HIV-infected patients with crusted scabies may have millions of mites. A proliferation of *Demodex folliculorum* within follicles causes papular demodicidoses.

Clinical Manifestations

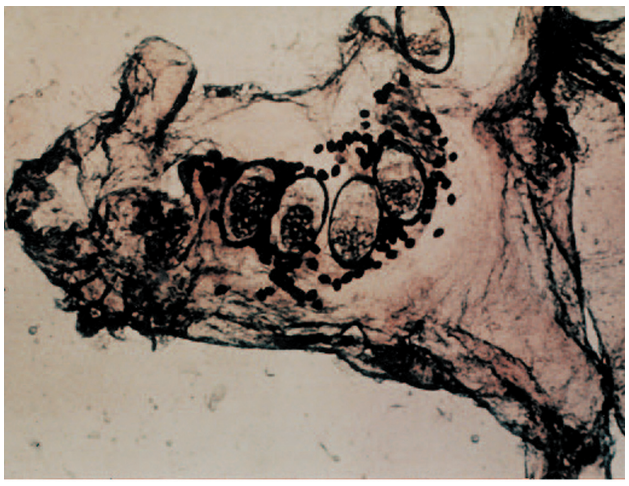
Scabies in patients with HIV infection (Figs. 14.28 and 14.29) may appear as hyperkeratotic plaques on the palms, soles, trunk, or extremities. In other patients, only scattered pruritic papules accompanied by slight scaling of the trunk and extremities may



(a)



(b)



(c)

Figure 14.28 Severely crusted scabies in a patient with AIDS (a, b). Head and neck involvement is common. (c) Scrapings of skin lesions usually demonstrate numerous live mites, eggs, and scybala.

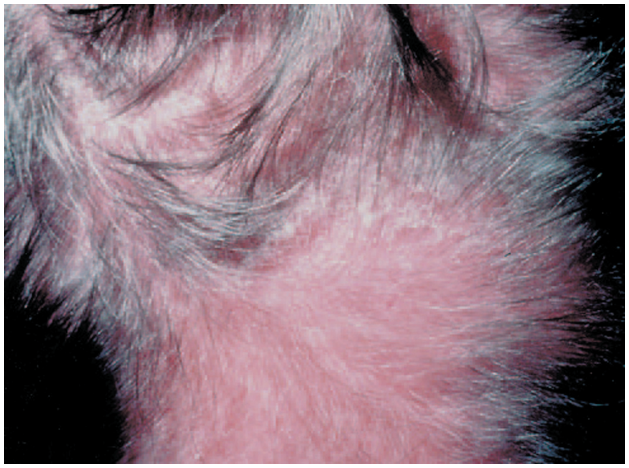


Figure 14.29 Crusted (Norwegian) scabies that mimicked seborrheic dermatitis.

be seen. Any patient with a scaly persistent pruritic eruption should have skin lesions scraped and examined histologically in search of mites. Patients complain of intractable pruritus that is worse at night. Usually contacts are infested, especially in the context of the number of mites present on the skin of these individuals. Severe forms of scabies may be associated with secondary infection, bacteremia, and fatal septicemia, especially in severely compromised hosts, but this has decreased in incidence in patients receiving HAART [66].

Demodicidosis generally consists of a persistent pruritic follicular eruption that may be confused with other responses to arthropods, including scabies as well as folliculitis (Fig. 14.30). Lesions may involve the face, trunk, and extremities.

Acanthamebiasis consists of painful nodular lesions with ulcerations, usually on the trunk or extremities; it can also be sexually transmitted (Fig. 14.31).

Histopathology

In crusted scabies there is usually a superficial and mid-to-deep perivascular and interstitial infiltrate of lymphocytes with numerous eosinophils. The epidermis is hyperplastic, with prominent crusting and many mites visible in the cornified layer.

Demodicidosis characteristically shows abundant *Demodex* mites within follicular infundibula associated with a mixed infiltrate of neutrophils and eosinophils within and around the infundibula of hair follicles.

Acanthamebiasis shows diffuse infiltrates of amebic cysts and trophozoites throughout the skin, especially around blood vessels and in the subcutaneous fat. Careful inspection is required, as these infiltrates may appear similar to histiocytes or other normal-appearing structures in the skin. Erythrophagocytosis may be noted.

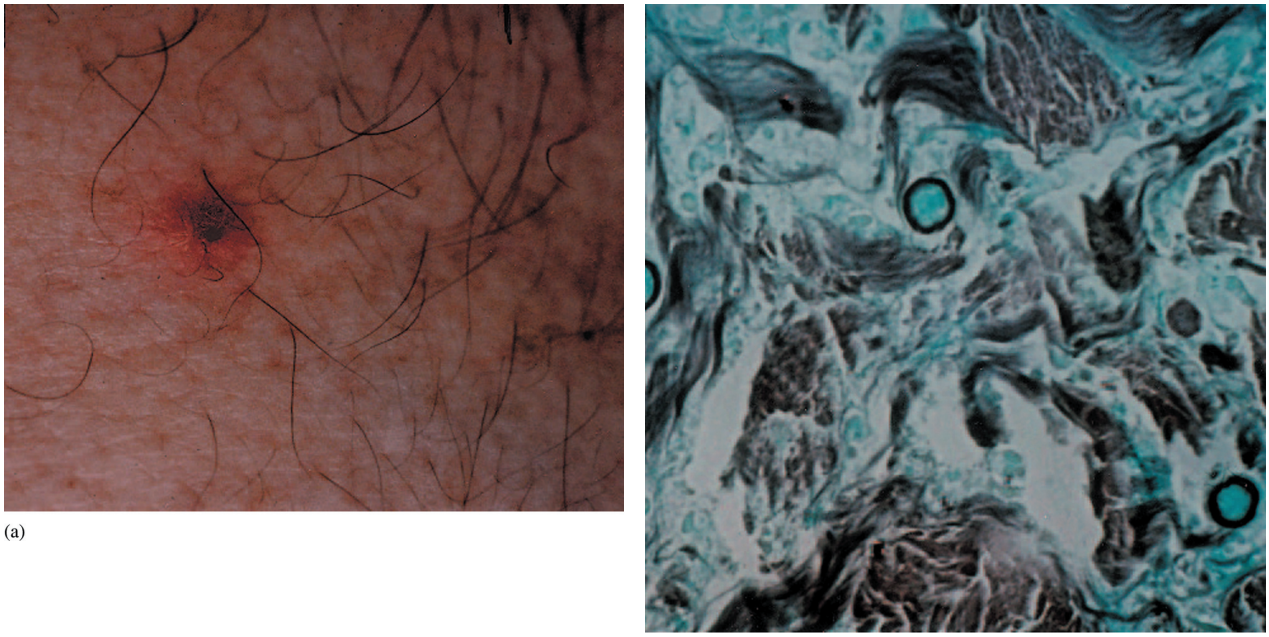


(a)



(b)

Figure 14.30 (a, b) Papular demodicidosis with scraping. (a) Note the similarity of the morphology of the lesions to acne rosacea and eosinophilic folliculitis. (b) Demodex folliculorum mites are visualized in large numbers. (Photographs courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)



(a) (b)

Figure 14.31 (a) Amebiasis in immunocompromised persons may appear as papules, pustules, or nodules and can be associated with liver abscesses. (b) Histological confirmation may be achieved by finding amoebic cysts in tissue. (Photographs a, b, courtesy of James Conners, M.D., Department of Dermatology, Yale University School of Medicine, New Haven, CT.)

Laboratory Findings

No specific laboratory findings are seen with any of these infestations, although elevated eosinophil counts are commonly noted.

Diagnosis

The diagnosis of scabies and demodicidosis depends primarily on the clinical appearance of skin lesions and demonstration of mites on microscopic examination of scrapings. Skin biopsies evaluated in the context of clinical history and appearance are important in the diagnosis of acanthamebiasis.

Treatment

The treatment of ectoparasite infestations is listed in Table 14.4. After treatment of scabies in some patients, recurrences may occur as a consequence of failure to treat areas under the fingernails and the intertriginous zones, although resistance to scabicidal medications may develop. Some have recommended alternating treatment with lindane and permethrin. Multiple treatments may be required. Oral ivermectin is very effective in the therapy of crusted scabies. Postscabetic id reactions must be treated with antihistamines, such as doxepin, 10–25 mg orally three to four times daily, with topical application of corticosteroid preparations to diminish inflammation. In cases of nodules, injection of triamcinolone acetonide may be required. Careful laundering of linen and clothing is necessary, and household and other contacts should be treated as well.

Table 14.4 Treatment of Parasitic Infestations

Symptom	Treatment
Scabies	Lindane cream or lotion applied from head to toe and washed off after 8–12 hours of treatment. This regimen is repeated in 1 week
	Permethrin 5% cream applied in the same manner
	5% precipitated sulfur in petrolatum applied from the neck down nightly for 3 nights may also be effective
	Oral ivermectin, 200 μg/kg, is highly effective and is considered the treatment of choice for crusted scabies
Demodicidosis	Metronidazole gel, applied 2–3 times daily, with or without the addition of topical benzoyl benzoate
	Systemic metronidazole, 250 mg to 750 mg orally three times daily, may be required in cases not responsive to topical treatment
Amebiasis	Metronidazole, 750 mg orally twice daily for 10 days
	Response may be poor in severely immunocompromised persons
Pneumocystosis	Intravenous pentamidine, which is the usual treatment for P. jiroveci pneumonia
Strongyloidiasis	Thiabendazole, 25 mg/kg twice daily, lasting 4–5 days to several weeks, depending on the immune status of the host
Leishmaniasis	Stibogluconate sodium, 20 mg/kg each day for 3–4 weeks
	Ketoconazole or other imidazole antifungal medications may also be effective
Pruritus associated with these infestations	Topical application of corticosteroids or antipruritic agents containing menthol and phenol, pramoxine, and antihistamines may be required
	Doxepin, 10% in aquaphor ointment, is a valuable antipruritic agent that may be used in patients with refractory pruritus
	Exposure to ultraviolet B irradiation and psoralen plus ultraviolet A are also helpful

Internal Parasites

Definition

A number of parasites may produce cutaneous manifestations of systemic disease. These include *Pneumocystis jiroveci* infection, leishmaniasis, strongyloidiasis, and toxoplasmosis.



Figure 14.32 Cutaneous Pneumocystis jiroveci infection. The lesions may be nondescript and simulate molluscum contagiosum (a). (Reprinted with permission, Arch Dermatol, 127:1699–1701, 1991.) (b) Nodular, and (c) plaque-like presentations have also been described. (Photograph c courtesy of Timothy Berger, M.D., Department of Dermatology, UC San Francisco, San Francisco, CA.)

Epidemiology

P. jiroveci infection, disseminated strongyloidiasis caused by *Strongyloides stercoralis*, and disseminated toxoplasmosis, caused by *Toxoplasma gondii*, are rarely seen now that HAART and oral prophylaxis are given [67]. By contrast, multiple cases of leishmaniasis in HIV-infected hosts have been diagnosed in India, Southeast Asia, Spain, and South America (especially Brazil) [68]. The most common infecting organism is *Leishmania donovani*, the protozoan responsible for the visceral form of the disease.

Pathogenesis

Cutaneous *P. jiroveci* infection is enhanced by the use of aerosolized pentamidine for the prophylaxis of *P. jiroveci* pneumonia. By creating a more unfavorable environment in the lung, organisms spread more widely to involve visceral organs as well as the skin.

Clinical Manifestations

P. jiroveci may have several different clinical manifestations. The most commonly reported form is that of friable reddish papules or nodules seen in the ear canal or the nares. Small translucent molluscum contagiosum-like papules (Fig. 14.32), bluish cellulitic plaque-like lesions, and deep-seated abscesses have also been observed. Given the diminishing frequency of systemic *P. carinii* infection secondary to administration of prophylactic antibiotics and HAART, skin lesions will be seen even less frequently.

Leishmaniasis does not have a uniform or specific appearance, but often appears symmetrically on acral zones. Manifestations have included erythematous papules, hypopigmented macules, small subcutaneous nodules, scaly violaceous plaques, and ulcers (Fig. 14.33) [68].

Histopathology

P. jiroveci in the skin has an appearance similar to that in the lung, with a diffuse infiltrate of foamy-appearing cells that highlight the microorganisms, resulting in the "teacup-and-saucer" appearance when they are stained with Gomori's methenamine silver or Steiner's stain. Strongyloidiasis generally shows a diffuse infiltrate of lymphocytes and eosinophils scattered throughout the dermis.

Laboratory Findings

No specific laboratory findings are seen with any of these infestations, although elevated eosinophil counts are commonly noted.

Diagnosis

Skin biopsies evaluated in the context of clinical history and appearance are important in the diagnosis of these conditions. Special serological and complement fixation tests may be helpful



(a) (b)

Figure 14.33 Widespread plaques (a) and ulcers (b) of disseminated leishmaniasis. (Photographs courtesy of Walmar Roncalli P. DeOliveira, M.D., São Paulo, Brazil.)

in confirming diagnoses. Treatment of parasitic infestations is shown in Table 14.4.

Systemic Fungal Infections

Definition

Blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis are some of the systemic fungal infections that occur in HIV-infected individuals (Table 14.5). These infections may occur in localized fashion involving a single tissue or as disseminated multiple-organ disease. Mucosal and cutaneous lesions may have many different clinical morphologies in HIV-seropositive patients, many of which may be unusual and challenge accurate clinical diagnosis.

Epidemiology

The most common opportunistic fungal infections to involve the skin in HIV-seropositive patients are histoplasmosis and cryptococcosis. Nearly 20% of HIV-seropositive individuals with disseminated histoplasmosis and up to 10% of those with disseminated cryptococcosis develop mucocutaneous lesions. Systemic and cutaneous coccidioidomycosis are both being recognized more frequently in HIV-infected patients, although they are still seen only sporadically. HIV-infected hosts with blastomycosis, paracoccidioidomycosis, or sporotrichosis have also been observed, although rarely. Similarly, although mucocutaneous candidiasis occurs commonly in HIV-seropositive individuals, disseminated candidiasis is seldom reported.

Clinical Manifestations

Mucocutaneous lesions associated with systemic fungal infections may assume a number of different features (Table 14.6). The most common lesions are pustules and ulcers, although papules and nodules are also frequently observed. Less often, patches, plaques, and mucosal ulcerations are seen.

Blastomycosis. Progressive disseminated blastomyeosis is characterized by *B. dermatitidis*-related pustules, nodules, and cutaneous ulcers.

Candidiasis. Oral thrush involving either the tongue and/or buccal mucosa, with or without esophageal infection, is the most common manifestation of candidiasis in HIV-seropositive patients (Fig. 14.34) and may be the initial sign of HIV infection. As an individual's immune status improves with HAART, oral candidiasis

Table 14.5 Mucocutaneous Manifestations of Systemic Fungal Infections in Human Immunodeficiency Virus–Seropositive Patients

Manifestation	Occurrence	Morphological appearance
Blastomycosis		
Acute pulmonary infection–associated reactive erythema	Rare	Erythema nodosum
Primary cutaneous (inoculation) infection	Rare	Solitary indurated chancre-like ulcer that can subsequently be accompanied by lymphangitis, lymphadenitis, and subcutaneous nodules extending along the involved lymphatic vessel
Disseminated infection: cutaneous lesions in 70% of patients; oral lesions in 25% of patients	Most common	Centrifugally enlarging plaques with a scarred area of central healing and a raised verrucous pustule–containing border
	Less common	Ulcers with granulating bases that rapidly develop from pustules; subcutaneous abscess
	Rare	Widespread or acrally distributed pustules
		Oral ulcers and friable masses of heaped-up tissue
Coccidioidomycosis		
Acute pulmonary infection–associated reactive erythemas	50% of patients	Erythema multiforme, erythema nodosum, and "toxic" erythema (an erythematous, macropapular, morbilliform, or urticarial diffuse exanthem)
Primary cutaneous (inoculation) infection	Rare	Same as primary cutaneous blastomycosis
Disseminated infection: only occurs in about 1/10,000 cases; of these 15–20% have cutaneous lesions	Most common	A solitary verrucous plaque or granulomatous nodule on the face, multiple papules, nodules, or pustules; subcutaneous abscesses (with or without overlying skin changes); sinuses, ulcers, and scars
Cryptococcosis		
Primary cutaneous infection	Rare	Variable
Disseminated infection	Usually seen in immunosuppressed individuals; mucocutaneous lesions occur in 10–20% of these patients	Erythematous papules that may develop into pustules or ulcerating nodules
		Other morphologies: abscesses, acneiform lesions, cellulitis, cutaneous ulcers, ecchymoses
		Oral ulcers (rare), purpura, pyoderma gangrenosum-like lesions, vasculitis, and verrucous lesions
Histoplasmosis		
Acute pulmonary infection–associated reactive erythemas		Erythema multiforme, erythema nodosum
Primary cutaneous (inoculation) infection	Rare	Same as primary cutaneous blastomycosis
Disseminated infection	Occurs in 1/1,000 to 1/500,000 cases; of these, 3% have cutaneous lesions and 21% have mucosal lesions	Acneiform or follicular lesions, exfoliative erythroderma, macules and patches, papules and nodules, petechiae, purpura, and ecchymoses, and plaques and ulcers (cutaneous and mucosal)
Paracoccidioidomycosis		
Disseminated infection	Common	Mucosal lesions of the larynx, month, nose, and pharynx, that begin as papules and nodules and subsequently enlarge to become infiltrated, granulomatous, and ulcerated (and often extend onto the adjacent skin of the face)
	Rare	Cutaneous lesions may appear as widely scattered nodules, papules, pustules, or ulcers
Sporotrichosis		
Lymphocutaneous infection	Most common	A painless papule or pustule at the site of inoculation that develops into an ulcerated nodule; subsequently, asymptomatic subcutaneous nodules develop in an ascending direction along the corresponding lymphatic with or without accompanying lymphangitis and lymphadenopathy
Fixed cutaneous infection		Lesion or group of lesions, of variable morphology, localized to the site of inoculation, cellulitis (facial), erosions (pyodermatous), papules (infiltrated), plaques (large and warty or scaly and psoriasiform), and ulcers (thick and crusted or pyoderma gangrenosum-like)
Disseminated cutaneous infection	Rare	Polymorphous lesions similar in morphological appearance to fixed cutaneous sporotrichosis infection
Multifocal systemic infection	Rare	Widespread, scattered nodules or subcutaneous abscesses that subsequently ulcerate

Table 14.6 Cutaneous and Mucosal Lesions of Systemic Fungal Infections in Human Immunodeficiency Virus–Infected Patients

Morphology	Blastomycosis	Coccidioidomycosis	Cryptococcosis	Histoplasmosis	Paracoccidioidomycosis	Sporotrichosis
Macule				+		
Nodule		+	+			+
Abscess		+				
Herpes-like			+	+		
Fistulas				+		
Kaposi's sarcoma–like			+			
Molluscum contagiosum–like			+			
Purpura		+				
Papule		+	+	+		+
Patch		+		+		
Plaque				+		+
Pustule	+	+	+	+		+
Cutaneous ulcer	+		+	+	+	+
Mucosal ulcer			+	+		

often resolves. Other manifestations that may develop include chronic paronychia and onychodystrophy, chronic refractory vaginal candidiasis, distal urethritis, and persistent monilial infection of the axilla, glans penis, groin, and/or inframammary area.

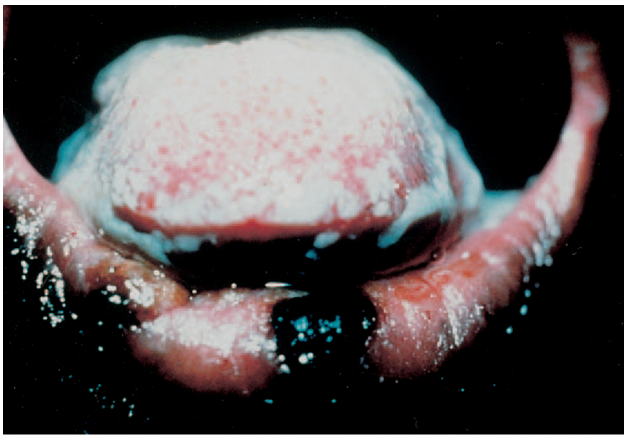
Disseminated candidiasis has been reported in a small number of HIV-infected patients. Administration of broad-spectrum antibiotics and total parenteral nutrition, extended placement of central intravenous catheters during prolonged hospitalizations, and, in children, previous oral candidiasis, are predisposing factors for systemic infection in these individuals [69].

Coccidioidomycosis. Although an increasing number of HIV-infected patients with coccidioidomycosis are being described, only a few have been reported with associated skin lesions [70]. These lesions may include ulcers, abscesses, nodules, purpura, and papulopustules.

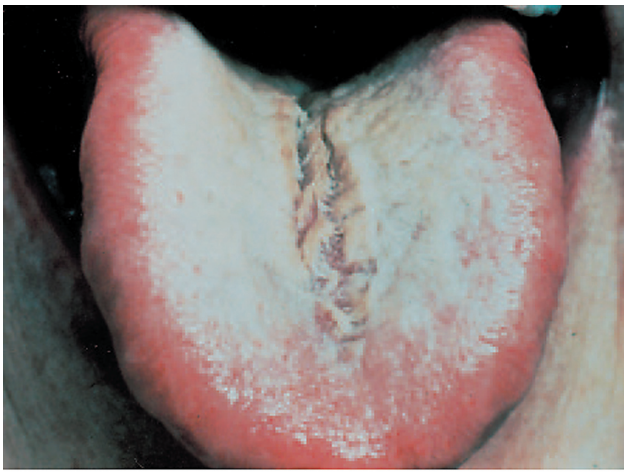
Cryptococcosis. Cryptococcosis is a common infection to develop in HIV-infected individuals with low incidence of cutaneous involvement [71]. Mucocutaneous lesions of cryptococcosis are polymorphous and may appear as erythematous papules, nodules, pustules, and/or ulcers of the skin and mucosa (Fig. 14.35).



(a)



(b)



(c)

Figure 14.34 Hyperplastic and erosive candidiasis of the mouth (a–c) in HIV-infected patients. (Photograph b reprinted with permission, Cutis 40:406–409, 1987.)



(a) (b) (c)

Figure 14.35 Widespread lesions of disseminated cryptococcosis may have different clinical appearances and may simulate (a) molluscum contagiosum or may be (b) nodular. (c) Histological diagnosis is necessary. (Photographs a and c courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

Cutaneous cryptococcosis, like other opportunistic infections that develop in these patients, may mimic the cutaneous morphology of other disorders, such as herpes simplex virus infection, cellulitis, or molluscum contagiosum infection, as well as of soft-tissue hypertrophic lesions such as rhinophyma and KS.

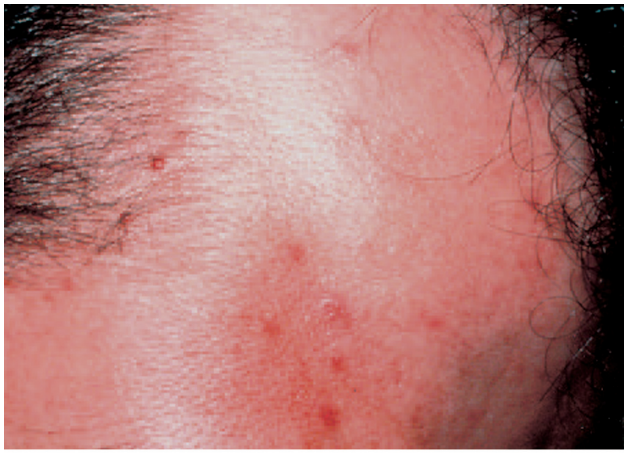
Histoplasmosis. A review of 280 HIV-infected individuals with disseminated histoplasmosis identified 48 patients (17%) with histologically and/or culture-proven mucocutaneous lesions of *H. capsulatum* [72]. Clinically, the lesions may appear as cutaneous and mucosal ulcers, erythematous macules and patches, fistulas, papules and nodules, pustules, and verrucous plaques [73] (Table 14.6) (Fig. 14.36). *H. capsulatum* and KS may coexist in a single skin lesion, and cases of concomitant psoriasis and histoplasmosis have also been described [73,74].

Paracoccidioidomycosis. Descriptions of disseminated paracoccidioidosis in HIV-infected individuals are increasing in Brazil (Fig. 14.37). *P. brasiliensis* organisms can be observed on hematoxylin and eosin stained sections prepared from a biopsy of the cutaneous ulcers.

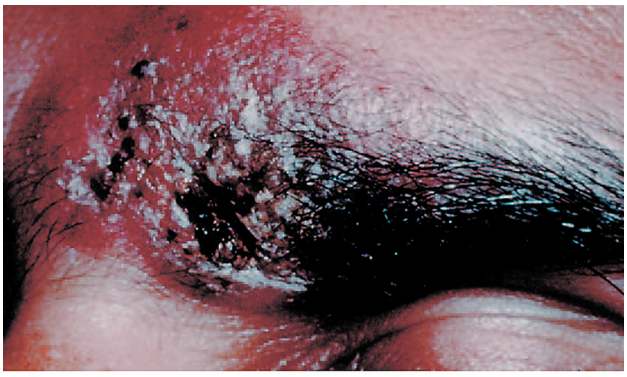
Sporotrichosis. Clinical forms of sporotrichosis include lymphocutaneous, fixed cutaneous, disseminated cutaneous, and systemic. The last may present as either localized pulmonary disease or as widespread involvement of numerous organs. In patients with HIV infection, skin lesions may be ulcers, papules, nodules, plaques, and/or pustules (Fig. 14.38). These may be widespread, and internal organ involvement may develop that often proves fatal.

Histopathology

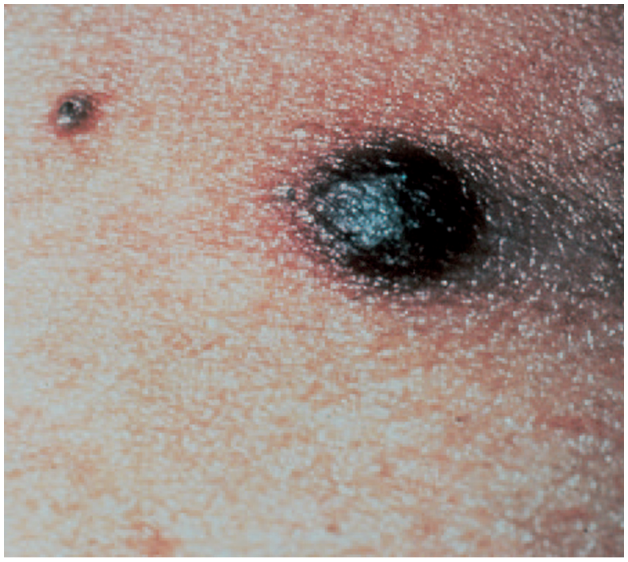
The epidermis in mucocutaneous lesions of systemic fungal infections usually exhibits pseudocarcinomatous hyperplasia. There is almost always a supporative and granulomatous inflammatory infiltrate in the dermis in blastomycosis, coccidioidomycosis,



(a)



(b)



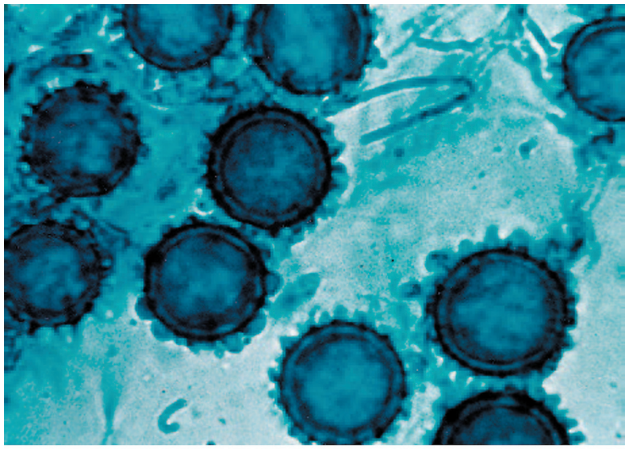
(c)



(d)



(e)



(f)

Figure 14.36 (a–d) Lesions of disseminated histoplasmosis may have multiple morphologies, including nondescript papules, plaques, ulcers, and psoriasiform lesions. (e) Oral ulcerations caused by disseminated Histoplasma capsulatum infection. (f) Histological diagnosis is necessary and may be confirmed by culturing the organism. (Photographs d and f courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)



Figure 14.37 Paracoccidioidomycosis in Brazilian AIDS patient. This mycosis can appear with cutaneous plaques. (Photograph courtesy of Walmar Roncalli P. DeOliveira, M.D., São Paulo, Brazil.)



Figure 14.38 Sporotrichosis in AIDS patients may produce widespread papules, nodules, and plaques. (Photograph courtesy of Walmar Roncalli P. DeOliveira, M.D., São Paulo, Brazil.)

paracoccidioidomycosis, and sporotrichosis. There may be transepidermal elimination of fungal spores. Histoplasmosis may exhibit a diffuse dermal infiltrate of histocytes, neutrophils, and leukocytoclasis. Cryptococcosis has a characteristic histopathological appearance in most cases. There is diffuse pallor of the dermis that correlates with the mucoid capsular material of the organisms, which are usually present in abundance. The organisms can often be identified on hematoxylin and eosin stained sections, although special stains such as the periodic acid-Schiff and Gomoris methenamine silver can be used to facilitate their detection.

Diagnosis

When the possibility exists that a mucocutaneous lesion in an HIV-infected patient is secondary to dissemination of a systemic fungal infection, a tissue biopsy of that lesion should be prepared for histological evaluation and microbiological cultures. The growth of a fungal organism in culture is definitive evidence that the lesion is caused by an opportunistic fungus. Unfortunately, several of these organisms require several days to weeks to grow in culture so that more rapid methods to establish a definitive diagnosis are often required. In cases in which the number of microorganisms is small, the sensitivity of diagnosis can be increased by immunoperoxidase staining using antibodies directed to fungi or mycobacteria that cross-react with them. The PCR technique has expedited the diagnosis of some of these infections, but, currently, diagnostic molecular mycology is still a research methodology that is not routinely available. Finally, since fungal infection-associated lesions in HIV-seropositive individuals have been reported to harbor more

Table 14.7 Treatment of Systemic Fungal Infections

Disease	Treatment
Blastomycosis	Amphotericin B
Disseminated candidiasis	Amphotericin B
	Fluconazole or itraconazole may be effective for initial and maintenance therapy
Localized superficial candidiasis	Topical antifungal preparations
	Systemic therapy with imidazoles may be required in refractory cases
Coccidioidomycosis	Amphotericin B, intravenously
	Concomitant intrathecal amphotericin B may be required in some cases
Cryptococcosis	Amphotericin B
	Imidazoles
	Flucytosine (rarely)
Disseminated histoplasmosis	Amphotericin B
	Imidazoles have been shown to be effective in both prophylaxis and therapy
Paracoccidioidomycosis	Amphotericin B
	Imidazoles have been shown to be effective in both prophylaxis and therapy
Systemic sporotrichosis	Amphotericin B
	Ketoconazole, fluconazole, or itraconazole are also effective
Lymphocutaneous sporotrichosis	Potassium iodide. (Careful monitoring is necessary to avoid recurrences, as this drug is not fungicidal)

than one pathogen, a diligent search for concurrent infectious organisms is warranted.

Treatment

Amphotericin B and imidazoles remain the drugs of choice for many systemic fungal infections, but many newer agents are under study [75] (Table 14.7). Fortunately, as more patients receive HAART, the incidence of these already rare complications may decrease.

Other Fungal Infections in Patients with Human Immunodeficiency Virus Infection

In addition to the fungal infections described previously, disseminated *Scedosporium inflatum*, *Pseudallescheria boydii*, and *Microsporum canis* occur, as have infections with other saprophytic fungi. Mycetomas, which may be either fungal or bacterial, may be found in AIDS patients as nodules with draining sinus tracts, most often on the feet (Fig. 14.39). Disseminated *Aspergillus* infection can manifest as facial palsy as a consequence of involvement of the mastoid sinus or as a retrobulbar lesion (Fig. 14.40). *Zygomycosis* infection of the head and neck may develop and manifest as local pain, cutaneous necrosis, and necrotizing ulcerations. Deep soft-tissue muscular aspergillosis has also been noted. These infections are being encountered more frequently as a consequence of better prophylaxis against other opportunistic infections and because of abnormal neutrophil function that has been demonstrated in these patients.



Figure 14.39 Eumycetoma in an AIDS patient in India. (Photograph courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

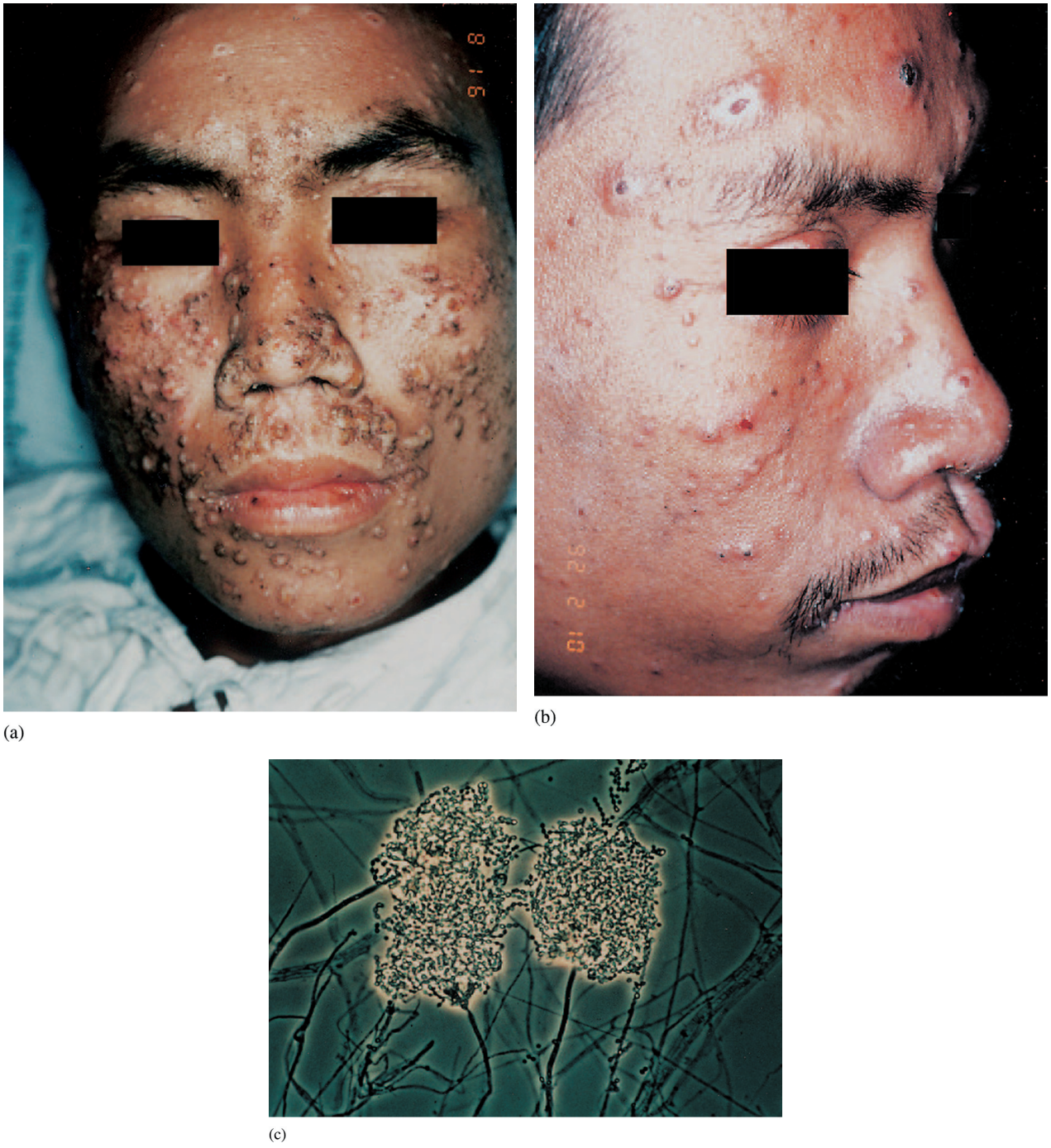


Figure 14.40 Retrobulbar aspergillosis. (Photograph courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

Penicillium marneffei, a fungus that is endemic in Asia, causes a common infection in patients with AIDS in Thailand. Some of the cutaneous manifestations include umbilicated papules that could be confused with those of molluscum contagiosum, ecthyma-like lesions, folliculitis, subcutaneous nodules, and morbilliform eruptions (Fig. 14.41). The diagnosis is established by histological evaluation of skin biopsies and by the performance of cultures. A study in Thailand showed that voriconazole is a safe and effective therapy for systemic *P. marneffei* infections [76].

Infection by dermatophytes in HIV-infected individuals may occur on any cornified epithelial surface (Fig. 14.42). Dermatophyte infection of the feet, toenails, or fingernails also occurs commonly in HIV infection, with proximal white subungual onychomycosis of the toenails frequently observed. In contrast to the classic form of distal subungual onychomycosis in which the fungus infects the nail distally and spreads proximally, proximal white subungual onychomycosis is characterized by involvement of the proximal nail plate beginning under the posterior nail groove and extending distally. *Tinea corporis* may be manifested as extensive widespread involvement of the trunk and extremities. In any individual with extensive tinea corporis, the possibility of underlying HIV should be entertained.

Pityrosporum ovale and *P. orbiculare* are normal residents of the hair follicles of the scalp and may cause or exacerbate seborrheic dermatitis in patients with HIV infection. The density of *P. ovale* of the involved skin may correlate with the severity of seborrheic dermatitis. Pityrosporum folliculitis characterized by pruritic papules and pustules on the trunk and extremities also may develop in HIV-infected hosts. Histological evaluation of potassium hydroxide preparations of scrapings from lesions shows yeasts and pseudohyphal forms of the organisms, and histopathological examination of skin biopsy specimens also demonstrates



(a) (b) (c)

Figure 14.41 Penicillium marneffei in (a, b) Thai AIDS patients as (c) confirmed by culture. (Photographs courtesy of Siri Chiewchanvit, M.D., Chiang Mai, Thailand.)

numerous organisms within hair follicles. In patients with HIV infection, extensive overgrowth of *P. ovale* of the glabrous skin leads to tinea versicolor, evidenced by scaling patches and plaques of the trunk. Treatment with oral imidazole antifungal medications, such as fluconazole, itraconazole, or ketoconazole, for 14 days is effective, although the condition tends to recur following its discontinuation.

Trichosporonosis caused by infection with *Trichosporon beigelii* generally causes white piedra, a superficial infection of the hair endemic to tropical and sub-tropical regions and parts of southeastern USA. *Cladosporium cladosporioides* can cause pustular nodules. Cutaneous alternariosis presenting as an eschar on the leg and *Curvularia* phaeohyphomycosis causing a keratotic lesion on the scrotum have both been observed in HIV-infected individuals.

NONINFECTIOUS SKIN DISORDERS

In addition to infectious disorders, one or more of the following noninfectious cutaneous signs may point to HIV infection as a possible underlying cause of these conditions.



(a)



(b)



(c)

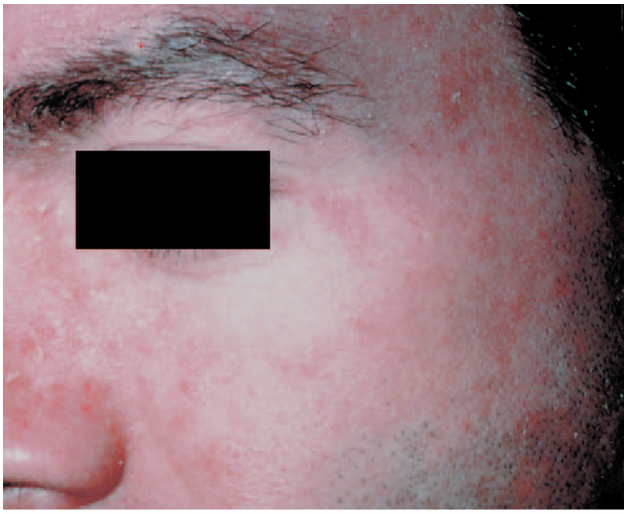


(d)

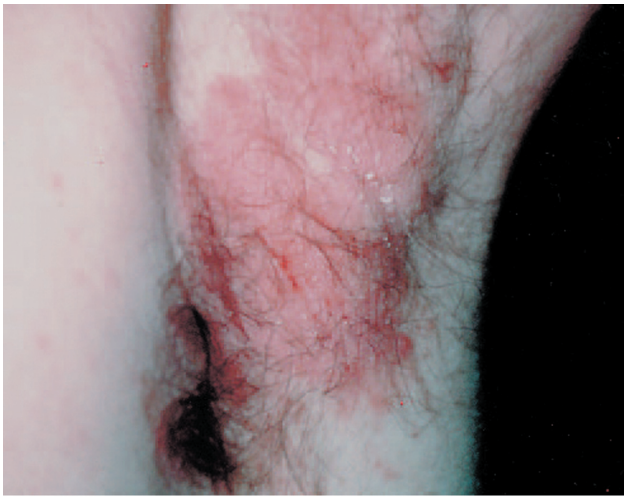


(e)

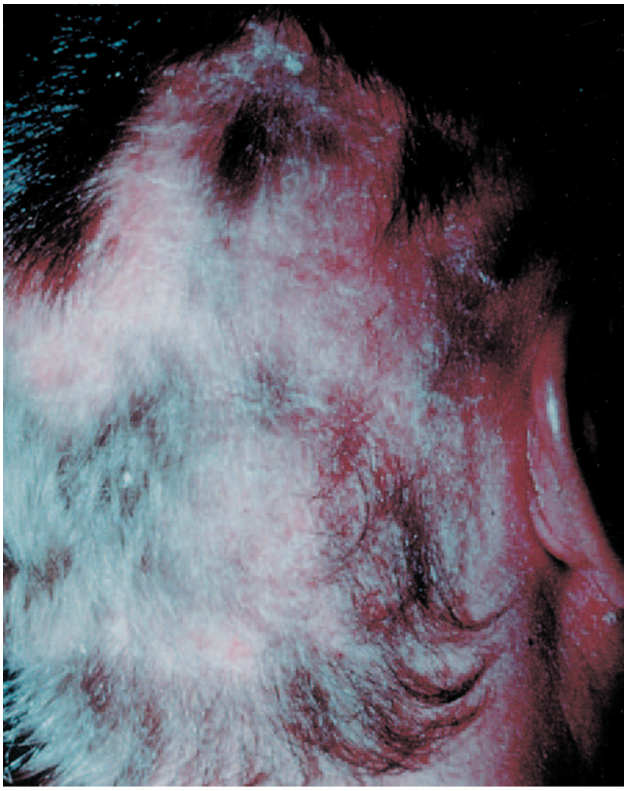
Figure 14.42 (a) Widespread dermatophytosis in a patient shown to be the first manifestation of HIV infection. (b, c) Severe manifestation of dermatophytosis in a patient with AIDS. Note the similarity to crusted scabies in Figure 14-28. (d) Proximal white subungual, and (e) total nail onychomycosis in patients with HIV infection. (Photograph d courtesy of J. K. Maniar, M.D., Department of Dermato-venereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)



(a)



(c)



(b)

Figure 14.43 (a) Seborrheic dermatitis as an early manifestation of HIV infection. (b, c) Severe seborrheic dermatitis with alopecia and inverse distribution in an immunocompromised patient with AIDS.

Seborrheic Dermatitis, Psoriasis, and Reiter's Syndrome

Definition

Seborrheic dermatitis and psoriasis are papulosquamous disorders associated with epidermal hyperplasia, increased epidermal turnover, and scaling. Reiter's syndrome is a condition consisting of urethritis, conjunctivitis, arthritis, and psoriasiform lesions of the glans penis and other parts of the body. Seborrheic dermatitis has a characteristic distribution involving the scalp, nasolabial folds, and presternal areas and occasionally intertriginous sites. Psoriasis occurs in a number of different forms and is seen most commonly as scaly plaques of extensor surfaces. All three of these conditions are increased in incidence in patients with HIV infection.

Epidemiology

Seborrheic dermatitis is one of the most common skin conditions to affect patients with HIV infection, previously occurring at least once in nearly 85% of all HIV-infected individuals. HIV-associated psoriasis and arthritis as well as Reiter's syndrome occur more frequently in HIV patients than in the general population.

Pathogenesis

The pathogenesis of seborrheic dermatitis remains unknown, although it has been postulated to be caused by a reaction to *P. ovale*. Dysregulation of the immune system may cause the skin of HIV-infected hosts to become acanthotic and psoriasiform, possibly owing to cytokine release or an exaggerated inflammatory reaction. Why psoriasis develops in patients with HIV infection remains unknown, although several studies have postulated that the pathogenesis of psoriasis may be related to underlying vascular proliferation. Infections may also cause psoriasis to flare in patients with HIV disease, especially those caused by *Candida*, *Staphylococcus*, and *Streptococcus*. Reiter's syndrome in immunocompetent hosts is commonly triggered by infections with *Shigella flexneri*, *Campylobacter fetus*, and *Ureaplasma urealyticum*. These organisms are rarely found in HIV-infected patients with Reiter's syndrome, although some patients do have a culture-negative diarrheal illness or culture-negative urethritis at the time of the onset of the disorder. In that HLA-B27 is significantly associated with Reiter's disease, autoimmunity associated with this allele may be important.

Clinical Manifestations

Seborrheic dermatitis occurs as slightly indurated, diffuse or confluent, pinkish-red scaly plaques involving the face and scalp (Fig. 14.43). These may be large, thickened, and heavily crusted and may be present on other areas such as the upper anterior



Figure 14.44 (a, b, c) Extensive eruptive psoriasis in HIV-infected hosts. (d) Inverse psoriasis.

chest, back, groin, and extremities. In some patients, the condition may involve large areas of the skin, leading to erythroderma. Still other cases may be associated with alopecia. With the advent of HAART, however, the incidence of refractory cases seems to be diminishing.

Psoriasis may have a number of different manifestations. The classic cases consist of reddish plaques with superficial micaceous scale on the extensor surfaces and nail changes of onycholysis, pitting, and subungual hyperkeratosis (Figs. 14.44 and 14.45). In other patients, severe psoriatic arthritis may be seen. Different forms of psoriasis may be found in the same patient, such as guttate psoriasis associated with classic psoriasis vulgaris. Severe exfoliative erythroderma may develop within several days, and acral pustular lesions of keratoderma blennorrhagicum coexisting with psoriasis or sebopsoriasis have been noted. Concomitant seborrheic dermatitis of the scalp is almost always seen. HIV-related psoriasis may develop in patients with mild pre-existing psoriasis that suddenly undergoes severe exacerbation



(e)



(f)

Figure 14.44 (continued). (e) Sebopsoriasis in an HIV-infected patient that progressed to widespread extensive involvement with erythroderma. (f) Nail changes of onycholysis and pitting with HIV-associated psoriasis.

once AIDS develops, or it may develop spontaneously at some point after HIV seroconversion in an individual who has never before had clinical disease.

Reiter's syndrome is characterized clinically by arthritis (especially sacroiliitis), urethritis, conjunctivitis, and pustular scaling lesions of the glabrous skin, glans penis, and scalp. Debilitating palmoplantar pustular disease is common, and there is generally striking nail dystrophy associated with periungual erythema, inflammation, and hyperkeratosis with prominent crusting (Fig. 14.46).

Histopathology

The histopathological findings of seborrheic dermatitis are similar to those seen in patients with non-HIV-associated disease, namely,



(a)



(b)

Figure 14.45 (a, b) Treatment may be effective with acitretin or low-dose methotrexate in this case of severe keratoderma.



(a)



(b)



(c)



(d)



(e)

Figure 14.46 (a–e) Pustular psoriasiform lesions of HIV-associated Reiter's syndrome. (Photographs a–d courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

psoriasiform hyperplasia of the epidermis with mounds of parakeratosis containing neutrophils near the ostia of hair follicular infundibula. An infiltrate of lymphocytes and scattered plasma cells are seen in the dermis. Seborrheic dermatitis in patients with HIV infection produces scattered individually necrotic keratinocytes, unlike its appearance in the general population. Some have likened this to cutaneous graft versus host disease.

Psoriasis, too, has histological features similar to those seen in non-HIV-infected patients. The pattern is generally that of marked acanthosis with regular elongation of epidermal retia associated with dilated tortuous blood vessels in the papillary dermis, thin suprapapillary plates, and mounds of parakeratosis containing neutrophils. In pustular cases, spongiform areas in the epidermis containing collections of neutrophils are noted. Reiter's disease has a histological picture similar to that of pustular psoriasis [77].

Laboratory Findings

No specific laboratory findings associated with these diseases have been reported other than the presence of HLA B27 in patients with Reiter's syndrome. CD4+ cell numbers may be at any level when seborrheic dermatitis develops; but when it becomes persistent and refractory to therapy, CD4+ cell numbers are generally lower than 250 cells/mm^3. Psoriasis, too, may develop at any point during the course of HIV infection, but has been reported to be worse when CD4+ cell numbers are less than 500 cells/mm^3.

Diagnosis

The diagnosis of a psoriasiform dermatosis in HIV-infected hosts is generally based on evaluation of clinical and histological features of the disease in question. In most cases, diagnoses are not difficult to render. Scrapings for microscopic examination should be done to exclude the possibility of fungi and scabies if any question in the diagnosis persists.

Treatment

Table 14.8 lists the treatment for seborrheic dermatitis and psoriasis. Both topical antifungals and topical steroids are used for therapy of seborrheic dermatitis.

Both spontaneous remission of psoriasis and complete unresponsiveness to all forms of treatment have been observed in HIV-infected patients. In many cases, systemic drugs, systemic psoralen, and ultraviolet A therapy may be required. Methotrexate may be used with extreme caution. Concomitant administration of trimethoprim-containing compounds is contraindicated because the folate reductase-inhibiting effect is synergistic with that produced by methotrexate.

There has been concern that exposure to ultraviolet radiation may cause worsening of immunocompromise in patients with HIV disease, as in vitro exposure of HIV-infected cell lines to such radiation has been shown to lead to increased production of HIV from latently infected cells [78]. In spite of this, in clinical practice no evidence of increased immunosuppression or worsening of HIV infection after exposure to ultraviolet radiation has been observed [79].

Table 14.8 Treatment of Seborrheic Dermatitis and Psoriasis

Symptom	Treatment
Seborrheic dermatitis	Topical hydrocortisone, 2.5% ointment or cream, applied twice daily Topical antifungal creams, applied twice daily Ultraviolet B phototherapy is often effective as an adjunct
Psoriasis	Combination of hydrophilic petrolatum, applied several times daily, 3–5% salicylic acid ointment applied one to two times daily (for keratolytic effect), and triamcinolone acetonide ointment 0.025%–0.1% (or its equivalent) for localized short-term therapy, is partially effective; 2% crude coal tar and petrolatum followed by ultraviolet B phototherapy may also be beneficial Anthralin 0.1–1% cream or ointment applied either overnight or for short duration Acitretin, 25 mg to 50 mg orally each day, with or without the addition of dapsone, 100–200 mg orally each day Psoralen, taken orally, followed by ultraviolet A phototherapy Methotrexate (orally), starting at 5–7.5 mg/week and gradually increasing the dose by 2.5 mg/week as needed. Monitor carefully, as immunosuppression may occur Note: Concomitant administration of trimethoprim-containing compounds is contraindicated because the folate-inhibiting effect is synergistic with that induced by methotrexate

Other Papulosquamous Disorders

Pityriasis rubra pilaris is a papulosquamous dermatosis characterized by widespread scaly plaques that involve the scalp, trunk, extremities, palms, and soles, with characteristic follicular involvement and islands of skin that are spared by the disease (Fig. 14.47). Several HIV-infected patients with this disorder have been reported, some of whom developed explosive cystic acne vulgaris in association with the follicular abnormality [80]. Elongated cutaneous follicular spines have been observed, and there was at least one report of histopathological evidence of mucin deposition [81]. Therapy with 13-*cis*-retinoic acid may be effective, and improvement following the administration of HAART may be noted.

Exfoliative erythroderma in patients with HIV infection is most commonly caused by psoriasis, although it may be caused by cutaneous T-cell lymphoma, atopic dermatitis, drug eruptions, and severe seborrheic dermatitis (Fig. 14.48). A hyperpigmented erythroderma associated with elevated immunoglobulin E levels has also been observed. Staphylococcal scalded skin syndrome as well as the toxic streptococcal syndrome are infectious causes of erythroderma and should be considered, as these can be treated with antibiotics.

Histologically, patients with psoriasiform dermatitis have been shown to have findings similar to those of seborrheic dermatitis as well as of spongiotic dermatitis. Severe xerosis and acquired ichthyosis may develop as a consequence of abnormal nutrition as well as secondary to diminished autonomic nervous system function, with decreased sweating and diminished sebaceous gland secretion. The problems may develop in 20–30% of HIV-infected patients (Fig. 14.49). Treatment consists of avoidance of soap and water and application of emollients, such as hydrophilic petrolatum or lotions containing 12% lactic acid. Pityriasis rosea may also occur in widespread fashion in patients with HIV disease.

Noninfectious Papular Pruritic Disorders

Definition

Aside from infestations, a number of cutaneous disorders are pruritic and lead to extreme discomfort. Some conditions



(a) (b) (c)

Figure 14.47 (a–c) Pityriasis rubra pilaris in patients with HIV infection. Note the prominent follicular involvement that led to the complication of explosive cystic acne. (Reprinted with permission, Br J Dermatol 126:617–620, 1992.)

associated with itchy papular and pustular dermatoses in these individuals include eosinophilic (pustular) folliculitis, severe xerotic dermatitis, papular dermatitis of AIDS, papular urticaria, and atopic dermatitis. Eosinophilic (pustular) folliculitis is a condition of widespread follicular papules and pustules that is characterized by an influx of eosinophils in the infundibula of hair follicles (Fig. 14.50). Papular urticaria generally refers to responses to insect bite reactions or possibly to hypersensitivity "recall" reactions to insect bites suffered previously (Fig. 14.51). The papular dermatitis of AIDS is a condition of nondescript papules on the trunk and extremities in patients with HIV infection, the etiology of which has not been determined (Fig. 14.52).

Epidemiology

Pruritic conditions in patients with HIV infection are quite common, although the precise incidence and prevalence are unknown. Approximately 5–30% of HIV-infected patients develop eosinophilic folliculitis [82]. Other pruritic dermatoses, such as papular dermatitis of AIDS, papular urticaria, and atopic dermatitis, are seen in variable percentages, probably ranging between 1 and 2% or less. Atopic dermatitis may be seen more commonly

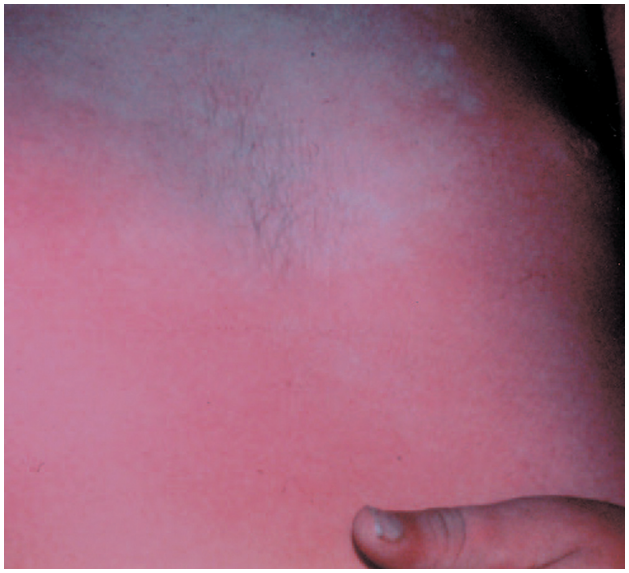


Figure 14.48 Erythroderma associated with AIDS. Many different factors may be etiological.

in children with HIV infection. Xerotic dermatitis may be seen to some degree in up to 85% of patients.

Pathogenesis

The pathogenesis of pruritic dermatoses in patients with HIV infection is not entirely clear, although there are several theories that may be germane. All patients should be evaluated for the presence of ectoparasites and other pathogens such as scabies and fungi, as these may lead to itching. Systemic parasites also may lead to itching by inducing urticarial reactions or as a consequence of migration through the skin. Other causes of hypersensitivity, such as drug eruptions and underlying atopic dermatitis, may produce itching and should be excluded on clinical grounds. Patients with HIV infection commonly have circulating IgE antibodies to HIV, the levels of which increase as CD4+ cell numbers fall [83]. This may correlate with the increased frequency of IgE-mediated disorders

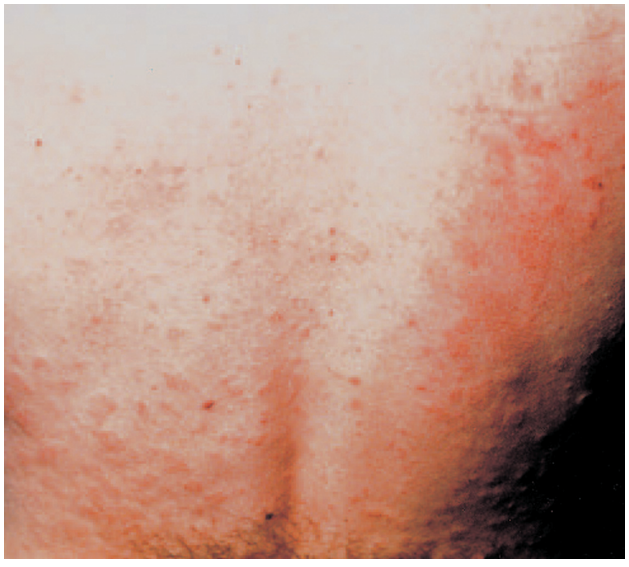


Figure 14.49 Severe asteatosis associated with HIV disease.



Figure 14.50 Eosinophilic (pustular) folliculitis. In some cases, the major presenting feature may be lichen simplex chronicus.

in HIV-infected patients, such as worsened atopic dermatitis and other hypersensitivity disorders. Basophils have been shown to be hyper-releasable in patients with HIV disease, and it is presumed

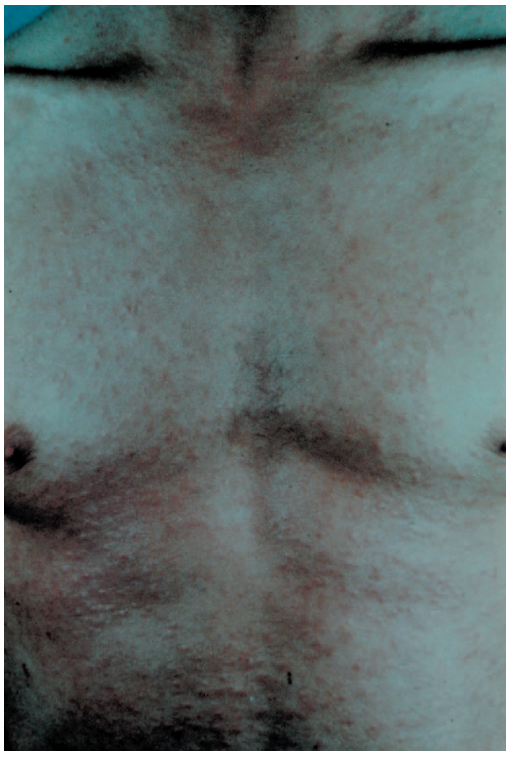


Figure 14.51 Papular urticaria associated with HIV infection.

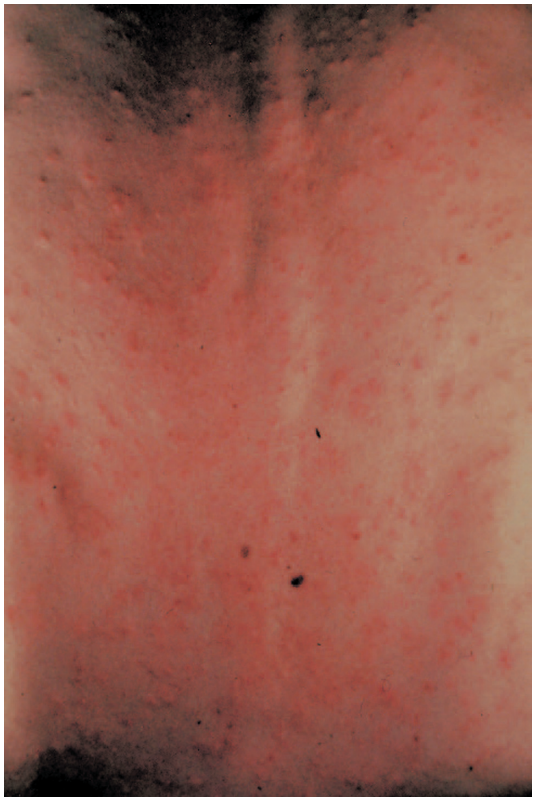


Figure 14.52 Acute papular urticarial reaction associated with acute seroconversion to HIV-1. Note the similarity to papular urticaria (Fig. 14–51).



Figure 14.53 Acute urticaria in HIV-infected patients.

that mast cells are similarly hyper-releasable. Enhanced degranulation of basophils and mast cells results in increased release of mast-cell mediators with attendant inflammatory reactions and pruritus. Patients with HIV disease may also have direct neural infection with neural irritation and enhanced sensations of itching. This may result in chronic excoriation, lichen simplex chronicus, and nodular prurigo. Sometimes, autonomic dysfunction is associated with diminished sweating and sebaceous gland secretion, worsening xerosis. In addition, patients infected with HIV are under severe stress for a number of reasons, and it is well known that stress may lead to urticaria and itching. Finally, patients with HIV infection may develop pruritus secondary to underlying circulating pruritogens associated with systemic disorders. Liver disease, renal disease, and systemic lymphoma all may be associated with pruritus. All these factors should be considered when dealing with an itchy HIV-infected patient.

The pathogenesis of eosinophilic (pustular) folliculitis is unknown, but has been postulated to be a consequence of an exaggerated reaction to *Pityrosporum* yeasts normally present within follicular infundibula.

Clinical Manifestations

Eosinophilic (pustular) folliculitis (EF) is one of the most characteristic and common pruritic dermatoses to develop in patients with CD4 lymphocyte counts below 200 cells/mm^3. The frequency declined significantly with the advent of HAART, but EF may reappear in patients with low CD4 cell numbers.

Patients often have widespread excoriated follicular papules that commonly involve the trunk, extremities, and head and neck areas [82]. It is important to exclude the diagnosis of scabies, which may look quite similar to EF, by performing scrapings and biopsies if necessary. It is rare to find intact pustules because patients are usually so uncomfortable that by the time they see the dermatologist, lesions have been excoriated.

Papular dermatitis of AIDS is a nondescript papular eruption in patients with HIV infection. The original description was that of an eruption of urticarial papules present on the trunk and extremities associated with excoriation and rubbing. Many believe that this may represent a reaction to insect bites or eosinophilic (pustular) folliculitis.

Atopic dermatitis produces erythematous patches and plaques with fine papulovesicles associated with scaling, crusting, and lichen simplex chronicus. Patients often have associated hyperlinear palms, allergic rhinitis, and asthma. HIV-infected individuals who develop atopic dermatitis may manifest severe forms of the disorder with erythroderma.

Xerotic dermatitis exhibits diffuse dryness of the skin with hyperpigmented scales and focal crusting. Many lesions may be fissured, and eczema craquele may develop. This latter complication enhances localized infection, as the broken skin serves as a portal of entry for bacteria and fungi.

Prurigo nodularis appears as hyperpigmented dome-shaped papules and nodules usually associated with lichen simplex chronicus. Lesions are produced by chronic rubbing and scratching.

Papular urticaria and chronic urticaria are manifested by pinkish-red erythematous papules and plaques, initially with little surface change (Fig. 14.53). Edema and a peau d'orange appearance of the skin are noted. Angioedema may be seen. Although papular urticaria may be excoriated, primary urticaria generally is not.

Histopathology

EF has a characteristic histopathological appearance – within the infundibula of hair follicles there are clusters of eosinophils that may be numerous. There is often a perifollicular inflammatory infiltrate of lymphocytes, neutrophils, and some eosinophils, especially when the follicles have ruptured.

The papular dermatitis of AIDS is similar to that of insect bite reactions, with a superficial and deep perivascular and interstitial infiltrate of lymphocytes, some histiocytes, and eosinophils.

Atopic dermatitis has microscopic features of a superficial perivascular infiltrate of lymphocytes and eosinophils, with epidermal hyperplasia and foci of spongiosis. Late lesions have the morphological appearance of lichen simplex chronicus. Asteatotic or xerotic dermatitis shows very little inflammation in the dermis, with slight epidermal hyperplasia, tiny amounts of spongiosis, and small zones of parakeratosis.

Laboratory Findings

Most patients with EF have low CD4+ cell counts. Eosinophilia may be found in patients with atopic dermatitis or papular urticaria. Although IgE levels are often elevated, no laboratory test is specific for any of these disorders. Underlying liver or renal impairment may be present.

Differential Diagnosis

The differential diagnosis of EF includes a number of other pruritic dermatoses that may be found in both HIV-infected individuals and immunocompetent patients. Bacterial folliculitis may be associated with pruritus and has clinical features similar to those of EF. Insect bite reactions, scabies, and dermatitis herpetiformis must all be excluded. If skin scrapings show no evidence of scabies, in most cases the diagnosis can generally be assumed to be EF and treated accordingly, without a biopsy.

Papular urticaria is thought to be a manifestation of insect bite reactions, thus it is important to exclude scabies and pediculosis by microscopic examination of skin scrapings. In some cases, careful histories reveal no evidence of insect bite reactions.

Atopic dermatitis must be differentiated from other psoriasiform dermatitides, such as psoriasis, cutaneous T-cell lymphoma, and psoriasiform drug eruptions. In general, the presence of severe pruritus and a history of atopy aid in this diagnosis. Xerotic dermatitis should be excluded from other forms of dry, scaly dermatoses, such as the characteristic "flaky-paint" dermatitis seen with kwashiorkor. In individuals with advanced AIDS, evaluation of nutritional status is essential.

Diagnosis

The diagnosis of noninfectious papular pruritus is based on history, physical examination, and performance of biopsies and scrapings. Evaluation for causes of chronic urticaria is similar to that undertaken in immunocompetent hosts, although searches for underlying parasitic and protozoal infestations and drug hypersensitivity reactions should be undertaken in all cases, as these are seen more commonly in HIV-infected hosts.

Treatment

Therapy of EF has been the subject of a number of studies because of the high incidence of the disorder and the morbidity it produces in HIV-infected individuals. Patients are generally treated with gradually increasing phototherapy units of ultraviolet B (UVB). Several studies have demonstrated that moderate exposure to UVB is safe in the treatment of HIV-related dermatoses if administered appropriately [79]. Therapy with itraconazole is also used, although its mechanism of action is unknown; it may act by diminishing the concentration of *Pityrosporum* yeasts within follicular infundibula. Other treatments are shown in Table 14.9. For papular urticaria, systemic antihistamines are generally used. In general, nonsedating antihistamines are not as effective as classic H-1 antagonists that induce somnolence, as these may aid in lessening the perceived sensation of itching. It is important to search for underlying causes of pruritus, such as ingestants that may be causing an allergic reaction. Chronic urticaria is often difficult to control in immunocompetent patients and may be especially problematic in HIV-infected hosts. It is usually difficult to establish an etiology. Atopic dermatitis usually responds to measures used for treatment in immunocompetent hosts.

Vasculitis and Other Vascular-related Abnormalities

Definition

Patients with HIV and AIDS develop a number of conditions that either involve primarily the blood vessels with inflammation or are associated with vascular proliferation. KS is discussed in the section on neoplastic disorders. Some of the conditions associated with vascular abnormalities include vasculitis, idiopathic thrombocytopenic purpura, hyperalgesic pseudothrombophlebitis, diffuse facial and truncal telangiectasia, and erythema elevatum diutinum.

Epidemiology

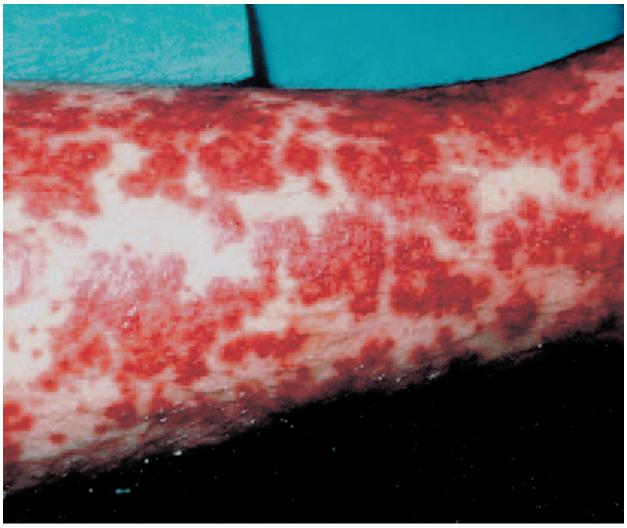
All these conditions have been reported only sporadically in patients with HIV disease.

Pathogenesis

Vasculitis and erythema elevatum diutinum represent manifestations of immune complex-mediated disease. Antigen–antibody

Table 14.9 Treatment of Noninfectious Papular Pruritic Disorders

Symptom	Treatment
Eosinophilic pustular folliculitis	Ultraviolet B phototherapy or natural sunlight exposure Itraconazole 100–200 mg orally twice daily Metronidazole orally may also be effective Oral 13-cis-retinoic acid may also be effective Doxepin, 10–20 mg orally every 6 hours, or other antihistamines for pruritus Topical application of antipruritic agents, such as pramoxine and menthol and phenol-containing lotions, may also be beneficial in diminishing itching
Papular urticaria	Systemic antihistamines Topical corticosteroid preparations (e.g., triamcinolone acetonide 0.1% ointment or more potent steroids) are beneficial in lessening inflammation; 10% doxepin compounded in aquaphor ointment is also effective
Xerotic dermatitis	Avoidance of excessive exposure to soap and water and other irritating factors Potent emollients, such as hydrophilic petrolatum and alpha-hydroxy acid–containing preparations; 12% lactic acid lotions are effective in lessening the severe dryness
Atopic dermatitis	Avoidance of irritants Emollient application Topical corticosteroid preparations Tacrolimus ointment (0.03% or 0.1%)



(a)



(b)

Figure 14.54 (a) Severe leukocytoclastic vasculitis of undetermined origin in an HIV-infected patient. (b) Severe vasculitis may result in deep ulcers. (a, Reprinted with permission, Arch Int Med 151:1295–1303, 1991; photograph b courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)

complexes collect within blood vessels, leading to deposition of fibrin in walls of blood vessels and attendant signs of inflammation. As the CD4+ cell count falls, the B-cell arm of the immune response may become hyperactive, leading to a relative overabundance of antibody secretion. The altered concentration of antigen to antibody in the circulation leads to precipitation and abnormal clearance of immune complexes [84]. This mechanism may be related to the development of idiopathic thrombocytopenic purpura as well. Extravasated erythrocytes lead to the characteristic clinical picture of palpable purpura and petechiae.

Hyperalgesic pseudothrombophlebitis is thought to be related to deep-seated KS, with associated secretion of cytokines and inflammatory mediators. Widespread telangiectasias may be associated with a circulating vascular proliferation factor that may be related to fibroblast growth factor or other vasoproliferative agents.

Clinical Manifestations

Leukocytoclastic vasculitis may progress clinically through several stages, beginning as urticarial papules or as small petechiae. In most cases, characteristic palpable purpuric papules develop most commonly on the extremities, although any body site may be involved. In patients with HIV infection, lesions may be more numerous and more florid than in immunocompetent hosts (Fig. 14.54). Pustules, ulcers, and bullae may also be seen. Erythema elevatum diutinum is a manifestation of chronic leukocytoclastic vasculitis that evolves into indurated reddish plaques, often over the joints (Figs. 14.55). The dorsal surfaces of the hands, especially over the knuckles and around the ankles and knees, are common sites of involvement. Plaques may assume a somewhat yellowish color as a consequence of the influx of numerous neutrophils and their degradation, which correlates with the clinical name of extracellular cholesterolosis that was previously applied to this condition. In time, plaques give way to firm, thick fibrotic nodules that may extend to involve volar skin surfaces. Generally, lesions are asymptomatic, but if they are located on weight-bearing sites, they may be painful [85]. Idiopathic thrombocytopenic purpura usually manifests as petechiae or palpable purpura and may simulate leukocytoclastic vasculitis.

Hyperalgesic pseudothrombophlebitis is associated with diffuse swelling of an extremity with extreme tenderness. Patients note marked sensitivity to even the lightest touch. No thrombophlebitic cords can be palpated. Diffuse telangiectasia has a



(a) (b)

Figure 14.55 (a, b) Erythema elevatum diutinum in AIDS. (a, Reprinted with permission, J Am Acad Dermatol 28:919–922, 1993).

clinical appearance somewhat similar to that of poikiloderma of Civatte (Figs. 14.56 and 14.57). The reddish telangiectatic areas on the cheeks, neck, chest, and trunk are not the result of sun exposure.

Histopathology

Leukocytoclastic vasculitis has a characteristic histopathological appearance that is usually diagnostic. Very early urticarial or petechial lesions are characterized by a perivascular and interstitial infiltrate that contains lymphocytes, neutrophils, and eosinophils, with abundant nuclear dust. Minimal involvement of actual blood vessels may be noted, so that no fibrin within the walls of vessels is appreciated. In time, inflammatory cells are noted within the walls of small and medium-sized blood vessels with abundant deposition of fibrin. In fully developed lesions, there may be significant thrombi within vascular lumina. Erythema elevatum diutinum is characterized by similar histological findings initially, but in due course, abundant fibrosis is noted around blood vessels and in the stroma. An increase in the number of MAC-387 positive histiocytes as well as fibroblasts can be demonstrated with immu-



(a) (b)

Figure 14.56 (a, b) Widespread telangiectasia and poikiloderma in HIV infection.



Figure 14.57 "Blotchy" matlike telangiectasia of the trunk.

noperoxidase stains. Only minimal granulomatous inflammation is seen, although in some lesions, cholesterol clefts are observed in the interstitium. Collections of neutrophils and eosinophils are seen in late fibrotic lesions, even though vasculitis may have abated.

Laboratory Findings

Elevated erythrocyte sedimentation rates may be found in patients with leukocytoclastic vasculitis and erythema elevatum diutinum. If an underlying cause of vasculitis is present, such as a connective tissue disease, characteristic laboratory findings of the underlying disease are found in most cases. CD4+ cell counts vary widely. Hypocomplementemia may be noted, and if vasculitis involves the kidneys, findings of renal dysfunction such as elevated serum creatinine levels may be present. Prolonged bleeding times will be noted in idiopathic thrombocytopenic purpura. Elevated antistreptolysin O titers or elevated immunoglobulin levels may be found in patients with erythema elevatum diutinum. No known abnormalities are found in patients with either hyperalgesic pseudothrombophlebitis or diffuse telangiectasia.

Diagnosis

Diagnosis of each of these conditions is based on characteristic clinical findings and exclusion of other diseases in combination with histopathological findings.

Treatment

The management of vascular-related disorders is outlined in Table 14.10. The treatment of vasculitis consists primarily of identifying the underlying cause and correcting associated abnormalities. Before cyclophosphamide, methotrexate, or other potentially immunosuppressive immunomodulators are administered, careful assessment of the immune status of the patient must be undertaken. All patients who are to be treated with agents such as these must be monitored carefully. In HIV-infected patients, the response of erythema elevatum diutinum to dapsone may be blunted or there may be no response at all.

Table 14.10 Treatment of Vasculitis and Vascular-related Abnormalities

Symptom	Treatment
Vasculitis	Nonsteroidal anti-inflammatory agents may be beneficial in some cases Colchicine, dapsone, or systemic corticosteroids such as prednisone may be required in severe cases Cyclophosphamide and methotrexate are occasionally needed in severe cases Splenectomy is effective for idiopathic thrombocytopenic purpura
Erythema elevatum diutinum	Dapsone therapy (oral) Surgical excision has been effective in some cases
Hyperalgesic pseudothrombophlebitis	Analgesics and nonsteroidal antiinflammatory agents are the primary treatment Narcotic analgesics may be required, as the condition is extremely painful Bed rest, warm compresses, and leg elevation may be useful
Diffuse telangiectasis	Selective laser destruction using argon or tunable dye laser Electrocoagulation may also be beneficial Cosmetic camouflage using green-tinted makeup is helpful in masking the red appearance of the skin

Photoinduced and Photoaggravated Conditions

Definition

Several skin disorders that are worsened by light exposure may be associated with HIV infection. These include chronic actinic dermatitis, porphyria cutanea tarda (PCT), photoexacerbated drug eruptions, photoexacerbated rosacea, and granuloma annulare.

Epidemiology

No specific figures exist regarding the prevalence of these conditions in that most have been reported only sporadically. PCT, however, is being reported with some frequency, although the overall prevalence of this condition remains low.

Pathogenesis

Chronic actinic dermatitis may be associated with HIV infection because of the exaggerated B-cell immunity that may be present in these individuals. Patients with HIV infection may develop allergies to drugs and other substances owing to alterations of the immune system and recall of underlying allergic phenomena. Patients with HIV infection produce greater concentrations of porphyrins, possibly as a consequence of abnormal liver function secondary to hepatitis, such as hepatitis C or other factors. This latter factor may be of prime importance, as over 50% of all patients with PCT have been found to be coinfected with this virus.

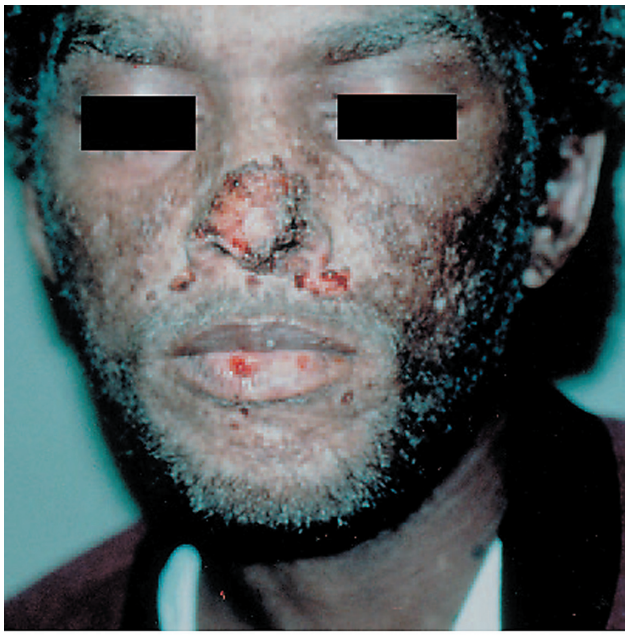
Clinical Manifestations

Chronic actinic dermatitis of HIV infection is characteristically manifested by psoriasiform lichenified plaques in the sun-exposed areas of the body; these plaques are often hyperpigmented, scaly, and pruritic [86]. Lesions are generally located on the dorsal surfaces of the hands, forearms, face, upper anterior chest, and the posterior neck. Extensive lichenification is often seen, and patients

may have an appearance similar to that described with actinic reticuloid. The appearance of PCT is virtually identical to that seen in immuno-competent hosts, with blisters on the dorsal surfaces of the hands and other sun-exposed areas (Fig. 14.58). These blisters are associated with crusting, milia formation, dyspigmentation, and scarring [87]. Frequently, there is also hyperpigmentation and hypertrichosis of the malar areas of the face. Patients may report the excretion of dark urine. Widespread granuloma annulare is manifested by small pinkish dermal papules distributed on sun-exposed areas. Photoexacerbated drug eruptions often appear lichenoid or erythematous and are distributed on photoexposed sites (Figs. 14.59 and 14.60). Actinically aggravated rosacea looks similar to acne rosacea in immunocompetent hosts, with an eruption of follicular papules and pustules on the face (Fig. 14.61). Extrafacial lesions may be seen. Dermal waxy papules may represent granulomatous rosacea, which may also be worsened by sunlight exposure.



(a)



(b)

Figure 14.58 Severe porphyria cutanea tarda in a patient with HIV infection. Most patients with this complication have been found to suffer from concomitant hepatitis C infection.



Figure 14.59 Lichenoid photodermatitis of unknown origin in a patient with AIDS.

Histopathology

Chronic actinic dermatitis is generally manifested by a superficial and often deep psoriasiform dermatitis with an infiltrate of lymphocytes and abundant eosinophils. In immunocompetent individuals, PCT has histological findings that are characterized by a subepidermal blister with minimal inflammation in the dermis. Preservation of dermal papillae, so-called "festooning," is seen, and there are thick hyaline periodic acid-Schiff stained-positive rims surrounding blood vessels in the upper dermis. Elongated aggregations of necrotic keratinocytes are often present in the epidermis, overlying the blister; these have been referred to as "caterpillar bodies" [88]. Granuloma annulare also has a histological pattern that resembles a diffuse infiltrate of palisaded histiocytes in the dermis, with mucin in the center of the palisade. Eruptive forms of granuloma annulare may be associated



Figure 14.60 Acute phototoxic reaction to dapsone.

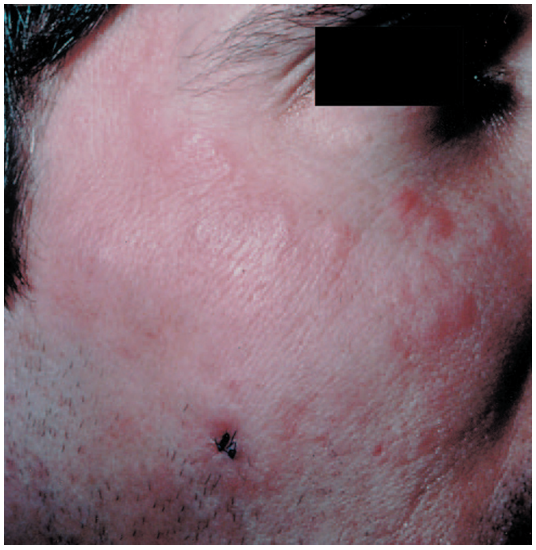


Figure 14.61 Acne rosacea may be photoexacerbated in HIVinfected hosts.

only with an interstitial infiltrate without significant palisading. Rosacea is manifested by a perifollicular infiltrate of lymphocytes, some neutrophils, and follicular pustules.

Laboratory Findings

The only significant laboratory findings associated with PCT are elevated circulating and urinary uroporphyrins (≤9000 IU/ml) and coproporphyrins. CD4+ cell counts range from 3 to >500 cells/mm^3, which indicates that the disorder may develop at any stage of HIV infection. Elevated serum glutamic-oxaloacetic transaminase and serum glutamate pyruvate transaminase enzyme levels and, occasionally, hyperbilirubinemia occur. Many patients with HIV infection and PCT are anemic rather than polycythemic, and treatment with phlebotomy cannot be undertaken in such patients. CD4+ cell counts below 200 cells/mm^3 are usually associated with photoaggravated disorders.

Diagnosis

The diagnosis of chronic actinic dermatitis involves a history of recent exposure to potential photoallergens or phototoxins, as well as a past history of exposure that may have been reactivated. PCT is diagnosed on the basis of clinical and histological findings, as well as demonstration of elevated urinary uroporphyrin and coproporphyrin levels. Actinically exacerbated granulomatous disorders are diagnosed on the basis of exclusion of infectious diseases in the context of characteristic clinical findings.

Treatment

The management of photoaggravated conditions is outlined in Table 14.11. In some cases of chronic actinic dermatitis, complete light avoidance may be essential, as even light emitted from television monitors may be sufficient to worsen the condition. Paradoxically, the use of psoralen and ultraviolet A therapy may "harden" the skin and lead to remission.

PCT is classically treated by repeat phlebotomy. In patients with HIV infection who are often anemic, this treatment cannot be used. Low doses of hydroxychloroquine may be effective in mobilizing accumulated porphyrin in the liver [89]. Erythropoietin has been shown to be effective in treatment of PCT by enhancing heme biosynthesis [90]. This results in mobilization of porphyrins. Although expensive, this might be the most beneficial form of treatment, as it will tend to correct the hematological deficit as well as the metabolic one. The effect of HAART on the incidence of HIV-associated PCT is unknown at this time.

Rosacea is often treated with the usual antirosacea regimen of tetracycline and topical benzoyl peroxide. Topical or systemic metronidazole may be beneficial, as *Demodex* mites are thought to play a role in the pathogenesis in some cases.

Table 14.11 Treatment of Photoinduced and Photoaggravated Conditions

Symptom	Treatment
Chronic actinic dermatitis	Avoidance of photoallergens and phototoxins Avoidance of ultraviolet light Application of topical corticosteroid preparations Hydroxychloroquine (Plaquenil) 200 mg orally one to two times daily, may also be beneficial
Porphyria cutanea tarda	Hydroxychloroquine starting at 25 mg/wk and gradually increased to 200 mg/wk Erythropoietin
Rosacea	Oral tetracycline and topical benzoyl peroxide combination Metronidazole gel applied twice daily is also effective Metronidazole, 250–750 mg orally three times daily Avoidance of ultraviolet light may be necessary in cases associated with photoexacerbation
Granuloma annulare	Nicotinamide may be effective Application of topical corticosteroid preparations may be effective Avoidance of ultraviolet light may be necessary in cases associated with photoexacerbation

Cutaneous Drug Eruptions

Definition

Drug eruptions are cutaneous disorders caused by the oral or parenteral administration of therapeutic drugs. Most are hypersensitive in nature, although others are a consequence of direct toxicity or unusual idiosyncratic reactions.

Epidemiology

Cutaneous drug reactions are the most common manifestation of drug hypersensitivity. A study of 684 HIV-infected patients in Boston revealed that 79% had one or more dermatological diagnoses, 188 of which included cutaneous reactions to drugs [91]. The incidence of many of these reactions is higher in HIV-infected patients than in the general population, including hypersensitivity to multiple drugs. The best known example of a drug that causes hypersensitivity reactions in HIV-infected hosts is trimethoprim-sulfamethoxazole. In some studies, 50–60% of HIV-positive patients were shown to develop a cutaneous eruption due to this



(a) (b)

Figure 14.62 (a,b) Unusual papular drug eruption in response to trimethroprim-sulfamethoxazole, mimicking eosinophilic (pustular) folliculitis.

agent. Up to 45% of patients develop maculopapular eruptions, with variable numbers of other reactions being reported. African-American patients seem to have a lower risk of cutaneous trimethoprim-sulfamethoxazole reactions. Stevens-Johnson syndrome and toxic epidermal necrolysis occur sporadically [92]. Other antibiotics are also common offenders, as maculopapular eruptions may often be seen in patients taking antituberculous regimens, amoxicillin-clavulanic acid, a combination of clindamycin and primaquine, intravenous clindamycin, and fusidate. Thalidomide used for treatment of aphthous ulcers may cause a widespread maculopapular exanthem in HIV-positive patients [93]. Zidovudine also may cause an exanthematous eruption in 1% of patients, which may mandate its discontinuation. Other eruptions and toxic drug effects have been reported to occur sporadically [94].

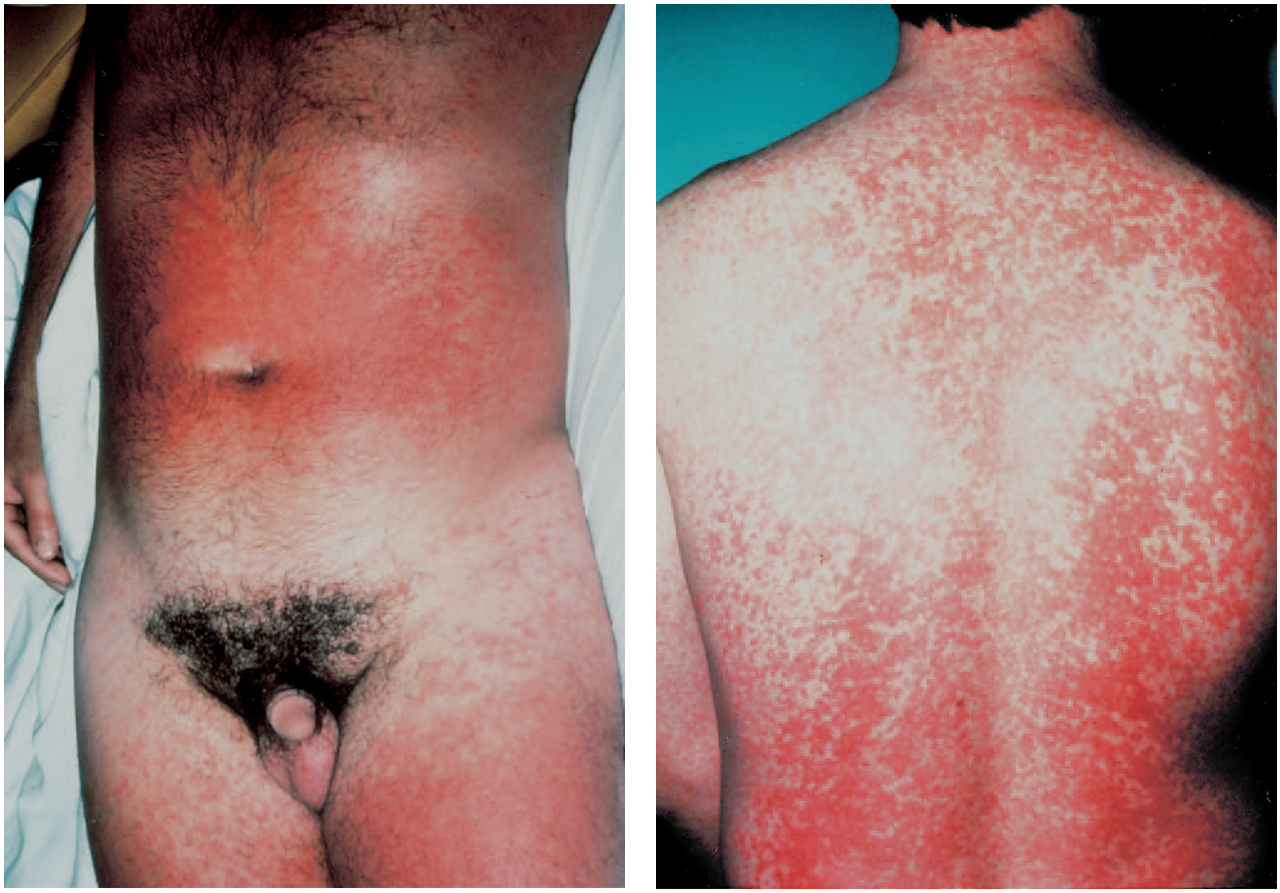
Pathogenesis

Drug eruptions develop as a consequence of any of the classic hypersensitivity reactions described by Coombs and Gell. Immediate hypersensitivity mediated by immunoglobulin E may lead to anaphylactoid and urticarial reactions. Type 2 reactions involving IgG and IgM antibodies may induce hemolytic anemia and thrombocytopenia. Immune complex-mediated reactions may produce serum sickness-like eruptions or drug-induced lupus erythematosus. Morbilliform eruptions may be present, although they may also be the result of cell-mediated (type 4) immune reactions. The pathogenesis of some of these eruptions is unknown. Underlying infection with CMV or EBV may predispose the patient to adverse drug reactions analogous to those seen with EBV-induced infectious mononucleosis and ampicillin [95].

Clinical Manifestations

Trimethoprim-sulfamethoxazole is the best known and most common allergic drug eruption to develop in patients with HIV infection (Fig. 14.62). In most cases, a widespread eruption of fine pink to red macules and papules involving the trunk and extremities develops 8–12 days after initiating therapy and reaches maximal intensity 1–2 days later. In some cases, desquamation may supervene. The eruption may disappear within 3–5 days even though therapy is continued. In some cases, the eruption may persist for days to weeks following discontinuation of the medication. Cutaneous eruptions caused by trimethoprim-sulfamethoxazole do not always recur with drug rechallenge in HIV-infected patients. However, if the agent is to be reinstituted, it should be done under controlled circumstances to monitor for possible anaphylactoid reactions characterized by fever, urticarial papules and plaques associated with angioedema, shortness of breath, and bronchospasm. Stevens-Johnson syndrome, characterized by fever, widespread blistering of the skin and mucous membranes of the eye, mouth, and/or genitals, may also develop. Toxic epidermal necrolysis (TEN) is a more serious manifestation that involves widespread areas of the skin with confluent bullae that often leads to loss of skin in massive sheets. Many cases of TEN have been reported in HIV-infected individuals. Other antibiotics, such as cephalexin and rifabutin, may produce morbilliform eruptions (Fig. 14.63).

NRTIs are associated with numerous cutaneous manifestations. Zidovudine may induce several different cutaneous complications. Blue to brown-black nail discoloration has been reported in over 40% of patients [96] (Fig. 14.64). It is more common in African American patients and usually begins 4–8 weeks after initiating treatment or may occur as late as 1 year. Longitudinal streaks are most common, but diffuse pigmentation and transverse bands may occur. The thumbnails are affected most frequently. Zidovudine may also cause hyperpigmentation of the mucous membranes and the skin that may mimic a clinical picture seen with adrenal insufficiency [97]. In addition to pigmentary abnormalities, severe exanthematous eruptions, such as lichenoid



(a) (b)

Figure 14.63 (a,b) Morbilliform eruptions in response to cephalexin and rifabutin, respectively, in patients with HIV infection.

reactions, that may appear almost identical to lichen planus may develop within 1 to 2 weeks following the initiation of zidovudine therapy. Other manifestations include acral and periarticular reticulate erythema that may simulate dermatomyositis. Abacavir, another NRTI, is associated with a life-threatening hypersensitivity reaction that occurs in 5–8% of patients. This reaction, which usually occurs within the first six weeks after treatment initiation, is characterized by fever and/or rash in 98% of patients. Other systemic manifestations include multivisceral involvement, hypotension, lymphocytosis, and eosinophilia. The rash is generally urticarial or maculopapular and of mild to moderate intensity. Treatment for this condition involves immediate and permanent discontinuation of the drug [98–100]. Emtricitabine, a newer NRTI, may cause rashes and hyperpigmentation. Rashes, which occur in 17–30% of patients, may be maculopapular, urticarial, vesiculobullous, pustular, or pruritic. Hyperpigmentation occurs almost exclusively in African American patients and usually affects the palms and soles. The incidence of hyperpigmentation is 3% overall and 32% in children [99].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), most notably nevirapine, are also associated with cutaneous eruptions. Approximately 20% of patients treated with nevirapine develop a rash, which is usually maculopapular and erythematous in nature. Risk factors for developing a rash due to nevirapine include a high baseline CD4 count, a low baseline viral load, Chinese ethnicity, and female gender [100]. Stevens-Johnson syndrome may develop; therefore, the clinician must terminate therapy if the rash involves the mucous membranes, is moist, or becomes extensive and is accompanied by fever [101]. Another NNRTI, efavirenz, causes maculopapular or erythematous rashes in 26% of patients. Rashes appear approximately 11 days after starting

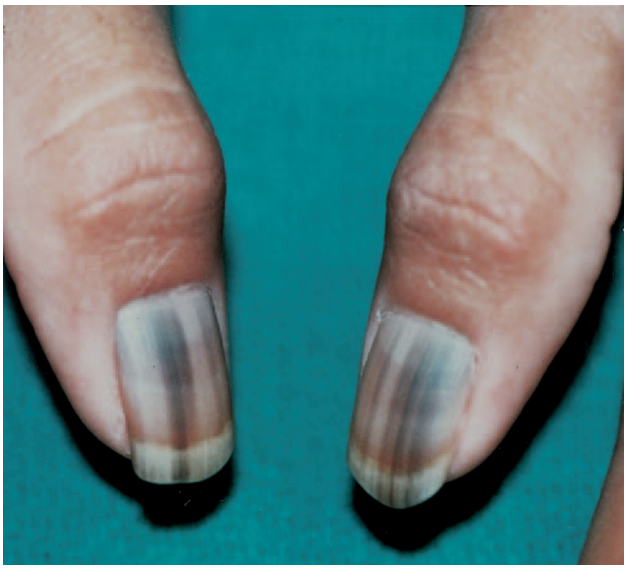


Figure 14.64 Longitudinal pigmented bands of multiple nails caused by zidovudine.

therapy and last for about 2 weeks. These rashes occasionally become vesicular, desquamated, or ulcerated. Efavirenz is also associated with photosensitivity and cutaneous leukocytoclastic vasculitis [99].

PIs may also cause numerous dermatological abnormalities. Indinavir has been associated with paronychia and pyogenic granuloma of the great toes [102], recurrent paronychia and ingrown toenails [103], hair loss of the lower extremities [104], and striae formation [105]. This drug, as well as the other PIs, has been associated with a form of lipodystrophy leading to abnormal fat accumulation in particular areas along with an overall wasting appearance in others [106,107]. The fat accumulation typically leads to the development of a cervicodorsal fat pad ("buffalo hump") [108–112], and/or an increased abdominal girth ("protease pouch," "crix belly") [109,110,113], or breast development [113]. Some of these patients may also develop elevated triglyceride and cholesterol levels. The metabolic factors involved in this adverse effect are unknown at this time, although several potential mechanisms have been suggested [114].

The fusion inhibitor, enfuvirtide, is associated with injection site reaction in 98% of patients. Most reactions occur during the first week of treatment and include erythema, mild induration, and nodules at the injection site. The infiltrate surrounding the site typically includes eosinophils, histiocytes, and other inflammatory cells. In long-term therapy with enfuvirtide, scleroderma-like lesions may develop [99,100].

Penile ulcerations caused by foscarnet develop about 11–16 days after initiation of therapy. Lesions range in number from two to five and are usually 1–5 cm in diameter and consist of erosive, bullous, tender ulcerations [115]. Sites of high deposits of urine concentration (urethral meatus and scrotum) are affected. Oral and esophageal ulcers may also develop. In addition to ulcerations, a generalized cutaneous eruption has been reported [116]. Widespread erythroderma has been reported in association with rifampin administration.

Parenteral pentamidine reactions range from morbilliform to urticarial eruptions. Sulfadoxine-pyrimethamine (Fansidar) may cause erythema multiforme and toxic epidermal necrolysis, while aerosolized pentamidine may cause a widespread erythematous maculopapular pruritic eruption. Other causes of toxic epidermal necrolysis include chlormezanone, fluoxetine, and thiacetazone. Unfortunately, patients sensitive to trimethoprim-sulfamethoxazole also often react to the most common substitute, dapsone. A sulfone syndrome has been observed when dapsone is used as a prophylaxis against *P. jiroveci* infection. Finally, systemic treatment with methotrexate for psoriasis and with corticosteroids for vasculitis has precipitated both rapid proliferation and the sudden appearance of non-Hodgkin's lymphoma (NHL), opportunistic infections, and KS.

Histopathology

The histopathology of morbilliform drug eruptions typically consists of a superficial perivascular inflammatory infiltrate of lymphocytes with scattered eosinophils associated with vacuolar alteration of the dermoepidermal junction and individually necrotic keratinocytes. Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis are all characterized by prominent vacuolar interface changes, with extensive keratinocytic necrosis of the epidermis. In toxic epidermal necrolysis, the number of inflammatory cells in the dermis may be minimal, although there is confluent epidermal necrosis with no parakeratosis, a consequence of the rapid progression of the eruption. Urticarial allergic eruptions are usually characterized by mixed infiltrates of inflammatory cells interstitially in the dermis with minimal epidermal change. Ulcerations caused by foscarnet generally show a mixed perivascular and interstitial infiltrate in the dermis with ulceration and epidermal necrosis, although inflammation may be minimal. Zidovudine-induced lichenoid eruptions may appear histologically identical to those of lichen planus, whereas zidovudine-induced nail pigmentation generally consists of an increase in the amount of melanin within melanocytes associated with scattered melanophages in the dermis.

Laboratory Findings

In most cases, laboratory findings are nonspecific, although patients with cutaneous drug eruptions have lowered CD4+ cell numbers ($\leq$250 cells/mm^3). Eosinophilia may be noted as a general sign of hypersensitivity. As drugs may induce a number of other systemic problems, it is not uncommon to see accompanying changes such as neutropenia, thrombocytopenia, hypoglycemia, elevation of transaminase levels, and anemia.

Diagnosis

Diagnosis is generally made on the basis of the clinical appearance of the eruption correlated with the history of drug intake. As a general rule, antibiotics are the most common offenders, followed by anticonvulsants, nonsteroidal anti-inflammatory agents, and antiretrovirals [91]. Furthermore, patients may be sensitive to multiple drugs. Biopsies may be required and, in some cases, rechallenge with the suspected offending allergen may be necessary to prove the diagnosis.

Treatment

The most serious cutaneous complication is epidermal necrolysis that may arise if the diagnosis is not made in timely fashion and the offending agent is not withdrawn. Other complications include systemic toxicity, such as hepatotoxicity or renal damage associated with the sulfone syndrome. Toxic epidermal necrolysis may lead to secondary infection with sepsis, volume depletion, and high output cardiac failure as a consequence of widespread denudation of the skin. Patients who develop this must be treated aggressively in intensive care settings. Whether systemic corticosteroids should be used remains controversial. Hypersensitivity to trimethoprim-sulfamethoxazole has been successfully treated with desensitization. Desensitization may also be attempted with other antibiotics when necessary.

Hair and Nail Abnormalities

A number of abnormalities of hair and nails may be encountered in patients with HIV infection. Chronic inflammatory and noninflammatory alopecia has been observed (Fig. 14.65). The hair may become lusterless and dull with straightening. Although these changes may be related to HIV infection and concomitant nutritional abnormalities, diffuse alopecia may also be associated with underlying connective-tissue diseases or syphilis. Diffuse,

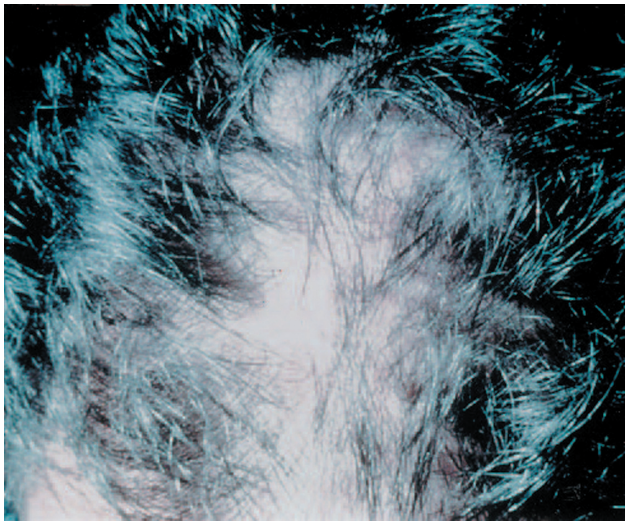


Figure 14.65 Noninflammatory alopecia associated with chronic HIV infection.

fine, downy alopecia may occur in patients with end-stage AIDS. Finally, patients with HIV infection may develop serious infections with fever leading to true telogen effluvium.

In addition to loss of scalp hair, there may be elongation (trichomegaly) of the eyelashes, a sign of a prolonged anagen phase (Fig. 14.66) [117]. Other changes of the hair seen in HIV-infected patients include premature canities (Fig. 14.67) and alopecia areata [118].

Nail disorders may develop in patients with HIV infection. Nail plate thickening with subungual hyperkeratosis and dystrophy may be associated with fungal infections caused by dermatophytes as well as by *Candida*, *Hendersonula toruloidea,* and other nondermatophyte fungi. The yellow nail syndrome secondary to metabolic abnormalities, lymphedema, and hypoxia is characterized by transverse and longitudinal ridging. As in immunocompetent patients, Beau's lines may be seen 2–3 months after an episode of a serious infection (Fig. 14.68). Diminished thickness of the nail plate may also be seen. Increased nail plate opacity as well as both Muehrcke's and Terry's nails (Fig. 14.69) have been



Figure 14.67 Premature canities in patients with AIDS.

seen. Ridging and nail thickness changes are most likely a consequence of diminished matrix growth with decreased nail plate turnover. Involvement of the periungual tissues by infectious agents, psoriasis, and erythema with features similar to Gottron's papules may also be seen.

Miscellaneous and Metabolic Skin Disorders Associated with Human Immunodeficient Virus Infection

Calciphylaxis is a disorder that represents a manifestation of hyperparathyroidism; it develops in association with renal failure



Figure 14.66 HIV-associated trichomegaly of the eyelashes.



Figure 14.68 Beau's lines in a patient recently recovered from Pneumocystis jiroveci pneumonia.



(a) (b)

Figure 14.69 (a) Terry's nails in a patient with advanced AIDS. Such nail changes should be distinguished from (b) "half-and-half" nails, which are associated with uremia. (Photograph b courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G. T. Hospital, Grant Medical College, Mumbai, India.)



Figure 14.70 Calciphylaxis in an HIV-seropositive patient with chronic renal failure. (Reprinted by permission, J Am Acad Dermatol 26:559–562, 1992.)



Figure 14.71 Calcinosis cutis in an infant infected with HIV in utero. (Photograph courtesy of San Chen, M.D., Department of Dermatology, University of Texas Medical Branch at Galveston, Galveston, TX.)

[119]. Sensitivity to elevated circulating levels of parathyroid hormone leads to widespread calcification of the skin, soft tissues, blood vessels, and viscera. Diminished levels of protein C may be important in the pathogenesis of the disorder. Histopathologically, there is extensive calcification of small and medium-sized blood vessels throughout the dermis and subcutaneous fat, with secondary cutaneous necrosis and prominent thrombosis. Painful skin lesions may appear as livedo reticularis-like areas of the skin with hemorrhage, purplish discoloration, and erythema (Fig. 14.70). Necrosis and gangrene may appear within a few days. Treatment consists of correction of serum calcium and phosphorus abnormalities as well as emergency parathyroidectomy. Some patients may have no detectable abnormalities in parathormone, calcium, or phosphorus. Calcinosis cutis has also been observed in an infant infected in utero with HIV (Fig. 14.71).

In addition to the diseases described, a host of poorly defined inflammatory skin disorders has been noted in patients with HIV disease. These are thought to occur as a consequence of cutaneous eruptions developing in the setting of an abnormal immune state

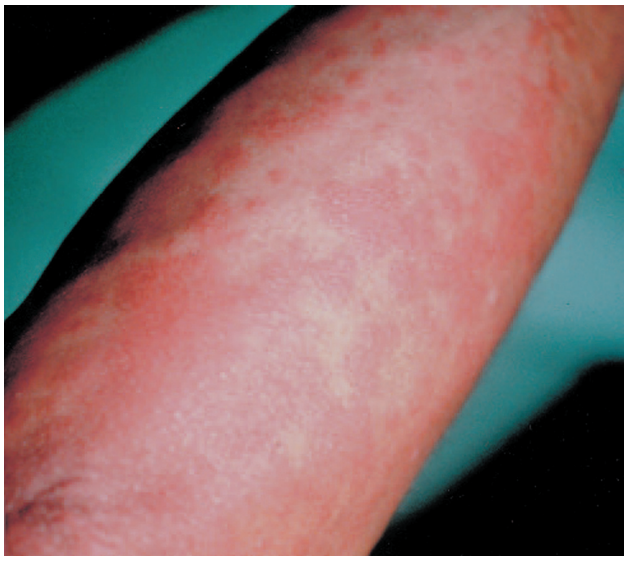


Figure 14.72 Evolving erythema multiforme.



Figure 14.73 Unusual gyrate erythema-like eruption of unknown etiology in an HIV-infected patient.

that includes diminished neutrophil function, elevated serum levels of IgE, abnormal T cell, B cell, and macrophage function, and the presence of circulating antiepidermal antibodies. Widespread scaly dermatoses, erythema multiforme (Fig. 14.72), diffuse noninfectious granulomatous dermatitis, gyrate erythema-like eruptions (Fig. 14.73), and serum sickness-like eruptions (Fig. 14.74) correlate poorly, if at all, with classically described clinical disorders. In addition to the unusual clinical picture, histopathological findings correlate with clinical findings in only 30% of cases. Other unusual cutaneous conditions include lichenoid granulomatous dermatitis, exaggerated responses to insect bites, Sweet's syndrome (Fig. 14.75), disseminated granuloma annulare (Fig. 14.76), and nonspecific cellulitis [120].

Features of adult Kawasaki's disease include the age of onset, pneumonia, arthritis, aseptic meningitis, and the absence of cardiac involvement or thrombocytosis. Clinically, patients had fever of more than 5 days' duration that was unresponsive to antibiotics and that was associated with bilateral conjunctivitis, a generalized confluent macular eruption with edema of the hands that underwent desquamation, oral mucous membrane changes, and cervical adenopathy.

Acute allergic contact dermatitis and acute anaphylactic reactions as a consequence of latex sensitivity have also been reported in HIV-infected patients [121].

Malnutrition becomes a common problem in individuals with HIV disease. Cutaneous manifestations of protein and vitamin deficiencies may be encountered. An eruption of multiple spiny follicular papules, known as phrynoderma, may be a manifestation of vitamin A deficiency. Vitamin C deficiency results in scurvy, which is manifested as bleeding gums and perifollicular petechiae. Pellagra (pyridoxine deficiency) is evidenced as a blistering photosensitive eruption with hyperpigmentation that is associated with diarrhea and dementia. Kwashiorkor presents with dry scaly areas of the skin, the so-called "flaky-paint" dermatitis. Diminished luster to the hair and a reddish-orange color may also be noted. Treatment with nutritional zinc replacement reduces periorificial erythema that is a manifestation of acrodermatitis enteropathica [122]. Advanced AIDS may also be associated with diffuse hyperpigmentation and necrotizing gingivitis (Fig. 14.77).

NEOPLASTIC DISORDERS

A number of different neoplastic disorders may develop in patients with HIV disease. These may be classified as epithelial, lymphoreticular, vascular, smooth muscle, and melanocytic.

Epithelial Cutaneous Neoplasms

Definition

Epithelial neoplasms are either benign or malignant proliferations, such as (1) neoplasms of the anorectal area, including anal



(a) (b)

Figure 14.74 (a, b) Serum sickness–like eruption in HIV-infected patient that developed shortly after a wasp sting.



Figure 14.75 Sweet's syndrome associated with a squamous cell carcinoma of the lung in an HIV-infected host.

intraepithelial neoplasia, squamous cell carcinoma in situ, fully developed squamous cell carcinoma, and cloacogenic carcinoma; (2) both cervical intraepithelial neoplasia and fully developed cervical carcinoma in HIV-infected women; (3) bowenoid papulosis; (4) basal cell carcinoma – multiple, primary, and metastatic; (5) multiple cutaneous squamous cell carcinomas associated with epidermodysplasia verruciformis; and (6) multiple sebaceous gland tumors. Other non-cutaneous epithelial neoplasms that have been observed in patients with HIV infection include small cell carcinoma of the lung, anaplastic carcinoma, testicular germ cell tumors, seminoma, transitional cell carcinoma of the bladder, and parotid gland tumors (Fig. 14.78).

Epidemiology

The incidence of epithelial neoplasms in patients infected with HIV is markedly increased, most commonly in oral, cervical, and anorectal locations [123]. Bowenoid papulosis, cloacogenic carcinoma, and transitional cell carcinoma are also increased in incidence. These neoplasms, as well as carcinoma of the cervix, are thought to be related to repeated trauma and HPV infection.

HPV infection is highly prevalent as vulvar HPV infection, condyloma acuminata, and vulvar intraepithelial neoplasia. Invasive squamous cell carcinoma arising in HPV-induced anal intraepithelial neoplasia or cervical intraepithelial neoplasia has become a major clinical problem as patients with HIV infection survive longer [124–126]. Epidermodysplasia verruciformis, a condition of widespread HPV infection with multiple carcinomas, has been reported in several patients with HIV infection.

Pathogenesis

HPV infection, deficient cell-mediated immunity, the HIV *tat* protein, and other, less understood factors interact to promote epithelial neoplasia in HIV-seropositive persons (see Chapter 12).

Clinical Manifestations

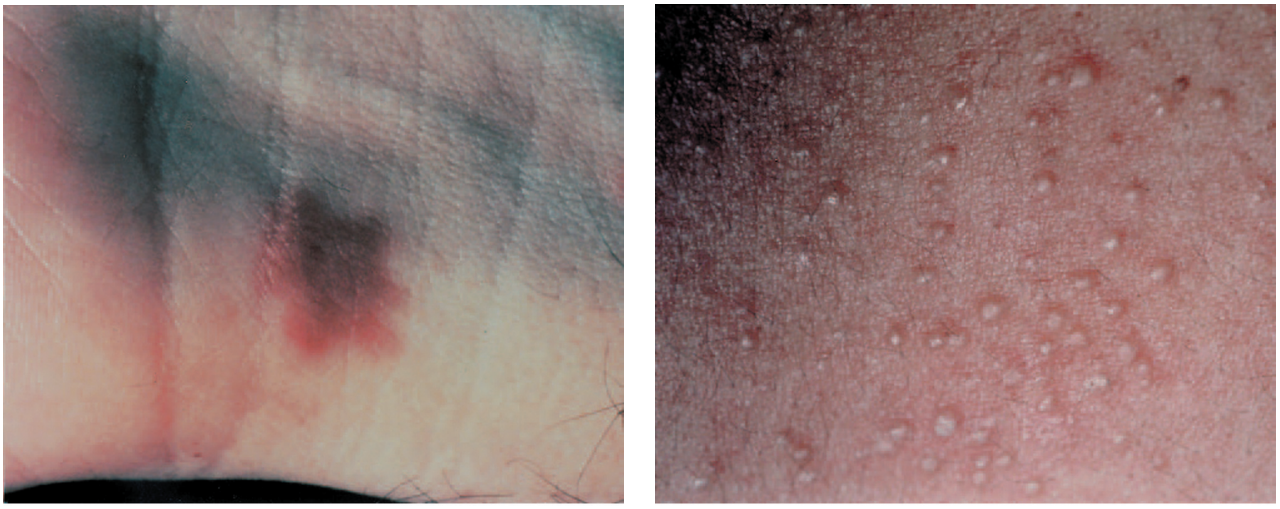
Invasive verrucous squamous cell carcinoma may occur either in the cervix or in the anorectal area (see Chapter 12). Bowenoid papulosis is generally manifested as brown-to-black flat-topped papules on the labia or penile skin. The same oncogenic HPV types can lead to squamous cell carcinoma of the penis or keratoacanthomas (Fig. 14.79). Epidermodysplasia verruciformis has a clinical appearance of widespread warty papules that are either pink or red. Metastases of basal cell carcinoma may occur, usually in draining lymph nodes and the lung.

Histopathology

The histopathological findings of these conditions range from subtle atypical intraepithelial proliferations within stratified squamous epithelial cells, to full-thickness involvement of the epithelium by atypical neoplastic keratinocytes (see Chapter 12).

Laboratory Findings

HPV genomic DNA can be identified with neoplastic cells by PCR in many cases (see Chapter 12).



(a) (b)

Figure 14.76 (a, b) Disseminated HIV-associated granuloma annulare. Plaques may mimic those of Kaposi's sarcoma.



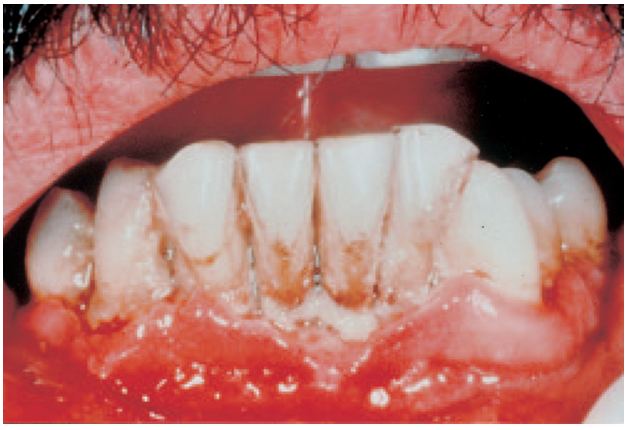
(a)



(b)



(c)



(d)



(e)

Figure 14.77 (a–c) Diffuse hyperpigmentation associated with advanced AIDS. (d, e) Necrotizing gingivitis with loss of teeth noted in E. (Photograph b courtesy of Jeffrey Callen, M.D., Division of Dermatology, Department of Internal Medicine, University of Louisville School of Medicine, Louisville, KY; photograph c courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G.T. Hospital, Grant Medical College, Mumbai, India.)



Figure 14.78 Parotid gland tumor in an HIV-seropositive patient. (Photograph courtesy of Axel Hoke, M.D., Novato, CA.)

Diagnosis

Diagnosis is established primarily on the basis of clinical appearance and skin biopsy (see Chapter 12).

Treatment

Treatment of squamous cell carcinoma usually requires excision or aggressive destructive measures (Table 14.12) (see Chapter 12). The use of HAART does not seem to affect patient prognosis [127].

Lymphoreticular Malignancies

Definition

A number of different lymphoreticular malignancies of both B- and T-cell lineage may involve lymph nodes and the reticuloendothelial system, although the skin may be involved primarily or secondarily. NHL, mostly high grade (small noncleaved cell and large cell immunoblastic) B-cell lymphomas, is seen most commonly in HIV patients, although cutaneous T-cell lymphomas, Hodgkin's disease, lymphomatoid granulomatous (angiocentric peripheral T-cell lymphoma), and adult T-cell leukemia-lymphoma caused by human T-cell lymphotropic virus (HTLV-1) have been reported.



Figure 14.79 Keratoacanthoma associated with HPV infection.

Table 14.12 Treatment of Neoplastic Disorders

Symptom	Treatment
Epithelial Cutaneous Neoplasms	
Squamous cell carcinoma	Surgical excision Carbon dioxide laser destruction
Bowenoid papulosis	Electrodesiccation and curettage; Other destructive surgical methods
Basal cell carcinoma	Surgical excision, cryosurgery
Epidermodysplasia verruciformis	Surgical excision Destructive treatment methods
Lymphoreticular Malignancies	
Cutaneous T-cell lymphoma	Psoralen and ultraviolet A* therapy Total body electron beam Topical nitrogen mustard
Systemic lymphoma	Methotrexate, prednisone, bleomycin, doxorubicin, cyclophosphamide, vincristine
Kaposi's Sarcoma	Cryotherapy with liquid nitrogen Radiation therapy Electron beam therapy Intralesional injections of vinblastine sulfate, 0.2–0.4 mg/ml at biweekly intervals Intralesional interferon alpha-2b Alitretinoin gel Liposomally encapsulated doxorubicin and daunorubicin Photodynamic therapy Isotretinoin plus interferon

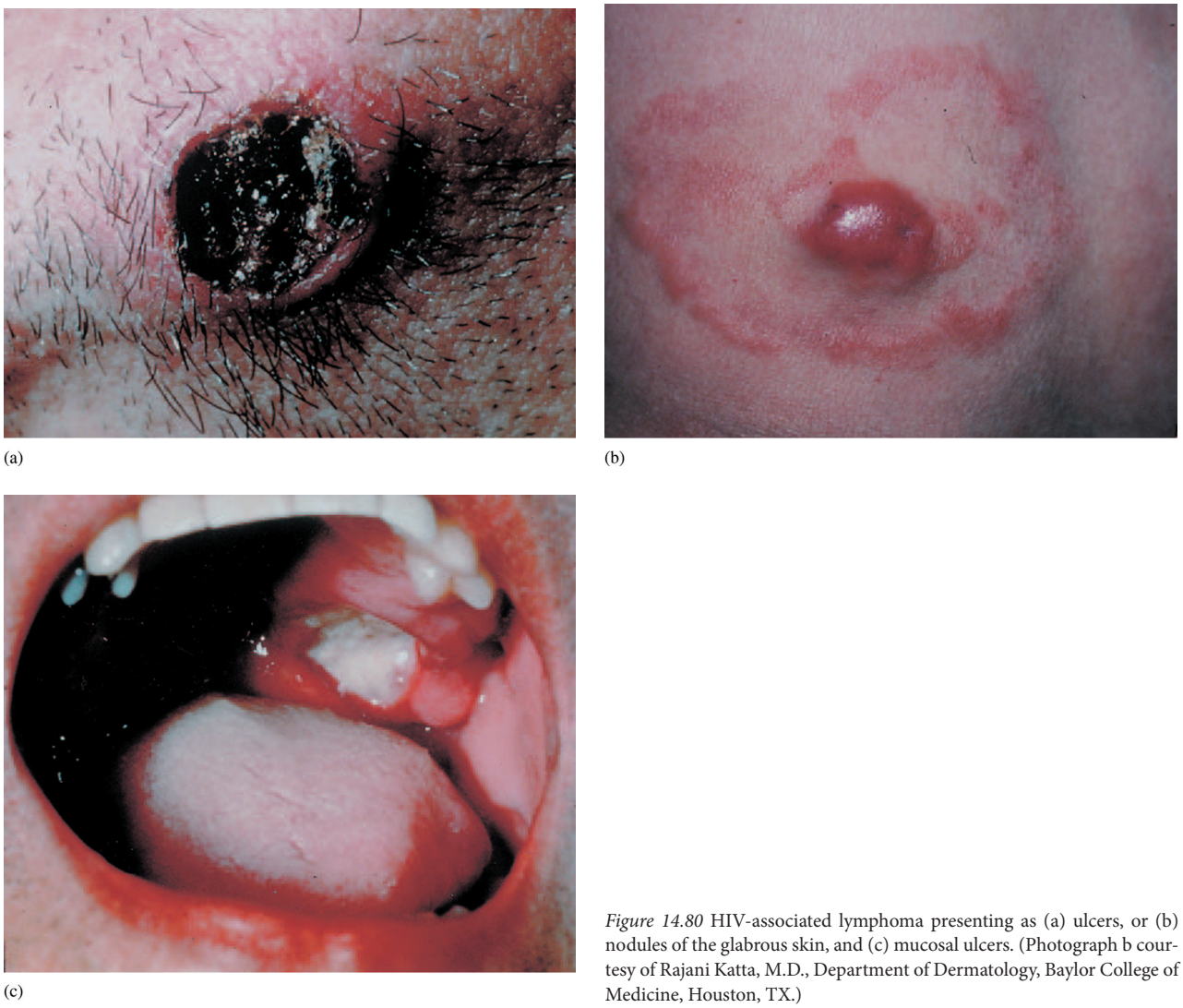
* Many of these agents may accelerate immunocompromise and accelerate death.

Incidence

NHL is the most common AIDS-defining malignancy and a frequent cause of death among HIV patients. The incidence of primary AIDS-related lymphoma of the central nervous system has decreased significantly since the institution of HAART [127]. Other lymphomas, such as cutaneous T-cell lymphoma, have been reported sporadically.

Pathogenesis

The incidence of NHL increases as the CD4 count decreases, thus HAART may reduce the risk of this cancer among HIV patients [127]. Approximately 25% of AIDS patients with NHL have had histological findings of follicular hyperplasia observed on biopsy. These lymph nodes contain polyclonal proliferations of B lymphocytes, a finding similar to that seen in African children with endemic Burkitt's lymphoma as well as in iatrogenically immunosuppressed patients. Polyclonal B-cell proliferation is thought to be caused directly by viral infection or as a consequence of loss of T-cell immunoregulation. Clonal immunoglobulin heavy-chain rearrangements, however, have been found in



(a) (b) (c)

Figure 14.80 HIV-associated lymphoma presenting as (a) ulcers, or (b) nodules of the glabrous skin, and (c) mucosal ulcers. (Photograph b courtesy of Rajani Katta, M.D., Department of Dermatology, Baylor College of Medicine, Houston, TX.)

HIV-associated lymph node hyperplasia, suggesting a premalignant nature of such proliferations.

EBV infection is another factor of importance in the pathogenesis of HIV-related lymphoma, as this virus may be found in a high percentage of HIV-associated NHL. Activation of the B-cell arm of the immune system develops in HIV-infected patients as a consequence of constant stimulation by foreign antigens. Concomitant infection by EBV may lead to immortalization of infected lymphocytes, resulting in uncontrolled lymphoproliferation and, eventually, malignancy.

Clinical Manifestations

Although lymphoma usually involves visceral sites, the skin may have pink to purplish papules or nodules with NHL (Fig. 14.80). Deep-seated soft-tissue involvement may expand superficially, forming dome-shaped nodules that often ulcerate. Cutaneous Hodgkin's disease appears similar to NHL either as diffuse nodular lesions or as a "panniculitis." HIV-related cutaneous T-cell lymphoma may have a clinical appearance similar to the widespread plaques of mycosis fungoides. HTLV-1 lymphoma may also resemble mycosis fungoides. Lymphomas can also result in osteolysis (Fig. 14.81). A unique malignancy described in HIV-seropositive persons is the CD30+ lymphoma (Fig. 14.82).

Histopathology

When the skin is involved by lymphoma, there is generally a diffuse infiltrate of atypical lymphoid cells that are monomorphous in appearance. Many of the cells are large, pleomorphic, and in mitosis. The infiltrate tends to be deeply situated, involving the lower portions of the dermis and subcutaneous fat, and there is often extensive necrosis as well as obliteration of pre-existing adnexal structures. Hodgkin's disease may have an appearance similar to that of an inflammatory infiltrate in the skin, although the diffuse nature of the infiltrate and the presence of large, atypical cells having a Reed-Sternberg-like morphology generally aid in making the diagnosis. Cutaneous T-cell lymphoma is usually manifested histologically by psoriasiform hyperplasia of the epidermis with a band-like infiltrate of atypical lymphocytes; many have convoluted nuclei with a cerebriform appearance. These cells are also present in the epidermis, where they often form small collections. In cases of HTLV-1-associated lymphoma, neoplastic lymphocytes are often extremely large and multilobulated, with a "clover-leaf" appearance. In addition, there



Figure 14.81 Lymphoma resulting in osteolysis. (Photograph courtesy of J. K. Maniar, M.D., Department of Dermatovenereology and AIDS Medicine, G. T. Hospital, Grant Medical College, Mumbai, India.)

is usually prominent exocytosis and, in that there is an associated leukemia, atypical lymphoid cells are often seen in blood vessels and lymphatics.

Laboratory Findings

Patients may have abundant circulating atypical lymphocytes that may number up to 600,000 cells/mm^3 in Sézary's syndrome and in adult T-cell lymphoma/leukemia. By contrast, when hemophagocytosis or extensive bone marrow involvement supervenes, there may be profound anemia and pancytopenia.

Diagnosis

The routine diagnosis of these neoplasms is based on the characteristic clinical appearance taken in the context of histopathological features. In many cases, gene rearrangement studies, flow cytometric immunological analysis, and the use of DNA probes are necessary to further characterize and subtype the neoplasm. Immunophenotyping of mycosis fungoides-like cutaneous T-cell lymphoma in HIV patients may be characterized by an infiltrate of CD8+ lymphocytes in some cases. HTLV-1-associated leukemia-lymphoma is characterized by an infiltrate of CD4+ cells with absent CD2+ and CD7+ antigens [128].

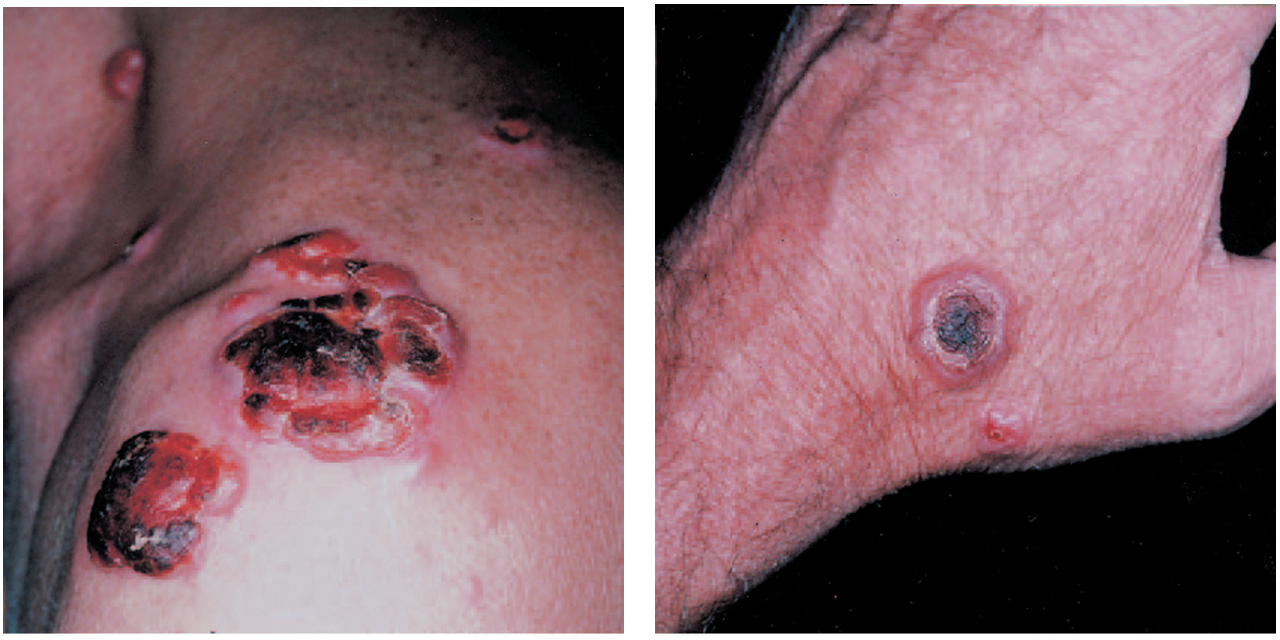
Treatment

Treatment consists of standard dose regimens for systemic lymphoma, usually rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. As these patients are already immunocompromised, administration of these agents may cause profound exacerbation of this condition with acceleration of death (Table 14.12). Use of hematopoietic growth factors and prophylaxis against opportunistic infections may help to prevent these complications [127]. Cutaneous T-cell lymphoma may respond to treatment with psoralen and ultraviolet A therapy, total body electron beam, and topical nitrogen mustard.

Kaposi's Sarcoma

Definition

KS is a vascular neoplastic disorder that normally occurs in an isolated subset of individuals. First described by Moritz Kaposi in



(a) (b)

Figure 14.82 (a and b), CD30 lymphoma producing cutaneous nodules. (Photographs courtesy of Jeffrey Callen, M.D., Division of Dermatology, Department of Internal Medicine, University of Louisville School of Medicine, Louisville, KY.)



(a)



(b)



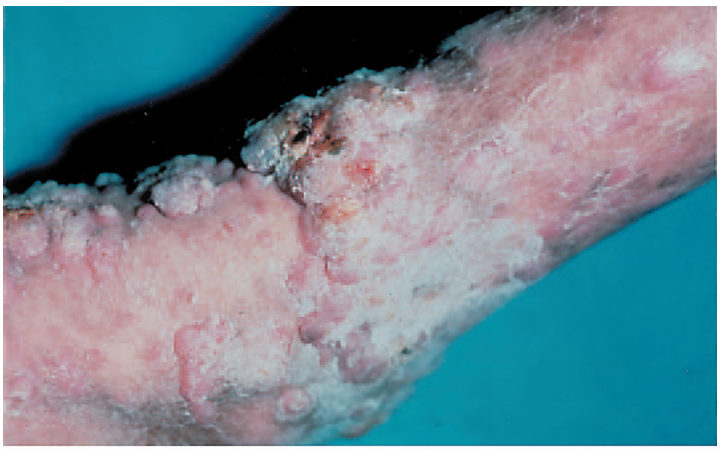
(c)



(d)



(e)

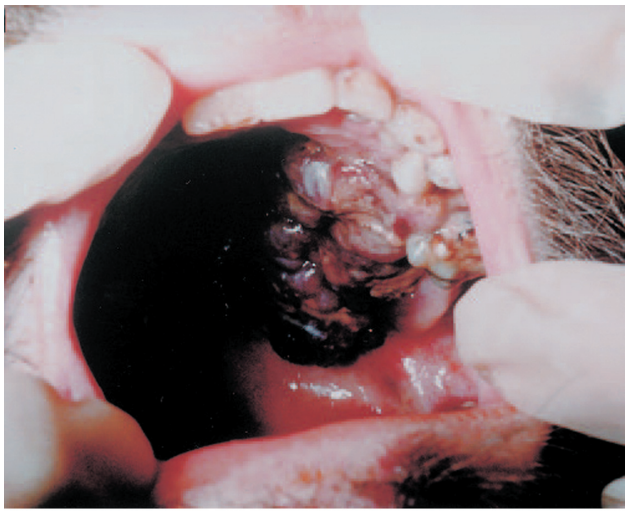


(f)

Figure 14.83 (a) Patch to early plaque stage of Kaposi's sarcoma. (b) Involvement of feet and legs in pattern similar to that of classic Kaposi's sarcoma. (c, d) Extensive disseminated plaques may be severely cosmetically disfiguring. (e, f) Nodular stage of Kaposi's sarcoma with f showing verrucous morphology.



(a)



(b)

Figure 14.84 (a, b) Oral mucosal involvement with Kaposi's sarcoma.

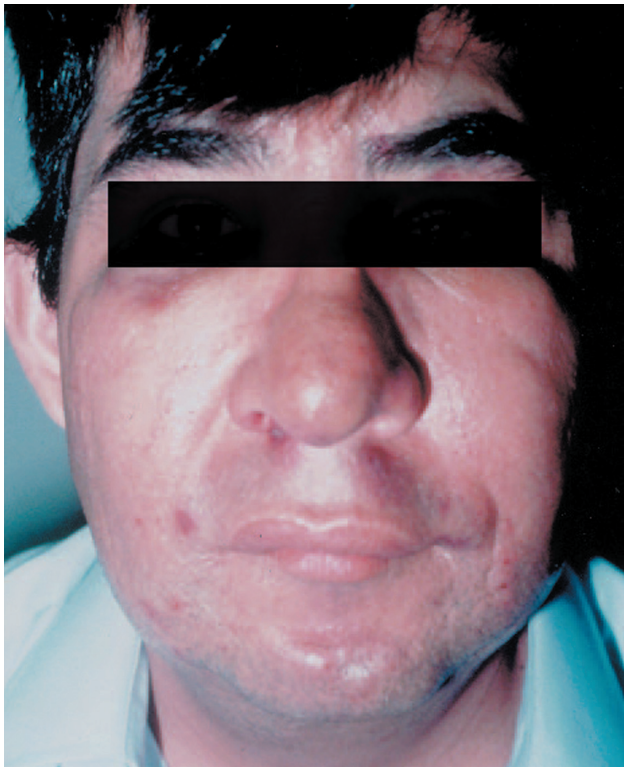


Figure 14.85 Diffuse edema may be caused by deep infiltrative involvement by Kaposi's sarcoma and lead to a vena cavalike syndrome.

1872, it is the second most frequent neoplastic disorder to develop in patients with AIDS [127].

Epidemiology

Shortly after the beginning of the AIDS epidemic, the frequency of occurrence of KS increased significantly. With the widespread use of HAART, the prevalence of KS dropped dramatically. The disorder has continued to be far less common among intravenous drug users and is rare in women, hemophiliacs, and their sexual partners. In some regions of Africa, the incidence of KS in women approaches 40% of the total number of KS cases related to HIV infection [129]. In patients with KS but no HIV infection, the disease tends to have a more indolent course similar to that observed in elderly Italian and Jewish men [130].

Pathogenesis

Many features suggest that KS may be transmitted by a sexually transmissible agent [131], as human herpesvirus 8 (HHV-8) DNA genomic sequences appear in almost 100% of KS lesions that have been studied [132] (see Chapter 10). HIV-positive patients have a high prevalence of HHV-8 coinfection, thus placing them at an increased risk of KS compared to the general population. Other risk factors for KS include immunosuppression and HIV replication [127].

Clinical Manifestations

Clinically, KS skin lesions may be pink, red, brown, or purple macules, patches, plaques, nodules, or tumors (see Chapter 10) (Figs. 14.83–14.85).

Histopathology

The histopathological findings of KS vary with the stage of the lesion in question (see Chapter 10).

Laboratory Findings

No specific laboratory findings are seen in patients with AIDS-related KS, but degree of immunosuppression is a correlate. As a result of marked improvement of the immune status in most patients treated with HAART, KS has become much less common.

Diagnosis

Diagnosis is generally based on the characteristic clinical features of purplish skin lesions in the appropriate clinical setting in conjunction with histopathological findings. The neoplasm occurs only rarely in women and children.

Treatment

In most patients, HAART leads to a decrease in the number and size of KS lesions. In patients with limited cutaneous lesions,

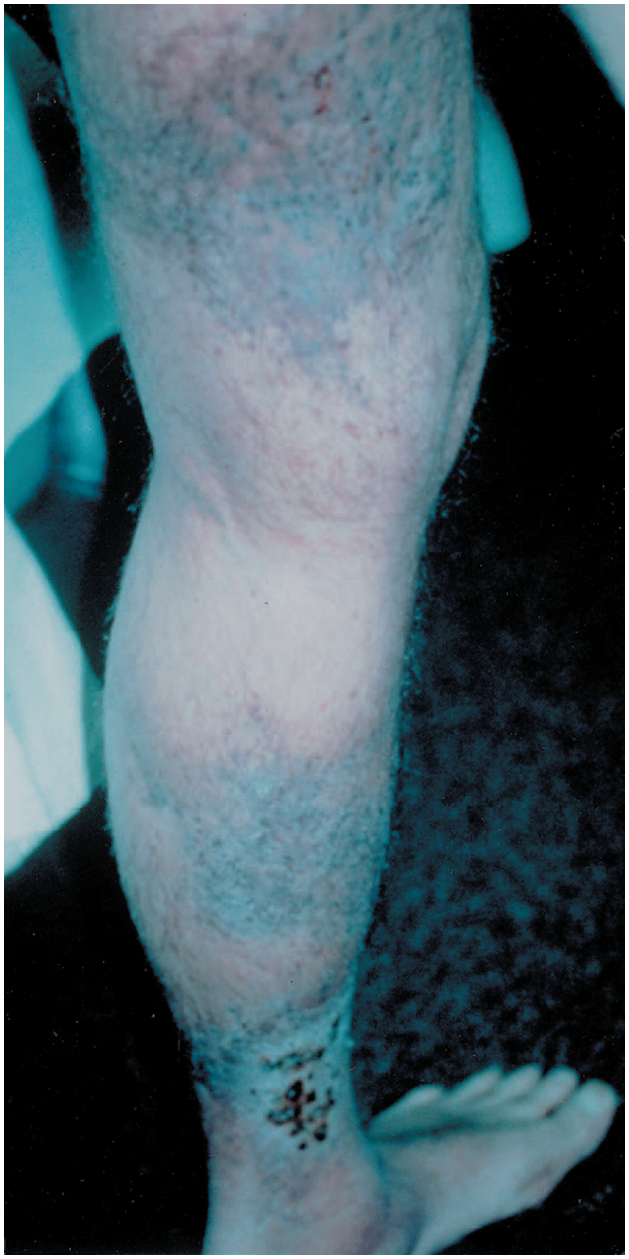


Figure 14.86 Kaposi's sarcoma following local irradiation. Often there is significant residual disease, as seen here.

HAART may be the only treatment required (see Chapter 10) (Fig. 14.86). However, systemic chemotherapy may be indicated for patients with visceral lesions or rapidly progressive disease [127]. Multiple studies have demonstrated that liposomal doxorubicin is the preferred first-line agent in patients who require chemotherapy [133–135]. Another study showed that a combination of liposomal doxorubicin and interleukin-12 is also highly effective [136].

Other Cutaneous Neoplasms

Several other cutaneous malignancies have been reported in HIV-seropositive patients. Malignant melanoma may be quite aggressive, even those with Breslow thicknesses of 0.6–1.4 mm. One patient had an amelanotic malignant melanoma of the neck that clinically mimicked molluscum contagiosum (Fig. 14.87). In addition to



Figure 14.87 Amelanotic melanoma in a patient with AIDS. Note the similarity to either a basal cell carcinoma or a giant molluscum contagiosum lesion.

melanoma, eruptive multiple dysplastic nevi have been observed in these individuals in some cases (Fig. 14.88).

Smooth muscle tumors, including leiomyoma, leiomyosarcoma, and nodal myofibroblastoma, have been described in children [137]. The synchronous development of multiple tumors in this age group is extremely rare; therefore, the association with HIV infection is likely to be definitive.

ANTIRETROVIRAL THERAPY

HAART is complex for both the physician and patient and usually consists of three or more antiretroviral drugs from two or three of the different classes of drugs (Table 14.13). An HIV expert is required to carry out the complex task of combining drug classes, negotiating treatment regimens, and monitoring laboratory parameters.

Serious side effects, patient compliance, and risk of resistant strains emerging from suboptimal or inappropriate dosing complicate current antiretroviral therapy (Fig. 14.89). The following antiretroviral drugs are currently available: (1) *NRTIs:* zidovudine (Retrovir) [AZT]; lamivudine (Epivir) [3TC]; lamivudine/zidovudine (Combivir); stavudine (Zerit) [D4T]; didanosine (Videx) [ddI]; zalcitabine (Hivid) [ddC]; abacavir (Ziagen); abacavir+lamivudine+zidovudine(Trizivir);abacavir+lamivudine

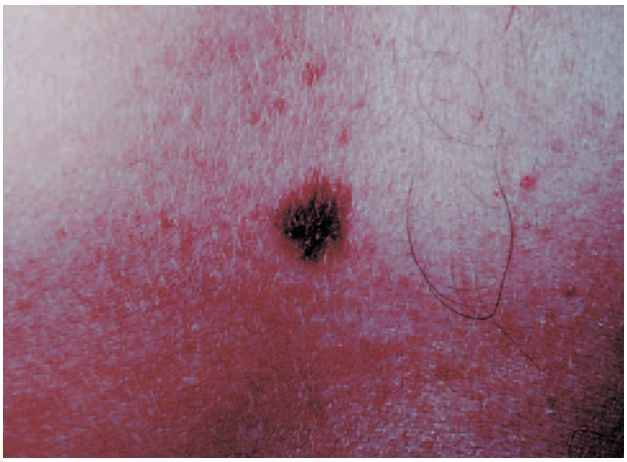


Figure 14.88 Dysplastic nevus in a patient with HIV infection.

Table 14.13 Antiretroviral Therapy

Drug	Form	Dose	Dietary	Adverse events	Laboratory tests
Nucleoside reverse transcriptase inhibitors (NRTIs)					
Zidovudine (Retrovir) AZT	100-mg caps 300-mg tabs 10-mg/ml IV solution 10-mg/ml oral solution	200 mg tid 300 mg bid	None	Bone marrow suppression: anemia or neutropenia GI: nausea, vomiting, hepatotoxicity, hepatic steatosis Others: fatigue, metabolic acidosis, myopathy, myositis, headache, insomnia, hyperpigmented and slow-growing nails, urticaria, pruritus, maculopapular rash	CBC (monthly) Electrolytes, creatine kinase, and liver function tests (every 3 months)
Lamivudine (Epivir) 3TC	150-mg tabs 10-mg/ml solution	150 mg bid	None	Nausea, vomiting, anorexia, lactic acidosis, hepatic steatosis, peripheral neuropathy, headache, malaise, pancreatitis, hyperglycemia, fatigue, psychosis, mania	Amylase, lipase
Stavudine (Zerit) D4T	15-mg caps 20-mg caps 30-mg caps 40-mg caps 1-mg/ml solution	40 mg bid	None	Peripheral neuropathy, lactic acidosis, hepatic steatosis, myopathy, pancreatitis	Amylase, lipase, liver function tests
Didanosine (Videx) ddI	25-mg tabs 50-mg tabs 100-mg tabs 150-mg tabs 200-mg tabs 167-mg sachets 250-mg sachets 400-mg EC caps	200 mg tabs bid; 250 mg powder bid 400 mg tabs once daily	30 min before meals	Nausea, vomiting, diarrhea, peripheral neuropathy, pancreatitis, hepatitis, lactic acidosis with hepatic steatosis, dry mouth, hypertriglyceridemia, hyperuricemia, optic neuritis, rash	Amylase, lipase, liver function tests, lipids
Zalcitabine (Hivid) ddc	0.375-mg tabs 0.75-mg tabs	0.75 mg tid	Avoid aluminum magnesium antacids	Peripheral neuropathy, neutropenia, pancreatitis, aphthous ulcers, somatitis, esophageal ulcers, hepatomegaly, steatosis, lactic acidosis, reported urticaria, one anaphylactoid reaction	CBC, amylase, lipase
Abacavir (Ziagen) ABC	300-mg tabs 20-mg/ml solution	300 mg bid	None; avoid alcohol	Hypersensitivity syndrome, fever, maculopapular rash, nausea, vomiting, fatigue, diarrhea, anorexia, malaise, myalgias, arthralgias, lactic acidosis with hepatic steatosis, hepatitis, respiratory symptoms such as sore throat, cough, shortness of breath	Amylase, lipase, creatine kinase, liver function tests
Emtricitabine (Emtriva) FTC	200-mg hard gelatin capsule; 10-mg/ml solution	200 mg daily	None	Lactic acidosis, hepatic steatosis, hyperpigmentation, skin discoloration	Amylase, lipase, liver function tests
Combivir (AZT+3TC)	300-mg AZT, 150-mg 3TC	bid	None	As above	CBC, electrolytes, creatine kinase, liver function tests, amylase, lipase
Trizivir (AZT+3TC+ABC)	300-mg AZT, 150-mg 3TC, 300-mg ABC	bid	None	As above	CBC, electrolytes, creatine kinase, liver function tests, amylase, lipase
Epzicom (3TC + ABC)	300-mg 3TC, 600-mg ABC	1 tablet daily	None	As above	Creatine kinase, liver function tests, amylase, lipase
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Nevirapine (Viramune) NVP	200-mg tabs 50-mg/5 ml suspension	200 mgx14 days then, 200 mg bid	No antacids within 1 hour	Rash, Stevens-Johnson syndrome, and hepatitis	Liver function tests
Delavirdine (Rescriptor) DLV	100-mg tabs 200-mg tabs	400 mg tid in 3 oz water	No antacids within 1 hour; low-fat diet	Rash, Stevens-Johnson syndrome	Liver function tests
Efavirenz (Sustiva) EFV	50-mg caps 100-mg caps 200-mg caps	600 mg at night	Low-fat diet	Dizziness, insomnia, nightmares, delusions, hallucinations, amnesia, confusion, impaired concentration, somnolence, agitation, euphoria, depersonalization, depression, maculopapular rash, increased liver function test values, false-positive cannabinoid test	Liver function tests
Etravirine (Intelence) ETV	100-mg tablets	200 mg bid	With food	Rash, Stevens-Johnson syndrome, nausea	None

(*Continued*)

Nucleotide reverse transcriptase inhibitor (NtRTIs)					
Tenofovir (Viread) TDF	300-mg tablets	300 mg once daily	With food	Gastrointestinal (diarrhea, nausea, vomiting, flatulence), lactic acidosis, hepatomegaly with steatosis	Liver function tests
Combinations of NRTIs, NNRTIs, and NtRTIs					
Truvada (TDF+FTC)	300-mg TDF, 200-mg FTC	1 tablet daily	None	As above	Amylase, lipase, liver function tests
Atripla (EFV+FTC+TDF)	600-mg EFV, 200-mg FTC, 300-mg TDF	1 tablet daily	None	As above	Amylase, lipase, liver function tests
Protease inhibitors (PIs)					
Saquinavir (Fortovase) SQV	200-mg caps, soft gel	1200 mg tid, soft gel	With food (within 2 hours of a meal)	Nausea, vomiting, diarrhea, hepatitis, lipodystrophy, hyperlipidemia, diabetes mellitus, hyperglycemia, headache, elevated liver function values, lipodystrophy	Liver function tests, lipids, glucose
(Invirase)	200-mg caps, hard gel	400 mg tid, hard gel			
Ritonavir (Norvir) RTV	100-mg caps 600-mg/7.5 ml solution	600 mg bid or 7.5 ml bid	With food; refrigerate caps not in solution	Nausea, vomiting, diarrhea, hepatitis, pancreatitis, hyperlipidemia, hyperglycemia, peripheral neuropathy, circumoral paresthesias, asthenia, abnormal fat distribution, unpalatable taste, maculopapular rash, increased creatine kinase, uric acid, liver function test values	Liver function tests, lipids, amylase, lipase, glucose
Indinavir (Crixivan)	200-mg caps 333-mg caps 400-mg caps	800 mg q 8 hours; separate dosing with ddI by 1 hour	With food (1 hour before or 2 hours after meals); drink plenty of water	Nausea, vomiting, diarrhea, hepatitis, indirect hyperbilirubinemia, nephrolithiasis, acute interstitial nephritis, acute renal failure, hyperglycemia, diabetes mellitus, hyperlipidemia, hemolysis, metallic taste, thrombocytopenia, rash, abnormal fat distribution, headache, asthenia, blurred vision, dizziness, paronychia	Liver function tests, lipids, glucose, urinalysis, creatinine
Nelfinavir (Viracept) NFV	250-mg tabs 50-mg/g powder	750 mg tid; or 1250 mg bid	With food	Diarrhea, hepatitis, hyperlipidemia, hyperglycemia, abnormal fat redistribution	Liver function tests, lipids, glucose
Amprenavir (Agenerase)	50-mg caps 150-mg caps 15-mg/ml solution	1200 mg bid; 1400 mg bid solution	Avoid high-fat meals	Nausea, vomiting, diarrhea, hepatitis, circumoral paresthesias, hyperlipidemias, diabetes mellitus, hemolytic anemia, rash, lipodystrophy	Liver function tests, amylase, lipase, glucose
Atazanavir (Reyataz) ATV	100-mg caps 150-mg caps 200-mg caps	400 mg once daily	With food; avoid antacids	Indirect hyperbilirubinemia, prolonged PR interval, nephrolithiasis, diabetes mellitus, lipodystrophy, hemolytic anemia, rash	Liver function tests, amylase, lipase, glucose, creatinine
Fosamprenavir (Lexiva) FPV	700-mg tablet 50-mg/ml solution	1400 mg FPV bid; 1400 mg FPV+200 mg RTV once daily; 700 mg FPV + 100 mg RTV bid; 1400 mg FPV + 100 mg RTV once daily	None	Nausea, vomiting, diarrhea, hyperlipidemias, diabetes mellitus, lipodystrophy, headache, elevated liver function values, hemolytic anemia, maculopapular rash	Liver function tests, amylase, lipase, glucose
Tipranavir (Aptivus) TPV	250-mg caps	500 mg TPV bid+200 mg RTV bid	With food	Hepatitis, hyperlipidemias, diabetes mellitus, lipodystrophy, hemolytic anemia, rash, rare cases of fatal and nonfatal intracranial hemorrhage	Liver function tests, amylase, lipase, glucose
Darunavir (Prezista) DRV	300-mg tablet	600 mg DRV+100 mg RTV bid	With food	Nausea, diarrhea, hyperlipidemias, diabetes mellitus, lipodystrophy, headache, elevated liver function values, hemolytic anemia, rash, Stevens-Johnson syndrome	Liver function tests, amylase, lipase, glucose
Kaletra (Lopinavir+RTV)	133.3-mg LPV+ 33.3-mg RTV; 80-mg LPV+20-mg RTV (solution)	400 mg LPV+100 mg RTV bid	With food	Nausea, vomiting, diarrhea, asthenia, increased transaminases, hyperglycemia, lipodystrophy, hyperlipidemia	Liver function tests, lipids, amylase, glucose, lipase
Fusion inhibitors					
Enfuvirtide (Fuzeon)	90-mg/ml injectable solution	90 mg bid	None	Injection site reaction, nausea, headache, dizziness, bacterial pneumonia, eosinophilia, hypersensitivity reaction	CBC

(*Continued*)

CCR5 antagonists					
Maraviroc (Selzentry)	150-mg tablet 300-mg tablet	150 mg bid, 300 mg bid, 600 mg bid	None	Upper respiratory tract infections, cough, fever, orthostatic hypotension, myalgia, abdominal pain, dizziness, rash, hepatitis	Liver function tests
Integrase inhibitors					
Raltegravir (Isentress)	400-mg tablet	400 mg bid	None	Diarrhea, nausea, headache, fever, elevated CPK	Liver function tests, CPK

(Epzicom); and emtricitabine (Emtriva). (2) *NNRTIs:* nevirapine (Viramune); delavirdine (Rescriptor); efavirenz (Sustiva); and etravirine (Intelence). (3) *Nucleotide Reverse Transcriptase Inhibitors (NtRTIs):* tenofovir (Viread). (4) *Combinations of NRTIs, NNRTIs, and NtRTIs:* emtricitabine+tenofovir (Truvada); efavirenz+emtricitabine+tenofovir (Atripla). (5) *PIs:* saquinavir (Fortovase); saquinavir (Invirase); ritonavir (Norvir); indinavir (Crixivan); nelfinavir (Viracept); amprenavir (Agenerase); lopinavir+ritonavir (Kaletra); atazanavir (Reyataz); darunavir (Prezista); fosamprenavir (Lexiva); and tipranavir (Aptivus). (6) *Fusion Inhibitors:* enfuvirtide (Fuzeon). (7) *CCR5 Antagonists:* maraviroc (Selzentry). (8) *Integrase Inhibitors:* raltegravir (Isentress).

Antiretroviral therapy is recommended for any symptomatic HIV-positive patient, for postexposure prophylaxis, and for pregnant women to prevent vertical transmission.

The decision to start treatment in asymptomatic patients is based on the patient's willingness to adhere to the complex drug regimen, both the clinical and immunological parameters, and a risk/benefit analysis. Patients with a history of an AIDS-defining illness or with a CD4 count less than 350 cells/mm^3 are candidates for treatment [16]. Other indications for institution of antiretroviral treatment include pregnancy, HIV-associated nephropathy, and coinfection with hepatitis B when treatment for hepatitis B is indicated [16].

The CD4 count is the most important predictor of clinical outcome, although both viral load and CD4 count are useful for monitoring response to therapy [16]. Maximal durable viral suppression, immunological restoration, improved quality of life, and reduced HIV-related morbidity are the ultimate goals of therapy [16]. First-line therapy generally consists of one NNRTI plus two NRTIs or one PI (with or without ritonavir-boosting) plus two NRTIs [16]. A triple NRTI regimen may be used for patients who desire a low pill burden and wish to avoid the side effects associated with PIs and NNRTIs; however, these regimens have suboptimal virologic suppression compared to PI- and NNRTI-based regimens [16].

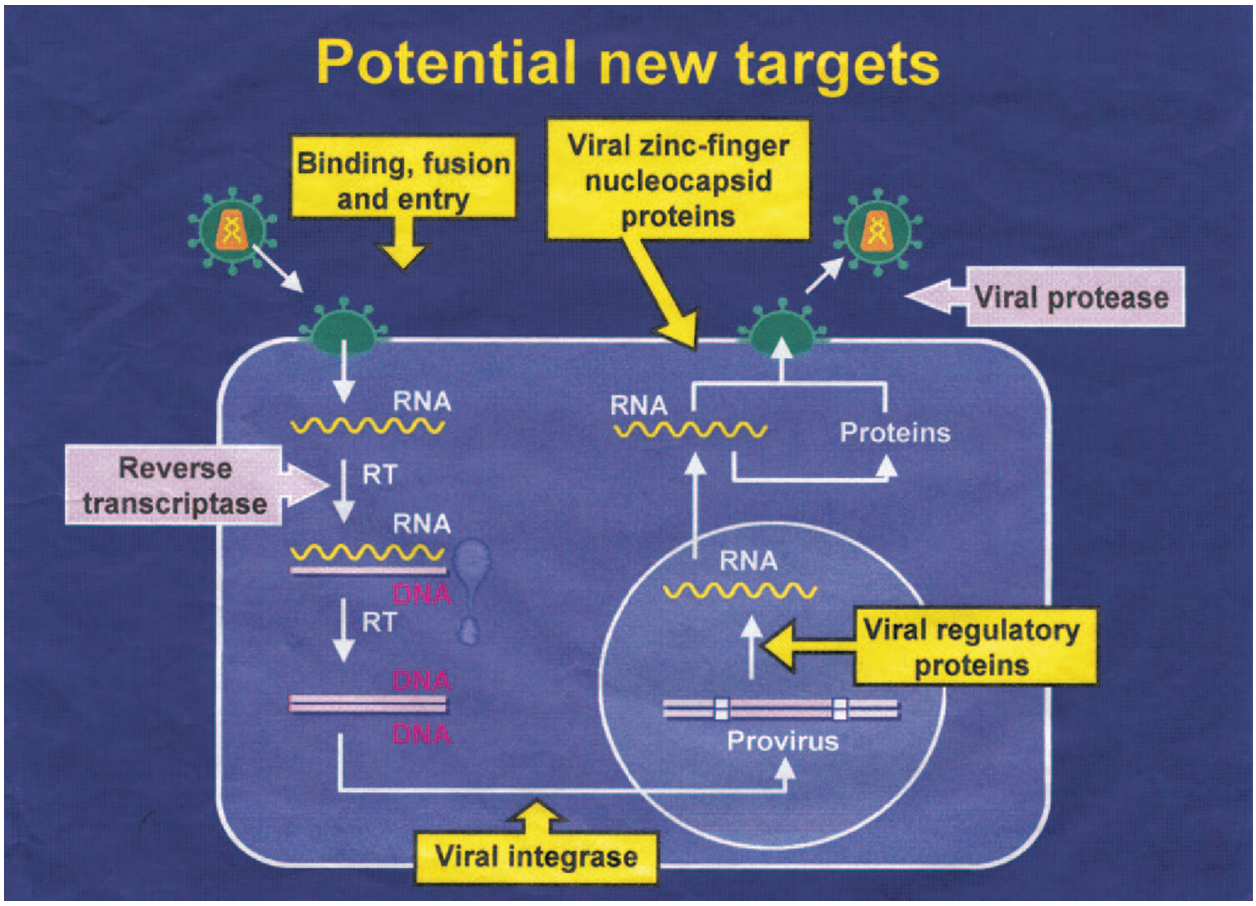


Figure 14.89 Sites of action of antiretroviral drugs. (Illustration courtesy of William O'Brien, M.D., Department of Internal Medicine, University of Texas Medical Branch at Galveston, Galveston, TX.)

Patients must be monitored for adverse events and treatment response following initiation of treatment. Optimal response is defined as (at least) a one log decrease in viral load at 8 weeks and no detectable virus (<50 copies/ml) at 4–6 months of therapy [16]. Viral load measurements should be monitored every 3–4 months once a patient is on therapy. In the case of primary treatment failure, HIV drug resistance testing should be performed to assist in selecting a new antiretroviral regimen [16].

Nucleoside Reverse Transcriptase Inhibitors

Starting with AZT, NRTIs were the first class of antiretroviral drugs introduced in 1987. They are dideoxynucleoside analogues, which are phosphorylated intracellularly into the active triphosphate form. The triphosphate metabolite acts as an alternate substrate for the enzyme, competitively inhibiting reverse transcriptase. Once the metabolite is incorporated into the developing DNA strand, chain termination ensues (Fig. 14.89). A common adverse effect is lactic acidosis with hepatomegaly; hepatic steatosis is rare, but is a potentially life-threatening toxicity seen with use of NRTIs (Table 14.13).

Zidovudine (Retrovir) [AZT]

The first NRTI introduced in 1987 was zidovudine, but it was synthesized in the 1960s as an antineoplastic drug. Monotherapy was the antiviral treatment of choice in HIV-infected patients when AZT was the only antiretroviral drug available, but zidovudine-specific resistant HIV strains have evolved. Delayed CD4 count decline and improved survival rates were observed among AZT recipients [138]. Reduced susceptibility isolates are recovered after only 6 months of monotherapy with zidovudine, and resistance increases with continued use [139]. When HAART is available, antiretroviral monotherapy is no longer a treatment option.

The recommended dose of zidovudine is 300 mg bid with no dietary restrictions. Since zidovudine alters methadone levels, special care must be taken in the methadone-dependent patient.

Lamivudine (Epivir) [3T3]

Because lamivudine is active against both HIV and hepatitis B, it is the drug of choice in HIV-infected patients with a concomitant hepatitis B infection receiving HAART therapy. Significantly lower mortality rates and longer AIDS-free survival were observed in HIV-infected patients who received initial therapy with regimens including either lamivudine or stavudine than in those receiving initial therapies with regimens limited to zidovudine, didanosine, and zalcitabine [140]. The dose of lamivudine is 150 mg bid, but adjustment is recommended for renal impairment. No dietary restrictions or significant drug–drug interactions are noted.

Lamivudine/Zidovudine (Combivir)

A combination of lamivudine (150 mg) and zidovudine (300 mg), marketed as Combivir, provides a convenient formulation that allows bid dosing with no dietary restrictions. Combivir is commonly used as the NRTI backbone in antiretroviral drug regimens.

Stavudine (Zerit) [D4T]

Patients who have failed or are intolerant to other more common antiretroviral agents may be treated with stavudine [141], 40 mg bid. No dietary restrictions are recommended. A sensory neurological examination, routine liver function tests, and monitoring of amylase and lipase values are recommended every 3 months.

Didanosine (Videx) [ddI]

Patients unable to tolerate zidovudine or are refractory to its effects may benefit from didanosine given as two 100-mg tablets bid. Didanosine must be taken 30 minutes prior to or 2 hours after a meal, since it is best absorbed in a nonacidic environment. Medications that require an acidic environment for absorption should not be given with it, as didanosine is formulated in an antacid buffer. Ketoconazole, itraconazole, dapsone, indinavir, delavirdine, pyrimethamine, quinolone antibiotics, and related medications that require an acidic environment for absorption should be given at least 2 hours before or 6 hours after administration of didanosine.

Isolated elevated amylase levels may be observed [142], but the rare occurrence of pancreatitis is normally reversible upon termination of didanosine. Use of medications that affect the peripheral nerves, such as zalcitabine (ddC), isoniazid, and chemotherapeutic drugs, may produce synergistic neurotoxicity. Routine testing of amylase and lipase levels, liver function tests, triglyceride checks, and a sensory neurological examination are recommended at least every 3 months.

Zalcitabine (Hivid) [ddC]

Zalcitabine is effective when used in combination therapy and is indicated in HIV infection demonstrating both immunological and virological failure. Probenicid increases the bioavailability of zalcitabine by 50%, but cimetidine, metoclopramide, and aluminum and magnesium hydroxide preparations decrease the bioavailability of zalcitabine. Amylase and lipase measurements, a complete blood count, and a sensory neurological examination must be performed every 3 months. The usual dose of zalcitabine is 0.75 mg tid.

Abacavir Sulfate (Ziagen)

Abacavir is a potent second-generation nucleoside analogue responsible for profound reductions in viral load and increases in CD4+ counts [143,144]. Cross-resistance to abacavir is seen, with resistance among the nucleoside analogues zidovudine and lamivudine. The dose of abacavir is 300 mg tablets bid with no meal restrictions. Alcohol causes a synergistic increase in abacavir and is thus the only dietary restriction. An evolving maculopapular rash that is centripetal in distribution, urticarial in appearance, and becoming confluent characterizes the reversible hypersensitivity syndrome. Preceding the rash, patients may experience fever, malaise, arthralgias, and myalgias. Patients should discontinue treatment if they experience a combination of these symptoms with a rash. They may continue the medication, but must have close follow-up examination if a rash and fever are the only symptoms. The hypersensitivity syndrome usually resolves within 1–2 days of discontinuing the medication; a rechallenge with abacavir is contraindicated because hypotension or death could occur. Liver function tests and monitoring of creatine kinase, amylase, and lipase levels every 3 months are the recommended laboratory parameters for patients on abacavir.

Abacavir+Lamivudine+Zidovudine (Trizivir)
Trizivir combines 300 mg of zidovudine, 150 mg lamivudine, and 300 mg of abacavir (Table 14.13). One tablet is taken twice a day with no diet restrictions. Recent studies have demonstrated that Trizivir is inferior to regimens that combine two NRTIs with efavirenz, a NNRTI. Trizivir may be used as an alternative therapy in patients intolerant of or resistant to PIs or NNRTIs [145].

Abacavir+Lamivudine (Epzicom)
Epzicom combines 600 mg of abacavir and 300 mg of lamivudine. One tablet is taken daily with no dietary restrictions. In patients with renal impairment, the dosage must be adjusted by separating the drug into individual components and reducing the lamivudine dose. It may be used in place of zidovudine-lamivudine (Combivir) as the NRTI backbone when patients are intolerant to the adverse effects of zidovudine [146]. When compared to Combivir, studies have shown that Epzicom has better CD4 cell count responses and is noninferior in term of virologic responses [16].

Emtricitabine (Emtriva)
Emtricitabine is a pyrimidine nucleoside analogue that is very similar to lamivudine in terms of its activity, adverse effects, and resistance profile. Like lamivudine, emtricitabine has activity against both HIV and hepatitis B [147]. In patients coinfected with both HIV and hepatitis B, emtricitabine or lamivudine in combination with tenofovir is the recommended NRTI backbone [16]. The dose of emtricitabine is 200 mg once daily, but adjustment is recommended in patients with renal impairment. Skin discoloration and hyperpigmentation, usually affecting the palms and soles, is a relatively unique side effect associated with emtricitabine. No dietary restrictions or significant drug–drug interactions are noted [147].

Non-nucleoside Reverse Transcriptase Inhibitors
NNRTIs are entirely unrelated to the nucleoside analogues, but inhibit HIV replication at the same stage. These drugs are not incorporated into the developing viral DNA chain, but noncompetitively bind directly to the active site of reverse transcriptase (Fig. 14.89). NNRTIs are highly active against HIV-1, but not HIV-2. They do not require phosphorylation and are active in their native state [148]. Monotherapy is not an option, since cross-resistance between other NNRTIs does occur [149,150]. Since their synergistic activity is more potent, these drugs are suited for combination therapy with NRTIs and PIs. All NNRTIs are metabolized by the cytochrome P450 and may cause a rash and increases in transaminase levels (Table 14.13).

Nevirapine (Viramune)
Nevirapine, the first NNRTI introduced in 1996, binds to the HIV reverse transcriptase and blocks RNA and DNA-dependent DNA polymerase. Nevirapine is indicated in patients who have demonstrated immunological and virological failure and should be used in combination with NRTIs. The usual dose is 200 mg bid. It is recommended that nevirapine be discontinued if the patient's clinical, immunological, and virological status does not improve (because resistance develops quickly) [139]. The cytochrome P450 system, in particular the isozyme cytochrome P450 3A inducer (CYP3A), metabolizes nevirapine. Nevirapine's induction of CYP3A causes a decrease in the concentrations of other drugs, such as PIs and rifampin, and dosage adjustment may be required because these drugs are similarly metabolized.

In about 20% of patients, a transient and self-limiting pruritic erythematous, macular, papular eruption develops on the trunk, face, and extremities within 6 weeks [100,149,151,152]. Cases of Stevens-Johnson syndrome have been reported [153]. Nevirapine decreases methadone levels and should not be administered with cisapride. It is recommended that liver function tests be performed routinely every 3 months because liver toxicity is also a known side effect.

Delavirdine (Rescriptor)
The primary indication for delavirdine is in combination therapy [154]. The metabolism of delavirdine, like the other NNRTIs, depends on cytochrome P450 metabolism, specifically the 3A inhibitor isozyme. Since delavirdine inhibits the CYP3A enzyme, it inhibits the enzymatic metabolism of itself and other drugs; therefore, increased plasma levels of medications like cisapride, clarithromycin, terfenadine, astemizole, warfarin, PIs, benzodiazepines, and calcium channel blockers are observed and may cause life-threatening side effects if they are coadministered with delavirdine [155]. Since antacids and meals high in fat significantly reduce the absorption of delavirdine, a dose of four 100-mg tablets tid or four 100-mg tablets dissolved in at least 3 oz of water tid should be given 1 hour apart from these foods.

When delavirdine was administered with PIs, significant drug–drug interactions occurred. The concentrations of both saquinavir and indinavir are increased by delavirdine. The use of certain PIs, like the soft gel saquinavir capsule (Fortovase), can cause potential synergistic liver toxicity. Liver function tests are recommended every 3 months.

Rash, Stevens-Johnson syndrome, and hepatitis are the most common side effects, as with other NNRTIs. Rashes develop within 1–3 weeks of starting treatment and resolve 3–14 days after onset in clinical studies [101,155].

Efavirenz (Sustiva)
Efavirenz, 600 mg qhs, must be administered in a combination cocktail with a PI and/or NRTI [101]. Monotherapy is contraindicated because viral resistance can emerge.

In clinical trials, as many as 50% of patients taking efavirenz reported mild side effects. Side effects were more common in patients with a history of psychiatric illness and substance abuse. Within the first few days of initiating therapy, the side effects appeared and then resolved within 7–14 days. In 27% of treated patients, a macular papular eruption developed within the first 1–2 weeks of therapy. Liver function tests should be done every 3 months.

Taking certain drugs concomitantly is contraindicated because efavirenz is a mixed P450 3A inducer-inhibitor. The metabolism of some drugs is inhibited as a result of the enzyme competition, which increases their concentrations. Cisapride, midazolam, triazolam, clarithromycin, or ergot derivatives should not be administered with efavirenz, since life-threatening complications, such as cardiac arrhythmias, prolonged sedation, or respiratory depression can occur. Significant drug–drug interactions are possible with the PIs. When indinavir is coadministered with

efavirenz, the levels of indinavir are decreased by 30%. Saquinavir levels are decreased by 60% with efavirenz.

Etravirine (Intelence)

Etravirine is a next-generation NNRTI that has activity against many strains of HIV-1 that are resistant to other NNRTIs. The dosage of etravirine is 200 mg bid following a meal. The drug is FDA approved for use in treatment-experienced patients who are infected with resistant strains of HIV. It must be administered in combination with a boosted PI and two NRTIs [156].

Rash is the most commonly reported adverse effect associated with etravirine, occurring in 17% of patients. Rashes generally develop within the first few weeks of treatment and are more common in women. The majority of rashes are erythematous or maculopapular and of mild to moderate severity [99].

Etravirine is a CYP3A4 and UDPGT inducer, and a CYP-2C9 and CYP-2C19 inhibitor. Efavirenz, nevirapine, rifampin, carbamazepine, phenytoin, phenobarbital, and St. John's Wort should not be administered with etravirine, since these drugs may significantly decrease concentrations of etravirine. Like other NNRTIs, significant drug–drug interactions are possible with PIs. When coadministered with etravirine, concentrations of indinavir, saquinavir, and atazanavir were reduced to a clinically significant extent. Coadministration of etravirine and nelfinavir led to significantly increased concentrations of nelfinavir. Tipranavir boosted with ritonavir significantly decreased etravirine levels [156].

Nucleotide Reverse Transcriptase Inhibitors

Tenofovir disoproxil fumarate (Viread) received FDA approval in 2001 for the treatment of HIV-1 in adults. Nucleotide analogues are similar to nucleoside analogues and block HIV replication in the same manner [157]. Tenofovir is to be used in combination with other antiretroviral drugs. It is available as a 300-mg tablet to be taken orally, with a meal.

Combinations of NRTIs, NNRTIs, and NtRTIs

When HAART was introduced, the most common reasons for nonadherence to treatment regimens were pill burden, dosing frequency, and regimen complexity [16,158]. In recent years, pills containing combinations of antiretroviral drugs from different classes have been developed to simplify regimens and reduce pill burden.

Emtricitabine+Tenofovir Disoproxil Fumarate (Truvada)

The coformulation of emtricitabine and tenofovir disoproxil fumarate (Truvada) was FDA approved in 2004 for the treatment of HIV infection in adults in combination with other antiretroviral medications. Emtricitabine and tenofovir disoproxil fumarate act synergistically against both HIV-1 and HIV-2. The dosage is one tablet consisting of 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate once daily. In patients with renal insufficiency and a creatinine clearance of 30–49 ml/min, the dosage frequency should be decreased to one tablet every 48 hours. Truvada should not be used in patients with a creatinine clearance less than 30 ml/min or in patients on hemodialysis [158].

Efavirenz+Emtricitabine+Tenofovir Disoproxil Fumarate (Atripla)

The combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) received FDA approval in 2006 for the treatment of HIV infection in adults, alone or in combination with other antiretroviral agents. The dosage is one tablet consisting of efavirenz 600 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg once daily. Atripla should not be used in renally impaired patients with a creatinine clearance less than 50 ml/min [16].

Protease Inhibitors

PIs were introduced in 1995. They act by inhibiting HIV protease, a virus-specific enzyme, thereby preventing the cleavage of viral polyproteins in the final stages of viral protein processing. This, in turn, prevents virus assembly, which results in a defective, noninfectious viral particle [159,160] (Fig. 14.89). PIs are effective in chronically infected cells and prevent replication in newly infected cells [161]. More effective in reducing the viral load than the nucleoside analogues, PIs are associated with increased body weight and improved quality of life [162–164]. However, they have been associated with a form of lipodystrophy resulting in abnormal fat accumulation in localized areas, commonly referred to as "protease pouch," "buffalo hump," and "crix belly" [107,110,111,165] (Table 14.13; Fig. 14.90). PIs have the disadvantages of high cost, common cross-resistance, poor central nervous system penetration, and significant drug–drug interactions [7]. All PIs are metabolized by the cytochrome P450 hepatic microsomal enzyme, CYP3A isozyme. Terfenadine, cisapride, triazolam, midazolam, or ergot derivatives cannot be given with PIs because plasma concentrations of either drug may require dosage adjustments to avoid potentially serious reactions.

Saquinavir (Fortovase) or Saquinavir (Invirase)

The first PI approved for the treatment of HIV was saquinavir in the hard gel capsule in a dose of 600 mg tid. Saquinavir was reformulated shortly thereafter into the soft gel capsule, which resulted in a fivefold greater absorption and increased reduction in viral load [166]. Liver function tests, as well as glucose and lipid level determinations, are recommended every 3 months. Since food increases drug levels sixfold, the standard dose of Fortovase is six 200-mg soft gel capsules three times a day (1200 mg) with a meal or within 2 hours after eating.

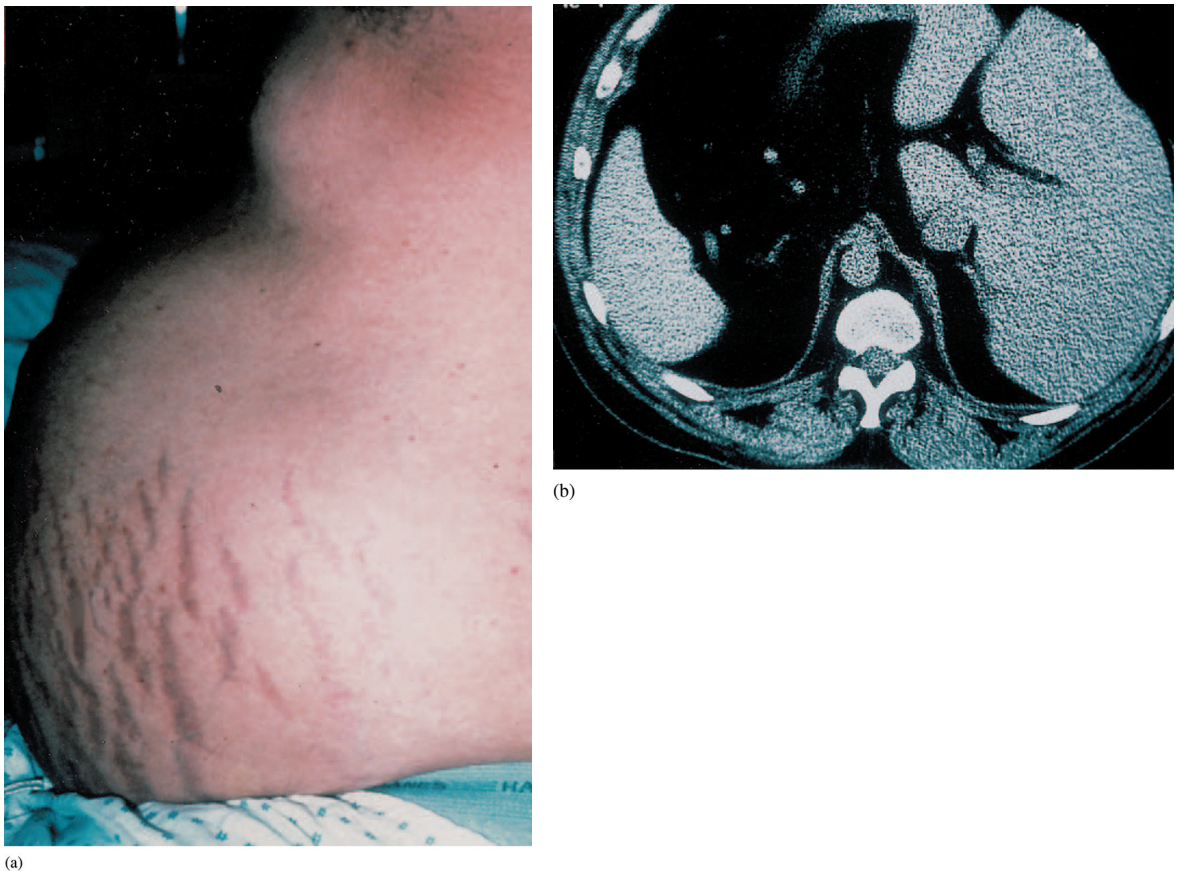
Ritonavir (Norvir)

The second PI to be approved for use in HIV patients was ritonavir [167]. A few cases of a maculopapular eruption and fever have been reported within a few days of treatment initiation. Several cases of hypermenorrhea have also been reported [168]. A large meal must be taken with both the liquid and capsule preparations to decrease diarrhea and increase plasma levels (600-mg capsule bid or 7.5 ml bid). To enhance tolerance, gradual dose escalation is recommended over 10–14 days.

Liver function tests and glucose, lipid, amylase, and lipase level values are recommended every 3 months. When administering ritonavir to patients with chronic hepatitis B or C infection, care should be taken as with other drugs that may be potentially hepatotoxic.

Indinavir (Crixivan)

Indinavir was approved by the FDA for use in HIV patients in 1997. The recommended dose is 800 mg tid [169]. Nephrolithiasis may occur [164], since indinavir is poorly soluble in urine [170,171]. Patients are encouraged to drink at least 64 oz of water each day to



(a) (b)

Figure 14.90 (a, b) Lipodystrophy in patients receiving HAART therapy for 5 years. (Photographs courtesy of Komal Chopra, M.D., Department of Dermatology, Columbia University School of Medicine, New York City, NY.)

maintain adequate hydration. Indinavir has also been associated with paronychia (Fig. 14.91).

Food can decrease drug levels by 77%, so indinavir may be taken on an empty stomach or ingested with one of the 24 recommended dietary choices. Agents such as ddI, antacids, and sucralfate, which interfere with the gastric pH, should be avoided if taken concomitantly, because indinavir requires an acidic pH for maximal absorption.

Nelfinavir (Viracept)

Prolonged viral suppression is observed when nelfinavir, approved for combination therapy in HIV patients in 1997, is used with two NRTIs [101,172]. Nelfinavir should not be given with other PIs. The nelfinavir dose is three 250-mg tablets tid or 1250 mg bid, taken with food to increase levels two to threefold.

Amprenavir (Agenerase)

Amprenavir, which received FDA approval in 1999, must be administered as a cocktail with two NRTIs [173]. A maculopapular rash occurs with rare progression to Stevens-Johnson syndrome. Amprenavir in 150-mg capsules, 1200 mg given twice a day, is administered with or without food. Liver function tests and amylase, lipase, and glucose level studies are recommended every 3 months. Each capsule of amprenavir contains 150 IU of vitamin E, but the long-term effect of 2400 IU (16 capsules) of vitamin E per day is not known.

Lopinavir+Ritonavir (Kaletra)

The coformulation of ritonavir and lopinavir (Kaletra) was FDA approved in 2000 for the treatment of HIV infection in adults and children 6 months and older in combination with other antiretroviral medications. Kaletra takes advantage of the ability of ritonavir to boost the levels of other PIs, creating a potent anti-HIV combination. The lopinavir-ritonavir (400/100 mg) combination given bid is the recommended regimen.

Atazanavir (Reyataz)

Atazanavir was approved by the FDA in 2003 for use in combination with other antiretroviral drugs. Atazanavir has fewer adverse effects on lipids than other PIs. The most common laboratory abnormality is reversible hyperbilirubinemia, which occurs in up to 41% of patients and leads to jaundice or scleral icterus in 7–8% of patients [174]. Rash occurs in 21% of patients taking atazanavir. Most of these are mild to moderate maculopapular skin eruptions [98]. Nephrolithiasis has also been reported [175]. The recommended dose of atazanavir is 400 mg once daily with food. The dosage must be decreased in patients with moderate hepatic impairment. Atazanavir is contraindicated in severe hepatic impairment [174,176].

Fosamprenavir (Lexiva)

Fosamprenavir received FDA approval in 2003 for use in combination with other antiretroviral agents for the treatment



Figure 14.91 Paronychia associated with indinavir therapy. (Photograph courtesy of J. K. Maniar, MD, Mumbai, India.)

of HIV in adults. In 2007, an oral suspension form was approved for use in children 2–18 years of age. Fosamprenavir is a prodrug of amprenavir and allows for reductions in pill number and size compared to amprenavir. The most commonly reported side effects are gastrointestinal symptoms, fatigue, headache, and insomnia [177]. Rashes occur in 19% of patients and are usually morbilliform and mild to moderate in severity. Rashes appear approximately 11 days after the onset of treatment and last approximately 2 weeks [98]. Four different dosing schedules are available: (1) fosamprenavir 1400 mg bid; (2) fosamprenavir 1400 mg and ritonavir 200 mg once daily; (3) fosamprenavir 700 mg and ritonavir 100 mg bid; (4) fosamprenavir 1400 mg and ritonavir 100 mg once daily [16]. The dosage must be decreased in patients with mild to moderate hepatic impairment. Fosamprenavir should not be used in patients with severe hepatic impairment [177].

Tipranavir (Aptivus)

Tipranavir is a nonpeptidic PI approved by the FDA in 2005 for use in combination with ritonavir in treatment-experienced adults with strains of HIV that are resistant to multiple PIs. The most common adverse effects are gastrointestinal disturbances, fever, fatigue, and headache [178]. Tipranavir has a black-box warning for increased risk of clinical hepatitis and hepatic failure, particularly in patients with chronic hepatitis B or C coinfection or elevated transaminases at baseline. Liver function tests should be obtained at the initiation of treatment and at regular intervals thereafter. In 2006, a black-box warning was issued for increased risk of fatal and nonfatal intracranial hemorrhage and inhibition of platelet aggregation [178,179]. Rash occurs in 8–10% of patients taking tipranavir. Rashes included urticarial rash, maculopapular rash, and photosensitivity. Most rashes were of mild to moderate intensity; however, some were accompanied by joint pain or stiffness, pruritus, or throat tightening [99]. The recommended dose is tipranavir 500 mg and ritonavir 200 mg bid with food. Tipranavir is contraindicated in moderate and severe hepatic impairment [178].

Darunavir (Prezista)

Darunavir is the newest PI and received FDA approval in 2006 for use in combination with ritonavir in patients who have experienced virologic failure on a previous antiretroviral regimen. Darunavir affects lipid profiles and insulin resistance similarly to other PIs. The most commonly reported side effects are gastrointestinal symptoms, headache, and rash [180]. Rashes occur in 7% of patients and most are mild to moderate and self-limited. Stevens-Johnson syndrome and erythema multiforme have been reported [99]. The dose is 600 mg of darunavir and 100 mg of ritonavir bid with food. No trials have evaluated the need for dosage adjustment in patients with hepatic or renal impairment [180].

Fusion Inhibitors

Enfuvirtide (Fuzeon) is the first fusion inhibitor to be approved by the FDA. Enfuvirtide acts by inhibiting glycoprotein 41-mediated fusion and viral entry (Fig. 14.89) [181]. Enfuvirtide was approved in 2003 for use in treatment-experienced adults and children 6 years of age and older. Studies have shown that enfuvirtide is effective in treating patients infected with HIV strains resistant to NRTIs, NNRTIs, and/or PIs. However, 49% of patients experienced virologic failure within 24 weeks of treatment with an average 21-fold loss in enfuvirtide susceptibility [182]. Thus, long-term clinical use is limited.

Injection site reactions were the most common adverse effect associated with enfuvirtide, occurring in 98% of patients. These reactions included erythema and induration in 89%, tenderness, nodules, or cysts in 76%, ecchymosis in 89%, and pruritus. Most reactions occurred soon after injection and lasted 5–7 days. Injection site reactions led to drug discontinuation in 3% of patients [182]. Other adverse effects include gastrointestinal disturbances, headache, and dizziness. Bacterial pneumonia and eosinophilia were also seen more frequently in patients treated with enfuvirtide compared to patients receiving an optimized background regimen. Studies have shown that enfuvirtide has a low potential for metabolic drug–drug interactions [182].

The dosage of enfuvirtide is 90 mg bid by subcutaneous injection in adults and 2 mg/kg bid in children. The annual cost of treatment with enfuvirtide is approximately $20,000 [182]. Given the high cost, inconvenient mode of administration, and limited long-term clinical benefit, enfuvirtide is likely to be useful only in heavily experienced patients for relatively short time periods.

CCR5 Antagonists

Maraviroc (Selzentry) is the first CCR5 antagonist to gain FDA approval. Maraviroc acts by selectively and reversibly inhibiting the binding of viral glycoprotein 120 to the CCR5 coreceptor. This, in turn, prevents the conformational changes required for the entry of CCR5-tropic strains of HIV-1 into CD4 cells [183]. Maraviroc received accelerated approval in 2007 and traditional approval in 2008 for the treatment of CCR5-tropic HIV-1 in treatment-experienced adults in combination with other antiretroviral agents.

The most common adverse effects associated with maraviroc included upper respiratory tract infection in 20%, cough in 13%, fever in 12%, and rash in 10%. Postural hypotension may be seen in patients receiving higher doses of maraviroc. Other adverse effects include musculoskeletal complaints, gastrointestinal disturbances,

and dizziness. No significant drug–drug interactions were noted at clinically relevant concentrations of maraviroc [183].

Maraviroc is available in three dosing schedules depending on which other antitretroviral drugs the patient is concomitantly taking. When given with strong CYP3A inhibitors, such as PIs, the dose is 150 mg bid. When given with drugs that are not strong CYP3A inhibitors, such as NRTIs and nevirapine, the dose is 300 mg bid. When given with CYP3A inducers, such as efavirenz, the dose is 600 mg bid [16]. Maraviroc should not be used in patients with severe hepatic impairment.

Integrase Inhibitors

Raltegravir (Isentress) is the first integrase inhibitor to be approved by the FDA. Raltegravir inhibits HIV replication by inhibiting required strand-transfer activities of viral integrase [184]. Raltegravir was approved in 2007 for use in treatment-experienced adults with resistant strains of HIV in combination with other antiretroviral medications.

The most common adverse effects associated with raltegravir included diarrhea in 17%, nausea in 10%, and headache in 10%. Raltegravir has the potential to cause an elevation in creatine phosphokinase (CPK), thus liver enzymes should be regularly monitored. Because raltegravir is not a CYP-450 inducer or inhibitor, no drug–drug interactions are expected [184].

The dose of raltegravir is 400 mg bid [16]. Caution should be used when administering raltegravir to patients at risk for rhabdomyolysis or myopathy due to the potential for increased CPK. Raltegravir should not be coadministered with rifampin. Studies have not yet evaluated the need for dosage adjustment in patients with hepatic or renal impairment [184].

Antiretroviral Treatment Toxicities

Bone Marrow Suppression and Anemia

Antiretroviral agents are the most common cause of anemia in HIV-positive patients. In the early 1980s, zidovudine was used in high doses as monotherapy and was frequently associated with significant anemia. Since the advent of HAART, zidovudine is used at much lower doses as part of combination regimens and the incidence of anemia requiring transfusion has decreased considerably [185]. The AIDS Clinical Trial Group demonstrated that a zidovudine dose of 500 mg daily did not cause anemia in asymptomatic patients; however, it could cause significant anemia in patients with advanced disease. Approximately 50% of cases of anemia can be attributed to bone marrow suppression. Erythropoietin has been shown to be effective in treating anemia in patients with low levels of circulating erythropoietin [185].

Lactic Acidosis and Hepatic Steatosis

Obese females and persons with prolonged use of NRTIs are most at risk for lactic acidosis and hepatic steatosis, which are associated with high fatality rates [186,187]. The NRTIs may be at fault since they are thought to induce mitochondrial toxicity. Gastrointestinal complaints such as abdominal distention, nausea, vomiting, abdominal pain, diarrhea, anorexia, weight loss, and hepatomegaly are observed. An increased anion gap and elevated levels of aminotransferases, CPK, lactate dehydrogenase, lipase, and amylase may be seen [188]. Toxicities may spontaneously resolve following discontinuation of NRTIs, and an NRTI-sparing regimen is recommended. Progressive lactic acidosis, dyspnea, tachypnea, and ultimately respiratory failure may result from failure to suspend NRTI therapy in the presence of lactic acidosis and hepatic steatosis. Bicarbonate infusions and hemodialysis may be used for therapy [189].

Pancreatitis

Pancreatitis has been reported in patients taking didanosine. Risk factors for the development of pancreatitis include high daily doses of didanosine, advanced disease, history of pancreatitis, substantial alcohol intake, hypertriglyceridemia, hyperamylasemia, and coadministration of other drugs potentially toxic to the pancreas [190]. Since the advent of HAART, didanosine is used at much lower doses and pancreatitis is rare. Changes in lipase and amylase levels should be monitored during treatment and didanosine should be discontinued if pancreatitis is diagnosed [190].

Peripheral Neuropathy

Peripheral neuropathy has been associated with several NRTIs including zalcitabine, didanosine, and lamivudine. Evidence suggests that this neuropathy is a result of NRTI-induced mitochondrial toxicity [191,192].

Psychiatric Disturbances

The NNRTI, efavirenz, has been associated with numerous psychiatric disturbances. These include acute psychosis, nightmares, irritability, difficulty concentrating, and depression [193]. Acute psychosis, resembling the effects of LSD, occurs soon after initiation of efavirenz and necessitates discontinuation of the drug. Problems with nightmares, irritability, and concentration disappear within the first 4 weeks of treatment. Depression may occur late in treatment, but must be differentiated from direct effects of HIV [193].

Hyperglycemia

Hyperglycemia, diabetic ketoacidosis, exacerbation of preexisting diabetes, and new-onset diabetes mellitus are reported in patients receiving HAART. The PIs are usually involved, although poor glycemic control can occur with many of the antiretroviral agents [194]. Although the exact cause of the hyperglycemia is not known, it is suspected that beta cell dysfunction and peripheral insulin resistance could be the cause [194–196]. During the first year of therapy with PIs, it is recommended that fasting blood glucose levels be checked at least every 3–4 months.

Lipodystrophy

Changes in body fat distribution known as lipodystrophy are observed in patients on HAART therapy. Lipodystrophy can occur with any antiretroviral therapy and even in the absence of therapy, but it is often associated with the use of PIs and NRTIs [108,197–200]. The morphological changes of lipodystrophy may not be apparent for months after therapy initiation. Lipodystrophy appears clinically as central obesity secondary to visceral fat accumulation. Successful treatment standards have not been established [201–203], but therapy is aimed at halting the progression of the fat maldistribution.

Hyperlipidemia

During HAART therapy, there are increases in cholesterol and triglyceride levels. It is suspected that PIs interfere with normal

cellular proteins involved in lipid metabolism, but the pathogenesis of these lipid abnormalities is not known [204]. Long-term studies will provide evidence to determine whether PIs result in progression to premature cardiovascular disease [205]. Fasting laboratory lipid evaluations are recommended for patients receiving PIs every 3–4 months. The effectiveness of lipid-lowering agents, exercise, and diet modification to control hyperlipidemia is not clear. Potential enhanced hydroxymethyl-glutaryl coenzyme A reductase inhibitor-related toxicity must also be carefully monitored [16].

Hyperbilirubinemia

The PIs, indinavir and atazanavir, are associated with unconjugated, benign, reversible hyperbilirubinemia. This laboratory abnormality occurs in up to 41% of patients receiving atazanavir 400 mg once daily, and leads to jaundice or scleral icterus in 7–8% of patients. Concomitant use of indinavir and atazanavir is not recommended due to their potentially additive effects on bilirubin levels. Liver function tests should be regularly monitored in persons with hepatic risk factors receiving these agents [174].

Nephrolithiasis

Several PIs are associated with nephrolithiasis. These include indinavir, saquinavir, nelfinavir, lopinavir, and atazanavir. Among these agents, indinavir has the highest propensity to cause nephrolithiasis and its associated complications [175]. One study showed that the incidence of nephrolithiasis among patients receiving indinavir was 67% at the beginning of treatment, decreasing to 25% after 2 weeks. Risk factors for nephrolithiasis include urine pH greater than 6, high daily dose of indinavir, dehydration, and warm environmental temperature. To prevent nephrolithiasis, patients should be encouraged to increase fluid intake [206].

Increased Bleeding Episodes in Patients with Hemophilia

Increased episodes of spontaneous bleeding into joints, soft tissues, brain, and gastrointestinal system are noted in hemophiliacs using PIs [207]. Additional coagulation factor is required for some patients while on PI therapy.

Osteonecrosis and Osteopenia

Osteonecrosis and osteopenia have been described in patients receiving HAART. The hips and shoulders are the most common locations. Risk factors for osteonecrosis include hypertriglyceridemia, corticosteroid use, and alcohol abuse. PI-induced hyperlipidemia and high levels of circulating antiphospholipid antibodies in HIV patients have been proposed as possible etiologies [192].

Immune Reconstitution Inflammatory Syndrome

When patients receive HAART, HIV replication is suppressed and CD4 cell counts increase. In most cases, this leads to a recovery of immune function. However, some patients experience a paradoxical worsening of their clinical status. This phenomenon has been titled the immune reconstitution inflammatory syndrome. The inflammatory response is thought to be due to increased hypersensitivity to various antigens. IRIS typically occurs within the first few months following the initiation of HAART [192].

IRIS is most commonly associated with mycobacterial infections, particularly *M. tuberculosis*. In this case, granulomatous and necrotizing inflammation is directed at mycobacterial antigens in a delayed-type hypersensitivity reaction. Risk factors for tuberculosis (TB)-associated IRIS include disseminated TB, a shorter delay between commencing TB treatment and HAART, low baseline CD4 count, high baseline viral load, and a greater reduction in viral load or increase in CD4 count while receiving HAART [208]. Other pathogens commonly associated with IRIS include CMV, *Cryptococcus neoformans*, *P. jiroveci*, *T. gondii*, and *Polyomavirus JC* [192].

Most cases of IRIS last approximately 57 days; however, the duration is longer in cases presenting with lymphadenopathy. Most cases are self-limited and death is rare [208]. Treatment includes therapy against the causative pathogen, continuation of HAART, and either nonsteroidal anti-inflammatory medications or corticosteroids. Temporary discontinuation of HAART may be necessary in severe cases [192,208].

Postexposure Prophylaxis

Postexposure prophylaxis is recommended for the management of health care workers who have been exposed to blood or body fluid that is tainted or is suspected as being from a patient with HIV.

Both basic and the expanded regimens are available for postexposure prophylaxis. For occupational HIV exposure for which there is a recognized transmission risk, the basic regimen is 4 weeks of zidovudine (300 mg bid) plus lamivudine (150 mg bid), or Combivir (one tablet bid) [209]. For occupational HIV exposures that pose increased risk of transmission, such as a high viral load or a large volume of blood, the expanded regimen is recommended. Lopinavir and ritonavir, given in combination as Kaletra (400/100 mg bid), are added to the basic regimen for the expanded regimen [209].

Investigational Drugs

Attachment inhibitors, CXCR4 antagonists, and maturation inhibitors are new drug classes under investigation. New agents from existing drug classes are also being developed.

Attachment inhibitors include agents that inhibit virion absorption or Env-receptor interactions. Cyanovirin-N interferes with CD4 and coreceptor interactions via interaction with high mannose carbohydrate residues on glycoprotein 120. Cyanovirin-N has been shown to inhibit fusion of various strains of HIV in vitro and in animal models, and is a promising candidate topical microbicide [210]. PRO 2000 is another candidate vaginal microbicide that acts by binding CD4 to prevent HIV attachment. BMS 378806 is a topical agent that prevents CD4-induced conformational changes required for viral fusion. BMS 378806 has potent activity against clade B HIV-1, but little activity against other subtypes [210].

CXCR4 antagonists inhibit the binding of viral glycoprotein 120 to the CXCR4 coreceptor, thereby preventing conformational changes required for the entry of CXCR4-tropic strains of HIV-1 into CD4 cells. AMD 070 is a CXCR4 antagonist that is currently in Phase II clinical trials. Concerns have been raised about the potential long-term adverse effects of this class, since the CXCR4 receptor plays an important role in nervous system development [211].



Figure 14.92 Fogo selvagem in a Brazilian AIDS patient. (Photograph courtesy of Walmar Roncalli P. DeOliveira, M.D., São Paulo, Brazil.)

Maturation inhibitors prevent the production of mature viral proteins. Bevirimat (PA 457) binds to a cleavage site on the viral gag polyprotein precursor, which is a major structural protein involved in assembly and budding of virions. This, in turn, inhibits the production of the mature capsid protein, p24. Bevirimat is currently in Phase II clinical trials [212].

Several drugs belonging to existing drug classes are currently in clinical trials. Rilpivirine (TMC 278), a NNRTI with a high genetic barrier to resistance, is in Phase III trials. Elvitegravir (GS 9137) is a highly selective integrase inhibitor in Phase II trials. Vicriviroc (SCH-D) is a CCR5 antagonist that has been associated with rare cases of malignancy. A direct relationship between vicriviroc and malignancy was not found, so Phase II and III trials have continued [211].

Conclusion

In summary, patients with HIV infection are prone to develop numerous cutaneous manifestations, especially if HAART is not available. The number of different expressions of disease in the skin is greater than that in any other organ and is the source of significant morbidity. By recognizing these signs and symptoms and performing appropriate diagnostic testing to establish correct diagnoses, these complications can be minimized significantly. It is possible, however, that the skin changes may be nonspecific, may be unique to one part of the world (such as fogo selvagem in Brazil) (Fig. 14.92), or may not be present. In the latter case, HIV seroconversion may still be associated with lymphadenopathy. In advanced AIDS, neurological defects may be caused by opportunistic infections that rarely have cutaneous manifestations (e.g., toxoplasmosis and the JC polyomavirus causing progressive multifocal leukoencephalopathy). If, however, these clinical manifestations of HIV seroconversion are not present or noticed, many months or even years may pass before symptoms become obvious. In such cases, HIV infection will be diagnosed only if serological testing is carried out for reasons other than illness (e.g., blood donations, job or insurance physical examination).

Maximal viral suppression, sustained durability, decreased morbidity and mortality, increased CD4 count, decreased evolving resistance, and fewer side effects combined with increased compliance remain the goal of therapy among the different classes and complexity of antiretroviral regimens. The direction of therapy is best guided by serial viral load measurements, CD4 counts, and clinical assessments. Since HAART costs approximately $10,500 per patient per year [213], it is not readily available to the vast majority of the estimated 33 million people living with HIV in the world [214]. Two NRTIs and a PI or NNRTI usually comprise HAART, but other combination regimens exist. Since antiretroviral agents are not virucidal, viral eradication with HAART cannot be achieved. Viral loads return to pretreatment levels when HAART is stopped. Available tools to control the epidemic include public awareness, education, condom use or abstinence, testing blood products, and not sharing needles. Despite these interventions, 2.7 million people become infected with HIV every year [214]. Therefore, it is clear that a safe and effective vaccine is needed to supplement these public health measures.

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15 Human T-Lymphotropic Virus 1

Francisco Bravo and Kristien Verdonck

Human T-lymphotropic virus 1 (HTLV-1) is a deltaretrovirus that causes a lifelong infection in humans [1]. The virus can be transmitted from mother to child through breastfeeding, among injecting drug users, via the transfusion of cellular blood components, and during sexual intercourse [1,2]. The clinical manifestations of the infection are diverse, and include (1) an asymptomatic status (in up to 90% of carriers), (2) a severe neoplastic disease (adult T-cell leukemia/lymphoma; ATLL), (3) inflammatory disorders (including HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and uveitis), and (4) infectious complications (such as strongyloidiasis, scabies, and tuberculosis). Infective dermatitis (ID) is a complication of HTLV-1 infection that generally affects children and appears to have both inflammatory and infectious features [1].

History

The descriptions of several of the diseases associated with HTLV-1 have preceded the discovery of the virus. The earliest report of a disease compatible with HAM/TSP dates back to 1897. The syndrome was described in Jamaica and was attributed to malaria [3]. ID was described for the first time in 1966, also in Jamaica [4]. In the 1970s, in Japan, hematologists described an autochthonous malignancy and named it adult T-cell leukemia [5]. In 1979, in the USA, the research group of Robert Gallo isolated HTLV-1 from a patient with a T-cell malignancy [6]. Through the 1980s, several pieces were fit together and the link between HTLV-1 infection on the one hand and ATL, HAM/TSP, ID, and uveitis on the other, became clear [5,7–9]. A quarter of a century after the discovery of HTLV-1, understanding of the interaction between virus and human host has improved markedly. Nevertheless, the spectrum of diseases associated with the infection remains unclear. There are no good surrogate markers for prognosis. There is no vaccine. Treatment options for HTLV-1 infection and its complications are limited [1].

Epidemiology

The ancestor of all primate T-lymphotropic viruses (PTLV) occurred in Africa. PTLV comprises HTLV types 1–4 and simian T-lymphotropic viruses (STLV) types 1–3. The human subtypes of HTLV-1 (a–g) arose through several interspecies transmissions between simians and humans [10]. For the subtypes HTLV-1 a, b, d, and e, these transmissions have been dated from 5,300 to 21,100 years ago [11].

It has been estimated that 20 million people worldwide are infected with HTLV-1 [12]. The infection is frequent in specific areas in Asia (Southern Japan, Taiwan, and Iran), Melanesia (Papua New Guinea), Eastern Europe (Romania), Central and West Africa, the Caribbean, and South America (French Guiana, Guyana, Surinam, Brazil, Colombia, and Peru) (Fig. 15.1) [1]. Factors associated with HTLV-1 infection in prevalence studies include older age, female sex, transfusion history, prolonged breastfeeding, sexually transmitted disease history, illicit drug use history, and low socioeconomic status [1,2].

Pathogenesis

The main target of HTLV-1 is human CD4 lymphocytes, but the virus can also infect CD8 lymphocytes and dendritic cells [13]. During the viral life cycle, single-stranded RNA is converted to double-stranded DNA and inserted into the genome of the human host cells. HTLV-1 is a cell-associated virus; it very rarely leaves its human host cell. Consequently, the virus is only transmitted via the transfusion of blood components that contain cells; and the HTLV-1 viral load in plasma is undetectable [14]. An alternative way to measure viral burden is the proviral load, which is the proportion of mononuclear cells in the peripheral blood that carry the HTLV-1 provirus in their genome. In contrast with HIV, HTLV-1 does not tend to kill its host cells. Rather, the virus interferes with host cell function: it stimulates mitotic cell division and inhibits cell death, and contributes in that way to its own survival and spread [1,15].

The mere presence of HTLV-1 is not sufficient to explain the clinical outcomes of the infection, because (1) the majority of HTLV-1 carriers remain asymptomatic, and (2) the diseases associated with the infection are diverse. It is as yet unclear which cofactors contribute to the development of the clinical complications of HTLV-1 infection. Evidence suggests that host genetic factors, the subgroup of the virus, the insertion site of the proviral DNA into the host DNA, and concurrent infections such as strongyloidiasis may be involved [1,16].

In the case of HAM/TSP, the interaction between virus and human host has been extensively studied. In comparison with healthy carriers of HTLV-1, HAM/TSP patients have an increased HTLV-1 proviral load and an exaggerated pro-inflammatory cellular immune response. This immune response appears to be based, at least in part, on the host genetic constitution, as specific class I human leukocyte antigen (HLA) alleles and polymorphisms in cytokine and cytokine promoter genes have been linked to HAM/TSP.

The biological basis of the infectious complications of HTLV-1 remains to be clarified. The association of HTLV-1 with strongyloidiasis appears to be based on the suppression by HTLV-1 of protective T_H2 immune responses. However, the same mechanism cannot be extrapolated to tuberculosis, where T_H1 responses are protective. A generalized immune suppression does not explain the phenomenon either, because not all the infections that are known to be prevalent in immunosuppressed individuals are associated with HTLV-1.

Clinical Manifestations

A practical approach to HTLV-1-related disorders is to divide the manifestations on the basis of the basic process: neoplastic (ATLL), inflammatory (HAM/TSP, uveitis), and infectious (crusted scabies,

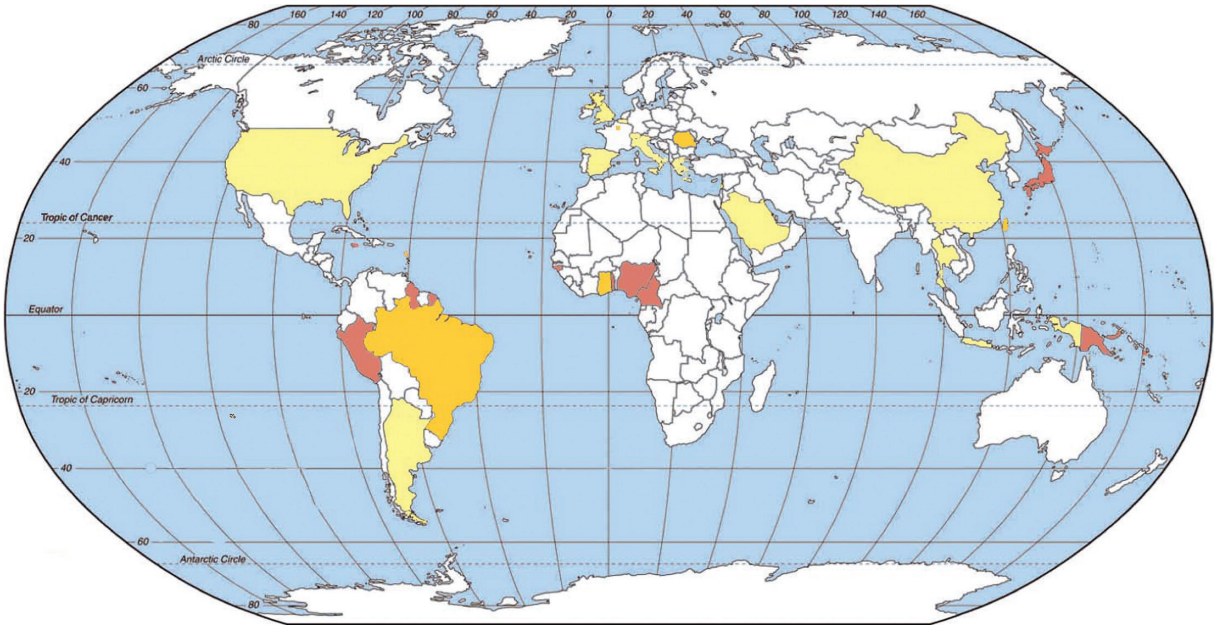


Figure 15.1 World distribution of HTLV-1 infection: estimation of population prevalence: red: ≥1%, orange: ≥0.1% and <1%, yellow: <0.1%, white: population prevalence unknown.

tuberculosis, strongyloidiasis, dermatophytosis). Some manifestations will be more difficult to categorize; ID, for example, is not just an infection, but more of a deregulatory immune process, similar in many ways to atopic dermatitis (AD). Staphylococcal and streptococcal infections will keep the dermatitis alive, but more than due to the bacteria themselves, the syndrome seems to be the result of altered cellular immune response. We will deal first with the cutaneous manifestations, followed by a brief discussion of conditions affecting other organs.

Cutaneous Manifestations

Infective Dermatitis

This particular type of dermatitis is a common manifestation of HTLV-1 infection in many countries where the infection is prevalent.

The first observations were made in Jamaican children by Sweet in 1966, as a peculiar eczema of the scalp [4]. A year later, Walsh described a series of 25 patients, associating the clinical findings to chronic staphylococcal and streptococcal infections; she proposed that they suffered from some form of immune suppression. The same author coined the name infective dermatitis for the condition [17]. The link to HTLV-1 infection was established by Louis La Grenade in 1990 [18]. ID has been well documented in endemic areas of the Caribbean (such as Jamaica, Trinidad & Tobago, Guadeloupe), South America (French Guiana, Colombia, Brazil and Peru), and Africa (Senegal) [18–21]. In Japan, ID has been described only in relation to ATLL [22].

Several major diagnostic criteria have been defined for this entity (see Table 15.1): an eczematous process affecting specific areas such as the scalp, axillae, groin, external and retroauricular areas, eyelid margins, paranasal skin, and the neck; a chronic nasal discharge with crusting of nares; a chronic course with rapid response to antibiotics, but with frequent relapses following their withdrawal; positive serology test for HTLV-1; and the common onset during childhood (Fig. 15.2). This last criterion has been challenged recently with the description of the disease occurring in adulthood, in Peru and Brazil, with an otherwise identical clinical picture (Fig. 15.3) [23,24]. One may theorize that whereas children with ID were infected through breastfeeding, adults with ID contracted the infection through either sexual contact or blood transfusions.

Minor criteria include the common isolation of *Staphylococcus aureus* and *β*-hemolytic streptococci from skin and nares; a generalized fine papular rash; lymphadenopathy; anemia; elevated erythrocyte sedimentation rate; hypergammaglobulinemia (either IgE or IgD) and elevated CD4 and CD8 counts, as well as an elevated CD4/CD8 ratio.

Table 15.1

Major criteria for the diagnosis of infective dermatitis

1. Eczematous process affecting specific areas such as the scalp, axillae, groin, external and retro-auricular areas, eyelid margins, paranasal skin, and neck
2. A chronic nasal discharge with crusting of nares
3. A chronic course with rapid response to antibiotics, but with frequent relapses following their withdrawal
4. Positive serology test for HTLV-1
5. Common onset during childhood (not an exclusion criterion)

Minor criteria for the diagnosis of infective dermatitis

1. Common isolation of *Staphylococcus aureus* and *β*-hemolytic streptococci from skin and nares
2. Generalized fine papular rash
3. Lymphadenopathy
4. Anemia
5. Elevated erythrocyte sedimentation rate
6. Hypergammaglobulinemia (either IgE or IgD)
7. Elevated CD4 and CD8 counts; elevated CD4/CD8 ratio

Modified from La Grenade L, Manns A, Fletcher V et al. Clinical, pathologic, and immunologic features of human T-lymphotrophic virus type I-associated infective dermatitis in children. Arch Dermatol 1998; 34: 439–44.



Figure 15.2 A boy with typical findings of ID: scaly scalp, face, and exudative dermatitis affecting the axillary areas.



Figure 15.3 An older man with ID with identical lesions in identical areas.



Figure 15.4 Psoriasiform scalp dermatitis in a young male. The clue to ID in this particular case was the rapid improvement of his "psoriasis" with oral antibiotics.

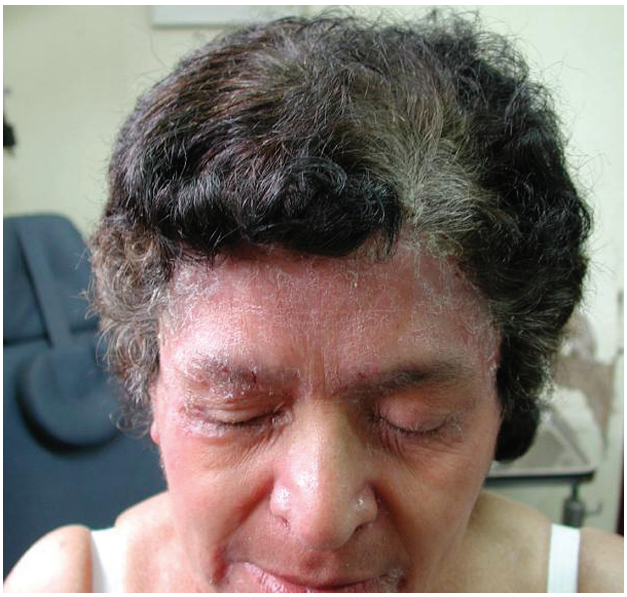


Figure 15.5 Facial and scalp dermatitis in a woman with ID, initially misdiagnosed as contact dermatitis, unknown origin.

The following clinical pictures may obligate a clinician to suspect the disease, regardless of the age of the patient: an apparently impetiginized scalp "psoriasis" that responds quickly to antibiotic treatment; an intractable, extremely pruritic eczema of the scalp (Figs. 15.4 and 15.5); facial and retroauricular "seborrheic dermatitis" with honey crusting (Figs. 15.6 and 15.7); honey-crusted intertrigo affecting the neck, axillae, and groin areas (Fig. 15.8); apparently "impetiginized" inverse psoriasis affecting any body fold; and, in fact, any form of chronic impetiginized eczema affecting multiple areas, such as head, trunk, and axillae (Figs. 15.9 and 15.10).

On histology, several patterns have been described: psoriasiform dermatitis with neutrophils, spongiotic dermatitis, and lichenoid dermatitis. Clues to the possibility of ID are the presence of exocytosis, atypical lymphocytes in the dermis, wiry bands of collagen in the papillary dermis, individual lymphocytes lined



Figure 15.6 Facial dermatitis, on a seborrheic distribution, with honey crust, typical of ID.



Figure 15.7 A boy with ID scalp dermatitis mimicking psoriasis or tinea amiantacea.

along the dermo-epidermal junction, plasma cells in a psoriasiform dermatitis, and any clinical presentation that reflecs a mixture of psoriasis, spongiotic dermatitis, and mycosis fungoides (MF). Any of these findings in the context of a chronic eczematous process affecting the scalp, face, upper trunk, and folds should alert the clinician to the possibility of ID.

The differential diagnosis includes psoriasis (especially scalp and inverse forms occurring simultaneously), seborrheic dermatitis, intertrigo, contact dermatitis and, most clearly, AD. This last diagnosis has been reported as the initial diagnosis in a series of



Figure 15.8 A more exudative form of ID on the posterior neck.



Figure 15.9 At this point, ID of the scalp may be easily confused with tinea.

ID cases [25]. AD may be particularly difficult to distinguish from ID, as some patients may have an overlap of both entities, such as involvement of scalp, face, intertriginous areas, as well as antecubital and retropopliteal areas. Patients with ID may have increased IgE levels as well. A fine point of differentiation for both entities may be based on the elevation of immunoglobulins other than IgE seen in ID patients. An interesting parallel can be made when studying both types of dermatitis: whereas AD is an eczematous process that commonly gets infected, ID is a chronic impetigo with common eczematization.

Therapy consists of the administration of antibiotics with an anti-staphylococcal and anti-streptococcal coverage. Many patients will require prolonged therapy with trimethoprim-sulfamethoxazole to avoid frequent recurrence. Topical steroids may be used if antibiotics fail to resolve ID completely.

The natural course of the disease as we have observed it in Peruvian cases may depend on the onset of the disease: children seem to self-resolve when reaching adolescence, in a similar



Figure 15.10 The fine papular rash of ID (minor criteria) in a young man who also had ID on the scalp.



Figure 15.11 Crusted scabies in a HTLV-1-positive man.

fashion to atopic patients; adults, instead, may have a more intractable course. In fact, later evolution of ID toward ATLL or their simultaneous occurrence has already been described in adulthood [26,27]. ID has also been described occurring simultaneously with HAM/TSP [28].

Crusted Scabies

This massive infestation by the *Sarcoptes scabiei* mite (formerly known as Norwegian scabies) was originally described in leprosy patients in Norway. Later, its frequent association with forms of immune suppression was clearly established, including chronic steroid therapy, radiation therapy, leukemia, lymphoproliferative disorders, diabetes, and retroviral infections (either HTLV-1 or HIV). Interestingly, it is also more common among people with certain genetic disorders, such as Down syndrome and Bloom's syndrome. On the other hand, it can also occur in otherwise healthy individuals. In 1993, Mollison described the simultaneous occurrence of crusted scabies and HTLV-1 infection in Australian aborigines [29]. Other authors have reported its occurrence in HTLV-1-infected patients, who are otherwise asymptomatic or suffering from any form of ATLL [30]. At least three countries, French Guiana, Brazil, and Peru, all with a high prevalence of HTLV-1 infection in the general population, have reported a series of patients with both crusted scabies and HTLV-1 infection [31–33]. In Guyana, Del Giudice described the association of crusted scabies with other infections, such as tuberculosis, tinea, and strongyloidiasis. The report by Blas established HTLV-1 infection as the most common risk factor for crusted scabies in Lima, over other causes, such as steroid therapy and diabetes. An important clue to the infection by HTLV-1 may be the tendency of crusted scabies to recur despite appropriate treatment (Figs. 15.11 and 15.12).

HTLV-1 infection status should be considered in the diagnostic workup of any otherwise healthy patient suffering from crusted scabies, especially in areas with high prevalence of HTLV-1 infection. The coexistence of HIV and HTLV-1 infection is well established in the medical literature; both infections share risk factors and mechanisms of transmission. As such, the possibility of a simultaneous HTLV-1 infection may also be considered in any patient with HIV and crusted scabies, either in immigrants or residents of areas with high prevalence.



Figure 15.12 Crusted scabies in a HTLV-1 young male. The scabies recurred in the same location several times, despite appropriate treatment.

Adult T-cell Leukemia/Lymphoma

ATLL is a malignancy of mature CD4 lymphocytes that develops in 1–5% of HTLV-1 carriers. The initial description and definition of ATLL was made in 1977 by Takatsuki in Kyoto, Japan [34], a few years before the discovery and isolation of HTLV-1. This first description focused on the leukemic form, which was commonly accompanied by skin lesions, lymphadenopathy, hepatosplenomegaly, and hypercalcemia. The T-cell nature and the particular cytological features of the proliferating cells were clearly established from the beginning. Later, other clinical forms were defined and a consensus classification was proposed in 1991, based on the Shimoyama criteria [35]. Four categories of disease were then defined: acute leukemia, chronic leukemia, lymphoma, and smoldering ATLL. This last category was characterized by very limited involvement of the peripheral blood with evident involvement of the skin or lung tissue.

Considering all categories, skin involvement is quite common; from 43 to 72% of patients may present with some sort of skin lesion.

In fact, some patients will present with exclusively cutaneous disease and no other organ involvement. Jhono proposed the idea of a fifth category, or purely cutaneous ATLL [36]. Two subcategories were then established: an erythemato-papular and a tumoral type, the latter clearly with a worse prognosis. Later studies by other investigators from Japan and Brazil tend to corroborate these findings: nodules and tumors on clinical examination, nodular and diffuse infiltration, larger cells, and proviral integration in the proliferating T cells define a subgroup with a shorter survival rate [37,38]. Other signs of bad prognosis include older age, hypercalcemia, large number of lesions, and high lactate dehydrogenase levels [39].

The age at onset of ATLL seems to be older in Japanese than in Caribbean patients (57 versus 50 years), but there is no difference in prognosis [39].

Retrospectively, ID seems to be present in the past medical history of many ATLL cases [38]. Prospectively, crusted scabies and massive strongyloidiasis could be markers of an increased risk of developing ATLL (E. Gotuzzo, personal communication). In Japan, TSP and ATLL have not been reported simultaneously. However, such association has been seen in South America [38].

The clinical spectrum may include various types of lesions, from erythroderma to macules, papules, nodules, and tumors. Diffuse eczematous and ichthyosiform varieties may be seen. Rare vesicular and pompholix cases have been reported. Patients tend to have one exclusive morphology type and there may be few or multiple lesions; disseminated lesions are quite common. The smoldering and chronic leukemic types are frequently associated with a clinical erythematous maculo-papular eruption (Fig. 15.13) and a MF-like histological picture. Tumors are associated with an aggressive primary category, as well as acute leukemic forms and lymphomatous forms (Figs. 15.14 and 15.15) [39]. Papular forms are seen in all categories. A patient may present with a purely papular rash and a few days later develop a leukemic form (Fig. 15.16). Small papules may evolve into large plaques by confluence of lesions. Peculiar forms include single unilateral tumors on a leg or multiple papules on the dorsum of



Figure 15.13 Lesions typical of mycosis fungoides in a woman with HTLV-1.



Figure 15.14 A solitary nodule on the chin of a woman with HTLV-1. The lesion was the only clinical involvement of ATLL evident in her case (purely cutaneous ATLL).



Figure 15.15 Multiple nodules in a patient with the chronic leukemic form of ATLL.



Figure 15.16 Papular eruption in a patient with the acute leukemic form of ATLL.

hands, mimicking large B-cell lymphoma or erythema elevatum diutinum, respectively.

On histology, the spectrum goes from a pattern identical to MF, to a superficial perivascular infiltrate with atypical lymphocytes, to a massive diffuse infiltration of the whole dermis, with and without epidermotropism, mimicking peripheral cutaneous T-cell lymphoma, anaplastic T-cell lymphoma or even large B-cell lymphoma of the leg. Marked epidermotropism, beyond what is usually seen in MF, may be a subtle clue to ATLL. A granulomatous pattern has been described. The phenotype is of T cells, mainly CD4 and few CD8 cells. CD25 cells may be numerous, and CD68 may be detected when histiocytes are present. Few cases show reactivity for CD30 cells.

If the cutaneous involvement takes place in the presence of pre-existing peripheral blood disease or solid organ infiltration, the diagnosis is quite obvious. For purely cutaneous forms, the first and most important differential diagnosis is MF; the most challenging situation is a patient with MF-like lesions, with histology of MF and with a positive serology for HTLV-1. To define the case as ATLL, one has to prove viral integration into the proliferating cells using Southern blot or long inverse polymerase chain reaction. Large tumors with diffuse dermal infiltration by atypical lymphocytes have to be differentiated from peripheral T-cell lymphoma, anaplastic large T-cell lymphoma, and large B-cell lymphoma of the legs. Papular forms have an extensive differential diagnosis. Only careful examination of the cytology of the perivascular infiltrate and the presence of epidermotropism may bring to consideration the possibility of ATLL.

Treatment options vary, from conservative therapy, to skin-directed therapy (such as phototherapy) for macular types, to aggressive chemotherapy or a combination of zidovudine and interferon alfa for high-risk groups such as acute leukemia, lymphomatous forms or large cutaneous tumors. The median survival time of the acute and lymphomatous forms is less than 1 year, and the response to chemotherapy is very poor [40,41]. The chronic and smoldering forms have a better prognosis, but may evolve into acute ATLL. Hematopoietic stem cell transplantation may be the last alternative for patients with several indicators of poor prognosis or with disease failing to respond to more conventional therapy [39].

Patients with ATLL are immunosuppressed and may present with opportunistic infections [40,41].

Other Cutaneous Manifestations

Other cutaneous manifestations have been reported in association with HTLV-1, including chronic and extensive dermatophytosis, xerosis, seborrheic dermatitis, candidiasis, palmar erythema, chronic eczema, folliculitis decalvans (Fig. 15.17), zoster, and extensive onychomycosis [42].

Human T-lymphotropic Virus 1 Manifestations Beyond the Skin

Human T-lymphotropic Virus 1-associated Myelopathy/Tropical Spastic Paraparesis

HAM/TSP affects an additional 1–4% of HTLV-1 carriers [43]. The syndrome presents as a chronic, symmetrical paraparesis of the lower limbs, with signs of pyramidal tract involvement, which progresses slowly and without remission. Patients often suffer from lumbar pain, urinary problems, and constipation [44]. HAM/TSP is more frequent in women than in men. Although the disease can affect HTLV-1 carriers at any age, the typical age of onset is around 50 years.

The disease mainly involves the lateral columns of the lower thoracic spinal cord. The predominant histopathological characteristic is a perivascular and parenchymal infiltration of T cells [45].



Figure 15.17 A woman with the typical findings of ID on her face and scalp; the morphology was that of doll hair folliculitis or folliculitis decalvans.

However, because manifestations of other inflammatory disorders such as acquired ichthyosis, uveitis, dry eye syndrome, and thyroiditis are quite common among HAM/TSP patients, some investigators consider that HAM/TSP should be regarded as a systemic inflammatory disease rather than a neurological disease.

Several drugs have been proposed for the treatment of HAM/TSP, such as corticosteroids, interferon-α, interferon-β1a, zidovudine, and lamivudine. Some of these therapies are directed at modulating the immune response, whereas others aim at decreasing the HTLV-1 viral antigen burden. The potential effect of these treatments is as yet unclear, as most have been evaluated only in small and/or uncontrolled studies, and among patients with long disease duration and varying disease severity.

Uveitis

Uveitis has been described more commonly in adult women with HTLV-1 infection. Common symptoms include blurred vision and floaters. Iritis and vitreous opacities are present on physical examination. Unilateral and bilateral uveitis are equally frequent. The disease tends to resolve spontaneously, but recurrences are seen in 90% of cases.

Strongyloidiasis

This infection is caused by *Strongyloides stercoralis*, an intestinal nematode that is capable of reproducing within the human host. It can produce either intestinal or disseminated disease, with subsequent invasion of lung, liver, kidney, and central nervous system. The disseminated disease, also called hyperinfection, is associated with a deficient immune state. HTLV-1 infection has been linked not only with hyperinfection, but also with strongyloidiasis in general and with relapses after appropriate treatment.

Tuberculosis

Studies from Japan, Brazil, and Peru suggest that HTLV-1 might increase the susceptibility to active tuberculosis as well as the severity of the disease. The underlying biological mechanisms are as yet unknown.

Conclusion

Infection by the HTLV-1 retrovirus is associated with several skin conditions, some of them with a characteristic clinical presentation, such as tumoral ATLL. However, other manifestations, such as ID, may be easily confused with rather common dermatoses, such as psoriasis, seborrheic dermatitis, contact dermatitis, or atopic dermatitis. More important, HTLV-1 infection may express itself in a very subtle way, e.g., as a more extensive or severe case of extremely common entities, such as dermatophytosis or scabies.

Dermatologists may be tempted to ignore this condition on the basis of its prevalence limited to specific areas of the world. However, in this era of globalization, where migration can bring people from around the world to temperate communities, cases of HTLV-1 may already be occurring and may be overlooked. HTLV-1 should be included in the diagnostic workup of any unusual dermatitis or T-lymphocytic proliferation in endemic countries or among immigrants from such regions.

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16 Reoviridae

Brenda L Bartlett and Stephen K Tyring

The Reoviridae family includes the Colorado tick fever virus (CTFV), a double-stranded RNA arbovirus (formerly classified as an orbivirus), of the genus *Coltivirus* [1,2]. A spherical virion, it has a diameter of 80 μm. The genome has 12 dsRNA segments that encode several important proteins [2,3]. As many as 22 strains of CTFV have been identified, many of which can lead to human disease. Humans are incidental hosts of the virus, with infection manifesting predominantly as a self-limited febrile illness with rare encephalitic or hemorrhagic manifestations [2] (Fig. 16.1).

History

In the 1850s, settlers of the Rocky Mountains first recognized the entity "Mountain fever," which described the clinical symptoms of a group of febrile diseases, mainly Rocky Mountain spotted fever, CTF, and typhus, among others. In 1930, Becker was the first to clearly distinguish the clinical manifestations of CTF, giving the disease its present name [4]. In 1944, Florio et al. successfully transmitted the disease to adult volunteers and animals [5], and in 1950, they isolated the virus from endemic *Dermacentor andersoni* ticks [6].

Incidence

Among tick-borne illnesses, CTF is of less importance as only 200–300 cases are reported annually in the USA [7]. Of these cases, approximately 5–10% develop meningoencephalitis [8]. The annual incidence may be underestimated because infection may go undetected due to a generally benign presentation [9]. Most cases occur in people aged 20–30 years with a 2:1 male to female ratio [10]. The epidemiology of CTF corresponds with the geographic distribution of its vector, the Rocky Mountain wood tick (*D. andersoni*), which is found at elevations of 4,000–10,000 feet in the western USA and southwestern Canada, particularly on south-facing brush slopes with dry rocky surfaces east of the Continental Divide [2,11]. Colorado and Idaho report most of the cases, occurring between March and September. The peak incidence occurs in April and May at low altitudes, when the ticks are most active. Hikers, campers, and forestry workers are most often affected. Second attacks are rare, and susceptibility is universal. Cases of CTF have only rarely been reported in non-endemic areas. A case of transfusion-related transmission has been reported [12], and CTF in persons exposed to ticks brought home on the clothing of relatives has occurred [13].

Pathogenesis

A wide variety of mammals, principally rodents, are naturally infected with CTFV, however, only humans develop clinical disease. The golden-mantled ground squirrel, the Columbia ground squirrel, the porcupine, the yellow-pine chipmunk, and the least chipmunk are amplifying hosts for the virus [14–17], while larger mammals (e.g., deer and elk) have no known role in virus perpetuation. The vector is a wood tick known as *D. andersoni*, which is a dark brown tick with white markings on the scutum [18]. The larvae and nymph of the tick acquire the virus while feeding on small viremic mammals [2]. The wood tick lifespan averages 2–3 years, and CTFV infection is present for the life of this species. However, only adult ticks, both male and female, are capable of transmitting the virus to humans [11].

Shortly after inoculation, CTFV invades the bone marrow and the host erythrocyte precursors. CTFV is unique among arboviruses in that it is harbored within erythrocytes during infection [19]. Persistence of the virus within peripheral erythrocytes prolongs the viremia long after acute infection has resolved [20]. Host immune mechanisms have little efficacy against the erythrocyte-sequestered virus. This evasion of immunity delays the development of complement fixation and neutralizing antibodies [19,20]. The involvement of bone marrow erythrocytic precursors is also associated with other marrow cell lines. Bone marrow invasion may result in hemorrhagic and vasculitic manifestations.

Clinical Manifestations

Clinical manifestations of CTF, including influenza-like symptoms, begin approximately 1 week post-inoculation and last 7–10 days [7] (see Table 16.1). Sudden onset of fever, chills, headache, and severe muscle aches occur early in the illness. The fever, the most distinguishing feature, is described as a biphasic or "saddleback" fever. Meaning, the initial fever lasts 2–3 days, remits for a similar duration followed by a second febrile period associated with leucopenia [18]. Fever has also been associated with meningitis, conjunctivitis, and rash [21]. Sore throat is seen in approximately one third of patients, while further involvement of the respiratory tract rarely occurs [22]. Gastrointestinal symptoms including abdominal pain, nausea, and vomiting are prominent with this infection. Additional symptoms include backache and vertigo [18].

The cutaneous manifestation of CTF is not a prominent, common, or characteristic feature of the illness. In two large clinical series, the incidence of skin eruption ranged from 5 to 12% [23,24]. The associated exanthem is often transient and faint, and it may be limited to the trunk or become generalized [9,23–25]. Macular, maculopapular, morbilliform, and petechial eruptions have been described [23]. The maculopapular rash may appear on the neck, face, arms, and legs [24]. The petechial lesions may appear over the flexor surfaces of the arms and legs or may be diffuse [26].

Most cases of CTF resolve completely without sequelae, however, rare complications may occur and tend to occur in children more often than adults [27]. Others at risk for complications include immunocompromised patients or patients who have undergone splenectomy [7]. Hemorrhagic diathesis has been reported, particularly in children less than 10 years of age, and has led to death in at least three cases [23,24,26–29]. This manifestation is typically associated with thrombocytopenia and sometimes with disseminated intravascular coagulation. Central nervous system (CNS) involvement may occasionally develop through CTFV

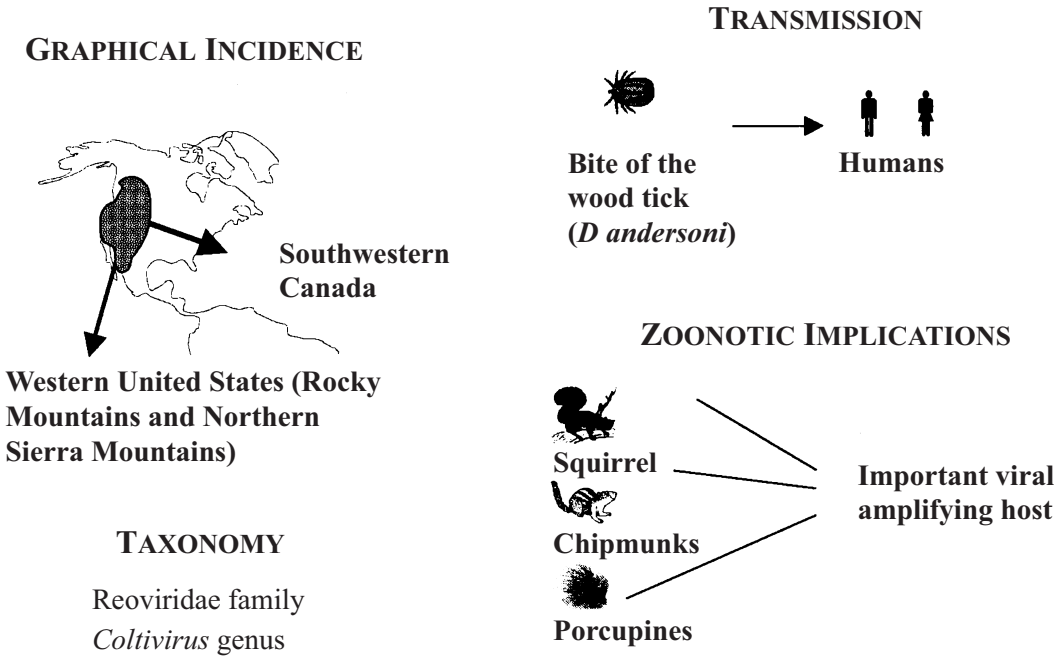


Figure 16.1 Incidence and transmission of Colorado tick fever.

invasion of the brain and meninges, with signs and symptoms consistent with aseptic meningitis or encephalitis. Nuchal rigidity has been reported as a manifestation of CNS involvement [24]. CNS complications may be self-limited with possible residual neurologic dysfunction or may progress to coma and death [23,28,30]. Other rare complications in adults include epididymoorchitis, pericarditis, hepatitis, and pneumonitis [12,18,31–33].

Laboratory Findings

The first laboratory sign of CTF is leucopenia with neutropenia either greater than or proportionate to the lymphopenia. Atypical lymphocytes may be seen along with neutrophils with toxic morphology [34]. Thrombocytopenia has also been seen, although less commonly [35]. CNS disease shows cerebrospinal fluid (CSF) findings common for viral disease – slightly elevated protein and lymphocytic pleocytosis. In addition, the virus may be isolated in the CSF [8].

Diagnosis

The differential diagnosis for CTF can be broad as it may include all febrile illnesses with influenza-like symptoms [36]. Differential diagnoses are shown in Table 16.2. Appropriate clinical symptoms, especially a biphasic fever, in the patient with recent tick exposure, in an endemic area, should lead the physician to suspect CTF. Clinicians should have a high index of suspicion even without a history of a tick bite if other factors are suggestive. In a large case study, 90% of patients with CTF reported exposure to ticks prior to illness, while only 52% were aware of an actual tick bite [24].

Viral isolation from blood (specifically erythrocytes) can confirm the diagnosis, and most patients remain viremic throughout the course of clinical symptoms [24]. Complement fixation and neutralizing antibodies appear late in the disease due to viral persistence and sequestration in red blood cells, which limits the use of serology for early diagnosis. Paired antibody titers can document prior infection, but are less useful than in other arboviral diseases. Immunoglobulin M is first detectable at the same time as neutralizing antibodies (14–21 days post-infection) and abruptly declines after 6 weeks [13,37]. Direct detection of viral antigens by immunofluorescence of erythrocyte smears is a rapid technique for diagnosis, and infected blood remains positive for up to 20 weeks after the onset of the illness. However, this method has low sensitivity during the first 7 days of disease, so a negative test should be repeated during the second week of clinical illness [38,39].

Table 16.1 Clinical Manifestations of Colorado Tick Fever

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–6 days	Acute onset of malaise, myalgia, high fever, chills, intense headache, painful skull, photophobia, retroorbital pain, and lumbar back pain. Nausea and vomiting may occur. This phase lasts for 5–10 days	Demonstration of viral antigens in erythrocytes by immunofluorescence Viral isolation from erythrocytes Serology (less useful)	A biphasic pattern occurs in half of patients, with initial febrile illness for 2–3 days, followed by an asymptomatic afebrile period for 1–2 days, then a second symptomatic febrile period lasting for 2 more days
8–16 days	Convalescent phase begins, with asthenia, weakness, and malaise resolving within a few weeks. Some patients may experience prolonged convalescence for months		

Table 16.2 Differential Diagnoses for Colorado Tick Fever

Rocky Mountain spotted fever: Fever, headache, and rash are typical manifestations of RMSF. It is seen predominately in children in the eastern United States, but a similar illness occurs in Brazil. A tick bite history is inconstant. Fever occurs 2–8 days later. The rash, a vasculitis due to endothelial cell involvement, blanches initially, then turns purpuric, perhaps hemorrhagic or even necrotic. It appears on the wrists and ankles frequently involving the palms and soles, then spreads centrally. Absence of the rash occurs in proven disease. The headache may be associated with meningeal signs, and altered mental status or coma may occur. Cardiac involvement results in failure and arrhythmias. Myositis and pneumonia are seen and edema may occur. Thrombocytopenia is common as is leukocytopenia, but leukocytosis occurs with secondary infectious complications. Treatment with chloramphenicol or tetracycline must be based on suspicion of diagnosis; untreated disease may be fatal

Lyme disease: A tick bite precedes the classic erythema migrans eruption early in the course of disease. Late manifestations are arthritis, aseptic meningitis, cranial nerve palsy, or heart block

Tularemia: Tularemia may be associated with a tick bite, but the site of inoculation becomes painful and ulcerated, with associated lymphadenopathy. The less common presentation with bacteremia or meningitis is similar to CTF but may be more severe

Enteroviral infections: Patients have fever, headache and nuchal rigidity. Cerebrospinal fluid studies show lymphocytic predominance with elevated protein. Enteroviral meningoencephalitis will be clinically indistinguishable from other central nervous system diseases. Serology, viral isolation, or where available, nucleic acid amplification testing will prove the etiology

Herpes simplex virus (HSV) encephalitis: HSV encephalitis should be excluded because of its severe outcome and response to antiviral therapy. Rapid testing for HSV is commonly employed. A hemorrhagic, necrotizing encephalitis of the temporal lobes is typical, but it may appear as meningitis or frank encephalitis with seizures and coma

Other Arboviral Infections: ONN is suggested by sub-Sarahan travel, fever, arthritis, a morbilliform rash, and lymphadenopathy.

Sindbis is suggested by fever, rash, arthritis with travel in Europe, Asia, Africa, or Australia, and mosquito exposure

Mayaro is suggested by fever, chills, headache, myalgia, arthralgia, and a maculopapular rash as the fever fades and travel to Brazil or Trinidad, with mosquito exposure. Travel to Australia, mosquito exposure, fever, arthritis, and rash suggests Ross River virus or Barmah Forest disease

Oropouche is suggested by travel to Trinidad or northern South America, fever, myalgia, anorexia, headache, photophobia, leukopenia, with exposure to Culicoides midges or suggestive season and habitat

Sandfly fever is suggested by travel to Africa, southern Europe, central Asia or the Americas in the summer, exposure to small flies, or habitat with fever, myalgia, photophobia, retro-orbital pain, and conjunctival injection

Other Arboviral Encephalitis:

Eastern equine encephalitis is suggested by encephalopathy (altered mental status, coma, seizures), by salt marsh habitat in North and South America, deaths in horses and pheasants, and mosquito exposure in hot, damp months

Western equine encephalitis is suggested by encephalopathy with mosquito exposure in western United States and Canada and an equine epizootic

Venezuelan equine encephalitis is suggested by encephalopathy with travel in South and Central America, the Florida Everglades, Mexico or Texas, inflammation of conjunctivae or pharynx, flushed facies and muscular tenderness, an equine epizootic, and exposure to mosquitoes in wet, warm months

West Nile fever is suggested by travel to rural Africa, southern Europe, central or south Africa, or northeastern United States, mosquito exposure, symptoms of headache, myalgia, lymphadenopathy, leukopenia, and a nonpruritic maculopapular rash

California encephalitis is suggested by encephalopathy with rural midwest United States travel in July through September

Japanese encephalitis is suggested by severe encephalopathy in children in Asia in the monsoon season

St. Louis encephalitis is suggested by encephalopathy with central and western United States travel, mosquito exposure in late summer to early autumn

Tick-borne encephalitis is suspected by tick exposure in Russia or central Europe in late spring or summer after heavy rainfall or exposure to raw milk in a patient with altered mental status, fever, thrombocytopenia, and leukopenia

Powassan encephalitis occurs in Russia, Canada, and the United States. Young boys are more commonly affected, and tick exposure is frequent

Other diagnostic tests, including enzyme-linked immunosorbent assay (ELISA) and Western blot, have been developed [40]. Real-time polymerase chain reaction (PCR) has also been developed and used for the early diagnosis of CTF infection. Diagnosis within the first days of symptoms can be made using reverse transcriptase (RT)-PCR, which has the specificity to differentiate between antigenic variants [2,41].

Prevention and Treatment

The use of proper clothing, limiting exposure by avoiding tick-infested areas, and prompt tick removal are somewhat effective strategies in preventing infection. Due to significantly prolonged viremia, blood donation should be prohibited for 6 months to 1 year after infection to prevent transfusion-related transmission. An experimental vaccine studied in the 1960s used inactivated virus and showed promising results, producing high antibody titers; however, it was not developed further [8].

No specific antiviral treatment is currently available for CTF [42]. Treatment is therefore supportive, although patients are sometimes treated empirically with doxycycline, tetracycline, or chloramphenicol to cover for other tick-borne diseases [7]. Ribavirin has shown activity against CTFV in vivo and increased survival in an animal model. However, no human data exists to support the use of ribavirin as a treatment [43]. The expected outcome without sequelae is good, except in cases with CNS involvement [44].

Conclusion

CTF is generally a benign tick-borne illness with rare complications. It occurs in endemic regions of the USA and requires a high index of suspicion in order to make a diagnosis. Treatment is supportive as no specific antiviral therapy exists.

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17 Paramyxoviruses

Thais Sakuma, Daniel Coimbra, Vera Y Soong, and Tricia J Brown

Measles is an acute exanthematous and enanthematous disease caused by the rubeola virus. This highly communicable illness is characterized by fever, cough, coryza, and a maculopapular eruption. Although measles is generally self-limited, serious complications of the respiratory and central nervous systems may occur. Measles remains a worldwide problem, with significant morbidity and mortality in developing countries (Fig. 17.1).

History

The name measles is thought to be derived from the Latin *misellus* or *misella*, from the word miser, meaning miserable. *Morbilli*, the diminutive of *morbus*, was used to distinguish this minor illness from bubonic plaque, *morbus*, the major disease. The term morbilliform is still in common use to describe a measles-like exanthem [1]. Measles has been recognized for over 2000 years, although it was frequently thought to be a mild form of smallpox. Rhazes, an Arabic physician, is credited with the earliest written description of measles in the 10th century AD in which he distinguished measles from smallpox [2]. Rhazes quoted El Yehudi, a Hebrew physician, who described measles in Syria in the 7th century AD [3]. Thomas Sydenham recorded a measles epidemic in London in 1670 [4,5]. Noah Webster wrote about the contagious nature of measles in 1799 after epidemics swept through the early American colonies. In 1846, Paul Panum, a Danish physician, published a landmark description of an outbreak in the Faroe Islands [6]. He described the incubation period, respiratory mode of transmission, and apparent lifetime immunity of previously infected persons. Koplik, in 1896, described the characteristic enanthem of measles that bears his name [7]. In 1905, Hektoen conclusively demonstrated the transmission of measles by infecting susceptible volunteers through the transfer of blood from acutely infected patients [8]. Goldberger and Anderson confirmed the viral etiology in 1911 after transmitting measles to rhesus monkeys by injection of filtered material from acutely ill human patients [9,10]. In 1954, Enders and Peebles were the first to report the propagation of wild measles virus (MV) in primary human renal tissue culture cells and to describe the characteristic cytopathic effects (CPE) of this virus [11]. This work led directly to the development of the live attenuated measles vaccine currently in use today [12].

Virology

MV is a single-stranded RNA virus belonging to genus *Morbillivirus* in the family Paramyxoviridae [13]. The organism is very labile and easily inactivated [14]. Low relative humidity is the most important factor that determines viral survival [15]. Viral decay increases dramatically in the range of 50–70% humidity. This may account for the increased incidence of measles in winter, when indoor relative humidity is low. The virus is also readily inactivated by heat, ether, light, acid pH, and trypsin. It survives less than 2 hours in the air or on objects and surfaces [16,17].

Humans are the only natural hosts of wild MV, although other primates can be infected. There is no animal reservoir. Human or simian renal cell cultures are most widely used to isolate the virus from infected patients. Two types of CPE are produced by MV in tissue culture: multinucleated giant cells and spindle cell transformation [18]. Multinucleated giant cells, analogous to Warthin-Finkelday cells seen in the reticuloendothelial system, appear in 6–10 days. Spindle cell transformation is produced by vaccine, rather than wild strains and is characterized by alteration of single cells into spindle or stellate shapes. Both forms of CPE may be present simultaneously in tissue culture. They provide reliable evidence of viral multiplication and are the basis for procedures for viral isolation, assays of infectivity, and determinations of neutralizing antibodies.

MV is an enveloped virus that presents two transmembrane glycoproteins, fusion protein (F) and hemagglutinin (H) protein. The former mediates membrane fusion after receptor binding by the latter.

Hemagglutinin (H) protein binds to two receptors, the signaling lymphocyte activation molecule (SLAM, CD150) and the membrane cofactor protein (MCP, CD46). CD150 is expressed on immature thymocytes, activated lymphocytes, macrophages, and mature dendritic cells (DCs). This distribution of SLAM determines MV lymphotropism and its immunosuppressive nature [19–21]

Epidemiology

Despite the availability of a safe and effective vaccine to prevent the disease, measles remains a leading cause of death among young children. For 2007, the World Health Organization (WHO) estimated 197,000 deaths worldwide due to measles. The burden of measles continues to be greatest in regions of Africa and South-East Asia, especially in countries that have not carried out mass vaccination campaigns and where routine immunization rates are low [22].

From 2000 to 2006, almost 500 million children aged between 9 months and 14 years received measles vaccine through supplementary campaigns in 46 out of the 47 priority countries with the highest burden of measles. During this time, mortality from measles fell by 91% in Africa (from an estimated 396,000 in 2000 to 36,000 in 2006) and by 68% worldwide (from an estimated 757,000 deaths to 242,000) [22,23].

Prior to available vaccination, approximately 130 million cases and 7–8 million deaths occurred annually worldwide due to measles infection [24,25]. During the pre-vaccine era, more than 95% of the US population contracted the disease before their 20th birthday, usually in early childhood. Epidemics in the late winter and early spring occurred every 2–3 years. Widespread measles vaccination began in the 1960s and has thus far reduced global measles morbidity and mortality [26]. Results of epidemiological data for 1998 suggest that measles is no longer an indigenous

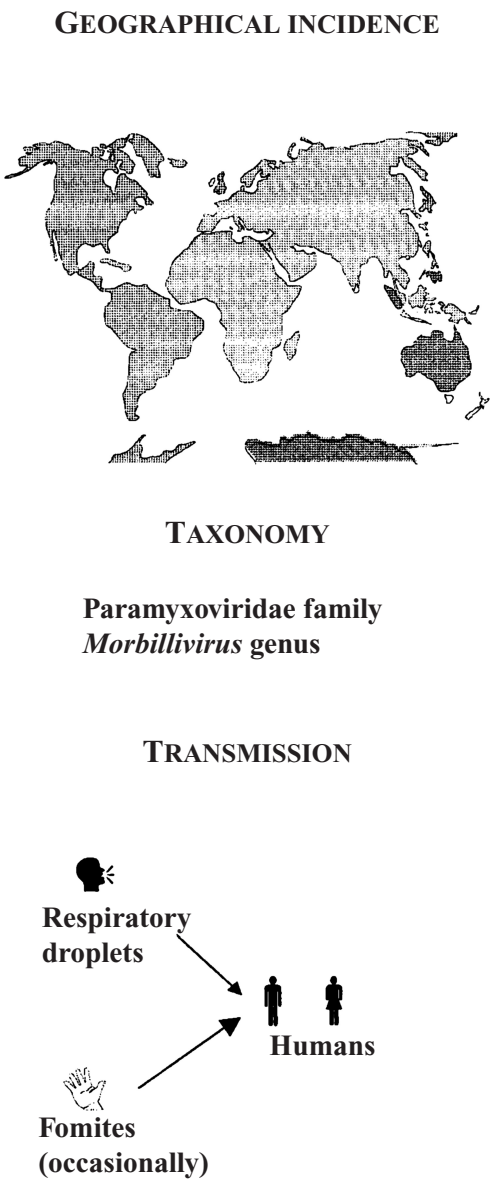


Figure 17.1 Incidence and transmission of measles.

illness in the USA [27]. Of the record low number of 100 cases that occurred that year, 71 cases were internationally imported or importation-associated.

Between January and July 2008, 131 measles cases from the USA were reported to the Centers for Disease Control and Prevention (CDC), compared with an average of 63 cases per year during 2000–2007. Among these measles cases reported during the first 7 months of 2008, 91% were in persons who were unvaccinated or of unknown vaccination status. Of the 131 cases, 89% were imported from or associated with importations from other countries, particularly countries in Europe, where severe outbreaks were occurring [28].

According to the WHO, from January to August 2008, Australia reported 63 measles cases, Japan 10,627 cases, and China reported 129,195 suspected cases [29]. Brazil and Mexico had no confirmed measles in 2007, while Canada reported 101 cases during the same year [30]. A total of 3,826 measles cases were registered in 2007 from 31 European countries. The highest reported indigenous incidence of measles was reported from Switzerland followed by the UK with 14.06 and 1.64 per 100,000 inhabitants, respectively [31].

The WHO's goal is to achieve a 90% worldwide reduction in the number of measles deaths by 2010 compared to the 2000 estimate [22].

Pathogenesis

Measles is one of the most communicable of infectious diseases. Transmission via respiratory droplets approaches 100% [32], although relatively close contact is required. The portals of entry of infection are the nasopharynx and perhaps the conjunctiva. Infection is typically acquired from inhalation of respiratory droplets as a consequence of face-to-face exposure to infected individuals who are coughing and sneezing during the prodromal stage [6,9,33]. As MV can survive for 2 hours in respiratory droplets [34], occasional transmission by contact with fomites is possible. Airborne transmission of measles in a physician's office [35–37] and in an elementary school [38] have been documented. Immunocompromised persons may shed the MV for extended periods. These individuals should be kept in respiratory isolation during hospitalization [34].

In 2000, SLAM CD150, expressed on subsets of thymocytes, macrophages, DCs and B- and T-lymphocytes, was identified as the main receptor for wild-type MV. As it is not expressed by epithelial cells of the respiratory tract or by monocytes, studies indicate that DCs and lymphocytes expressing CD150 are the primary target cells for MV infection. MV may also inefficiently infect $SLAM^-$ cells through an independent pathway, probably when high virus loads are present [39,40].

DCs, which are abundantly present in the upper respiratory tract, may transport the virus to the regional lymph nodes, and primary viremia occurs by day 3. Inside the lymph nodes, MV are transmitted to lymphocytes, which during the second viremia that occurs on days 5–7, disseminate the virus throughout the body resulting in the establishment of generalized infection [39,40].

During the second week of infection, the virus can be found in blood, skin, respiratory tract, and other organs. During days 10–12 after exposure, the prodromal period of measles occurs, followed a few days later by a generalized maculopapular skin rash. Infectivity is greatest in the 3 days before rash onset. It appears that prodromal measles corresponds to a period of intense viral multiplication and dissemination during which tissue damage occurs, resulting in the clinical illness. During days 14–17, viremia diminishes as viral multiplication slows. This rapid decline in tissue viral content coincides with the appearance of measles antibody during days 14–18. As serum antibody levels increase, the virus becomes undetectable in blood, urine, and nasopharyngeal secretions. Patients shed MV from the nasopharynx and are considered infectious from the beginning of the prodrome until approximately 4 days after the appearance of the rash [41].

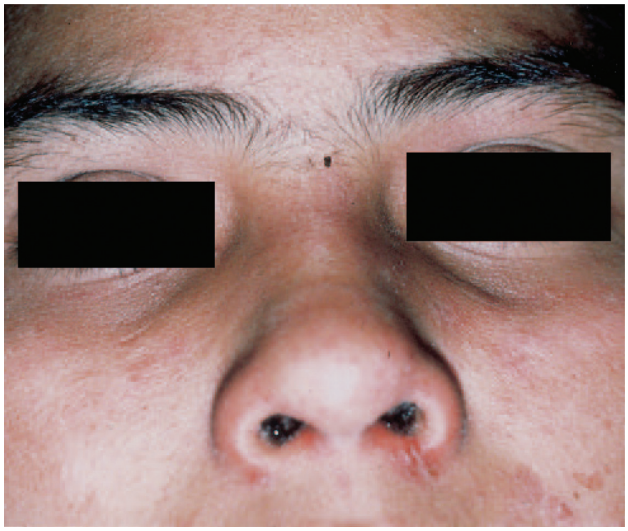


Figure 17.2 Coryza associated with measles. (Photograph courtesy Lourdes Tamayo, M.D., and Edith Garcia-Gonzalez, M.D., Ph.D., Department of Dermatology, Instituto Nacional de Perinatologie, Mexico City, Mexico.)

Measles-associated immunosuppression and lymphopenia are not well understood. It starts before the onset of the rash and lasts for up to 1 month. Possible underlying mechanisms are: (1) infection and subsequent destruction of $SLAM^+$ cells of the immune system, (2) MV-SLAM interaction may affect signal transduction of immune cells, and (3) TH2 polarization response because of preferential infection of TH1 cells, which express higher levels of SLAM [40]. It results in suppression of delayed-type hypersensitivity, as demonstrated by anergy to skin test antigens [42].

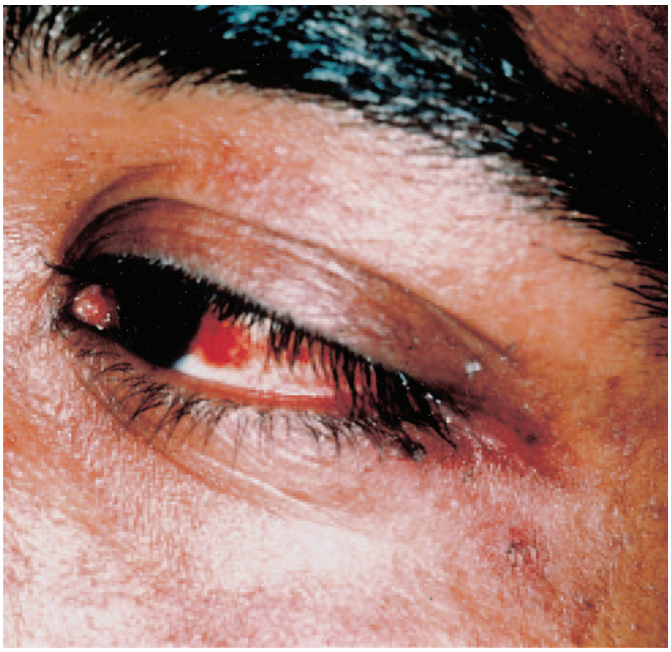


Figure 17.3 Conjunctivitis associated with measles. (Photograph courtesy of Mark Lebwohl, M.D., Department of Dermatology, Mt. Sinai School of Medicine, New York, NY.)



Figure 17.4 Erythematous macules and papules of acute measles.

Clinical Manifestations

Measles infection is only rarely associated with sub-clinical infection. After an incubation period of 8–12 days, measles starts with fever, cough, coryza, and conjunctivitis (Figs. 17.2 and 17.3), followed a few days later by the onset of characteristic macules and papules in a uniform morbilliform eruption (Figs. 17.4–17.7)

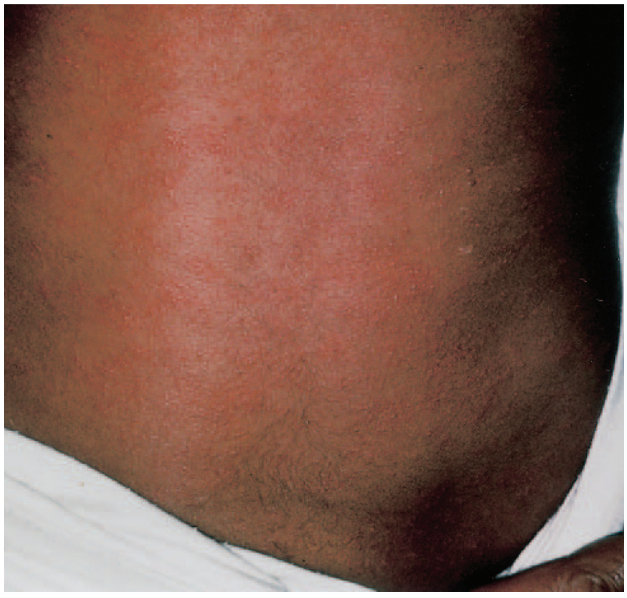


Figure 17.5 Erythematous macules and papules of acute measles.

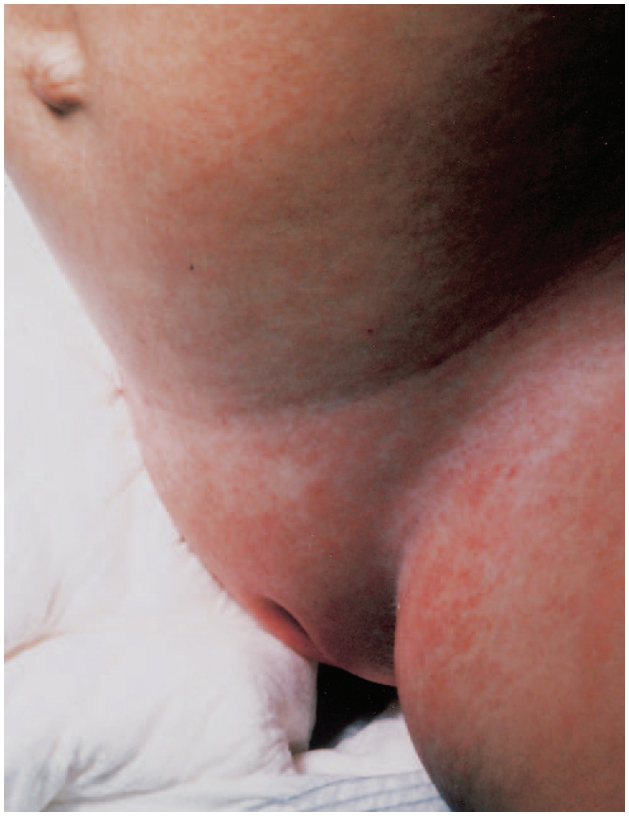


Figure 17.6 Erythematous macules and papules of acute measles.

(Table 17.1). The symptoms, usually first noted on the face and neck, peak on the first day of rash. For 2 or 3 days, the lesions increase in number, especially on the trunk and face, and also spread toward the distal extremities, where more discrete lesions are seen. The rash lasts for 3–7 days and then ends with fine desquamation [42]. Fever associated with measles infection may exceed 40°C (104°F), and the patient may appear extremely ill and toxic. Pharyngitis and cervical lymph node enlargement are common with measles; generalized lymphadenopathy may also be seen. Diarrhea, vomiting, laryngitis, croup, and abdominal pain may occur, particularly in children.



Figure 17.7 Erythematous macules and papules of acute measles.

Koplik's spots have been reported in 60–70% of persons with measles and are pathognomonic of the disease. They usually appear 1 day before the onset of rash and last for 2–3 days. They are initially seen as clusters of punctate blue-white papules on an erythematous base and are located on the buccal mucosa adjacent to the upper molars (Figs. 17.8 and 17.9) [42]. These lesions rapidly increase in number and can involve the entire buccal and lower labial mucosa (Fig. 17.10). Initially about 1 mm in size, the lesions may coalesce as they become more numerous. The background oral mucosa has a characteristic red, granular appearance. Koplik's spots are often described as having the appearance of a grain of salt on a red background.

Clinical recovery begins after the appearance of the rash in uncomplicated measles. In severe cases, the exanthem may have associated edema, particularly on the face. The copper to brownish discoloration of the rash that develops as the exanthem fades is thought to be due to capillary hemorrhage (Figs. 17.11–17.13). In fair-skinned persons, the rash may become purpuric instead of fading, although this is not related to hemorrhagic manifestations of measles [43].

Children infected by human immunodeficiency virus (HIV) not treated with highly active antiretroviral therapy (HAART) have a decreased response to measles vaccination, and the vaccine-induced immunity declines faster. They also have prolonged virus shedding. However, there is no consensus on whether measles in HIV-infected children presents a higher case-fatality rate than in non-HIV-infected hosts [17,42,44].

Modified Measles

Modified measles is a milder form of measles that is seen in persons with passive immunity to the virus. It occurs in infants less than 9 months of age with transplacentally acquired antibody to the virus, in persons who receive blood products that contain antibody to the virus, in susceptible patients given immune globulin after exposure to rubeola, after vaccine failure, or rarely in recurrent disease [42,45–49]. Patients with modified measles have an attenuated illness with a shortened prodromal period; fever, coryza, and cough are mild. Koplik's spots may not occur. The exanthem evolves as in typical measles, but the lesions do not become confluent. The illness may not fulfill the CDC clinical criteria for the diagnosis of measles, most often due to absent or low-grade fever. Undiagnosed modified measles occurring after secondary vaccine failure may lead to under-reporting of measles cases and falsely elevated vaccine efficacy rates in highly vaccinated populations [47].

Atypical Measles

The live attenuated measles vaccine available today affords most persons with effective immunity against natural measles infection. A killed vaccine, which was used in the USA during the years 1963–1967, was withdrawn after the emergence of the atypical measles syndrome in patients exposed to wild MV [50–53]. Although atypical measles has rarely been reported in recipients of the live attenuated vaccine [54], this syndrome occurs almost

Table 17.1 Clinical Manifestations of Measles

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
8–12 days	Prodromal symptoms, including fever, malaise, coryza, cough, conjunctivitis, photophobia, and periorbital edema	Serology, particularly IgM Detection of measles virus antigen in tissues Viral culture (difficult)	The cough has a brassy or barking quality, and may be severe Symptoms increase in severity over the next few days As the exanthem progresses, initially discrete lesions become confluent, especially on the face, neck and shoulders Fever peaks on the 2nd or 3rd day of the rash, followed by rapid defervescence (unless complications occur) Fine desquamation may be seen with resolution of the rash. Conjunctivitis and coryza resolve at this time, but dry cough may persist for 10 days or more
16–20 days	Koplik's spots appear at the end of the prodromal period and remain discrete for 2–3 days		
10–14 days	Exanthem begins on the 3rd or 4th day of fever, beginning as prominent, blanchable, erythematous macules and papules on the neck, hairline, forehead and postauricular areas. The exanthem spreads to the trunk and extremities over the next 2–3 days, reaching the feet in 3 days		
11–16 days	Exanthem reaches its peak after 3 days, which conicides with the peak of the prodromal symptoms		
15–19 days	Exanthem begins to clear, in order of appearance. As the rash fades, it becomes a copper color, then leaves a brown nonblanching discoloration		

IgM, immunoglobulin M.

exclusively in recipients of the killed vaccine. Atypical measles rarely occurs, and it is now an infrequent disease of young adults.

The pathogenesis of atypical measles remains unclear. The illness is characterized by the occurrence of excessively high measles antibody titers. Often immeasurable or low at the onset of the exanthem, antibody titers rise dramatically to levels as high as 1:128,000 within 2 weeks [55]. It has been found that the antigenicity of the F glycoprotein of the viral envelope is destroyed by the inactivation of the virus during preparation of the killed vaccine. Therefore, the killed measles vaccine does not induce an antibody response to the F protein, which mediates cell fusion and cell-to-cell spread of the virus. The spread of infection in recipients of the killed vaccine is unchecked due to lack of these neutralizing antibodies. By contrast, the antigenicity of the H glycoprotein is preserved and may simultaneously induce later hypersensitivity to natural measles infection. This results in the syndrome of atypical measles, with hypersensitivity responses in multiple organs, despite partial immunity [53].

After an incubation period of 7–14 days, atypical measles begins abruptly with high fever, headache, photophobia, myalgias, arthralgias, abdominal pain, tachypnea, pleuritic chest pain, nonproductive cough, and prostration. Coryza and conjunctivitis are absent. Koplik's spots are not seen. After 2–3 days, the exanthem appears. Unlike typical measles, the eruption begins peripherally on the hands, wrists, feet, and ankles and spreads centripetally (Figs. 17.14–17.16). The exanthem usually begins as erythematous macules and papules, but may progress to vesicular or petechial lesions. The vesicular lesions appear singly or in crops, primarily on the trunk, and may resemble the exanthem of varicella. The petechial lesions may be associated with purpura and occur predominantly on the trunk and extremities with relative sparing of the face. This cutaneous pattern may be confused with Rocky



Figure 17.8 Koplik's spots seen on the buccal mucosa. (Photograph courtesy Lourdes Tamayo, M.D., and Edith Garcia-Gonzalez, M.D., Ph.D., Department of Dermatology, Instituto Nacional de Perinatologie, Mexico City, Mexico.)



Figure 17.9 Koplik's spots seen on the buccal mucosa. (Photograph courtesy Lourdes Tamayo, M.D., and Edith Garcia-Gonzalez, M.D., Ph.D., Department of Dermatology, Instituto Nacional de Perinatologie, Mexico City, Mexico.)



Figure 17.10 Red, granular, manifestations of measles on the oral mucosa. (Photograph courtesy Lourdes Tamayo, M.D., and Edith Garcia-Gonzalez, M.D., Ph.D., Department of Dermatology, Instituto Nacional de Perinatologie, Mexico City, Mexico.)

Mountain spotted fever, meningococcemia, Henoch-Schonlein purpura, or Gianotti-Crosti syndrome. The exanthem may also be predominantly an erythematous maculopapular eruption that has been confused with scarlet fever [53,56,57]. Erythematous papules coalescing into plaques in an inverse photo-distribution have been reported [58]. Peripheral edema is commonly seen.

Involvement of the respiratory tract in atypical measles is prominent, with hilar adenopathy, pulmonary infiltrates, and pleural effusion frequently seen [53,57]. Pulmonary infiltrates may be diffuse, segmental, or nodular. Patients may present with hypoxemia, and acute respiratory failure has been documented. Pulmonary function tests reveal severe restrictive lung disease. Although pulmonary disease is self-limited, residual calcified

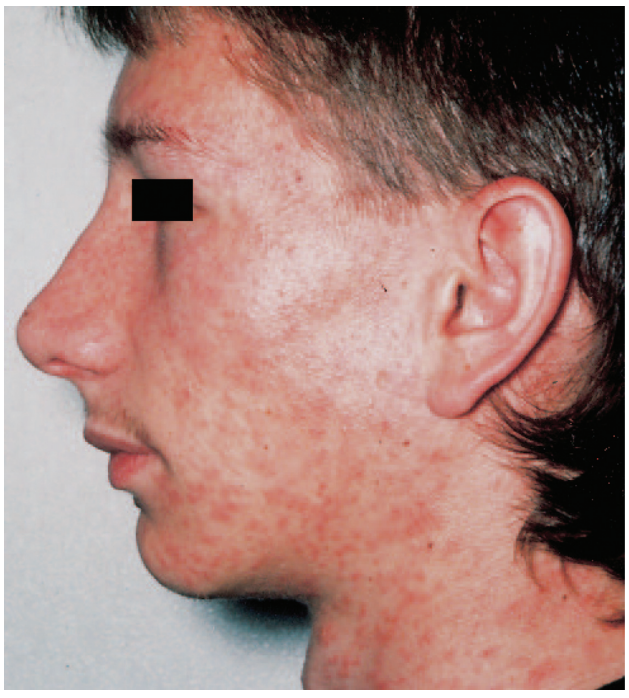


Figure 17.11 Exanthem of measles after resolution of fever and other symptoms.



Figure 17.12 The exanthema becomes a copper color as it begins to fade (after two weeks).



Figure 17.13 After three weeks, the exanthema has faded significantly, leaving a brown, nonblanching discoloration. (Photograph courtesy of Shirley Pren, M.D., Department of Pediatrics, University of Miami School of Medicine, Miami, FL.)



Figure 17.14 The eruption of atypical measles begins on the extremities and spreads centripetally. (Photograph courtesy of Mark Lebwohl, M.D., Department of Dermatology, Mt. Sinai School of Medicine, New York, NY.)

nodular lesions may persist for years [59]. Transient hepatitis may complicate atypical measles [55]. Skin biopsy differs from that of classic measles in that a prominent mixed vasculitis is seen and the typical measles histologic complex is absent [53]. Although the morbidity of atypical measles is greater than that of classic measles, it is generally a self-limited illness with a good prognosis. Atypical measles is not thought to be contagious. However, viable



Figure 17.15 The eruption of atypical measles begins on the extremities and spreads centripetally. (Photograph courtesy of Mark Lebwohl, M.D., Department of Dermatology, Mt. Sinai School of Medicine, New York, NY.)



Figure 17.16 The eruption of atypical measles begins on the extremities and spreads centripetally. (Photograph courtesy of Monica McCrary, M.D., Department of Dermatology, Medical College of Georgia, Augusta, GA)

MV has been cultured from the nasopharyngeal aspirate of one patient [58].

Complications

Respiratory Manifestations

According to the CDC, approximately 30% of reported measles cases have one or more complications, which are highest among children less than 5 years and adults over 20 years. From 1985 to 1992, otitis media was the second most frequent measles complication, being reported in 7% of cases, preceded only by diarrhea that accounted for 8% of the cases [17]. Laryngitis and laryngotracheitis also occur frequently. Pneumonia is a common, often serious, complication of measles with reported rates of 3.5–50%. Pneumonia may be the result of direct viral invasion of the lungs, secondary viral infection with adenovirus or herpes simplex virus, or secondary bacterial infection [42,60–63]. Primary measles pneumonitis is seen more frequently in children and is characterized by the presence of multinucleated giant cells with intranuclear and intracytoplasmic inclusion bodies [64,65]. Studies demonstrated bacteria as the cause of 25–35% of measles-associated pneumonia. The most commonly cultured organisms were *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenza*. Other less commonly isolated bacteria were *Pseudomonas species, Klebsiella pneumonia*, and *Escherichia coli* [42]. Radiographic findings are nonspecific, with a fine multilobular reticulonodular infiltrate as the most common finding (Fig. 17.17).

Pneumonia is the most common cause of death associated with measles, with the greatest mortality occurring in pediatric, malnourished, and immunocompromised patients. This complication accounts for about 60% of measles-related deaths [17,66]. An immunocompromised child exposed to measles may develop fatal giant cell pneumonia with or without a rash [65,67].

Malnourishment, intense exposure due to crowded living conditions, vitamin A deficiency, and immunosuppression (e.g., congenital defects in T-lymphocyte function, bone marrow transplantation, chemotherapy, immunosuppressive doses of steroids) contribute to high mortality rates [42,68]. Patients with B-cell immune deficiency syndromes with normal T-cell



Figure 17.17 The fine, multilobular reticulonodular infiltrate of measles pneumonia.

function do not appear to have increased measles-related complications [42]. Although measles pneumonia increases the morbidity of the disease in healthy adolescents and young adults, deaths are rare.

Encephalitis

The incidence of post-infectious encephalitis is 0.5 to 1/1000 cases of measles infection [69]. The decline in measles encephalitis has paralleled the decline in the incidence of measles [70]. Although MV has already been detected in cerebrovascular endothelial cells of a person who died during the first days of rash, viral invasion of the brain is not an obligate step in measles encephalomyelitis [71]. Measles encephalitis appears to be caused by an abnormal immune response that affects myelin basic protein [42] and presents with an abrupt recrudescence of fever, seizures, headache, lethargy, irritability, and depressed level of consciousness, including coma [72,73]. Most cases occur within 7 days of the onset of the exanthem, often after the eruption has faded and fever has abated. The mortality rate of acute measles encephalitis is approximately 15%. Another 25% of patients have serious neurological sequelae, including mental retardation, seizures, deafness, behavioral disorders, hemiplegia, and paraplegia [70,74].

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic neurological disease caused by a persistent MV infection in the central nervous system [42]. This late complication of measles was first described by Dawson in 1933, who proposed a viral etiology due to the presence of intranuclear inclusion bodies in brain tissue [75]. SSPE is rare, with an incidence of 5–10 cases per million cases of measles. SSPE occurs less frequently following measles vaccination [3]. Most cases occur in children between the ages 5 and 14 years. Nearly half of all patients have a history of acquiring measles before 2 years of age. The mean latent period between acute measles infection and the onset of SSPE is 7 years, with a range of 6 months to 18 years [76]. The disease is two to three times more common in males than females. The incidence is higher in rural areas, especially farms, and in persons exposed to birds, pigs, and dogs with canine distemper, which suggests some form of associated zoonotic infection. A serious head injury is also a risk factor for SSPE [77]. The disease has also been reported in immunocompromised patients [67]. SSPE is not considered contagious [41].

SSPE is a progressive, degenerative neurological disease with an average survival of 6–9 months after onset. The onset is gradual, with intellectual decline and abnormal behavior that may initially be diagnosed as a psychological problem. After 1–2 months, seizures, mycolonic jerks, ataxia, dyskinesia, and visual impairment may suddenly develop without headache or fever [78]. The disease is relentlessly progressive in most cases, eventuating in coma, opisthotonus, emaciation, and death over the next few months. Patients who do not die remain in the fourth stage, characterized by severe loss of cerebral cortex function. Remission is rare but has been reported [79]. No effective treatment has been developed.

With laboratory evaluation, one finds that the electroencephalogram (EEG) is abnormal, showing periodic bursts of high voltage activity at 3–5 second intervals. An increased level of gamma globulin in the cerebrospinal fluid (CSF) is seen [78]. Antibody to MV is present both in the serum and CSF of patients with SSPE [78,80]. A significant titer of intrathecal measles antibody is the most valuable single test for establishing the diagnosis [81]. The MV has been cultured from the brain of patients with SSPE as well [82,83]. Isolation of infectious virus was accomplished only with co-cultivation techniques, which suggests that the virus is present in a defective or latent form.

Other Manifestations

Hepatitis occurs in measles, with 80% of cases reported in adults [84,85]. It is seen most commonly in severely ill patients. Jaundice may occur, but liver involvement is self-limited with no long-term sequelae. However, a clear correlation between the severity of hepatic involvement and the occurrence of secondary bacterial infections may occur.

Black measles, a rare form of rubeola, differs from typical measles in that confluent hemorrhagic exanthem, gastrointestinal and respiratory tract bleeding, and severe hyperpyrexia are seen. It is frequently complicated by pneumonia and encephalitis or encephalopathy and has a significant mortality. Little is known about the pathogenesis of black measles [1,49].

Measles complicating pregnancy has been associated with spontaneous abortions, premature delivery, and low-birth-weight infants. There is no convincing evidence that measles infection early in pregnancy causes congenital anomalies [86–88]. During the measles epidemic in Houston in 1988–1989, 13 patients with gestational measles were hospitalized. The most common maternal complication was pneumonia, and one patient died. Four of the

thirteen patients had an adverse fetal outcome (premature labor, spontaneous abortion). The other mothers delivered healthy, full-term infants [89].

Transitory hypocalcemia of unknown etiology, with tetany as a rare complication, has been reported [90,91]. Transient development of a lupus anticoagulant after measles in an otherwise healthy child has been documented [92]. Noma-like post-measles ulcerations occur in African children after desquamation of the skin eruption. Ulcerations occur at the lips and in the perioral, perinasal, and periorbital areas with resultant scarring and mutilation [93]. Non-erosive stomatitis may result in severe oral stenosis that requires commissurotomy after natural measles and has been reported in the USA [94]. Other unusual manifestations of measles include myocarditis, pericarditis, thrombocytopenic purpura, Stevens-Johnson syndrome, pneumomediastinum, subcutaneous emphysema, appendicitis, ileocolitis, mesenteric lymphadenitis, acute glomerulonephritis, corneal ulceration leading to blindness, and gangrene of the extremities [49].

Pathology

The distinctive pathological feature of measles is multinucleated giant cells [67]. Two types have been described: reticuloendothelial giant cells (Warthin-Finkelday cells) and epithelial giant cells. The Warthin-Finkelday cells, first described in 1931, are found in tonsils (Fig. 17.18), lymph nodes, Peyer patches, appendix, thymus, spleen, and bone marrow. They are large, with up to 50 nuclei and scant cytoplasm. These cells are seen in prodromal measles and disappear within 2–4 days after the onset of the exanthem when serum antibodies appear. Epithelial giant cells are found predominantly in the respiratory mucosa, but have been described in the oral mucosa, skin, salivary glands, liver, kidney, bladder, and gastrointestinal tract. During the prodromal period, these cells are sloughed from respiratory epithelium and can be found in pharyngeal smears.

The histological changes of measles in skin and oral mucosa are distinctive [95,96]. The most characteristic feature of the exanthem is syncytial-type multinucleated giant cells in the epidermis (Fig. 17.19). These cells have 3–26 nuclei, abundant cytoplasm, and contain pink intranuclear and intracytoplasmic inclusion bodies. Other epidermal changes include focal parakeratosis, dyskeratosis, and spongiosis associated with a few lymphocytes. Some epidermal cells show intracellular edema. Spongiosis progresses to intraepidermal vesiculation in a minority of cases. The epidermal changes are strikingly focal, associated primarily with hair follicles and eccrine sweat ducts. In the dermis, a sparse superficial perivascular lymphohistiocytic infiltrate is seen.

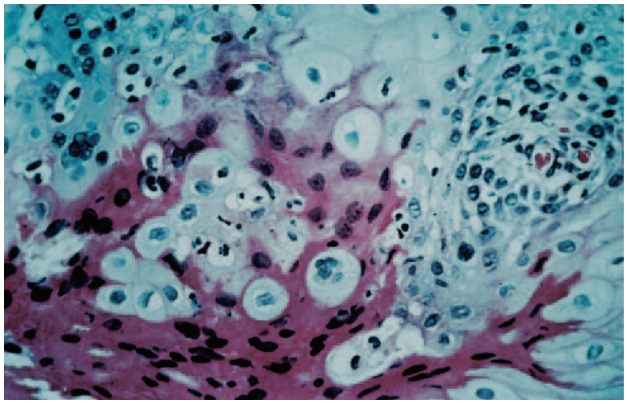


Figure 17.19 Syncytial-type multinucleated giant cells of measles in the epidermis.

The histological changes seen in Koplik's spots are similar to those seen in skin. Giant cells are more numerous and contain more nuclei (Fig. 17.20). Intracellular edema is more prominent, whereas spongiosis and the dermal infiltrate are less pronounced. Electron microscopy reveals aggregates of microtubules characteristic of paramyxovirus within the cytoplasm and nuclei of giant cells (Fig. 17.21). These viral microtubular aggregates lend support to the hypothesis that direct viral invasion of the skin and oral mucosa causes the cutaneous manifestations of measles.

Laboratory Findings

Patients may have mild leukopenia, often with relative lymphocytosis. With measles encephalitis, the cerebral spinal fluid typically shows an increase in protein and a slight increase in lymphocytes, while the glucose level remains normal.

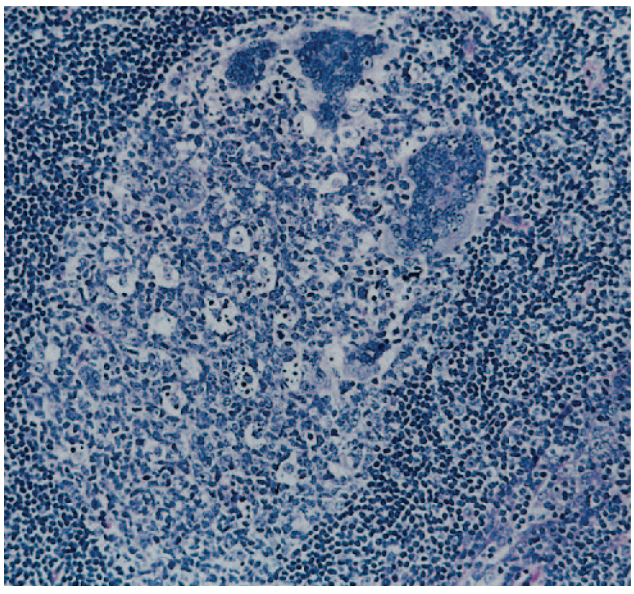


Figure 17.18 Warthin-Finkelday giant cells of measles in the tonsils.

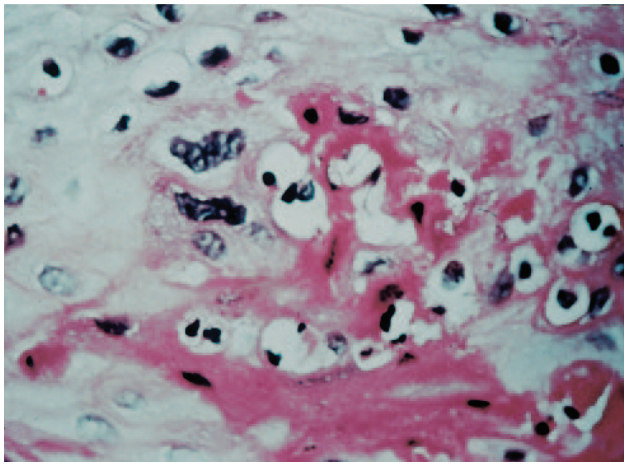


Figure 17.20 Multinucleated giant cells of measles in Koplik's spots.

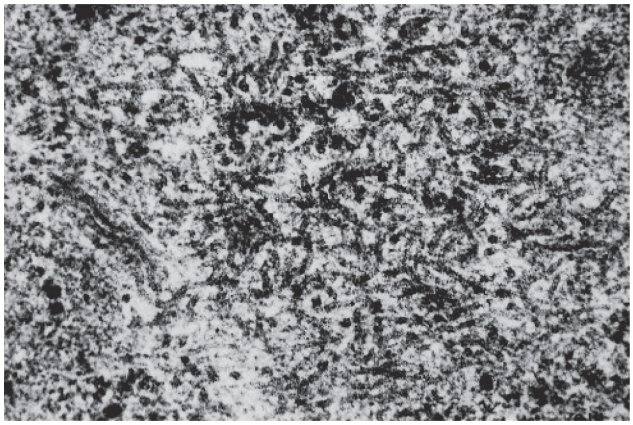


Figure 17.21 Electron microscopy showing aggregates of microtubules characteristic of paramyxovirus (e.g., measles) within the cytoplasm and nuclei of giant cells.

Table 17.2 Differential Diagnosis of Measles

Mycoplasma pneumoniae: The fever, cough, and other manifestations associated with this infection may mimic measles. An exanthem commonly occurs, typically as an erythematous maculopapular rash, most prominent on the trunk and back. This rash may either be rubelliform and discrete or morbilliform and confluent.

Infectious mononucleosis: This infection typically consists of fever, lymphadenopathy, hepatosplenomegaly, sore throat, and fatigue. A morbilliform or papular rash is present in 5–15% of cases, particularly in young children. This exanthem is typically present on the arms or trunk. The ampicillin-associated rash begins on the trunk and spreads to the face and extremities

Rubella: The rash and severity of this disease are less striking than that of measles, and the course of disease is of shorter duration. The rubella rash fades as it spreads and is associated with prominent posterior cervical lymphadenopathy

Erythema infectiosum: The infection typically has a prominent "slapped cheek" appearance to the rash on the face

Meningococcemia: The rash with this infection may be similar to that of measles, but it is usually petechial and purpuric. Also, cough and conjunctivitis are usually absent

Rickettsial infections: With these infections cough may be present, but the rash typically spares the face

Scarlet fever: The rash of this infection is typically diffuse and finely papular, with a "goose flesh" or sandpaper-like texture on an erythematous base. Scarlet fever is also usually accompanied by a sore throat and pharyngeal exudate

Exanthem subitum (roseola infantum): The rash of this disease appears as the high fever disappears. This exanthem begins on the trunk, neck, or behind the ears, and only occasionally spreads to the extremities

Enteroviral infections: The rash and severity of these diseases are less striking than that of measles.

Drug eruptions: There is an absence of cough and other characteristic prodromal symptoms with a drug eruption. A patient history of recent drug ingestion may explain rash

Diagnosis

The diagnosis of classic measles was easily made on clinical grounds during the pre-vaccine era when it was extremely common. However, many clinicians today are unfamiliar with the illness, as the incidence has declined with widespread vaccination. Also, measles occurring in immunocompromised hosts (Fig. 17.22) and modified or atypical measles can be difficult to diagnose on clinical criteria alone (Table 17.2).

Criteria for the clinical diagnosis of measles as defined by the CDC [97] are: (1) a generalized rash lasting 3 or more days, (2) a temperature of 38.3°C (101°F) or greater, and (3) the presence of cough, coryza, or conjunctivitis. Cases are further classified as suspect, probable, or confirmed. A case is considered confirmed if it meets the clinical case definition and is epidemiologically linked to a confirmed case, or if it is laboratory confirmed. Measles is a notifiable disease in the USA and in all 53 EUR member states. Measles cases are epidemiologically differentiated, according to the CDC, as internationally imported or US-acquired case. The latter is defined as a case in which the patient had not been outside the USA during the 21 days before the rash onset or was known to have been exposed to measles within the USA. US-acquired cases can be sub-classified in import-linked case, imported-virus case, endemic case, and unknown source case [98,99].



Figure 17.22 Acute measles in an human immunodeficiency virus seropositive male. (Photograph courtesy of Walmar Roncalli P. de Oliveira, M.D., Sao Paulo, Brazil.)

Laboratory confirmation of measles can be done by serological testing, viral culture, or by RT-PCR:

(A) Detection of measles-specific immunoglobulin M (IgM) antibodies in serum is widely available and is the standard test for laboratory diagnosis of measles. It is commonly performed using enzyme-linked immunoassay (EIA or ELISA) and may be diagnostic if done at the appropriate time. The IgM ELISA test for measles is more sensitive between days 4 and 28 after the rash onset [17,100].

(B) Although no longer routinely used for diagnosis of acute measles, detection of a significant rise of measles-specific IgG during the acute and convalescent phases can be used to confirm infection. The first blood sample should be drawn as soon as possible after onset of rash, and the second 10–30 days later. The specific criteria to determine an increase in titer depend on the test [17,100].

(C) MV can be isolated in cell culture from urine, nasal aspirates, throat or nasopharyngeal swabs, or whole blood collected in EDTA tube. Ideally, samples should be collected simultaneously with the blood samples for serological diagnosis, as soon as possible after onset of rash. It is not recommended for routine laboratory diagnosis [17,100].

(D) MV can be detected through RT-PCR in the same samples of virus isolation. As it can detect inactivated virus particles,

the period of time that virus can be detected after rash onset is often several days to weeks longer than for virus isolation. Its importance relies on epidemiologic studies for genetic characterization of wild MV [100].

Prevention

Since 1976, the live, further attenuated vaccine that has been used exclusively in the USA is the Moraten strain. It is available in a monovalent formulation or in combination with rubella (measles and rubella [MR]), with mumps and rubella (measles-mumps-rubella [MMR]), or combined with mumps, rubella, and varicella vaccine as MMRV (ProQuad) [17]. Improper storage or handling may inactivate the vaccine virus and cause primary vaccine failure. The lyophilized vaccine must be reconstituted properly and used within 8 hours or discarded [41,101]. It contains a small amount of human albumin, neomycin, sorbitol, and gelatin [17].

The measles vaccine produces a sub-clinical or mild, non-communicable infection. A measles antibody response develops in at least 95% of susceptible children vaccinated at 12 months of age and 98% of children vaccinated at 15 months of age. The incidence of primary vaccine failure is approximately 2–5% of children who receive only one dose of MMR vaccine. Studies demonstrate that more than 99% of persons who receive two doses of measles vaccine (with the first dose administered after 1 year of age) develop serologic evidence of measles [17]. Immunity appears lifelong in most individuals with occasional secondary vaccine failure [45–48].

Persons are considered immune to measles if they: (1) were born before 1957; (2) have documentation of physician-diagnosed measles; (3) have laboratory evidence of measles immunity; or (4) have documentation of adequate vaccination. All other persons, except for those with a medical contraindication or religious or philosophical exemption, should be vaccinated. The CDC currently recommends a two-dose vaccination regimen for measles, as combination MMR, with the first dose given between 12 and 15 months [17]. The second dose should be given no earlier than 1 month later, but is typically given at 4–6 years of age. It is a second opportunity to produce measles immunity for those who failed to respond to the first dose (primary vaccine failure). Children vaccinated before 12 months of age with measles-containing vaccine should be considered unvaccinated and should be vaccinated as outlined above.

The measles vaccine now in use has an excellent safety record. Fever (temperature 39–40°C or greater) begins 5–12 days after vaccination and lasts several days in 5–15% of vaccinees. These patients are otherwise well. Transient rashes occur in 5% of vaccine recipients. Arthralgias and transient lymphadenopathy are also reported. Allergic reactions, parotiditis, and deafness are rare [17]. It has been suggested that side effects are more common and severe in adults [17,102]. Serious neurological disease, including encephalitis, transverse myelitis, encephalopathy, aseptic meningitis, Reye's syndrome, cranial nerve palsy, cerebellar ataxia, and Guillain-Barré syndrome, occurs in fewer than one per one million cases [103]. The incidence of encephalitis is lower than encephalitis of unknown etiology, which suggests that the vaccine is not the cause. Thrombocytopenic purpura [104] and toxic epidermal necrolysis [105] in vaccine recipients has been reported.

Medical contraindications and precautions to the measles vaccine according to the CDC [17] are:

(A) Pregnancy, which should also be avoided for 4 weeks following MMR vaccine. Close contact with a pregnant woman is not a contraindication to MMR vaccination of the contact.

(B) Severe allergic reaction to a vaccine component or following a prior dose. History of hypersensitivity to egg ingestion does not contraindicate the vaccine, as the subsequent risk for serious allergic reactions by egg-allergic persons is extremely low.

(C) Immunosuppression or immunodeficiency. Severely immunocompromised patients should not be given live measles vaccine because of the possibility of severe infection with the vaccine virus. Based on the fact that measles may be a severe, sometimes fatal disease in HIV-infected patients, and that the incidence of complications from the vaccine is low in HIV-infected patients without evidence of severe immunosuppression, MMR is recommended for asymptomatic HIV-infected persons and should be considered for symptomatic persons who are not severely immunosupressed [17,106,107].

(D) Moderate or severe acute illness. Until the illness has improved, the vaccine should not be administered.

(E) It is recommended that vaccination be delayed in patients who have recently received antibody-containing blood products. This is recommended because Ig, and products such as whole blood or blood plasma, may contain sufficient measles antibody to neutralize the vaccine virus.

In susceptible persons exposed to measles, the administration of live measles vaccine within 72 hours may prevent the disease. For patients in whom contraindications exist for vaccination, prophylaxis with Ig given within 6 days of exposure can prevent or modify the disease. Persons who may need passive immunization include susceptible household contacts (particularly infants less than 1 year of age), infants born of mothers with measles, and immunocompromised patients for whom the risk of complications is greatest. The recommended dose of Ig for the normal host is 0.25 ml/kg (max 15 ml) intramuscularly. Immunocompromised patients should receive 0.5 ml/kg (max 15 ml).

Treatment

Treatment of measles is supportive, as there is no specific antiviral agent yet available (Table 17.3). Antibiotic therapy should not be given unless the patient has bacterial superinfection. Prophylactic antibiotics during acute measles fail to prevent bacterial complications and may even predispose the person to infection with a resistant organism [108]. Ribavirin has been used to treat measles both aerosolized or by intravenous administration, associated or not with hyperimmunoglobulin. However, the therapeutic use of ribavirin has demonstrated variable efficacy and is limited by its toxicicity, which consists mainly of anemia and teratogenicity [109–111]. In developing countries where malnutrition is common, vitamin A significantly reduces the mortality and morbidity of severe measles infections [112–115]. The WHO recommends that all children in developing countries with measles infection should receive two doses of vitamin A given 24 hours apart, with the dose based on the child's age [22].

Table 17.3 Treatment of Measles

Symptom	Treatment
Fever	Antipyretics (acetaminophen or non-steroidal anti-inflammatory drugs) Maintain fluid balance, with ingestion of adequate liquids Bed rest and limited activity (Measles infection damages the ciliated respiratory epithelium, which can predispose for bacterial pneumonia in persons who resume activity too soon and are exposed to other persons.)
Cough	Antitussive medicines (narcotic cough suppressants should be avoided)
Conjuctivitis	Humidification of the room Daily rinsing of the eyes with sterile saline solution
Otitis media	Antibiotic therapy
Pneumonia	Antibiotics should be given, since bacterial and primary viral pneumonias are difficult to differentiate. Aerosolized ribavirin can be considered for the treatment of known primary viral pneumonia
Laryngotracheitis	Humidification of air
Encephalitis	Supportive care of symptoms, such as maintenance of fluids and electrolytes, and anticonvulsants for seizures
Malnutrition	Vitamin A supplementation

Conclusion

Measles is an acute systemic viral illness that is self-limited in most cases; however, serious complications involving the respiratory and central nervous systems may occur. Measles remains a major public health concern around the world despite intensive efforts to eradicate the disease. The rapid diagnosis of measles and prompt containment of outbreaks is hampered by the fact that many health care providers today have never seen a patient with measles. Physicians must maintain a high index of suspicion when seeing a febrile patient with an exanthem and cough. Importation of measles from other countries where measles remains an endemic disease will continue. In addition, the typical features of this illness may be obscured in the setting of immunocompromised patients and in those with atypical or modified measles. Health care practitioners must remain vigilant in the coming years if measles is to be eradicated.

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18-I Filoviruses: Pathology and Effects on the Innate Immune Response

Ramin Mollaaghababa Hakami and Derron A Alves

Introduction

Ebola (EBOV) virus and Marburg virus (MARV) are the only known viruses belonging to the Filoviridae family and are among the deadliest of human pathogens, causing an acute multisystemic debilitating disease characterized by bleeding diathesis and rapid fatality. After cell entry, filoviruses paralyze the innate immune cells and prevent them from properly co-stimulating and activating filovirus-specific T-cells. Incomplete humoral and T-cell immunity responses and eventual immune subversion allow the virus to survive and propagate, leading to a rapid demise of the infected host. In this chapter, we highlight gross and histopathologic findings associated with filovirus infection of cutaneous and mucosal tissues, and provide a broad overview of the pathogenic aspects of filovirus infections in relation to innate immunity.

Filovirus Structure

To date, four species of EBOV have been reported, each named after the geographical locations in which outbreaks have been documented: EBOV-Cote d'Ivoire (1994), EBOV-Reston (1989), EBOV-Sudan (1976), and EBOV-Zaire (formerly, Democratic Republic of Congo, 1976). Also, laboratory analysis conducted by the Centers for Disease Control and Prevention (CDC) has indicated that the 2007 EBOV outbreak in Bundibugyo District, Uganda, was different from those previously documented and represents a new and fifth species, named *Bundibugyo ebolavirus* [1]. Unlike EBOV, however, only one species of MARV has been found to date, designated as Lake Victoria, although different strains with varying degrees of potency do exist.

Filoviruses are encoded by non-segmented, negative-sense, single stranded (ss) RNA that is approximately 19 Kb long [2,3]. Both MARV and EBOV encode for seven structural proteins, with EBOV also encoding for one additional non-structural product, as described below. The transcribed open reading frames of filoviruses are arranged linearly along the single-stranded RNA: 3'-NP-VP35-VP40-GP-VP30-VP24-L-5'. Proteins encoded by these reading frames consist of the major nucleocapsid protein (NP); the virion structural proteins (VP) VP35, VP40, VP30, and VP24; the glycoprotein (GP); and the L protein, which based on sequence homology studies is presumed to function as a RNA-dependent RNA polymerase. The NP is a putative P-like protein. VP30 and VP35 become part of the ribonucleoprotein complex that contains the NP, the L protein, and the genomic RNA. The VP40 protein forms oligomers that associate with microtubules, and along with the other matrix protein VP24 and the GP gets incorporated into a host-derived membrane bilayer that encloses the viral nucleocapsid. A "variable" region exists in the middle of the GP gene that appears to be subtype-specific [4]. It is of note that this "variable" region of GP is highly immunogenic, based in part on characterization of monoclonal antibodies against MARV GP [5,6]. In contrast with MARV, the GP open reading frame of EBOV produces two gene products, an N-terminal soluble fragment of GP (sGP, 60-70-kDa) and a full-length GP (150-170 kDa) that carries a transmembrane region [7,8].

Mucosal and Subcutaneous Manifestations of Filoviruses

Early cellular targets of filovirus infection include the fibroblastic reticular cells (FRC), the dendritic cells (DCs), monocytes, and macrophages of the immune system [9–11], although filoviruses show broad host-cell recognition and are found in multiple non-lymphocytic cells during later stages of infection. Interestingly, while filoviruses have the capacity to invade innate immune cells, the lymphocytes of the adaptive immune system are completely refractory to invasion by filoviruses [12–14]. Filoviruses cause widespread necrosis and destruction of tissues in humans, particularly in internal organs such as the liver, spleen, lymph nodes, and kidney [15]. Gross pathologic findings observed at autopsy include widespread petechial and ecchymotic hemorrhages, not only in these vital internal organs but also in the skin and mucous membranes. For instance, based on IHC analysis of post-mortem human samples (i.e., late infection stage), Zaki et al. reported the presence of EBOV antigen in the dermis and also within the endothelial cells and fibroblasts of the subcutaneous tissue, with various degrees of swelling, necrosis, and drop-out of the endothelial cells [16]. At relatively late stages of EBOV infection in NHPs (5 days post infection), electron microscopy (EM) studies of the liver showed characteristic intracytoplasmic EBOV inclusions in rare endothelial cells lining hepatic sinosoids [17]. Also, late infection (6–7 days post infection) EM studies of the mesenteric lymph nodes of EBOV-infected NHPs showed the presence of EBOV inclusions in the endothelial cells of high endothelial venules and in FRCs [9]. Because human outbreaks are sporadic and cause high fatalities, filovirus animal model development has become paramount in the study of the pathogenesis of these deadly viruses. Non-human primates (NHPs) such as cynomolgus macaques (*Macaca fascicularis*), rhesus macaques (*Macaca mulatta*), African green monkeys (*Chlorocebus aethiops*), and hamadryad baboons (*Papio hamadryas*), experimentally infected with either MARV or EBOV can develop clinical symptoms and lesions that are reasonably similar to those seen in humans. In addition, mouse and guinea pig animal models that show a significant degree of similarity to NHP phenotypes have been developed [18–20]. The use of hamsters has also been reported although it is the least developed and characterized of the animal models [21]. It is important to note that animal models do have their limitations with regard to recapitulating all aspects of the human disease phenotypes and therefore need to be regarded with some level of caution. For instance, guinea pigs and rodents fail to develop the characteristic cutaneous maculopapular rash often seen in human and NHP filoviral infections [19]. Nevertheless, many aspects of the disease, including defined cellular hallmarks, are reasonably well represented and the gross histological and IHC findings have been well described in filovirus animal models, especially for

EBOV infection. Here we provide a brief synopsis of the gross, histologic, and IHC changes associated with filovirus infection of skin and mucosal surfaces, with an emphasis on MARV-infected NHPs.

Similar to humans, the maculopapular rash observed in EBOV- or MARV-infected NHPs typically occur on the face (around the eyes, nose, and mouth), across the chest, and bilaterally in the axillary and inguinal regions and extending down the arms and legs (Figs. 18-I.1A and 1B). At least during acute infection, except for dermal congestion and fibrinocellular thrombi, significant vascular lesions are not consistently observed in either the skin or other organs of EBOV-infected NHPs [11,17,22]. This observation is consistent with the original histological observations in fatal human cases [23]. Furthermore, ultrastructural examinations of hemorrhagic skin areas in EBOV-infected baboons revealed that endothelial cells in hemorrhagic areas do not disintegrate to a greater extent than in other skin regions [24]. These findings are supported by both in vivo and in vitro studies indicating that direct virus-induced cytolysis of endothelial cells occurs after the onset of hemorrhagic abnormalities that characterize EBOV hemorrhagic fever [17], suggesting that congestion of capillaries and veins with subsequent diapedesis of erythrocytes is the likely cause of hemorrhages seen in skin and other organs.

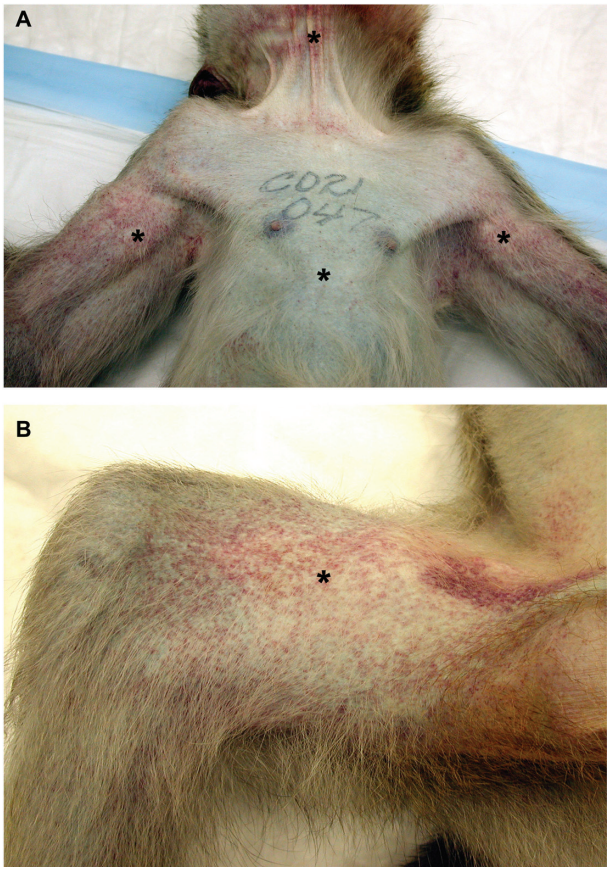


Figure 18-I.1 The cutaneous manifestation of MARV infection in a cynomolgus macaque at days 7 and 8 after experimental infection with aerosolized MARV-Ci67. A, B: A maculopapular cutaneous rash (asterisks) that progressively worsens is consistently observed in infected humans and nonhuman primates, particularly on the face, under the chin, across the chest, and bilaterally in the axillary and inguinal regions. It should be noted that the occurrence of a maculopapular cutaneous rash is not unique to filovirus infections.

Although not consistently seen, Baskerville et al. observed that outer epidermal layers in the skin of EBOV-infected rhesus macaques were separated from the basal layers [25]. We similarly observed this in MARV-infected cynomolgus macaques (Figs. 18-I.2A–C). Another histological finding in the epidermis of MARV-infected NHPs was the presence of scattered shrunken epidermal cells with hypereosinophilic cytoplasm and pyknotic nuclei, interpreted as single cell epidermal necrosis (Figs. 18-I.2B and 2C). Furthermore, IHC analysis indicates that EBOV antigen is occasionally localized to acinar and ductular epithelium of apocrine glands, the bulbs of hair follicles, the nasal and oral epithelium, and the epidermis [9,22]. Viral antigen is similarly distributed in MARV-infected NHPs, particularly on the face (Figs. 18-I.2D–2F). Within the dermis and/or underlying subepithelial connective tissue, free viral antigen and variable numbers of infected immunoreactive macrophages, DCs, FRCs, and/or endothelial cells may be detected in filovirus-infected NHPs. These findings are consistent with results obtained from the IHC analysis of formalin-fixed postmortem skin biopsies obtained from EBOV-infected humans [16]. Despite the presence of either EBOV or MARV antigen in the epidermis, adnexa, the subjacent dermis, and subepithelial connective tissue, the subtle epidermal histological changes described here are not consistently observed.

NHPs infected by aerosol exposure to EBOV show the presence of respiratory tract lesions [26]. Consistent with this finding, we observe the presence of MARV antigen in the respiratory tract of NHPs infected by aerosolized MARV (Fig. 18-I.3). In humans, limited information on filovirus-induced pulmonary pathology exists. Nevertheless, it has been shown that the lungs are usually hemorrhagic and show features of diffuse alveolar damage [15]. Similarly, infected NHPs can also develop pulmonary hemorrhage and alveolar damage as well as show significant epithelial involvement of larger airways of the respiratory system. These pulmonary lesions vary considerably in severity between individual animals and depending on the stage of infection. Nevertheless, documented respiratory epithelial lesions in NHPs include desquamation, necrosis, or loss of few to low numbers of laryngeal, tracheal, bronchial, and/or bronchiolar epithelial cells, as well as damage and dystrophic changes to alveolar epithelial cells and type II pneumocytes [9,22,24,25]. Immunostaining in the respiratory tract of EBOV-infected NHPs, especially during the terminal stage of disease, identified EBOV-positive mucosal epithelial cells of the trachea and larynx, bronchial and bronchiolar epithelial cells, and type II pneumocytes. We observed similar histological and IHC findings in MARV-infected NHPs (Fig. 18-I.3).

We and others noted that erosion and necrosis of the intestinal epithelium with variable hemorrhage and necrosis within the adjacent lamina propria is occasionally observed in both EBOV- and MARV-infected NHPs, especially at the gastroduodenal junction, the proximal duodenum, and in the ileum near the ileocecocolic junction [22,24,25] (Figs. 18-I.4A and 4B). Random luminal surface enterocytes as well as epithelial cells of the gastric glands, duodenal Brunner's glands, and crypts of the ileum are multifocally positive for filoviral antigen (Fig. 18-I.4C). Furthermore, filoviral antigen is often observed in the lamina propria and submucosa, and localizes to macrophages, fibroblast-like cells, and endothelial cells [9,11,22] (Fig. 18-I.4C). These findings are supported by the presence of EBOV viral inclusions detected

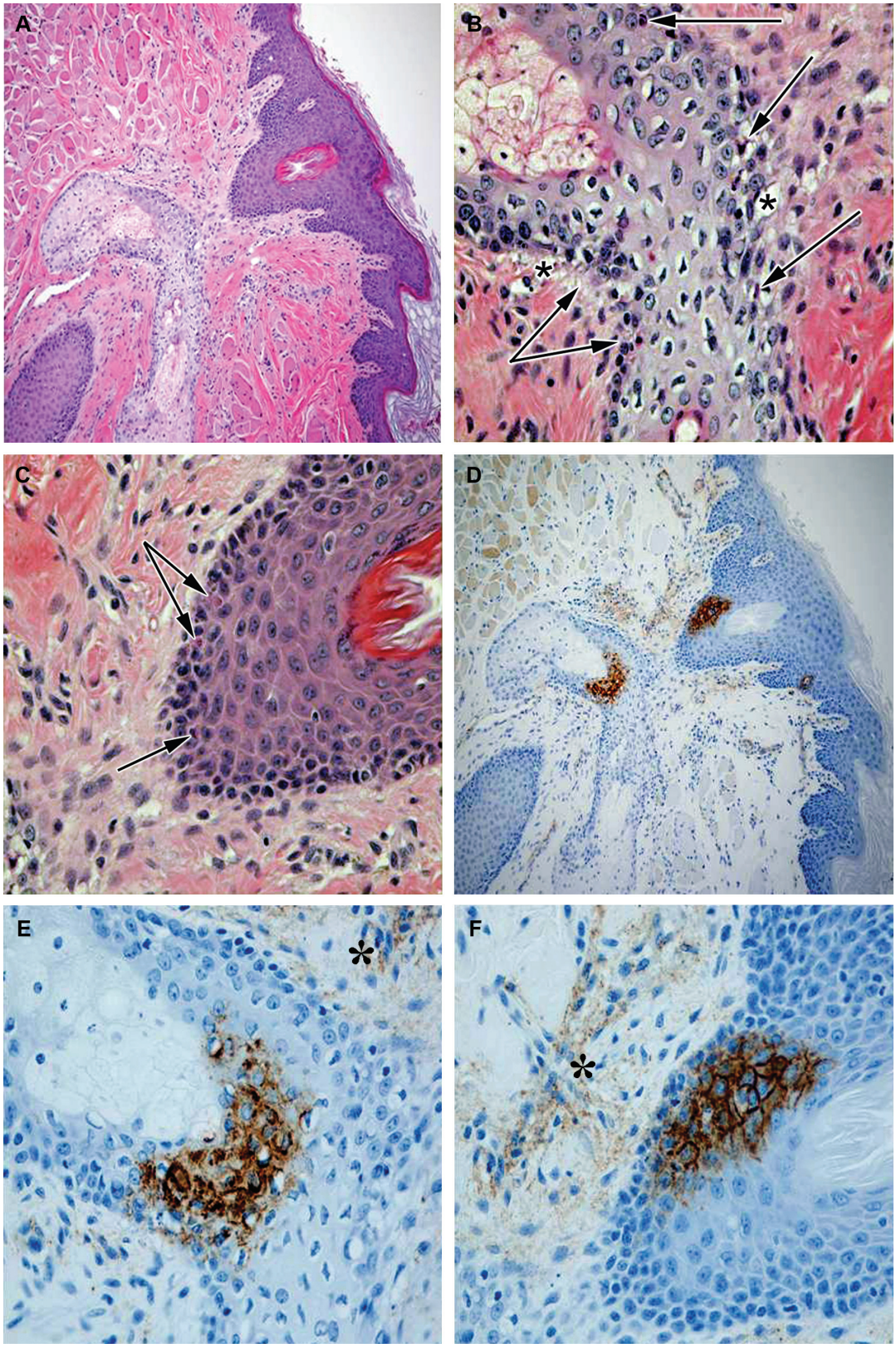


Figure 18-I.2 Histological and immunohistochemical findings in the haired skin (nares) of a cynomolgus macaque 7 days after experimental infection with MARV-Ci67 (1000 pfu im). A: No significant histologic epidermal lesions are observed at this magnification. B, C: Occasionally, epidermal cells of the stratum basal and stratum spinosum are necrotic (arrows) and separated by increased amounts of clear space (asterisk). These changes are not consistently observed in filovirus-infected NHPs. D-F: Individual and nests of virus-positive epidermal cells are present, adjacent to a sebaceous gland (E) and in the external root sheaths of hair follicles (F). The presence of free viral antigen (non-cell associated MARV staining) is observed in the superficial dermis (E and F, asterisk). MARV antigen appears brown. Magnifications are 10X for panels A and D and 40X for panels B, C, E, and F.

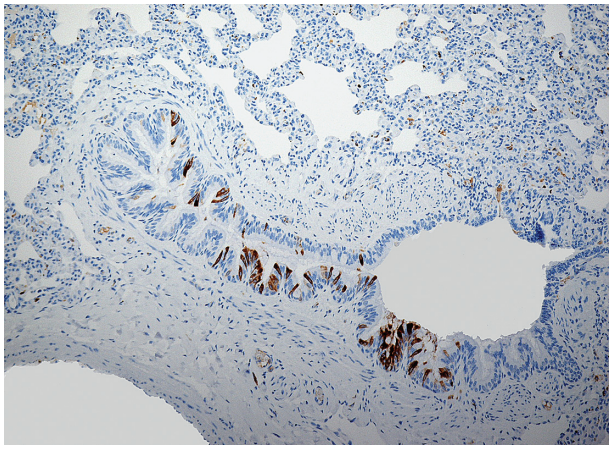


Figure 18-I.3 Immunohistochemical findings in the lung of an African green monkey 10 days after experimental infection with MARV. Multifocally, bronchiolar epithelial cells are strongly immunoreactive. MARV antigen appears brown. Magnification is 10X.

by ultrastructural examination [9,22]. Although gastrointestinal epithelial cells are occasionally immunoreactive, the changes observed histologically may be attributed to hemostatic impairment, as described previously, rather than a direct cytopathic effect on the epithelial cells. Additionally, nests of squamous epithelial cells in the tongue, tonsil, and esophagus and salivary gland ductular epithelial cells are also sporadically immunoreactive in both EBOV- and MARV-infected NHPs (Figs. 18-I.4D and 4E).

Petechial hemorrhages are occasionally observed on the urinary bladder mucosa of filovirus-infected NHPs during post-mortem gross examination. Histologically, however, with the exception of vascular thrombosis and rare hemorrhages, no marked changes are observed in EBOV-infected NHPs [11,22,24,25]. Similarly, besides scattered individual necrotic mucosal epithelial cells, significant histologic lesions are not routinely observed in the urinary bladders of MARV-infected cynomolgus macaques (Figs. 18-I.5A and 5C). Both EBOV and MARV immunoreactivity can occasionally be observed in the urothelium of infected NHPs as well as in macrophages, fibroblast-like cells, and endothelial cells in the lamina propria (Fig. 18-I.5B). Additionally, Jaxx et al. reported EBOV immunoreactivity in the oviduct epithelium of EBOV-infected rhesus macaques [22].

Filoviral Subversion of the Innate Immune Response

Both innate and adaptive immune responses are critical in the ability to provide protection against filoviruses. The innate immune responses provide the primary defense mechanisms after infection, while the T-cell-dependent adaptive immunity responses play a significant role at later stages. As we described in this chapter, the filoviruses have the capacity to invade a variety of cell types and adversely affect their function/survival, including cells of the innate immune system such as macrophages, DCs, and neutrophils. What are the molecular mechanisms by which filoviruses evade and subvert the innate immune response? The ability of the virus to replicate and also the recovery of the host and filoviral death are determined by the occurrence of an early immunological cascade [27]. This cascade consists of a balanced inflammation response that must be properly phased and regulated to achieve pathogen elimination without causing damage to the self due to the various immune responses [28]. Specific checkpoints and critical positive and negative feedbacks exquisitely regulate the inflammatory process to allow escalation or suppression of the inflammatory response. Recent reports suggest that dysregulated inflammatory responses play a crucial role in how filoviruses may perturb the immunity of the infected host. For instance, blood samples from individuals infected with EBOV [29–34] had elevated levels of inflammatory cytokines (tumor necrosis factor (TNF)-α, interferon (IFN)-α, IFNγ) and interleukin (IL)-10 [35,36]. Filoviral infection of monocytes, macrophages, or neutrophils can cause the release of inflammatory cytokines such as TNFα from these cells [37–39]. On the other hand, it has been shown that filoviral infection significantly inhibits the costimulatory machinery of DCs [40]. There is similarity in the pattern of inflammatory response between humans and NHPs infected with filoviruses.

Several specific C-type lectins have been shown to facilitate filoviral cell entry, apparently via their interaction with N-linked carbohydrates of GP on the filoviral surface. These include DC-specific intercellular adhesion molecule 3 (ICAM3)-grabbing non-integrin (DC-SIGN; also known as CD209), the liver/ lymph node-SIGN (L-SIGN; also known as CLEC4M), the human macrophage C-type lectin specific for galactose/*N*-acetylgalactosamine, and the hepatocyte-specific asialoglycoprotein receptor [14]. Triggering receptor on myeloid cells (TREMs), which are a class of immunorecognition receptors that were recently identified [41], have also been implicated in filovirus-induced immune response. TREM-1 is rapidly induced in neutrophils after filovirus infection [27] and it has also been shown that a specific peptide that inhibits TREM-1 interaction with its ligand significantly reduces filovirus-induced TNFα levels [27]. The TREM receptors regulate various immunological pathways in neutrophils, monocytes, and DCs and, interestingly, TREM-1 appears to play a significant role in TLR-mediated production of proinflammatory cytokines during septic shock [42]. Accordingly, it would be of interest to learn if, during filoviral infections, the induction of TREM-1 coincides with an increase in the levels of proinflammatory cytokines such as TNFα, IL-1β, or IL-8. Recent data suggest that the receptor-type tyrosine kinase Axl may also play a role in cell entry of EBOV [43,44].

Interferons also play a major role in the activation of immune cells and viral clearance, and are another class of host molecules that are targeted by filoviruses. It has been shown that the filoviral proteins VP35 and VP24 inhibit the synthesis of IFNs in infected cells [45,46], thus stripping them of the antiviral effects of IFNs. The VP35 protein suppresses IFNα/β by inhibiting IFN regulatory factor 3 [45], and VP24 inhibits IFNα/β and IFNγ signaling by interrupting the nuclear accumulation of tyrosine-phosphorylated STAT1 [46]. This IFN inhibition indirectly affects the natural killer (NK) cells, which mount an effective early defense against filovirus infection in mice [47]. Transcriptional profiling and bioinformatics analysis suggest that in addition to antagonistic effects on IFN pathway VP35, VP24, and other subunits may perturb multiple other immune-related genes in filovirus-infected cells such as human liver cells [48]. These results together suggest that a subversion of multiple immune-related pathways by filoviruses may cause severe mis-regulation of the

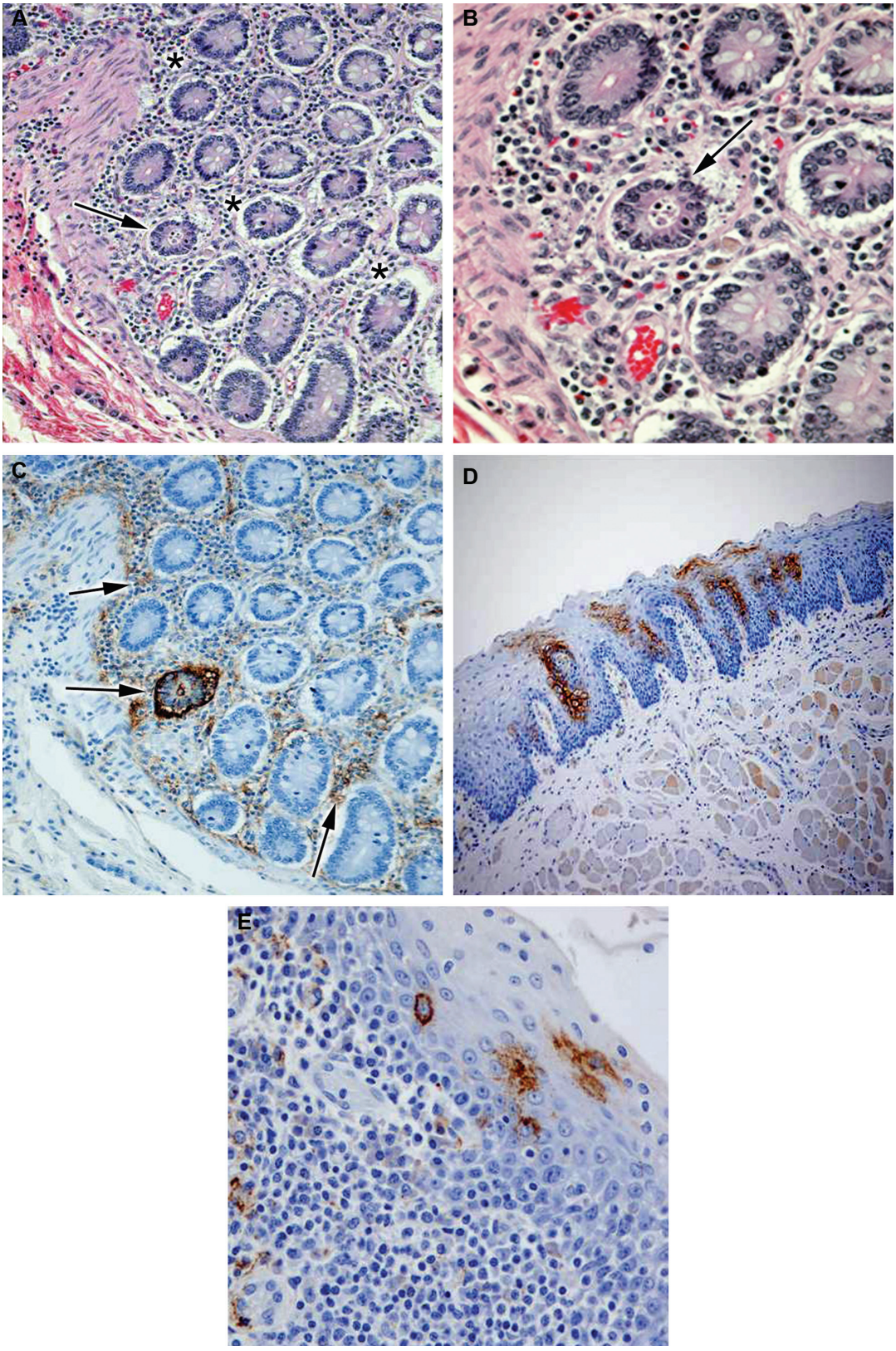


Figure 18-I.4 Histological and immunohistochemical findings in the colon (A-C) of a cynomolgus macaque and also tongue (D) and tonsil (E) of a second cynomolgus macaque, 7 days after experimental infection with MARV-Ci67 (1000 pfu im). A, B: Focally, there is necrosis of crypt epithelial cells with apoptotic-like debris (arrows) and a mild increase in the number of mononuclear cells within the lamina propria (*). C: Strong viral immunoreactivity is observed in crypt epithelium. Viral immunoreactivity is also observed within the adjacent lamina propria, indicating the presence of either free viral antigen or antigen localized to macrophages and fibroblast-like cells (arrows). D, E: The squamous mucosal epithelial cells of the tongue and tonsil are also multifocally immunopositive. MARV antigen appears brown. Magnifications are 20X for panels A, C, and D and 40X for panels B and E.

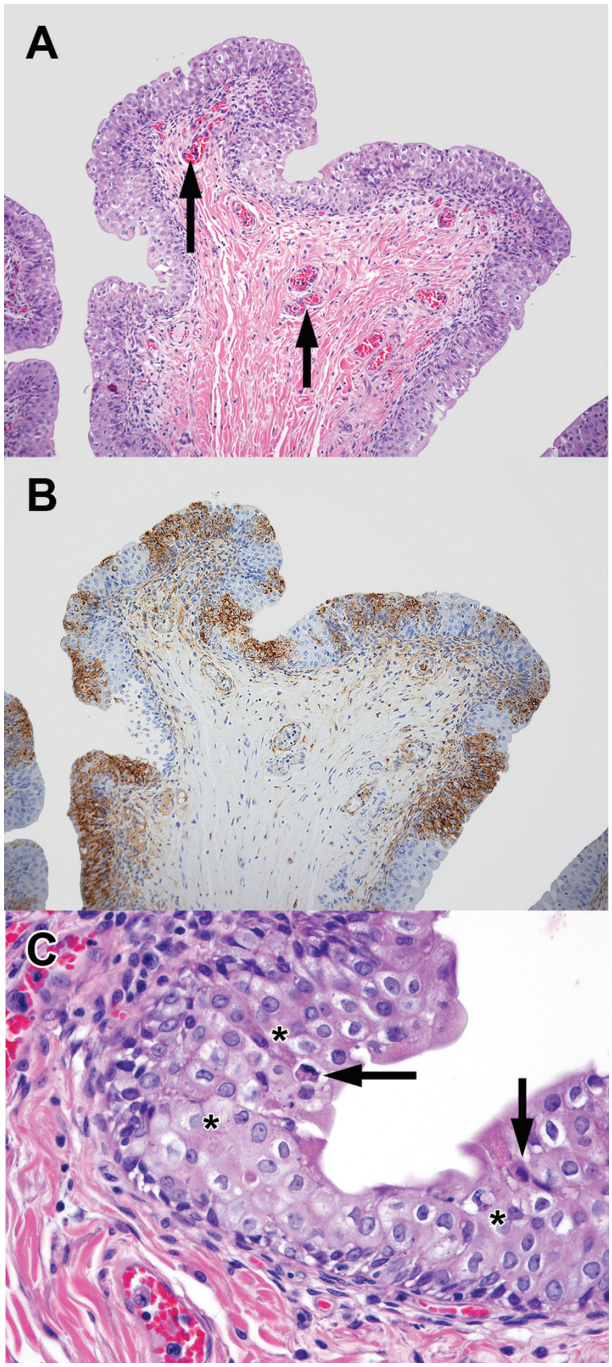


Figure 18-I.5 Histological and immunohistochemical findings in the urinary bladder of a cynomolgus macaque 7 days after experimental infection with MARV-Ci67 (1000 pfu im). A: No significant histologic epidermal lesions are observed at this magnification; however, congested vessels and mild hemorrhage in the lamina propria are present (arrows). B: Multifocally, nests of mucosal epithelial cells are strongly positive for the viral antigen. C. Similar to the epidermis, there is occasional necrosis (arrows) and cytoplasmic vacuolation of mucosal epithelial cells (asterisk). MARV antigen appears brown. Magnifications are 10X for panels A and B and 40X for panel C.

immune system, adversely affecting antiviral activity and the ability to coexist peacefully with less harmful pathogens such as *E. coli* that normally reside in the gut. Future studies should shed further light on the specific roles of innate immune component cells such as DCs, macrophages, neutrophils, and monocytes during such processes.

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18-II Filoviruses: Clinical Manifestations

Dieudonné Nkoghe, Eric Leroy, Médard Toung Mve, and Jean Paul Gonzalez

Introduction

The Filoviruses belong to the Filoviridae family, order of Mononegavirales, a large group of viruses whose genome consists of a strand of RNA of negative polarity [1]. The term "filovirus" refers to their elongated filamentous form shown by electron microscopy. The other three main families of this order, genetically closer to the filoviruses, include the Paramyxoviridae (i.e., measles virus), the Rhabdoviridae (i.e., rabies virus), and the Bornaviridae (*bornavirus*). The filoviruses are divided into two distinct genera: *Marburgvirus* (MARV) and *Ebolavirus* (EBOV). MARV includes one species (*Lake Victoria Marburgvirus*), while EBOV is subdivided into five species: *Zaire*, *Côte d'Ivoire*, *Sudan*, *Reston* [2], and *Bundibugyo* recently discovered in Uganda [3].

These viruses are among the most virulent and hazardous pathogens for humans and non-human primates. In terms of biological risk, filoviruses are classified as "Level 4 security" agents. Filoviral infections have been described in Africa, Europe, USA, Russia, and Asia (Fig. 18-II.1). They induce epidemics and fulminant hemorrhagic fever (HF), mostly from equatorial Africa, more rarely in Europe. Since 1967, 23 outbreaks of EBOV have been confirmed by virus isolation or by unequivocal diagnosis using molecular and biological methods, and nine manifestations of MARV have been notified [4]. EBOV presents a different pathogenicity, depending on the species. *Ebola zaire* species is more virulent than other species, with a case-fatality rate about 80–90%; *Ebola sudan* has a case-fatality rate of 50–55%; and the new *Ebolavirus bundibugyo* seems less virulent with a 36% case-fatality rate. *Ebolavirus cote d'ivoire* caused a single non-fatal HF case in a human, while *Reston ebolavirus* was only described in Asia and in a non-human primate. Finally, the pathogenicity of MARV (80–90%) seems close to that of *Ebolavirus zaire* [5,6], with regard to the outbreak in Uige province in northern Angola in 2004–2005.

With respect to the natural history of these viruses, the reservoirs of these viruses are not fully known; however, recent studies identified four fruit bat species, *Hypsignathus monstrosus*, *Epomops franqueti*, *Myonycteris torquata*, and *Roussetus aegyptiacus*, as more probable natural host/reservoirs of EBOV and MARV, circulating in Gabon. [7,8].

Associated with some physiological and environmental conditions, transmission to the great apes (gorillas, chimpanzees) occurs by direct contact with blood and/or placenta from the female bat during delivery [9]. The spread of outbreak into these species is due to direct contact between animals in the course of fights and breastfeeding, and through other species when licking carcasses. Human infections are accidental and occur in three ways: (1) by direct contact with biological fluid of large non-human primates (i.e., poaching practices), contamination when handling infected animal carcasses, as described for EBOV transmission during epidemics [10]; (2) by direct contact with the potential virus host/reservoir through various natural infected fluids [7, 11–13]; and (3) more rarely involving experimental laboratory worker accidents [14]. The most common human transmission occurs by close physical contact, extended through blood or body fluids (feces, vomit, urine, saliva, and semen) [15] during medical care (by family, healthcare workers, traditional healers, and burial practices) [16].

The clinical picture has been fully documented: after a variable incubation period, patients present with high fever accompanied by digestive and respiratory disorders, skin signs followed, in severe cases, by shock with multivisceral hemorrhages and death within a few days. The diagnosis of filovirus infection during outbreaks is provided by the detection of circulating antigen and viral genetic material by polymerase chain reaction (PCR), which leads to virus type identification [17,18]. There is no specific treatment or vaccine, so the treatment is supportive and patient management requires specific measures of isolation and a septic burial to avoid any risk of transmission by contact as described above [16,19].

Clinical Manifestations

It is virtually impossible to distinguish between the two clinical etiological infections of Ebola fever and Marburg disease. Moreover, there are no cardinal signs, and clinical diagnosis during an epidemic period is done by the combination of epidemiological characteristics and the occurrence of HF symptoms. However, clinical manifestations can also diverge according to the virus species (Table 18-II.1).

After an incubation period that can range from 3 to 7 days for MARV [4] and 4–6 days for EBOV, the clinical picture evolves in a series of symptoms that can be considered as three successive phases: a first phase characterized by non-specific symptoms; a second phase with multiple lesions in different organs; and a third terminal phase, which can evolve either toward recovery or a fatal issue depending on host and virus factors. Here, these theoretical phases are deliberately divided for a better clinical understanding. In fact, they often overlap.

Phase I

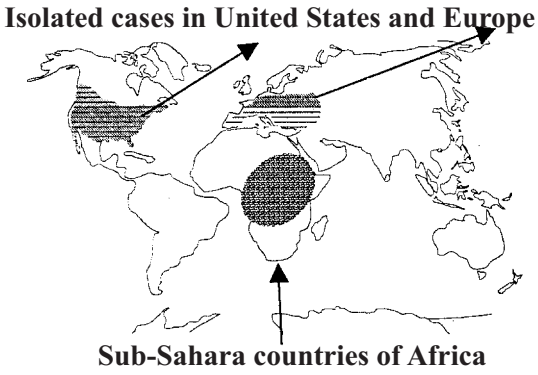
The disease typically begins with a flu-like syndrome followed by a sudden onset of fever of 39–40°C, with violent headache localized primarily in the occipital region and then spreading to parietal and frontal regions; a generalized fatigue is always associated with myalgia and arthralgia. Sometimes, myalgia with concomitant muscle tension spreads into the cervical area and is rarely due to true meningitis. Patients can also present with prostration, malaise, as well as sensitivity to pressure on the eyeballs, photophobia, and vertigo with MARV.

Phase II

The second phase is marked, on day 2–4 after onset, by the appearance of severe organ damage and lasts for 7–10 days. At

Geographical Incidence

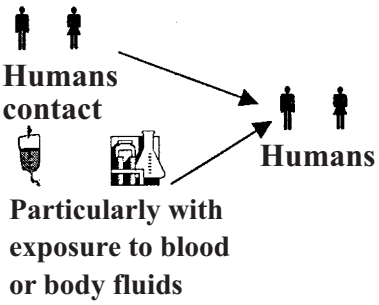
All natural outbreaks have occurred in southern countries of Africa, while laboratory cases have occurred in the United States and Europe from importation from Africa or the Philippines.



Taxonomy

Filoviridae family

Transmission



Zoonotic Implications



Monkeys } **Source of isolated laboratory infections although not naturally infected.**

Figure 18-II.1 Incidence and transmission of Marburg and Ebola hemorrhagic fevers

first, a digestive syndrome appears with severe abdominal pain and nausea followed by watery diarrhea and anorexia. Within a few days, these symptoms induce weight loss and marked dehydration. At this stage, the patient has "a ghost appearance" with deep-set eyes, an expressionless face, and extreme lethargy. Respiratory symptoms appear concurrently with a severe sore throat accompanied by chest pain and a dry cough, resulting from damage to the pharynx, and is strongly evocative of filovirus infection (patients have the feeling of a "ball" in the throat). Consequently, swallowing is hindered, and the subsequent lack of food intake exacerbates malnutrition. A non-pruritic rash appears between the 2nd and 7th day, followed by a fine scaling. The latter features will be the subject of a separate description (see below). Also frequently, but not constantly present, bleeding appears characterized by petechiae in variable sites, burning and injected conjunctivae, melena, hematemesis, hematuria, epistaxis, and hemoptysis, and bleeding at the site of injection. Moreover, pregnant women often present with uterine bleeding, generally resulting in an abortion. Ultimately, the nervous system can be affected with behavioral disorders (aggressiveness, confusion, delirium crises), sensitivity disorders (paresthesia, hyperesthesia), and often convulsions.

Phase III

The third phase will evolve to either death or recovery. A severe syndrome evolves with bleeding; also tachypnoea is observed with hiccups followed by anuria; death occurs in 2–3 days by shock with capillary extravasations and multiorgan failure. Meanwhile, beginning 2 weeks after onset, some patients will survive with a long, i.e., a period of 1 month or more, painful convalescence with intense fatigue, loss of appetite, profound prostration, weight loss, and migrant arthralgias. Some survivors developed partial amnesia and were unable to recall the most severe period of illness. Others developed bacterial infections or psychoses [4].
Sequelae are noted, such as orchitis, recurrent hepatitis, transverse myelitis, and uveitis [20,21]. Psychiatric sequelae have also been described and include confusion, anxiety, restless and aggressive behavior [4].

Mucocutaneous Manifestations

Although skin manifestations accompanying filovirus HF (FHF) syndrome are limited and are not life-threatening by themselves, their appearance supports the diagnosis. Skin damage has been reported in the early epidemics [22,23] and is useful in the clinical diagnosis in patients with light skin [5]. Skin damage usually appears in phase II after onset, i.e., 4–5 days following the first clinical symptoms [6,20,24]. Skin and/or mucous membrane signs are common and can be found in more than half of cases during an epidemic [21]. They are more often see and are more characteristic during MARV infections than EBOV infections.

More specifically, skin lesions appear as macular or maculopapular exanthema giving the appearance of a non-pruritic pseudomeasles rash [4,25,26] (Fig. 18-II.2). In most cases it is recognized by a flaky appearance in subjects with dark skin. Initial lesions, consisting of pin-point, dark red papules, are first observed around the hair roots, in the buttocks, the upper parts of the arms, legs, and face, and then extend to the trunk and the rest of the body. In some cases, exanthema extension is rather centripetal from the arms and legs to the trunk [27,28]. Around day 8, a dark, livid, diffuse cutaneous erythema develops over the entire body of most patients and is sometimes accompanied by cyanosis [4,21,29,30]. The severity of the erythema correlates with the severity of disease, but disappears within several days. Patients with rash show desquamation of the affected parts of the skin. The desquamation lasts from a few days to 2 weeks and is most severe on the palms of the hands, soles of feet, and extremities [4].

Table 18-II.1 Clinical Manifestations of Marburg and Ebola Hemorrhagic Diseases

Time After exposure	Clinical manifestations	Laboratory analyses	Other notes
6–9 days	Abrupt onset of fever, severe headache, profound malaise, and myalgia	Antigen detection in blood or serum by IFA	Prostration and obtundation occur with progression of disease. A mask-like or ghost-like facies is described in the most severe cases, along with wasting
8–11 days	Clinical deterioration, with severe nausea and vomiting, pharyngitis, diarrhea (+/− blood), and abdominal pain. Bleeding occurs during the first week of disease, with ecchymoses, petechiae, and bleeding from gastrointestinal tract, mucous membranes, vagina, and venipuncture sites	Serology, with IgM or fourfold rise in IgG Viral isolation from blood products Positive direct Coombs tests	Cutaneous hemorrhage is unusual The rash is a characteristic feature, and is useful for differential diagnosis Abortion commonly occurs in pregnant women as a result of infection
13–15 days	A nonpruritic, maculopapular rash appears on the trunk and spreads to the extremities, and desquamates after 7 days		
16–20 days	Intractable shock with pulmonary insufficiency, often progressing to adult respiratory distress syndrome. This stage often progresses to death		
Over 5 more weeks	Slow recovery in survivors, with prostration and weigh loss. Sequelae may include uveitis, orchitis, deafness, arthralgia, pancreatitis, myelitis, psychosis, or myositis		

Mucosal lesions are also common on the eyes, mouth, and pharynx, and 50% of patients have bilateral conjunctival congestion with some photophobia, which can be the start of a more severe hemorrhagic manifestation [31] (Figs. 18-II.3–18-II.5).

A cold sore- like lesion [4,22,31,32], gingivitis, and glossitis accompanied by fissuring [23,27,33] have been described. Sore throat and dysphagia are the result of pharyngitis. Such inflammation appears as a dryer enanthema with a grayish exudate [4,23,32], often accompanied by small, whitish, clear lesions resembling "tapioca granules," localized on the soft palate. Enanthema can also extend to the tonsils and palatal floor [22,27]. All these mucosal lesions can often be associated with bleeding of variable severity [21].

In addition to these manifestations, one can also observe, among survivors, hair loss during the late period of remission [4,20,27].

Diagnosis

If the FHF common denominator is fever, bleeding may be discreet and sometime missed. Such diagnostic uncertainty is predictable regarding the occurrence of an isolated case (sporadic) or the beginning of an epidemic [13], and also in cases imported from the tropics [34].

In endemic areas, the diagnosis is made from the case definition based on clinical and biological arguments. Five levels of case definition have been proposed: (1) a highly potential case; (2) a suspected case (to the attention of non-medical staff); (3) a probable case; (4) a confirmed case; and (5) a contact case (in the case of evaluation by a physician) [16]. However, malaria, typhoid, shigellosis or other enteric bacterial infections, viral hepatitis, leptospirosis, other HF (yellow fever, Lassa, Crimean-Congo, Dengue, Chikungunya), must be considered in the differential diagnosis (Table 18-II.2). The first Ebola epidemic in Nzara, Sudan, was initially considered to be an epidemic of bacillary dysentery [23], and the initial epidemic in Gabon in 1994 was confused at first with a yellow fever epidemic [35,36]. Outbreaks of typhoid fever and shigella occurred simultaneously with Ebola HF in western Kasai (Democratic Republic of Congo) in 2007 [37].

Thus, even characteristic skin lesions were insufficient for the diagnosis. Such difficulty occurred during the Ebola outbreak

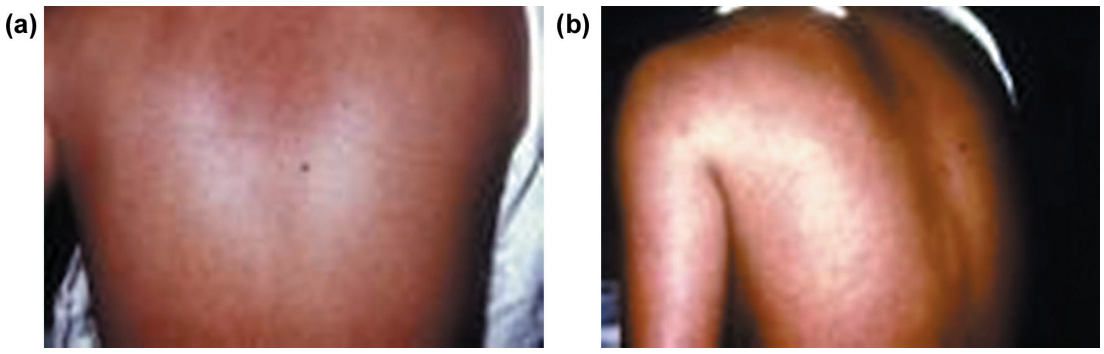
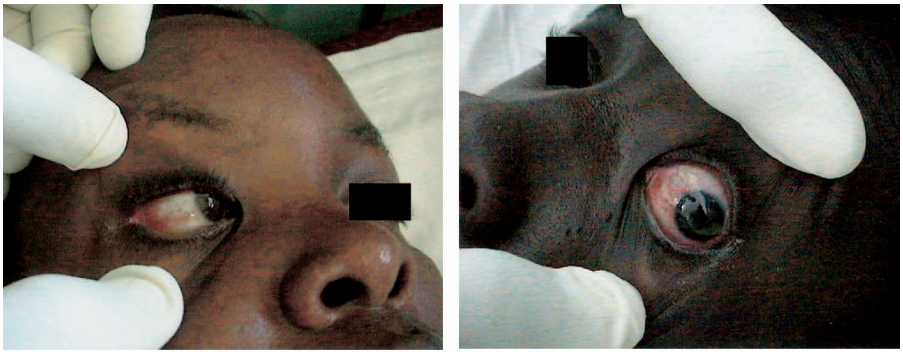


Figure 18-II.2 View of a female Marburg patient's back depicting a measles-like rash. She was hospitalized in Johannesburg, South Africa in 1975. The maculopapular rash usually appears on Marburg patients around the 5th day after the onset of symptoms, and may be found on the patient's chest, back, and stomach. This patient's skin blanched under pressure, which is a common characteristic of a Marburg virus rash. (From CDC's Public Health Image Library at http://phil.cdc.gov/phil/home.asp. Accessed February 5, 2009.)



(a) (b)

Figure 18-II.3 Conjunctivitis typically found in Ebola patients. (a) Early onset of Ebola conjunctivitis. (b) Latter manifestations of Ebola conjunctivitis. (Photographs courtesy of Dr. Ben Naafs.)

in Yambio (southern Sudan) in 2004, where a majority of cases involved children and was accompanied by a concurrent measles outbreak challenging case selection and typing, thus delaying immediate isolation and care [38]. Consequently, differences in the fundamentals of infection, epidemiological features of the epidemic, lethality, and the high number of hemorrhagic presentations were used for the differential diagnosis. During recent epidemics, the diagnosis of suspected cases was based on antigen detection and viral RNA detection by PCR. When clinical symptoms were clearly identified, biological diagnosis was done by IgG detection and PCR. Cutaneous presentation plays another important role in HF diagnosis: confirmation can be made from skin biopsies [39–41]; filoviruses can be detected from a sample of skin via immunohistochemistry by the Molecular Pathology Unit of the Center for Disease Control. Moreover, formalin preserved skin biopsy is not infectious and can be sent abroad without risk, to specialized laboratories for histological analysis, serology, and electron microscopy (Figs. 18-II.6 and 18-II.7). The histopathology examination shows some non-specific skin alterations mainly restricted to endothelial cells and fibroblasts in the dermis and epidermis. Lesions appear uniform, with varying degrees of swelling and necrosis. Furthermore, a large amount of viral antigens can be detected by enzyme-linked immunosorbent assay (ELISA) and viral inclusions identified by electron microscopy in the extracellular matrix and around the sweat glands [39]. These observations provide valuable arguments for the possibilities of virus transmission through skin. Immunohistochemical examination of skin is useful for post mortem diagnosis, both in human and animal.

Patient Management and Treatment

There is no specific treatment or vaccine available for FHF. In this chapter, we will not discuss global outbreak containment (with import and export controls and enhanced disease surveillance), which decrease the risk of filovirus introduction and spread to non-endemic countries by infected animals and humans. We will focus on patient management, especially in African countries. Outbreak response is organized at the local level. Many recommendations have been established, including case definition and surveillance, case management and isolation, social mobilization, education, communication and medical anthropology, and logistics such as finances. The important role played by medical anthropologists in understanding local people's perception, feelings, and responses to disease, and identifying specific features of clinical care and intervention efforts that are not culturally sensitive or appropriate, must be emphasized [42]. Thus, our interventions with local people can be more humanistic.



(a) (b)

Figure 18-II.4 View of Ebola-caused edema in leg. (a) Pressure being applied to leg. (b) View of edema pit after release of pressure. (Photographs courtesy of Dr. Ben Naafs.)

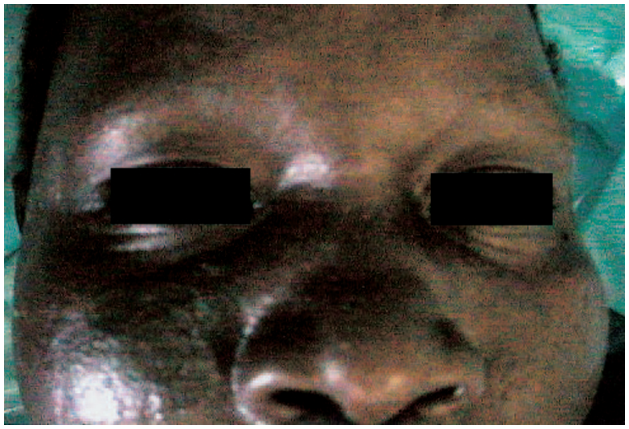


Figure 18-II.5 View of Ebola patient showing facial edema. (Photograph courtesy of Dr. Ben Naafs.)

Epidemic and patient management

During epidemics, management is carried out by international multidisciplinary teams and emphasis is placed on rapid aseptic isolation of suspected cases in order to avoid further transmission in the hospital setting between filovirus-infected patients, medical personnel, and other medical workers. When several patients are under care, they should be separated by insect proof screens. The convalescent patients are placed in different rooms, away from acute patients. Observing aseptic measures for patient isolation and the enforced use of effective means of protection for medical staff will avoid any further transmission in hospital settings. All hospital personnel should be informed of the nature of the disease and its transmission routes. Hospital staff should wear gowns, gloves, masks, and goggles. Major attention must focus on medical workers' basic activities, such as setting up a perfusion, handling blood or secretions, or any potentially infected biological product or device (e.g., catheter, suction device), which will be used strictly in accordance with isolation principles. The techniques for disinfection of the skin, equipment, bedding, and destruction of waste must be strictly enforced to prevent nosocomial transmission.

Non-specific treatment

The treatment remains essentially symptomatic (Table 18-II.3). Because of the risk of bleeding, oral medications are preferred over injections (IV or IM); also, in case of fever, use of antipyretics such as acetaminophen is the rule (bleeding risk prohibits the use of aspirin). The treatment seeks to combat dehydration induced by pyrexia, vomiting, and diarrhea, when possible (limited pharyngitis) oral hydration may be efficient, while serious cases must be placed in an intensive care unit.

The development of effective treatments against filoviruses is underway following two different approaches, including the direct inhibition of viral replication and the reduction of damage induced in the host. For the latter, considerable progress has been noted, in particular with the use of a promising anticoagulant (rNAPc2) tested in clinical trials of experimentally infected primates [43,44]. Survival and prolongation of disease course in treated animals was associated with attenuation of coagulation and proinflammatory responses.

Table 18-II.2 Differential Diagnoses for Marburg and Ebola Hemorrhagic Diseases

Yellow fever: The keys to diagnosis of yellow fever are exposure to mosquitoes and travel to tropics of Africa or the Americas toward the end of rainy season. Jaundice is profound with hemorrhagic manifestations

West Nile fever: Suggested by travel to rural Africa, southern Europe, central or south Africa, or northeastern United States, mosquito exposure, symptoms of headache, myalgia, lymphadenopathy, leukopenia, and a nonpruritic maculopapular rash

Rift Valley fever: This febrile influenza-like illness has infrequent occurrence of hemorrhagic disease, encephalitis, or retinitis. Jaundice is significant feature. Animal epizootics occur during periods of excessive rainfall. Patients have occupational animal exposure

Influenza: The coryza, cough, myalgia, and fever without rash, jaundice, frequent hemorrhage or encephalitis lead to the suspicion of influenza. Secondary bacterial complications—pneumonia and meningitis—compound the differential diagnosis and require specific antibiotic therapy

Malaria: Patients have periodic paroxysms of fever along with constitutional and gastrointestinal symptoms. Splenomegaly, pallor, and jaundice are common. Plasmodium falciparum in a nonimmune host may lead to cerebral malaria, blackwater fever, hepatic failure and respiratory failure

Typhoid fever: Insidious onset of fever, anorexia, abdominal pain, and constipation precede dramatic fever spikes. Rose spots may be evident. Liver function tests are abnormal. Low white cell and platelet counts are typical. Stool cultures document the etiology

Shigellosis: The acute onset of fever, toxic appearance, diarrhea (+/− blood), and abdominal pain are indicative of shigellosis. Shigellosis does not develop a skin eruption and has leukocytosis with leukocytes in the stool

Lassa fever and the South American hemorrhagic fevers: Suspect for travel to Nigeria, Argentina, Bolivia or Venezuela; rodent or nosocomial exposure; and in a patient with pharyngitis, retrosternal pain, and proteinuria. Fever, edema, conjunctivitis, and hemorrhage are also seen

Crimean-Congo hemorrhagic fever: Suggested by fever, prostration, hepatitis, hemorrhage, and tick or nosocomial exposure in Africa or eastern Europe, middle East, or Asia

Dengue: Suggested by worldwide travel in the tropics and mosquito exposure. Children predominantly affected with a capillary leak syndrome resulting in hemorrhage with shock

Kyanasur Forest disease: Suggested by tick or nosocomial exposure in India with resulting fever, myalgia, lymphadenopathy, hemorrhage, or encephalitis

Omsk hemorrhagic fever: Suggested by tick exposure in western Siberia in the spring, summer, or fall, or by muskrat hunting in the winter. The patient is usually male and may have hemorrhage and encephalopathy

Colorado tick fever: Suggested by exposure to ticks in western United States or Canada at altitudes above 4000 feet, in May to June, outdoor activities. Characterized by fever, rarely encephalitis or hemorrhage, with leukopenia and thrombocytopenia

Hantavirus hemorrhagic fever: Suggested by rodent exposure, travel to Asia or Korea, the Balkans, Scandanavia, Russia, and western Europe in the summer or fall. Characterized by a patient with fever, conjunctivitis, retro-orbital pain, hemorrhage, shock, proteinuria, and renal failure

Chikungunya fever: Suggested by severe arthralgia with hemorrhagic manifestations like dengue, yet milder. Most recognized disease is urban in the rainy season in sub-Sarahan Africa, India, southeast Asia, or the Philippines. A maculopapular rash, lymphadenopathy with conjunctival injection and periorbital edema are suggestive

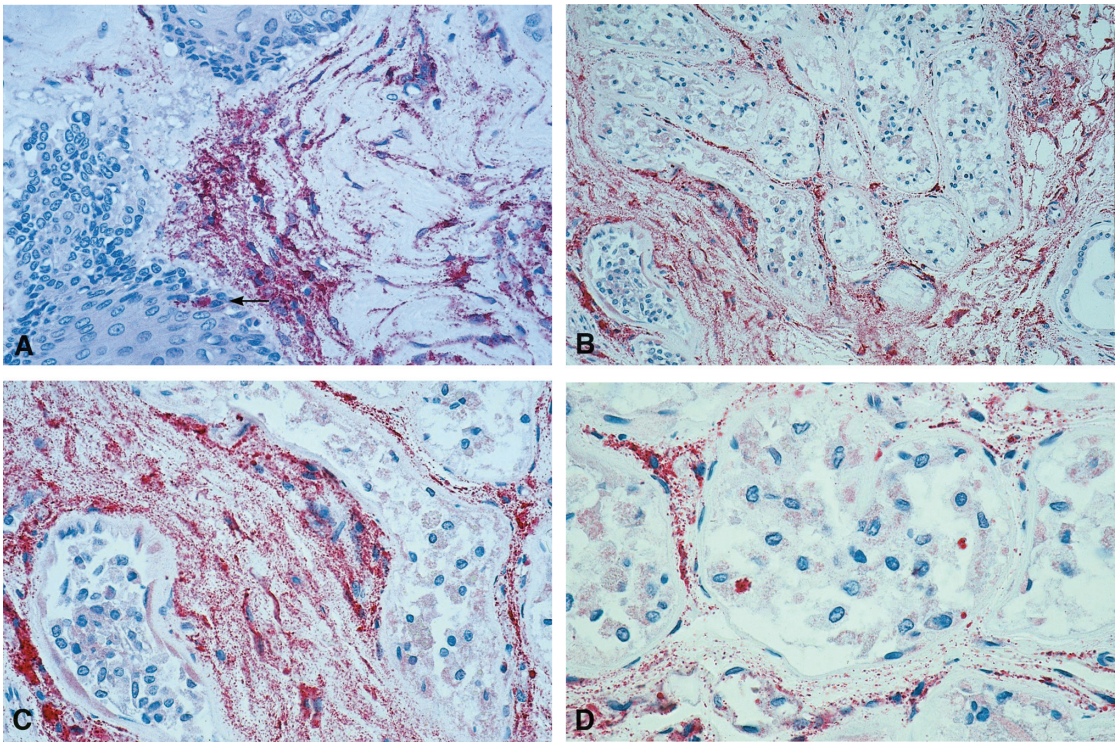


Figure 18-II.6 Histopathology of cutaneous lesions. Ebola (EBO) antigen distribution in skin specimen of EBO hemorrhagic fever patients as determined by immunohistochemistry. (A) Extensive amounts of EBO virus antigens are seen primarily within endothelial cells and fibroblasts in dermis. Note the rare immunostaining of cells (arrow), perhaps Langerhans, in the epidermis. Original magnification: 1100. (B) Massive amounts of viral antigens are seen in connective tissue surrounding sweat glands. Original magnification: 150. (C) Higher-power magnification of (B) showing immunostaining of endothelial cells and fibroblasts. Note also the abundant extracellular antigens and the absence of staining within sweat glands. Original magnification: 1100. (D) Antigen-positive cell and immunostaining within sweat glands. Original magnification: 1158. (A–D) Immunoalkaline phosphatase staining, naphthol fast red substrate with light hematoxylin counterstain. (From Zaki SR et al. 1999, with Editor's permission.)

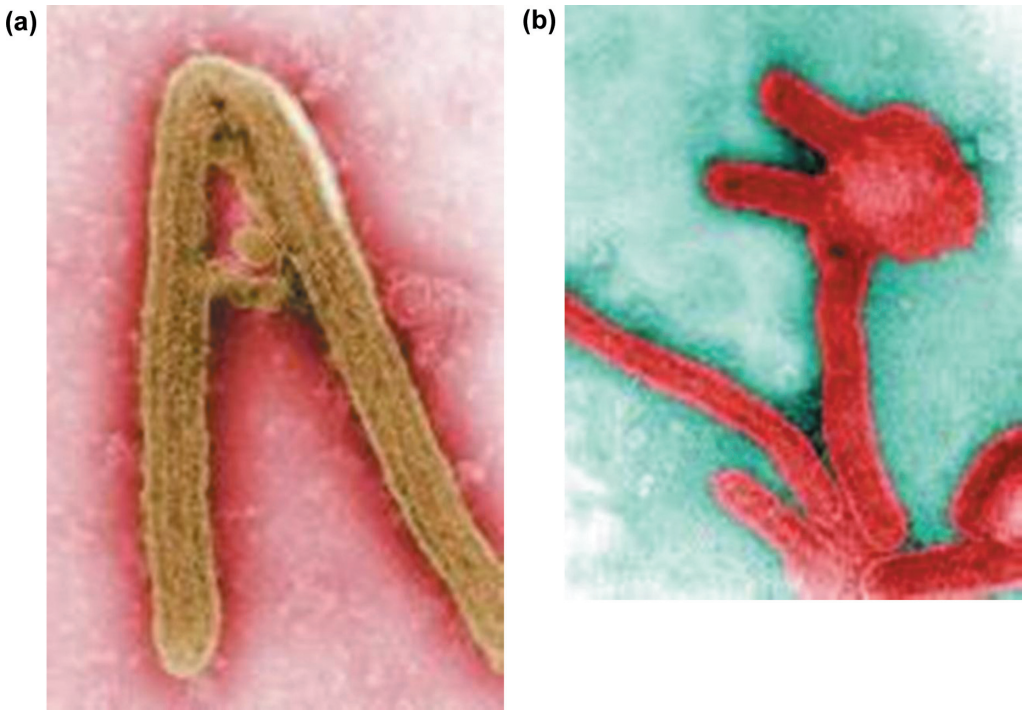


Figure 18-II.7 Virus structure in electron microscopy. Negative-stained transmission electron micrograph (TEM), captured by F.A. Murphy in 1968, depicts a Marburg virus virion, which had been grown in an environment of tissue culture cells. (Photos obtained from CDC's Public Health Image Library at http://phil.cdc.gov/phil/home.asp. Accessed February 5, 2009.)

Table 18-II.3 Treatment of Marburg and Ebola Hemorrhagic Diseases

Symptom	Treatment
Fever	Antipyretics (avoid medications which interfere with platelet function, since the infection is already associated with thrombocytopenia and abnormal platelet aggregation)
Vomiting, diarrhea and dehydration	Oral rehydration is preferred to limit the potential for viral exposure to medical staff as well as to preserve the integrity of the skin (patients are at risk for hemorrhage from venepuncture sites). The electrolyte balance, particularly potassium, should be maintained. Antiemetics may be useful. With intractable vomiting and diarrhea, intravenous hydration is unavoidable, but special care should be exercised with these patients
Shock	Volume expanders (intravenous fluids or albumin) and blood transfusions are critical. Renal function should be monitored closely. Oliguric patients may benefit from mannitol, whereas anuric patients often need dialysis treatment
Hemorrhage	Fresh blood transfusions, platelets transfusions, fibrinogen, and/or clotting factor concentrates may be useful

Also, several candidate vaccines are currently being tested and at least two are in the experimental phase: the VSVΔG/ZEBOVGP and VSVΔG/MARVGP (a live attenuated recombinant of vesicular stomatitis virus expressing either the EBOV or MARV glycoprotein), and the ADV-GP/NP (an inactivated recombinant adenovirus expressing the EBOV glycoprotein and the nucleoprotein) [45,46]. They protected experimentally infected animals such as guinea pigs and rhesus macaque monkeys and seemed well tolerated.

Conclusion

Mucocutaneous manifestations of filovirus infection are frequent. Generally, they occur between the 2nd and 7th day of the appearance of symptoms, but also during the survivors' convalescence phase. They are important in the differential diagnoses of tropical diseases, particularly fevers accompanied by exanthema from arboviral infections. Histopathology and electron microscopy of skin specimens are useful for confirmation of the diagnosis. Skin biopsy is a powerful and conservative tool for diagnosis and research. The role of the skin in the transmission of filoviruses by physical contact must be emphasized.

It is necessary to note the importance of dermatology and histopathology, via skin biopsy, in the diagnostic confirmation, by the detection of viral antigens and the identification of viral inclusions in electron microscopy. Skin biopsy appears as a powerful, conservative, and safe to perform tool for diagnostics and also research. Finally, the role of the skin in transmission by physical contact must be underlined.

ACKNOWLEDGEMENTS

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19 Bunyaviruses

Omar Lupi, Cinthia Diniz, Fabiana de Carvalho Serra, and Elba Regina Sampaio de Lemos

Bunyaviridae is a family of negative-stranded RNA viruses. Though generally found in arthropods or rodents, certain viruses in this family occasionally infect humans. Bunyaviridae are vector-borne viruses. The Bunyaviridae family consists of more than 200 different viruses, several of which are human pathogens. With the exception of hantaviruses, transmission occurs via an arthropod vector (mosquito, tick, or sandfly). Hantaviruses are transmitted through contact with deer mice feces. The incidence of infection is closely linked to vector activity, for example, mosquito-borne viruses are more common in the summer.

HANTAVIRUSES

Definition

In the last few decades, despite intensive research and great efforts to eradicate infectious diseases, a significant number of unknown or underestimated pathogens have emerged as health hazards of the human population. Almost all of these emerging pathogens are zoonotic agents [1]. Rodent-borne zoonoses have grown markedly in the last few decades and constitute an important health problem worldwide. Hantavirus are causative agents of rodent-borne viral hemorrhagic fevers all over the world, and their ubiquity and potential for causing severe human illness make these viruses an important public health concern.

Hantaviruses are enveloped RNA viruses of the genus *Hantavirus*, a member of the family Bunyaviridae. Similar to other Bunyaviridae, the genome of hantaviruses consists of three single-strand, negative-sense RNA segments, large (L), medium (M), and small [2–4]. With the exception of hantaviruses, Bunyaviridae are maintained in arthropods and are amplified in animal or plant hosts that are often killed by the infecting virus. By contrast, hantaviruses are maintained by cyclical transmission between persistently infected rodents, with incidental infection of humans [3,5].

Currently, the genus *Hantavirus* includes aproximately 50 genotypes, each one generally carried by its specific natural host. Wild rodents of the subfamily *Sigmodontinae* (family Cricetidae), which comprises more than 420 species, is the major reservoir of hantavirus in the Americas. In Asia and Europe, the subfamily *Murinae* is responsible for the transmission of hemorrhagic fever with renal syndrome (HFRS) to humans (Table 19.1).

The transmission to humans is believed to occur occasionally from inhalation of virus-contaminated aerosols of rodent excreta and, according to the genotype involved, can result in two distinct clinical syndromes: HFRS, endemic in Asia and Europe, and hantavirus pulmonary syndrome (HPS), an emergent disease with growing numbers of cases in the Americas. Person-to-person transmission is associated only with Andes virus in Argentina and Chile [6–11] without evidence of this kind of transmission in other places [12–15]. Vertical transmission, although suggested by some authors [16], could not be confirmed by other studies [17].

History

Although the diseases associated with hantaviruses have been unrecognized for many years, they are not new for humankind. A syndrome similar to HFRS was described as early as 960 AD in China [30]. Reports of HFRS date back to 1913 in Russia [30], and sporadic epidemics have been described in Manchuria, Siberia, and Lapland during the 1930s and 1940s [30]. In 1940, Japanese researchers first inoculated humans and monkeys with bacteria-free serum from patients with HFRS. The serum recipients then developed the same syndrome, proving the etiology to be infectious and viral [30]. This syndrome first received worldwide attention when more than 3000 United Nations troops stationed in Korea during 1951–1954 (Korean War) became infected. However, the infecting agent remained unknown until 1976, when the Korean researcher, Ho Wang Lee, discovered that lung tissues of the rodent *Apodemus agrarius*, captured near the Han River, contained a specific antigen reactive with HFRS patient serum samples [30].

No human disease had been known to be caused by hantaviruses in the Americas until 1993 when a cluster of unexplained respiratory illnesses leading to death was found in the Four Corners region of southwestern USA [30]. This "new" syndrome was demonstrated to be due to a new genotype of hantavirus, called Sin Nombre virus (SNV), which is related to, but distinct from, those causing HFRS. This syndrome, known as HPS, is also rodent-borne and is associated with a high case-fatality rate [30].

Incidence

It is estimated that more than 150,000 cases of hantavirus infection are diagnosed annually worldwide. Three endemic foci are recognized. The first is situated in southeast Asia, where Hantaan and Seoul viruses cause moderate to severe cases of HFRS, although Seoul, the virus associated with *Rattus norvegicus* and *R. rattus* has a worldwide distribution [31,32]. The second focus includes southwest, north, and central Europe, where the mildest cases of HFRS are reported. The third endemic focus includes virtually the entire Americas, where the clinical syndrome HPS predominates [30,33].

The Hantavirus group is distributed worldwide in rodents [36] and the localization of each hantavirus genotype and, consequently, its associated clinical syndrome, are usually restricted to its reservoir (Table 19.1).

HFRS occurs in early summer and late fall in a band-like distribution from Scandinavia across Europe and Russia to China and Korea [30]. In certain countries, such as China, Korea, and eastern Russia, hantaviruses continue to cause a considerable number of infections with over 100,000 known cases in China each year [30]. Milder disease characterizes the European condition, while the Asian variety is quite severe (Korean hemorrhagic fever) (Fig. 19.1).

For HPS, the case count started when the disease was first recognized in May 1993. More than 35% of all reported cases have resulted in death in the Americas.

Table 19.1 Hantaviruses: Major Reservoir, Geographic Distribution, and Clinical Presentation

Virus	Disease	Reservoir	Country	Distribution
Order Rodentia; Family Cricetidae				
Subfamily Murinae				
*Dobrava-Belgrade	HFRS[a]	*Apodemus flavicollis*	Slovenia	Europe
*Hantaan	HFRS	*Apodemus agrarius*	Korea	Asia, Europe
Saarema	HFRS	*Apodemus agrarius*	Europe (East and Center)	Europe
*Seoul	HFRS	*Rattus norvegicus*	Korea	Asia, Europe, Americas
*Thailand	ND[b]	*Bandicota indica*	Thailand	Asia
Subfamily *Arvicolinae*				
Bloodland lake	–	*Microtus ochrogaster*	USA	North America
*Islā Vista	–	*Microtus californicus*	USA	North America
*Khabarovsk	–	*Microtus fortis*	Russia	Asia
*Puumala	EN[c]	*Chletrionomys glareolus*	Finland	Europe
*Prospect Hill	–	*Microtus pennsylvanicus*	USA	North America
*Topografov	–	*Lemmus sibiricus*	Russia	Asia, North America
Tabetsu	–	*Chletrionomys glareolus*	Japan	Asia
*Tula	–	*Microtus arvalis*	Russia	Europe
Subfamily *Sigmodontinae*				
Alto Paraguai	–	*Holochilus chacarius*	Paraguay	South America
*Andes	HPS[d]	*Oligoryzomys longicaudatus*	Argentina	South America
Anajatuba	–	*Oligoryzomys fornesi*	Brazil	South America
Araraquara	HPS	*Bolomys lasiurus*	Brazil	South America
*Bayou	HPS	*Oligoryzomys palustris*	USA	North America
Bermejo	–	*Oligoryzomys chacoensis*	Argentina	South America
*Black Creek Canal	HPS	*Sigmodon hispidus*	USA	North America
Blue River	–	*Peromyscus leucopus*	USA	North America
Calabazo	–	*Zygodontomys brevicauda*	Panama	Central America
*Caño Delgadito	–	*Sigmodon alstoni*	Venezuela	South America
Castelo dos Sonhos	HPS	Oligoryzomys moojeni	Brazil	South America
Central Plata	HPS	*Oligoryzomys flavescens*	Uruguay	South America
Choclo	HPS	*Oligoryzomys fulvescens*	Panama	Central America
*El Moro Canyon	–	*Reithrodotomys megalotis*	USA	North America
HU39694	–	unknown	Argentina	South America
Itapuã strain 16	–	*Akodon montensis*	Paraguay	South America
Itapuã strain 37	–	*Oligoryzomys nigripes*	Paraguay, Brazil	South America
Itapuã strain 38	–	*Oligoryzomys nigripes*	Paraguay, Brazil	South America
Jaborá	HPS	*Akodon montensis*	Brazil	South America
Juquitiba	HPS	*Oligoryzomys nigripes*	Brazil	South America
*Laguna Negra	HPS	*Calomys laucha*	Paraguay, Brazil	South America
Lechiguanas	HPS	*Oligoryzomys flavescens*	Argentina	South America
Limestone Canyon	–	*Peromyscus boylii*	USA	North America
Maporal	–	*Oligoryzomys fulvescens*	Venezuela	South America
Maciel	–	*Bolomys obscures*	Argentina	South America
Monongahela	HPS	*Peromyscus maniculatus*	USA	North America
*Muleshoe	–	*Sigmodon hispidus*	USA	North America
Neembuco	–	*Oligoryzomys chacoensis*	Paraguay	South America
*New York	HPS	*Peromyscus leucopus*	USA	North America
Oran	HPS	*Oligoryzomys longicaudatus*	Argentina	South America
Pergamino	–	*Akodon azarae*	Argentina	South America
*Rio Segundo	–	*Reithrodontomys mexicanus*	Costa Rica	Central America
*Rio Mamore	–	*Oligoryzomys microtis*	Bolivia	South America
Rio Mearim	–	*Holochilus scireus*	Brazil	South America
*Sin Nombre	HPS	*Peromyscus maniculatuss*	USA	North America
Order Insectívora				
*Thottapalayam	–	*Suncus murinus*	India	Asia
Asama	–	*Urotrichus talpoides*	Japan	Asia

[a]Hemorrhagic fever with renal syndrome; [b]none documented; [c]epidemic nephritis; [d]hantavirus pulmonary syndrome; *officially recognized by the International Committee on Taxonomy of Viruses (ICTV) database.

In North America, especially in the USA, of persons ill with HPS, 63% have been male, 37% female. The mean age of confirmed case patients is 38 years (range: 10–83 years). HPS can strike anyone; however, Caucasians currently account for 78% of all cases, American Indians for about 19% of cases, African Americans for 2% of cases, and Asians for 1% of cases. About 14% of HPS cases have been reported among Hispanics (ethnicity considered separately from race). As of March 1999, 211 cases of HPS had been confirmed by the Centers for Disease Control (CDC), with a case fatality rate of 34% and overall fatality of 43%. By March 26, 2007, a total of 465 cases of HPS had been reported in the USA. Cases have been reported in 30 states, including most



Figure 19.1 Hemorrhagic conjunctivitis secondary to infection with Hantavirus (Korean hemorrhagic fever). (Photograph courtesy of Drs. Monica McCrary and Jack Lesher, Medical College of Georgia, Augusta, GA.)

of the western half of the country and some eastern states as well. Over half of the confirmed cases have been reported from areas outside the Four Corners area. About three quarters of patients with HPS have been residents of rural areas [32,33].

In Latin America, cases of HSP had already been described in Argentina, Bolivia, Brazil, Chile, Panamá, Paraguay, Uruguay, and Venezuela [9–11,13,20,33–40]. In Costa Rica and Peru, although lacking evidence of human cases, many genotypes have been genetically characterized in wild rodents [37,39]. In Colombia, the serologic evidence of human infection confirms the wide circulation of those viruses in the Americas [41].

The majority of HPS cases have been identified in Brazil. From the recognition of the first cases in Brazil until September 2008, more than 1100 HPS cases have been reported, with a 39% case fatality rate, mainly in southern and southeastern states [42]. Araucaria, Juquitiba, and Araraquara (Fig. 19.2) viruses are the most important strains in Brazil.

Pathogenesis

Although there are many unknown aspects about the pathogenesis of hantavirus-associated human diseases, available data indicates exacerbated immune response as the major pathogenic mechanism involved in both clinical syndromes [43].

The virus presumably enters the human body via the respiratory mucosa and penetrates cells through specific receptors. Recent studies suggest β1 and β3 integrins, receptors of endothelial cells, platelets, and macrophages, as the entry mechanism involved in this process [27,44]. Viruses can be detected in plasma during the first 7 days of clinical illness.

Immunohistochemistry (IHC) analysis has shown that viral antigens are distributed primarily within the endothelium of capillaries throughout various tissues from patients with HPS and mainly within the capillary endothelium of renal tubules in HFRS [45,46]. Marked accumulations of hantaviral antigens are seen in the pulmonary microvasculature and in follicular dendritic cells within the lymphoid follicles of spleen and lymph nodes. Hantaviral nucleic acids can also be localized to endothelial and inflammatory cells in tissues from HPS cases using in situ hybridization. Electron micrographic studies confirm the infection of endothelial cells and macrophages in the lungs of HPS patients. Typical hantaviral inclusions are frequently seen in pulmonary endothelial cells, and their identity can be confirmed by immunolabeling. In the heart, endothelial staining is mainly in the capillaries of the myocardium and varies from focal immunostaining in some cases, to diffuse and extensive staining in others. Occasionally, staining of endothelial cells lining the endocardium is observed. Functional impairment of vascular endothelium is central to the pathogenesis of HPS. However, the pathogenesis of HPS is complex, and a myocardial depressant may contribute significantly to the mortality of this disease. It is also unclear how the shock syndrome relates to factors such as viral distribution and immunologic and pharmacological mediators of capillary permeability. There appears to be compartmentalization of a selective immune response in the lungs of HPS patients in combination with extremely high levels of viral antigens in the pulmonary vasculature. This feature suggests that the mechanism of inflammatory cell recruitment in the lungs of HPS patients may result from specific attraction and adherence of a selective population of inflammatory cells to an activated pulmonary microvascular endothelium [46].

Indeed, in HPS, as a result of increased permeability of pulmonary capillaries, there is an intense plasma leakage into the alveolar spaces that results in pulmonary edema and respiratory distress. A similar effect is seen in HFRS, in which the vascular dysfunction represents the central point of the pathogenic mechanism, represented locally by renal failure and systemically by hypotension and shock. The hemorrhagic picture seen in HFRS can be, in turn, explained by the vascular damage associated with the decreased number of functionally active platelets, which seems to be related to the hantavirus capacity to cause platelet adhesion through β3 integrin receptors [47].

In rodents, hantavirus seems to cause a persistent, asymptomatic and non-lethal infection that can lead them to a reservoir state for the rest of their lives. In those animals, viral particles can be

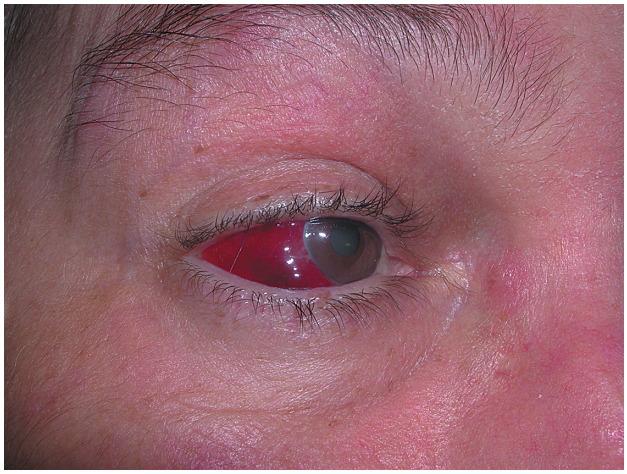


Figure 19.2 Eye involvement related to Araraquara virus infection.

Table 19.2 Clinical Manifestations of Hantavirus Hemorrhagic Fever with Renal Syndrome (HFRS)

Time after exposure	Clinical manifestations	Other notes
4–21 days	Abrupt onset of influenza-like prodrome, with high fever, chills, headache, dizziness, myalgias, abdominal pain, backache, and anorexia	
18–28 days	Abrupt defervescence of the febrile stage, followed by hypotensive stage, lasting 2 h to 3 days. Patients have nausea, vomiting, and typically develop severe clinical shock	One third of deaths due to HFRS occur during the hypotensive stage
18–31 days	Recovery from hypotension coincides with the development of the oliguric stage, lasting 3–7 days. Patients have varying degrees of renal failure, with pulmonary edema, pneumonitis, transient hypertension, and mucosal bleeding. More extensive hemorrhage may occur, with ecchymoses, hemoptysis, hematemesis, hematuria, melena, and central nervous system hemorrhage (rare)	Two thirds of the deaths due to HFRS occur during the oliguric stage, particularly due to pulmonary edema and cerebrovascular accidents (likely due to coagulopathy)
21–38 days	The polyuric stage begins in survivors of the illness and may last for weeks to months during recovery. Renal function is spontaneously restored and urine output of 3 to 6 L/day may occur. Massive fluid and electrolyte shifts may result with the diuresis	Patients who survive generally make a complete recovery, except those who develop central nervous system hemorrhages

isolated from many organs like the spleen, liver, kidney, parotid glands and lungs, being eliminated in large amounts through saliva, urine, and feces for a long period [48].

Clinical Manifestations

Two clinical syndromes are associated with hantaviruses: HFRS and HPS.

Hemorrhagic Fever with Renal Syndrome

Prototypic HFRS involves fever, hemorrhage, and renal failure [47,48] (Table 19.2). Classically, HFRS evolves in five phases: febrile, hypotensive, oliguric, diuretic, and convalescence, which can be superposed in milder cases, or may even be absent [47]. Severe HFRS presents with headache, abdominal pain, lumbar pain, proteinuria, and hemorrhagic manifestations with shock and renal insufficiency. Of these cases, 30–40% consist of minimal illness, and only 20–30% of patients have moderate to severe disease [47].

After a medium incubation period of 5–42 days, there is a febrile phase, followed by hypotension, then by oliguria. Diuresis follows, leading to prolonged convalescence. Survival is usually associated with complete recovery, but chronic renal insufficiency may ensue. During the febrile stage, ciliary muscle involvement may cause blurred vision associated with photophobia, pain of extraocular muscles, and retro-orbital pain. The face, neck, and back are flushed, and pharyngeal and conjunctival suffusion is noted. Petechiae are seen in the conjunctivae, axillae, and at points of pressure. Costovertebral angle pain reflects retroperitoneal edema. Proteinuria, disseminated intravascular coagulation (DIC), and an active urinary sediment become evident.

During the hypotensive period, a rising hematocrit corresponds with the capillary leak syndrome. There is isosthenuria along with massive proteinuria and oliguria. The presence of atypical lymphocytes and activation of kinins provides evidence for immunological activity in this stage [49,50].

The oliguric phase is associated with severe hemorrhagic phenomena and the majority of deaths. Less severe cases of HFRS (Seoul virus) develop fever with gastrointestinal symptoms followed by brief oliguria, then hyposthenuria. The clinical course with mild disease is of shorter duration [49].

Nephropathia epidemica is a milder variant of HFRS, usually caused by the Puumala virus [54,55]. The HFRS lethality rate is low, varying from 1 to 10%; Puumala infections have the lowest rates (usually less than 1%) [49,50].

Hantavirus Pulmonary Syndrome

HPS is typically an acute febrile disease, characterized by severe cardiovascular commitment and respiratory distress [51–53] (Table 19.3).

After a median incubation period of 15 days, which can vary from 9 to 33 days [54), patients present in a very nonspecific way with a relatively short febrile prodrome lasting 3–6 days [45]. In addition to fever and myalgias, early symptoms include headache, chills, dizziness, non-productive cough, nausea, vomiting, and other gastrointestinal symptoms. Malaise, diarrhea, and lightheadedness are reported by approximately half of all patients, with less frequent reports of arthralgias, back pain, and abdominal pain. Patients may report shortness of breath (respiratory rate usually 26–30 times per minute). Typical findings on initial presentation include fever, tachypnea, and tachycardia [52,53].

The diagnosis is seldom made at this stage, as cough and tachypnea generally do not develop until approximately day 7. Once the cardiopulmonary phase begins, the disease progresses rapidly, evolving with progressive plasma leakage into interstitial and alveolar spaces, causing pulmonary edema, progressive hypoxia, hypotension, and shock, necessitating hospitalization and often ventilation within 24 hours. If frank shock with severe hypoxemia and respiratory failure appear promptly, there are severe manifestations of abnormal capillary permeability, with high mortality rates despite good medical care. The case fatality rate is up to 10 times that seen in HFRS [53–55].

Cutaneous and conjunctival manifestations that are seen in other hemorrhagic fevers are rare in HPS, thus arguing against North American hantavirus infection, although rash and conjunctivitis can be seen in patients with HPS in South America (Fig. 19.2). Although changes in blood clotting are frequently seen, rash, petechiae, hyperemia, or hemorrhage of conjunctiva or other sites, makes HPS an unlikely diagnosis [53,55].

Pathology

In HFRS, capillary dilation and red cell diapedesis are present, along with retroperitoneal and other interstitial edema. Hemorrhage occurs in the skin, mucous membranes, and various organs.

Table 19.3 Clinical Manifestations of Hantavirus Pulmonary Syndrome

Time after symptom onset	Clinical manifestations	Laboratory analyses	Other notes
7–4 days	Sudden onset of prodromal symptoms, with fever, headache, myalgia, and cough, progressing to hypoxia. Over half of patients have gastrointestinal symptoms, with nausea, vomiting, abdominal pain or diarrhea, mainly mild. Some patients may also complain of malaise, dyspnea, and dizziness	Serology, with IgM acutely or fourfold rise of IgG in paired sera Detection of viral antigens in infected tissue by PCR	
9–7 days	Rapid development of bilateral interstitial pulmonary infiltrates develop along with adult respiratory distress syndrome (ARDS). With this, the pulmonary capillary wedge pressures are <10 mm Hg. Hypotension, rhabdomyolysis, and thrombocytopenia also develop. In some patients, myocardial depression and hypovolemia develop, although systemic vascular resistance is high		The degree of hypoxia generally progresses to require mechanical ventilation The rapidity of cardiopulmonary decompensation is the hallmark of HPS
10–18 days	Hospitalization is usually required with 3–4 days of symptom onset		
12–21 days	Maximal hemodynamic compromise peaks, with severe hypotension and pulmonary edema. Renal failure may occur in some cases but is uncommon Survivors typically develop diuresis and recover without sequelae		Most deaths occur within 2 days of hospitalization

IgG, IgM, immunoglobulin G, M; PCR, polymerase chain reaction; HPS, hantavirus pulmonary syndrome.

Table 19.4 Differential Diagnoses of Hantavirus Hemorrhagic Fever

Leptospirosis: A biphasic febrile illness with myalgia precedes central nervous system manifestations. Jaundice and exposure to animals are epidemiological clues. The rash is a trunchal, erythematous, maculopapular rash. It may be urticarial, petechial, purpuric, or desquamative

Acute renal failure: A variety of etiologies leads to hematuria, proteinuria, azotemia, and/or hypertension. These include toxins/drugs, systemic lupus, HSP, malaria, and severe dehydration and shock

Murine typhus: Fever, headache, and a trunchal rash that spreads peripherally are typical. The condition is mild. Exposure to rat flea environment is necessary

Scrub typhus: Travel to the southwest Pacific, eschar from a mite bite, lymphadenopathy, hepatosplenomegaly, a rash, and pneumonia are suggestive of scrub typhus

Meningococcemia: Fever, petechiae and purpura; altered mental status; and leukocytosis precedes shock

Pyelonephritis: Fever, pyuria, bacteriuria, and costovertebral angle tenderness precede sepsis and endotoxic shock

Hemolytic uremic syndrome: A hemolytic anemia, thrombocytopenia, and azotemia follow gastroenteritis. A Shiga-like toxin has been implicated

Scarlet fever: Exudative pharyngitis, cervical adenitis, and a fine maculopapular rash with coarse, sand paper texture are characteristic. Group A β- hemolytic streptococcus on throat culture is diagnostic. This infection may lead to sepsis or necrotizing fasciitis

Acute abdomen (e.g., appendicitis): Diffuse pain migrates to the right lower quadrant, with fever and leukocytosis lead to peritoneal signs and abscess or septic shock

Heatstroke: A history of insufficient fluid intake for the circumstances precedes extreme temperature elevations and seizures. Lacking is the specific geography and vector exposures, specific rash, or hepatic dysfunction

Goodpasture's disease: Azotemia, hematuria, and proteinuria are seen with pulmonary insufficiency

Anaphylactoid purpura (Henoch-Schönlein purpura [HSP]): A purpuric rash of dependent areas (hands, feet, buttocks) is seen with hematuria of renal insufficiency, arthritis, gastrointestinal pain or bleeding, and/or intussusception

Rocky Mountain spotted fever

Other arboviral infections:
- **ONN**
- **Sindbis**
- **Mayaro**
- **Oropouche**
- **Sandfly fever**
- **Hantavirus pulmonary syndrome**

} See Table 16.2

Other hemorrhagic fevers:
- **Rift Valley fever**
- **Kyasanur Forest disease**
- **Omsk hemorrhagic fever**
- **Colorado tick fever**
- **Crimean-Congo hemorrhagic fever**
- **Lassa fever and the South American hemorrhagic fevers**
- **Chikungunya fever**

} See Table 18-II.2

Dengue: Suggested by world-wide travel in the tropics and mosquito exposure. Children predominantly affected with a capillary leak syndrome resulting in hemorrhage with shock

Ebola and Marburg hemorrhagic fevers: Suggested by laboratory (Europe) or wild (Africa) exposure to monkeys, patients' tissue, or secretions; by pharyngitis; conjunctival injection; toxic appearance; dehydration; basilar rales; edema; and hemorrhage

Kidneys are edematous and hemorrhagic, and hemorrhage can also develop in the pituitary gland and right atrium [49,53].

HPS pathology involves pulmonary endothelial and reticulo-endothelial findings. The lungs are dense and rubbery in a serous pleural fluid. Intra-alveolar edema and interstitial mononuclear infiltrates are seen. The endothelium shows generalized capillary dilatation and edema. Viral inclusions are seen on electron microscopy, with viral antigen at high levels. Cardiac endothelium is affected and may result in the myocardial depression seen clinically. Lymphoid tissues show immunoblasts in the spleen and lymph nodes.

Laboratory Findings

The laboratory findings are often nonspecific. Neutrophilia, circulating atypical lymphocytes, hemoconcentration, and

Table 19.5 Differential Diagnoses of Hantavirus Pulmonary Syndrome

Pneumonia with sepsis: Sudden onset of fever, cough, respiratory insufficiency, possibly empyema, progressing to shock and multiple organ failure, and adult respiratory distress syndrome (ARDS)	
Fungal pneumonias: Coccidioidomycosis occurs in desert habitat, more often in males, and may have erythema nodosum. Usually is self-limited except to immune compromised hosts. Histoplasmosis occurs in moist areas with aerosolization of excreta of birds. In blastomycosis, pulmonary involvement results from inhalation of the agent, leading to fever, malaise, cough, and chest pain. Consolidation results in chronic respiratory compromise	
Plague (*Yersinia pestis*): Travel to endemic area is key with high index of suspicion when seeing chills, fever, lymphadenopathy, headache, pneumonia, DIC, purpuric skin lesions, or meningitis	
Tularemia: Also may be associated with a tick bite, but the site of inoculation becomes painful and ulcerated, often with associated lymphadenopathy	
Relapsing fever: Recurrent fevers, exposure to lice or ticks, headache, photophobia, nausea, vomiting, myalgia, arthralgia, and hemorrhage from skin, gastrointestinal, or GU track occur. A diffuse macular rash may appear. Hepatitis and encephalitis may occur	
Brucellosis: Occurs world wide with exposure to domestic animals or unpasteurized dairy products. Triad of fever, arthralgia/arthritis, and hepatosplenomegaly is classic	
Legionella: Progressive respiratory insufficiency with atypical pneumonia, chills, abdominal pain, myalgia, headache, fatigue; low or absent fever; in spite of routine antibiotic treatment progresses to respiratory failure. A variety of species and serotypes in the genus Legionella is etiologic	
Psittacosis: An exotic avian exposure, abrupt onset of fever, chills, sweats, headache, nonproductive cough, rales, abnormal chest radiograph, pleural effusion, mild leukocytosis, and abnormal liver function tests characterize infection with Chlamydia psittaci	
Rocky Mountain spotted fever	See Table 16.2
Leptospirosis	See Table 19.4
Murine typhus	
Scrub typhus	
Heatstroke	
Goodpasture's disease	
Meningococcemia	
Pyelonephritis	
Pulmonary hemorrhage with Henoch-Schönlein purpura	

DIC, disseminated intravascular coagulation; GU, genitourinary.

thrombocytopenia are frequent with both syndromes. Hepatic function is also impaired in most cases, with elevated aminotransferase levels and hypoalbuminemia. The white blood cell count tends to be raised with a marked left shift. The percentage of white blood cell precursors may be as high as 50% and atypical lymphocytes are frequently present, usually at the time of onset of pulmonary edema. In about 80% of individuals with HPS, the platelet count is below 150,000 [55,56]. A dramatic fall in the platelet count may herald a transition from the prodrome to the pulmonary edema phase of the illness. HPS shows varying degrees of hypoxia and respiratory insufficiency, progressing to respiratory failure with hypoxia, hypocapnea, and metabolic acidosis. Lactic dehydrogenase levels are usually elevated until convalescence and plasma lactate can rise in severe cases, indicating a bad prognosis [49,50,57].

Chest radiography reveals a typical evolution in HPS. Initially, minimal evidence of interstitial pulmonary edema is seen. After some days or hours, bilateral alveolar edema and pleural effusion can be evident [53,58].

The HFRS, in turn, has proteinuria, azotemia, oliguria with electrolyte abnormalities, and evidence of renal insufficiency, then polyuria.

Diagnosis

A positive serological test result, evidence of viral antigen in tissue by IHC, or the presence of amplifiable viral RNA sequences in blood or tissue, with a compatible history of HPS or HFRS, is considered diagnostic (Tables 19.4 and 19.5).

Serologic assays

Routinely, hantavirus infections are diagnosed by serologic tests. Though many methods are available, e.g., indirect immunofluorescence assay (IFA), Western blot, rapid immunoblot strip assay (RIBA), IHC and neutralization tests, enzyme-linked immunosorbent assay (ELISA) using IgM capture and IgG is the preferred one [6,7,9,59,60].

The laboratory criteria for diagnosis are: (a) the presence of IgM in acute-phase sera, or (b) a fourfold rise in IgG antibody titer from acute- and convalescent-phase sera. One should remember that acute-phase serum sent as an initial diagnostic specimen may not yet have IgG. IgG antibody is long lasting, and sera of patients retrospectively identified appear to have retained antibody for many years. The IgG ELISA has therefore been used in serologic investigations of the epidemiology of the disease and appears to be appropriate for this purpose [59,60].

In 1993, cross-reactive antibodies to the previously known hantavirus genotypes were found in the acute- and convalescent-phase sera of some of the initial HPS patients. Tests based on specific viral antigens from SNV have since been developed and are now widely used for the routine diagnosis of HPS. The CDC uses ELISA to detect IgM antibodies to SNV and to diagnose acute infections with other hantaviruses [55].

Nowadays, at least four recombinant antigens based on the S-segment sequences of Argentinean and Brazilian hantavirus for detecting antibodies against hantavirus in indirect enzyme immunoassays (EIA) are used to diagnose HPS (Andes, Araraquara, Maciel, and Araucària) [9,10,24,25,61,62].

The use of genotype-specific antigens for each region is ideal, but still not feasible. However, because of the satisfactory similarity in genotypes, amino acid sequencing is not a problem [63].

Polymerase Chain Reaction

Reverse transcriptase-polymerase chain reaction (RT-PCR) can be used to detect hantaviral RNA in fresh frozen lung tissue, blood clots, or nucleated blood cells. However, it is important to highlight that it is very prone to cross-contamination and differences in viruses of each region complicate its use and sensitivity for the routine diagnosis of hantaviral infections [49,50].

Immunohistochemistry

IHC testing of formalin-fixed tissues with specific monoclonal and polyclonal antibodies can be used to detect hantavirus antigens and has proven to be a sensitive method for laboratory confirmation of hantaviral infections. IHC has an important role in the diagnosis of HPS in patients from whom serum samples and frozen tissues are unavailable for diagnostic testing and in the retrospective assessment of disease prevalence in a defined geographic region [55].

Table 19.6 Treatment of Hemorrhagic Fever with Renal Syndrome (HFRS) and Hantavirus Pulmonary Syndrome (HPS)

Symptom	Treatment
General	Intravenous ribavirin therapy for severe cases of HFRS. Bed rest
Fever	Antipyretics. Acetaminophen is preferred over aspirin and other nonsteroid anti-inflammatories, since thrombocytopenia is already present with these syndromes
Capillary leak and hypotension	Cautious repletion with intravenous fluid and colloids. Overhydration should be avoided to prevent exacerbation of pulmonary edema
Cardiac depression	Vasopressor and inotropic agents may be beneficial
Renal insufficiency	Careful fluid and electrolyte maintenance
Renal failure	Peritoneal dialysis or hemodialysis
Respiratory insufficiency	Oxygen therapy, or if necessary, mechanical ventilation. Pulmonary artery catheterization with wedge pressure tracings is necessary in most cases

Isolation

Isolation of hantaviruses from human sources is difficult, and the viruses causing HPS seem to be no exception. Therefore, virus isolation is not a consideration for diagnostic purposes [55].

Laboratory testing should be performed or confirmed at a reference laboratory. Because the clinical illness is nonspecific and acute respiratory distress syndrome (ARDS) is common, a screening case definition can be used to determine which patients to test. In general, a predisposing medical condition (e.g., chronic pulmonary disease, malignancy, trauma, burn, and surgery) is a more likely cause of ARDS than HPS, and patients who have these underlying conditions and ARDS need not be tested.

Treatment and Prevention

The high case fatality rates, particularly for HPS, attest to the difficulty of treatment (Table 19.6). There is no specific treatment for hantavirus infection. Intravenous ribavirin, a guanosine analogue, has not been shown to be effective for treatment of HPS [64] despite its effects on HFRS, especially when started before the fourth day of disease [65]. Controlled trials showed a reduction in case-fatality for HFRS patients treated with ribavirin. However, despite in vitro activity of ribavirin against SNV, neither an open-label trial conducted during the 1993 outbreak nor an attempted placebo-controlled trial demonstrated clinical benefit for HPS. Ribavirin is not recommended for treatment of HPS and is not available for this use under any existing research protocol.

Supportive care continues to be the mainstay of treatment. Patients should receive appropriate, broad-spectrum antibiotic therapy while awaiting confirmation of a diagnosis of HPS. Care during the initial stages of the disease should include antipyretics and analgesia as needed. Fluids should be administered carefully due to the potential for capillary leakage [49,50,61,62]. Some authors have recommended treatment with corticoids, although the real benefit of this therapy is controversial.

The control and prevention of hantavirus infections is based on systematic measures of sanitation and environmental and domestic changes that keep humans from direct or indirect contact with rodents or their excreta and secretion. Eradicating the reservoir hosts of hantaviruses is neither feasible nor desirable because of the wide distribution of those rodents and their importance in the function of natural ecosystems. Therefore, the best currently available approach for prevention is risk reduction through avoidance of contact with all wild and peridomestic rats and mice. Rodent control in and around the home remains the primary strategy in preventing hantavirus infection. The interior and exterior of the home should be carefully inspected regularly for any openings where rodents could enter the home and if any evidence of rodent infestation is detected inside the home or in outbuildings, precautions should be taken. Complete precaution guidelines are also available on CDC's website: All about Hantaviruses (http://www.cdc.gov/ncidod/dvrd/spb/mnpages/rodentmanual.htm).

Laboratory worker exposure is minimized by the use of suitable precautions while handling rodents. A formalin-inactivated Hantaan virus vaccine is not commercially available.

CALIFORNIA/LA CROSSE ENCEPHALITIS

Definition

The California encephalitis serogroup consists of mosquito-transmitted, enveloped RNA viruses that cause human encephalitis or milder disease. The prototype virus is La Crosse (LAC), which causes disease predominantly in children. Three viral subgroups, A–C, are distinguished by RNA techniques. LAC virus causes nearly all of the infections attributed to the California group viruses in the USA [66].

Other viruses of the California serogroup that cause encephalitis in humans include the California virus, snowshoe hare virus, Inkoo and Tahyna viruses, trivittatus virus, and Jamestown Canyon virus. California virus is found in southwestern USA [66]. Jamestown Canyon virus is found in Alaska and northeastern USA. It is transmitted by Culiseta mosquitoes and amplified in whitetail deer. Snowshoe hare virus, named after its mammalian host, is found in Canada, Alaska, and the Rocky Mountains. Trivittatus virus is present in midwestern and southeastern USA. Tahyna occurs in southern Europe and Inkoo occurs in Finland. Reindeer and moose are natural hosts.

History

In 1960, LAC virus was first isolated from a 4-year-old patient who died from encephalitis in La Crosse, Wisconsin, hence the name. Epidemiological and serological studies demonstrated that the LAC virus was a significant cause of "rural encephalitis," which had infected a number of children in the upper midwest, particularly Wisconsin and Minnesota. A virus previously isolated in 1943 in California (California virus) [66] proved to be a similar, but much less common cause of encephalitis. Except for epidemics due to St. Louis encephalitis virus, LAC virus is the most prevalent mosquito-borne arboviral infection and the most commonly identified cause of encephalitis in the USA [67].

Incidence

Most LAC infections result in subclinical infection or fever alone, while encephalitis with fever is much less frequent. Serological studies suggest that LAC virus may infect more than 300,000 humans each year in the USA, with more than 1000 subclinical or

Table 19.7 Clinical Manifestations of La Crosse Infection

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–7 days	Prodrome of fever (102° –104° F) malaise, headache, irritability, drowsiness, and vomiting, lasting 2–3 days. Diarrhea is usually absent	Specific serology with IgM or fourfold rise in IgG titers. Isolation of IgM in CSF fluid is most specific	Fever and somnolence are the only universal characteristics. Some cases may present with only a sudden convulsion
6–11 days	Half of patients progress to focal or generalized seizures or disorientation. Other patients gradually improve		10% of cases develop status epilepticus
10–15 days	Resolution of disease without sequelae in most patients		Patients who develop encephalopathy or coma require more time for recovery, typically at least 2 weeks

CSF, cerebrospinal fluid; IgG, IgM, immunoglobulin G, M.

mildly symptomatic infections per reported clinical case [68,69]. Most cases of LAC occur in Wisconsin, Illinois, Ohio, and Minnesota. Sporadic infections have been found in 20 other states, predominantly in areas east of the Mississippi River. In endemic areas, the annual incidence of LAC encephalitis is 10–30 cases per 100,000 persons, which exceeds that for all types of bacterial meningitis [68,69]. In the USA, an average of 73 cases of LAC encephalitis is reported to the CDC each year [67]. The majority of cases occur between July and September, when the specific mosquito vector is most active. Cases of encephalitis occur almost exclusively in children less than 15 years of age [68,69]. Boys develop infection twice as often as girls, probably because of increased outdoor exposure in this group [70–72]. Most cases occur in rural areas or forested suburbs and small mammals are potential amplifying hosts [73]. Seroprevalence rates rise with age, reaching about 20% by age 60 years. There are few deaths (0.3%), and low rates of sequelae.

Pathogenesis

Aedes triseriatus, the tree hole mosquito, is the mosquito vector of LAC virus and also a reservoir in nature. Once infected, these mosquitoes carry the virus for life. The female breeds in small collections of rain water, such as tree holes, cans, and discarded containers. She transmits the virus to offspring, constituting an over-wintering mechanism for the virus. There is also venereal transmission to uninfected females during mating. Small mammals, such as chipmunks and squirrels, serve as amplifying hosts [9]. Humans are dead-end hosts, as they do not have a prolonged viremia with LAC infection. Related viruses have a variety of natural hosts, mosquito vector species, and biotypes.

After the virus is introduced into human skin and subcutaneous tissue by the feeding mosquito, viral replication occurs in nearby muscle tissue. This leads to dissemination into the blood. With viremia, further viral replication occurs in vascular endothelial cells, reticuloendothelial cells, and chondrocytes. This amplification results in further viremia with central nervous system (CNS) invasion. Access to the CNS is gained by infection of the vascular endothelial cells, followed by infection of neurons and glial cells [74,75].

Clinical Manifestations

LAC virus and related viruses share a common clinical pattern (Table 19.7). Encephalitis is less common than inapparent or nonspecific mild infection. Symptomatic disease occurs in less than 1% of infections. Children have more severe disease, a higher frequency of encephalitis, and more frequent sequelae. Mild cases involve meningeal signs and disorientation. More severe cases have seizures and altered states of consciousness with paresis, aphasia, and abnormal reflexes. Only 25% of cases develop nuchal rigidity, and only 50% of cases have any signs of meningeal irritation. No associated cutaneous manifestations have been described. Seizure disorders constitute the principal sequelae. Less than 2% of patients have significant neurological sequelae, such as focal weakness or spasticity [72]. Common migraine headaches may occur after encephalitis, particularly in those children who developed localization-related epilepsy [76]. Poor school performance in some children is a possible consequence, but epidemiological studies have difficulty distinguishing this manifestation from background rates in the general population [77,78].

Laboratory Findings

A peripheral leukocytosis with a left shift is frequent. The cerebrospinal fluid (CSF) shows a moderate mononuclear pleocytosis with mildly elevated protein (in one third of cases) and normal glucose. Computed tomography (CT) scans may show focal abnormalities, as do brain scans. However, most CT scans appear normal [78]. Electroencephalographic findings are frequent, usually consisting of generalized symmetrical slow waves [79].

Pathology

Cerebral edema, perivascular cuffing, glial nodules, and neuronal degeneration are evident. All are common findings in other arboviral CNS diseases.

Diagnosis

Recovery of virus from brain tissue has been reported, but viral isolation from CSF has never been successfully performed [80–82]. Detection of viral antigens is also problematic. Therefore, serology remains the cornerstone of diagnosis. Serological diagnosis requires a fourfold titer rise in hemagglutination inhibition (HI), neutralization (N), or complement fixation (CF) antibodies. Immunoglobulin M (IgM) by ELISA is sensitive early in the disease [19], but IgM remains elevated in the serum for at least 9 months in more than 50% of patients. Thus, demonstration of IgM in CSF is the most sensitive and specific diagnostic method for patients living in endemic areas [82] (Table 19.8).

Table 19.8 Differential Diagnoses of California/La Crosse Encephalitis

Herpes simplex virus (HSV) encephalitis: HSV encephalitis should be excluded because of its severe outcome and response to antiviral therapy. Rapid testing for HSV is commonly employed. A hemorrhagic, necrotizing encephalitis of the temporal lobes is typical, but it may appear as meningitis or encephalitis with seizures and coma

Enteroviral aseptic meningitis: Patients have fever, headache and nuchal rigidity. CSF studies show lymphocytic predominance with elevated protein. Enteroviral meningoencephalitis will be clinically indistinguishable from other viral CNS diseases. Serology, viral isolation or, where available, nucleic amplification testing will prove the etiology

Bacterial meningitis: A history of fever, nuchal rigidity, and headache with Kernig's and Brudzinski's signs are expected. Leukocytic predominance in the CFS with low glucose and high protein are expected as are positive bacterial cultures, gram stain, or antigen tests. Diagnosis is based on laboratory analysis of CFS

Tuberculous meningitis: Usually an insidious process associated with a miliary chest radiograph or tuberculous osteomyelitis

Cerebral malaria: Patients have periodic paroxysms of fever along with constitutional and gastrointestinal symptoms. Splenomegaly, pallor and jaundice are common. Plasmodium falciparum in a non-immune host may lead to cerebral malaria, blackwater fever, hepatic failure, and respiratory failure

Dengue virus with encephalopathy: Dengue is suggested by world-wide travel in the tropics and mosquito exposure; children predominantly affected with a capillary leak syndrome resulting in hemorrhage with shock

Intracranial hemorrhage/Stroke: Intracerebral hemorrhage is associated with adults; smoking or hypertension, and a variety of neurological deficits but without fever

Heat stroke: A history of insufficient fluid intake for the circumstances precedes extreme temperature elevation and seizures. Lacking is the specific geography and vector exposures, specific rash, or hepatic dysfunction

Toxic encephalopathy: Exposure to toxic substance producing altered mental status and varying symptoms, including memory loss, personality changes, depression, lack of concentration, seizures, involuntary movements, nausea, fatigue, or decreased arm strength.

Lead encephalopathy: Exposure to automobile or battery destruction or repair, smelter activities, or lead based paint aid in diagnosis. Patient is usually a child with encephalopathy with anemia but normal white blood count

Brain abscess: Fever, signs of increased intracranial pressure, focal seizures, focal EEG, abnormal imaging (nuclear scan, CT scan, MRI), and bulging fontanelle or spread sutures are seen

Brain tumor: Afebrile, signs of increased intracranial pressure, progressive neurologic deficits, abnormal imaging (nuclear scan, CT scan, MRI), and bulging fontanelle or spread sutures are seen

Postinfectious encephalitis: Guillain-Barré presents as afebrile loss of reflexes with ascending weakness; it may progress to respiratory depression. Acute cerebellar ataxia follows varicella and shows only ataxia that appears suddenly and resolves without residual deficits

Metabolic encephalopathy: Coma or altered mental status occur with elevated ammonia or BUN, depressed glucose, or history consistent with inborn error of metabolism. Absent fever and absent focal findings typify this group of conditions

Status epilepticus (SE): A prior history of a seizure disorder, sudden onset of unresponsiveness, perhaps with stereotypic behavior and abnormal EEG, SE may resolve with antiepilepsy drugs administered acutely

Acute confusional or basilar migraine: Altered mental status or coma appear suddenly, perhaps following an aura. Episodes are quite similar. Though not postictal, somnolence may follow each attack. Fever and seizures are absent

Reye's syndrome: Depressed mental status following varicella or influenza treated with aspirin is associated with hypoglycemia, bleeding disorder, elevated ammonia, and altered liver function tests

Other arboviral encephalitides:

Japanese encephalitis is suggested by severe encephalopathy in children in Asia in the monsoon reason

Eastern equine encephalitis
Western equine encephalitis
Venezuelan equine encephalitis
West Nile fever
St. Louis encephalitis
Tick-borne encephalitis
Powassan encephalitis
Rocky Mountain spotted fever
} See Table 16.2

Rift Valley fever
Kyasanur Forest disease
Colorado tick fever
} See Table 18-II.2

BUN, blood urea nitrogen; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogy; MRT, magnetic resonance imaging.

Table 19.9 Treatment of La Crosse Encephalitis

Symptom	Treatment
General	Close monitoring for changes in consciousness. If the child is disoriented, admission to an intensive care unit is necessary
Fever	Antipyretics
Headaches	Analgesics
Altered consciousness	Institute measures to limit the cerebral metabolic rate, such as fever control and seizure management. Prevention of cerebral edema is important, with maintenance of serum osmolality, avoiding hypotonic IV fluids, and monitoring for hyponatremia. Other methods include sedation, elevation of the head of the bed, hyperventilation, and osmotic agents
Seizures	Control with anticonvulsants. If this treatment is required, at least one major anticonvulsant should be continued for 1 year to reduce the risk of post-encephalitis epilepsy
Choreoathetosis Irritability and confusion	Haloperidol, lorazepam

Treatment and Prevention

Mild cases are the most common and require only symptomatic treatment (Table 19.9). Encephalitis cases must be supported with therapy available for sudden seizure development or acute neurological deterioration. Ribavirin has been shown to have in vitro efficacy against LAC virus [83,84], but no clinical trials have yet been completed to confirm an in vivo benefit. The control of the mosquito vector requires eradication of the principal breeding sites by cementing holes of trees and removing discarded containers. Aggressive mosquito control programs in a county in Wisconsin reduced the number of cases in that area. Mosquito repellents and insecticides prevent the risk of infection by minimizing exposure to the mosquito vector.

LAC and related viruses employ a variety of mosquitoes and natural hosts endemic to the biotype or climate. Asymptomatic infection and mild disease predominate. Clinical encephalitis has a favorable outcome in most cases, and sequelae are uncommon [85].

Table 19.10 Clinical Manifestations of Crimean-Congo Hemorrhagic Fever

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–6 days	Abrupt onset of influenza-like symptoms lasting 7–10 days, with fever, incapacitating chills, and severe headache. Severe myalgia, particularly of the limbs and lumbar area, nausea, vomiting, abdominal pain, diarrhea, and anorexia are also common. Conjunctival injection, pharyngeal hyperemia, flushing and edema of the face and neck, and palatal petechiae are often visible	Viral isolation Serology, with IgM or rise in IgG Detection of antigen in cells	Hepatosplenomegaly occurs in 50% of patients The mouth is dry and the breath has a foul odor. Patients appear depressed and somnolent Bradycardia is typically present, unless shock develops
6–10 days	Hemorrhagic manifestations appear in most patients, with a diffuse fine petechiae rash, ecchymoses, bruising, melena, hematemesis, epistaxis, bleeding gums, and jaundice. The petechiae typically begin on the back and spread to the entire body. Purpura and large hematomas may also develop on the skin		Hematuria, proteinuria, and azotemia are associated with severe infection and indicate a poor prognosis
11–16 days	Recovery begins, with slow improvement over 2 to 6 wk		

IgG, IgM, immunoglobulin G, M.

CRIMEAN-CONGO HEMORRHAGIC FEVER

Definition

The Crimean-Congo hemorrhagic fever (CCHF) virus is in the genus *Nairovirus*. A related *Nairovirus* causes Nairobi sheep disease. It causes severe disease, whether tick-borne or nosocomial, and occurs across a wide area of the eastern hemisphere.

History

From 1944 to 1945, over 200 agricultural workers in the Crimea developed a new syndrome of high fever, prostration, and occasional hemorrhagic disease with a 10% mortality rate. Ixodid (hard) ticks were implicated in the transmission [86], and the virus was isolated early in the disease. Antibodies to the virus were demonstrated in several of the patients. In the 1960s, a new virus was isolated from patients with severe febrile illness, in what is now the Republic of Congo [87]. These two viruses were later found to be identical, and the disease was termed Crimean-Congo hemorrhagic fever after both locations [88,89].

Incidence

CCHF occurs in eastern Europe, the Middle East, Africa, and Asia, where *Hyalomma* species are the predominant ticks. Most patients are animal husbandry workers or medical personnel. The severity of the disease described in Europe is not generally seen in Africa. Countries with reported disease include China, India, Pakistan, Afghanistan, Iran, Iraq, United Arab Emirates, Syria, Bulgaria, Hungary, Yugoslavia, South Africa, Zimbabwe, and countries of East and West Africa [90–96]. The virus or antibody has also been found in Egypt, France, and Greece [92,94].

Pathogenesis

Ticks demonstrate complex natural cycles that some arboviruses exploit. Three cycles occur: one involves generations of ticks; a second, large animals and adult ticks; and a third, small animals and immature ticks. A natural cycle limited to ticks occurs with transtadial and transovarial transmission [94]. Larval ticks feed on small mammals and become infected. As these infected larval ticks feed on noninfected animals, the cycle is completed as the virus is transmitted. In maturity, these ticks are infective for large animals, which serve as amplifying hosts. This mature tick–large animal cycle permits uninfected mature ticks and large animals to acquire and transmit the virus. Large ticks transmit the virus transovarially to offspring, constituting a third natural cycle.

Infected adult *Hyalomma marginatum* or *H. anatolicum* ticks transmit the virus to large animals and humans. *Boophilus* ticks and other *Hyalomma* species are involved in some cases. Infected birds offer the opportunity for wider virus distribution beyond the boundaries of any particular enzootic or epizootic area. Human disease occurs from tick feedings, from exposure to infected large animals or their milk or blood, or from exposure to infected humans.

Humans are accidental dead-end hosts of the virus and appear to be the only species that develops severe disease from infection. After inoculation, the virus is hematogenously spread throughout the body, resulting in a short incubation period. The exact pathogenesis of CCHF is not well understood. The virus is known to preferentially invade the capillary endothelial cells and reticuloendothelial cells [97]. During the acute disease process and viremia, thrombocytopenia and lymphopenia occur. Although the virus involves the liver, CCHF is not primarily hepatic. Hemorrhage develops in many organs and resulting blood loss may lead to death.

The mechanism of hemorrhage is associated with DIC, and hepatic necrosis with lymphocyte depletion and necrosis in the spleen is evident. White blood cell counts over 10,000/mm^3, platelets below 50,000/mm^3, transaminase values over 150 mg/dL, and coagulopathy within 5 days of onset predict a case fatality rate approaching 100% [98].



Figure 19.3 Ecchymoses and petechiae secondary to infection with Crimean-Congo hemorrhagic fever virus. (Reprinted from Samlaska CP. Viral Hemorrhagic Fevers. In: James WD ed. Military Dermatology. In: Textbook of Military Medicine. Washington, D.C., Dept. of the Army, Office of the Surgeon General, Borden Institute, 1997:201, 197–212. Photograph courtesy of David I.H. Simpson, Department of Microbiology and Immunology, The Queen's University of Belfast.)

Clinical Manifestations

Inapparent, subclinical infections with CCHF must be common, as some endemic areas have significant serological evidence of viral exposure [99,100] (Table 19.10). The fever associated with this infection is usually continuous, but may sometimes be remittent or biphasic. Most cases of disease have signs of hepatitis, with hepatomegaly, jaundice, and elevated transaminases. Bleeding may occur from multiple organs and, in decreasing order of frequency, may affect the nose, gums, buccal mucosa, stomach, uterus, intestines, and lungs. CNS involvement, with nuchal rigidity, agitation, meningeal symptoms, or coma, occurs in 10–25% of cases and is typically associated with a poor prognosis. Capillary leakage may lead to pulmonary edema, while significant blood loss results in hypovolemic shock. These findings also signify a poor prognosis. Mortality rates vary from 10 to 50%, and death usually occurs during the second week due to severe hemorrhage, hypovolemic shock, pulmonary edema, and renal failure [99] (Fig. 19.3).

Pathology

Petechiae, echymoses, and bruising are seen as manifestations of the bleeding diathesis. No specific skin lesions are described in CCHF. Hepatic and splenic necrosis is evident, as is lymphocyte depletion [98].

Laboratory Findings

Profound thrombocytopenia (as low as 20,000), leucopenia, elevated liver enzymes (transaminases), and abnormalities of hemostasis are expected. Leukocytosis with thrombocytopenia and hepatic dysfunction occur in patients with the poorest outcomes [98].

Diagnosis

The virus can be isolated from blood onto cell culture or suckling mice during the first weeks of the illness. Serological diagnosis

Table 19.11 Differential Diagnoses of Crimean-Congo Hemorrhagic Fever

Gastric ulcer: Epigastric pain, relieved by food, possibly transmitted to the back. Anemia, hematochezia, and the absence of fever characterize this *Helicobacter pylori* infection or anti-inflammatory medication reaction.	
Appendicitis: Diffuse pain migrates to the right lower quadrant with fever and leukocytosis leading to peritoneal signs and abscess or septic shock	
Stevens-Johnson syndrome: Various skin lesions with mucous membrane involvement (conjuctivitis, stomatitis, urethritis, proctitis) result from drug reactions	
Yellow fever	See Table 18-II.2
Rift Valley fever	
Other hemorrhagic fevers:	
Dengue	
Kyasanur Forest disease	
Omsk hemorrhagic fever	
Colorado tick fever	
Crimean-Congo hemorrhagic fever	
Hantavirus hemorrhagic fever	
Lassa fever and the South American hemorrhagic fevers	
Chikungunya fever	
Other arboviral infections:	See Table 16.2
Hantavirus pulmonary syndrome	
ONN	
Sindbis	
Mayaro	
Oropouche	
Sandfly fever	
Ebola/Marburg hemorrhagic fevers	See Table 19.4
Leptospirosis	

Table 19.12 Treatment of Crimean-Congo Hemorrhagic Fever

Symptom	Treatment
General	Immediate hospitalization and strict bed rest Ribavirin may be useful, and is given orally as a 2 g loading dose, followed by 1 g every 6 hr for 4 days, then 0.5 g every 6 hr for 6 days High titer immune convalescent plasma may also be of benefit
Fever	Antipyretics: Acetaminophen is a better choice than nonsteroidal anti-inflammatory drugs, since patients often have profound thrombocytopenia and hemorrhage
Shock	Intravenous infusions of crystalloid and colloid. Avoid overhydrating the patient since this illness may be associated with a leaky capillary syndrome. Pulmonary edema may also result from fluid overload
Anemia and acute blood loss	Transfusion of red blood cells or whole blood
DIC	Fresh frozen plasma infusion
Renal failure	Fluid restriction, diuretic therapy, electrolyte management, and dialysis, if necessary

DIC, disseminated intravascular coagulation.

Table 19.13 Clinical Manifestations of Rift Valley Fever

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–6 days	Sudden onset of biphasic fever, chills, myalgias, arthralgias, and headache. Some patients may have nausea or vomiting, abdominal discomfort, photophobia, and retro-orbital pain. The face is flushed, the tongue is furred, and the conjunctivae are injected. The liver may be enlarged and tender. Jaundice may be evident in skin and conjunctiva	Viral isolation Serology (IgM or increase in IgG) Detection of viral RNA in tissue or acute sera	Viremia lasts during the acute clinical illness Less than 5% of cases are serious or fatal, with possible complications of hemorrhage and liver necrosis, retinitis and visual impairment, or meningoencephalitis Hemorrhagic manifestations of mucous membranes and skin include petechiae, ecchymoses, and bruising
7–11 days	Full resolution of symptoms in most patients		

IgG, IgM, immunoglobulin G, M.

by ELISA, HI, IFA, immunodiffusion or plaque reduction neutralization test of paired sera is useful, as is IgM antibody ELISA. In nonfatal cases, IgG and IgM antibodies become demonstrable 7–10 days after symptoms begin [101]. Antigen can also be detected in inoculated cells. This is best performed with immunofluorescent antibody techniques (Table 19.11).

Treatment and Prevention

The treatment of CCHF generally involves supportive therapy (Table 19.12). Intravenous ribavirin and high titer immune convalescent plasma may have a role in the treatment of CCHF [102]. The efficacy of these treatments depends on the rapid institution of therapy early in the course of disease. For prevention of disease, protection against ticks is beneficial and low cost. Use of universal precautions for exposure to bodily fluids limits nosocomial spread. A vaccine, prepared from inactivated mouse-brain culture, has been used in Bulgaria and Russia [103]. However, no data on the efficacy of this vaccine are available.

CCHF is occasionally a severe infection with the potential for a major occupational and nosocomial risk, if not a major risk for travelers. Clinical hemorrhagic fever is complicated by extensive hepatic damage, similar to yellow fever and Rift Valley fever (RVF). Though the tick exposure mechanism suggests a rural habitat, nosocomial infection may be more suburban.

RIFT VALLEY FEVER

Definition

RVF virus is in the genus *Phlebovirus* of the sandfly fever group. RVF virus causes epizootic disease in sub-Saharan Africa in the wettest of rainy seasons. It affects domestic animals, sheep most severely, but also cattle and goats. Among humans, slaughterhouse workers, ranchers, and other domestic animal handlers are most commonly affected [104,105].

History

RVF was first isolated in 1930 during an investigation of an epidemic among ewes and lambs on a farm in the Rift Valley in Africa [104,105]. Humans in the endemic area were found to have a mild influenza-like febrile illness, with 1–2% having hemorrhagic disease. Other patients developed encephalitis or retinitis. By protecting parts of herds from mosquitoes while other parts were not protected, the role of mosquito vectors was first demonstrated. In 1944, the virus was isolated from wild-caught mosquitoes found in Uganda. While mild human disease was mainly recognized in the 1970s, the first cases of fatal infections were reported in South Africa in 1975 [105]. Although most cases occur in sub-Saharan Africa, epidemics of the disease have been reported twice in Egypt as well as in Madagascar [107–110].

Incidence

Epizootic disease occurs in sub-Saharan Africa during periods of excessive rainfall and affects sheep, cattle, and goats, in descending order. Young animals die, pregnancies are aborted, and ewes are lost perinatally. During an epidemic, animal infections occur first, followed by disease in humans. The economic impact of this agent is significant. In the Kenyan epidemic of 1997, 70% of animals died, though not necessarily all from RVF. Several hundred human deaths occurred in an estimated 18,000 infections in Egypt in 1977. The case fatality rate in hospitalized Egyptian patients was 14% [107]. During the 1997–1998 RVF epidemic in East Africa, approximately 89,000 cases and 200 deaths were reported.

Pathogenesis

Epizootic diseases are associated with a variety of mosquitoes and, therefore, with a variety of habitats. Excessive rainfall is a constant feature of outbreaks [107,111]. The most common vectors include *Culex pipiens* in Egypt, *C. theileri* in South Africa, and *Aedes* species in East Africa [111–113]. In laboratory experiments, malaria parasites present in the mosquito enhance the transmission of RVF [114]. Mosquito viral transmission may be more complex than originally thought. This phenomenon may apply to other mosquito vectors and arboviral diseases in malaria endemic areas.

Close contact with infected animals increases risk for human infection. This suggests that the mosquito vector is less important than animal contact [104,105]. After dermal injection of the virus during feeding, local nodes are infected first and then the liver. The virus replicates in the endoplasmic reticulum of the hepatocytes. Hepatic necrosis occurs and virions are released. Encephalitis or retinitis occurs after an interval of time, which suggests an immunologic role in pathogenesis.

Clinical Manifestations

Inapparent or mild disease is frequent, and most clinical cases are uncomplicated (Table 19.13). This clinical pattern is similar to phlebotomus fever and other arboviral fevers. Bradycardia is often evident on physical examination. Many patients become delir-

Table 19.14 Differential Diagnoses of Rift Valley Fever

Yellow fever	See Table 18-II.2
Crimean-Congo hemorrhagic fever	
Lassa fever	
Other encephalitides:	
Colorado tick fever	
Eastern equine encephalitis	See Table 16.2
Western equine encephalitis	
Venezuelan equine encephalitis	
West Nile fever	
California encephalitis	
Japanese encephalitis	
St. Louis encephalitis	
Tick-borne encephalitis	
Powassan encephalitis	
Other hemorrhagic fevers:	See Table 18-II.2
Kyasanur Forest disease	
Omsk hemorrhagic fever	
Hantavirus hemorrhagic fevers	
Chikungunya fever	
Ebola and Marburg hemorrhagic fevers	See Table 19.4
Dengue	

ious, sometimes with hallucinations. Hemorrhagic fever, similar to yellow fever, develops in 1–2% of patients with a case fatality rate of 15–50%. Most deaths occur during the second week, due to hemorrhagic complications with hepatic involvement. DIC seems central to the hemorrhage, compounded by hepatic disease [115]. Deaths may be due to hepatic failure from necrosis of the liver. Less than 1% of patients develop encephalitis, though much later in the course of the infection. This complication is clinically similar to Japanese encephalitis or other viral encephalitis, and patients typically develop intense headache, confusion, and stupor. Few patients die from the encephalitis, and most patients recover completely without permanent sequelae. In less than 1% of patients, a retinal vasculitis may occur quite late in the disease. This complication usually develops 1–3 weeks after the onset of the fever. Retinal edema, hemorrhage, and infarction may lead to permanent visual impairment. However, most patients gradually regain normal vision.

Pathology

Limited pathological studies have been performed on humans. Hepatocellular necrosis is evident, since the virus is cytocidal. Hemorrhage, interstitial pneumonitis, and myocardial fiber degeneration may also be present. The CNS and ophthalmologic manifestations are inflammatory, suggesting an immunological mechanism or an immunological failure [116].

Laboratory Findings

Leucopenia, thrombocytopenia, abnormal liver function tests, and indicators of DIC are seen in cases with hemorrhagic fever. If meningoencephalitis develops, the CSF findings resemble other viral encephalitides, with pleocytosis (particularly lymphocytes), a normal glucose, and a slightly increased protein level.

Hemorrhagic manifestations can simulate other hemorrhagic fevers, but the hepatic injury is uncommon except in yellow fever and CCHF. Ebola, Lassa, and Marburg viruses are considerations.

Table 19.15 Treatment of Rift Valley Fever

Symptom	Treatment
Fever	Antipyretics. Avoid nonsteroidal antiinflammatory drugs, which may impair platelet function since thrombocytopenia is already present with this disease
Arthralgias and myalgias	Analgesics such as acetaminophen
Hemorrhagic diathesis	Transfusion of fresh frozen plasma and platelets. Avoid hepatotoxic drugs that could potentiate the condition

Other infectious encephalitides can mimic the encephalitis, for example, herpes simplex. Retinitis is uncommon and, in the habitat of RVF epizootic disease, should be suspected and identified. If the travel history is incomplete or includes multiple geographic regions, there may be failure to recognize the importance of coexisting RVF epizootic disease or excessive rainfall in a sub-Saharan rainy season biotype.

Diagnosis

Specific viral diagnosis may be difficult in the nonspecific phase. Virus isolation is more useful for vector surveillance than for disease detection. Serological methods (HI, CF, IgM ELISA) document human and animal disease and viral exposure. Either acute sera for IgM or paired sera (acute and convalescent) for IgG, showing a fourfold increase, can be used. IgM antibodies can also be detected in the spinal fluid in patients with encephalitis. PCR is available for detection of viral RNA in acute sera or tissue [116] (Table 19.14).

Treatment and Prevention

The treatment for RVF centers on palliative care (Table 19.15). Supportive therapy for DIC and circulatory integrity is pivotal. In animal studies, treatment with interferon [117], ribavirin, and passive antibodies have demonstrated efficacy, but these agents have yet to be tested in humans. Complications, such as retinitis and encephalitis, occur after antibody development, so antiviral therapy or immune sera would not be advantageous.

Prophylaxis for RVF includes protective gear, such as gloves and masks, in high-risk individuals to prevent contact with infected animal tissue. Unfortunately, in many poor areas of Africa, animals are kept in close proximity to family quarters, and sick or dying animals are often killed to salvage the meat for food. Animal immunization is available with live-attenuated and killed virus vaccines. For humans with high risk of exposure, a formalin-inactivated vaccine produced in cell cultures has been developed [118]. However, this vaccine has not been licensed and is not commercially available.

While RVF primarily affects sheep and cattle in endemic areas of Africa, sporadic epidemics in humans can occur. Effective animal vaccines are available and offer the potential for control. Human vaccines for animal handlers would limit disease in known high-risk personnel, but not travelers or out-of-area animal handlers who might handle infected imported animals. Laboratory workers are protected by appropriate precautions and vaccination [107].

Conclusion

Bunyaviruses are vector-borne RNA viruses. While hantaviruses are transmitted through contact with deer mice feces, most bunyavirus transmission occurs via an arthropod vector. Hantaviruses can cause HFRS or HPS. California/LAC encephalitis viruses produce CNS manifestations. CCHF and RVF can cause hemorrhagic complications.

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20 Arenaviruses

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Definition

The Arenaviridae are a family of viruses whose members are generally associated with rodent-transmitted disease in humans. Each virus is usually associated with a particular rodent host species in which it is maintained. Arenavirus infections are relatively common in humans in some areas of the world and can cause severe illnesses.

The family Arenaviridae consists of a unique genus (Arenavirus) that currently contains 24 recognized viral species [1,2], of which five can cause viral hemorrhagic fevers, with a case fatality rate of about 20% (Table 20.1).

The virus particles are spherical and have an average diameter of 110–130 nm. All are enveloped in a lipid membrane. Viewed in cross section, they show grainy particles that are ribosomes acquired from their host cells. It is this characteristic that gave them their name, derived from the Latin "arena," which means "sandy." Their genome is composed of single-stranded, bi-segmented RNA, and while their replication strategy is not completely understood, we know that new viral particles, i.e., virions, are created by budding from the surface of their hosts' cells [2–4].

According to their antigenic properties, the arenaviruses are classified into two groups: the New World or Tacaribe complex, which includes viruses indigenous to the Americas, and the Old World or Lassa/lymphocytic choriomeningitis (LCM) complex, which includes viruses indigenous to Africa and the ubiquitous LCM virus (LCMV) that is associated with *Mus musculus* (Fig. 20.1).

These viruses are zoonotic, meaning that, in nature, they are found in animals. Each virus is associated with either one species or a few closely related rodents, which constitute the virus' natural reservoir. Tacaribe complex viruses are generally associated with the New World rats and mice belonging to the family Cricetidae, subfamily *Sigmodontinae* (Figures 2 and 3). The Lassa/LCM complex viruses are associated with the Old World rats and mice (family Muridae, subfamily *Murinae*). Taken together, these types of rodents are located across the greater proportion of the Earth's land mass, including Europe, Asia, Africa, and the Americas. One notable exception is Tacaribe virus, found in Trinidad, which was isolated from a bat [4,5].

History

The first recognized arenavirus, LCMV, was isolated in 1933 during a study of an epidemic of St. Louis encephalitis. Although not the cause of the outbreak, LCMV was found to be a cause of aseptic (nonbacterial) meningitis [6].

Lassa fever (LF) was described in 1969 when two missionary nurses died in Nigeria. The cause of the illness was found to be Lassa virus, named after the town in Nigeria where the first cases originated [2,7,8].

The virus was isolated and found to be an arenavirus closely related to LCMV [6,8]. Epidemics have since occurred in Sierra Leone and other countries of West Africa.

Four other related arenaviruses have been found to cause hemorrhagic fever, although they are endemic in South America rather than Africa. All South American arenaviruses have been identified during the second half of the 20th century. However, there is a hypothesis that arenaviruses are quite ancient and have existed in nature for years as silent zoonotic foci. It is believed that some outbreaks that caused catastrophic demographic collapse in Mexican populations during the 16th century may have been due to arenaviruses [8].

Argentine hemorrhagic fever (AHF) was clinically described in 1955, followed by isolation of the etiologic Junin virus in 1958 [9]. Initially, this virus caused AHF in a limited agricultural area of the pampas in Argentina, but the region at risk is progressively expanding [9]. Subsequently, Tacaribe virus was found in 1956, although it could not be associated with any disease until now [10]. On average, every 1–3 years, new arenaviruses have been discovered. In 1959, an illness similar to AHF was recognized in eastern Bolivia, in the remote savannas of the Beni province, but only in 1963 was the causative agent (Machupo virus) isolated [11]. A major epidemic of Bolivian hemorrhagic fever (BHF) occurred from 1962 to 1964 in San Joaquin, Bolivia, as the rodent vector population soared and inhabited the village housing [11]. The next member of the virus family to be associated with an outbreak of human illness was identified in Venezuela in 1991 and named Guanarito, responsible for more than 200 cases of Venezuelan hemorrhagic fever (VHF) [12]. In 1994, another virus was added to this family. Sabia virus was isolated from a fatal case of hemorrhagic fever in Brazil [13,14]. Two additional occupational cases reported in laboratory workers were associated with this virus, but its natural reservoir remains unknown [14–16].

Incidence

The LF-specific rodent reservoir is restricted to endemic bush areas. This infection only arises in persons who live or have traveled to such areas or have had exposure to infected individuals. LF and BHF are generally contracted in or close to homesteads, and they affect both sexes and all ages. Machupo virus (BHF) has been clearly associated with nosocomial transmission as well [11,17]. Guanarito (VHF) is typically acquired in gardens near homes and typically affects only adults. Junin (AHF) is normally contracted during the harvest of maize, and generally affects adult male agricultural workers [4,18]. However, since the development of a live attenuated vaccine in the late 1980s, the epidemiology of AHF has been dramatically modified [1,2].

LF estimates range from 100,000 to 300,000 cases annually with 5000 deaths. Unfortunately, such estimates are crude, because surveillance for cases of the disease is not uniformly performed [7]. Since the first description of AHF, Junin virus is estimated to have caused approximately 30,000 symptomatic cases [9]. In Bolivia, Machupo virus was involved in a series of outbreaks that affected

Table 20.1 Arenaviruses: Clinical Presentation, Main Reservoirs and Geographic Distribution [1–4]

Virus	Human disease	Main reservoir	Geographic distribution
Old World arenavirus or Lassa/LCM complex			
LCM	Febrile syndrome Aseptic meningitis	Mus musculus	Europe Americas
Lassa	Lassa fever	Mastomys sp.	Occidental Africa
Mopeia	–	Mastomys sp.	South Africa
Mobala	–	Praomys sp.	Central Africa
Ippy	–	Arvicanthis sp.	Central Africa
Kodoko	–	Mus (Nannomys) minutoides	West Africa
New World arenavirus or Tacaribe complex			
Allpaahuayo	–	Oecomys sp.	Peru
Amapari	–	Neacomys guianae	Brazil
Bear Canion	–	Unknown	–
Cupixi	–	Unknown	Brazil
Guanarito	Venezuelan hemorrhagic fever	Zygodontomys brevicauda	Venezuela
Flexal	–	Oecomys bicolor	Brazil
Junin	Argentine hemorrhagic fever	Calomys musculinus	Argentina
Latino	–	Calomys callosus	Bolivia
Machupo	Bolivian hemorrhagic fever	Calomys callosus	Bolivia
Oliveros	–	Necromys obscurus	Argentina
Pampa	–	Necromys amoenus	Argentina
Parana	–	Sooretamys angouya	Paraguay
Pichinde	–	Nephelomys albigularis	Colombia
Pirital	–	Sigmodon alstoni	Venezuela
Sabiá	Brazilian hemorrhagic fever	Unknown	Brazil
Tacaribe	–	Artibeus sp. (bat)	Trinidad
Tamiami	–	Sigmodon alstoni	USA
Whitewater Arroyo	–	Neotoma albigula	USA
Rio Cacarana	–	Unknown	–

Adapted from 1 and 2.

more than 1000 patients in the 1960s, with 180 deaths [11]. After that, an effective rodent control was established and was responsible for the lack of reported cases. Then, in the 1990s, a new series of 19 cases was reported [1]. Until 1998, approximately 200 cases of VHF were confirmed [5]. In 2002, when a new outbreak was detected, 18 additional cases with two deaths were reported [1,2].

The mortality rates for these arenavirus hemorrhagic infections are similar, ranging from 15 to 20% in the absence of specific therapy. However, overall, only about 1% of infections with Lassa virus results in death [7]. The death rates are particularly high for women in the third trimester of pregnancy, and for fetuses, about 95% of which die in the uterus of infected pregnant mothers. Case fatality ratios for hospitalized patients with LF approximate 16%. In endemic areas of Sierra Leone, 10–16% of hospitalized patients have LF, indicating the serious impact of the disease on the population of this region [7]. While LF is mild or has no observable symptoms in about 80% of people infected with the virus, the remaining 20% have a severe multisystem disease. The seroprevalence rates for the population in endemic areas ranges from 35 to 50% [7].

LF occurs throughout the year, but most hospitalizations occur during the dry season from February to May [7]. AHF is a typical seasonal disease, occurring in the harvest season from April to June [9]. The frequency of BHF corresponds to the end of the rainy season from March to July in a tropical savannah biotype [11].

Pathogenesis

The rodent hosts of arenaviruses are chronically infected with the viruses; however, the viruses do not appear to cause obvious illness in them, which is crucial for the long-term persistence of arenavirus in nature. Human infection occurs when: (1) an individual inhales infectious particles present in aerosolized excretions and secretions of infected rodents; (2) an individual comes into contact with materials contaminated with the excretions of an infected rodent, such as ingestion of contaminated food, or by direct contact of abraded or broken skin with rodent excrement; (3) broken skin or mucous membranes come in contact with rodent body fluids. The types of incidental contact depend on the habits of both humans and rodents. These events happen more often when workers are hunting rodents or preparing them for food. LF is also occasionally transmitted from person-to-person through close contact. The nosocomial infection occurs through human secretions from patients in or out of hospitals [20]. Transmission through sexual intercourse or nursing an infant has also been described. By contrast, the South American hemorrhagic fevers are rarely transmitted from person to person [9–12] (Fig. 20.1).

Knowledge of the multiplication of arenaviruses is fragmentary. Most of what is known comes from studies with LCMV, which replicates in a wide variety of cell types [6]. Although the virus receptor has not been identified, it must be highly conserved and widely distributed. Transcription of the genome and replication are confined to the cytoplasm. The small RNA in the virion encodes in the negative sense a nucleoprotein, and in the positive or message sense a precursor glycoprotein (GP), which is cleaved into two virion GP components (GP1 and GP2). The large RNA in the virion encodes in the negative sense a zinc-binding protein

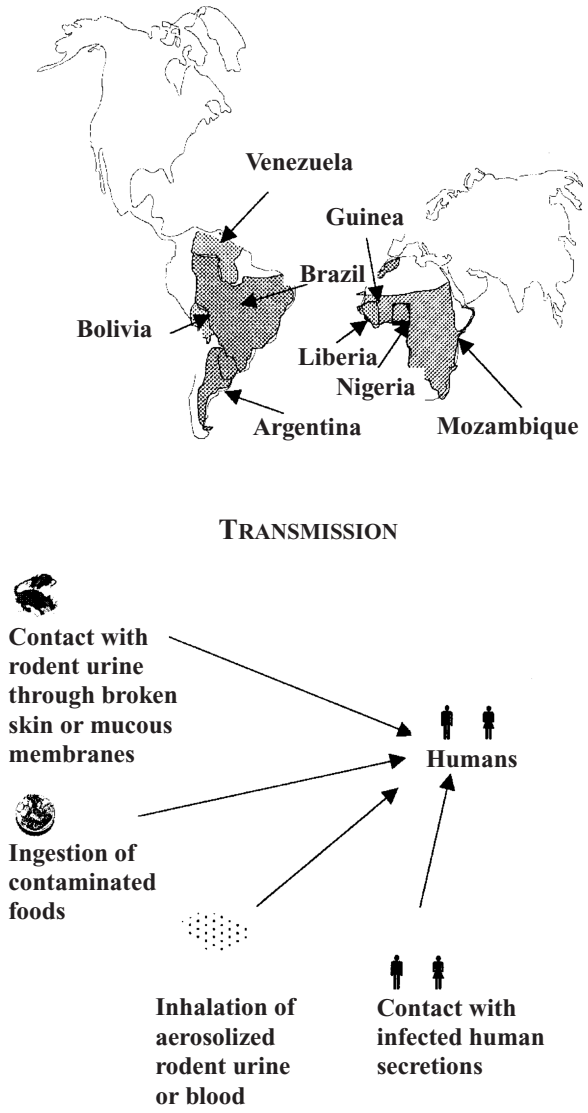


Figure 20.1 Incidence and transmission of Lassa Fever and South American hemorrhagic fevers

that binds to the ribonucleoprotein complex. The virus buds from the plasma membrane [6].

Clinical Manifestations

LF virus infection usually has mild or nonspecific symptoms or is asymptomatic. Serologic evidence of prior infection is common in endemic areas. Patients hospitalized with other diagnoses frequently prove to have LF [20]. Conversely, infection with the South American viruses generally results in symptomatic illness. Unlike most hemorrhagic fevers, the onset of LF is insidious with a progressive course (Table 20.2).

Signs and symptoms of LF typically occur 1–3 weeks after the patient comes into contact with the virus. These include fever, retrosternal pain, sore throat, back pain, cough, abdominal pain, vomiting, diarrhea, conjunctivitis, facial swelling, proteinuria, and mucosal bleeding. Neurological problems have also been described, including hearing loss, tremors, and encephalitis [2,3,19,21].

The fever produces moist skin until shock ensues. Pulse and respiratory rates are elevated with fever, but blood pressure is low. Patients appear anxious and acutely ill. The abdomen is tender, but with active bowel sounds and no localizing signs [1,2]. There is no rash, but pharyngitis and conjunctivitis are evident in some patients. More than two thirds of patients have pharyngitis, sometimes with pharyngeal and tonsillar exudates, edema, swelling, and diffuse inflammation. The conjunctival hemorrhage is less common and is a poor prognostic sign [3]. The pharyngeal pain may lead to expectorated saliva due to dysphagia. Other respiratory symptoms are not prominent.

Hemorrhage is not frequent with LF (15–20% of cases), and develops only in the most severe cases. It usually occurs from the gums or nose, gastrointestinal (GI) or genitourinary (GU) tracts. While hemorrhage is minor and does not typically cause complications, capillary leak syndrome may become severe and lead to hypovolemic shock. Capillary leak syndrome is the hallmark of LF and the South American hemorrhagic fevers [2,4,7,9–11]. It may lead to facial and nuchal edema without peripheral edema, as well as pleural and pericardial rubs and effusions later in the course of disease. Hair loss and loss of coordination may occur in convalescence [3]. Very young children may develop a "swollen baby syndrome," which consists of widespread edema (anasarca), abdominal distention, and spontaneous bleeding [21]. The most common complication of LF is deafness [7]. Various degrees of deafness occur in approximately one third of cases, and in many cases, hearing loss is permanent [7]. Deafness with tinnitus, confusion, tremors, seizures, encephalopathy, and neurologic findings are common. As far as is known, severity of the disease does not affect this complication: deafness may develop in mild as well as in severe cases. Besides neurosensory hearing loss, complications and sequelae include uveitis, orchitis, effusions of pleura or pericardia, and ascites. Generally, tremors precede death in fatal cases [7,21].

South American hemorrhagic fevers have a very similar clinical picture. After a mean incubation period of 7–14 days, there is a gradual onset of fever and malaise. Secondarily, other nonspecific symptoms like myalgia, back pain, headache, and dizziness appear. In this phase, hyperesthesia of skin is also common. Subsequently, the disease evolves with important neurologic and hemorrhagic manifestations, which occur combined or separately [9–13].

Generally, around the fourth day of illness, petechiae of skin and bleeding of the gums, vagina, or GI tract appear and herald the hypovolemic shock [1,9,10] (Fig. 20.2). AHF and BHF have a similar insidious onset, but hemorrhage is more common, particularly of the skin [9,11]. In AHF, micro-vesicular lesions can also be seen on the palate along with enlargement of the gums [3,11]. Patients with severe cases of VHF often show signs of

Table 20.2 Clinical Manifestations of Lassa Fever

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
8–14 days	Insidious onset of progressive fever, weakness, and malaise	Viral isolation Serology, with IgM or paired sera for IgG Detection of viral antigens	
Slow development over the next several days	Development of generalized myalgias, arthralgias, lower back pain, and a nonproductive cough. Many patients complain of a headache, usually frontal, sore throat, retrosternal chest pain, vomiting, diarrhea, and abdominal pain		Hyperesthesia of the skin is common with AHF and BHF
12–18 days	In some patients, petechiae develop on the skin (rare in LF) and mild hemorrhage occurs from the gums, gastrointestinal tract and vagina. These signs herald the onset of hypovolemic shock. Capillary leak syndrome leads to facial edema and effusions. Neurological manifestations may occur in some patients		Hemorrhagic and neurological manifestations are more common in AHF and BHF
15–26 days	Some patients develop rapid clinical deterioration, with possible death due to hypovolemic shock or neurological sequelae. The majority of patients improve and recover completely		Patients who survive severe disease often have a slow recovery and may have significant generalized muscle wasting and limb contractures

AHF, Argentine hemorrhagic fever; BHF, Bolivian hemorrhagic fever; LF, Lassa fever.

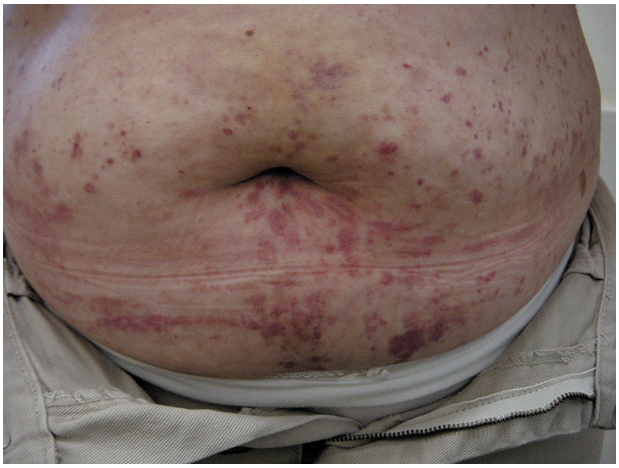


Figure 20.2 Petechiae and purpura associated with Sabia infection (Brazilian hemorrhagic fever).

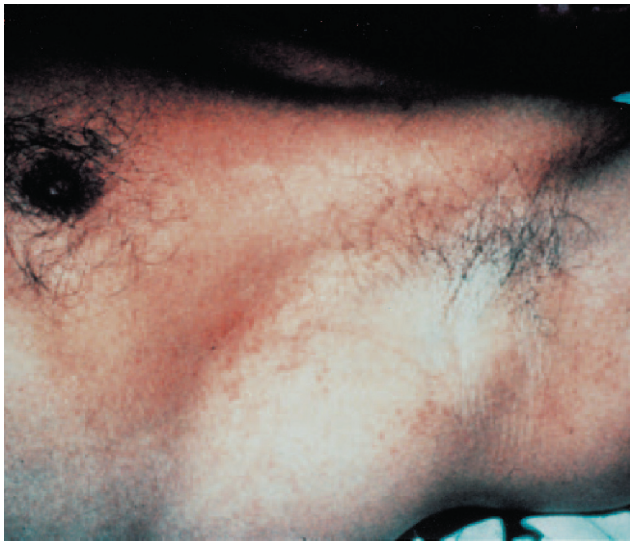


Figure 20.3 Macular eruption in a patient with Argentine hemorrhagic fever (Junin virus). (Reprinted from Samlaska CP. Viral Hemorrhagic Fevers. In: James WD, ed. Military Dermatology. In: Textbook of Military Medicine. Washington, D.C., Dept. of the Army, Office of the Surgeon General, Borden Institute, 1997:201, 197–212. Photograph courtesy of David I.H. Simpson, Department of Microbiology and Immunology, The Queen's University of Belfast.)

bleeding under the skin, in internal organs, or from body orifices like the mouth, eyes, or ears. Although they may bleed from many sites around the body, patients rarely die because of blood loss. Petechiae are common; there is hyperemia of the face and trunk and a macular enanthem [3] (Fig. 20.3).

In South American hemorrhagic fevers, neurologic findings are similar to those of LF, but are more commonly observed. Manifestations such as delirium, tremors, and inability to swallow or to speak may develop and can progress to convulsions, coma, and death, even in the absence of significant capillary leak or hemorrhagic signs [1,2].

Additionally, some types of VHF are associated with renal failure. A rising hematocrit and proteinuria precede and predict clinical crises; these may be lethal without appropriate supportive care. Fatal outcomes occur in patients with high levels of circulating virus or with conjunctival hemorrhage, hemorrhage with pharyngitis, or an elevated serum aspartate transaminase. Usually, with the progression of the disease, there is an increase in vascular permeability that can evolve to hypovolemic shock and death [19,21]. Pregnancy carries a 20% fatality rate and an 80% late abortion rate. Pregnancy termination improves maternal outcome. In those patients with severe disease who present an

unfavorable outcome, death usually occurs 7–12 days after the onset of illness, however, those who survive generally make a complete recovery [1,2].

Pathology

The clinical severity is strikingly out of proportion to the pathology. Focal hepatic necrosis is mild to moderate in severe LF. Otherwise, LF and the South American hemorrhagic fevers do not cause parenchymal histological damage. CNS pathology lacks inflammation, showing only edema. Interstitial edema reflects the capillary leak. Minor hemorrhagic manifestations are evident, but these are less striking than that seen in other arboviral hemorrhagic fevers [22].

Complete autopsies have not been performed on patients with LF, however, autopsies performed on patients with AHF show a lack of deposited immunoglobulin (Ig) and complement component C3 in the kidneys and small blood vessels. Mediators released from infected cells have a potential role in the pathogenesis of dysfunction of some target organs. Although LCMV can produce severe human disease, characterized by prominent neurologic manifestations, pathologic lesions have not been studied extensively. However, in the mouse model, the immune response against LCMV (specifically the T cells) is central to the development of fatal neurologic disease [6]. Furthermore, mice infected with a lethal dose of this virus can invariably be saved by treatment with antibody to interferon αß, raising the possibility that endogenous interferon αß enhances the immunopathology.

Laboratory Findings

The normal white blood cell count in LF shows a relative lymphopenia, and thrombocytopenia is evident. Neutrophilia appears late in severe cases. The hematocrit is elevated with intravascular volume depletion from capillary leakage. Blood urea nitrogen rises with dehydration and may be moderately elevated. Proteinuria is common and occurs in two thirds of patients. The South American hemorrhagic fevers typically have leukopenia (<4000/mm^3) and thrombocytopenia (<100,000/mm^3). As in LF, proteinuria is common. Microscopic hematuria may also be present.

Diagnosis

The wide spectrum of manifestations and the insidious onset of these infections make the diagnosis difficult. Pharyngitis, proteinuria, and retrosternal chest pain in endemic areas are a specific triad for these arenaviral infections. Although this triad is present in 80% of patients with LF in endemic areas, it may only detect about 51% of cases [1,2].

The LF is most often diagnosed using enzyme-linked immunosorbent serologic assays (ELISA), which detect IgM and IgG antibodies as well as Lassa antigen [23]. Half of all patients have measurable antibodies by day 5 of the illness, and most patients have antibodies by day 14. Conversely, antibodies with the South American hemorrhagic fevers do not appear until the third week of illness, which is 1–2 weeks later than that for LF [23]. The level of neutralizing antibody rises with the declining viremia, but viremia in Lassa persists for some time after the appearance of specific antibody (up to 3–4 weeks with severe disease).

The virus may be detected by culture in 7–10 days, or by reverse transcription-polymerase chain reaction (RT-PCR), however, these methods are primarily a research tool. In South American hemorrhagic fevers, virus can be isolated from 2 to 14 days after the onset of symptoms [23].

Immunohistochemistry can also be performed on tissue specimens, being useful to make a post-mortem diagnosis (Table 20.3).

Table 20.3 Differential Diagnoses of Lassa Fever and the South American Hemorrhagic Fevers

Influenza: The coryza, cough, myalgia, and fever without rash, jaundice, frequent hemorrhagic complications or encephalitis lead to the suspicion of influenza. Secondary bacterial complications, pneumonia and meningitis, compound the differential diagnosis and require specific antibiotic therapy.	
Rocky Mountain spotted fever	} See Table 16.2
Typhoid fever	} See Table 18-II.2
Malaria	
Rift Valley fever	
Other hemorrhagic fevers:	
Kyasanur Forest disease	
Omsk hemorrhagic fever	
Colorado tick fever	
Crimean-Congo hemorrhagic fever	
Hantavirus hemorrhagic fever	
Chikungunya fever	
Hemolytic uremic syndrome	} See Table 19.4
Leptospirosis	
Dengue	
Ebola/Marburg hemorrhagic fevers	
West Nile fever	} See Table 16.2

Treatment

Ribavirin initiated in the first 6 days of LF symptoms (for patients with AST greater than or equal to 150 IU/l) decreased mortality from 55 to 5% [24,25]. If initiated 7 or more days after the onset of fever, the drug is not as effective, but is still recommended [24]. Limited studies have shown that ribavirin may also be effective in AHF and BHF, but further clinical trials are needed [24,25]. In 1994, the laboratory-acquired Sabiá virus infection was treated with ribavirin for 3 days and the patient recovered without any sequelae [16]. Although there is little data concerning ribavirin's efficacy, in light of its broad spectrum of action against distinct arenaviruses, it is probable that most, if not all, of these viruses are susceptible to this drug [1,2].

Protocols for ribavirin use were defined for Lassa virus infections. For therapeutic use, the drug should be given intravenously as follows: a loading dose of 30 mg/kg, then 16 mg/kg every 6 hours for 4 days, then 8 mg/kg every 8 hours for 6 days. For prophylactic use, ribavirin can be given orally, in a dose of 500 mg every 6 hours for 7 days [1,2,10,24]. Currently, ribavirin is contraindicated in pregnancy, although it may be warranted if the mother's life is at risk [25].

Immune therapy is another choice for the treatment of arenavirus-associated hemorrhagic fevers. Administration of human convalescent plasma reduces the mortality of AHF from 16% to less than 1% if initiated within the first 7 days of clinical illness [1,2]. This treatment is associated with an unusual late neurological syndrome in 10% of survivors, although usually benign. Convalescent plasma has been used for the treatment of BHF as well, although studies have not proven its efficacy. Plasma therapy for LF has had equivocal results, likely due to the comparatively lower quantity of virus-neutralizing antibodies in convalescent patients with LF [2].

Table 20.4 Treatment of Lassa Fever and South American Hemorrhagic Fevers

Symptom	Treatment
General	Ribavirin administered intravenously as a 2 g loading dose, followed by 1 g every 6 hr for 4 days, then 0.5 g every 8 hr for 6 days Human convalescent plasma in some cases (see text)
Fever	Analgesics. Avoid aspirin and nonsteroidal anti-inflammatory drugs, which can interfere with platelet function since thrombocytopenia is already present with these infections
Dehydration	Adequate fluid replacement and management of electrolyte and acid-base balances
Hypotension and shock	Intravenous fluid replacement. Renal function, pulmonary status, and blood pressure should be monitored closely to avoid overhydration, since excess fluids may exacerbate laryngeal or pulmonary edema, and capillary leak syndrome may already be present
Neurologic deterioration	Attention to cerebral edema and seizure control without compromising cerebral perfusion and ventilation
Concurrent pregnancy	Elective termination of pregnancy by uterine evacuation, particularly in the third trimester, substantially improves maternal survival

While ribavirin and human plasma therapy are available options for the treatment of these infections, supportive care of symptoms and complications is critical. Without specific treatment, arenavirus-associated hemorrhagic fevers present a case-fatality ratio of approximately 20–30% [17] (Table 20.4).

During the care of these patients, barrier nursing methods should be strictly practiced to prevent nosocomial spread of the viruses.

With the exception of AHF, for which vaccines have been developed, no vaccines exist that can protect against these diseases. Therefore, prevention efforts must concentrate on avoiding contact with host species. If prevention methods fail and a case of hemorrhagic fever occurs, efforts should focus on preventing further transmission from person to person.

Conclusion

Arenavirus hemorrhagic infections range from minimally or mildly symptomatic to severe and lethal. The epidemiology is defined by complex interactions with the rodent hosts during pest control of crops, encroachment into the rodent habitat, or securing food. The triad of pharyngitis, proteinuria, and retrosternal pain is useful in identification of severe disease, but it does not identify all cases. The less frequent but more severe manifestations result in morbidity and mortality in endemic areas, particularly in late pregnancy. Rodent control and vaccines would provide potential solutions, except for the rural nature of arenaviral hemorrhagic disease. Scientists and researchers are challenged with developing containment, treatment, and vaccine strategies for these diseases. Another goal is to develop immunologic and molecular tools for more rapid disease diagnosis, and to study how the viruses are transmitted and exactly how the disease affects the body (pathogenesis). A third goal is to understand the ecology of these viruses and their hosts in order to offer preventive public health advice for avoiding infection.

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21 Enteroviruses

Kelly B Conner and Stephen K Tyring

Introduction

Enteroviruses, consisting of coxsackieviruses, echoviruses, polioviruses, and newer enteroviruses are among the most common viruses affecting humans worldwide. While the vast majority of enteroviral infections in man result in mild or asymptomatic clinical syndromes, enteroviruses may also result in serious, potentially fatal conditions, such as aseptic meningitis, encephalitis, paralysis, myocarditis, and enteroviral sepsis. Although polioviruses were of great historical importance worldwide, this chapter will focus on the mucocutaneous manifestations of the nonpolio enteroviruses. More than 30 enteroviruses have been associated with rashes and are very common causes of exanthematous disease in childhood [1]. The cutaneous and mucosal manifestations of enterovirus infections can be bewildering to even the most experienced clinician because many are not specific enough to allow differentiation on clinical grounds alone. One clinical syndrome may be produced by several different enteroviruses, while seemingly different patterns of illness can be traced to a solitary enteroviral cause.

The enteroviruses comprise a large group of distinct serotypes of viruses belonging to the viral family Picornaviridae ("pico"=small, "rna"=ribonucleic acid) and the genus *Enterovirus*. Within the genus, there are three types of polioviruses, 23 group A coxsackieviruses (A1–22, 24), 6 group B coxsackieviruses (1–6), and 32 echoviruses (e.g. types 1–7, 9, 11, 27, and 29–34). This traditional system of classifying the enterovirus subtypes was based on the symptoms of the disease or the characteristics of growth of a virus in experimental animals and tissue cultures. This method resulted in overlapping characteristics, blurred lines, and confusion [2]. A new method of taxonomy was developed, resulting in all newly discovered enteroviruses being categorized numerically (enterovirus 67–71) [3,4]. Current taxonomy [5], which divides enteroviruses into four species (A–D), takes into account the molecular morphology and distinct biochemical characteristics of the viruses. See Table 21.1 for a breakdown of the current classification of enteroviruses. The traditional names for individual subtypes (e.g., coxsackievirus A16) are still widely used and will be used for the purposes of this chapter. All these subtypes are immunologically distinct and are identified with type-specific antisera.

The enteroviruses are all morphologically similar. They are very small (approximately 30 nm) and are composed of a single–stranded, positive-sense RNA core surrounded by a naked icosahedral protein capsid that consists of four structural proteins (VP1–VP4) [2]. Isolates of the same serotype characteristically diverge in the VP1 region by less than 25 and 12%, respectively, within corresponding nucleotide and amino acid sequences [6].

History

Clinical disease due to enteroviruses has been recognized since ancient times. An Egyptian stele from the 18th dynasty (1580–1350 BC) depicting a man with an atrophied, shortened, paralytic leg represents the earliest documentation of poliomyelitis [7]. The first medical description of poliomyelitis is attributed to Michael Underwood, a London pediatrician, who in 1789 published his depiction of the disease in *A Treatise on the Diseases of Children* [8]. John Badham made the first report of a poliomyelitis outbreak in 1834 [9]. Poliomyelitis outbreaks were frequently met with public hysteria and the campaign to isolate an etiology for the disease, potentially finding a cure, received a great deal of publicity and funding from private and governmental agencies. In 1909, Landsteiner and Popper intraperitoneally administered cerebrospinal fluid (CSF) from a patient with fatal paralytic disease to monkeys, with the result that the monkeys exhibited a paralytic syndrome indistinguishable from that seen in humans, thus demonstrating a causative agent [10,11]. The use of animal inoculation became the method of choice for isolating and studying polioviruses over the following decades. A major breakthrough occurred in the study of polioviruses when it became possible to propagate the virus in human tissue [12,13]. This allowed easy isolation of polioviruses from human specimens and resulted in the eventual isolation of three poliovirus subtypes.

The extensive study of the viral etiology of poliomyelitis led to the unanticipated discovery of other related viruses. In 1948, viruses were isolated from mice inoculated with the stool of children suffering paralysis during a poliomyelitis epidemic in Coxsackie, New York. The viruses were not neutralized by antisera against the three types of polioviruses [14]. These new viruses, distinctly different from the polioviruses, were named coxsackieviruses and were further categorized into groups A and B based on their biological properties in mice [2]. Over the years, numerous additional strains of coxsackieviruses would be identified. The first recognized outbreak of what is now known as hand-foot-and-mouth disease (HFMD), which is most commonly caused by coxsackievirus A16, occurred in 1957 in Toronto, Canada [15]. The patients affected by the epidemic exhibited a febrile illness with cutaneous and oropharyngeal lesions. This unique clinical syndrome received its namesake from Alsop and colleagues after a similar epidemic of coxsackievirus A16 occurred in Birmingham, England in 1960 [16].

Another set of previously undiscovered viruses, the echoviruses, were uncovered during the quest to rid the world of poliomyelitis. While echoviruses produced cytopathic effects in cultured cells, they were found not to be pathogenic in laboratory animals and were isolated from both seemingly healthy children as well as patients with aseptic meningitis [17]. These viruses were grouped together and called "orphan" viruses because they were not yet linked to human diseases. They were later to be known as enteric cytopathic human orphan (ECHO) viruses, or echoviruses. Echoviruses were differentiated from coxsackieviruses by their inability to cause disease in mice. Some echovirus strains were later found to be pathogenic in infant mice, while some strains of

Table 21.1 Current Genomic Classification of Enteroviruses

Species Designation	Subtypes
Human enterovirus A	Coxsackievirus A2-8, 10, 12 ,14, 16 Enterovirus 71
Human enterovirus B	Coxsackievirus A9, B1-6 Echovirus 1-9, 11-21, 24-27, 29-33 Enterovirus 69
Human enterovirus C	Coxsackievirus A1, 11, 13, 15, 17-22, 24
Human enterovirus D	Enterovirus 68, 70
Poliovirus	Poliovirus 1, 2, 3

coxsackievirus failed to produce disease in mice. The lines drawn between these two groups became blurry and overlapping properties accumulated. As a result, newly discovered enteroviruses were simply named enterovirus followed by a number (i.e., enterovirus 67–71) [3]. The echoviruses have since been attributed to numerous clinical syndromes [13].

Epidemiology

In a survey of enteroviral infections in the USA from 1970 through 2005 [18], the 15 most commonly reported enteroviruses accounted for 83.5% of reports with a known serotype, and the five most commonly reported serotypes (echovirus 9, 11, 30, 6, and coxsackievirus B5) accounted for 48.1%. The diseases associated with enteroviruses frequently occur during epidemics, most of which appear during the summer months, with nearly 80% occurring between the months of June and October. In tropical locations, there is no seasonal pattern and outbreaks commonly occur throughout the year. In adults over 20, both sexes and all racial groups are similarly affected, but in persons less than 20, the surveillance study found a slight male predominance. Children, especially infants, tend to be more readily affected because they are relatively immunologically susceptible and their predilection for insanitary habits facilitates spread [19]. Children less than 1 year comprise nearly half of all reported cases [18].

Transmission of the virus can be accomplished by both direct person-to-person contact or indirectly. The fecal-oral route is the most common mechanism of transmission, but the virus may also be disseminated from the respiratory tract. Direct contact with feces occurs with activities such as diaper changing. Poor sanitary conditions may contribute to indirect transmission via contaminated water and food [20]. During the summer months, swimming and wading pools may serve as a potential means of transmission [21]. Long-term circulation trends of individual serotypes were consistent with both epidemic and endemic patterns [19]. Recently, it has been postulated that the enteroviruses may play a role in the pathogenesis of diabetes mellitus and chronic fatigue syndrome [22,23].

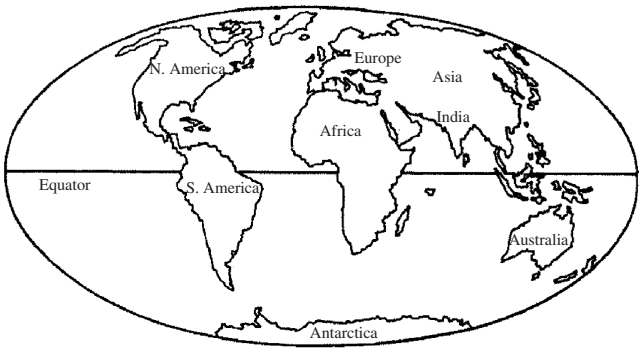
Pathogenesis

Enterovirus implantation occurs in both the buccal mucosa and lower gastrointestinal tract, more specifically, the terminal ileum. At these implantation sites, the virus begins to replicate rapidly and spreads directly to lymphoid tissue throughout the body. Subsequent replication at sites such as the tonsils, cervical lymph nodes, intestinal Peyer patches, and mesenteric lymph nodes produces a minor viremia. This stage of viremia, which usually coincides with the onset of symptoms, occurs approximately 72 hours after initial implantation and results in the spread of virus to secondary locations, such as the skin of the hands and feet

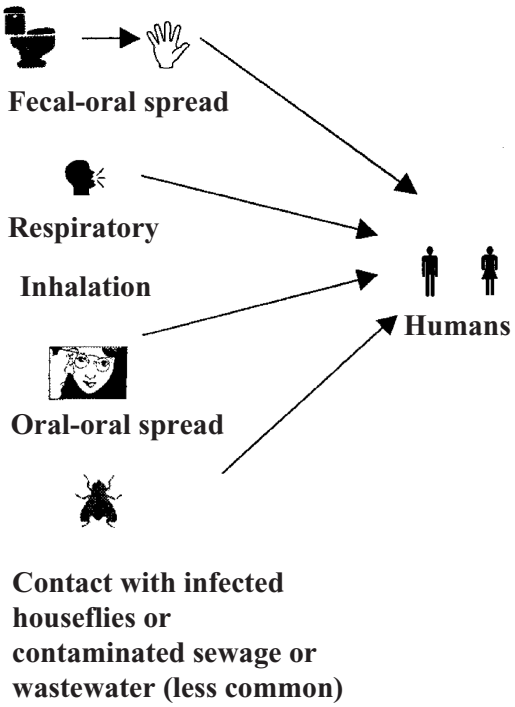
TAXONOMY

Picornaviridae family
Enterovirus genus

WORLDWIDE GEOGRAPHICAL INCIDENCE



TRANSMISSION



ZOONOTIC IMPLICATIONS

None

Figure 21.1a Incidence and transmission of enteroviral infections.

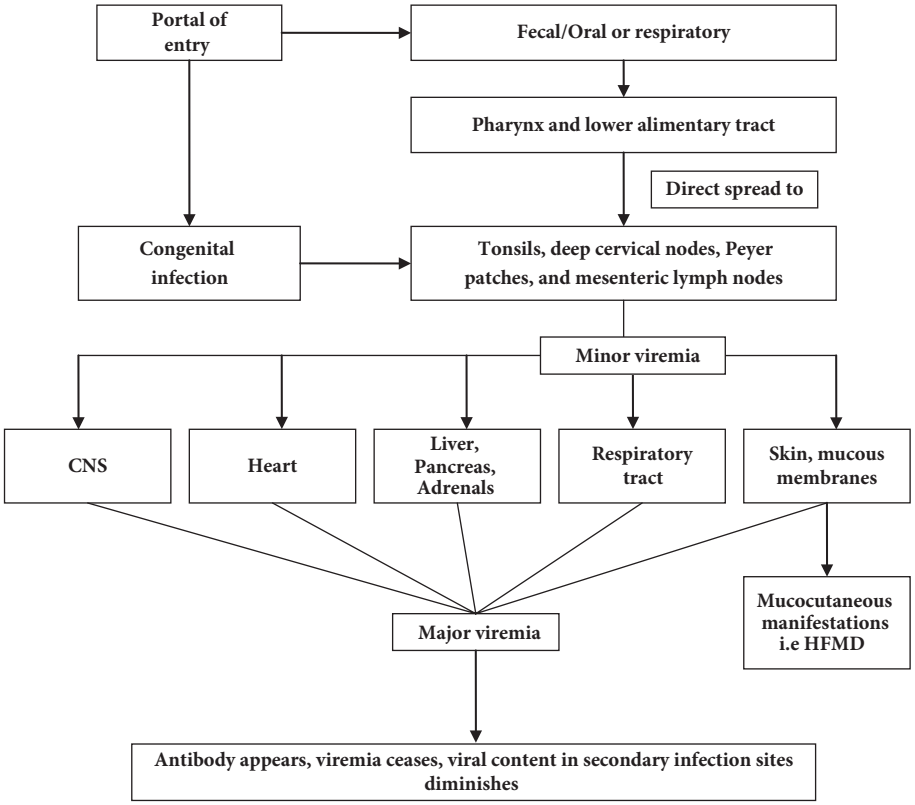


Figure 21.1b Pathogenesis of Enteroviral infections.

and the oral mucosa, as in HFMD. Secondary spread occurring in the central nervous system may result in aseptic meningitis, while spread to the heart may result in myocarditis. The pattern of spread and the resulting clinical syndromes are as variable as the enterovirus subtypes themselves. The viremia disappears with the appearance of serum antibody, and viral concentrations at secondary infection sites decrease around the 7th day after the initial infection. Some sites, such as the lower intestinal tract, may harbor virus for 1 month or longer. See Fig. 21.1 for diagrams of the classification, incidence, transmission, and pathogenesis of enteroviral infections [1,19,24].

Clinical Presentation

Infections with enteroviruses are extremely common, and the rashes produced are protean. The confusion arising from these presentations is partially clarified by two tables adapted from charts organized by Dr. James D. Cherry [19]. Table 21.2 indicates certain of the most prevalent enteroviral types, the age group of most affected patients, the frequency of the rash, its most common morphological features, and the associated clinical manifestations of the outbreak. Table 21.3 indicates the morphology of the rash and the common, occasional, and rare enteroviral illnesses producing these specified lesions. Table 21.3 summarizes and clarifies information from hundreds of outbreaks and will be an aid to every interested clinician.

The most common exanthems are macular or maculopapular eruptions. In certain cases, these may coalesce into a morbilliform pattern. Such rashes have been associated with numerous enteroviral types, such as coxsackievirus A6, A9, A16, and B5, but it is important to know that some of these patients also exhibited vesicles [22], petechiae, purpura, urticaria, and/or maculopapules while suffering their particular enteroviral infection (Figs. 21.2–21.11). Vesiculobullous eruptions mimicking herpes zoster have been described with echovirus 6 (see Fig. 5.38) [25], and petechial eruptions simulating meningococcemia have been described with echovirus 9 [26]. Acute hemangioma-like lesions have been associated with echovirus 25 infection (Fig. 21.11).

From these tables, it is possible to deduce that certain patterns of illness, such as HFMD, herpangina, and roseola-like illnesses, are fairly frequent enteroviral presentations. These manifestations are discussed more fully, but the clinician should consider the diagnosis of enteroviral illness every time a child or adult presents with any combination of fever, gastrointestinal symptoms, headache, meningismus, meningitis, rashes, and/or mucous membrane lesions.

Hand-Foot-and-Mouth Disease

The term hand-foot-and-mouth disease conveniently identifies anatomically the most common sites of the vesicles and ulcers associated with this illness. Unlike many of the exanthems caused by enteroviruses, the clinical syndrome associated with HFMD is recognizable and easily identified clinically. The most common virus responsible is coxsackievirus A16, but several other enterovirus subtypes, such as coxsackievirus types A5, A7, A9, A10, B2, B5, and enterovirus 71 (EV71), have been associated with this exanthem [1]. The virus is highly contagious and typically affects children between the ages of 2 and 10 years. Adults exhibit clinical symptoms much less frequently, but are not entirely spared. While

Table 21.2 Clinical Exanthematous Manifestations of Coxsackieviruses and Echoviruses

Clinical feature	Associated virus subgroup	Common	Occasional	Rare
Macular rash	*Coxsackievirus A*			
	Coxsackievirus B		*1, 2,* 5	
	Echovirus and enterovirus		*2, 4,* 5, 13, 14, 17, 19, 30	*18, 71*
Maculopapular rash	*Coxsackievirus A*	*9*	*2, 4,* 5, 10, 16	*6, 7*
	Coxsackievirus B		*1–5*	
	Echovirus and enterovirus	*4, 9*	*2, 5–7,* 11, 16–19, 25, 30, 71	*1, 3,* 13, 14, 22, *27, 33*
Vesicular rash	*Coxsackievirus A*	*5, 16*	*8–10*	*4, 7*
	Coxsackievirus B			*1–3, 5*
	Echovirus and enterovirus		*11, 71*	*6, 9,* 17
Petechial or purpuric rash	*Coxsackievirus A*	*9*	*4*	
	Coxsackievirus B		*2–5*	
	Echovirus		*4, 7*	*3*
Urticarial rash	*Coxsackievirus A*	*9*	*16*	
	Coxsackievirus B		*4, 5*	
	Echovirus		*11*	
Erythema multiforme or *Stevens-Johnson syndrome*	*Coxsackievirus A*		*9*	*10, 16*
	Coxsackievirus B			*4, 5*
	Echovirus			*6, 11*
Exanthem and meningitis	*Coxsackievirus A*		*2, 9*	*7*
	Coxsackievirus B		*1, 2,* 4, 5	
	Echovirus and enterovirus	*4, 9*	*6, 11,* 17, 18, 25, 30	*3, 14,* 33, 71
Exanthem and pneumonia	*Coxsackievirus A*		*9*	*7*
	Coxsackievirus B		*6*	*1*
	Echovirus			*9, 11*
Hand-foot-and-mouth syndrome	*Coxsackievirus A*	*16*	*5, 10*	*7, 9*
	Coxsackievirus B			*1, 3,* 5
	Echovirus and enterovirus		*71*	
Hemangioma-like lesions	*Coxsackievirus A*			
	Coxsackievirus B			*25, 32*
	Echovirus			
Herpangina and exanthem	*Coxsackievirus A*		*4*	*9*
	Coxsackievirus B			*2*
	Echovirus		*16, 17*	
Roseola-like illness	*Coxsackievirus A*			*6, 9*
	Coxsackievirus B		*5*	*1, 2,* 4
	Echovirus		*16, 25*	*9, 11,* 27, 30
Anaphylactoid purpura	*Coxsackievirus A*			*4*
	Coxsackievirus B			
	Echovirus			*9, 18*
Zoster-like rash	*Coxsackievirus A*			
	Coxsackievirus B			
	Echovirus			*5, 6*
Chronic or recurrent rash	*Coxsackievirus A*	*16*		
	Coxsackievirus B			
	Echovirus			*11*

Source: JD Cherry. Enteroviruses: coxsackieviruses, echoviruses, and polioviruses. In: RD Feigin, JD Cherry, eds. Textbook of Pediatric Infectious *Disease, 4th* edition, Philadelphia: WB Saunders, 1998, p. 1811, modified with permission.

up to 100% of infected preschool-age children develop a rash, only 38% of school-age children and 11% of adults exhibit cutaneous manifestations of infection [27]. The disease is most prevalent in the summer and early fall.

The clinical syndrome develops after an incubation period of 3–6 days and may begin with a prodrome characterized by low-grade fever, malaise, and abdominal pain or respiratory symptoms lasting from 12 to 24 hours. Patients may present with either enanthem or exanthem alone, but most manifest both (Figs. 21.12–21.15). As oral lesions typically appear first, a common early presentation is the complaint of sore throat or mouth and a refusal to eat. Classically 5–10 mm in diameter, oropharyngeal lesions appear initially as macules that develop into grayish vesicles that eventually ulcerate. Lesions may occur anywhere in the mouth as opposed to herpangina (discussed below). Typically 5–10 painful, ulcerative oral lesions may be present on the tongue, hard palate, buccal mucosa, and gingivolabial groove. The tongue may be diffusely red and edematous [1,24,28,29].

The exanthem, characterized by cutaneous lesions of the hand and foot, usually develops after the oral lesions. Beginning as 2–8 mm macules or papules, the lesions quickly evolve into vesicles that are set on an erythematous base [24]. These cutaneous lesions may be asymptomatic, tender, or even painful and may number from a few to nearly 100. Frequently, the vesicles take on linear or arcuate forms, with the long axis running parallel to skin lines. While characteristically found on the palms and soles (see Figs. 21.12 and 21.13), especially on the sides of fingers and toes, lesions may develop in other areas of the body, such as the

Table 21.3 Frequency of Exanthem in Outbreaks of Illness Due to Coxsackieviruses and Echoviruses

Virus type		Age group	Occurrence of rash	Characteristic of rash	Associated manifestations
Coxsackievirus	A2	Children	Rare	Maculopapular	Fever
	A4	Children	Rare	Maculopapular, vesicular	Fever, herpangina, hepatitis
	A5	Mainly children	Occasional	Hand-foot-and-mouth syndrome	Fever
	A7	Children and adults	Rare	Morbilliform, hand-foot-and-mouth syndrome	Meningitis, pneumonia, pancarditis
	A9	Mainly children	4%	Maculopapular, vesicular, urticarial, petechial, hand-foot-and-mouth syndrome	Fever, meningitis, pneumonia
	A10	Mainly children	Occasional	Hand-foot-and-mouth syndrome	Fever
	A16	Children and adults	88%, <5 yr old 38%, 5–12 yr old 11%, adults	Hand-foot-and-mouth syndrome	Fever
	B1	Children	Occasional	Maculopapular, vesicular, (roseola-like illness)	Fever, meningitis
	B2	Children	Rare	Maculopapular, vesicular, petechial	Fever, herpangina, meningitis
	B3	Mainly children	Occasional	Maculopapular, vesicular, petechial	Fever, hepatosplenomegaly
	B4	Mainly children	Occasional	Maculopapular, vesicular, urticarial	Fever, respiratory symptoms
	B5	Mainly children	10%	Maculopapular, petechial, urticarial, roseola-like	Fever, meningitis
Echovirus	B6	Children and adults	20%	Morbilliform	Pneumonia
	1	Children	Rare	Maculopapular	Conjunctivitis
	2	Children	Rare	Macular, maculopapular	Fever, pharyngitis
	3	Children	Rare	Petechial	Fever, meningitis
	4	Mainly children	10–20%	Macular, maculopapular, petechial	Fever, meningitis
	5	Infants and adults	Occasional	Macular	Fever
	6	Mainly children	Rare	Maculopapular, macular, papulopustular, vesicular	Fever, meningitis
	7	Children	Occasional	Maculopapular	Fever, meningitis
	9	Children and adults	57%, <5 yr old 41%, 5–9 yr old 6%, >10 yr old	Maculopapular, petechial, vesicular	Fever, meningitis
	11	Mainly children	Occasional	Maculopapular, vesicular, urticarial, roseola-like	Fever, meningitis
	13	Children	Rare	Maculopapular	
	14	Mainly children	Rare	Maculopapular, scarlatiniform	Fever, meningitis
	16	Children	Occasional	Roseola-like	Fever, herpangina
	17	Children	Occasional	Macular, maculopapular, papulovesicular	Fever, diarrhea, herpangina, meningitis
	18	Children and adults	Occasional, 1 epidemic	Rubelliform	Fever, meningitis
	19	Children and adults	Occasional	Maculopapular	Fever, meningitis, upper respiratory symptoms
	22	Infants	Rare	Morbilliform	Respiratory symptoms
	25	Children	Occasional	Maculopapular, hemangioma-like	Fever, pharyngitis
	30	Children and adults	Occasional	Macular, maculopapular	Fever, meningitis
	32	Children	Rare	Hemangioma-like	Fever
	33	—	Rare	—	Meningitis
Enterovirus	71	Children and adults	Occasional Four epidemics	Macular, maculopapular, vesicular, hand-foot-and-mouth syndrome	Mild-to-severe illness with: fever, meningitis, herpangina, encephalitis, paralytic disease, pulmonary edema and hemorrhage, myocarditis, facial paralysis, death especially with children less than 5 yr old

Source: JD Cherry. *Enteroviruses:* coxsackieviruses, echoviruses, and polioviruses. In: RD Feigin, JD Cherry, eds. Textbook of Pediatric Infectious Diseases, 3rd ed. Philadelphia: WB Saunders, (1992), Table 157–11, p. 1718, and 4th ed. (1998). Table 170–16, p. 1813, modified with permission.

buttocks (Fig. 21.15a). Vesicles on the palms and soles usually do not rupture, but those in other areas may rupture and form erosions and crusts. The clear, water-like, vesicular fluid contains numerous viral progeny and provides a mode of transmission through person-to-person direct contact [1].

HFMD is typically characterized by a benign course that is roughly 1 week in duration. While the prognosis is typically very good, a more severe, chronic, or relapsing course may occur, but is rarely seen. One chronic case in an elderly woman persisted 2½ years [30]. Serious organ involvement has been reported in rare instances, especially during epidemics, such as interstitial pneumonitis, pulmonary edema, aseptic meningitis, encephalitis, or myocarditis leading to significant morbidity and mortality [31].

Enterovirus 71

Special mention should be made to the epidemics of EV71 reported in Southeast Asia. The first major epidemic occurred in Taiwan in 1998. This epidemic of HFMD (75%) or herpangina (11%) was documented to affect 129,106 patients by 850 sentinel physicians (8.7% of MDs). The vast majority of these patients had self-limited infections and required little or no medical treatment. There were 405 severe cases that required hospitalization and 78 resulted in



Figure 21.2 Papular, erythrodermic eruption associated with enterovirus infection.



(a)

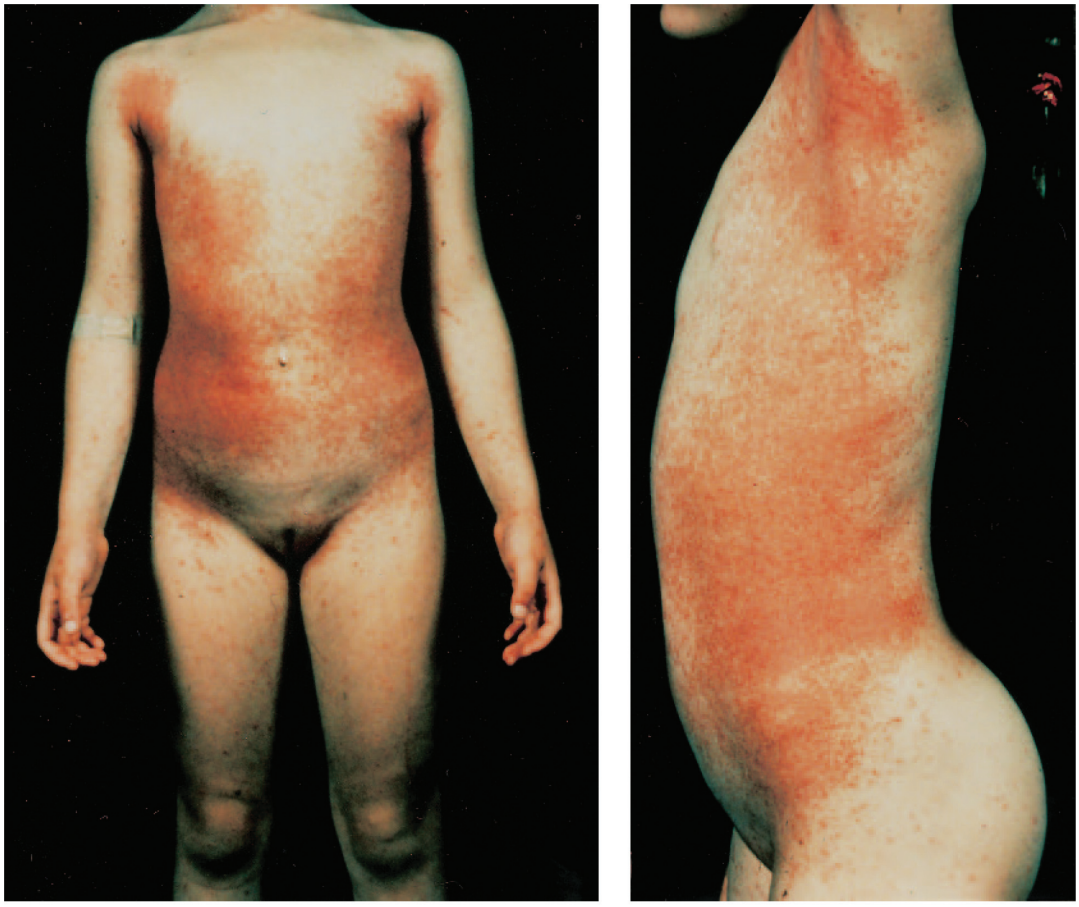


(b)



(c)

Figure 21.3 (a-c) Pustular eruption associated with echovirus 6.



(a) (b)

Figure 21.4 (a,b) Purpuric rash due to coxsackievirus B6.

mortality [32,33]. See Figs. 21.13–21.15 for images of a patient during the outbreak in Taiwan. Outbreaks were also reported in the Shandong Province of China in 2007, resulting in 14 deaths.

When the 2008 Olympic Games began in August 2008, another epidemic in China resulted in significant worldwide media attention. From January 1 to May 9, 2008, 61,459 HFMD cases and 36 deaths were reported through the disease reporting system in Mainland China. From March 27–29, 2007, a hospital clinician became alarmed when three consecutive deaths of preschool children presented with severe pneumonia and rapid deterioration in Fuyang City, Anhui Province. By mid April, 15 similar deaths were reported. All fatal cases presented with an acute onset of fever and then rapidly deteriorated, developing tachypnea, cyanosis, and some with seizures. All fatal cases died of complications such as neurogenic pulmonary edema. An investigation was conducted



Figure 21.5 Purpuric lesions secondary to coxsackievirus B4.



Figure 21.6 Papular lesions resulting from coxsackievirus B4.

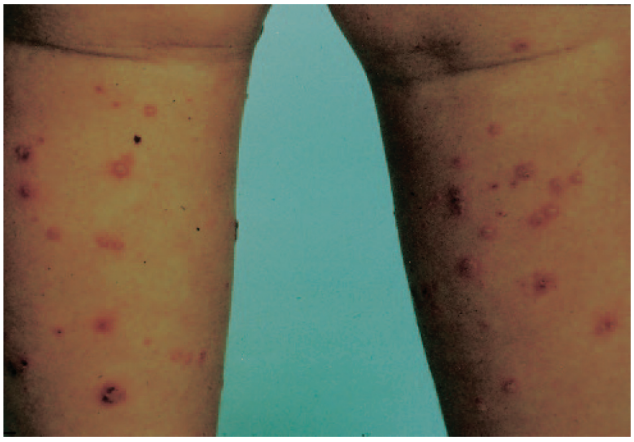


Figure 21.7 Acral pustular eruption due to enterovirus infection.



Figure 21.9 Linear distribution of papules due to coxsackievirus B5 in a patient with aseptic meningitis.

and it was found that there were simultaneous outbreaks of children presenting with symptoms consistent with HFMD.

Testing of initial cases for a variety of diseases, including seasonal and avian influenza and SARS did not reveal conclusive results. The Chinese Center for Disease Control and Prevention determined that 5 out of 12 fatal cases (42%) tested EV71 nucleic acid positive by PCR. The EV71 genotype C4 was isolated in specimens of both mild and fatal cases.

The initial outbreak in Fuyang City exhibited a high case-fatality rate of 2.9% (18/610). This was attributed to rapid disease progression, late clinical presentation, and limited local medical capacities. HFMD was not previously categorized as a notifiable infectious disease, but it was quickly added to the web-based national disease surveillance system. Once the etiology of the disease was known, enhanced surveillance, implementation of prevention and control measures, and early treatment was provided for severe patients, resulting in a significant decrease in the case-fatality rate to 0.07% (4/5439) [34].

While most cases of EV71 infections result in a mild clinical syndrome, the fatalities reported in these recent epidemics remind us of the pathogenic potential and deadly virulence of this virus. It is a painful lesson indeed, with most of the victims being infants and young children, but there is hope on the horizon. Researchers and



Figure 21.8 Erythema multiforme-like rash associated with coxsackievirus infection.



Figure 21.10 Photodistribution of macules associated with coxsackievirus infection.



(a)



(b)

Figure 21.11. (a,b) Acute hemangioma-like lesions associated with echovirus 25 infection.

clinicians in Southeast Asia, those most closely affected by these recent events, are continuously at the forefront of EV71 research. New prophylactic and treatment methods are being meticulously studied in hopes that in the future, morbidity and mortality from EV71 will be greatly reduced.

Herpangina

Herpangina is the term used to describe a febrile illness accompanied by a vesicular enanthem that is caused by several different enteroviruses. Despite its name, the illness has nothing to do with herpesviruses. Numerous enteroviruses have been implicated in this particular clinical syndrome, such as coxsackievirus A1–6, 8, 10, 22, coxsackievirus B (strains 1–4), and echoviruses. The disease presents both sporadically and during periods of epidemics, most of which occur in the summer months. It is characterized by the presence of small vesicles or ulcers on the anterior faucial pillars, soft palate, uvula, tonsils, and pharynx (see Fig. 21.16).

The illness may be heralded by the sudden onset of fever, malaise, headache, dysphagia, anorexia, and sore throat typically without a history of prodromal symptoms. The enanthemous lesions are usually few in number (2–6), but the entire visible pharynx may be studded with them. Typically small (2–4 mm), they progress from gray-white papules to vesicles and then to ulcers with a red halo. The lesions frequently present as small clusters that later coalesce,



Figure 21.12 Palmar vesicles of hand-foot-and-mouth disease.



Figure 21.13 Palmar vesicles of hand-foot-and-mouth disease caused by enterovirus 71 (courtesy of Luan-Yin Chang, M.D., Ph.D. Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University).



Figure 21.14 Palmar Vesicles of hand-foot-and-mouth disease in child with leukemia.

leaving a shallow, punched out, grayish crater. The pharyngeal mucosa is usually diffusely hyperemic and swallowing causes severe pain. The illness may be accompanied by drooling (100%), sore throat (50%), coryza (45%), vomiting or diarrhea (25%) or both (36%), and headache (18%). In the outbreak in Taiwan (see above), 10% of fatal cases had herpangina [32,33].

Lesions typically disappear in 5–10 days from their onset and treatment is primarily supportive, consisting of topical anesthetics. The location of the lesions in the posterior oropharynx as well as isolation of an enterovirus, help to narrow the differential diagnosis.

Histopathology

Biopsies are rarely performed in patients with herpangina. Dermatopathological findings in HFMD show nonspecific intraepidermal vesicles filled with neutrophils, mononuclear cells, and proteinacous eosinophilic material. The dermis exhibits a perivascular mixed cell infiltrate. Electron microscopy may reveal intracytoplasmic particles in a crystalline array characteristic of coxsackieviral infections [24]. Tissues may be examined for specific enteroviral antigens by immunofluoresence and for RNA by polymerase chain reaction (PCR) [35].

Laboratory Findings

Patients with HFMD typically have leukocyte counts ranging from 4000 to 16,000/mm^3, sometimes with atypical lymphocytes. Laboratory findings for herpangina are nonspecific.



Figure 21.15 (a-d) Mucocutaneous manifestations of hand-foot-and-mouth disease caused by enterovirus 71 during an outbreak in Taiwan. (courtesy of Luan-Yin Chang, M.D., Ph.D. Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University).

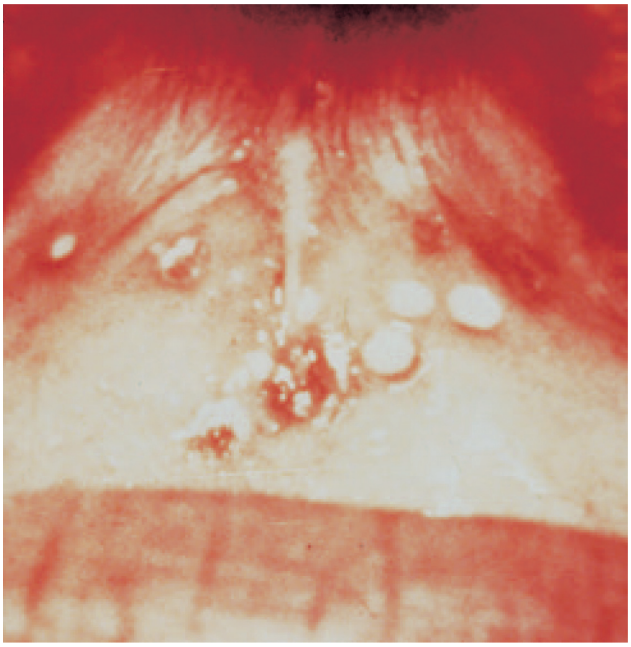


Figure 21.16 Oral vesicles of herpangina.

Diagnosis

With the exception of some of the more characteristic clinical syndromes such as HFMD, enteroviral infections are difficult to diagnose clinically. It is important to carefully review the clinical symptoms, taking into account the season of the year, the geographic location, exposures with sick contacts, and the incubation period. Specific laboratory tests may guide the clinician who suspects an enteroviral etiology based on clinical findings.

Specimens may be taken from vesicular fluid, throat, stool, blood, urine, CSF, and other body fluids. Most viral diagnostic laboratories have facilities for the isolation of most enteroviruses that cause illness, and tissue culture evidence of enteroviral growth typically takes a few days to a week to detect. Serology studies may detect neutralizing antibodies to particular enterovirus subtypes. While serological studies are useful in some circumstances, such as in the study of an enteroviral outbreak in a community, they are impractical in most clinical situations. In recent years, numerous reports have described enteroviral PCR methods and their use in the clinical setting [36]. PCR has proved to be useful in the identification of enteroviruses in CSF, blood, urine, and throat specimens [37]. A shortcoming of PCR is that while enteroviral RNA is identified, the specific subtype is not identified.

Treatment and Prophylaxis

Good hygiene and sanitation, including careful handwashing, is the most important step in preventing the spread of enterovirus infections. Supportive treatment of symptoms is the mainstay of therapy for most patients with enteroviral disease. One study investigated the use of milrinone, a phosphodiesterase inhibitor, in the treatment of EV71-induced pulmonary edema [38]. The mortality rate was significantly reduced in a milrinone-treated group versus a nontreated group (36.4 versus 92.3%). Milrinone seems to attenuate the changes in cytokines seen in severe cases of EV71 infection. Immunodeficient patients, especially neonates and patients with hypogammaglobulinemia, may benefit from intravenous immunoglobulin.

No specific antiviral agents are currently available to treat or prevent infections due to enteroviruses (except poliovirus vaccines). Many efforts have been made to develop compounds targeting the virus, the most promising target being the viral capsid protein, VP1. One such capsid inhibitor, pleconaril, showed promising results in the treatment of picornaviral respiratory tract infections, meningitis, and other life-threatening infections. It reached advanced stages in clinical trials (Phase III), but was rejected due to safety concerns [39]. While these failed efforts have been disappointing, the development of this drug and perhaps others in its class gives rise to great hope for useful therapy in the future.

Investigations for a potential vaccine for EV71 are currently underway. Chen et al. reports the development of an EV71-like particle with similar appearance, capsid and protein composition that may serve as a potential vaccine. This EV1-like particle induced a potent immune response in mice, protecting them against a lethal challenge with virus [40]. Chen and colleagues were also able to produce transgenic mice that expressed the VP1 protein in their milk. Infant mice that suckled this milk generated EV1 specific antibodies and fared better when exposed to the virus [41].

Conclusion

Enteroviral infections cause variable patterns of illness with mucocutaneous manifestations and can be difficult to identify by even the most astute clinician. While these infections are usually associated with a benign course and a fairly good prognosis, clinicians should conscientiously be on the alert for rare complications that may lead to severe morbidity and mortality for their patients.

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22 Flaviviruses

Omar Lupi and Carlos Gustavo Carneiro

The Flaviviridae family consists of almost 60 different viruses, several of which are pathogenic to humans. These viral infections are primarily mosquito- or tick-borne, and the clinical diseases associated with them range from asymptomatic infection to severe encephalitis or hemorrhagic fever. With the morbidity and/or mortality that is associated with dengue fever (DF), yellow fever, and Japanese encephalitis (JE), among others, this family of pathogenic viruses deserves a significant amount of medical interest. Hepatitis C virus, a member of the Flaviviridae family not arthropod-borne, will be discussed in Chapter 24.

DENGUE FEVER

Introduction

Currently, dengue is considered the most important viral infection transmitted by an arthropod vector globally in terms of mortality and morbidity [1].

History

The earliest known documentation of dengue-like symptoms was recorded in the *Chinese Encyclopedia of Symptoms* during the Chin Dynasty (AD 365–420). The disease was associated with flying insects near water and was known as "the water poison" [1,2].

At the end of the 18th century (1779–1780), the first epidemic flares of dengue were reported in Asia, Africa, and North America [2]. However, dengue was most likely present for a long time before it was first reported in the medical literature. By that time, dengue was not considered an important tropical disease like malaria and yellow fever, since only the benign form of the disease was known [3–5]. Moreover, the epidemiologic efforts to decrease the cases of urban yellow fever diminished the number of cases of dengue disease (both diseases are transmitted by the *Aedes aegypti*). For all these reasons, dengue was not considered a relevant public health issue during the 18th century [4].

Benjamin Rush was the first person to report a case of dengue in 1789 [1]. He coined the term "breakbone fever" because of the symptoms of arthralgias and fever. During a Caribbean outbreak in 1827–1828, the term dengue arose and it represented a Spanish attempt at the phrase "*ki denga pepo*" (Swahili language). This phrase means: "cramp-like seizure by an evil spirit." Eventually, in the 20th century, the viral etiology and the transmission of the disease by mosquitoes were discovered [1,4].

The importance of dengue from the public health standpoint changed drastically in the 20th century, mainly for two reasons: the occurrence of a high number of endemic cases and the appearance of new epidemic flares in Asia [2]. The importance of the disease was recognized due to the discovery of the more severe hemorrhagic form of the disease in 1954 in the Philippines. World War II induced important socioeconomic changes in the world, leading to a significant spread of the disease worldwide. After World War II, a pandemic of dengue started in southeast Asia and has spread around the world since then [1,2]. The dissemination of the disease occurred quickly, due to migration of people to different countries or simply due to international air travel. Furthermore, several locations in Latin America in the 1970s had similar demographic conditions as in Asia, offering an optimal environment for the dissemination of the disease and the development of epidemic flares.

The lapse in mosquito eradication programs in the Americas had relevant consequences for dengue. In the early 1970s, the *Ae. aegypti* eradication programs to combat yellow fever were discontinued and, consequently, a reinfestation of the Americas with the *Ae. aegypti* occurred [6]. This reinfestation combined with uncontrolled urbanization and increased travel and commerce have played an important role in the increase of dengue and the emergence of dengue hemorrhagic fever (DHF) in the Americas [6].

Since 1977, successive introduction of new serotypes has occurred in the Caribbean, Central and South America [6]. In 1981, a case of DHF was reported in the Caribbean and since then epidemics have occurred in Latin America affecting more than 10 countries in the region [6]. The areas of the globe affected by dengue in the 1990s were Latin America, northern Australia, Africa, China, India, southeast Asia, and various Pacific Islands [3,5]. In 2001, more than half of the total cases of dengue reported in Latin America [610,000] occurred in Brazil. Currently, Brazil has the highest number of cases of the disease in the Americas [5]. However, Venezuela has the highest number of hemorrhagic cases. One hundred million cases of dengue are reported in the world every year. As the disease spreads to different areas worldwide, the number of cases and the number of explosive outbreaks has been increasing [3,5]. The expanding geographic distribution of the four dengue virus strains and their mosquito vectors are responsible for the spread of dengue. The most important mosquito vector of dengue is the predominantly urban species *Ae. Aegypti* [3,5,6]. A rapid increase in urban populations, especially in areas that are adequate for mosquito breeding (e.g., areas where solid waste disposal is not properly done and areas where household water reservoirs vulnerable to mosquito larvae are common), is increasing the numbers of people in contact with this vector.

Synonym

Dengue, "breakbone fever," "*ki denga pepo*," Dandy fever, "water poison" [1].

Epidemiology

Dengue is the most severe and prevalent disease caused by arthropod-borne flavivirus [7]. The prevalence of dengue worldwide has increased dramatically in recent decades [3,5,6]. At present, the disease is endemic in more than 100 countries in the Americas, Africa, southeast Asia, western Pacific, and the eastern Mediterranean. More than 40% of the population of the world (2.5 billion people) is at risk for the disease [3,5,8].

Currently, all dengue virus serotypes are present in the Americas [6]. In 1994, DEN-3 was reintroduced in Central America [3,5]. This type of dengue virus is now found in many countries in the region. However, since it had been absent from Central America for many years, the level of immunity of the population is low and the virus can spread very fast. Epidemics caused by multiple types of dengue virus can occur (hyperendemicity).

The virus may circulate in endemic cycles; however, it periodically causes widespread acute epidemics [9]. The burden of severe disease has considerably increased in recent years in the Americas, but it remains proportionately much greater in the Pacific and Asian countries. Inadequate mosquito control, uncontrolled urbanization, growth of urban population in tropical countries, and the increase in air travel (providing the ideal mechanism for infected human transport of dengue viruses between population centers of the tropics) have contributed to the increase in epidemic activity [9].

Annually, between 100 and 200 suspected cases of dengue are introduced into the USA by travelers. At present, the evolution of the disease in the Americas is similar to southeast Asia during the 1950s and 1960s [2,9,10].

The estimated incidence of cases of DF annually in the world is 50–100 million [7]. The mortality rate of DF is less than 1%. The estimated cases of DHF are also high (several hundred thousand cases per year). The fatality rate of DHF is approximately 5% [9]. When people go on to develop dengue shock syndrome (DSS), the mortality rate can be as high as 40%. Currently, dengue is considered the most important viral infection transmitted by an arthropod vector in terms of mortality and morbidity [9,10].

In order for a dengue epidemic to occur, it is necessary to have the arthropod vector, the virus, and a high number of susceptible human hosts. The outbreaks can be progressive or explosive, depending on the strain and serotype of the dengue virus, the number of susceptible people in the population, the amount of contact between the vector and humans, and the density and efficiency by which the vector can be infected [4,69]. Control of the arthropod vectors can significantly decrease the dengue infection rates. In the 1950s and 1960s, the Pan American Health Organization was able to eradicate the vector *Ae. aegypti* from many areas of South and Central America [4]. Epidemics of the disease were rarely seen during those decades. However, when the eradication program was discontinued, *Ae. aegypti*, and subsequently dengue, returned.

In the USA, the *Ae. aegypti* is seasonably abundant in some southeastern and southwestern states including Arizona, Texas, New Mexico, Mississippi, Louisiana, Alabama, Georgia, and mid to South Florida. In addition, it is sporadically reported from some areas of North Carolina, Tennessee, South Carolina, Arkansas, New Jersey, and Maryland. Isolated dengue outbreaks have occurred in the continental USA and the last reported dengue occurred in Texas in 1999 [9].

At the present time, *Ae. albopictus*, a species from Asia that can also transmit dengue, is found in most states in the eastern half of the USA and in some areas of Brazil, Bolivia, Cuba, Colombia, Cayman Islands, El Salvador, Dominican Republic, Mexico, Guatemala, Honduras, and Europe (3–5). The rapid geographic spread of *Ae. albopictus* has been largely attributed to the international trade of used tires. Dengue infections due to autochthonous transmission by *Ae. albopictus* mosquitoes occurred in 122 Hawaii residents from mid 2001 through early 2002 [9]. The epidemic that occurred in Hawaii in 2001 is a reminder that several states in the USA are susceptible to dengue epidemics, since they harbor the particular types of mosquitoes that transmit it.

Most dengue cases in US citizens occur due to endemic transmission in some of the US territories. However, limited outbreaks and travel-associated dengue also occur in the continental USA. Annually, 100–200 cases of dengue are reported to the Center of Disease Control and Prevention (CDC). Most of these cases occur in people who have recently traveled abroad [9].

Besides typical dengue, DSS and DHF have also increased in many areas of the world. Women and men are equally affected by the disease, however, more cases of DHF and DSS have been reported in women. Individuals of all ages can be affected, but elderly individuals are more likely to be at risk because of coexisting medical conditions; 90% of patients with DHF are younger than 15 years. All races can be affected by the disease [4,9].

Notification of the public health authorities is essential, once a case of the disease is confirmed. In 2005 and 2006, outbreaks of dengue occurred in Thailand, Vietnam, Costa Rica, Cambodia, Indonesia, India, Malaysia, Martinique, Philippines, Singapore, and Sri Lanka. More than 1000 deaths occurred in Indonesia [3,5].

Natural disasters, such as hurricanes, increase the habitat for mosquito growth in urban areas by increasing garbage and rubble, which function as water reservoirs. Since more than 90% of the mosquito breeding sites are produced by humans, the best way to control the disease is through education of the mosquito population [10].

Etiologic Agent and Reservoir

The disease can be caused by any one of four serotypes of dengue virus. People can be infected by at least two if not all four serotypes during different times in their lifetime, but only once by the same serotype [1,9,11]. Humans are the only vertebrate hosts of dengue virus. There is a jungle cycle between arthropod vectors and monkeys that plays no role in human disease.

Virology

Dengue viruses can be classified into four different serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), which have 60–80% homology between each other [4]. They are RNA enveloped viruses and are members of the *Flavivirus* genus and the Flaviviridae family. Flaviviruses are 40–50 nm in diameter, enveloped viruses with an icosahedral capsid that contains single-stranded RNA [1,4,9,10]. Dengue viruses are classified as arboviruses (i.e., arthropod-borne viruses).

Dengue viruses have three main proteins present in their structure: protein C of the viral capsid, M protein that is associated with the viral membrane, and protein E of the viral envelope that interacts with receptors present on the cells of the host (mainly phagocytic mononuclear cells). Protein E is also responsible for the neutralization reaction mediated by antibodies. Dengue viruses also have some proteins that are non-structural. These proteins are NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5, but their functions have not been clarified [10,11]. E glycoprotein and protein NS1 have been associated with protective immunity.

Transmission

The main vector is *Ae. aegypti*. After they become infected, the arthropod vectors remain infective for life [10].

Ae. aegypti is a highly domesticated, small, black and white member of the sub-genus *Stegomyia*. Since the mosquito typically lays its eggs in artificial containers that accumulate water, dengue is often an urban-acquired disease. The flight range of the vector is considered short and, especially in urban areas, house-to-house spread of dengue occurs.

Since infection with one of the dengue serotypes provides immunity with only this serotype for life, persons living in endemic areas can develop more than one dengue infection during their lifetime. *Ae. aegypti* prefers to feed on humans in the daytime. The mosquito is not only the vector of the disease, but also a true reservoir. Humans are the main source of infection. *Ae. aegypti* is a species completely adapted to the urban environment and is the main vector of the disease. However, another species (*Ae. albopictus*) can also transmit the disease. This species was recently introduced in the Americas and can be seen not only in the urban setting, but also in the semi-rural environment. This is worrisome because the mosquito can act as a bridge for the return of urban yellow fever [10,11].

The arthropod vectors usually acquire the virus while feeding on blood of an infected person. The bite of the infective female *Aedes* mosquitoes is responsible for the transmission of dengue viruses to humans. The infected female mosquitoes can transmit the virus to their offspring by trans-ovarian transmission. However, the role of this vertical transmission in sustaining transmission of the virus to humans has not been established. Some studies have shown that monkeys may become infected and possibly serve as a source of dengue virus for uninfected mosquitoes. However, the main amplifying hosts of the virus are humans. The disease is not contagious from person to person. The viral circulation in the blood of infected people occurs over 2–7 days [10,11] and is accompanied by fever. The viral infection is acquired when the mosquito feeds on an infected human during this period. The arthropod vector injects anticoagulants that prevent blood clotting while it is feeding. The virus multiplies in the gut of the arthropod vector and attains a high number in its salivary glands. The vector is not adversely affected by the virus. The life span of *Ae. aegypti*, the primary vector in the Americas, is generally 3 weeks. The incubation period depends on the rainfall and temperature in the geographic area. Virus replication occurs 8–12 days (10–13) after it is ingested by the vector from an infected individual.

DHF is most likely to occur when an individual previously infected with one type of dengue virus is later infected with a different viral strain.

The period of time needed for an individual to start developing symptoms after the bite of an infected mosquito ranges from 3 days to 2 weeks with an average of 4–6 days. An infected individual can be a source of dengue virus for vectors for about 6 days (11–13).

Cases of vertical transmission of the disease have already been reported, but they are very rare.

Pathogenesis

After being inoculated in humans by the bite of the arthropod vector, the virus multiplies initially inside the regional lymph nodes and subsequently enters the circulation [14,15]. An increase in body temperature lasting 5–8 days can then be observed. The virus has a second replication cycle, this time inside the blood monocytes [14,15], and proliferates through the body inside these cells or in the plasma. Dengue virus has a tropism mainly for monocytes and macrophages. However, the virus also has a tropism for muscle cells, which explains the intense myalgia that can be seen during the course of DF [16]. The viremia can be maintained by viral replication inside the macrophages of the reticuloendothelial system. The production of cytokines by the macrophages is directly stimulated by replication of dengue virus. In addition, specific T-helper lymphocytes that interact with HLA class II antigens present on the macrophages are indirectly stimulated by the viral replication to produce cytokines. The release of tumor necrosis factor alpha and interleukin 6 is probably related to the development of the fever [16,17].

Both the antibody-mediated immunity and the cell-mediated immunity are involved in the control of the infection by the organism. In the first week of the disease, the immune system starts to respond to the infection. With the help of specific antibodies, CD8+ cytotoxic T lymphocytes can destroy the cells infected by dengue virus, i.e., antibody-dependent cytotoxicity [18].

The antibodies can interact with dengue viruses and neutralize them directly. Anti-dengue immunoglobulin M (IgM) can be observed in the blood from the fourth day of the disease. The peak of IgM antibodies occurs by the end of the first week. The IgM antibodies can continue to be present in the blood for months (16–18).

The IgG antibodies can be observed in the first week and peaks by the end of the second week. The IgG antibodies can continue to be present in the blood for years and are responsible for the serotype-specific immunity against the virus, probably for the lifetime of the individual.

DHF is usually seen in patients who already had an infection by one of the dengue viruses serotypes and, years later, acquired another infection by a different serotype of dengue virus. When the second infection is caused by the dengue virus serotype 2, the patient's risk of having hemorrhagic dengue is even higher (16–18).

The evolution from DF to DHF occurs in a small percentage of individuals with the disease (0.3–4%). This is caused by complex mechanisms between the virus and the host immune response, and also because of epidemiologic factors and some comorbidities that can increase the risk of this progression from DF to DHF [18].

Dengue serotype 2 is considered the most virulent of the dengue viruses, followed by serotypes 3, 4, and 1, in decreasing order of virulence [11].

During the primary infection, neutralizing antibodies are produced by the individual's immune system against this first serotype of dengue virus and persist during the lifetime of the individual. These antibodies are able to protect the organism against other serotypes over a short period of time. This is known as cross immunity and lasts for months or a few years [19]. If a different serotype of dengue virus is inoculated in the same individual years later, producing another infection (secondary infection), those antibodies will not be able to neutralize this other serotype and will have a sub-neutralizing character. This finding

is the basis for the most important pathogenic theory of hemorrhagic dengue, which is called "the theory of Halstead" [20].

The Theory of Halstead

The viral penetration in the macrophage by opsonization is facilitated when the antibodies bind to the new serotype of dengue virus inoculated in the organism without neutralizing it. Thus, a much higher number of viral copies can penetrate in the phagocytes and can replicate very intensively. This leads to an increase in the viremia and stimulates the production of more cytokines (interleukin-6 and tumor necrosis factor alpha), as well as proteases that activate the complement system, and thromboplastin, which is a pro-coagulant factor. Interferon gamma released by the T-helper CD4+ lymphocytes specific for viruses acts on infected macrophages and enhances the viral internalization and the expression of HLA class II molecules in their membrane. Additional specific T-helper CD4+ lymphocytes are activated by these HLA class II molecules located in the membrane of the macrophages, establishing a positive feedback mechanism [20].

Another example of the presence of the sub-neutralizing antibodies leading to the manifestations of hemorrhagic dengue is seen when the anti-dengue I antibodies from the mother pass through the placental route to the fetus. Since these antibodies are passive, they tend to decrease in amount during the initial 9 months, reaching sub-neutralizing levels. In this situation, the phenomenon of the Halstead theory can be seen after the same viral serotype is inoculated in the individual [16,18].

Children can have up to 50% mortality with DHF, but are generally unaffected by classic dengue. Long-time residents in endemic areas usually get DHF, whereas recent arrivals to the same regions generally contract the classic form [19].

Currently, immune enhancement is the most commonly accepted explanation for the mechanism of progression from DF to DHF. The immune enhancement hypothesis states that individuals who were previously infected with one of the four types of dengue virus have circulating non-neutralizing antiviral antibodies [11]. When another type of dengue virus infects the individual (i.e., secondary infection), the dengue virus is recognized by the non-neutralizing antiviral antibodies, but the viral replication is not inhibited or neutralized by these antibodies. An antigen–antibody complex is subsequently formed. Receptors on macrophages recognize the complex and the immune complex is then internalized. The virus is allowed to replicate unchecked and this phenomenon is called immune enhancement. Vasoactive mediators are released by the macrophages leading to an increase in the vascular permeability and consequently, vascular leakage, hypovolemia, and shock (16–18).

Some cytokines are believed to induce the leakage of plasma through the capillary vessel walls and are seen in elevated levels in DHF. These proteins include tumor necrosis factor alpha, interleukin 2, interleukin 6, interleukin 8, interleukin 10, and gamma interferon. After being stimulated, the endothelial cells show an increased expression of the adhesion molecules VCAM 1 and ICAM 1 [16,17].

The genotypic variation of a viral strain and the viral serotype possibly have some influence in the progression of DF to DHF [11,17].

Possible causes of the thrombocytopenia that can be seen during the course of the disease are: periphery destruction of the platelets caused by the action of immunocomplexes or by the complement system and/or by inhibition of the medullar hematopoiesis.

Clinical Presentation

Infected people can have a spectrum of clinical illness ranging from a nonspecific viral syndrome to severe and fatal hemorrhagic disease (Table 22.1). Dengue virus infection can lead to one of four different consequences: classical dengue, hemorrhagic dengue, asymptomatic infection, and less frequent manifestations such as hepatitis [20,21].

Classical dengue, also called dengue fever, is characterized by fever, headache, myalgia, and rash (Figs. 22.1 and 22.2). DHF is a separate, more virulent, clinical entity [1,9,22,23].

In the past, dengue used to be called "break-bone" fever because the disease sometimes causes severe joint and muscle pain that feels like bones are breaking [2,4].

Mild hemorrhagic symptoms (including gingival bleeding, petechiae, and a positive tourniquet test) can be seen in approximately one third of the patients with DF [1,9,23].

Regain of appetite is considered a sign of recovery after DSS or DFH.

Classical Dengue

The most frequent form of disease in the setting of primary infection is classical dengue. Fever is the initial manifestation and has an abrupt onset. Fever can be associated or followed by headache, severe myalgia, retro-orbital pain, anorexia, vomiting, nausea, arthralgia, and fatigue. On the third or fourth day following onset of the symptoms, a morbilliform eruption or a scarlatiniform rash can be seen (21–24). This rash is centrifugal, spares the palmoplantar region, and can be associated with pruritus (Figs. 22.1 and 22.2). In children, abdominal pain is more frequent. In classical dengue, the headache occurs predominantly in the frontal region and can be the chief complaint because of its intensity [1,9,24]. Although the rash is usually maculopapular, it can also be macular or even urticarial (Fig. 22.3); in this case it is not easy to differentiate the rash from an allergic reaction to the medications used to control the symptoms.

Patients with classical dengue can also have lymphadenopathy and tender hepatomegaly. Hemorrhagic manifestations are not exclusively seen in DHF and can be observed in classical dengue (21–26) (Fig. 22.4).

Hemorrhagic Dengue

The most important risk factors for this form are [27,28]:

- Infants born from mothers who had dengue
- A history of another episode of dengue in the past (preferably a confirmed episode)
- Children younger than 12 years of age (in southeast Asia)
- Female patients
- When serotype 2 causes the infection
- When the patient is Caucasian

In DHF, the fever usually begins in the same manner as in classical dengue; however, in the period between the 3rd and

Table 22.1 Clinical Manifestations of Dengue Fever

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
4–7 days	Sudden onset of high fever, chills, headache(commonly retro-orbital), eye pain, joint pain, and severe myalgia (termed breakbone fever). A transient, generalized erythematous flush-like rash of the face, neck, and chest, and sparing the palms and soles may be present during the first 24–48 hr of fever. Other symptoms include anorexia, nausea, vomiting, taste alteration, nonspecific respiratory symptoms, marked lassitude, cutaneous hyperesthesia, and conjunctival suffusion ↓	Serology, with acute demonstration of immunoglobulin M (IgM), or a fourfold rise in IgG titers between paired sera Viral isolation	Onset of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) is similar
7–12 days	In some patients, the fever and symptoms completely remit at this time and the patient recovers completely. In others, a second rash may appear as the fever subsides. This eruption can be scarlatiniform, maculopapular, petechial, or purpuric and typically begins on the trunk and spreads to the face and extremities. The rash typically desquamates after 1–3 days, leading to recovery. The hemorrhagic manifestations of DHF appear at this stage, often with petechiae and bleeding diathesis. Signs of circulatory insufficiency may appear in some patients, which may progress to DSS ↓		
11–17 days	Patients with dengue fever have complete recovery. Time to recovery varies in DHF and DSS, but is not as rapid as that in classic dengue fever		Patients with DHF will be restless and sweaty with cold extremities. Pleural effusion and abdominal ascites may be present. With treatment, this period lasts 24–48 hr in DHF. DSS will have these symptoms as well as rapid pulse, hypotension, generalized vasculitis, and disseminated intravascular coagulation (DIC)

8th day of disease evolution, the characteristic findings of DHF appears. In this period, plasma leakage, bleeding, and low platelet levels can be observed [27].

The hemodynamic and systemic changes caused by the increase in the vascular permeability leads to a relative hypovolemia (eventually shock), interstitial edema, and serosal effusion [1,9,27]. This sequence of events characterizes DHF. Thus, DHF is not defined and characterized by the presence of hemorrhagic manifestations, despite the name.

When present, however, the hemorrhagic manifestations of DHF are more severe than in classical dengue. The patients with hemorrhagic DF can have moderate to severe thrombocytopenia and coagulation disturbances. The lethality rate ranges from 5 to 50% and averages 12% (27–29). Recovery is observed in most of the patients.

The initial clinical picture of DHF is similar to the initial presentation of classical dengue. Hemorrhagic manifestations and cavitary effusions can be observed from the second or third day of the disease (Figs. 22.5–22.7). However, hemorrhagic manifestations are not always seen in the course of DHF [27,30]. The tourniquet test usually gives a positive result in DHF [27] (Fig. 22.8).

Hepatomegaly is seen more commonly in DHF than in classical dengue and, eventually, can be associated with mild splenomegaly [30,31]. Patients with simultaneous presence of hematemesis, hepatomegaly, and abdominal pain have a bad prognosis [31].

The hemodynamic signs can be observed between the 3rd and 7th day of the disease when the fever starts to subside. Patients can develop premonitory signs and symptoms in relation to the hemodynamic changes: cold sweating, tachycardia, perioral cyanosis,

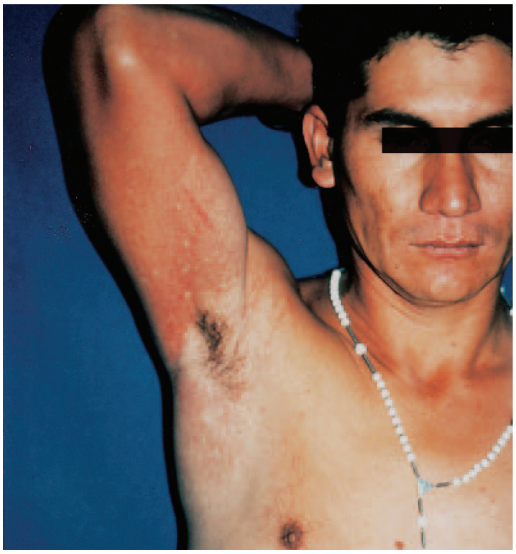


Figure 22.1 Scarlatiniform eruption of dengue fever. The "white islands within a sea of red" is a classic description for the cutaneous findings of dengue fever. (Photograph courtesy of Anna Cardenas, M.D., Walter Reed Army Medical Center, Washington, D.C.)



Figure 22.2 Scarlatiniform eruption of dengue fever. (Photograph courtesy of Paulo Emerich, MD.)

intense abdominal pain, and agitation. The progression to shock is very fast with a convergent, very low arterial blood pressure, which can even be inaudible. The patient can develop lethargy and metabolic acidosis; disseminated intravascular coagulation (DIC) can be observed. If the patient does not receive therapy for shock, death can result in 24 hours or less (29–34).

Edema and serosal effusion are caused by plasma leakage through the capillary vessels. Red blood cell leakage through the capillary vessel wall is also observed. Pleural effusion occurs in 80% of the cases and is usually small and located bilaterally, but can be unilateral (Fig. 22.9). Ascites can also be seen [35].

Complications

Complications are uncommon but can include encephalopathy, seizures, myocarditis, liver failure, and brain damage from intracranial hemorrhage or prolonged shock (36–39). Although there is an association between liver failure and dengue hemorrhagic syndrome/DSS epidemics, it is not clear whether this is caused by lack of perfusion or by a viral effect. Other complications that can be attributed to dengue include neuropathies, encephalitis, transverse myelitis, and Guillain-Barré syndrome [27,28,35,36].



Figure 22.4 Macules and petechiae of primary dengue infection in a Thai infant. (Photograph courtesy of Dr. Douglas Walsh, Armed Forces Institute Medical Sciences, Bangkok, Thailand.)

Some complications of DHF are: shock, fulminant liver insufficiency, renal insufficiency, myocardial dysfunction, encephalopathy (with seizures), and respiratory acute distress syndrome. These findings can occur as part of the multiple organic dysfunction syndrome seen in shock or they can be isolated [35,36].

Differential Diagnosis

The exclusion of other diseases in the differential diagnosis is very important because the diagnosis of dengue made solely on a clinical basis is not reliable (Table 22.2). Since the clinical picture of



Figure 22.3 Macules and urticaria of dengue fever. (Photograph courtesy of Ivo Castelo Branco, MD, PhD.)



Figure 22.5 Oral petechiae of dengue hemorrhagic fever. (Photograph courtesy of Paulo Emerich, MD.)



Figure 22.6 Conjunctival hemorrhages in dengue hemorrhagic fever. (Photograph courtesy of Paulo Emerich, MD.)

dengue is often marked, the diagnosis of dengue can be done very easily in endemic areas [36,40]. The differential diagnoses include typhoid fever, malaria, yellow fever, viral hepatitis, lymphocytic choriomeningitis, poisoning, St. Louis encephalitis, leptospirosis (anicteric type), influenza, rickettsial infection, hemorrhagic viral fevers, pharyngitis, sepsis, endocarditis, and pyelonephritis. Meningococcemia and meningococcal meningitis are included in the differential diagnosis of DHF. Circulatory shock and purpuric lesions usually occur only after the first 48 hours in the severe forms of dengue. In the case of meningococcemia and meningococcal meningitis, these signs occur generally in the first 2 days of the disease [1,9,27]. The epidemiological history is very important to distinguish dengue from malaria, yellow fever, and leptospirosis. In addition, laboratory examinations can be very helpful to differentiate dengue from yellow fever and leptospirosis, since their initial clinical presentation can be very similar [40]. Some viral diseases that can be considered in the differential diagnosis with dengue include West Nile, influenza, Marayo fever, Sindbis, chikungunya, Rift Valley fever, and Ross River [36].

Dengue is often under diagnosed and sometimes reported as influenza or measles because of the rash.



Figure 22.7 Conjunctival hemorrhages in dengue hemorrhagic fever (DHF). (Photograph courtesy of Anna Cardenas, M.D., Walter Reed Army Medical Center, Washington, D.C.)



Figure 22.8 Strongly positive tourniquet test in DHF. (Courtesy of Dr. Siripen Kalayanarooj, Chiang Mai, Thailand.)

A significant leukocytosis, especially if there is also a shift to the left, is compatible with pyogenic bacterial disease or leptospirosis and practically discards the diagnosis of dengue [41,42].

Severe cytopenia and fever can be observed in acute leukemia and in aplastic anemia. Moderate and severe anemia can be seen in these conditions and helps to differentiate them from dengue [42].

Diagnosis

1. Clinical history [27]:
   - Patients have a history of recent travel to an area where dengue is endemic
   - Initial symptoms include sudden onset of high fever (temperature >101°F), chills, and a severe aching of the head, back, and extremities
   - DSS can be seen after dengue hemorrhagic syndrome, with symptoms of respiratory and circulatory failure that can result in death
   - Uncommonly, patients with DF can have diarrhea
2. Physical examination [27]:
   - Hemorrhagic manifestations as epistaxis, purpura, petechia, and ecchymosis can occur in patients with DHF
   - The tourniquet test can be positive in more than 50% of the DHF cases



Figure 22.9 Right pleural effusion in DHF. (Courtesy of Dr. Chaicharn Phothirat, Chiang Mai, Thailand.)

Table 22.2 Differential Diagnoses of DF/DHF

Roseola infantum (exanthem subitum): Caused by human herpesvirus 6, roseola displays fever for 3 days, then a fine maculopapular rash appears as the fever vanishes	
Scarlet fever: Exudative pharyngitis, cervical adenitis, and a fine maculopapular rash with a coarse, sandpaper texture characteristic of scarlet fever. Group A beta hemolytic streptococcus on throat culture is diagnostic. This infection may lead to sepsis or necrotizing fasciitis	
Rocky Mountain spotted fever	See Table 16.2
Influenza	See Table 18-II.2
Typhoid fever	
Malaria	
Other hemorrhagic fevers:	
Rift Valley fever	
Chikungunya fever	
Kyasanur Forest disease (KFD)	
Omsk hemorrhagic fever (OHF)	
Colorado tick fever	
Crimean-Congo hemorrhagic fever	
Hantavirus hemorrhagic fever	
Lassa fever and the South American hemorrhagic fevers	
Ebola and Marburg hemorrhagic fevers	See Table 19.4
Meningococcemia	

3. Complementary tests: many serologic tests have been used for the diagnosis of dengue: IgM-capture enzyme-linked immunoabsorbent assay (MAC-ELISA), indirect immunoglobulin G ELISA, complement fixation, hemagglutination-inhibition and neutralization test. The high cross-reactivity observed with these tests is considered limitations of these techniques. Some commonly used methods for viral isolation are: inoculation on mosquito cell cultures, inoculation on mammalian cell cultures, intrathoracic inoculation of adult mosquitoes, and intracerebral inoculation of newborn mice. Some useful new diagnostic techniques that have been developed are: real-time polymerase chain reaction (RT-PCR) and nucleic acid hybridization [41,42].

Viral isolation has a high cost and should not be routinely done for the diagnosis of dengue. However, it is considered the best method available to identify the viral serotype and consequently, it is useful in the context of epidemiological vigilance. For viral isolation during the viremic phase of the disease, the appropriate period of time for blood collection is between the 3rd and 4th day (but can be done until the 6th day) [41].

ELISA is a commonly used technique for the diagnosis of dengue by serology. RT-PCR is a very important test, since it can detect dengue viruses up to the 10th day after onset of symptoms. However, ELISA does not identify the dengue virus serotype causing the current infection, thus molecular techniques have a very important role in the diagnosis of dengue (42–44).

At present, the diagnosis of dengue is based on viral isolation, serology, and RNA detection.

During the first few days of the infection, the PCR-based methods are considered more effective, however, the MAC-ELISA becomes more sensitive 5–6 days after the onset of the disease [41,42]. The combination of immunological and PCR-based tests is considered the best method for the diagnosis of the disease. Besides being more sensitive than the nested RT-PCR approach, RT-PCR is reproducible, rapid, and highly specific [45].

The MAC-ELISA test can detect the antiviral IgM. It is considered a very useful test and can begin to give a positive result in the 6th day of the disease. It can continue to be positive for up to 30–90 days. This long duration of positive testing can predispose to false-positive interpretation; for example, in a situation where the patient acquired an asymptomatic dengue virus infection 1 month previously and is having fever caused by another viral infection at the moment that the blood is collected for the test [27,41,42].

An accurate and fast diagnosis of dengue is extremely important for effective control of dengue outbreaks. The following laboratory tests can be ordered [27,46,47]:

- CBC: a complete cell count can show an increase of 20% in the hematocrit (hemoconcentration), thrombocytopenia, and leucopenia. In order to facilitate the early recognition of DHF, platelet count monitoring should be done every 24 hours. Up to 50% of patients with DF can have thrombocytopenia. In patients with DHF and DSS, platelet counts less than 100,000 can be observed and occur before defervescence and the onset of shock. Near the end of the febrile phase of the disease, leucopenia, frequently with lymphopenia, is seen. However, lymphocytosis with atypical lymphocytes is often observed before defervescence or shock. An increase in the hematocrit greater than 20% precedes shock and is a sign of hemoconcentration. The hematocrit level should be evaluated at least every 24 hours to facilitate early recognition of DHF and every 3–4 hours in severe cases of DSS and DHF. Thrombocytopenia and leucopenia are commonly seen in cases of DF and are believed to be related to direct destructive actions of the dengue virus on bone marrow precursor cells. The hematocrit is essential to confirm the hemoconcentration [46,47]. Criteria adopted by the World Health Organization (WHO) can be used to evaluate hemoconcentration in different age ranges:
  - patients up to 15 years of age: hematocrit greater or equal to 45% (20% greater than the limit of 38%)
  - adult females: hematocrit greater or equal to 48% (20% greater than the limit of 40%)
  - adult males: hematocrit greater or equal to 54% (20% greater than the limit of 45%)
- Leucopenia (mild to moderate) associated with relative leukocytosis and eventually with atypical lymphocytosis, is the most frequent laboratory finding of classical dengue. Mild thrombocytopenia, usually not less than 100,000/mm^3 can be observed. Usually, the hematocrit is seen in the normal range. An increase in the transaminases can be seen, especially an increase in alanine transaminase (ALT) [27,46,47].
- Chemistry panel: it can show increased blood urea nitrogen (BUN), electrolyte derangements, and acidosis. The most common electrolyte abnormality seen in patients with DHF or DSS is hyponatremia. In patients with shock, an increase in BUN can be seen. Metabolic acidosis can also be seen in patients with shock [46,47].
- Isolation of dengue virus from a clinical specimen
- Detection of dengue viral material in a clinical specimen
- A significant increase in the level of a dengue virus-specific IgG proven by neutralization or another specific test
- Use of IgM-capture ELISA serological tests

- In order to exclude or confirm other potential causes of the patients' signs and symptoms, cultures of urine, cerebrospinal fluid (CSF), blood, and other body fluids should be performed, as necessary [46]
- Since administration of blood products can be necessary in cases of severe DHF or DSS, typing and cross-matching of blood should be ordered in these situations
- Liver function tests can be ordered, since the patients can have mild increases in the transaminase levels and low albumin
- In patients with severe hemorrhagic manifestations, coagulation studies can be very helpful. Some findings that can be observed are: prolongation of the prothrombin time, prolongation of the activated partial thromboplastin time, and low fibrinogen and increased fibrin degradation product levels [46,47]
- Hematuria can be seen
- Total protein and fractions: hypoalbuminemia can be observed and is a result of the leakage of plasma to the third space
- A right-sided pleural effusion can typically be seen on the chest radiograph (Fig. 22.9). Patients with DSS commonly have bilateral pleural effusions
- Ultrasound of the abdomen: thickening of the gallbladder wall can be observed and this can be a sign that the patient may develop cavitary effusions in the near future [47]
- In severe cases, arterial blood gas determination should be performed in order to evaluate ventilation, oxygenation, and pH
- Some clues to evaluate the possibility of plasma leakage in DHF are: an elevation of 20% in the basal hematocrit, a decrease of the hematocrit by 20% after hydration, hypoalbuminemia, and cavitary effusion
- The diagnosis of DHF (Table 22.3) can be made when there is a confirmed or probable case of dengue infection and hemorrhagic changes demonstrated by one of the following [27,48]:
  - Bleeding from mucosa, gastrointestinal tract, infection sites, or other sites
  - Ecchymoses, purpura, petechiae
  - A positive tourniquet test
  - Melena or hematemesis and thrombocytopenia (<100,000 cells/mm^3) and evidence of plasma leakage caused by increased vascular permeability demonstrated by one or more of the following: an increase in average hematocrit level greater than 20% for the age and sex, a decrease in hematocrit level greater than 20% following volume replacement compared to baseline, or signs of plasma leakage (e.g., ascites, hypoproteinemia, pleural effusion)

Table 22.3 World Health Organization Diagnostic Criteria for DHF and DSS

DHF
Fever
Hemorrhagic manifestations, with either minor or major bleeding phenomena or a positive tourniquet test (except in shock cases)
Thrombocytopenia, with platelet count ≤ 100,000/mm3
Evidence of increased capillary permeability, such as hemoconcentration (hematocrit increased by≥ 20%) or pleural effusions (on radiographs or other imaging study)
DSS
All of the above, plus hypotension or narrow pulse pressure (≤20 mm Hg)

Table 22.4 Treatment of Dengue Fever

Symptom	Treatment
General	Bed rest (during the febrile period) and adequate oral fluids. Intravenous fluid therapy is the mainstay of treatment for patients with DHF
Fever and pain	Antipyretics and analgesics. Aspirin and nonsteroidal anti-inflammatory drugs are contraindicated, because they may potentiate the hemorrhagic diathesis
Shock	Intravenous fluid therapy, with Ringer's lactate, normal saline, or a plasma expander. Close monitoring with frequent vital signs and central venous pressure measurements is recommended. The urinary output should be followed. Serial hematocrits should be performed to follow the patient's hemoconcentration. Acid-base and electrolyte disturbances should be corrected. Oxygen therapy should be given.
Hemorrhage	Fresh whole blood or red blood cell transfusions are required for uncontrollable, massive bleeding
DIC	Fresh frozen plasma or platelet transfusions. Heparin infusions may be helpful

The diagnosis of DSS can be made in cases meeting all the above criteria plus evidence of circulatory failure, such as the following [27,48]:

- Hypotension
- Narrow pulse pressure (<20 mmHg)
- Rapid, weak pulse
- Altered mental status
- Cool, clammy skin

Treatment

The treatment of dengue is supportive and nonspecific (Table 22.4). Hydration is a very important component of the therapy for dengue. Besides fluid replacement, the patients can also benefit from bed rest and the use of analgesics [49]. Patients with hypotension or DIC need to be admitted to the intensive care unit.

The vast majority of patients with dengue are cured after 1 week from the beginning of the appropriate therapy. In the case of classical dengue or uncomplicated hemorrhagic dengue, patients can be discharged after 2 days without fever. The average time that the patient is away from work is 10 days from the onset. Prolonged fatigue can be seen in the convalescence period [27].

The mortality of DHF may be reduced to less than 1% with adequate intensive supportive therapy. The main feature of DHF clinical management is the maintenance of an adequate circulating fluid volume. The use of high doses of corticosteroids has not been shown to change the mortality rates in the case of severe bleeding and shock syndrome [50,51].

Acetaminophen (paracetamol) is the drug of choice for the treatment of fever and pain. Aspirin and NSAIDs are contraindicated, since they are associated with the increased risk of hemorrhagic manifestations. At present, there is no specific antiviral drug to treat dengue infections (52–57).

Prognosis

- With an early diagnosis and adequate supportive therapy, fatalities are rare
- Cases of DHF and DSS that do not progress to death usually have no associated sequelae

- Patients with DF have an excellent prognosis and a complete recovery is the norm

Disease Classification

Hemorrhagic dengue is classified by the World Health Organization as follows [27]:

- Level I: positive tourniquet test and absence of hemorrhagic manifestations and hemodynamic instability
- Level II: presence of hemorrhagic phenomena that occur spontaneously
- Level III: weak pulse, arterial hypotension, tachycardia, pulse pressure of 20 mmHg, agitation, and clammy, cold skin
- Level IV: profound shock without pulse and inaudible arterial pressure

Prophylaxis

Currently, the only method of preventing or controlling dengue or DHF is to combat the arthropod vector. At present, there is no vaccine available for public health use. Insecticides, barrier measures, such as protective clothing, insect repellents and mosquito nets, are important for prevention and control of the *Ae. aegypti*. Prevention of the disease should not be centered solely on the use of insecticides, since dengue has an important epidemiological complexity [56,57]. The best preventive method for people living in areas infested with *Ae. aegypti* is to eliminate the places where the mosquito lays eggs. In the Americas and Asia, the arthropod vector breeds primarily in manmade containers, such as earthenware jars, metal drums, and concrete cisterns used for domestic water storage, as well as other items that accumulate rainwater, such as plastic food containers and automobile tires. In the African continent, the mosquito also breeds in natural habitats, such as leaf axils and tree holes. The use of appropriate insecticides on larval habitats, particularly those that are considered useful by the householders, e.g., water storage containers, prevent mosquitoes breeding for many weeks; however, it must be reapplied periodically. New techniques for rendering the arthropod vector sterile have recently been reported from Oxford University [53].

Biocontrol efforts using small, mosquito-eating fish and copepods (tiny crustaceans) have also been done with some success.

Emergency control measures, which can be done during outbreaks, include the application of insecticides as air sprays to kill adult mosquitoes using portable or truck-mounted machines or even aircrafts; however, the effectiveness of such measures are variable and transient. In addition, this strategy is costly and very demanding operationally. In order to ensure the appropriate choice of chemicals to combat the vectors, regular monitoring of the mosquitoes' susceptibility to the most widely used insecticides is necessary. Surveillance and monitoring of the vector population can be used to evaluate the impact of the programs [27].

Environmental management and chemical methods are used for the control of the vector. Improved water storage practices and an adequate solid waste disposal are important measures that can be done in community-based programs. Education of the entire population at risk in a region, utilizing media vehicles and health agents is crucial. It is very important to discard any object that can potentially accumulate rainwater. Vases with fresh flowers and pet watering containers should be emptied and scoured at least once a week. This measure can help in the elimination of the mosquito eggs and larvae and, consequently, decrease the number of mosquitoes. Moreover, covering containers to avoid access by egg-laying female arthropods is another relevant measure. In endemic areas, risk of being bitten by mosquitoes indoor is reduced by the use of screened windows and doors and by the use of air conditioning. The use of mosquito repellents with 20–30% DEET, as the active ingredient on the exposed skin, is useful as a preventive measure. Since *Aedes* mosquitoes are active in the daytime, personal protection strategies differ somewhat from those for mosquitoes active in the night-time (e.g., members of the genera *Culex* and *Anopheles*). Primary prevention of the disease mainly resides in eliminating or reducing the arthropod vector. The risk of dengue infection by international travelers appears to be low, except when an epidemic is in progress [3,5].

A coordinated community effort is important to increase awareness about the disease, how to recognize it, and how to combat the arthropod vector, decreasing the risk of an epidemic. A community-based and sustainable integrated mosquito control should be the emphasis for dengue prevention and control.

Immunization

Since there are four different types of the virus that can cause the disease, vaccine development for dengue and DHF is difficult. In addition, protection against only 1 or 2 dengue viruses can potentially increase the risk of more severe disease. However, efforts are currently ongoing to produce vaccines for protection against all four types of dengue viruses. The control of dengue will only be possible after an efficient tetravalent vaccine is available, since there is no cross-protection between the four serologically distinct types of the virus and because of the possibility of immune enhancement by monotypic antibody leading to DHF with subsequent natural infections [27].

Currently, there are several ongoing vaccine development programs. One of them, the Pediatric Dengue Vaccine Initiative, was set up in 2003 with the goal of accelerating the development and introduction of dengue vaccine(s) that are accessible and affordable to poor children in endemic countries.

Future Perspectives

- Genetic mapping of the arthropod vectors can help advance viral containment efforts
- Because of the short generation time and the adaptability of dengue viruses, the development of an effective vaccine produced by recombinant DNA technology will probably continue to be a challenge

The immune mechanisms responsible for DHF are complex and need to be clarified further for the development of therapeutics as well as efficacious and safe dengue vaccines. The role of enhancing antibodies in dengue pathogenesis is still not clear.

Conclusion

Millions of dengue cases occur worldwide each year. Dengue is usually a nonspecific febrile illness, but the spectrum ranges from asymptomatic to severe hemorrhagic fever and sudden fatal shock. Global warming and the observation that *A. albopictus* strains have adapted to temperate conditions could lead to increased cases of dengue and other mosquito-borne diseases. Control of dengue currently requires control of the principal vector

mosquitoes. Vaccine development, the use of repellents, mosquito barriers, and habitat control have the potential to limit dengue outbreaks. Life-saving intervention and management of a patient with complications depend on a high level of suspicion, especially in persons with a history of travel to endemic areas. Once a person is infected, the key to survival is early diagnosis and appropriate treatment for life-threatening complications, such as DHF and DSS.

JAPANESE ENCEPHALITIS

Definition

JE is an acute infection of the central nervous system (CNS). This flavivirus causes the greatest number of cases of childhood viral encephalitis in Asia with significant mortality and morbidity. The virus is a member of the St. Louis complex related to St. Louis, Murray Valley, West Nile, Ilheus, and Rocio encephalitis viruses. There are two immunotypes, the Nakayama strain and the JaGAr01 (Beijing-1) strain. There are also four geographically distinct genotypes: type I in Japan, China, Taiwan, Vietnam, Nepal, India, and Sri Lanka; type II in northern Thailand and Cambodia; type III in Indonesia, Malaysia, and southern Thailand; and type IV in eastern Indonesia. Types I and II occur in an epidemic pattern, and types III and IV occur as endemics [58].

History

As early as 1871, JE was recognized as a disease. In 1924, a severe epidemic occurred in Japan, with 6125 documented cases. However, it was not until 1935 that the etiological agent was serologically established as the prototypic (Nakayama) strain. In 1938, the virus was isolated from *Culex tritaeniorhynchus* [58]. Scherer and associates [59] showed that the host cycle involved pigs and birds, with transmission by *C. tritaeniorhynchus* to humans.

Incidence

The disease occurs throughout Asia in the following countries: Japan, China, Cambodia, Indonesia, Malaysia, Korea, Philippines, India, Laos, Myanmar, Thailand, Vietnam, and southeastern Russia (Fig. 22.10) [58,60]. An estimated 1 in 300 JE infections present as symptomatic illness [60,61]. The reported annual incidence of clinical infections in endemic regions is 50,000 cases, with 10,000 of these being fatal [60]. An increase in epidemics has been seen in India, Nepal, and northern southeast Asia in the past 25 years. China and Taiwan have seen a decrease in epidemics, owing to vaccination programs and improved socioeconomic and agricultural conditions [60].

The majority of people in endemic regions are infected by the age of 15 years, and children are most commonly clinically infected. In nonendemic regions, epidemics have a bimodal distribution affecting the elderly as well [58].

Temperate climates maintain transmission during the monsoon season of April or May through October, with incidence being highest in rural areas and in young males. Tropical areas have endemic disease with few epidemics.

Pathogenesis

The JE vector is the *Culex* mosquito, particularly *C. tritaeniorhynchus.* Other species involved in transmission occur geographically: *C. vishnui* in India; *C. gelidus* and *C. fuscocephus* in India, Malaysia, and Thailand; *C. annulus* in Taiwan; and *C. annulirostris* in Guam. The mosquito breeds in flooded rice fields and water pools. The vector rate of infection is 1–3% [60]. JE virus has also been isolated from *Aedes* and *Anopheles* mosquitoes. Humans and equines are not considered to be reservoirs, but are "dead-end hosts" because of the short viremic period. Transmission of the virus has been shown to occur both vertically (transovarially) and sexually (venereally) in mosquitoes. Other suggested methods of overwinter maintenance include alternate vectors (ticks or mites),

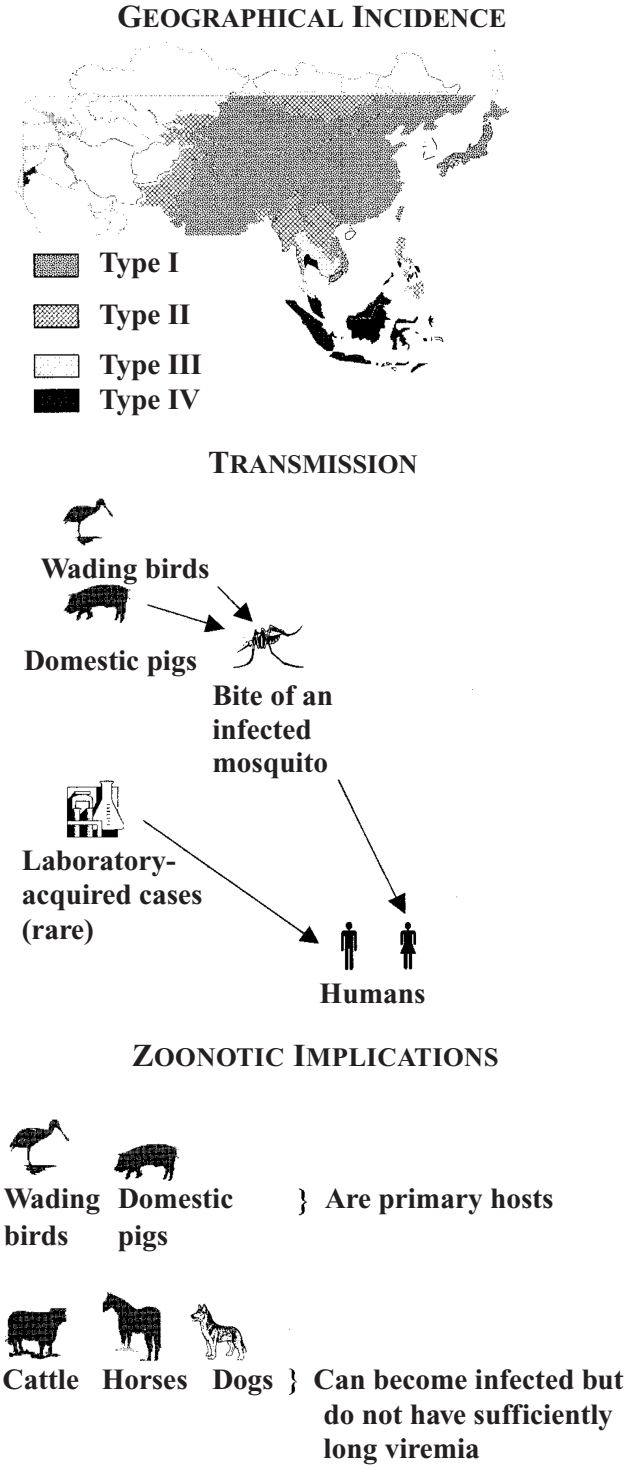


Figure 22.10 Incidence and transmission of Japanese encephalitis (JE).

Table 22.5 Clinical Manifestations of Japanese Encephalitis (JE)

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
4–14 days	Sudden onset of prodromal symptoms lasting 2–4 days, with headache, fever, chills, malaise, anorexia, nausea, and vomiting. Abdominal pain and diarrhea may be quite prominent in children. During this time, lethargy increases and behavioral changes may develop	Serology, with demonstration of IgM or a fourfold rise in IgG Viral isolation (uncommon)	
	↓		
7–18 days	The encephalitic phase consists of central nervous system (CNS) signs, with mental status changes (typically coma or stupor), pathological reflexes, lower motor neuron deficits, incoordination, rigidity, paresis, tremors, and cranial nerve palsies		Convulsions frequently occur in children, but develop in less than 10% of adults. Meningismus occurs more frequently in adults. Death, when it occurs, typically comes on the 5th–9th day of clinical illness (days 9–23). During recovery from coma and paralysis, common complications include pneumonia, bacteremia, stasis ulcers, and urinary tract infections. These may sometimes be secondary causes of death.
	↓		
12–23 days	Fever begins to defervesce and neurological function slowly improves		
	↓		
22–33 days	Convalescent phase begins, with gradual improvement in neurological function over weeks, months, or sometimes years		

vertebrate infections, reintroduction by migrating birds, and survival in hibernating mosquitoes [58,61].

After an infected mosquito feeds on a human, the virus replicates in local and regional lymph nodes. This leads to viremia, with infection of various organs including the brain. Access to the CNS is thought to occur through invasion of the endothelial cells of the cerebral capillaries [62].

Clinical Manifestations

The spectrum of clinical disease with JE ranges from a febrile headache syndrome to aseptic meningitis or encephalitis (Table 22.5). During the acute phase of illness, the most frequent complications include secondary infections (particularly pneumonia) and hyponatremia due to inappropriate antidiuretic hormone (ADH) secretion. The case-fatality rate with this disease is 5–40%, and may be as high as 70% in epidemics. Children and the elderly are at highest risk for mortality. A high percentage (45–70%) of survivors have permanent neurological and psychiatric sequelae, particularly in children younger than 10 years old [63]. These complications include seizure disorders, paralysis, mental retardation, and Parkinsonism.

There is evidence for latent and congenital human infections. A high rate of miscarriage occurs in women infected during the first and second trimester of pregnancy, but not in the third trimester [64]. Concurrent infection with JE and herpes simplex virus (HSV) suggests that JE invasion of the CNS occurs with disruption of the blood-brain barrier [65].

Pathology

CNS involvement acutely includes cerebral edema, congestion, and hemorrhage. Gray matter degeneration and necrosis, neuronophagia, perivascular inflammation, and microglial proliferation occur. Infection appears to be specific to neurons [66], with the thalamus and brainstem being most commonly involved [58]. Myocarditis, Kupffer cell involvement, pulmonary alveolar inflammation, and renal hemorrhages may be seen [58].

Laboratory Findings

A mild leukocytosis occurs. When urinary symptoms occur, the urinalysis reveals sterile pyuria, microscopic hematuria, and albuminuria. The CSF may have a high opening pressure, with leukocytes generally 10–500/mm^3, but rarely up to 1000/mm^3 (predominantly neutrophils initially followed by lymphocytes), and protein mildly elevated at 50–100 mg/dl. An electroencephalogram (EEG) shows decreased activity, generalized slowing, and dysrhythmia. Brain computerized tomograms reveal abnormalities in the thalamus and basal ganglia. Magnetic resonance imaging (MRI) of survivors with sequelae generally shows abnormalities of the thalamus, globus pallidus, hippocampus, and substantia nigra [58,60].

Diagnosis

Serological testing with IgM-capture ELISA of the CSF or blood is specific within 4–7 days of disease onset [60]. Dot blot or immunoprecipitation IgM assays may also be used. A fourfold rise in titer of paired sera with HI, CF, or N tests is diagnostic, although there may be a cross-reaction with other viruses [58]. Virus isolation from blood is uncommon, but may be successful if performed in the early stages of disease (during the first 6–7 days of symptoms); virus may be isolated from the CSF in some cases, and is generally associated with a poor prognosis (Table 22.6) [58].

Treatment and Prevention

There is no specific treatment for JE. Supportive care is essential, especially for hyperthermia, seizures, and acute neurological deterioration (Table 22.7). No specific antiviral agents are known to have efficacy against this disease. In addition, corticosteroid therapy was not shown to be beneficial [67]. Appropriate antibiotics and antiviral agents should be considered early in the course of disease until bacterial CNS disease or herpetic encephalitis can be excluded.

There are three types of JE vaccines in use. The first is a mouse brain-derived inactivated vaccine, the only one commercially

Table 22.6 Differential Diagnoses of JE

Herpes simplex virus (HSV) encephalitis	See Table 16.2
Enteroviral aseptic meningitis	See Table 19.8
Bacterial meningitis	
Tuberculous meningitis	
Cerebral malaria	
Dengue virus with encephalopathy	
Intracranial hemorrhage/stroke	
Heat stroke	
Lead encephalopathy	
Toxic encephalopathy	
Brain abscess	
Brain tumor	
Postinfectious encephalitis	
Metabolic encephalopathy	
Status epilepticus	
Acute confusional or basilar migraine	
Reye's syndrome	
Rocky Mountain spotted fever	See Table 16.2
Other arboviral encephalitides:	
Eastern equine encephalitis	
Western equine encephalitis	
Venezuelan equine encephalitis	
West Nile fever	
California encephalitis	
St. Louis encephalitis (SLE)	
Tick-borne encephalitis (TBE)	
Powassan encephalitis	
Rift Valley fever	See Table 18-II.2
Kyasanur Forest disease	
Colorado tick fever	

available internationally. Because of the relatively high cost, large-scale immunization is less likely in poorer countries. Initial injections are given at an interval of 1–2 weeks, but the booster dosing intervals are poorly defined and have regional variation. A second vaccine is a cell culture-derived inactivated vaccine manufactured in China. It is inexpensive, but is being replaced by a third vaccine, a cell culture-derived live attenuated vaccine. This vaccine is also manufactured in China and is inexpensive.

Side effects of immunization include local reactions in 20% of patients, and systemic effects in 20%, such as headache, fever, myalgia, and gastrointestinal symptoms. Acute encephalitis has been associated with immunization, and two fatal cases have occurred [60]. Hypersensitivity reactions may also develop, including urticaria, angioedema, respiratory distress, erythema nodosum, erythema multiforme, and rarely, anaphylaxis, with two reported fatalities [60,61]. The only contraindication to vaccination is hypersensitivity to previous vaccination. In endemic areas, JE immunization is recommended over 1 year of age.

Vector control with pesticides, improvement of agricultural practices, and personal protective measures remain important methods of decreasing JE. Mosquito repellents and protective clothing are recommended during outdoor exposure in endemic areas as well as the use of bednets for sleep.

Table 22.7 Treatment of JE

Symptom	Treatment
Fever	Antipyretics
Increased intracranial pressure	Mannitol infusions, hyperventilation, elevation of head of bed
Convulsions	Anticonvulsant therapy
Altered mental status	Supportive care, with respiratory support as needed, control of fluid balance, and prevention of secondary infections
Extrapyramidal symptoms	Trihexphenidyl

Conclusion

The frequency and severity of JE make it an important arboviral infection. Vector control affects the frequency of disease, but vaccination constitutes the ultimate solution to human disease. Methods of interrupting the natural cycle of disease will be problematic.

KYASANUR FOREST DISEASE

Definition

Kyasanur Forest disease (KFD) is a tick-borne virus, occurring in an endemic area of India. Other antigenically related flaviviruses include those that cause Omsk hemorrhagic fever (OHF) and Far Eastern tick-borne encephalitis (TBE). There is early fever and myalgia with occasional hemorrhagic symptoms. A later phase with encephalitis is seen. The maintenance of virus in the environment involves a tick–tick cycle and two tick–vertebrate cycles, with wild monkey epizootics and human disease.

History

First isolated in 1957 in India from a monkey, thousands of human cases have since been reported. During the first documented epidemic in 1958, the virus was isolated from infected humans [68,69]. Further research showed that the human epidemic followed disease in monkeys [70]. Local villagers had already named this illness "monkey disease" because of the known association with dead monkeys. In 1968, Boshell and coworkers isolated the virus from ixodid ticks [71]. The disease had been limited to an area of 77 square miles of the Kyasanur Forest, which is in the state of Karnataka (formerly Mysore) in southern India. However, infection has been progressively spreading, as evidenced by more recent epidemics that encompassed larger areas of the region (Fig. 22.11) [72].

Incidence

Annual epidemics occur in India during the pre-monsoon season, mid-November to mid-April. Between 400 and 500 proven cases occur annually, predominantly in persons with exposure to forested areas of the endemic region. Outbreaks often develop as a result of increased human activity in the endemic forest area, such as deforestation, commercial lumbering, and cattle ranching. The density of the tick vector correlates with frequency of human disease.

Pathogenesis

A variety of ixodid tick species are implicated in the transmission of KFD virus. Nymphal *Haemaphysalis spinigera* is the vector for human disease in over 90% of cases. Epizootics occur in wild monkeys, and monkey deaths provide a sentinel for viral activity.

In human infection, viremia is present between the 2nd and the 12th day of clinical illness. During this period, the virus is

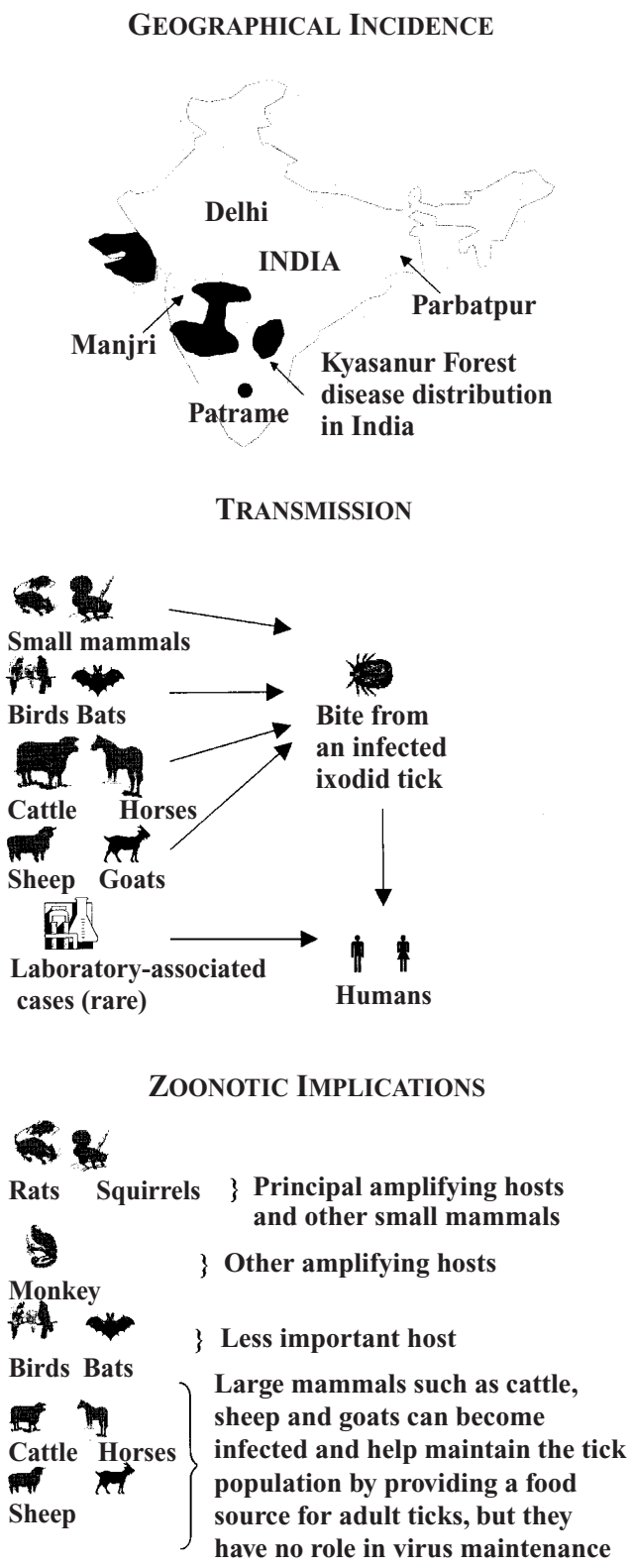


Figure 22.11 Incidence and transmission of Kyasanur Forest disease.

widely disseminated and can be demonstrated in various organs, such as heart, lung, kidneys, liver, spleen, and skeletal muscle. The virus can occasionally be isolated from the CSF in severe cases. The neurological symptoms that develop late in the course of disease are due to delayed infection of the CNS rather than a post-infectious phenomenon.

Clinical Manifestations

During the acute phase of illness, lymphadenopathy (particularly axillary and cervical lymph nodes) and bronchiolar involvement are common, and bradycardia is expected [73]. No skin discoloration or cutaneous eruption is observed with most cases of this illness [73], although petechiae have been reported in patients (Tables 22.8 and 22.9). Death is unusual, but can result from coma or pneumonia [74]. Most patients recover completely.

Pathology

Degeneration of hepatic and renal parenchyma, hemorrhagic pneumonia, an increase in the hepatic and splenic reticuloendothelial tissues, and erythrophagocytosis characterize the pathology [75]. Skin lesions relate to mucus membrane and cutaneous hemorrhagic phenomenon, probably due to DIC.

Laboratory Findings

Leukopenia and elevated serum aspartate transaminase (AST) are frequently seen. The presence of atypical lymphocytes is a consistent feature [73]. Thrombocytopenia of varying degree and anemia may also be present. Albuminuria occurs in most cases during the acute febrile period, and granular casts may occasionally be observed. In the presence of hemorrhage, laboratory documentation of DIC is expected. Patients with meningeal signs later in the course of disease may have abnormalities in the CSF, with a mild mononuclear pleocytosis and an increase in protein.

Diagnosis

Viremia occurs on days 2–12, during the nonspecific phase, earlier than the more severe and more specific findings. The virus can be isolated during this acute phase of disease. Standard serological testing (IgM ELISA or paired sera for CF, HI, or N testing) can also give the diagnosis, but cross-reaction from previous flavivirus infections may complicate results (Table 22.10).

Treatment and Prophylaxis

The treatment for KFD is supportive, particularly for shock, DIC, and acute neurological deterioration (Table 22.11). No specific antiviral therapy is available. A formalin-inactivated vaccine made in chick embryo fibroblasts is effective and available to high-risk groups and during epidemics in India.

Conclusion

KFD virus is a significant problem in its endemic area. The variety of tick vectors, the tick–small animal perpetual cycle, the use of large animals by the tick population, and the tick–tick transmission are potent transmission strategies for the virus. The increase in worldwide travel and commerce has the potential to further disperse this already spreading virus.

OMSK HEMORRHAGIC FEVER

Definition

OHF is caused by a flavivirus of the TBE complex. It occurs in a remote part of northwestern Siberia. Virologically and clinically, it is closely related to KFD.

History

The OHF was first isolated during the 1945–1949 epidemic in western Siberia. Travel to this area was restricted, and experience

Table 22.8 Clinical Manifestations of KFD

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–8 days	Sudden onset of fever and severe headache. Back pain, myalgias, listlessness, and prostration follow. Cough, sore throat, diarrhea, or vomiting may or may not be present. Conjunctival and pharyngeal suffusion appear, with papulovesicular palatine lesions	Viral isolation during the first 12 days of clinical disease Serology with acute IgM or fourfold rise in IgG	Hemorrhagic signs include hematemesis, melena, hemoptysis, and gingival bleeding
	↓		
7–15 days	In over half of patients, the illness progresses to involve hemorrhage, neurological signs indicative of brain involvement, or pulmonary findings of dyspnea and cyanosis		Hepatosplenomegaly or splenomegaly may occasionally develop
	↓		
17–22 days	The acute phase of illness resolves, with recovery for some patients at this time. In 15% of cases, an afebrile period of 1–3 wk occurs, followed by recurrence of fever and prodromal symptoms along with hemorrhage and mild meningoencephalitis		Signs of CNS involvement include severe headache, neck stiffness, coarse tremors, abnormal reflexes mental disturbance, and giddiness. Generalized convulsions indicate a poor prognosis. Death may sometimes occur in this second phase of illness
	↓		
19–34 days	Recovery begins in the remaining patients. Convalescence in survivors is prolonged and may last up to 4 wk.		

was limited to Soviet physicians. An evolving Russian tourist industry may change the western medical experience, although the disease frequency has diminished in recent years.

Incidence

Few cases are now seen in rural residents of the forest-steppe Omsk region of western Siberia (Fig. 22.12). Almost 1500 cases were reported in the endemic area between 1945 and 1958 [76]. Seroprevalence rates in some areas of the endemic region are higher than 30%. There is a spring-summer-fall distribution coinciding with *Dermacentor pictus* activity and a more common winter disease distribution related to muskrat hunting. The mortality rate with this disease is less than 5%.

Pathogenesis

The vector for OHF is an ixodid tick, *D. pictus*, possibly *D. reticularus* or *D. marginatus*. A maintenance cycle is thought to involve another tick, *Ixodes apronophorus* [58]. The host animals excrete virus in urine and feces, which plays a role in horizontal infection [77]. Infection of humans generally occurs in muskrat hunters with direct contact while skinning the animals. Family members of hunters account for 28% of infections [77], likely owing to exposure of the infected animal's tissue or fluids. Individuals prone to tick-borne disease are agricultural workers of the area and gatherers of mushrooms and wild berries. No direct human–human transmission of the virus has been documented [72].

Table 22.9 Signs and Symptoms of KFD

Signs	Percent of cases	Symptoms	Percent of cases
Fever	99	Fever	99
Hypotension	61	Weakness	90
Conjunctival congestion	54	Headache	69
Hemorrhage	54	Vomiting	55
Facial flushing	50	Hemorrhage	54
Hepatomegaly	50	Severe myalgia	53
Gingival hyperplasia	46	Altered sensorium	45
Neurological signs	45	Diarrhea	22
Pulmonary signs	45	Convulsions	22
Second phase of fever	14	Cough	13
Petechiae	13	Arthralgia	13
Stomatitis	11	Sore throat	6
Anemia	7		
Splenomegaly	3		

Table 22.10 Differential Diagnoses of KFD

Tick-borne encephalitis	See Table 16.2
HSV encephalitis	
Bacterial meningitis	See Table 19.8
Leptospirosis	See Table 19.4
Other hemorrhagic fevers:	
Dengue	
Ebola and Marburg hemorrhagic fevers	
Other arboviral encephalitides:	See Table 16.2
Eastern equine encephalitis	
Western equine encephalitis	
Venezuelan equine encephalitis	
West Nile fever	
California encephalitis	
Japanese encephalitis	
St. Louis encephalitis	
Powassan encephalitis	
Influenza-like illnesses	See Table 18-II.2
Other hemorrhagic fevers:	
Rift Valley fever	
Omsk hemorrhagic fever	
Colorado tick fever	
Crimean-Congo hemorrhagic fever	
Hantavirus hemorrhagic fever	
Lassa fever and the South American hemorrhagic fevers	

Clinical Manifestations

Clinical illness with OHF closely resembles that of KFD, except that hemorrhagic manifestations have an earlier onset. In addition, OHF more commonly has sequelae of psychomotor retardation, hearing loss, hair loss, and depression (Table 22.12).

Pathology

Autopsies show scattered hemorrhages, endothelial damage, interstitial pneumonia, normal lymphoid tissues, and focal necrosis of brain tissue. The pathology is not specific to OHF and is common to other hemorrhagic fevers.

Laboratory Findings

Leukopenia, thrombocytopenia, and plasmacytosis are common. Transaminases may be elevated. Hemoconcentration, albuminuria, and hematuria are evident in the most severely ill.

Table 22.11 Treatment of KFD

Symptom	Treatment
Fever and myalgias	Antipyretics and analgesics. Aspirin and nonsteroidal antiinflammatory drugs should be avoided because thrombocytopenia and hemorrhage can occur with this infection.
Hypotension and shock	Intravenous fluids
Convulsions	Anticonvulsants
Hemorrhage	Blood transfusions for severe bleeding
DIC	Fresh frozen plasma or platelet transfusions, as needed

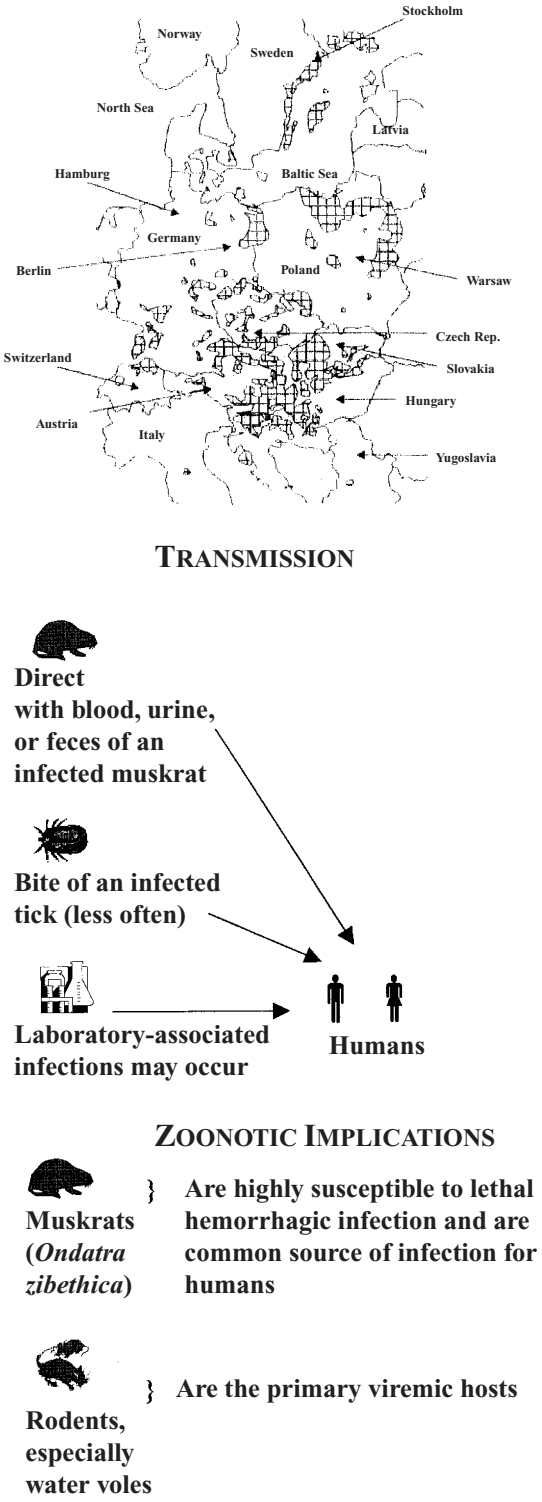


Figure 22.12 Incidence and transmission of OHF.

Diagnosis

Diagnosis is made by isolation of the virus during the acute phase of illness or by serological testing with ELISA, N, HI, and CF antibodies [77,78]. Paired serum in infected individuals will show seroconversion or a fourfold rise in IgG titers (Table 22.13).

Table 22.12 Clinical Manifestations of OHF

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–7 days	Sudden onset of fever and chills, followed by headache, myalgias, and prostration. Conjunctivitis, cervical adenopathy, and gastrointestinal symptoms often occur ↓	Isolation of virus during acute disease Fourfold rise in IgG or seroconversion in paired sera	
10–17 days	Uncomplicated cases resolve after 7–10 days of symptoms. 30–50% of cases have remission of symptoms, with an afebrile period lasting 1–2 wk followed by recurrence of fever ↓		
17–31 days	Development of second phase of fever, with headache, vomiting, meningismus, or other CNS symptoms. Hemorrhage may occur, with epistaxis, gastrointestinal bleeding, metrorrhagia, and hemorrhagic pneumonitis. A papulovesicular eruption may also occur on the soft palate. Hyperemia of the face, upper body, and mucous membranes often occurs ↓		The second febrile phase is typically more severe than the first Hemorrhage tends to be less severe than that of KFD. Bleeding predominately occurs from the nasal, enteric, lung, and uterine tissues Complications include bronchopneumonia, meningoencephalitis, shock, and rarely, death
Days to weeks	Most patients recover completely, but sequelae may occur (see text). Convalescence may be prolonged with weeks of persistent weakness		

Treatment and Prevention

Treatment remains supportive, aimed at controlling hemorrhage and replacing blood loss. The mainstay of prevention is limiting exposure to the tick vector and careful handling of muskrat hosts in endemic areas, as well as laboratory safety measures. A vaccine was reported to be available in the former Soviet Union [78]. TBE vaccine may provide cross-protective immunity and is used in high-risk populations [58].

Table 22.13 Differential Diagnoses of OHF

Enteroviral aseptic meningitis	See Table 19.8
HSV encephalitis	
Leptospirosis	See Table 19.4
Other hemorrhagic fevers:	
Dengue	
Ebola and Marburg hemorrhagic fevers	
Crimean-Congo hemorrhagic fever	See Table 18-II.2
Hantavirus hemorrhagic fever	
Lassa fever and the South American hemorrhagic fevers	
Chikungunya fever	
Other encephalitides:	
Rift Valley fever	
Kyanasur Forest disease	
Colorado tick fever	
Eastern equine encephalitis	See Table 16.2
Western equine encephalitis	
Venezuelan equine encephalitis	
West Nile fever	
California encephalitis	
Japanese encephalitis	
St. Louis encephalitis	
Powassan encephalitis	
Tick-borne encephalitis	

Conclusion

OHF occurs in an isolated part of the world, and there is limited medical experience with this disease. As the former Soviet Union is increasingly open to industry and travel, more cases may be seen. Alternately, the virus may eradicate the non-native muskrat population, which would lead to eradication of the disease.

ST. LOUIS ENCEPHALITIS

Definition

St. Louis encephalitis (SLE) disease is defined by the CNS manifestations caused by the SLE virus. Wild birds and mosquitoes constitute the natural cycle of the virus, which has the potential to cause massive epidemics in the USA. The large epidemic in St. Louis and Kansas City in 1933 gave rise to the name.

History

The first recognized epidemic occurred in Paris, Illinois, in 1932, and was followed by the St. Louis epidemic. The etiological virus was isolated from the brain of a fatal case in 1933, and the disease was later proved to be mosquito-borne [79]. Outbreaks have subsequently occurred in the Pacific coast states, other western states, Texas, Florida, and the Ohio-Mississippi river valley. During these various outbreaks, different vectors were identified for each region [58].

Incidence

In the USA, SLE is the most common pathogen transmitted by mosquitoes [80]. It occurs in epidemics in the midwest and southeast, but the virus can be found throughout the continental 48 states. A single outbreak of disease was reported in northern Mexico [81]. Although natural disasters such as floods and hurricanes increase the vector density, there is no evidence of increased transmission to humans [82]. Most cases of SLE occur in late summer or early autumn, during the period of increased mosquito activity.

Pathogenesis

Culex mosquitoes transmit SLE among wild birds. Humans are incidental dead-end hosts and are not involved in the transmission cycle [80]. The vectors involved in the Ohio-Mississippi basin and eastern Texas are *C. pipiens* and *C. quinquefasciatus. C. nigripalpus* is the vector in Florida, whereas the western states have *C. tarsalis* as the vector species. SLE may occur in conjunction with western equine encephalitis (WEE), because *C. tarsalis* is the vector for WEE as well. Various amplification mechanisms exist, including vertical transmission and possibly overwinter maintenance by bats.

After inoculation from an infective mosquito, the virus replicates in local tissue and regional lymph nodes. This leads to viral dissemination in the blood, with replication at secondary sites, such as lymphoreticulum, endocrine, muscle, and other tissues. Access to the CNS most likely occurs through involvement of the vascular endothelial cells [62]. The most affected regions of the brain are the substantia nigra, thalamus, and hypothalamus, and the virus spreads from cell to cell [83].

Clinical Manifestations

Less than 1% of cases of SLE are clinically apparent [80]. Although approximately 75% of symptomatic cases involve encephalitis, other clinical illness may include aseptic meningitis or a febrile illness with associated headache (Table 22.14) [84]. The disease is typically more severe in the elderly. Significant comorbidity, such as diabetes, hypertension, and alcoholism, are also associated with increased severity and poor outcome.

Physical examination may reveal an altered level of consciousness, nystagmus, tremor, ataxia, meningeal signs, myoclonus, abnormal reflexes, and cranial nerve abnormalities (most commonly cranial nerve VII) [58]. Urinary frequency, urgency, and dysuria occur in 25% of cases [85]. Possible complications of illness include bacterial infection, such as pneumonia, thrombophlebitis and pulmonary embolus, stroke, and gastrointestinal hemorrhage. Permanent neurological sequelae may occur, particularly psychomotor retardation in infants.

Pathology

During autopsy, histopathological examination of the brain reveals perivascular and parenchymal inflammation. Pathological changes are widely dispersed throughout the brain and spinal cord, but the midbrain, thalamus, brain stem, cerebral cortex, and cerebellum have more pronounced involvement.

Laboratory Findings

Leukocytosis, elevated transaminases, and increased BUN and creatinine phosphokinase may be seen. Urinalysis may show hematuria, proteinuria, and pyuria. In patients with CNS involvement, the CSF has pleocytosis and increased protein. Hyponatremia and hypo-osmolarity can be seen with the syndrome of inappropriate ADH. Radionuclide brain scans are normal, and computerized tomographic scans of the head are either normal or reveal mild, generalized edema. The EEG shows generalized diffuse slowing and delta waves.

Diagnosis

Diagnosis can be made with serology of paired sera, demonstrating a fourfold rise in antibody titers (Table 22.15). HI may be used after the first week. Cross-reactions may occur with dengue. CF antibodies are present from the second week up to a year. Neutralization tests may be used in the first week and for years after infection. IgM-capture ELISA is useful from 3 to 5 days up to 60 days. IgM antibodies may persist in some individuals for up to a year, making this diagnostic modality less specific of acute infection. The demonstration of IgM in the CSF is a more accurate and rapid means of diagnosis. Other diagnostic tests are indirect fluorescent antibody test and use of monoclonal antibodies [80,82]. The virus has rarely been successfully isolated from blood or CSF in infected patients.

Treatment and Prevention

The treatment of SLE remains supportive (Table 22.16), and includes treatment of complications, such as septicemia, bacterial pneumonia, pulmonary embolism, and gastrointestinal bleed. No vaccine is available against SLE. The mainstay of prevention continues to be personal protective measures, such as limiting vector exposure times, proper clothing, and mosquito repellent. Public insecticide spraying is also an important factor, particularly during epidemics.

Conclusion

SLE continues to be a significant cause of viral encephalitis in the USA. During epidemic periods, this virus is the most common

Table 22.14 Clinical Manifestations of SLE

Time after Laboratory exposure	Clinical manifestations	Laboratory analyses	Other notes
4–21 days	Insidious onset of malaise, myalgia, headache, fever, nausea, cough, and anorexia ↓	Serology, with IgM in the acute phase or fourfold rise in IgG titers in paired sera	In elderly patients, illness may first present with delirium, seizures, coma, or a focal neurological deficit
5–25 days	Progressive CNS involvement, with a stiff neck, disorientation, altered consciousness, vomiting, and photophobia. Clumsiness, tremor, dysarthria, or ataxia may occur. 10% of patients have seizures ↓	Viral isolation (rarely successful)	Seizure is a poor prognostic sign. The overall mortality rate is 7%, although up to 22% of cases in the elderly result in death.
Over several days	The fever resolves and neurological improvement begins in survivors. A prolonged convalescence is typical, often with emotional disturbance, forgetfulness, headache, tremor, unsteadiness, and dizziness. These symptoms may persist for months to years after acute illness, particularly in the elderly		Convalescent patients may also have gait or speech disturbances and sensorimotor impairment.

Table 22.15 Differential Diagnoses of SLE

HSV encephalitis	See Table 19.8
Enteroviral aseptic meningitis	
Bacterial meningitis	
Tuberculous meningitis	
Cerebral malaria	
Dengue virus with encephalopathy	
Intracranial hemorrhage/stroke	
Heat stroke	
Lead encephalopathy	
Toxic encephalopathy	
Brain abscess	
Brain tumor	
Postinfectious encephalitis	
Metabolic encephalopathy	
Status epilepticus	
Acute confusional or basilar migraine	
Reye's syndrome	
Other arboviral encephalitides:	
Japanese encephalitis	
Eastern equine encephalitis	See Table 16.2
Western equine encephalitis	
Venezuelan equine encephalitis	
West Nile fever	
California encephalitis	
Powassan encephalitis	
Rocky Mountain spotted fever	
Tick-borne encephalitis	
Rift Valley fever	See Table 18-II.2
Kyasanur Forest disease	
Colorado tick fever	

cause of viral encephalitis in the USA. Lacking specific therapy and a vaccine, prevention rests on protective measures, vector control, and surveillance of sentinel avians.

TICK-BORNE ENCEPHALITIS

Definition

The TBE viruses consist of 14 antigenically related viruses, eight of which cause human disease. The most common infections include Far Eastern TBE (Russian spring-summer encephalitis, RSSE) and Central European TBE (CEE). A unique feature of these viruses is the relative resistance to low pH, such as gastric secretions. This characteristic has favored the oral transmission of these viruses in infected milk, causing a condition previously known as biphasic milk fever.

History

RSSE was first described in 1934 in Siberia, with virus isolation and tick transmission shown in 1937 [86,87]. CEE was first seen in a 1948 epidemic in the former Czechoslovakia, an area of high disease frequency. Milk-borne transmission of these viruses was first recognized during an outbreak in 1951–1952. The disease has been recognized in all central and eastern European countries, with Scandinavia, Italy, Greece, Albania, and France frequently reporting cases (Fig. 22.13).

Table 22.16 Treatment of SLE

Symptom	Treatment
General	Maintenance of fluid and electrolyte balance
Fever and myalgia	Antipyretics and analgesics
Seizures	Anticonvulsants
SIADH (syndrome of inappropriate antidiuretic hormone)	Water restriction

Incidence

Two thousand cases a year are observed for these European outbreaks. Asymptomatic and mild infections are much more common, over 30 times as frequent as apparent clinical disease.

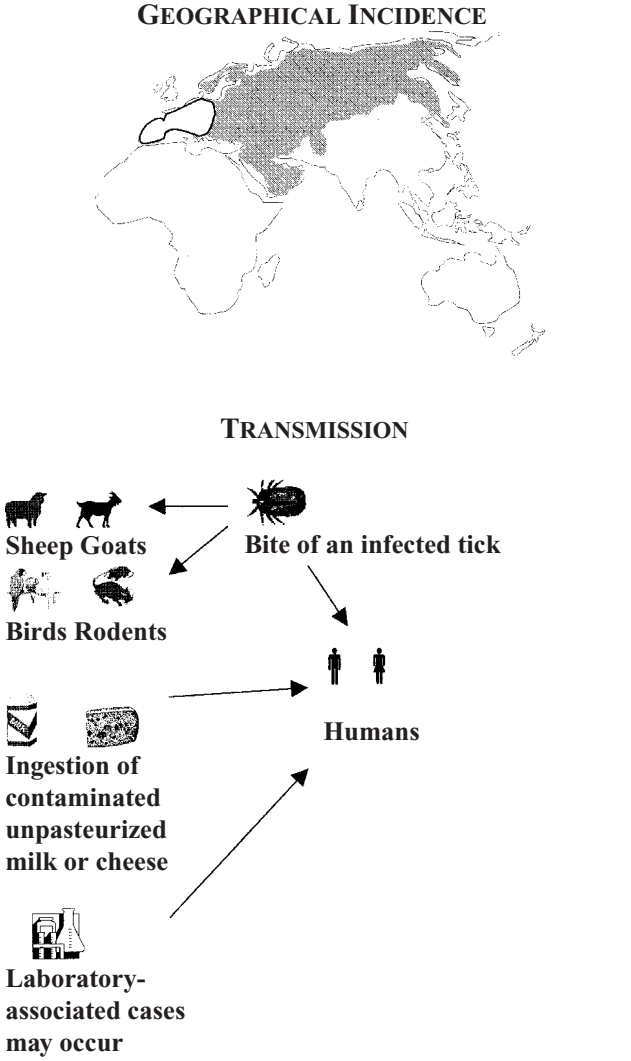


Figure 22.13 Incidence and transmission of tick-borne encephalitis.

In outbreaks, infection rates have ranged from 5 to 20 cases per 100,000 persons [88]. The tick-borne virus has two peaks of activity in Europe – May to June and September to October – corresponding to adult tick activity. A single late-summer peak occurs in Scandinavia. The 10 days following excessively heavy rainfall is a period of greatest disease activity [89]. Outbreaks occur in families as a result of ingestion of unpasteurized milk or cheese, usually from goats [90]. Laboratory infections can occur if suitable precautions are not implemented [91]. RSSE has a case fatality rate of 20% with 30–60% having sequelae. The CEE case fatality rate is 1–5% with infrequent sequelae [92].

Pathogenesis

Ix. ricinus and *Ix. persulcatus* are vectors in Europe and Russia, respectively. The virus cycles between ticks and vertebrates, usually small animals. Transmission occurs transovarially to offspring and transtadially as the tick matures. Transmission of the virus from an infective tick to another unaffected tick has been shown. Viremia in the host is not involved, shown by transmission in immune animals. The mechanism has to do with local virus replication at the feeding site and migration of infected cells to other feeding sites [93].

After inoculation, infection of the local dermal cells leads to seeding of the regional lymph nodes, where further replication takes place. This results in viral dissemination in the blood, with generalized infection, particularly involving the reticuloendothelial cells. A second period of viremia leads to neuroinvasion, which occurs through infection of mononuclear cells and vascular endothelial cells. Failure to establish an early CSF IgM response has been associated with clinical encephalitis [94]. Viral infection of macrophages alters the cellular ability to manufacture nitric oxide, important in antiviral defense [95].

Clinical Manifestations

Children are less severely affected than adults. With neurological involvement, physical examination may reveal signs of meningeal irritation, photophobia, and irritability (Table 22.17). Seizures, altered level of consciousness, and focal neurological signs are less frequent in children. Overall, there is a case fatality rate of 1–2%. Of the individuals with severe disease, 10–20% develop long-term or permanent neuropsychiatric sequelae, although generally mild.

In contrast to the biphasic course of CEE, RSSE has a monophasic course, with fatalities after a week of symptoms. Children are more severely affected than adults. The variety of neurological disturbances that may occur with this disease include paralysis, paresis, sensory loss, and seizures. Neurological sequelae are frequent (30–60%) [92], particularly flaccid paralysis of the upper extremities consistent with the anterior horn cell pathology. The virus has a propensity to develop persistent infection in immune-impaired animals and by implication in humans. The Central European disease has lower mortality and neurological sequelae.

Laboratory Findings

Thrombocytopenia, leukopenia, and occasional abnormal liver function define the hematological and chemistry abnormalities [96]. The CSF pleocytosis is initially neutrophilic, but becomes lymphocytic [97].

Pathology

Gross CNS changes include edema and petechiae. Histologically, there is perivascular and meningeal inflammation, neuronal necrosis and neuronophagia, and glial nodule formation. These pathological changes predominantly involve the anterior horn cells, but also affect the cerebral and cerebellar cortices, basal ganglia, and brain stem [98].

Diagnosis

Diagnosis is most commonly made by serology, especially with demonstration of IgM antibodies by ELISA (Table 22.18) [99,100]. However, with sensitive methods, IgM may be detected for up to 9–10 months after acute disease [101]. A fourfold rise in IgG titers between paired sera can also make the diagnosis. Antibodies to IgG or IgM can be detected in the CSF by ELISA [102]. Virus can be isolated from blood early in the disease or from brain in fatal cases. This method uses infant mice, embryonated eggs, or chick embryo cell cultures, but is usually unrewarding, being positive in only 10% of patients.

Table 22.17 Clinical Manifestations of TBE

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–7 days	Onset of fever, headache, myalgia, and malaise, mimicking influenza.	Serology, with acute IgM or fourfold rise in IgG titers in paired sera	Central European tick-borne encephalitis (CEE) is milder than Russian spring-summer encephalitis (RSSE) and usually has a biphasic course. The onset of RSSE illness is normally gradual, rather than acute
	↓		
10–14 days	Symptoms remit for 1 wk, other than fatigue. Most patients have no further symptoms and recover completely	Alternatively, antibodies can be detected in the cerebrospinal fluid	RSSE has a longer prodromal phase, with fever, headache, anorexia, nausea, vomiting, and photophobia, but it has a shorter course overall. These symptoms are followed by nuchal rigidity, visual disturbances, neurological dysfunction, or sensorial changes.
	↓		
17–21 days	In some patients (up to 33%) a second phase abruptly begins, with high fever, headache, and emesis. CNS involvement develops in this phase, with aseptic meningitis, myelitis, encephalitis, or radiculitis	Viral isolation is possible, but is less successful	
	↓		
20–25 days	In uncomplicated cases, the fever remits and convalescence begins. Most patients recover completely. In patients with encephalitis, the fever may persist for up to 1 wk		

Table 22.18 Differential Diagnoses of TBE

HSV encephalitis	See Table 19.8
Enteroviral aseptic meningitis	
Bacterial meningitis	
Tuberculous meningitis	
Cerebral malaria	
Dengue virus with encephalopathy	
Intracranial hemorrhage/stroke	
Heat stroke	
Lead encephalopathy	
Toxic encephalopathy	
Brain abscess	
Brain tumor	
Postinfectious encephalitis	
Metabolic encephalopathy	
Status epilepticus	
Acute confusional or basilar migraine	
Reye's syndrome	
Rocky Mountain spotted fever	See Table 16.2
Other arboviral encephalitides:	
Japanese encephalitis	
Eastern equine encephalitis	
Western equine encephalitis	
Venezuelan equine encephalitis	
West Nile fever	
California encephalitis	
St. Louis encephalitis	
Powassan encephalitis	
Rift Valley fever	See Table 18-II.2
Kyasanur Forest disease	

Table 22.19 Treatment of TBE

Symptom	Treatment
General	Bed rest
Fever and myalgias	Antipyretics and analgesics. Acetaminophen is preferred, owing to the thrombocytopenia associated with this disease
Convulsions	Anticonvulsants. Chronic anticonvulsive therapy is rarely indicated
Increased intracranial pressure	Hyperventilation, elevation of head of bed, and mannitol infusions, if needed

Treatment and Prophylaxis

No specific antiviral therapy is currently available. Passive protection with specific TBE globulin is preventive if given within 96 hours of tick exposure, but is not therapeutic (Table 22.19). This treatment could have detrimental effects if administered to a patient with current disease [103,104]. A vaccine is used for persons with high risk of exposure, such as forest workers, military, and laboratory workers. Repellents and protective clothing are recommended, but are of little utility for those with constant or repeated exposure. Avoiding habitat and unpasteurized milk is beneficial.

Related Viruses

Louping ill is a disease of sheep in Scotland, England, Ireland, and Wales. It occurs infrequently in humans, usually in laboratory workers or in abattoir workers, butchers, and veterinarians directly exposed to sick animals. The disease in humans is biphasic with fever lasting 2–10 days, then remission for 5 days followed by fever and meningoencephalitis for 4–10 days. Abortive influenza-like disease occurs, as does asymptomatic disease [105,106]. *Ix. ricinus* is the agent for humans, sheep, and grouse. A killed vaccine for Louping ill has been used. TBE vaccine may provide protection due to cross-reaction of TBE antibody with the Louping ill virus. A similar virus has been recovered in Norway from sheep [107]. A distinct virus causes Turkish sheep encephalitis [108].

Rocio encephalitis appeared in epidemics in 1975–1976 in Sao Paulo State, Brazil, and then vanished. It caused a disease similar to SLE, although it is more closely related to JE antigenically. The specific vector was probably a mosquito. Wild birds may have completed the natural cycle.

Powassan virus encephalitis occurs in Russia, Canada, and the USA. Small mammals and ixodid ticks appear to be the natural cycle. Virus has also been isolated from ticks and mosquitoes, but mosquito transmission is unproved. Cases have been more common and more severe in the young, usually boys, probably due to outdoor activities. Disease is severe, and sequelae are common [58]. The virus is more widely distributed than reported cases, a situation suggesting that many cases are mild and unrecognized. The increasing distribution of *Ix. dammini* portends greater disease frequency in the future. These two factors predict more recognized clinical disease in northern USA and Canada in the future.

Modoc is a virus isolated from the white-footed deer mouse in California, Oregon, Montana, and Ontario. A single proven case of human disease presented as aseptic meningitis.

Negishi was isolated from two fatal cases and a febrile laboratory infection. Human cases occur in China, but the frequency is unknown. The agent is a member of the TBE virus complex, but is similar to the JE agent.

Conclusion

TBE viruses constitute a group of several agents that cause human disease. Tick-bite history is incomplete, usually only in half of the cases. Transmission occurs between infected and noninfected ticks feeding on the same non-viremic animal. Personal protection from tick exposure, particularly after heavy rainfall periods, is recommended. Laboratory workers handling the virus and persons in contact with sick animals are at substantial risk and are vaccine candidates.

YELLOW FEVER

Definition

The yellow fever virus is the prototypic virus of the family Flaviviridae. The name for this virus resulted from the jaundice that occurs in severe cases. This mosquito-borne hemorrhagic fever causes severe hepatic injury and was one of the great scourges of the world. The clinical course of this infection involves two distinct phases that are separated by a transient remission. The first phase has viremia, and the second involves multiorgan dysfunction and hemorrhage of varying degree. In spite of an effective vaccine, yellow fever remains a major public health problem in Africa and the Americas.

History

Yellow fever was initially recognized in the Yucatan in 1648. Although this illness was first recognized in the New World,

yellow fever probably originated in Africa and was spread to the Americas through the slave trade. The tropical areas of the Americas experienced large outbreaks from the 17th to the 20th century. Nott first suggested that mosquitoes were the vector. In 1900, Walter Reed demonstrated the agent and transmission by the *Ae. aegypti* mosquito. Soper initially proposed the concept of jungle yellow fever, and later it was shown that this cycle involved wild monkeys and sylvanic mosquito species [109]. In 1927, the virus was isolated by Mahaffy and Bauer [110].

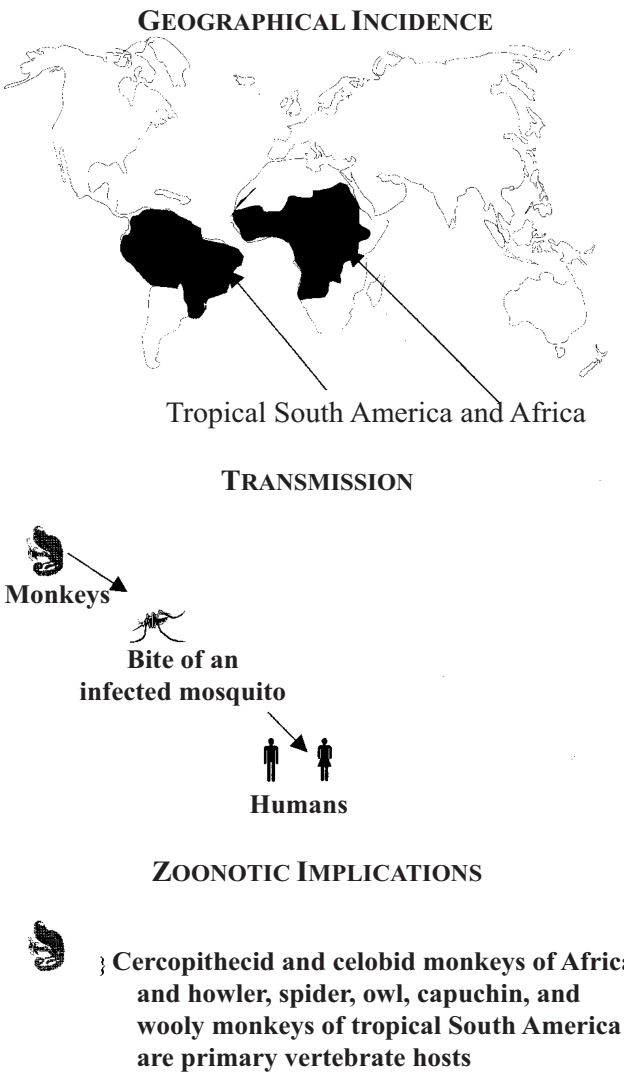


Figure 22.14 Incidence and transmission of yellow fever.

Incidence

Yellow fever is a serious public health concern in tropical South America and sub-Saharan Africa (Fig. 22.14). WHO estimates 200,000 cases annually with 30,000 deaths, although significant under-reporting and misidentification occur. Prior to the 1900s, there were also outbreaks in Europe, the Caribbean, and Central and North America. Yellow fever has never been reported in Asia, although WHO considers the area to be at risk, because the appropriate vectors and primates exist there. Nine South American countries have endemic yellow fever, with Bolivia, Brazil, Ecuador, Columbia, and Peru considered the highest risk [111]. Incidence in South America occurs via sylvanic transmission, primarily in young adult males from January to March due to peak rain and humidity during forest-clearing activities. Incidence in Africa occurs during the late rainy season, with background immunity the primary factor in determining age distribution. African countries in which yellow fever is endemic include Angola, Benin, Cameroon, Congo, Gabon, Gambia, Ghana, Guinea, Liberia, Nigeria, Sierra Leone, and Sudan [58].

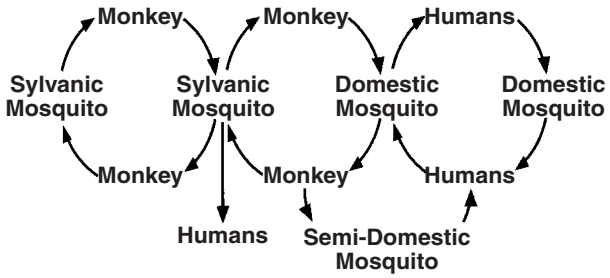


Figure 22.15 Yellow fever transmission.

Pathogenesis

There are four topotypes (geographic genetic types): two in Africa (one occurring in the eastern countries and the other occurring in the western countries), and two in South America (only one of which has been identified as causing outbreaks) [79,80]. The virus primarily affects humans and primates. Transmission can be horizontal by the biting mosquito as the vector between one animal and another, or vertically (transovarial). The mosquito vectors include the *Aedes* species or, in South America, *Haemagogus* species. There are three cycles of yellow fever: sylvatic, urban, and intermediate (Fig. 22.15). In sylvatic yellow fever, an infected monkey is bitten by a wild mosquito, which is then able to transmit the virus to uninfected monkeys. Sporadic human cases occur when infective mosquitoes enjoy a human blood meal from an itinerant worker or traveler. This occurs primarily in tropical rainforests. Urban yellow fever is transmitted directly from human to human via an infective domestic mosquito. There is no monkey involvement, and large epidemics occur. Intermediate yellow fever involves transmission from a semi-domestic mosquito to both monkeys and humans. This mode occurs in the "zone of emergence" in the African savannah, which borders equatorial forests and has high concentrations of vector and monkey [113]. Intermediate yellow fever results in small-scale epidemics.

After inoculation, the virus replicates in regional lymph nodes, followed by dissemination through the bloodstream to other tissues, such as bone marrow, myocardium, liver, and spleen. In the liver, the virus infects Kupffer cells and then certain hepatocytes, leading to coagulative necrosis of these cells. The bleeding diathesis that occurs with yellow fever is a result of depletion of hepatic clotting factors, platelet dysfunction, and intravascular coagulation.

Clinical Manifestations

The spectrum of disease with yellow fever ranges from a nonspecific febrile illness to a fulminating, sometimes fatal illness (Table 22.20). The characteristic course of disease progresses through three phases, known as the periods of infection, remission, and intoxication. Patients with yellow fever infection may

Table 22.20 Clinical Manifestations of Yellow Fever

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3–6 days	Abrupt onset of fever, chills, headache, significant lumbosacral pain, myalgia, anorexia, nausea, vomiting, and possibly, mild epistaxis or gingival bleeding. This "period of infection" typically lasts 3 days	Serology, with acute IgM or fourfold rise in IgG titers	During this phase, the patient has a high viral titer and is infective to the mosquito
	↓		
6–9 days	The "period of remission" begins, with defervescence. Most patients begin to recover without further symptoms	Viral isolation during the acute phase of illness	
	↓		
7–10 days	In severe cases, the disease progresses. The "period of intoxication" consists of a recurrence of fever and other symptoms, which progress to worsened vomiting, epigastric pain, prostration, altered consciousness, and jaundice. Hemorrhage occurs from multiple sites, with coffee-ground emesis ("vomito negro"), melena, petechiae, ecchymosis, metrorrhagia, oozing from mucous membranes, and DIC. Renal and CNS involvement may occur		During this period, viremia is absent and antibodies are present Dehydration results from vomiting and increased insensible losses Death occurs in 20–50% of cases, typically 7–10 days after disease onset
	↓		
14–28 days	Survivors begin to recover, typically without sequelae. Convalescence involves significant weakness for 1–2 wk		

demonstrate the Faget sign, which is a paradoxically slow pulse with high fever, a common feature of arboviral disease. The most significant dermatological manifestations other than icterus (Fig. 22.16) are the petechiae and ecchymoses associated with the bleeding diathesis. This is likely due not only to decreased synthesis of vitamin K-dependent factors, but also to increased vascular permeability, altered platelet function, and ultimately, disseminated intravascular coagulopathy. The eyes may become jaundiced.

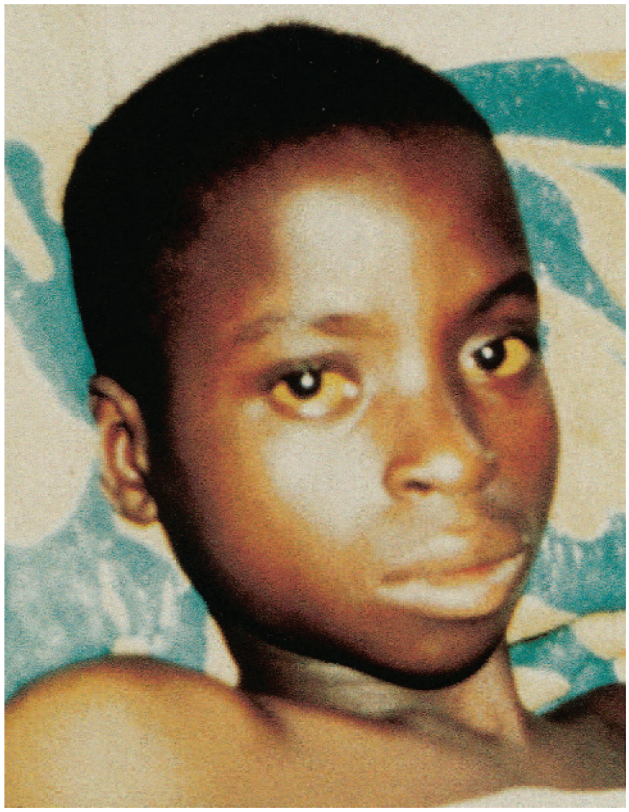


Figure 22.16 Jaundice and scleral icterus in a patient with yellow fever. (Reprinted from Samlaska CP. Viral Hemorrhagic Fevers. In: James WD, ed., Military Dermatology. In: Textbook of Military Medicine. Washington, D.C. Department of the Army, Office of the Surgeon General. Borden Institute, 1997, vol. 201, pp. 197–212.) (Courtesy of Thomas P. Monath, M.D., formerly Walter Reed Army Institute of Research, Washington, D.C.)

During infection, renal manifestations may include albuminuria and oliguria or frank renal failure and anuria. CNS involvement can be seen as delirium, seizures, and coma. The jaundice associated with yellow fever may not be significant and may be undetectable until after death. Signs that often precede death include worsening jaundice, hemorrhage, hypotension, oliguria, azotemia, and rising pulse. Poor prognostic indicators include hypothermia, intractable hiccups, agitation, delirium, hypoglycemia, stupor, and coma. Rarely, late death during convalescence occurs owing to cardiac or renal involvement.

Laboratory

Findings are nonspecific and include leukopenia, elevated bilirubin and transaminases, albuminuria, thrombocytopenia, and prolonged prothrombin and bleeding time. Transaminases remain elevated for at least 2 months. An electrocardiogram may show nonspecific ST changes.

Pathology

Numerous changes occur in the liver. Initially, there is swelling of the hepatocytes, followed by coagulation necrosis. This mainly occurs in the midzone of the lobule and spares the cells bordering the central vein. Eosinophilic degeneration of hepatocytes produces Councilman bodies. When these degenerate, as occurs with delayed death, they are known as Villela bodies. Torres bodies are hepatocytes with intranuclear eosinophilic granular inclusions. Fatty changes occur, and there is minimal inflammatory response. In recovered cases, there is complete healing. Renal manifestations include acute tubular necrosis and fatty changes. Glomerular changes are insignificant. The glomerular basement membrane undergoes Schiff-positive transformation, possibly

causing altered permeability and albuminuria. Myocardial fibers degenerate with fatty infiltration and edema. The CNS can be affected by edema, and petechial hemorrhage can occur in the brain. The reticuloendothelial system may show depletion of lymphocytic elements in the spleen and lymph nodes, as well as accumulation of monocytes and histiocytic cells in the spleen [112].

Diagnosis

Isolation of the virus is usually best during the first 4 days of disease, but serum up to 14 days after disease onset and from the liver at death can also be used (Table 22.21). Antibodies can be detected by HI, CF, and N tests, indirect immunofluorescence, ELISA, and radioimmunoassay (RIA). Clinical suspicion must be high in patients from endemic or epidemic areas or with recent travel history. Specific IgM or a rise in antibody titer in paired serum samples is diagnostic. Serological cross-reaction does occur with other flaviviruses [114].

Treatment and Prevention

The mainstay of treatment continues to be supportive care. Antiviral therapies are not effective against this virus, and no specific therapy is available (Table 22.22).

The most important factor for prevention is immunization. This is recommended 7–10 days prior to travel to endemic areas. Seroconversion occurs in 95% of recipients within 1 week. Although the vaccine is recommended every 10 years, immunity may be lifelong. Serious side effects from the vaccine are rare. The vaccine is not recommended for children under 6 months of age, pregnant women (except during an emergency vaccination campaign), persons with allergy to egg, and persons with immunodeficiency or taking immunosuppressive medications [111].

Table 22.21 Differential Diagnoses of Yellow Fever

Q fever: Is a self-limited febrile illness with pneumonitis and granulomatous hepatitis, headache and myalgia. Leukopenia and thrombocytopenia may occur. Chronic endocarditis with negative blood cultures occurs. Diagnosis is serological	
Viral hepatitis: A prodrome of malaise is followed by hepatic tenderness, possibly jaundice and markedly elevated transaminases. Specific antigen or antibody identifies the actual viral etiology. Risk factors may be identified, e.g., travel, intravenous drug use, sexual, household, or daycare contact with known hepatitis or high-risk patients. Anicteric disease occurs. Coagulopathy, cutaneous or gastrointestinal bleeding, and progression to hepatic failure are uncommon	
Drug-induced hepatitis: A variety of natural products, herbal treatments, and medications results in hepatic injury. Fever, rash, and arthralgia are seen clinically, with hepatic enzyme elevation and chemical and clinical evidence of hepatic dysfunction in the most severe injuries	
West Nile fever	See Table 18-II.2
Malaria	
Typhoid fever	
Murine typhus	See Table 19.4
Scrub typhus	
Leptospirosis	
Other hemorrhagic fevers:	
Ebola and Marburg hemorrhagic fevers	
Dengue	
Rift Valley fever	See Table 18-II.2
Kyasanur Forest disease	
Omsk hemorrhagic fever	

Table 22.22 Treatment of Yellow Fever

Symptom	Treatment
General	Bed rest, maintenance of fluid and electrolyte balance, and close monitoring of vital organ function. Supplemental oxygen may be helpful in some cases
Fever	Analgesics. Aspirin and nonsteroidal anti-inflammatory agents that impair platelet function should be avoided because of the associated hemorrhage and thrombocytopenia
Dehydration	Oral fluid replacement, or if necessary, intravenous fluid infusions
Hemorrhage	Transfusion of fresh whole blood or packed red blood cells is useful for severe bleeding
DIC	Transfusion of fresh frozen plasma is indicated. Heparin therapy is controversial, but may be helpful in certain situations that have a predominant fibrinolytic process
Renal insufficiency	Close monitoring of fluid balance and electrolytes. Hemodialysis may become necessary for severe renal impairment

The Pan American Health Organization had vector control programs in the 1950s and 1960s that virtually eliminated *Ae. aegypti* in most countries. However, the programs were not continued, and reinfestation has occurred in all Latin American countries except Chile and Uruguay [115]. Mosquito control programs against sylvanic infections are not cost-effective. For the urban cycle, elimination of mosquito breeding sites, treatment of potable water, and organophosphate spraying are beneficial, but must be continuously supported. The USA has *Ae. aegypti* vector present in the southeastern region, and is therefore a potential area of epidemic in the future.

Conclusion

Vigilant surveillance is necessary for early recognition of yellow fever, with control of epidemics through emergency vaccination campaigns. Urban areas where yellow fever has been eradicated, such as the southeastern USA, may face potential future outbreaks owing to lapsing vaccine use in current endemic areas and inattention to vector control.

WEST NILE VIRUS

Introduction

West Nile virus (WNV) is a mosquito-borne flavivirus found in rural Africa, southern Europe, and Central and South Asia [116]. The virus name could wrongly suggest an Egyptian origin but the WNV was highly prevalent in a poor slum area of Uganda known as the "West Nile district" [116,117]. Many patients who become infected with WNV may not experience any signs or symptoms or may only experience rash and headache. However, some patients who become infected with WNV develop a life-threatening illness that includes meningitis.

Since its introduction into the United States in 1999, WNV has become endemic in North America, and it is now found in all 48 American contiguous states, and has emerged as the most common cause of epidemic meningoencephalitis in North America and the leading cause of arboviral encephalitis in the United States.

Exposure to mosquitoes where WNV exists increases the risk of getting WNV infection [116].

Etiologic Agent and Reservoir

WNV is maintained in nature by cycling between mosquito vectors and bird hosts; humans are incidental hosts. Transmission to humans occurs predominantly after a bite from an infected mosquito but has also occurred via transfusion of blood products, via organ transplantation from infected donors, transplacentally, and percutaneously through occupational exposure [116,118].

In the United States, wild birds, especially crows and jays, are the main amplifying hosts of WNV, but the virus is actually spread by certain species of mosquitoes belonging to the genus *Culex*. When a mosquito bites a bird infected with the WNV, the virus enters the mosquito's bloodstream and circulates for a few days before settling in the salivary glands [116–118].

Although the exact mechanism of illness is unknown, WNV probably enters the host's bloodstream, multiplies, and moves on to the brain, crossing the blood-brain barrier. WNV transmission occurs mostly during warm weather, when mosquito populations are active.

Epidemiology

The overall risk of getting WNV infection depends on the time of the year, geographic region and time spent outside. In temperate regions, WNV follows a seasonal pattern starting in early spring, with the peak time for infection occurring in late summer and early fall. Persons living in southern climates have a year-round risk of infection. Visiting or living in areas where mosquito-borne viruses are common increases the risk of exposure to WNV, but it has been reported in all 48 contiguous American states, including desert regions such as Arizona [118, 119].

Even if a patient is infected, the risk of developing a serious WNV-related illness is extremely small — less than 1% of people who are bitten become severely ill. And most people who do become sick recover fully [119].

Clinical Presentation

Following an incubation period of three to six days, small children usually have a nonspecific febrile illness. Adults have a dengue-like condition with fever, headache, backache, myalgia, lymphadenopathy, and leucopenia [120].

The WNV rash is non-pruritic and usually macular, mainly on the trunk, and resolves without desquamation. Sore throat and gastrointestinal symptoms may occur. Meningeal signs occur infrequently, but are more common in the elderly, for whom the disease may prove fatal. Generally, the disease is brief, 3–6 days, and self-limited. Weakness and fatigue may persist after the acute phase for 1–2 weeks [116,120].

Approximately one of 150 patients develops central nervous system manifestations, including meningitis, encephalitis, and acute flaccid paralysis/poliomyelitis. Risk factors for neuroinvasive disease include older age (over 50 years) and immunosuppression [116, 121].

Diagnosis

The diagnosis is made in most patients on serological examination by the presence of a rising level of antibodies to the WNV or, directly, by a positive ribonucleic acid (RNA) test for the virus or by viral isolation during the acute phase. Reverse transcription polymerase chain reaction tests are useful to screen blood products and for surveillance of birds and mosquitoes. Paired sera can be attempted, but cross-reactions with related flaviviruses limit its usefulness [116,122].

Meningitis and encephalitis can be diagnosed by lumbar puncture and brain imaging such as CT or MRI scan. Imaging findings are usually nonspecific, and cerebrospinal fluid findings include pleocytosis, elevated protein, and normal to decreased glucose. The pathological findings are typical of a viral meningoencephalitis and include microglial nodules, perivascular chronic inflammation, and variable neuronal loss with necrosis or neuronophagia [122].

Treatment and Prevention

Treatment is largely supportive. Most patients recover from WNV without any treatment. Even those who develop encephalitis or meningitis may only need supportive therapy with intravenous fluids and analgesics. Interferon therapy may be useful for WNV encephalitis. Because no vaccine for WNV exists, prevention of mosquito bites is critical for control of WNV infection [123].

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23 Togaviruses

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ALPHAVIRIDAE

Alphaviridae, a group of arthropod-borne (arboviruses), single-stranded, positive RNA viruses, consist of 29 species with distribution patterns covering large areas of the world [1]. They are transmitted to their human hosts by mosquitoes. The most common clinical signs of alphavirus infection in humans are fever, arthralgias, and rash [2]. If patients do not develop this triad of symptoms, isolated cases are difficult to recognize. In case of an epidemic, with increased awareness, the diagnosis is made more easily [3].

The first part of this chapter will focus on alphavirus infections from the Old World (arthritogenic) group, which are most relevant in clinical dermatology since they can cause rashes: Chikungunya (CHIK), O'nyong-nyong, Ross River virus, Barmah Forest virus, Sindbis virus and Mayaro virus. The alphaviruses from the New World (encephalitic) groups, like Eastern equine encephalitis virus, Western equine encephalitis virus, and Venezuelan equine encephalitis virus leading to encephalitis in humans, will not be discussed since they normally do not cause skin-associated signs. Genetically, alphaviruses are closely related to the dengue-related arboviruses (Flaviviruses). The clinical picture of dengue and alphavirus infection can be quite similar, and both will need to be considered in patients who live in, or come from, an endemic area and present with an acute picture of fever, rash, and arthralgia.

Pathogenesis

Much of the knowledge on the genomic structure, proteins, replicative cycle, and functions of the alphaviruses and the pathogenesis in the host originates from murine models, especially used in the studies of the encephalitic alphaviruses [4]. Data on host responses and pathogenesis arising from these encephalitic models are not fully applicable to the pathogenesis and host reactions met in disease caused by the arthritogenic Old World alphaviruses. Alphaviruses are small, enveloped viruses with a message-sense RNA genome that encodes for four non-structural proteins (nsP1–4) and three structural proteins (C, E1–2) [5]. The replication cycle starts with the attachment of the viral envelope to receptors in the host cellular membrane. The exact receptors remain to be elucidated, but based on relevant molecules in some alphaviruses, the laminin receptor, glycosaminoglycans, and DC-SIGN molecules are possible candidates relevant in vertebrate cell infection. Next, the virus enters the cell cytoplasm through endocytosis. The viral envelope complex subsequently fuses with the endosomal membrane. Viral replication proceeds along parallel pathways. The viral genome serves as mRNA encoding for non-structural proteins and RNA replication occurs with transcription and translation processes leading to the formation of precursor, and finally, mature structural viral proteins. Viral assemblage takes place partly in the endoplasmic reticulum and Golgi complex. The assembled viral particle is transported to the cell membrane to become enveloped, and finally, bud through the cell membrane as an enveloped virion.

The host reaction to an alphavirus infection differs between vertebrates and invertebrates (e.g., the vector). Whereas in vertebrates (including man) the infection is usually cleared within a few days, in invertebrates the infection persists lifelong. Possibly, alphavirus-induced programmed host cell apoptosis in vertebrate cells, but not in invertebrate cells, could explain this difference in viral elimination [6]. Moreover, for unknown reasons, vertebrates' viral proteins need to interact with the nuclei of host cells; this is not the case in invertebrate cells.

The host response to alphavirus infection and the subsequent hypothetical pathophysiology is based mainly in studies performed in murine models [4]. Subsequent to the bite of an infected mosquito, viral particles are deposited in the subcutaneous layer, followed by local viral replication. Migration of the infection towards regional lymph nodes may follow either through infected dendritic cells, macrophages, or also via free (extracellular) virus. Viral replication continues in the regional lymph node and systemic dissemination via the thoracic duct can occur. Viremia is essential in further transmission following blood meals by the arthropod vector.

In mouse models using Sindbis viruses, a strong and consistent age-dependent resistance to fatal viral infection was found. Recent studies suggest that the age-dependent resistance may be common to most alphaviral infections. Contributing factors in age-dependent resistance are restriction of replication in first-infected cells, which may augment attenuating effects, such as increasing neuronal resistance and apoptotic death of infected cells [4]. Knockout mice models suggest that specific T cell, B cell, and natural killer (NK) cell-mediated immune responses do not play a vital role in age-dependent resistance. Recently, it was elucidated in knockout mice models that type-I interferon signaling pathways play an important role in the control of alphavirus-induced infections [5]. In the same study, CHIK-associated symptoms (e.g., muscle and joint ache, skin rash) matched with viral-infected tissues and cell tropisms, and skin fibroblasts were a major target cell for CHIK. It was concluded that CHIK-associated disease closely reflects CHIK tissue tropism, in contrast to other acute viral diseases in which most symptoms are caused by the systemic immune response to the infection. The antiviral activity of interferon (especially interferon alpha and beta, but also interferon gamma) consists of the induction of multiple proteins that interfere at different points in the viral replication cycle. In vitro studies suggest that alphaviruses are capable of antagonizing innate immune responses by shutting off host cell functions, thus preventing the induction of interferon production. Interferon beta treatment shows promising effects, since it combines antiviral activity with relatively little effect on the host cell viability. Secondly, the interferon-induced potent antiviral proteins could serve as prototypes for antiviral drug design [4].

Antigen-presenting cells, like dendritic cells and macrophages, also play an important role in antiviral immunity immediately after transmission in vertebrate hosts. Immature migratory dendritic

cells can detect viral products, like pathogen-associated molecular patterns (PAMPs), through pattern recognition receptors (PRRs), e.g., toll-like receptors (TLRs). Via PRR signaling, viral PAMPs (like ssRNA, dsRNA) trigger dendritic cells to mature, produce cytokines, and migrate to lymph nodes. Alongside the appropriate co-stimulatory molecules, protective immunity should be induced via T-cell recognition and virus-specific T-cell clonal expansion. The lineage of myeloid dendritic cells seem to play an important role in interferon-elicited antiviral responses, such as serum and mucosal antibody production [4].

Chikungunya

In 1955 [7], Chikungunya was first described from an epidemic that took place on the Makonde plateau in the southern province of Tanganyika, affecting 60–80% of the population. It was clinically indistinguishable from dengue; however, dengue had not been reported in this area and the inhabitants did not remember a similar epidemic in the past. Due to the severity of the joint pains and the sudden onset, a local name was given: "Chikungunya," which means "that what bends up." After an incubation period of 3–12 days, there was a sudden onset of clinical symptoms with fever and acute joint pain described as "frightening in its severity," and an "irritating" maculopapular eruption mainly on the trunk and extensor sides of the limbs in about 80% of the cases; it generally accompanied or followed a second rise in temperature around the 5th to 7th day. It is the incapacitating arthralgia that distinguishes it from dengue; recurrence of joint pains could continue until 4 months after the acute stage of the disease [7].

It is suggested that CHIK epidemics occurred much earlier, as early as 1779 in Batavia, Indonesia, but were mistaken for dengue [8].

Between the 1960s and 1990s, the virus was isolated from cases in many countries in central, east, and southern Africa, as well as in some countries in western Africa. Also, from the 1960s to 2003, outbreaks occurred in several Asian countries. Since 1986, CHIK has resurged with outbreaks in Senegal, Ivory Coast, Democratic Republic of Congo, and Indonesia [1]. An outbreak with hundreds of thousands of cases occurred almost continuously in the period 2004–2007 around the Indian Ocean [1,9]. The epidemic started with an outbreak in Kenya in December 2004, and from there to the Comoros in January 2005 [9]. It then spread to Madagascar, Mayotte, Mauritius, and the Seychelles with an estimated 9000 cases in the Seychelles, 7290 in Mayotte, and 6000 in Mauritius, and more than 250,000 cases in La Réunion, affecting approximately one third of the population [10].

In December 2005, a CHIK outbreak was recorded in India. It started in Andra Pradesh, and subsequently spread to 16 other states and northwards to Delhi. A total of 1.39 million cases have been recorded, with attack rates of 45% in some areas [10]. In a study from Andra Pradesh, varying attack rates within villages were found (from 0 to 22%), which were highest in adults and females. Attacks rates were highest in neighborhoods with brick houses and many water storage containers, in which larvae of *Aedes aegypti* were found [11]. In July and August 2006, cases were reported on the Andaman and Nicobar islands in the Bay of Bengal [12]. In October 2006, CHIK reached Sri Lanka, and in the period until August 2007, 37,667 cases were reported [10]. In Malaysia, 200 cases were reported in March–April 2006, after a period of 7 years in which no cases were reported [13]. In 2007, there was an outbreak in Gabon with 17,618 reported cases [10]. Between January 2001 and April 2007, with a peak in 2003, 15,207 cases were reported throughout Indonesia after a nearly 20-year interval, mostly on the island of Java (Fig. 23.1) [10,14].

Historically, CHIK originated in Africa and spread from there to other parts of the world. In Africa, it appears to be maintained

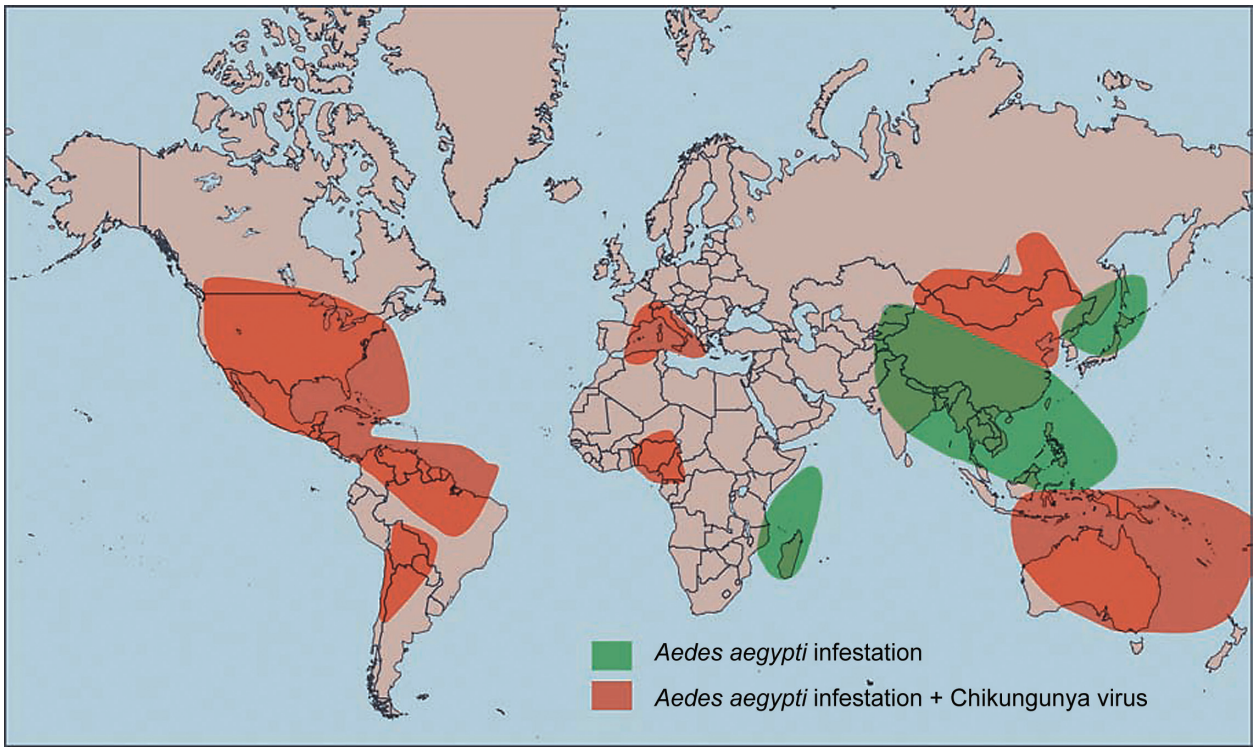


Figure 23.1 Geographical distribution of Chikungunya cases 2001–2007. (With permission of the New England Journal of Medicine.)

in a sylvatic cycle involving wild primates and forest dwelling *Aedes* species; in Asia, it is maintained in an urban cycle with *Ae. aegypti* mosquito vectors [1]. A phylogenetic study on isolates obtained from different parts of Africa and from southeast Asia showed two lineages: one containing western African isolates and the other southern/eastern African as well as Asian isolates; the Asian strains showing a different genotype [6]. CHIK outbreaks follow the start of the rainy season when vector density is high. In Africa, it appears endemic in rural areas with continuous transmission and smaller rural outbreaks, whereas in Asia it tends to be epidemic and urban. During epidemics, humans serve as a virus reservoir [9]. It has been reported that the recent outbreak in the Indian Ocean was caused by central/eastern African strains [15]; a single mutation may have enhanced its effective transmission by *Ae. albopictus* [16]. *Ae. albopictus* has spread to all continents in the last 50 years [17], and nowadays has a wide geographical distribution (Fig. 23.2); it has also been present in the Indian Ocean region for a long period of time [9]. The outbreak in India, in which *Ae. aegypti* is the vector, was caused by an African strain of the same lineage as that in the Indian Ocean islands, in contrast to those viruses isolated in the period 1963–1973, which were the Asian genotype [15]. The outbreak in Malaysia in March–April 2006 was, however, caused by already known Malaysian strains, and not by those causing the epidemic in the Indian Ocean islands, suggesting the possibility that the virus is endemic in Malaysia [13]. In Gabon, *Ae. aegypti* is common in the city, but *Ae. albopictus* was collected for the first time in 2006, and the virus was isolated from this species at the time of the outbreak [10].

In association with the outbreak on the Indian Ocean islands, cases have been imported in many countries, with more than 800 reported cases in Europe [18] by 2008; the great majority of cases in France were in patients infected on the island of Réunion [19]. In a study of 680 patients with CHIK virus infection in Germany, Belgium, Switzerland, Denmark, and Poland, it was found that the majority were infected on the Indian Ocean islands as well as in India, Sri Lanka, Kenya, and Indonesia. In the USA, 37 cases were imported in 2006, of which 32 were infected in India [20]. Nowadays, CHIK is the most frequent diagnosis in travellers with fever and enanthema, arriving from destinations in the Indian Ocean, Africa, and Asia [21].

In 2006, two main risk factors for CHIK virus transmission in Europe were identified. First is the importation of the virus into Europe by people travelling from high incidence areas in the Indian Ocean to Europe. As the majority of travellers are visitors to families and friends, there may be diminished attention for preventive measures to reduce CHIK virus infection. Secondly, the *Ae. albopictus* mosquito, the epidemic vector in Réunion in the Indian Ocean, was already introduced in Europe by the trade of used tires and ornamental plants, in particular "lucky bamboo" [22].

In 2007, CHIK fever was transmitted in Italy, in the province of Emilia-Romagna near Ravenna, for the first time [23]. Since then, 205 cases have been identified, by laboratory confirmation (85%) or clinical epidemiological criteria (15%), in the period July–September 2007. The presumed index case was a man from India, having visited relatives in a village. CHIK virus sequences were also detected in *Ae. albopictus*; the strains from humans

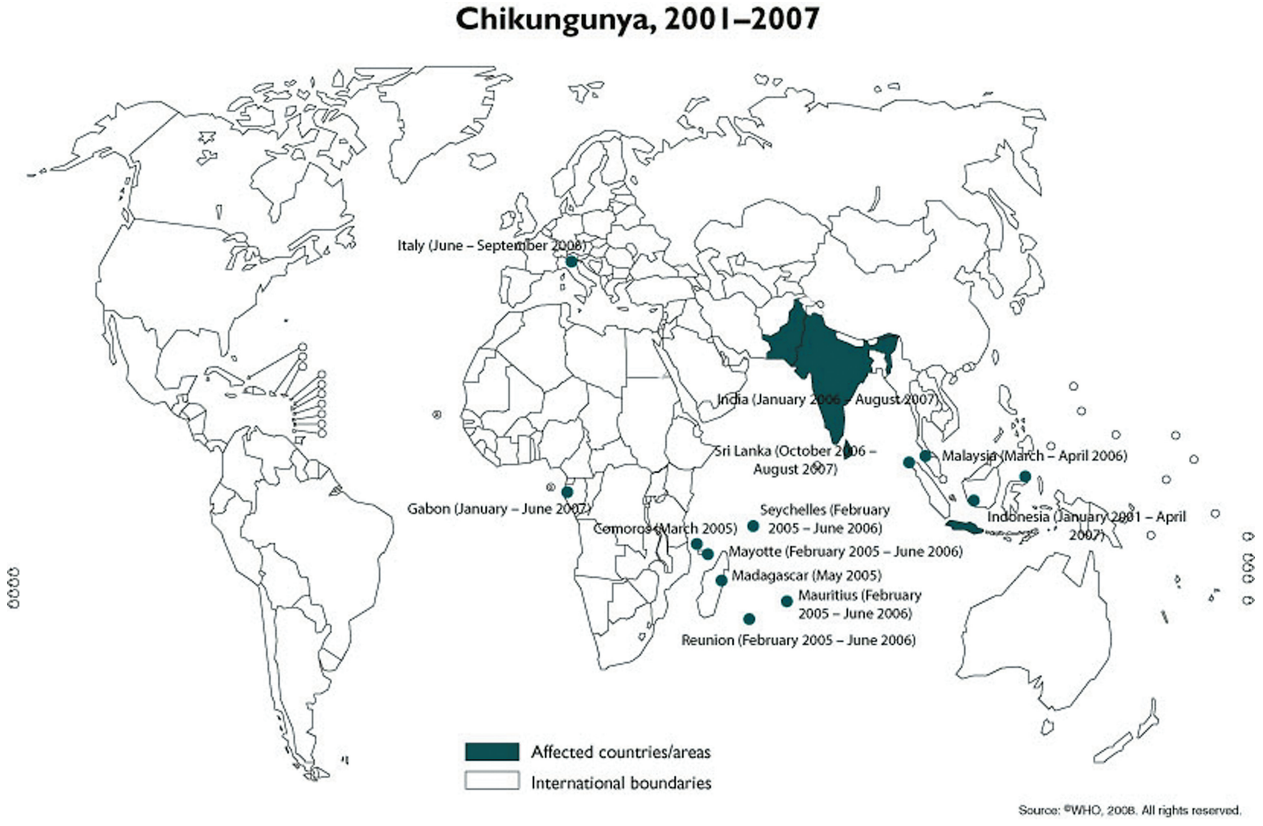


Figure 23.2 World distribution of the Aedes albopictus mosquito. (With permission of the WHO.)

Table 23.1 Clinical Manifestations of Chikungunya Fever

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
2–6 days	Sudden onset of high fever, significant arthralgia, muscle pains, and headache (frontal or orbital). Patients may often have photophobia, nausea, vomiting, and diarrhea. A flushed face often develops early in the disease and lasts 24 hours ↓	Viral isolation during the first 2 to 4 days of illness Serological tests, with acute IgM or fourfold rise in IgG among paired sera	Small children may have seizures and fever only. Arthritic manifestations are less common in children The fever is often biphasic, with an afebrile period that develops after 1–4 days and lasts 1–2 days before return of fever The rash may recur with repetitive waves of viremia
5–11 days	A generalized, fine and discrete maculopapular exanthem develops along with lymphadenopathy. The rash involves the trunk and limbs as well as the palms and soles. The rash either fades or desquamates after 1–5 days ↓		
10–13 days	Resolution of symptoms, with persistence of myalgia and arthralgia from 1 week to more than a year at times		Middle-aged adults experience more prolonged joint manifestations than younger patients

and mosquitoes showed a high similarity with strains identified during the preceding outbreak on the islands of the Indian Ocean [24]. *Ae. albopictus* had arrived in Italy by 1990, and is able to survive through the Italian winters. It was hypothesized that this outbreak was caused by globalization rather than by climate change [25].

Clinical Disease

CHIK is an acute illness characterized by fever, rash, and incapacitating arthralgias (Tables 23.1 and 23.2) [9]. Much of the pathogenicity of CHIK remains to be elucidated. What is assumed is based on predictive models based on other more extensively studied alphaviruses [26].

After an incubation period of 2–4 days (range: 1–12 days), the disease starts with sudden onset of high fever, headache, back pain, myalgias, and arthralgia [7,9].

Skin signs in the acute phase of the disease are found in one third to two thirds of the patients. They are described as a macular erythema or maculopapular erythematous rash (Figs. 23.3 and 23.4).

The rash most commonly starts during or after a secondary rise in temperature, although it has been described on the first day of illness; it may, however, also occur after the fever has subsided [7,21]. Trunk and limbs are almost without exception affected, and in a minority with involvement of palms and soles (Fig. 23.5). Involvement of the face has been reported to be absent [21] or present in a minority of the cases, and was in one study described as transient nasal erythema [27]. On the other hand, in one study facial



Figure 23.3 Maculopapular rash of Chikungunya. (With permission of Anke Heitkamp, MD.)



Figure 23.4 Maculopapular rash of Chikungunya. (With permission of Professor Arun C. Inamadar, MD, PhD.)

Table 23.2 Differential Diagnoses of Chikungunya Fever

Dengue fever	**See Table 18-II.2**
Hantavirus pulmonary syndrome	
Other arbovirus infections:	
O'nyong-nyong	**See Table 16.2**
Sindbis	
Mayaro	
Oropouche	
Sandfly fever	
Lyme disease	

Parvovirus B19: Parvovirus B19 causes erythema infectiosum or Fifth disease in infants. In adults, arthritis or anthralgia is common. Fever is not prominent, and other manifestations are lacking except for aplastic crisis in patients with hemolytic anemia

Rheumatic fever: Fever, arthritis, carditis, chorea, and subcutaneous nodules in combination typify the condition

Reiter's syndrome: Fever, arthritis, urethritis, and conjunctivitis are typical of this condition

Coxsackievirus: This virus usually causes minor disease but may cause carditis and viral sepsis with multisystem failure

Mumps: The clinical spectrum spans mild, self-limited febrile illness with parotitis or orchitis to encephalomyelitis, nephritis, pancreatitis, or diabetes

Rubella: Associated with fever, posterior cervical adenopathy, and maculopapular exanthem. Adults frequently have anthralgia, but frank arthritis is uncommon. The disease is self-limited except in the fetus. The embryopathy is significant, with cardiac and central nervous system involvement the most significant

Disseminated gonococcal infection: Fever and a petechial rash that is gram positive along with positive cervical culture are diagnostic

Hepatitis B prodrome: The prodrome is associated with malaise and anorexia. Anthralgia and arthritis may occur, along with glomerulonephritis and a variety of skin lesions (Gianotti-Crosti is classic). Jaundice and abnormal liver function tests are seen

Henoch-Schönlein purpura

Rheumatological conditions: Fever, arthritis, carditis, chorea, and subcutaneous nodules in combination typify the conditions

Autoimmune disease: Most patients have gradual onset of fever and joint symptoms. Conditions persist well beyond the time course of CHIK

flush was described as an early sign during the first 2 days, and in another study, edema of the face was a common finding [28]. Accompanying subjective symptoms described as itching, stinging, or burning are common in approximately 50% of cases [7,21]. The skin lesions fade spontaneously with or without scaling after a duration of 2–7 days [7,21]. Hemorrhagic signs are rare, and have been described as purpura and echymoses, sometimes simulating vasculitis, as well as asymptomatic subungual haemorrhages and gingival and nasal bleeding. Histopathology shows a perivascular lymphocytic infiltrate in the upper dermis, with erythrocyte extravasation around superficial capillaries [29]. Bullous lesions have been described that, clinically, appear intraepidermal and heal without scarring. Ulcerative lesions appear as aphthous ulcers of the month and ulcers of the flexural areas of the skin (Fig. 23.6) [27,30,31]. In one case, long-lasting ulcers of the lower legs [32] were described. Histopathology of aphthous-like ulcers show vascular endothelial changes with a dense, perivascular, lymphocytic infiltration [27]. In children, systemic signs tend to be less severe, but vesiculobullous lesions and hemorrhagic signs are more common (Fig. 23.7) [9,10,27].

Hyperpigmentation was the most common skin manifestation in 61 out of 145 cases in a study from India with a clinical diagnosis of CHIK. Freckle-like macules predominantly involved



Figure 23.5 Involvement of the palms from Chikungunya. (With permission of Anke Heitkamp, MD.)

the center of the face and lasted an average of 3 weeks (Fig. 23.8). Histopathology of these lesions showed diffuse hypermelanosis with an intact basal layer and no evidence of melanin incontinence [27]; which is unlike the histopathological picture of post-inflammatory hyperpigmentation as a consequence of an interface dermatitis.

Late cutaneous manifestations consist of hyperpigmentation, maculopapular lesions, aphthous-like ulcer, subungual haemorrhage, lichenoid eruption, lymphedema, and ankle edema [27].

Arthralgia is reported in a varying but generally high percentage of the patients [9,30], i.e., up to 100% in studies in travellers [31,33]. Joints are usually symmetrically involved, affecting mainly the extremities, but large joints can also be affected [3,7,31]. Persisting joint pains for more than several months are found in the majority of cases [30,33], and are described as intermittent and affecting different joints at different times [7].

CHIK is not considered to be a life-threatening disease; however, in the Réunion outbreak, patients required intensive care, and several deaths may have been caused by this infection [9]. Eight out of forty-seven imported cases in France were hospitalized, of which two had life-threatening infections [28].



Figure 23.6 Aphtous ulcer in the groin from Chikungunya. (With permission of Professor Arun C. Inamadar, MD, PhD.)



Figure 23.7 Vesiculobullous lesions in a child from Chikungunya. (With permission of Professor Arun C. Inamadar, MD, PhD.)



Figure 23.8 Freckle-like hyperpigmentation of the face from Chikungunya. (With permission of Professor Arun C. Inamadar, MD, PhD.)

Management

Treatment is symptomatic and supportive (Table 23.3). During the acute phase, antipyretic and non-steroidal anti-inflammatory drugs (NSAIDs) can be prescribed to control fever and arthralgia, and can be given for a prolonged period of time in case of persistent joint pains. Short-term steroids, given in cases of contraindication or failed response to NSAIDs, resulted in dramatic improvement of locomotor complaints [28]. The maculo-papular eruption needs no specific treatment as it resolves spontaneously. Aphthous ulcers were treated with local cleansing and topical antimicrobials, and healed in a period of 7–10 days. Hyperpigmentation was treated with sunscreens and topical steroids. Infants with vesiculo-bullous lesions and adults with vasculitis were given systemic steroids in some cases [27]. A vaccine against CHIK virus is not available.

Ae. aegypti is clearly associated with human habitation, indoors as well as outdoors, whereas *Ae. albopictus* has a wider range of habitats, both natural and artificial, explaining its existence in rural areas, parks, and suburbs. Elimination of breeding sites, i.e., stagnant water, is important [18,27]. Application of insecticides and larvicides to potential breeding sites is an important measure to prevent transmission, as are mosquito nets.

O'nyong-nyong

During the first half of 1959, an epidemic, which originated in northwest Uganda, broke out with fever, headache, agonizing joint and back pain, pruritic rash, and lymphadenitis. Different tribes gave this disease various names, usually referring to the painful joint manifestations. The name "O'nyong-nyong" was selected as the definitive name [34]. O'nyong-nyong in the Acholi language signifies pain in the joints and general weakening of the body [35]. The disease spread rapidly southward over Uganda into Kenya, as well as the former Belgian Congo and Sudan [34]. Later, it spread to southern Uganda and the former Tanganyika. It was estimated that nearly two million people were affected by mid 1961 [36]. This epidemic spread further to Tanzania and Zambia, and from there northwards into southwest Uganda where it subsided [37].

Attack rates could be very high (up to 80%), and using antibody assays it was suggested that approximately 90% of the population were infected [38]. The virus was isolated from sera of patients in the early stage of the disease, generally in the first 2 days [36].

In 1996, after an absence of 35 years, a new epidemic of O'nyong-nyong fever started in southwest Uganda, this time with a restricted spread in a few districts and over the border into Tanzania [37]. At that time, based on a household-based seroprevalence study in affected areas, an infection rate of 40% and an attack rate of 29% were estimated [39]. It appeared that the virus isolates from this epidemic were closely related to the strains isolated in the 1959 epidemic [40].

Although human and mammal infections, based on serological evidence, have been reported from west Africa, human infections have only been documented in east Africa [41,42]. In a study of viral infections in travellers, O'nyong nyong virus antibodies were found in 4 out of 86 patients who had visited countries in west Africa [43]. In 2003, an outbreak of a disease with fever, a maculopapular rash, pruritus, myalgias, and arthralgia took place in a refugee camp in Côte d'Ivoire. By means of serological tests or an O'nyong nyong-specific real-time polymerase chain reaction assay, it was shown to be O'nyong-nyong fever [42]. In 2004, a French soldier was infected in Chad [41].

From field studies in locations in Uganda and Kenya, it appeared that *Anopheles funestus* was the main vector, and that *A. gambiae* might have transmitted the virus in certain areas [44]. This was supported by the isolation of the virus from pools of *A. funestus*, and to a lesser degree from pools of *A. gambiae* [45]. *A. funestus* favors clear permanent water with some water movement and with moderate shade, whereas *A. gambiae* breeds in small, freshly formed rainwater pools without vegetation or shade; and both are anthropophilic, biting especially at night. It is the first example of an anopheline mosquito being recognized as the principal vector

Table 23.3 Treatment of Chikungunya Fever

Symptom	Treatment
Fever	Antipyretics. Because of the hemorrhagic potential for CHIK, aspirin and any medicines that inhibit platelet function should be avoided. Bed rest is indicated during the febrile period
Arthralgia	Analgesics and, if needed, mild sedation
Nausea or vomiting	Oral rehydration for fluid losses
Seizures	Anticonvulsants

in an epidemic viral disease in man [44]. A vertebrate reservoir has not been identified [6].

Clinical Disease

The clinical picture, as it was initially described, consisted of joint pains, rash, and lymphadenitis; headache, fever, and post-orbital pain were also prominent. The rash is reported in the majority of patients and is described as irritating or pruritic in quality. It generally starts on the face, extending to the trunk and extremities, and is generalized over the body; it is mostly papular or maculopapular, initially discrete, but tending to become confluent later. In general, it starts 4 days after the onset of symptoms, but this may vary from day 1 until day 7, and is often followed by an improvement of the general symptoms; it lasts for 4–7 days and fades without desquamation. Pruritus in the absence of rash occurs frequently. Although on clinical grounds it was initially considered to be a dengue-like disease, it mostly resembles CHIK. There are, however, important differences: lymphadenopathy is not a feature of CHIK; joint pains are generally less severe, whereas headache and eye complaints, post-orbital pain, and red eyes are much more pronounced in O'nyong-nyong fever. Lymphadenopathy is found in approximately half of the patients, and the cervical glands are nearly always affected and can be visibly enlarged. Eye involvement has been reported as throbbing post-orbital pain in 60% and red eyes in 44% of the cases [35,46]. Hemorrhagic features have been described in only one patient who was suffering from bleeding gums [46]. Although it leads to substantial morbidity, it is self-limiting, and no fatal cases have been reported [35,46].

In the 1996–1997 epidemic in south central Uganda, it was found that the duration of the arthralgia was 6 days (range: 2–21 days) with knee and ankle joints most commonly affected. In this study, a combination of fever, arthralgia, and lymphadenopathy had a specificity of 83% and a sensitivity of 61% for the identification of O'nyong-nyong fever [46].

Ross River Virus and Barmah Forest Virus

Two different alphaviruses, Ross River virus and Barmah Forest virus, are implicated in human disease in Australia. They are zoonotic and associated with rural disease [47]. Ross River virus disease is the most common and most widespread arboviral disease in Australia; on average, 4800 cases per year are reported [48].

Ross River Virus

The disease symptoms caused by Ross River virus were initially named epidemic polyarthritis, but nowadays the term Ross River virus disease is used; not all patients present with fever and joint pain and epidemic polyarthritis includes disease caused by Ross River virus as well as Barmah Forest virus [49,50]. Ross River virus was isolated from *Ochlerotactus vigilax*, previously *Ae. vigilax* mosquitoes, in 1959 near the Ross River in Townsville [51], and from the blood of a patient in 1971 [52].

In 1928, the first descriptions of Ross River virus disease were of an "unusual epidemic," of a disease with "pain, skin eruption and general manifestations" in which "painful swelling of the joints" predominated [53]. The disease is endemic in all states of Australia, but local epidemics occur in rural areas. Epidemics usually follow periods of heavy rain or after high tides that inundate salt marshes and coastal wetlands. However, Ross River virus has also been detected in major urban areas [48]. In 1979, Ross River virus spread to the South Pacific, probably imported by a viremic person infected in Australia, with high numbers of cases in Fiji, the Cook Islands, and Samoa [50]. Currently, it is endemic throughout Australia, Papua New Guinea, East Timor and adjacent islands of Indonesia, and the Solomon Islands [48]. Two new cases have been described from Fiji, where it had been not been reported since the 1979–1980 epidemic [54].

The virus is transmitted by different mosquitoes in a mosquito-mammal cycle, the reservoir being native macropods (kangaroos, wallabies), but horses and fruit bats are also implicated. The vectors are: *A. vigilax*, breeding in temporary brackish and saline water along the coast and intermittently in urban areas, excluding the southern part of Australia; *A. camptorhynchus*, breeding in salt marshes along the southern coast; and *Culex annulirostris*, breeding in temporary or semipermanent ground waters and run-off all over Australia except Tasmania. A human-mosquito cycle may be present during large outbreaks. Vertical transmission in desiccation-resistant eggs of certain mosquito species, by which the virus can persist for long periods of time, may explain the appearance of Ross River virus disease after early season rains. Antibody prevalence studies have shown that the risk of infection is greater in the north of Australia.

Clinical disease

After an incubation period of 7–9 days (range: 3–21 days), Ross River virus disease manifests with fever, rash, and joint manifestations. Fever and other constitutional symptoms as myalgias and upper respiratory tract symptoms are much less severe than in CHIK fever, and are found in about half of the patients. The most common complaints are lethargy, joint pain, and swelling [55,56]. Fatigue and lethargy affect over 50% of patients [50,56]. Lymphadenopathy is a common manifestation. The pruritic rash, which is seen in approximately half of the patients, may occur between 2 weeks before until 2 weeks after the constitutional symptoms, and lasts from 2 to 10 days. It may be the sole manifestation of the disease. Characteristically, it is maculopapular, but vesicles and haemorrhagic lesions may also be found. It is localised mainly on the trunk and extremities, and may also involve the face and scalp; it fades with desquamation in the minority of patients [53,57]. Mucosal lesions of the mouth have been described [48,50,57]. Joint involvement, in the form of arthralgia or arthritis with swelling, redness, and restriction of movement, is found in the majority of patients, with ankles, knees, fingers, and wrists most commonly and symmetrically involved. Joint pains generally resolve in 14 days, but persistent, intermittent, or continuous joint pains for a period of years have been reported [50]. A low attack rate in children suggests less severe infection in this age group [58].

Management

NSAIDs can give dramatic symptomatic relief. Physical therapy is beneficial for a minority of patients. Systemic steroids have been prescribed, but their usefulness is not clear, and are not recommended [50]. Control measures consist of mosquito control measures, personal protection (long sleeves and pants, mosquito repellents and mosquito coils), and avoidance of areas where the dusk to dawn biting vectors are abundant. There is no commercial vaccine available [48].

Barmah Forest Virus

Barmah Forest disease, characterized by fever, arthralgia, and rash, has been reported only from the mainland of Australia; although in much lower numbers than Ross River virus disease. Several outbreaks were reported in the 1990s after a period without Barmah Forest virus activity in that area. The largest outbreak involved 135 cases in 1995 on the south coast of New South Wales following unusually high rainfall coupled with high tides [59]. In 2005–2006, the largest outbreak took place with 1895 cases [60]. Different mosquitoes are supposed to be involved in the transmission of the virus [61]. Barmah Forest virus antibodies have been found in kangaroos, cattle, horses, and sheep in south Australia [61], and studies from the Brisbane area, Queensland, have implicated horses and brushtail possums as possible non-human hosts in that area [62]. The virus is transmitted in a mosquito-mammal cycle, and there is no evidence for human-to-human transmission [61].

In 1974, Barmah Forest virus was first isolated from *C. annuloristis* mosquitoes in the Barmah Forest near the Murray River, Northern Victoria, and first cultured from a patient from North Queensland in 1988 [61,63].

Clinical disease

After an incubation period of 7–10 days (range: 3–21 days), Barmah Forest virus disease manifests similar to Ross River virus disease, although the rash is more common and more extensive in Barmah Forest virus disease, and arthralgia is more common and more prominent in Ross River virus disease [49,61,63]. The most common symptoms are lethargy, joint pain, and rash, which are, in general, the first symptoms. Patients with a rash suffer less from chronic sequelae [64]. The rash of Barmah Forest virus disease has been described as maculopapular. It lasts for an average of 7 days and resolves spontaneously, in a minority with desquamation [65,66]. In a clinical study of 5 patients, facial signs, i.e., erythema with an urticarial component, were found. A more diverse eruption can be seen consisting of papules, papulovesicles, and, in a minority, purpuric lesions on the trunk and extremities [65]. Pruritus is reported by a minority of patients [64,65]. The most common histopathologic feature is a mild to dense lymphocytic infiltrate around superficial dermal vessels [65]. Arthralgia, myalgias, and lethargy are less long lasting than in Ross River virus disease [63]. There is a low disease rate in children [61].

Sindbis Virus: Ockelbo, Pogosta, Karelian Fever

Sindbis viruses are the most widely distributed of the alphaviruses, as they have been recovered from Europe, Africa, Asia, Australia, and the Philippines [3]. Transport of Sindbis strains over long distances can be accomplished by infected mosquitoes by air or by ship; the finding of a genetic cluster comprising north European and South African strains points to migrating birds as a transport mechanism [67].

Sindbis virus infections have been described in several reports from northwestern Europe. They have been described as Pogosta disease, after the local name of Ilomantsi parish "Pogosta" in Finland, Ockelbo disease in Sweden, and Karelian fever in Russia [68,69]. Lundström states that all western European alphavirus strains are Sindbis [70].

Ockelbo disease occurred annually, with a peak incidence in August, since the 1960s in central Sweden with the majority of the cases between the 60th and 63th parallels. In an outbreak in 1982, a positive antibody test was found in 2–3% of healthy individuals (blood donors) in the endemic area, and in 8% in foci with high incidence [71]. In 1982, the virus was isolated from *Culiseta* mosquitoes in Sweden [72].

In Finland, Pogosta disease peaks in late August, with epidemics occurring at 7-year intervals. It appears that the snow cover and the temperature in the spring predict the number of cases. By means of serological tests, the estimated seroprevalence in fertile-age females in Finland is about 2%; however, after the 1981 epidemic, seroprevalence in the general population in the Ilomantsi parish was as high as 39%. The seroprevalence in game animals was highest, i.e., 65% in black grouse and capercaillie birds [68]. Antibodies were present in all passerine bird samples tested in different locations in Sweden [73]. The relatively high proportion of antibodies against Sindbis virus found in sera of resident birds in the UK in 2001 and 2002 suggests an efficient transmission from the migrant bird population [74].

Ockelbo virus RNA has been detected in 4 out of 10 biopsies from the typical rash, but not from acute and convalescent sera or from lymphocytes collected during the covalent phase [75].

Pogosta virus has been isolated from four skin biopsies from papulopustules and one whole blood sample [76].

Clinical disease

The main features of Sindbis virus infections are rash, arthralgia, and (moderate) fever.

In the1982 outbreak of Ockelbo disease in Sweden, 48 out of 50 patients had a rash, which was pruritic in 4; 47 patients reported joint pain, with swelling in 29 and fever in 17. Nearly all patients had myalgias, with general malaise and headache in a minority. The characteristics of the rash were not mentioned, but it started before, on the same day, or after the joint symptoms; the duration in the majority of the patients was between 2 and 10 days with a peak between 5 and 7 days. Fever in general was moderate. The large joints, i.e., wrist, hip, knee, and ankle were most commonly involved [71]. In a follow-up study of patients with confirmed Ockelbo disease, it was found that nearly 60% of the patients had fully recovered from the arthralgia within 3 months; however, nearly 30% had arthralgias for 3–4 years, and of these, the great majority still had arthralgia after 5–6 years. Complaints were often asymmetric, and often involved the joints most severely affected in the acute disease period [77].

The clinical picture of Pogosta disease was accurately recorded during the outbreak in 1981. The main clinical manifestations were fever in 23%, rash in 88%, and joint symptoms in 93% of the cases. The rash was described as papular, and in some cases morbiliform, with oral involvement in some cases.

In half of the patients the rash was the first sign; the duration was slightly shorter than in Ockelbo disease, but more frequently reported as pruritic (55%). Joints most commonly affected were ankles, knees, wrists, and fingers, and patients having arthralgia and arthritis were equal in Pogosta and Ockelbo disease. Malaise, headache, and nausea were found in nearly half of the patients, and muscle pains and retro-orbital headache in the minority [69].

In the 2002 outbreak, rash and joint symptoms were found in higher percentages. The rash was, in general, localized on the

trunk, thighs, and was pruritic in 50%; oral lesions were found in 8%. The duration of the rash was often >5 days.

Fatigue, mild fever, headache, and muscle pain were early symptoms, and occurred in about half of the patients. The same joints as previously reported were most commonly affected and symptoms were mostly fluctuating. Fifty percent of the patients still suffered from joints symptoms after 12 months [78]. In a follow-up study in 26 patients with serologically confirmed Pogosta disease, only 50% were symptomless after 2.5 years; 11 patients had chronic musculoskeletal problems: three fibromyalgia, six occasional arthralgia, and two chronic arthritis [79].

Mayaro virus

Mayaro virus was first isolated from patients in Mayaro country, Trinidad, in 1954. The clinical picture of these five original patients consisted of fever and generalized systemic complaints like headache, chills, and body pain [80].

In 1955, an outbreak of a disease characterized by fever and headache occurred on a plantation in the Amazon region, Brazil, in which Mayaro virus was isolated from 6 patients [81]. In 1978, an outbreak was recorded in the rural village of Belterra, Para, Brazil, in which approximately 20% of the residents were infected, and a very high proportion had clinical disease; based on serological assays, an attack rate of 19.4% and a clinical history of 20.5% were calculated. The highest number of cases was seen in people living near the forest. The virus was isolated from *Haemagogus janthinomys* mosquitoes, living in the canopy and at ground level in the forest [82]. Although the virus is supposed to be maintained in the sylvatic cycle involving tree-dwelling primates and *Haemogogus* mosquitoes, the maintenance cycle has not yet been definitely identified [83].

Based on serological studies, it has been found that Mayaro virus infection is relatively common in people living in the rural areas of the north part of South America and the Amazon Basin [84,85]. In 2000, Mayaro virus disease was also documented in four family members after a visit to a rural area in Venezuela [86].

Clinical disease

In the 1955 outbreak on the plantation in Brazil, the major symptoms and signs were severe frontal headache (in all cases) and epigastric pain, backache, nausea, photophobia, vertigo, conjunctival injection, and slight icterus (in the majority of cases) [81].

In the Belterrra outbreak in 1978, it presented with a clinical syndrome of fever, arthralgia, and rash. Fever and arthralgia were seen in all confirmed cases. Arthralgia was reported as severe with wrists, fingers, ankles, and toes most commonly affected; in about 20%, swelling of the joints was found. In contrast to previous reports, a maculopapular or papular rash that appeared around the 5th day of illness and was more commonly observed in children, was found in two thirds of the cases. The rash started on the 5th day and resolved within 3–5 days. Over 80% of the patients reported headache, myalgias, and chills, and more than 50% of the patients presented with inguinal lymphadenopathy [87].

In a study from Peru spanning several years, rash was found in 32%. It was hypothesized that this lower percentage was due to the fact that patients were seen, in general, in the early phase of the disease and before the appearance of skin signs [88]. In the Belterra outbreak, the incubation period could not be determined; in one case, clinical signs appeared 6 days after entering the epidemic area. However, in the study from Venezuela, clinical disease started 3 days after a single day-visit to a rural area [86].

Conclusion

Alphaviruses are mosquito-borne togaviruses that produce disease in many parts of the world. The clinical manifestations are similar to those of many flaviviruses, e.g., dengue, and include fever, rash, and arthralgias.

RUBIVIRIDAE

Rubella, also known as German measles or 3-day measles, is typically a subclinical or inconsequential viral exanthem of childhood. However, the serious potential for teratogenic effects with congenital rubella syndrome makes this infection of great importance to public health.

History

It is known that early Arabian physicians recognized a rash that presumably was rubella. They considered it to be a variant of measles and referred to it as al-hamikah. In 1752 and 1758, Bergen and Orlow, respectively, described rubella as a separate entity from measles. German physicians in the early 1800s called it Rötheln [89]. Warner, in 1829, distinguished this infection from measles and scarlet fever. In 1866, the Scottish physician Henry Veale described 30 cases of this disease and proposed the current name "rubella" [90]. The commonly known name, German measles, was used in several European countries because of the continued interest that Germans had in this disease during the 18th and 19th centuries [91].

In 1938, Hiro and Tasaka, inoculated humans and monkeys with filtered nasal secretions taken from infected individuals and demonstrated the viral etiology of rubella. This infection was considered to be a benign disease until 1941, when Sir Norman McAlister Gregg first linked rubella to congenital cataracts and malformations [92]. This observation was quickly confirmed by others. In 1942, Habel was able to reproduce the disease in monkeys, and in 1953 Krugman isolated the rubella virus from blood. In 1962, two different groups first isolated the virus in tissue cultures. Soon thereafter, the worldwide pandemic of rubella began. In the United States, this resulted in 12 million cases of rubella infection, with 30,000 stillbirths and 20,000 deformed infants caused by congenital rubella. These devastating figures prompted the rapid development of the rubella vaccine, which would soon turn the tables in the fight against this viral disease (Fig. 23.9).

Incidence

This worldwide infection most frequently occurs in the spring months. Epidemics occur every 5 to 7 years. Both sexes are equally affected, although most infections are subclinical. The ratio of subclinical to overt disease is 2:1 [93]. Infection is more frequent in schoolchildren, adolescents, and young adults, but prior to widespread immunization younger children were more often affected [93].

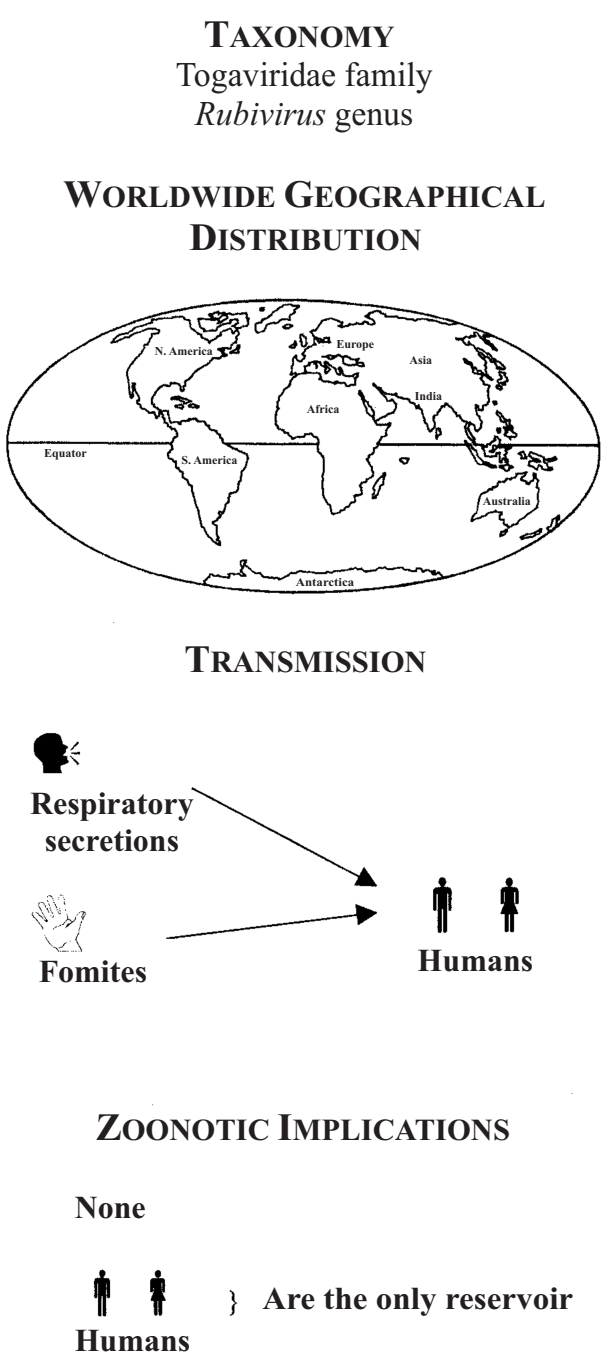


Figure 23.9 Incidence and transmission of rubella.

Pathogenesis

The rubella virus is transmitted from person to person via inhalation of infected droplets from respiratory secretions. Transmission of the secretions by contact and fomites is also possible [91]. Rubella is a moderately communicable infection. In the family setting, less than 50 to 60% of susceptible family members acquire rubella from the infected person [93].

The portal of entry for the rubella virus is primarily the nasopharynx. Viral replication begins in the respiratory epithelium and then spreads via the lymphatics to regional lymph nodes. Seven to nine days after exposure, viremia develops, and the virus spreads to multiple sites of the body. The extent of viremia peaks immediately before the development of the exanthem, then disappears quickly thereafter. Viral excretion from the nasopharynx persists for 6 days after onset of the exanthem and may continue for up to 13 days after the onset of rash (Fig. 23.10) [94].

Clinical Manifestations

Rubella produces a mild exanthematous macular rash (Figs. 23.11 to 23.13) except when it is transmitted in utero [95]. Subclinical infections represent 50 to 80% of the infections [96]. When eruption is present, it starts on the face and neck with mild pink erythematous macules and papules that spread, fade quickly, and leave no desquamation (Fig. 23.14) [97]. The clinical manifestations of postnatal rubella infection are outlined in Table 23.4. Up to 25 to 40% of rubella patients do not develop a rash [98], and 50 to 80% of infections are clinically inapparent [96]. Lymphadenopathy with prominent enlargement and tenderness, particularly involving the suboccipital and preauricular nodes, is the main prodromal characteristic of rubella infection [99–101]. Forschheimer's sign is also present in 20% of cases; this is an enanthem consisting of dull red petechiae on the soft palate. This manifestation generally appears during the prodromal period or during the first day of the rash [98]. In younger children there is usually no prodrome; in older individuals there is fever, malaise, sore throat, nausea, lymphadenopathy and painful eye movement. Cutaneous petechiae and purpura may develop infrequently with rubella infection [100]. Thrombocytopenic purpura develops in 1 out of 1500 to 3000 cases and more commonly affects children [102,103]. This complication may persist for weeks or even months but typically resolves completely.

Polyarticular arthritis or arthralgias are common complications of infection, more frequently involving adolescent girls and women. These sequelae affect 30% of females and 5% of males [104] and typically begin 1–6 days after the appearance of the rash. Articular symptoms may include pain, swelling, effusions, warmth, erythema, arthritis, and decreased movement of the joint. Joint manifestations may persist for one month up to several months and only rarely lead to chronic arthritis. Rubella virus has been isolated from peripheral blood lymphocytes in women with rubella-associated arthritis [105] and from synovial cells of patients with juvenile rheumatoid arthritis [106].

Complications involving the central nervous system, such as encephalitis, develop in 1 out of 6000 cases and more commonly affect adults [102]. Neurological symptoms, which may include headache, vomiting, nuchal rigidity, lethargy and seizures, suddenly appear 2 to 6 days after the rash onset in most cases. Encephalitis resulting from rubella is clinically similar to that of measles, although less severe [91]. Examination of the cerebrospinal fluid commonly reveals a mild increase in white blood cells (20 to 100 cells/mm^3), predominantly composed of lymphocytes. The protein concentration may be normal or slightly increased, and the glucose concentration is normal [91]. Rare neurological complications reported in rubella infection include panencephalitis (107,108), optic neuritis (109), peripheral neuritis (110,111), Guillain-Barré syndrome (112), and polyradiculoneuritis associated with encephalitis (113). Potential differential diagnoses are shown in Table 23.5.

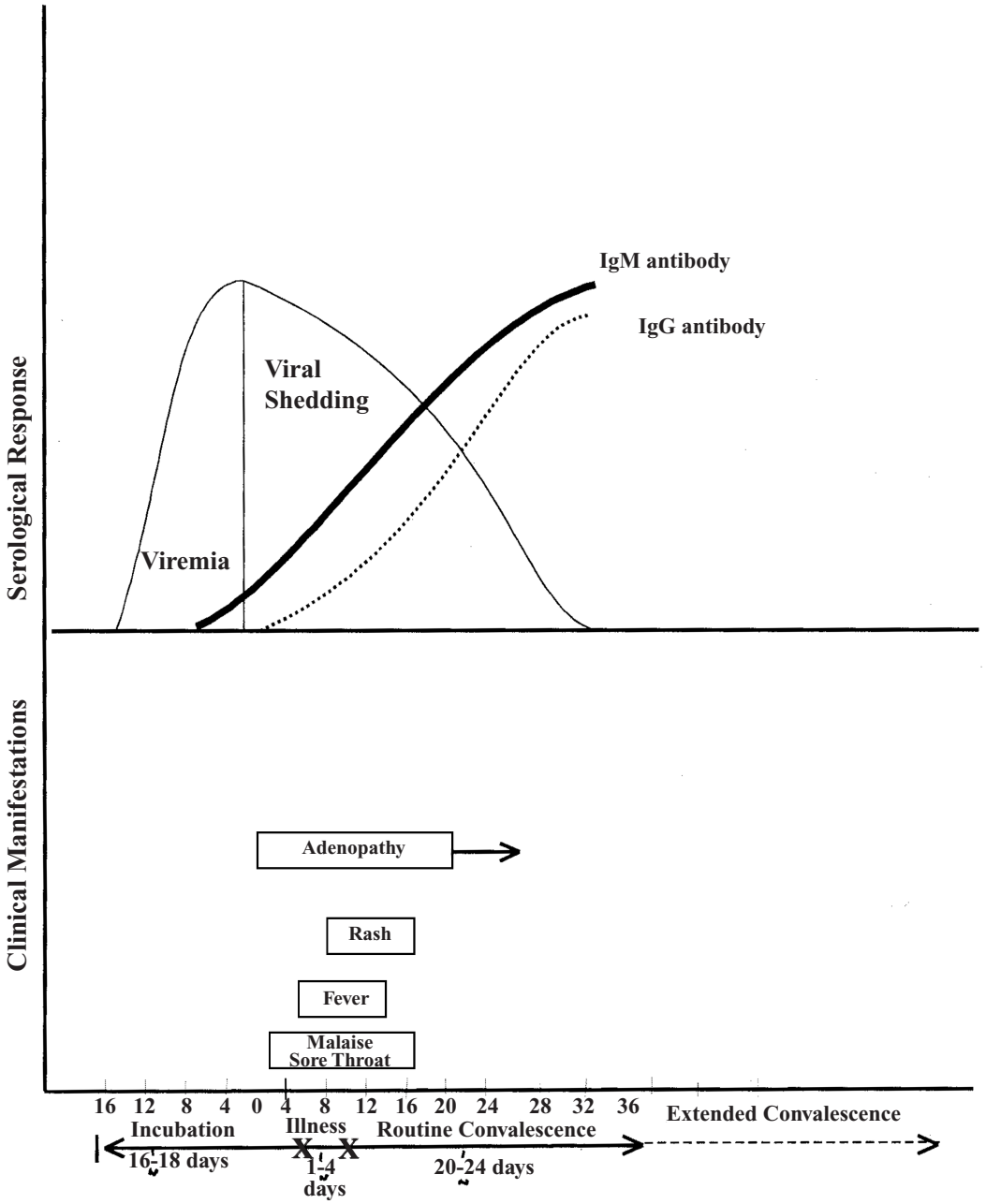


Figure 23.10 Pathogenesis and acquired immunity in postnatal rubella infection. The interaction of serological and clinical manifestations are shown over time. Although IgM antibody expression occurs most rapidly, most of the antibody disappears in less than a year. IgG levels, however, develop more slowly but are associated with lifetime immunity.

Congenital Rubella Syndrome

Rubella infection of the embryo or fetus occurs equally in all races and is most commonly the result of infection acquired during the first trimester of pregnancy. After Sir Normal Gregg first linked congenital rubella infection to cataract formation, the many effects of this syndrome were recognized during the large rubella pandemic of 1962 to 1965.

Not all infants exposed in utero become infected. In addition, not all infected infants have signs of disease during the neonatal period. Of all infected neonates, approximately 30% have clinical signs of rubella at birth whereas nearly 70% have subclinical infections [114].

There is a risk of 65% for congenital rubella if the infection occurs in the first 16 weeks of pregnancy [112]. The skin manifestations in the immediate neonatal period include multiple "blueberry-muffin spots" (Fig. 23.15), which are areas of extramedullary hematopoiesis. These sequelae develop in 20 to 50% of cases [116]. The lesions appear at birth or during the first 48 hours after birth. They can be macular or papular and are dark blue, dark red, or blue-grey in color. These lesions are frequently diffuse but often have a predilection for the trunk, scalp, and neck [114]. Thrombocytopenia commonly occurs in infants with congenital rubella syndrome, although actual petechiae and purpura are uncommon [114]. The hair, nails,



Figure 23.11 Erythematous macules of acute rubella. The exanthem starts on the face and neck. In young children, there is no prodromal syndrome. The lesions are mild, pink, erythematosus macules and papules that spread and fade in 2 or 3 days with no desquamation.

and mucous membranes are spared in congenital rubella syndrome, but necrosis of the inner enamel of the teeth has been described [117].

Visceral abnormalities can be present in up to 75% of patients with congenital rubella syndrome. The manifestations of congenital rubella syndrome are listed in Table 23.6. The classic triad of congenital rubella syndrome includes cataracts (Fig. 23.16), deafness, and heart defects (e.g., patent ductus arteriosus). If the mother is infected with rubella virus before becoming pregnant, the virus is not transmitted across the placenta. The greatest impact of viral transmission is during the first trimester. If the virus is transmitted after the first trimester, the impact of viral transmission declines until it nearly disappears at 20 weeks of gestation. The interval of viral transmission from the onset of rash in the mother is about 10 days to the placental villi and 20–30 days to the fetus. A phylogenetic tree of 61 virus isolates suggested no difference in virulence or teratogenicity among the virus isolates [118]. If infection occurs before the 20th week of gestation, the fetal damage and clinical findings are more severe. These neonates frequently have multiple congenital defects, particularly those of the classic triad, and often are of low birth weight and mentally retarded. Infection acquired after the 20th week of gestation rarely leads to congenital defects [102]. These neonates who are infected



Figure 23.13 Erythematous macules of acute rubella.

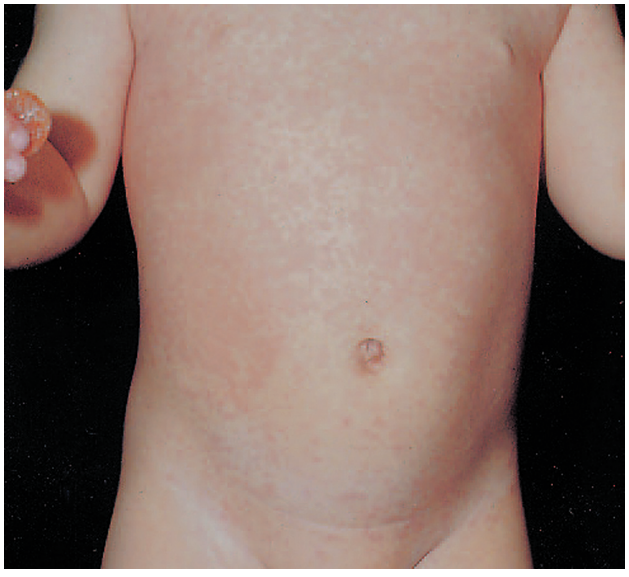
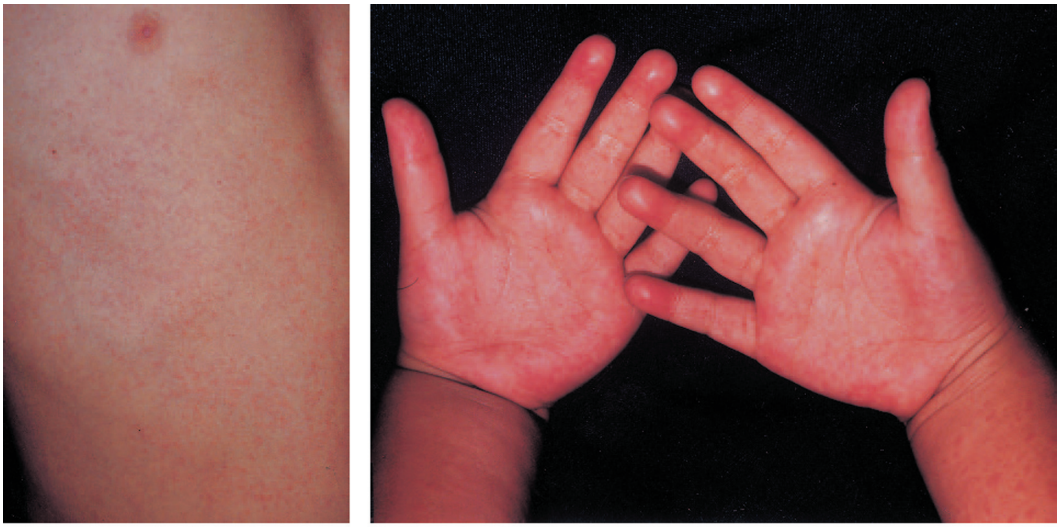


Figure 23.12 Erythematous macules of acute rubella.



(a) (b)

Figure 23.14 (a, b) The macular erythematous rash spreads to the trunk and goes to the extremities in 24 to 48 hours, as seen here.

in utero after complete organ development often have a different array of manifestations, which may include myocarditis, hepatitis, encephalitis, pneumonitis, or other sequelae. In infants with congenital rubella, the virus can be isolated from peripheral leukocytes, stool, and urine for months to years after birth [100]. These infants are considered infectious for the first 6 to 12 months of life [114]. Sequelae of rubella virus infection include three distinct neurological syndromes: a postinfectious encephalitis following acute infection, a spectrum of neurological manifestations following congenital infections, and progressive rubella panencephalitis (PRP). PRP is an extremely rare neurodegenerative disorder that may follow either congenital or postnatal infection. The pathogenesis of the three neurological syndromes is not understood. There may be an autoimmune reaction triggered by molecular mimicry between viral and host epitopes, as there is an apparent lack of virus in the brain except in cases of PRP [115].

Dermatopathology. There are no specific well-known histopathological findings in rubella infection. Some examined cases have shown a sparse superficial perivascular infiltrate of atypical lymphocytes (Türk's cells) with mild spongiosis [119].

Laboratory Findings. Leukopenia may be present early and may be followed by an increase in plasma cells or atypical lymphocytes. Little is known about the cellular immune response to rubella virus structural proteins, although both helper T-lymphocyte proliferation and cytotoxic T-lymphocyte responses occur during viral infections [120]. Most rubella virus infections produce lifelong immunity mediated by circulating antibodies and specific T lymphocytes [121].

Table 23.4 Clinical Manifestations of Rubella (German Measles)

Time after exposure	Clinical manifestations	Laboratory analysis	Other notes
13–l5 days	Viral prodrome of low-grade fever and the following symptoms lasting 1–3 days: headache, conjunctivitis, sore throat, rhinitis, malaise, cough, and diffuse lymphadenopathy. Petechiae may be seen on the soft palate at the end of the viral prodrome. ↓	Serological tests, with rubella-specific IgM or a fourfold rise in IgG. Isolation of the virus by nasal or throat swabs	Prodromal period is not always apparent in children Extremely elevated temperature is rare, and patients are not generally ill to a significant degree Tender lymph nodes resolve rapidly, but lymphadenopathy may remain for weeks The rash is not exceptionally distinctive and may look similar to an enteroviral or heat rash
16–18 days	Pink-red maculopapules appear. The rash initially begins on the forehead and spreads down to the face, trunk, and extremities during the first day. Lesions on the trunk may become confluent. The viral prodrome remits quickly after appearance of the rash. ↓		
17–19 days	The facial rash begins to fade. ↓		
18–21 days	The viral exanthem completely disappears after 2 to 3 days. Mild scaling may occur.		

Table 23.5 Differential Diagnoses of Rubella (German Measles)

Measles: Koplik's spots in the oral cavity, and the viral exanthem lasts 3–5 days. Rubella does not include photophobia, fever is slight or absent, and the rash persists for no more than 3 days. Lymph node enlargement strongly supports the diagnosis of rubella
Scarlet fever: Puncate, pinhead-sized yellow-red lesions on erythematous skin. There is a sandpaper-like quality to the skin rash. Scarlet fever typically has a significant postexanthem desquamation, particularly on the hands and feet
Infectious mononucleosis: Similar to rubella, this disease may have a diffuse rash and lymph node enlargement but is distinguished by the characteristic hematological findings
Exanthem subitum (roseola infantum): Rash appears after resolution of the febrile prodromal stage rather than at the peak of these symptoms
Enteroviral infections: These viral infections may also cause a diffuse rash but can typically be differentiated by respiratory and/or gastrointestinal manifestations and the absence of retroauricular adenopathy
Drug rash: Exanthem may appear similar, but lymphadenopathy is lacking

Table 23.6 Manifestations of Congenital Rubella Syndrome

Transient Sequelae
Extramedullary hematopoiesis (blueberry-muffin rash)
Diffuse lymphadenopathy
Thrombocytopenia (+/– petechiae, purpura)
Hepatosplenomegaly
Hepatitis
Hyperbilirubinemia and jaundice
Interstitial pneumonitis
Myocarditis
Myositis
Meningoencephalitis
Nephritis
Bony radiolucencies
Hemolytic anemia
Growth retardation (intrauterine and postnatal)
Permanent Sequelae
Ocular defects: cataracts, retinopathy, glaucoma, microphthalmia
Sensorineural hearing loss
Heart defects: patent ductus arteriosus, pulmonary artery stenosis, pulmonary valvular stenosis, ventricular septal defects
Mental retardation, psychomotor retardation, behavior disorders

Diagnosis. The most definitive form of diagnosis is made by isolation of the rubella virus in sensitive tissue culture. Throat or nasal swabs can readily isolate the virus for 6 days before or after the onset of the viral exanthem [122]. In infants with congenital rubella syndrome, virus can be isolated from the nasopharynx, conjunctivae, urine, feces, blood buffy coat, and cerebrospinal fluid.

Despite the accuracy of viral isolation, most cases of rubella are diagnosed by serological testing. A fourfold rise of rubella-specific IgG in sequential serum samples taken during the acute and convalescent phases (at least 1–2 weeks apart) is diagnostic of rubella infection. Some experts recommend drawing the convalescent phase serum at least 28 days after exposure [102]. For those patients who do not present sufficiently early in the course of disease, the presence of rubella-specific IgM is diagnostic of recent infection. Rubella-specific IgM becomes detectable quickly after the rash onset, and testing for this antibody can be done as early as 1–2 days after the appearance of the rash [102]. The rubella-specific antibodies can be identified by complement fixation, hemagglutination-inhibition, immunofluorescence, enzyme-linked immunosorbent assay, or platelet aggregation [123–127]. Hemagglutination-inhibition testing has been the predominant screening method for rubella antibodies in the past, but enzyme-linked immunosorbent assay and other newer methods



Figure 23.15 Blueberry-muffin lesions are characteristic of congenital rubella infection (20–50% of affected children), although congenital cytomegalovirus infection can also produce these lesions. They are areas of extramedullary hematopoiesis that can be associated with petechiae and purpura.

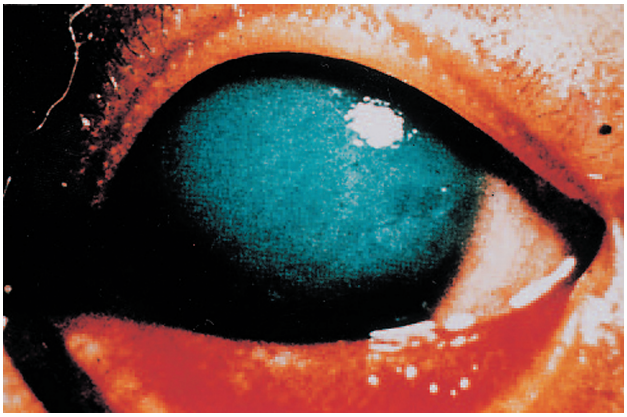


Figure 23.16 Glaucoma and cataracts are seen with the congenital rubella syndrome.

are now more commonly employed [102]. The presence of IgM and the persistence of IgG antibody in neonates are both indicative of congenital infection [98]. If exposure to rubella is suspected in a pregnant woman with uncertain rubella immunity, serological testing should be performed close to the time of exposure. If the woman already has antibodies to rubella, she is considered immune. If no rubella antibody is detected on serological examination, the test should be repeated in 3–4 weeks. Seroconversion at that time would confirm exposure to rubella, and information regarding the risks and alternative approaches for congenital rubella syndrome should be discussed with the mother [128].

Treatment and Prophylaxis. Antiviral agents such as amantadine and interferon have been tried in some cases of rubella infection with equivocal results at best. The mainstay of treatment for this condition continues to be supportive therapy (Table 23.7). Infected individuals should refrain from exposure to others for 7 days after the onset of the rash because of infectivity.

Because no antiviral treatment is available for rubella, widespread vaccination has been a priority. The World Health Organization set the goal to eliminate indigenous measles and congenital rubella in Europe by the end of the year 2000; however, some outbreaks have continued to occur. The immunization of children and susceptible women of child-bearing age is now a standard public health measure.

Several live-attenuated rubella vaccines have been used since 1966. The rubella vaccine is typically given as part of the combined MMR (measles, mumps, rubella) vaccine in childhood. One vaccine dose, usually given between 12–15 months of age, generally confers durable immunity against rubella. However, most experts recommend giving a second dose at 4–6 years of age [102]. Immunity after two vaccine doses is considered to be long-lasting, and waning immunity with increased susceptibility to rubella has not been observed in long-term surveillance [129]. Infants with colds or upper respiratory infections at the time of immunization have a significant seroconversion failure rate [130]. Interferon induced by a concomitant viral illness may be responsible for the vaccine failure. However, it is currently recommended that immunization be postponed for persons with severe illnesses only and not for those with minor illnesses [102].

Rubella vaccination is contraindicated in the following situations: pregnancy; persons on systemic corticosteroids for more than 2 weeks; leukemic or immunosuppressed patients; recipients of immune globulin treatment other than anti-Rho(D) therapy during the previous 3 months or in the following 2 weeks; and those with a history of anaphylactic reaction to neomycin [102].

Table 23.7 Treatment of Rubella Infection

Symptom	Treatment
Pruritus	Starch baths or antipruritics
Arthritis in adults	Aspirin or nonsteroidal antiinflammatory drugs and bed rest, if needed
Encephalopathy or encephalitis	Maintenance of fluids and electrolytes and other supportive care

Conclusion

Although widespread rubella immunization has significantly diminished the frequency of occurrence of this disease, many developing countries continue to have epidemics and high rates of infection because of the lack of vaccine availability. Although most cases of rubella are subclinical or insignificant, the possibility of fetal involvement with congenital rubella syndrome demands accurate diagnosis and monitoring of all potential infections.

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24 Hepatitis Viruses

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Introduction

Viral hepatitis is a worldwide health problem caused by several distinct DNA and RNA viruses, with the incidence of disease varying significantly among different populations (Fig. 24.1). This condition is most commonly caused by one of three viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Hepatitis D (HDV) and hepatitis E (HEV) occur less frequently and, to date, are not associated with any specific cutaneous findings. Hepatitis G virus (HGV) has been discovered more recently, but its role in hepatitis is not well established [1]. Other viruses are known to cause hepatitis. This chapter provides a brief introduction to hepatitis A, D, E, and G viruses before detailed discussion of HBV and HCV, since the predominant cutaneous manifestations occur in these diseases.

Hepatitis A Virus

HAV infection produces a transient, discrete, maculopapular, urticarial, or petechial rash in 14% of cases [2,3]. Papular acrodermatitis of childhood (PAC) has been described in association with HAV in at least one case [4], and after hepatitis A vaccination [5]. On rare occasions, persistent cholestatic hepatitis A infection may develop as cryoglobulinemia with cutaneous vasculitis [6–9].

Hepatitis D Virus

HDV, also called the delta virus, is a defective pathogen that requires the presence of HBV for infection. Because it requires concurrent involvement with HBV, dermatological manifestations with this infection are similar to those for HBV infection [10]. The hepatitis D virion antigen is found within the outer envelope of the surface antigen of the HBV (HBsAg) and requires this coat for transmission. It is transmitted parenterally along with HBV. The inner ribonucleoprotein structure is delta-AG (HDAg). HDV infection can occur simultaneously with HBV (coinfection) or occur in someone already infected with HBV (superinfection).

Hepatitis E Virus

HEV is a single-stranded RNA virus that causes an enterically transmitted acute viral hepatitis. HEV infection is a major public health problem in many developing countries. Hepatitis E infection is clinically indistinguishable from other types of acute viral hepatitis, although the disease can be more severe compared to HAV infections. The highest incidence of HEV infection is in Asia, Africa, Middle East, and Central America [11–15], and HEV is the second most common cause of sporadic hepatitis in North Africa and the Middle East [16].

HEV is enterically spread by fecally contaminated water in endemic areas [17,18]. Person-to-person transmission is uncommon. HEV can be transmitted by blood transfusion, particularly in endemic areas [19]. HEV can infect pigs, suggesting that some cases of human transmission may be due to contact transmission across species [20,21].

The highest attack rates are among persons aged between 15 and 40 years. The case fatality ratio is estimated to be 1–3%. For reasons that are not understood, fulminant hepatic failure occurs more frequently during pregnancy, resulting in a high mortality rate of 15–25% [22,23].

The clinical symptoms of HEV hepatitis are similar to HAV infection. HEV infection is usually acquired during young adulthood, while HAV is usually acquired very early in life. HEV infection can cause disseminated intravascular coagulation, and cutaneous signs of this disorder may be evident [24]. Commercially available antibody-based tests are available in Europe, Canada, and Asia. In the USA, testing for HEV is only available in research laboratories, which can be located through the Centers for Disease Control. A genotype 1 HEV recombinant protein (rHEV) vaccine was tested in a high-risk population, and was effective in the prevention of hepatitis E. It is not yet commercially available [25].

Hepatitis G Virus

Two viral agents related to hepatitis have been isolated and designated HGV and hepatitis GB virus type C (HGBV-C). Molecular characterization of these flaviviruses has shown them to be virtually identical isolates of the same virus [26,27]. HGV was initially cloned from a surgeon whose initials were GB, hence the term GB virus.

HGV has been found in a large proportion of HCV-infected individuals. Several different studies have determined that this virus plays no role in the pathogenesis of mixed cryoglobulinemia (MC) [28,29], vasculitis [30,31], or other extrahepatic manifestations [32]. The clinical significance of HGV infection is not well understood. HGV RNA has been detected in patients with chronic hepatitis of presumed viral etiology, in patients with cryptogenic cirrhosis, and in some patients with primary hepatocellular carcinoma. However, it is often difficult to tease out the direct role of HGV in these settings, since coinfection with HCV is so common.

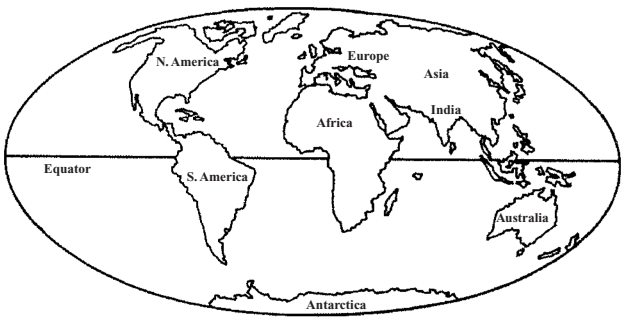
Hepatitis B Virus

HBV is a complex DNA virus, which is transmitted mainly percutaneously or sexually in western countries, but primarily by the perinatal route or in early childhood in the Far East and in Africa. The intact virion of HBV, known as the Dane particle, is composed of double-stranded DNA that contains the core antigen (HBcAg). The "e" antigen (HBeAg) is closely associated with hepatitis B infectivity, whereas the surface antigen (HBsAg) consists of various antigens, which allows for subtyping.

History

Hepatitis with associated jaundice has been a recognized clinical entity since antiquity, although the differentiation of the various causes is a more recent event. Lürman, in 1885, first suggested that parenteral inoculation and icterus were associated with

GEOGRAPHICAL INCIDENCE



Worldwide Incidence

TAXONOMY

Picornaviridae family (hepatitis A virus)
Hepadnaviridae family (hepatitis B virus)
Flaviviridae family
Hepacivirus genus (hepatits C virus)
Deltaviridae family (hepatitis D virus)
Caliciviridae family (hepatitis E virus)
Flaviviridae family (hepatitis G virus)

Figure 24.1 Incidence and taxonomy of viral hepatitis.

hepatitis [32]. He noted that almost 200 shipyard workers in Germany developed jaundice between 2 and 8 months after they received smallpox vaccination prepared from a human lymph node. Blumberg and colleagues [33] found a unique antigen, initially termed the Australia antigen, which is now known as the hepatitis B surface antigen (HBsAg).

Incidence

The World Health Organization estimates that there are approximately 350 million carriers of HBV worldwide, with over 1 million deaths each year caused by hepatocellular carcinoma or HBV-associated cirrhosis [34]. The seroprevalence of HBV carriers varies from 0.1 to 2% in low prevalence areas (USA, Canada, Australia, New Zealand), to 3–5% in intermediate prevalence areas (Mediterranean countries, Japan, Central Asia, Middle East), and 10–20% in high prevalence areas (southeast Asia, China, sub-Saharan Africa). In the USA in 2005, there were 5100 acute HBV infections, 1.25 million with chronic HBV, and 5000 deaths from associated cirrhosis or hepatocellular carcinoma [35].

Pathogenesis

The predominant mode of HBV transmission varies with location. In high prevalence areas, approximately half of infections are acquired perinatally. In intermediate prevalence areas, the virus is more often acquired during the first decade of life, with exposure to infected family members or other children, and later through sexual intercourse. In industrialized nations and low prevalence areas, HBV is usually acquired through sexual exposure or intravenous drug use. Prior to universal screening of blood, transfusions were a prominent source of infection. Transmission of the virus may occur from infected persons to health care workers, tattoo recipients, barbers, and others if appropriate preventive and protective measures are not employed [36]. It is estimated that up to 30% of needlestick exposures to HBV in nonimmunized people lead to seroconversion [37]. In addition to its presence in blood, HBsAg has been found in various body fluids, including semen, saliva, tears, urine, and in impetiginous skin lesions [38]. However, HBV infection only rarely develops after exposure to these other body fluids.

During infection, hepatitis B virions are present in highest concentrations in the blood and liver. Rather than exerting a direct cytopathic effect on infected hepatocytes, HBV alters the antigenic structure of the membrane of infected cells. Minute quantities of HBsAg, HBcAg, and HBeAg combine with HLA class I antigens on the cell surface of infected cells and act as a target. This results in an immune response against the HBV-infected cells. The sensitized cytotoxic T lymphocytes and cell-mediated immune system are considered responsible for destruction and necrosis of infected cells.

The extent of the necrosis may vary with the degree of immune response and the particular subtype of virus with which a person is infected. Chronic hepatitis develops when there is failure of the T lymphocytes to respond adequately to infected hepatocytes and HBsAg is not cleared. The presence of neutralizing antibody to HBsAg (anti-HBs) strongly correlates with the development of immunity to HBV.

Clinical Manifestations

Acute HBV may be symptomatic or asymptomatic. Asymptomatic infection is common in neonates and young children. Adults and adolescents usually develop symptoms, although only 25% develop jaundice. Acute symptomatic HBV infection is described in Table 24.1. In less than 1% of adults, fulminant hepatitis occurs and manifests as hepatic encephalopathy or hepatic synthetic dysfunction. The risk of remaining chronically infected in immunocompetent adults is less than 5% [39]. Approximately 90% of neonates and 30% of children under the age of 6 with HBV acquisition develop chronic infection. Patients with impaired immunity, such as organ transplant recipients or human immunodeficiency virus (HIV)-infected persons, also have a greater risk of chronic infection.

The outcome of chronic infection is variable. Patients with a normal alanine aminotransferase (ALT), absence of HBeAg, and HBV DNA $<10^4$ IU/ml have a good prognosis. Those with an elevated ALT, HBeAg, and/or HBV DNA $>10^4$ IU/ml have a high risk for developing cirrhosis and hepatocellular carcinoma [34].

Cutaneous Findings in Acute Hepatitis B Virus Infection

The majority of the skin findings in early hepatitis other than those of PAC appear to be caused by the development of immune complexes involving HBsAg. Antigen (HBsAg) appears prior to the onset of symptoms. As the individual begins to develop antibodies, symptoms begin to appear. As the titer of antibody rises, the immune complexes formed become less soluble and are cleared rapidly from the circulation with a decrease in symptoms and clinical findings.

Table 24.1 Clinical Manifestations of Hepatitis B

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
4 months (ranges from 2–6 months)	Insidious onset of prodromal period, with nonspecific symptoms of anorexia, nausea and vomiting, right upper quadrant abdominal pain, fever, headache, malaise, fatigue, myalgia, coryza, and/or perversions of taste or smell. 10% of patients may have a serum-sickness like illness, with fever, malaise, urticaria, and symmetrical small joint arthritis	Serological assays, with detection of HBsAg, HBcAg, and others Detection of HBV DNA in serum (although this method is not widely available)	Minimal symptoms may be present during the prodrome. Fewer then 50% of patients experience a prodromal period
	↓		
4 months and 10 days	Progression to the jaundice phase, with subsidence of prodromal symptoms shortly thereafter. A yellowish discoloration of the skin, sclera, conjunctiva, and mucous membranes becomes evident. The stools turn pale, and urine becomes dark		Approximately 50% of patients remain anicteric Less than 0.5% of cases develop fulminant hepatitis, with encephalopathy, coagulopathy, and fluid electrolyte imbalance, which has a high rate of mortality
	↓		
4 months and 2–3 weeks	Jaundice and symptoms begin to fade, and convalescence begins. Increased fatigue may persist for months		
	↓		
5 months	The majority of cases are completely resolved		Some patients have persistent antigenemia and elevated liver enzymes, with or without associated symptoms

Serum Sickness-like Syndrome

Of patients infected with HBV, 20–30% may develop a serum sickness-like illness due to immune complexes involving HBsAg [40,41]. This syndrome consists most commonly of urticaria, angioedema, arthropathy, lymphadenopathy, and proteinuria or hematuria. The onset is usually 1–6 weeks prior to the commencement of jaundice and it frequently improves or clears when jaundice appears. The articular involvement generally involves the small joints of the hands, the shoulders, knees, and ankles [42], lasting about 20 days. Urticaria is the most common skin manifestation. Angioedema occurs in approximately 4% of patients. Renal involvement is less frequent than the articular and dermatological manifestations and is commonly mild with complete resolution.

Papular Acrodermatitis of Childhood (Gianotti-Crosti Syndrome)

PAC is another skin eruption frequently associated with HBV infection in areas of the world with a relatively high incidence of hepatitis B, such as Europe and Japan. This eruption is seen most frequently in children between the ages of 1 and 6 years and rarely after the age of 10. Two 5-mm papules frequently erupt first on the buttocks and thighs, and then generally extend to involve the arms, legs, face, and ears, with relative sparing of the trunk (Fig. 24.2) [43]. Koebnerization of the papules frequently occurs. The eruption tends to be relatively persistent, but generally clears by the 11th week. PAC is not a specific skin finding for hepatitis B infection, although in southern Europe, the majority of cases appear to be associated with hepatitis B, subtype ayw. The eruption is seen most frequently with an anicteric form of the disease. In the USA, this eruption has more commonly been associated with viral infections other than hepatitis [44]. Currently, Epstein-Barr virus is the most common cause in the USA [45].

Other

Nonspecific macular papular eruptions, a scarlatiniform rash, petechiae, palpable purpura and Henoch-Schönlein type purpura, erythema multiforme, erythema nodosum, angioedema of the tongue, and a lichenoid dermatitis have all been described in the acute phase of HBV infection [46–49].

Cutaneous Findings in Chronic Hepatitis B Virus Infection

About 5% of patients with hepatitis B fail to clear HBsAg from the blood and become chronic carriers. Several nonspecific skin manifestations may be seen with acute fulminant hepatitis or liver damage from chronic hepatitis. These include findings such as jaundice, pruritus, spider nevi, palmar erythema, and purpura. The most common specific skin lesions associated with chronic hepatitis B are those seen with MC and polyarteritis nodosa (PAN). However, MC is more commonly seen with hepatitis C infection.

Mixed Cryoglobulinemia

MC is caused by immune complexes that have the physical characteristics of precipitating at temperatures below 37°C. Approximately 70–90% of individuals with MC type II have now been found to have an associated HCV infection, whereas only 5% of cases have been associated with HBV infection [50]. The cryoglobulin precipitates have a mixed pattern, with almost equal amounts of IgG and IgM [51], and are further described under the HCV section. Symptoms of cryoglobulinemia associated with



Figure 24.2 (a) Skin eruption of papular acrodermatitis of childhood (Gianotti-Crosti syndrome) on the legs of infants. Note that some of the papules appear to be slightly umbilicated, which is a frequent finding in this eruption. (b) The papules have coalesced above the knee. (c) This close-up view shows the papules on the dorsal hand.

hepatitis include palpable purpura or small vessel vasculitis (95%), arthropathy (45%), and renal disease (48%) [40]. Other findings may include Raynaud's phenomenon, urticaria, livedo reticularis, and acrocyanosis [52]. An acquired form of cold-induced urticaria has been reported in association with hepatitis B and cryoglobulins [53]. Small vessel vasculitis manifesting as palpable purpura may be associated with hepatitis in the absence of demonstrable cryoglobulinemia (Fig. 24.3).

Classic Polyarteritis Nodosa

HBV infection is thought to be an etiologic trigger in approximately 7% of patients with classic PAN [54].

Classic PAN is a systemic vasculitis that develops less than 6 months after infection with HBV, and it may be the initial manifestation of the infection. The vasculitis related to HBV is not anti-neutrophil cytoplasmic antibody (ANCA) related.

Classic PAN is an immune complex disease with decreased clearance of immune complexes by the reticuloendothelial system [55].



Figure 24.3 Small vessel vasculitis (palpable purpura) on the legs of a 37-year-old man with HBV infection.



Figure 24.4 Cutaneous lesions of polyarteritis nodosa on the calf of the leg. Lesions began as tender nodules that progressed to painful ulcerations.

PAN affects both medium and small arteries in various organs of the body, including the kidneys, central nervous system, and skin. This classic form of PAN is characterized by fever, polyarthralgia, calf pain, and systemic complaints related to involved organ systems. Dermatological manifestations occur in about 10–15% of cases [56]. The most common skin finding is tender subcutaneous nodules, approximately 1–2 cm in diameter, on the lower extremities. These nodules may progress to painful ulcerations (Fig. 24.4).

Livedo may be present, with occasional urticaria or angioedema. With end artery involvement, ulcers and acral gangrene are a common finding.

A cutaneous form of PAN without apparent systemic involvement has rarely been described in association with HBV [57]. It is more commonly associated with other infections, including streptococcal (especially in children), parvovirus B19, and HIV [58]. This entity probably represents part of the spectrum of PAN rather than a separate disease. Cutaneous PAN may rarely progress to systemic disease many years after the initial more limited involvement. Careful clinical pathological correlation is needed to separate systemic and cutaneous PAN.

Dermatopathology

Specimens from one series of patients with urticarial and maculopapular eruptions demonstrated a primarily lymphocytic venulitis with focal necrosis in patients [46]. Histologically, the lesions of the serum sickness-like prodrome may show a neutrophilic vasculitis of small vessels. PAC reveals one of three patterns, a spongiotic superficial perivascular lymphocytic infiltrate with some mild endothelial swelling, lichenoid changes, or possibly vasculitis without fibrin [59]. Skin lesions of palpable purpura associated with MC show a leukocytoclastic vasculitis of small vessels that has positive immunofluorescence for IgM, IgG, or complement.

PAN is a necrotizing vasculitis of small- and medium-sized muscular arteries. The lumina of vessels are often partially or completely thrombosed and the vessel wall is thickened, variably necrotic, and infiltrated with neutrophils. Eosinophils and extravasated red blood cells are frequently present in the adjacent dermis. The vascular lesions of PAN are characteristically focal and segmental. The involvement of both arterioles and capillaries with vasculitis may favor a diagnosis of systemic PAN over the cutaneous form. Multiple histological sections may have to be obtained to demonstrate the characteristic vascular changes. HBsAg, IgM, and complement are characteristically detected in endothelial membranes by immunofluorescence and electron microscopy.

Laboratory Findings

Patients with acute HBV infection typically have elevated serum ALT and serum aspartate aminotransferase (AST) levels. ALT is usually more elevated than AST. These enzymes begin to increase 2–4 weeks before the onset of clinical symptoms. Bilirubin levels may be modestly elevated as well. The white blood cell count is often low, with a relative lymphocytosis. A decreased complement level may be present with active vasculitis. In the presence of renal involvement with vasculitis or PAN, elevated blood urea nitrogen, serum creatinine levels, or abnormal urinalysis may be evident.

Diagnosis

The diagnosis of HBV is usually made by obtaining appropriate serological tests. The diagnosis of associated skin diseases is made by clinical findings and, when appropriate, histological examination of skin lesions and confirming laboratory tests. A patient with a typical case of hepatitis B infection has a predictable serological response. HBsAg is detectable in the serum 2–8 weeks before the onset of clinical illness and may persist into the convalescence period. IgM antibody to hepatitis B core antigen (anti-HBc) is generally detectable with the onset of clinical illness. Following clinical illness, the titer of HBsAg declines and eventually is undetectable. Hepatitis B surface antibody (anti-HBs) appears after the HBsAg disappears. Occasionally, there is a lag period between the disappearance of HBsAg and the appearance of anti-HBs, which is referred to as a serological "window phase." Diagnosis of acute HBV infection at this time is made by finding a positive IgM anti-HBc. A positive anti-HBc result alone may indicate either active HBV infection in the "window phase" or a healthy asymptomatic chronic carrier, but may also be found in patients previously infected with HBV in whom the titer of anti-HBs is undetectable [34].

The association of HBeAg or HBV DNA $>10^4$ IU/ml with HBsAg indicates the presence of infectious virus and correlates with high infectivity and more active disease. Failure to clear the HBsAg and develop anti-HBs, 6 months after infection, constitutes chronic hepatitis B. Patients who have received a series of hepatitis B vaccinations have anti-HBs only in their serum.

HBV DNA can be detected in serum with polymerase chain reaction (PCR). The presence of HBV DNA level $>10^4$ IU/ml correlates with active viral replication and greater infectivity than if HBV DNA is $<10^4$ IU/ml [34].

Treatment

Treatment for acute hepatitis B is supportive. Antiviral therapy for chronic hepatitis B includes immunomodulatory agents (interferon and peginterferon) and oral antiviral agents (the nucleoside and nucleotide analogues). Six drugs are currently approved by the FDA

for treatment of HBV infection: interferon alfa-2a, peginterferon-alpha-2a, lamivudine, adefovir, entecavir, and telbivudine. Among the six drugs licensed for the treatment of chronic hepatitis B in the USA, the preferred agents in 2009 are entecavir and peginterferon alpha-2a [60].

Treatment of the skin eruptions associated with hepatitis is the same as for skin eruptions from other etiologies (Table 24.2). The serum sickness-like syndrome, which occurs during acute HBV infection, is typically benign and self-limited. The urticaria and angioedema are most commonly treated with antihistamines, as is pruritus. Mild palpable purpura and MC without systemic involvement do not require specific treatment, but when causing ulceration or when associated with systemic involvement, these conditions may require systemic corticosteroids. The treatment of MC should first be directed toward any underlying disease. Corticosteroids in conjunction with cytotoxic agents may be necessary to control organ-threatening disease. Plasmapheresis [61], IVIg, and rituximab are reported to be effective in cryoglobulinemic vasculitis [62]. Other drugs, such as dapsone or colchicine, can also be tried in less severe disease [63].

Gianotti-Crosti syndrome (PAC) is a benign and self-limited disease that does not require specific therapy. Affected children with chronic hepatitis B infection should typically receive therapy for the underlying viral disorder.

The treatment of HBV-associated PAN is aimed at eradication of the virus [54]. Combination therapy with short-term corticosteroids (to control the inflammatory response), plasma exchange (to clear the circulating immune complexes), and antiviral agents (to reduce the production of viral antigens) has been effective in several open-label trials [64,65]. Approximately one half of patients with PAN will achieve remission or cure with corticosteroids. For patients who are refractory to corticosteroids or who have major internal organ involvement, cyclophosphamide should be added to their regimen [64].

For treatment of any associated condition, immunosuppressive agents should be used cautiously to avoid enhancing the risk of chronic infection.

Prevention

Active immunization is recommended using vaccines of human-derived or recombinant surface antigen for people at risk of infection with hepatitis B, such as health care workers, hemodialysis patients, and intravenous drug abusers. Hepatitis B vaccine is now also recommended as a routine childhood vaccination in the USA and other countries. Newborn babies of hepatitis B carrier mothers or unvaccinated adults following accidental exposures are given high-titer anti-hepatitis B human immunoglobulin (HBIG) in conjunction with vaccine [66]. Adults, especially health care workers who have been vaccinated without an antibody response are termed nonresponders and should be treated as unvaccinated. The first dose of vaccine should be given as early as possible, within 12 hours. If the source is known or suspected HBsAg positive, one dose of HBIG should also be administered in another site. The patient should complete the immunization series according to the normal schedule.

Recombinant DNA techniques have permitted the development of vaccines to hepatitis B that are prepared by cloning and expressing the HBsAg gene in yeast cells. Two yeast-derived recombinant thimerosal-free vaccines have been developed (Recombivax HB and Engerix-B) and are widely available. A combination vaccine (Twinrix) is approved for prevention of HAV and HBV.

There are two cutaneous reactions associated with the recombinant vaccines. The immediate reactions include anaphylaxis, urticaria, and angioedema. This is probably triggered by the minute quantities of yeast lipid, the aluminum hydroxide, or the thimerosal found in some vaccines [67,68]. Recombivax HB and Engerix-B vaccines are thimerosal free. Delayed reactions include lichenoid eruptions, lichen planus (LP), erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, cutaneous vasculitis, serum sickness-like illness, systemic lupus erythematosus, and hair loss resembling telogen effluvium [69–74]. Once a serious, life-threatening adverse event occurs, a patient should not undergo further vaccination.

Table 24.2 Treatment of HBV-Related Skin Disorders

Symptom	Treatment
Serum sickness–like syndrome	Antihistamines for urticaria, angioedema, or pruritus of the maculopapular eruption
Mixed cryoglobulinemia	HBV treatment Systemic corticosteroids Cytotoxic drugs such as azathioprine or cyclophosphamide for severe disease Dapsone or colchicine for milder disease or to spare steroids and cytotoxic drug
Giannotti-Crosti syndrome	Supportive
Polyarteritis nodosa	HBV treatment Systemic corticosteroids Plasma exchange Cytotoxic drugs for severe disease, Cyclophosphamide

Hepatitis C Virus

Definition

HCV is also a worldwide health problem. The predominant cutaneous manifestations of hepatitis viruses are associated with HCV. Hepatitis C is a single-stranded RNA virus. It was the most common cause of post-transfusion hepatitis prior to appropriate screening measures. Today, other routes (e.g., intravenous drug use, needlesticks, tattoos, sexual transmission) are responsible for over 90% of new cases of HCV [75].

History

In 1974, Prince and colleagues analyzed a group of post-transplantation hepatitis patients with no serological evidence for HBV or cytomegalovirus infection [76]. In 1988, the genome of HCV was first isolated and cloned from the liver and plasma of an experimentally infected chimpanzee [77,78].

Incidence

The World Health Organization has declared hepatitis C a global health problem, with approximately 3% of the world's population infected with HCV, and 170 million chronically infected individuals. In the USA, 2.7–4 million people are chronically infected with HCV, making it four times more common than HIV. HCV often remains undiagnosed and untreated. The incidence of new HCV infections has decreased substantially during the 1990s by

increased public and health care awareness; however, the incidence of HCV-related morbidity and mortality may increase for many years in the USA and elsewhere due to the propensity of the virus to cause chronic infection [79]. HCV has a prevalence of 1–2% in most countries. However, some areas, such as particular regions of Egypt and Japan, have significantly higher rates, with 20–40% of the population infected.

Transmission

Injection drug use is the predominant risk factor for HCV transmission in low endemic countries. In a 1992 study of 175 intravenous drug users in the USA, 83% were positive for HCV [80]. The risk of transmission of HCV by needlestick is 1.8% (range: 0–7%), demonstrating less infectivity than HBV [79–81]. Although it is not as efficiently transmitted as HIV or HBV, up to 20% of cases of HCV may be due to sexual transmission. Although HCV prevalence rates are consistently higher in persons with multiple sexual partners, sexual transmission of HCV between monogamous partners is rare [82]. Transmission from mother to infant is less than 5%. Nosocomial transmission of HCV has also been reported [84]. This virus is the primary cause of chronic liver disease in many countries, such as the USA, Japan, and Egypt [79].

Pathogenesis

The incubation period for clinical evidence of HCV infection is typically 6–7 weeks, but viremia has been detected within 2 weeks of exposure.

Infection with HCV can result in both acute and chronic hepatitis. The acute process is most often asymptomatic and rarely causes hepatic failure.

Natural history studies indicate that 55–85% of persons who develop acute hepatitis C will remain HCV infected. Among these individuals, 5–20% are reported to develop cirrhosis over periods of approximately 20–25 years [85]. They are at risk for end-stage liver disease and hepatocellular cancer. Chronic HCV is the most common cause of chronic viral hepatitis and the most frequent indication for liver transplantation in the USA.

Factors known to increase the probability of HCV disease progression include male sex, older age at infection, alcohol abuse, and concurrent HBV or HIV. Prior to effective therapy for HIV, AIDS-related mortality exceeded that from liver disease, but the advent of highly active antiretroviral therapy (HAART) has greatly improved HIV survival.

Clinical Manifestations

The clinical course of HCV infection is reviewed in Table 24.3. Clinical illness occurs less frequently in children compared with adults. Some patients with HCV will have a persistently normal ALT. In general, such patients have less severe liver disease and a better prognosis than patients with an abnormal ALT.

Cutaneous Findings in Hepatitis C Virus Infection

Nonspecific findings of urticaria [86,87], erythema multiforme-like reactions [88], erythema nodosum [89], prurigo [90], livedo reticularis [91], and Henoch Schönlein [92] have been associated with hepatitis C infections. Hepatitis C appears to be a much less frequent cause of PAN than hepatitis B [55,58]. Patients with liver disease may also have nonspecific conditions, such as generalized pruritus, palmar erythema, spider telangiectasia, jaundice, or purpura. The specific skin findings of MC with leukocytoclastic vasculitis [93–108], necrolytic acral erythema (NAE) [109,110], porphyria cutanea tarda (PCT) [111–120], and LP [121–133] are discussed in detail.

Mixed Cryoglobulinemia

About 80% of MC is secondary to HCV infection [107,134]. Cryoglobulins are anti-immunoglobulin immunoglobulins, which precipitate at temperatures less than 37°C. There are three types of cryoglobulins [98,63]. Type I consists of monoclonal immunoglobulins without rheumatoid factors and is generally paraneoplastic. Type II consists of polyclonal IgG and monoclonal IgM rheumatoid factors. In type III, both IgG and IgM are polyclonal. Most cases of MC, including those associated with HCV, are the type II variety [63,134].

MC typically results in vasculitis that may manifest with a classic triad of purpura, weakness, and arthralgias and may cause glomerulonephritis and peripheral neuropathy. Anti-HCV antibody and HCV RNA concentrate can be found in the cryoprecipitate [104]. The cutaneous lesions reported with this condition include palpable purpura or small vessel vasculitis, petechiae, urticaria, vascular occlusions, and ulcerative lesions with and without necrosis (Fig. 24.5). Raynaud's phenomenon and Sjögren's syndrome may also be present. The typical palpable purpura start on the legs, develop in crops, and may develop into vesicles or bullae with ulceration.

Porphyria Cutanea Tarda

HCV tends to induce PCT in predisposed individuals. (Figs. 24.6 and 24.7) [111,112,117–119,135–137]. The reported prevalence of antibodies to HCV in PCT varies from 8 to 79%, with a higher prevalence in southern Europe, the USA, and Japan [111,112]. In theory, it is thought that viral-induced liver damage decompartmentalizes hepatic iron stores. This results in increased free iron radicals that alter cytochrome P450. This leads to the reduction in uroporphyrinogen decarboxylase activity, an enzyme active in the metabolism of uroporphyrins, and a subsequent buildup of uroporphyrins [136]. PCT is often the first sign of hepatocyte

Table 24.3 Clinical Manifestations of HCV

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
6–7 weeks (varies from 2 weeks to 6 months)	Symptoms begin with a clinical course that is indistinguishable from that of HBV and other hepatitis viruses. Refer to Table 24–1	Serological tests, with selection of anti-HCV in serum Detection of HCV RNA in serum by polymerase chain reaction	At least two thirds of cases are anicteric and mild or completely asymptomatic



Figure 24.5 (a, b) Leukocytoclastic vasculitis in a hepatitis C patient with mixed cryoglobulinemia manifested as palpable purpura and ulcerations. (c) HCV: mixed cryoglobulinemia and leukocytoclastic vasculitis

injury provoked by HCV and manifests as subepidermal bullae, superficial erosions, hypertrichosis, and hyperpigmentation in sun-exposed skin. The skin lesions are a result of photosensitization by porphyrins [111]. All patients with PCT should have iron studies, screening for hemochromatosis (HFE) mutations and screening for HCV [118–120]. This testing is also important for PCT therapy because patients with HFE and HCV should undergo vigorous iron removal in addition to treatment for HCV. [118].

Lichen Planus

There is a possible association of chronic HCV infection with LP [121,122,131,132,], It is possible that the association is due to the frequency of each disease in the population [124]. There is particular interest with the erosive type of chronic oral LP (Fig. 24.8) [125–130], although there are also studies with no clear association [128]. The association with LP tends to be strongest in populations at greatest risk of exposure to HCV [138]. The prevalence of HCV infection in patients with LP varied considerably from one geographic area to another, ranging from 11.4% in southern Italy [128] to 62% in Japan [120].

Skin involvement typically consists of flat-topped violaceous papules, most commonly on the dorsal hands and wrist (Fig. 24.9). HCV RNA has been detected by PCR in the tissue of oral LP, suggesting a pathological role of HCV in this disease [129]. HCV RNA was also detected in skin lesions of 3 patients, suggesting that HCV-associated LP may be sites of HCV replication [121]. The role of HCV in the development of LP remains unclear. Nonetheless, consider HCV testing in patients with chronic LP, particularly those with oral involvement or HCV risk factors [122].



Figure 24.6 Slightly hemorrhagic bullae of porphyria cutanea tarda.

It is also interesting that the effects of anti-HCV therapy are highly variable, and some LP lesions actually appeared or were exacerbated during therapy [123,138–141].

Necrolytic Acral Erythema

NAE is a distinctive acral skin lesion with dusky erythematous plaques that evolve into hyperkeratotic lesions that resemble psoriasis. These lesions affect the dorsa of the feet. All 30 patients with NAE in a dermatology clinic in Cairo, Egypt, were infected with HCV. The eruption extended to involve the lower leg and other regions in some patients, but never affected palms or soles, the nail bed, nail plate, or mucous membranes. Skin biopsy specimens from fully evolved lesions displayed psoriasiform changes in association with more characteristic findings of keratinocyte necrosis and papillomatosis [110].

In another report of 7 patients with NAE, all were found to have HCV infection [109]. Therapy has included HCV treatment and zinc [110,142]. This condition should alert practitioners of the need for viral testing in this disorder. (Fig. 24.10)



Figure 24.7 Healing erosions and scarring lesions of porphyria cutanea tarda on the dorsal hand.

Other

A variety of skin manifestations can appear during therapy with interferon and/or ribavirin. These include erythema at injection site, maculopapular drug eruptions, transient alopecia, dry skin, acne, nail disorders, photosensitivity, sarcoid and exfoliative dermatitis, as well as exacerbation of psoriasis or LP [123,128,139–141].

Pathology

Skin biopsy samples in essential MC reveal evidence of a vasculitis, with destruction of dermal blood vessels and infiltration of neutrophils in and around the vessel wall [133]. Histologically, LP lesions show degeneration of keratinocytes and dense infiltration of lymphocytes in the upper dermis, which are hugging the border of the epidermis. PCT lesions show subepidermal cell-poor blisters.

Diagnosis

The usual approach is to test initially for antibodies to HCV (anti-HCV), then to use HCV RNA to document viremia. HCV RNA can be detected 1–2 weeks after exposure, which is long before symptoms or liver enzyme abnormalities develop. Detection of HCV RNA indicates current infection and transmissibility of HCV. Specific antibodies to HCV are not usually detected earlier than 3–4 months after initial exposure.

There are 6 major HCV genotypes. The genotype does not predict the outcome of infection, but can predict the likelihood of treatment response, and determine the duration of treatment [143–145].

Unfortunately, no simple diagnostic modalities are able to differentiate acute disease from chronic involvement with HCV, except the persistence of viremia for at least 6 months.

Treatment of Hepatitis C Virus

Table 24.4 lists the characteristics of persons for whom therapy is widely accepted [75]. In randomized clinical trials, the highest overall sustained virological rates (SVR) have been achieved with the combination of weekly subcutaneous injections of peginterferon alfa and oral ribavirin, which represents the current standard of care [75,146,147]. There are special situations for use of peginterferon alfa-2a as monotherapy [75]. Ribavirin is teratogenic and contraindicated in pregnancy.

"Cure," or sustained virological response, is usually defined as lack of detectable HCV RNA in serum by sensitive PCR assay at least 6 months after cessation of therapy.

Genotype is the main predictive factor in sustained virological response. The factors associated with a greater likelihood of sustained virological response are: genotype 2 or 3, HCV RNA level $<$600,000 IU/ml, age $<$40 years, or female sex. The presence of symptomatic cryoglobulinemia is an indication for HCV antiviral therapy, regardless of the stage of liver disease (Table 24.5). This indicates the importance of screening all patients with vasculitis for HCV infection, as it would be more beneficial to these patients to treat them with antiviral therapy rather than systemic corticosteroids or cytotoxic drugs. Although treatment for HCV infection attenuates



(a) (b)

Figure 24.8 (a) Lichen planus of the tongue in a patient with hepatitis C infection. (b) Chronic erosive lichen planus on the tongue of a 60-year-old woman. Not infrequently, such lesions appear to be associated with HCV infection.

MC in most of these cases, there may be relapse after treatment [148]. Rituximab (a B-cell-depleting antibody) has been shown to benefit patients with refractory HCV-associated cryoglobulinemic vasculitis, as well as those with recalcitrant HCV-negative MC [62]. Plasmapheresis or immunosuppressive agents (cyclophosphamide and azathioprine) may sometimes be necessary for treatment of the most severe forms of the disease [61,107,149].

Patients with PCT should receive standard PCT treatment with avoidance of liver toxins, alcohol, and estrogen as well as treatment for HCV (Table 24.5). Several reports have described the complete resolution of this condition after treatment for HCV [116,150,151]. Hemochromatosis genotyping can help to further classify patients with PCT and associated hemochromatosis. Simple or compound heterozygosity of hemochromatosis mutations does not affect the therapeutic response to chloroquine in PCT. In patients with homozygous mutations for hemochromatosis and PCT, phlebotomy should be first-line treatment to remove toxic iron.

LP is most commonly treated with topical steroids and/or calcineurin inhibitors. (Table 24.5). Numerous reports have indicated the beneficial effect of alpha interferon in the treatment of LP associated with HCV infection [126,152,153]. However, there have also been reports of worsening or induction of LP with the use of this drug [123,128,139,140].

Hepatitis C Virus-infected Children

An estimated 240,000 children in the USA have antibodies to hepatitis C. The seroprevalence is 0.2% for children under 12 years of age and 0.4% for those aged 12–19 years [143].

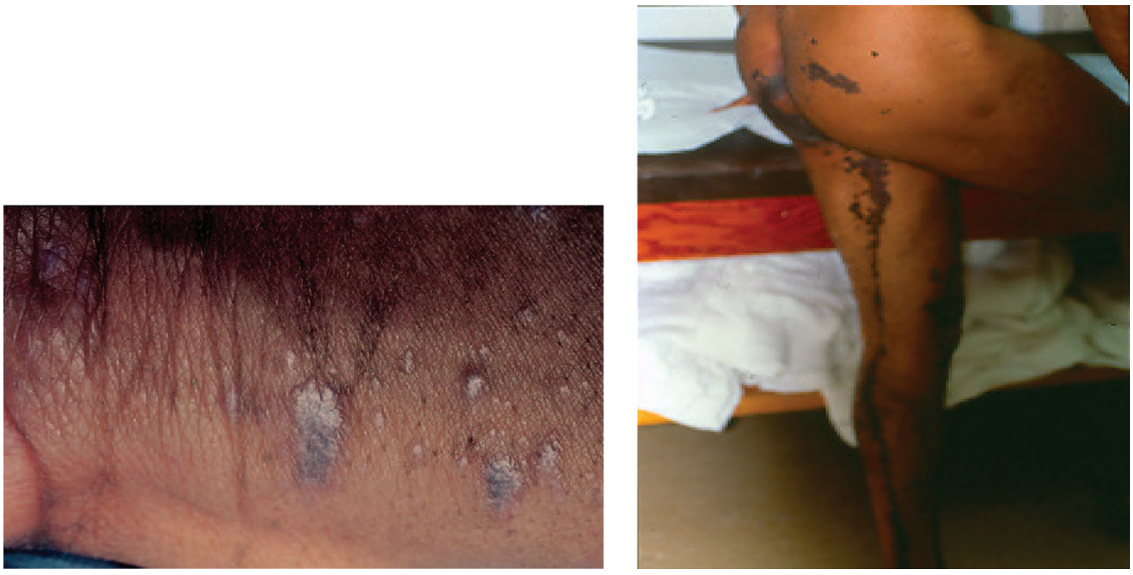


Figure 24.9 (a) Violaceous flat-topped papules and plaques typical of lichen planus. Lesions are located near the wrist. (b) Linear lichen planus in patient with HCV.

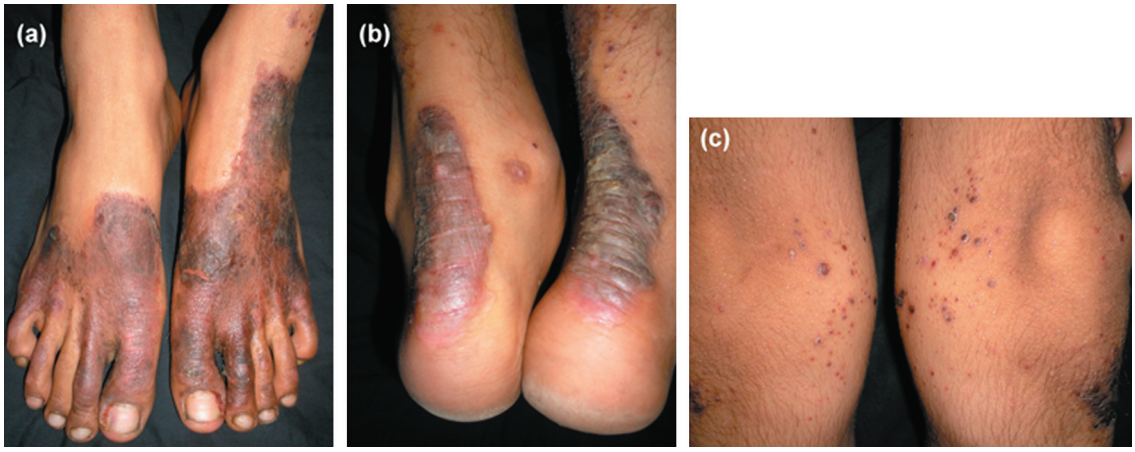


Figure 24.10 Typical lesions of necrolytic acral erythema over the dorsal surfaces of feet (a), Achilles tendon (b) and elbows (c). (Reprinted with permission. Int J Dermatol 47: 1073–1075, 2008).

Routine testing for HCV RNA in infants born to HCV-infected mothers is not recommended because of the high rate of clearance of the HCV virus within the first year of life, and the level of anxiety that may be caused by an early positive test. Testing with anti-HCV may be performed at 18 months or later. If an earlier diagnosis is desired, PCR for HCV RNA may be performed at or after the infant's first well-child visit at 1–2 months [143]. Children aged 3–17 years who are infected with hepatitis C and are considered appropriate candidates for treatment may receive therapy administered by those experienced in treating children [154,155].

Prevention

Immunoglobulin is not effective in preventing hepatitis C. A prototype vaccine that induces antibodies to HCV envelope protein is being studied, but is currently not available. The major difficulty in vaccine development is that HCV is a heterogenous virus with a high mutation rate. Despite recent screening for hepatitis C antibody in blood donors, hepatitis C remains the most common (although rare) cause of transfusion-related hepatitis, most probably because of the 3- or 4-month period between the time of infection and the development of circulating antibodies.

Conclusion

Hepatitis A and E virus are enterically transmitted with acute infections causing typical skin findings of liver disease. HDV is transmitted only with HBV. The significance of HGV is still being studied. HBV can cause specific skin lesions found in MC and PAN. HCV can be associated with specific skin findings of MC, PCT, LP or NAE.

Table 24.4 Justification for treatment of HCV

Liver biopsy with chronic hepatitis with significant fibrosis
Compensated liver disease (total serum bilirubin 1.5 g/dl; INR > 1.5; albumin 3.4 g/dl; platelet count < 75,000/mm^3; and no evidence of hepatic encephalopathy or ascites)
Acceptable hematological biochemical indices
Willing to be treated and to conform to treatment requirements.
Absence of major untreated neuro-psychiatric disease, especially depression
Extrahepatic manifestations

Table 24.5 Treatment of HCV related cutaneous disorders.

Symptom	Treatment
Mixed cryoglobulinemia HCV treatment	Systemic corticosteroids Rituximab Immunosuppressive drugs such as azathioprine or cyclophosphamide for severe disease Dapsone or colchicine for milder disease or to spare steroids and cytotoxic drug Plasma exchange
Porphyria cutanea tarda	HCV treatment Limit liver toxins Sun protection Phlebotomy-especially with associated hemochromatosis
Lichen planus	Topical steroids and/or topical calcineurin inhibitors
Necrolytic acral erythema	HCV treatment and/or zinc

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25 Prions

Omar Lupi

Introduction

The exact nature of transmissible spongiform encephalopathies (TSE) perplexed scholars for decades, until Prusiner [1] identified and defined prion infections in 1982. Prusiner [1] classified a prion as an infectious particle composed of a protein (PrP) that causes fatal neurodegenerative disorders. According to Collinge [2], prions are infectious agents by biological and medical criteria, sharing many characteristics with some viruses, but with fairly unique properties that differ from those of conventional microbes. There is evidence indicating that prions and viruses could be related in some aspects of their basic structure and they also share a common capability of self-assembly [3].

Prions cause a variety of degenerative neurologic diseases that can be infectious, inherited, or sporadic in origin [3]. The cause of the sporadic forms is unknown; inherited forms are caused by up to 20 different mutations of the human PrP gene; and the infectious forms are transmitted through contact with or consumption of previously infected tissues [3].

Well known human prion diseases include Creutzfeldt-Jakob disease (CJD), kuru, German-Straussler-Scheinker syndrome (GSS), and fatal familial insomnia [3]. Other well-known prion diseases that affect animals include scrapie (sheep and goats), bovine spongiform encephalopathy (BSE or "mad cow disease"), transmissible mink encephalopathy, chronic wasting disease (CWD) in wild cervids in North America, feline spongiform encephalopathy, and exotic ungulate encephalopathy [2,3]. BSE has already been described affecting humans through ingestion of contaminated meat, causing new variant CJD (nvCJD) in Europe [4,5].

PrP^{C} is the normal, cellular prion protein, and it is converted into PrP^{Sc} (from scrapie). The normal protein consists of mainly alpha helices with a spiral backbone, but the new, mutated prion protein is predominately formed by beta strands with a fully extended backbone [1]. This alteration in tertiary structure provides evidence for post-translational modification of the protein [2].

The mechanism of replication involves the synthesis of polypeptides in the absence of nucleic acid templates and the post-translational modifications of cellular proteins [1,2]. For the prion, replication involves converting conventional proteins into prions. The resulting PrP^{Sc} is a four-helix bundle protein with four regions of secondary structure, numbered H1 through H4 [2]. Prions replicate by recruiting normal proteins to their cause, "flipping" them into a rogue prion-like shape that can go on to infect other cells and animals [2]. This change initiates a chain reaction, and newly converted prions convert other proteins with which they come into contact on the interior of their respective cell membrane [1]. The PrP^{Sc} accumulate in lysosomes and eventually fill the lysosomes until they explode, releasing the prions to attack other cells [2].

Horizontal Transmissibility of Human Prions

Prion diseases of humans are undoubtedly transmissible, but only under particular circumstances [3]. The oral route is already correlated with the dissemination of kuru, BSE, and nvCJD [2–5], but many other routes are probably important in prion dissemination [3].

Several studies have suggested that some ectoparasites might harbor scrapie in farms and could act as vectors to infect previously healthy animals [6–10]. The human skin is a natural target for ectoparasites and also expresses PrP protein in large amounts [11,12]. In favorable circumstances, a case of myiasis, caused by tissue infestation by fly larvae, could act as an important source of the abnormal isoform of prion protein [10,13]. The autocatalytic method of prion dissemination would probably reduce the amount of PrP^{Sc} necessary to induce infection [2].

Direct transmission of brain-derived material from patients suffering from CJD to normal persons has resulted in documented transmission of the disease several times [13,14]. In these circumstances, electrodes, used for cortical recordings from CJD patients, were sterilized with formaldehyde and alcohol and then used for other patients. The disease state was transmitted to the young recipients [14,15]. Transplantation of corneas also has most likely resulted in transmission of the disease [14].

Apparently, iatrogenic CJD has been transmitted by implantation of dura mater homografts in 14 patients [3,16], and when contaminated neurosurgical instruments were used [17]. The most common source of iatrogenic CJD has been contaminated human growth hormone (hGH) from cadaveric human pituitaries (58 cases) [14], before recombinant hGH became available. In addition, four cases of CJD in young women following treatment of infertility with human gonadotropin have been reported in Australia [14].

Zobeley et al. [18] have demonstrated that prions can adhere easily to metal surfaces, and prion-contaminated metal wires are an efficient vehicle for experimental transmission of prion disease. It was also observed that when the stainless-steel wires were washed exhaustively with 10% formaldehyde for 1 hour, the prions were still present. Appel et al. [19] showed that prion rods have a much higher heat stability (over 150°C) compared to the normal PrP protein. Considerable concern has been expressed that blood from asymptomatic donors incubating nvCJD may pose a risk for iatrogenic transmission of nvCJD [3,20]. The crucial issue in all cases of iatrogenic and workplace infection is the awesome power of the prion to resist inactivation; none of the usual physical or chemical decontamination methods fully sterilized its infectivity [14,18]. The most effective methods have proven to be immersion for 1 hour in undiluted, freshly opened bleach (5% sodium hypochlorite) or 1N sodium hydroxide, or autoclaving for 1 hour at 132°C [14].

General Considerations about Prion Infections in Dermatology

The human skin is a potential target for prion infections [3,11–13]. Several cell types found in the human skin, including fibroblasts and keratinocytes, are able to express the prion

protein under several circumstances [13]. This expression might transform the skin and the mucous membrane in a primary site for prion infection, since the mechanism of propagation involves the physical contact between the pathological and cellular isoforms of PrP. The PrP^{Sc} form propagates itself by contacting PrP^{C} molecules and causing them to unfold and flip from their usual conformation to the scrapie configuration in an autocatalytic reaction [1,2]. Mutations in the PrP gene render the resulting proteins susceptible to flipping from an alpha-helical to a beta-sheet shape, solving the paradox of a genetic disease that can also be transmissible to previously normal hosts [1,2,13].

The dermatological implications of the prion infections can be divided into two main categories: those related to the accidental exposure of the skin and mucous membranes to potentially contaminated materials used for dermatologic procedures [3], and the theoretical possibility of a prion transmission due to ectoparasites that can eventually infest the skin [6–10,13].

The Bovine Connection: How Cosmetic Procedures can be Related to Prion Infection

BSE and nvCJD epidemic has been exhaustively discussed in the last few years [2]. The food chain was implicated with the dissemination of both diseases and the oral route was correlated to the human contamination by prion rods [2,4,14]. Other routes are even far more possibly associated with prion dissemination than the gastrointestinal route [3,4]. BSE could be transmitted readily to humans after bovine collagen use and normal hospital sterilization procedures that are not likely to completely inactivate prions [3,13,14]. Extrapolations based on the known incubation periods in the acquired human prion diseases, such as growth hormone-related iatrogenic CJD or kuru, would suggest mean incubation periods of BSE in humans of perhaps 30 years or more [3,14]. Then, we would expect that collagen-transmitted CJD, a hypothetical but possible new type of nvCJD, could also have a long period of incubation.

Bovine collagen has long been recognized as a safe and highly biocompatible material to perform dermal implants. It has been used for almost 20 years with few complications [21]. Bovine collagen has been used in natura, as a filling material, and is potentially associated with prion rod transmission because BSE reached epidemic proportions for almost 8 years in Europe and there are still new cases of the disease in the UK [3,13,14].

The use of sterile techniques in cell cultivation is absolutely essential. Sterilization by autoclaving relies on steam pressure and high heat. However, many biological products, including standard cell culture medium, cannot be sterilized by this procedure. Such medium is composed of a complement of amino acids, vitamins, inorganic salts, glucose, and serum as a source of growth factors, hormones, and attachment factors [22,23]. Laboratories from all over the world add fetal bovine serum (FBS) and newborn calf serum (NCS) to most culture media as a supplement [3,22]. Each sample of FBS and NBS is obtained from a pool of animals, increasing the risk even more [3]. Bovine trypsin is also a standard product worldwide to work with cell cultures, especially when it is necessary to set up new colonies from a previously attached monolayer of cultured cells [22,23].

Prions have a theoretical risk of being transmitted to the cell culture medium by previously infected FBS or NCS [3,24] and some cell lines are very susceptible to this infection, such as fibroblasts, neuronal cells (N-2A), and hypothalamic cell lines (GT1-trk) [25]. After transmission to these cells, all the resultant products will also be infected with prions. The dermatological use of these products, such as hyaluronic acid from rooster combs for soft tissue augmentation [26] and skin grafts for wound healing, theoretically, could transmit the disease [3]. In fact, Manna et al. [27] reported a large number of proteins of unknown origin in two commercially available derivatives of hyaluronic acid used for cosmetic purposes.

Another possible source of contamination would be skin grafts, because keratinocyte cultures are also fed mainly with NBS and FBS [3,13]. Most of these skin grafts are maintained in culture for several days or weeks, with daily replacement of the culture medium, in order to develop the necessary amount of tissue to perform skin surgeries [22,23]. Carruthers et al. [28] also described the risk involved in the transmission of CJD and other prion infections due to the use of botulinum toxin for cosmetic use. The product is manufactured with human or bovine albumin in order to stabilize the chemical compound [28].

All biological products derived from bovine origin should be considered at risk for prion transmission. The amount of risk will be related to the origin of the cattle and to the source of the bovine tissue. European cattle, mainly of UK origin, are at high risk for prion transmission [2–4,14]. Some tissues, such as the brain, lymphoid tissues, and bone marrow, present a much higher risk than collagen or the skin [2,4,24].

The Center for Biologics Evaluation and Research (CBER) assessed the risk for nvCJD from vaccines manufactured with processes that use bovine materials potentially contaminated with the BSE agent. CBER concluded that the risk was "theoretical and remote" [20]. Further, the benefits of vaccination outweigh any remote risk for nvCJD. The risks associated with cosmetics and cosmetic procedures however, require a more substantial discussion of the potential for prion transmission.

The Ectoparasite Hypothesis

Infestations by ectoparasites are very common among domestic and wild animals. The invasion of mammalian tissues by the larvae of Diptera (fly) is known as myiasis [29]. The eggs, living larvae, or both are deposited on the skin or mucous membranes, where they hatch and produce larvae, which burrow into the skin and produce mild or severe inflammatory changes [29]. Some varieties of flies puncture the skin and extrude the ova beneath the surface (furuncular myiasis), whereas others deposit their eggs on open wounds and ulcers [30,31]. Myiasis in humans can also arise in any natural cavity of the body and cause extensive destruction of healthy tissue. Ophthalmomyiasis is a common manifestation of the disease; it is associated with the deposition of the larvae directly on the eyes or after minor ocular damage caused by sand particles or wind [32].

Dermatobia hominis, also known as human or tropical botfly, is a fly about 12 mm long of the Cuterebrinae subfamily. *D. hominis* and their vectors are silvestrian, inhabiting forests and woods, but is a very common cause of human myiasis worldwide. Cattle are attacked most; humans and dogs are occasionally infested. While

going through the skin, a sensation of pruritus is felt [29]. After a bite, an inflammatory reaction occurs with edema and erythema. Finally, a furuncle-like lesion with a central hole appears, which drains a serosanguinous fluid; ophthalmomyiasis is eventually observed [13,33].

Hypoderma bovis is the agent of the "cattle botfly." It is found in temperate regions, including North America and Europe, and is a major cause of morbidity in cattle [34,35]. Humans and other mammals are occasionally infested [36,37]. Man is an abnormal host and the larvae cannot mature fully [38]. After penetrating the skin, the larvae produce migratory subcutaneous swellings, in a life cycle very different from that observed in human myiasis due to *D. hominis* [13,39–43]. They may also invade the eye, causing severe damage, known as "fly-blown eye" [10,38,44–49].

Oestrus ovis, the sheep nasal botfly found in all major sheep-raising regions, has been particularly implicated in human ophthalmomyiasis [50–53]. Female flies directly deposit first-instar larvae in the nostrils of sheep for obligate development in the upper respiratory tract. The condition is relatively common among shepherds of middle-eastern countries, sometimes with very severe ocular involvement [54–56].

Lupi [10,13] suggested the possibility that some ectoparasites, such as myiasis and mites, could act as vectors for prion diseases, in order to explain the maintenance of scrapie for many centuries in endemic European areas, despite the huge efforts to sacrifice infected animals as well as quarantine affected farms [30,31]. These three myiasis agents, *H. bovis*, *O. Ovis*, and *D. hominis* are potentially correlated with prion dissemination because of their high incidence in both human and other mammals very susceptible to prion infections, such as cattle and sheep [10,13].

Post et al. [6] analyzed experimental transmissibility of PrP^{Sc} by the larvae of *Sarcophaga carnaria*, another common species related to human myiasis. Scrapie was transmitted to monkeys and hamsters, either orally or after intracerebral injections, in the past [57]. In Post's study [6], larvae of *S. carnaria* were fed with brains of scrapie-infected hamsters. All the larvae expressed the abnormal isoform and were given orally to 4 hamsters [6]. Two developed clinical signs of scrapie after 215 days and 3 expressed PrP^{Sc}. Another 8 hamsters were fed with infected larvae and 5 died of scrapie. These results confirm that PrP^{Sc} was presented in high enough levels to infect hamsters [6].

This study supports the concept that fly larvae can harbor the prion agent, but it was not possible to know if the PrP^{Sc} truly replicated in *S. Carnaria* [6]. However, Raeber et al. [58] developed evidence of a prion replication in adult flies, since they were able to detect the expression of prion proteins in *Drosophila melanogaster* ("fruit fly"). Transgenic flies were generated by introducing the Syrian hamster prion protein (ShaPrP) gene into the *D. melanogaster* germ line. The pathological protein was synthesized in transgenic flies by continuously subjecting them to heat pulses. Deleault et al. [59] recently confirmed the ability of *D. melanogaster* neurons to express the protein in culture. Driscoll and Gerstbrein [60] observed that if invertebrate neurons are injured by hostile environments or aberrant proteins, such as prions or amyloid misfolded proteins, they die much like human neurons. According to Muqit and Feany [61], transgenic insects coding for the pathologic prion proteins are able to transmit the trait to their offspring, however, there is no data about the viability of infected larvae.

Using epidemiological and laboratory data, Carp et al. [7], Wisniewski et al. [8], and Rubenstein et al. [9] have already confirmed that mites are able to transmit the disease to new hosts. Seventy-one mice were infected with an intracerebral injection of a homogenate of different species of mites (*Lepidoglyphus destructor*, *Acarus farris*, *Tyrophagus longior*, *Cheyletus eruditus*, *Tydeus interruptus*, and *Tarsonemus* spp) gathered from infected animals in Iceland, where scrapie is endemic. Ten mice died of scrapie in the following few months, and immunoblotting detected PrP^{Sc} in the brains [8].

Further evidence that insect vectors may spread spongiform diseases has been shown in a study of hay mites collected from 5 different farms by Carp et al. [7] and Rubenstein et al. [9]. They observed that hay mite preparations from 5 Icelandic farms with a history of scrapie were able to transmit the disease into mice, after long incubation periods. Brain homogenates from the sick mice were then injected into a second set of mice, which developed the disease more rapidly, as is often found when prion diseases cross the species barrier [7,9]. All mice in this study showed spongiform changes in the brain, and showed scrapie-like Western-blot patterns [7,9].

These three studies suggest that the scrapie agent may replicate in mites [7–9], which would mean that mites could function as a reservoir or a vector involved in the occurrence and spread of transmissible encephalopathies [10]. They can also play a role in the continuing occurrence of BSE, even after UK authorities forbade the use of ruminant animal products for cattle feed [10]. Wisniewski et al. [8] concluded that Icelandic hay mites were potentially a self-sustaining reservoir for scrapie, since hay mites collected from infected animals transmitted the disease to previously healthy hamsters by the oral route. The mite assemblage, collected well after the normally short life span of the individual mite host and species, lends exceptional credence to the assumption of prion replication within the mite corpus, both individually and communally, being subsequently passed to the mite offspring [7,8]. The argument that the same old residual abnormal prionic material is passing through multiple generations of mites also seems quite far-fetched under the severe conditions of insect to offspring dilution and the biological necessities of active growth and transport to create the separate and distinct bodies of the new offspring [9]. The more logical conclusion is that the agent itself can reproduce within the diverse and seemingly adverse environment of the mite body [10,13].

Post's experiment [6] did not reproduce the natural conditions where fly larvae infect human or animals, although intestinal myiasis after accidental ingestion of fly eggs and larvae is not rare [13,29,62]. However, it is important to consider that iatrogenic CJD was already transmitted following corneal transplantation [2,63]. Scott et al. [64] transmitted scrapie to mice by instilling brain homogenate into the conjunctiva of healthy animals. Retinal damage is also a common finding in mice infected with scrapie, reinforcing the importance of this route in the etiopathogeny of some cases of prion infection [65]. Since then, some ophthalmologic procedures, especially corneal transplantation, were considered at high risk for prion transmission due to the physical proximity to the brain and because of the almost direct contact between the eye and the central nervous system (CNS) [63–65].

Prion proteins can be largely expressed in cutaneous cells, especially in chronic ulcers, according to Pammer et al. [11,12]. It would also be reasonable to discuss the possibility of contamination of fly larvae fed on cutaneous ulcers of prion-infected sheep and cattle. Since the adult form of flies is also able to express prion protein [58], a new generation of flies could, theoretically, transmit the disease to new hosts during their life cycle.

Hypodermosis

Since the theoretical capability of fly larvae to transmit prion rods is well established in the literature, it is critical to evaluate the life cycle of these myiasis agents to analyze if they have close contact to potentially infected tissues, such as the CNS and lymphoid tissues [13,63]. Cattle have been tested for prion infection around the world in the last decade and the recognition of the real impact of nvCJD in many European populations is probably far from being concluded [4]. A new BSE epidemic is not likely in the future, but some isolated cases of the disease are still happening in the UK, Canada, and the USA [66,67]. Since cattle were the source of the most disseminated contamination by prions in the human population, it is necessary to understand better the natural history of hypodermosis, the most common cause of myiasis in cattle. According to Haine et al. [34], the herd seroprevalence of *Hypoderma* spp. among 390 animals was 48.7% in Belgium. Cattle hypodermosis in China reaches 98% of the animals and maximum intensities exceed 400 warbles for each animal [68].

The female can deposit up to 100–800 eggs on a single cow [69]. There are two species of *Hypoderma* that affect cattle. *H. lineatum* appears at the start of warm weather and remains for 2 months [13]. *H. bovis* appears when *H. lineatum* is done and will persist throughout the summer months [13]. The eggs of *H. lineatum* and *H. bovis* hatch within 1 week and the larvae burrow through the skin, migrating in the connective tissue. Five months later, the larvae of *H. lineatum* accumulate in tissues of the esophagus, where they remain for 3 months [13].

The larvae of *H. bovis*, however, accumulate in the spinal canal and epidural fat, anatomical structures very rich in prion rods, where they remain for about 3 months ("winter resting sites") [39–42]. The larvae migrate once more to the back of the cow [43]. Once on the dorsum, the larvae will cut breathing holes for their posterior spiracles [13,63]. The larvae will continue to grow while spending 2 months in the warble. Finally, the larvae will enlarge the hole and fall to the ground where they will spend 1 month as pupae before emerging as an adult. The whole life cycle takes about 1 year [43].

It is important to point out that ataxia and posterior paralysis are commonly observed in animals infested by *H. bovis*, due to invasion of the spinal cord [39–41,63]. Aberrant migration intracranially or into the brain may cause acute neurological disease [70–73]; blindness is a common complication due to the invasion of the eye [38,44–49]. The huge amount of fly larvae in each animal and the very specific life-cycle pattern of *H. bovis* in cattle, with a very long period of accumulation in nerve structures that are very susceptible to prion infections, raise the possibility of a BSE transmission to other animals and even to humans [10,13,63].

Oestriosis

Scrapie, a prion infection of sheep, has been recognized in Europe for over 200 years and is endemic in many countries [74]. Remarkably, little is known about its natural routes of transmission. Horizontal transmission has been suggested to explain the dissemination of scrapie to previously healthy animals [63,74]. In contrast to BSE, where almost all cases are restricted to the UK [4,5], scrapie occurs worldwide [74]. The origin of the BSE epidemic can be traced back to changes in rendering operations in recycled cattle carcasses [4,5], but scrapie origins remain unknown [74]. There are instances in which the disease affects a flock with no previous cases or occurs in farms that were repopulated with new sheep [74]. Scrapie-free flocks of sheep start to develop the disease if put in fields alongside infected sheep, indicating that horizontal transmission is occurring in farm conditions [70], in a similar way to CWD [2,13].

These findings have led to the suggestion that a natural reservoir may be present in such places [6–10,13,63]. Oestriosis is the infestation by *O. ovis* larvae, the most common cause of myiasis in sheep [75–76]. Since scrapie is the most disseminated prion infection in the world and is present in several countries, infecting sheep and goats, oestriosis is a disease that should be considered in its transmission [10,13,63].

O. ovis fly is known as the sheep nasal bot fly [75]. It is very prevalent among sheep, affecting 59% of the animals in Mexico [76] and 50% in southwestern Germany [77]. Abo-Shehada et al. [78] evaluated 520 goats slaughtered in northern Jordan and detected that 126 (24%) were infected with *O. ovis*. Amin et al. [79] observed a similar result among sheep in an Egyptian abattoir. The adult is active during warm weather and bright sunlight. The larvipositing female flicks her abdomen and leaves glue-covered larvae on the nostrils of sheep and goats [75,76].

Once the larvae are deposited on the nostrils, they crawl onto the mucous membranes of the nasal passage and use the hooks in their mouths to anchor themselves [80]. The larvae will remain there for at least 2 weeks, but if it is late in the season, the larvae can remain arrested for 1–9 months. The larvae then travel to the frontal sinuses and continue to develop, feeding on the mucous membranes in the sinus cavity [78,79]. Moderate numbers of this bot fly may only cause an annoyance. If the parasite is present in great numbers, it can cause sneezing, nasal discharge, and even blockage of the nasal passages [76,78]. Other clinical signs observed are head shaking, labored breathing, and blind staggers. Some animals can develop neurological symptoms, since the larvae can affect brain structures near the sinus cavity because of the erosion of the cribiform plate [78–80]. Direct injury to the brain is common among sheep and may cause signs that mimic gid [73], a neurological manifestation of the infestation by *Taenia multiceps coenurus*, and characterized by blindness, anorexia, dullness, and paresis of one or both hind limbs [81,82].

In the last stage of its life cycle, *O. ovis* third stage larvae crawl out of the nasal passages or are sneezed out by the sheep, and pupate in the soil. In warm weather, the adults will emerge in 4 weeks, but in cold weather, the adults will not emerge until spring [76–78].

Human ophthalmomyiasis due to the sheep nasal bot fly is quite common around the world [51–56,83–87]. Those working in fields with sheep are at greatest risk. Of 112 shepherds of the Etnean area in Sicily, Italy, 90 (80.3%) have once or more contracted myiasis by *O. ovis* [88]. The most frequent sites of involvement were the pharynx (77 cases), the conjunctiva (56 cases),

followed by the nose (32 cases) and, rarely, the ear [88]. The larvae will cause a painful, but temporary ophthalmomyiasis.

Gregory et al. [89] described one of several reports of ophthalmomyiasis in American soldiers in the Middle East; the disease caused by *O. ovis* is endemic in tropical areas of the Middle East, Asia, and Africa. Hira et al. [90] and Torok et al. [91] also described cases of ophthalmomyiasis due to *O. ovis* during the Gulf conflict in Kuwait. US troops stationed in Iraq and surrounding areas are vulnerable to eye infestation [92–95].

General Considerations about Protein Folding

Dermatological diseases have different pathogenetic mechanisms, such as infections, nutritional, immunologic, and genetic disorders. Specifically, genetic disorders involve mutations in the sequence of a protein, which may lead to its malfunction or complete absence. On the other hand, a malfunctioning protein can cause a dermatologic disease, even though a genetic alteration in its sequence cannot be found. One possible explanation is that certain modifications in the protein structure occur during its lifespan, inducing malfunction and disease. For the majority of these so-called conformational diseases, the exact mechanism that alters protein structure is not known, but insights from general protein folding and misfolding processes will help to understand the pathogenesis of such dermatological diseases, and to discover efficient therapeutic methods.

For a long time, it has been known that proteins are a major constituent of cells. At the start of the 20th century, it was shown that some proteins have specific biological functions (e.g., catalytic activity, transport, storage). In 1951, Linus Pauling and Robert Corey proposed the first model for local structures of proteins. Twelve years later, Max Perutz showed the first atomic resolution model of a protein. This was a great step towards understanding how a protein functions, and it proved that proteins have a defined conformation, differing from the former notion that proteins were amorphous colloid-like masses.

The primary structure is the linear sequence of amino acids that comprise a protein (its polypeptide chain) as it is encoded by genetic information, and produced by the ribosome. The secondary structure represents the first spontaneous step of the normal folding pathway of the polypeptide chain, and follows certain typical models that Linus Pauling called alpha-helices and beta-sheets. These two structures are present in almost all globular proteins. Globular proteins are composed of a defined number and sequence of these elements of secondary structure that form and organize the whole molecule: the exact spatial arrangement of the atoms in the protein is called its tertiary structure. A drop-like organization, where the hydrophobic amino acids stay in the center, far away from the solvent, and the hydrophilic residues are on the surface, is characteristic of the tertiary structure of globular proteins. In addition to its occurrence in this subtype of proteins, a similar arrangement is also found in the fibrous proteins of our organism. The most common and well-characterized fibrous proteins in the human body are keratin, collagen, and elastin. They have simple structures, composed mainly or exclusively of helical elements, which give this kind of proteins a high stability, and that is the reason why these proteins have protective, connective, and supportive roles in living organisms.

The effectiveness of the normal folding pathway is critical to the determination of the protein function, a fact that can easily be observed with hemoglobin; many diseases are related to single or multiple mutations on the DNA sequence and will cause diseases because the mutation could change the final protein conformation, just as in sickle cell anemia, thalassemias, and other hemoglobin disorders. Another possibility that is now being studied is that even without any DNA mutation, some protein conformations could be modified with severe clinical consequences.

In 1973, Christian Anfinsen proposed that all the information required for the generation of the native three-dimensional conformation of a protein is contained in its amino acid sequence [96]. The big question of folding is to understand how a polypeptide chain can fold rapidly enough to be of use for biological processes. It is clear that a random search of all possible conformations until the best one has been found would not be possible, because this process would take an astronomical amount of time to complete (approximately 20 billion years – Cyrus Levinthal's calculation) [97]. This question has not been completely solved, but some findings have brought new insights to it. For example, it has been shown that some proteins, called chaperones, have the function of helping bigger proteins to fold properly [98–99]. But how do the chaperones fold in the first place? The discovery of intermediates in the folding pathway has also brought new light to the folding question.

Previously in protein folding studies, small proteins were generally considered to fold via a two-state transition involving a totally unfolded state, without any structure, that progresses directly to a completely folded structure [100]. However, diverse studies showed that many proteins fold through several sequential steps to the final completely folded state: a completely unfolded protein first acquires its secondary structure, then proceeds to the formation of an intermediate with secondary structure, but without a stable tertiary structure, and finally forms a native folded protein [101]. The finding of protein intermediates in the normal folding process led to the important discovery that the same protein can have different stable states, which may participate with different functions in the cell [102]. What seemed at first to be an academic question was proved to have medical significance when it was discovered that errors in this folding pathway can lead to many different diseases.

Misfolding of Proteins

Misfolding represents a mistake in the folding pathway that leads to the formation of a protein with a stable final structure, but very different from its native one. Misfolded proteins probably occur all the time in the cell, when a protein is produced in the cytoplasm or in the endoplasmatic reticulum, or when an already folded protein suffers a temporary loss of structure in the cell. They can also arise when a mutation in one of the amino acids of a protein's sequence alters the folding process. These proteins do not normally accumulate and provoke diseases, because the cell has an efficient mechanism to detect and destroy these misfolded proteins (through proteasomal degradation).

The biological functions of proteins are directly dependent on the acquisition of their precise three-dimensional structures. Failure of the intracellular folding mechanism or of the quality control machinery that detects and eliminates misfolded or

non-folded proteins [103] may lead to major pathological conditions collectively described as conformational diseases [104]. This failure in the control machinery of the cells may represent a sign of cell aging, and may explain why some of the conformational diseases manifest themselves in aged patients.

The misfolded proteins that are not destroyed by the cell tend to accumulate inside or outside the cell, and they can associate to form large aggregates of proteins. Actually, aggregation is the most common destiny of a misfolded protein, if it is not destroyed [103]. Until some years ago, it was believed that these aggregates were extremely toxic for cells and were the main cause of cell death, for example, the deposition of beta-amyloid fibrils in Alzheimer's disease. Today, an increasing quantity of new data suggest that the first stages of aggregation, which are called protofibrils or pre-fibrillar aggregates, are much more toxic and dangerous than the mature fibrils [105]. This may explain the lack of a direct correlation between the density of fibrillar plaques in the brains of patients with Alzheimer's disease (often proposed to cause dementia) and the severity of clinical symptoms [106]. The new question is: are the large fibrillar aggregates the major pathologic event that leads to cell death and tissue dysfunction or are they the last option for cells to get rid of the misfolded protein? Future therapeutic approaches should be directed to answering this question.

The exact pathologic mechanisms that lead to cell death are not yet completely understood. Some evidence shows that the pre-fibrillar aggregates have some exposed amino acid regions that can mimic regions of the surface of the native protein. These regions are, therefore, likely to be able to interact inappropriately with the binding partners or receptors of the native proteins [107]. Indeed, it has been shown that some pre-fibrillar aggregates can interact with cell membranes, possibly destabilizing them, leading to cell death [108].

Furthermore, the protein misfolding process might have a direct toxic effect on the cell, and/or it might provoke the loss of a vital function of the cell due to the absence of the correctly folded protein: in both cases it leads to cell death. This theory is called "gain of function or loss of function" and explains the pathologic mechanism of the conformational diseases.

The amyloidoses and the prion diseases are the most well-known and important conformational diseases.

Amyloidoses

The first person to detect the protein aggregates mentioned above and to associate them with disease was Virchow in 1854, after reacting the fibril aggregates present on hepatic tissue with iodine and sulfuric acid. Since that is the same reaction used to stain starch (*amylum*), Virchow gave the name amyloid to this type of aggregate. More than 70 years later, Divry and Florkin stained the amyloid aggregates with the dye Congo Red and recognized that they showed an apple-green birefringence when analyzed under polarized light [109]. To the present day, this is the most widely used method to diagnose an amyloid disease. Later, electron microscopic analysis showed that all such aggregates exhibit a similar fibrillar structure, with bundles of straight, rigid fibrils ranging in width from 60 to 130 Å and in length from 1000 to 16,000 Å [110].

The amyloid diseases comprise important pathologies, including Alzheimer's and Parkinson's diseases, type II diabetes mellitus, and various forms of systemic and cutaneous amyloidoses. The prion diseases are not universally considered amyloidoses because it is not clear if the amyloid aggregates present in the prion diseases are directly implicated with the neurodegeneration or only represent an epiphenomenon in the disease (see below); however, the prion diseases were included in this review because of the possibility of a cutaneous infection route.

Some of the amyloidoses are genetically inherited, and point mutations of normally occurring proteins have been described for many familiar forms of amyloidosis. These point mutations may not always alter the protein structure, but somehow favor the aggregation of the protein, and lead to its accumulation in the tissue and disease. Some examples of familial forms of amyloidosis are familial amyloidotic polyneuropathy I, or Corino de Andrade's disease, caused by transthyretin mutants [111]; familial forms of Alzheimer's disease, caused by β-amyloid peptide [112], and Huntington's disease, caused by huntingtin [113]. Since these mutations favor the aggregation of the respective proteins, the disease symptoms are seen rather early in the afflicted members of the families and do not reflect simply a cell-aging process. Recently, a familial form of primary cutaneous amyloidosis has also been described and linked to alterations on chromosome 5 [114].

The most peculiar aspect of the amyloid diseases is the fact that many proteins associated with this condition do not have any similarity in size, sequence, or native structure. However, they are all able to form amyloid fibrillar aggregates, which when closely studied, showed a marked similarity in morphology and internal structure. In general, the amyloid fibers are insoluble, resistant to proteolysis, and show an extremely high content of beta-sheet [107]. Another interesting aspect of the amyloidogenic process is that, apparently, under the right conditions, any protein can form amyloid aggregates, even disease-unrelated proteins [115]. The required conditions can be, for example, low pH, lack of specific ligands, high temperature, presence of salts or co-solvents that disrupt the protein's native structure; and in many cases, the fibrils formed do not represent a physiological reality. However, the possibility to study such artificial amyloid fibrils was helpful in understanding the amyloidogenic process better, and the mere existence of these fibrils proved that the ability to form amyloid fibrils is a generic property of peptides and proteins. It seems that the disease-causing mutations in familiar amyloidosis merely facilitate and accelerate the formation of such fibrils.

The exact process by which a soluble protein forms insoluble aggregates is not totally defined, although the understanding of the mechanism by which a protein assumes an amyloidogenic conformation is crucial to the development of future therapeutic approaches.

The following is an overview of the systemic and localized amyloidoses, including their cutaneous symptoms. Since it is not the objective of this review to give an extensive analysis of these forms of amyloidosis, only the more important features are mentioned.

Systemic Amyloidosis

The most frequent types of systemic amyloidosis are the AL (primary) and the AA (secondary) types [116]. AL amyloidosis is caused by the accumulation of the AL protein that is derived from the light chain of immunoglobulin, more precisely from the lambda region in 75% of the cases, and from the kappa in

the remaining cases [117]. This accumulation causes deposition of the protein aggregates in different tissues, and finally, organ dysfunction. The AL amyloidosis can be associated with multiple myeloma and Waldenstrom macroglobulinemia. AL amyloidosis can affect only one organ, or have a multi-organic involvement, and the main clinical presentations are: renal involvement with nephrotic syndrome, restrictive cardiomyopathy, peripheral neuropathy (frequently presenting as carpal tunnel syndrome), hepatomegaly with or without splenomegaly, macroglossia, and many non-specific cutaneous signs. The most common cutaneous presentations include a waxy thickening of the skin, ecchymoses, purpura (characteristically after Valsalva maneuver) and subcutaneous nodules and plaques. The ecchymoses and purpura are due to the perivascular infiltration of the amyloid deposits, which cause a local inflammatory reaction, and are found more frequently in flexural regions, such as the eyelids, nasolabial folds, neck and axilae, besides the mouth. The nails can also be affected, and brittleness, crumbling, subungual striations, and partial anonychia may be present.

AA amyloidosis is a secondary form of amyloidosis that may complicate chronic diseases in which there is chronic or recurrent inflammation, such as rheumatoid arthritis or spondyloarthropathy, chronic infections, or periodic fever syndromes. The fibrils are composed of fragments of the acute phase reactant serum, amyloid A. Just as in AL amyloidosis, the organs most affected are kidneys, liver, and heart.

The diagnosis can be suspected by the history and findings in the physical examination, and by the presence of the light chains in a urine sample. However, the diagnosis can only be confirmed by tissue biopsy and the demonstration of amyloid deposits. There is no optimal biopsy site: biopsy can be directed at dysfunctional organs, such as kidneys or nerves, or at other sites, such as subcutaneous fat, salivary glands, or rectal mucosa. A new diagnostic method available in some specialized centers is mass spectroscopy of the paraffin-embedded specimen, which allows a precise identification of the protein involved in the amyloid formation [118].

In conclusion, both forms of systemic amyloidosis have in common a high expression rate of a specific protein, immunoglobulin light chain in the AL amyloidosis, and serum amyloid A in the AA form. But how an excess of these proteins leads to their aggregation and the formation of amyloid fibrils is still not clear.

Localized Amyloidosis

In contrast to systemic AL amyloidosis, there are some patients who present localized deposition of the immunoglobulin light chains; this will cause damage to the affected site, usually the upper respiratory tract (nasopharynx, lips), colon, orbit, skin, and nails [119–120].

The primary localized cutaneous amyloidosis comprises the macular, papular (or lichen amyloidosus), and nodular forms. The nodular form can be considered a localized plasmacytoma because a high production of immunoglobulin light chains by clonally expanded plasma cells is observed, just as in the systemic AL amyloidosis, but locally [121]. On the other hand, the other forms of localized cutaneous amyloidosis are not associated with immunoglobulin production, and their pathogenesis is not completely clear. It is believed that focal epidermal damage is involved, with a local degeneration of keratinocytes, followed by apoptosis and conversion of filamentous masses (colloid bodies) into amyloid material in the papillary dermis [122]. Indeed there is evidence that the keratinocytes are involved with the formation of the fibrils [123]; the presence of keratins has been detected in the fibrils [124]. The exact mechanisms that cause the epidermal damage and how the amyloid fibrils are formed are still unknown. Some believe that chronic pruritus might lead to keratinocyte degeneration and initiation of the amyloid formation [125,126].

The clinical presentation of nodular amyloidosis is the presence of one or more nodular lesions in the limbs, trunk, face, or genitalia. The size of the nodules can vary from a few millimeters to several centimeters [127]. It is a benign lesion, but in a few patients it can evolve to systemic paraproteinemia and systemic amyloidosis [128–129]. A possible treatment is the excision of the lesion [130].

In the lichen amyloidosis form, the individual lesions are smooth or hyperkeratotic papules that may coalesce to form pruritic plaques, presenting principally on the shins. Finally, the macular form is characterized by poorly delineated, hyperpigmented patches with a chronic evolution and affects the upper back, limbs, and occasionally the chest and buttocks. This form can be pruriginous. In both cases, the diagnosis is made through biopsy of the affected region with the demonstration of the amyloid deposits in the papillary dermis. There is no effective treatment for these two forms of cutaneous amyloidosis; topical steroids combined with antihistamines can be used to alleviate the pruritus in some cases. Calcipotriol, etretinate, or acitretin therapy has also been tested [131–132]. The use of topical dimethylsulphoxide (DMSO) is still controversial [133,134].

Prions and Amyloids: The Emerging Concept of Transmissible Cerebral Amyloidosis

The amyloid plaque has long been recognized as a hallmark of the neuropathology of some TSEs, especially GSS and kuru [135–139]; it was established that the amyloid plaque of TSE was mostly composed of misfolded PrP. As a result, Gajdusek suggested calling PrP 27-30, the shortest truncated form of PrP that still retains infectious properties, a "scrapie amyloid" [140].

Fibrillar structures isolated from TSE-affected brains (prion rods) are morphologically very similar to, but distinguishable from, other amyloid fibrils when visualized by negative-staining electron microscopy [141]. Direct evidence for a cross pleated secondary structure of PrP^{Sc} was obtained within the last few years via infrared spectroscopy, which correlates the infrared spectrum with the secondary structure of proteins and does not require the protein to be in solution. Caughey et al. showed that PrP 27-30 contains a high proportion of pleated sheet [142]. Denaturation by either SDS or high pH reduces both scrapie infectivity and pleated content [143].

PrP fragments are able to form either helices or pleated sheets and conversion from helix into a sheet may underlie the formation of prions. Indeed, using hamster recombinant protein, Mehlhorn et al. demonstrated that the same peptide may form stable helix or sheets with several intermediates [144]. All these data point to an inherent propensity of PrP to exist in different conformations.

Riek et al. described the secondary structure of mouse PrP in solution to consist of three helices and two antiparallel strands at the globular C-terminus [145]. A comparison between human,

mouse, and bovine PrP demonstrated that human and bovine PrPs exhibit virtually identical conformations [146], and because species susceptibility is strongly influenced by PrP conformational similarity, humans are very susceptible for BSE infection.

As detailed above, it is now widely accepted that structurally diverse proteins can misfold and cause so-called "conformational diseases," including systemic and cutaneous amyloidosis, Alzheimer's disease, and Parkinson's disease [136–138]. All these diseases are characterized by amyloid plaques that may be causally connected to the pathological process. In the prion diseases of GSS, vCJD, and some murine scrapie models of disease, "classical" or multi-centric (in GSS) amyloid plaques are frequent, but they are often absent in human TSE cases [147], in BSE, and in most ovine scrapie.

All of these neurodegenerative diseases are "infectious" in the sense that misfolded sheeted conformers form in a nucleation process in which a preformed metastable oligomer acts as a seed to convert a normal into an abnormal protein [136–138]. However, in none but TSE has infectivity in a microbiological sense (from one organism to another) ever been observed, and even in TSE, the formation of misfolded protein is not necessarily accompanied by the generation of infectivity de novo. Lundmark et al. [148–149], recently described the transmissibility of systemic amyloidosis by a prion-like mechanism. Mice were orally infected by a homogenate of amyloid extracted from the liver of mice previously exposed to silver nitrate, a substance that is classically related to the induction of AA amyloidosis, or by naturally occurring amyloid fibrils [149]. The transmission occurred in a very effective way and suggested that at least some forms of amyloidosis may be transmissible diseases, akin to the prion-associated disorders [136–138,150].

Conclusion

Prion diseases of humans are undoubtedly transmissible by affected brain-derived and cornea material [2,7]. Skin and conjunctival membranes are possible sites for a direct contamination by prions [11,12]. The transmissibility of the agent by direct iatrogenic manipulation (blood transfusion, organ transplants) has been reported [8].

A serious discussion of the potential of prion transmission via filling materials from bovine origin and products obtained from cultured cells fed with bovine serum should be initiated by dermatologists [3]. Other dermatologic procedures associated with the use of biological products originated from donors, such as botulinum toxin that is stabilized in vitro by human or bovine albumin [3,28], are also at risk.

Ectoparasites, such as myiasis and mites, are common agents of skin infestation worldwide. Ophthalmomyiasis and oral myiasis are quite common manifestations of myiasis in both developed and underdeveloped countries [38,44–49,51–56,83–87]. The disease is far more common in tropical areas, such as India [53], Tunisia [55], Iran [56], Jordan [78], and Egypt [79], where it can reach epidemic proportions. It is important to point out that a great proportion of cases of ocular myiasis in humans are caused by the larvae of *O. ovis* and by *H. bovis*, respectively, the most common cause of myiasis in sheep and cattle [38,44–49, 51–56,83–87]. Both are the only domestic animals that are commonly infected by prions.

Even wound and ulcer myiasis are candidates for the dissemination of prion infections [10]. The specific immune system displays a natural tolerance to PrP^{Sc}, and lymphocytes are probably involved in the dissemination of the disease to the CNS [92,93]. Aucouturier et al. [92] observed that immunodeficient hamsters were resistant to prions after peripheral inoculation. In normal animals, however, cells of the immune system allowed neuroinvasion. Pammer et al. [11,12] detected that the expression of PrP^{C} was strongly upregulated in keratinocytes of patients with skin ulcerations. Tabouret et al. [93] investigated the cellular and humoral responses in sheep experimentally infected with *O. ovis* and detected a huge local recruitment of both lymphocytes and macrophages. The local humoral response was mainly directed against larval salivary gland antigens and the sinusal mucosa of infected animals was extremely thickened; the epithelium exhibited hyperplasia, metaplasia, and eosinophilic exocytosis [93]. The high expression of PrP^{C} on the skin and mucosa and the common occurrence of ocular myiasis could readily increase the efficiency of acquisition and transmission of prions in both animals and humans [10,13,63].

It is very difficult to confirm the exact source of infection in prion infection, as the experience demonstrated both with kuru in New Guinea and with BSE in the UK, because these diseases are associated with an incubation period of many decades [3,13]. However, the fact that it is difficult to confirm a clinical case does not invalidate the hypothesis of prion dissemination by ectoparasites, which is supported by several other lines of evidence, such as laboratory work with flies, fly larvae, fly pupae, hay mites, etc. [7–10]. Also important is the epidemiological data for scrapie [2], the amazing dissemination of CWD in the USA in the last 35 years [94], as well as the chronic and almost endemic infection of sheep in Iceland [2,7–9].

It is important to point out that most medical specialties are analyzing possible roles for prion transmission in their fields of influence, such as transmission by dura mater homografts, retinal transplants, vaccines, blood donors, contaminated surgical instruments and dental implants, use of gonadotropin and growth hormones [2,3,17,20,95].

Another important approach for prion infections is to recognize that they are related to wrong conformational patterns during the protein pathway [138–138]. This new class of diseases, called conformational diseases, is characterized by the formation of misfolded proteins that have the ability to aggregate into fibrils and cause tissue/organ dysfunction and disease [136]. The exact mechanisms that lead to this misfolding and aggregation are not yet known for all diseases of this class.

It seems critical to recognize both prion diseases and the different forms of amyloidosis, such as systemic and cutaneous amyloidosis, as different examples of conformational diseases that depend on the conversion of normal proteins into an "amyloidogenic," mostly beta-sheet structure liable to aggregation. In this interpretation, prion diseases distinguish themselves by their cerebral localization, and their transmission between organisms has been proved beyond doubt; a cutaneous transmission seems possible [136–138]. Systemic amyloidosis, on the other hand, afflicts several organs of the body, among them the skin, and its transmission between organisms has yet to be shown to occur outside the laboratory. The same is true for cutaneous amyloidosis [136].

The precise identification of the conformational diseases and the understanding of their pathogenesis are fundamental for the development of new and effective treatment.

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26 Oral Manifestations of Viral Diseases

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Keywords: herpes simplex virus, recurrent herpes infection, varicella zoster virus, herpes zoster, Kaposi's sarcoma, exanthema subitum, Epstein-Barr virus, oral hairy leukoplakia, human papilloma viruses, coxsackievirus infections, hand-foot-mouth disease, herpangina, verruca vulgaris, condyloma acuminatum, focal epithelial hyperplasia

Viral infections are common occurrences in the oral cavity. They are caused by DNA or RNA viruses that use the host cell to replicate viral genomic material and make progeny. Infections occur at all ages and as lytic, latent, or persistent infections. Lytic infections (e.g., human herpesviruses, coxsackieviruses) often produce acute symptoms and oral mucosal ulcerations. By contrast, latent and persistent infections (herpesvirus and human papillomavirus (HPV) infections) can result in episodic ulcerations, benign epithelial growths, and/or induce premalignant and malignant transformations. Viral infections are a concern to dental and medical professionals because of their influence on oral health, infection control, risk of transmission, and associations with systemic illnesses. Management is dependent on the infectious agent, clinical features, immune status of the patient, available drugs, and desires of the patient.

DNA VIRUS

Oral Herpetic Infections

Introduction

In the past 20 years, at least 80 herpesviruses have been described and eight of them are known to cause infections in humans. These include herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV-6), human herpes virus 7 (HHV-7), and human herpes virus 8 (HHV-8) (Table 26.1).

Herpes virus contains a DNA nucleus and can remain latent in host neural cells, thereby evading the host immune response. All herpesviruses contain four layers: an inner core of double-stranded DNA, a protein capsid, the tegument, and a lipid envelope containing glycoproteins derived from the nuclear membrane of host cells [1]. They cause a primary infection when the patient is initially exposed to the virus and then remain silent within the nuclei of specific cells for the life of the individual. The site of latency is different among the herpesviruses. HSV-1, HSV-2, and VZV remain latent in the sensory nerve ganglia; CMV remains latent in monocyte progenitors and salivary gland tissue; and HHV-6 and HHV-7 remain latent in CD4 lymphocytes [2]. HHV-8 also remains latent; although the exact site is unknown; it is most likely associated with B lymphocytes circulating the hematopoietic system [3]. After reactivation, herpesviruses can produce localized symptomatic or asymptomatic recurrent infections. They are transmitted from host to host by direct contact with saliva, dermal lesions, or genital surface secretions. HHV-8 may be transmitted by organ transplantation [4]. Herpesviruses are shed in the saliva of asymptomatic hosts, who act as constant reservoirs for new primary infections in previously uninfected individuals [5]. Herpesviruses are known to transform cells in tissue culture. EBV is associated with malignancies in humans, such as nasopharyngeal carcinoma and B-cell lymphomas [6]. Other malignancies are associated with EBV, including a nasal T-cell/natural killer (NK) cell lymphoma seen most commonly in South East Asia [7]. HHV-8 has been definitively linked to malignant processes such as Kaposi's sarcoma (KS), to several lymphoproliferative disorders, and to Castleman's disease [8].

HERPES SIMPLEX VIRUSES

HSV-1 and HSV-2 are the main types of HSV, and HSV-1 is responsible for the most common intraoral herpesvirus infections.

Primary Herpes Simplex Infections

HSV infects the skin and mucosa and travels to neurons of the sensory ganglia, where it causes lifelong latent infection. The virus periodically reactivates, resulting in progeny spread down neurons to axons in spinal or trigeminal nerves, and either to be shed symptomatically in saliva or genital secretions, or to cause disease of the skin, mucosa, and occasionally major organs. Primary HSV-1 infection occurs when a susceptible person, usually a child, comes into close contact with a person with primary or recurrent infection. Primary infection in children is asymptomatic 90% of the time, but can cause a severe herpetic gingivostomatitis that often requires hospitalization for fluid management. Symptoms are more common in adolescents and adults. Most HSV-1 seroconversions occur in the first 5 years of life, and by adulthood 80% of individuals have HSV-1 antibodies [9]. Symptomatic primary HSV-1 disease is preceded by generalized symptoms that may include fever, headache, malaise, nausea, and vomiting. In the oral cavity, vesicles and ulcers appearing on the oral mucosa is the primary feature coupled with generalized acute marginal gingivitis that occurs 1 or 2 days after the prodromal symptoms start. The generalized gingivitis is an important clinical feature in the differential diagnosis. Primary HSV-1 in healthy children is usually a self-limiting disease with fever disappearing in 3 or 4 days and oral lesions healing in 10–20 days.

Treatment of primary HSV infection is generally palliative. Milder cases can be managed by supportive care, including fluids, use of acetaminophen to reduce fever, and use of topical anesthetics such as viscous lidocaine to decrease oral pain. Aspirin and nonsteroidal medications should be used cautiously in patients with acute, systemic viral infections, especially children because of the risk of development of Reye's syndrome [10]. If the patient presents to the clinic within 72 hours of the beginning of the vesicles, antiviral medications may be helpful in decreasing healing time [11]. Acyclovir, a DNA chain terminator, has been shown to decrease symptoms of primary HSV infection in children, including days of fever and viral shedding [12]. Newer antiherpes drugs are available, including valacyclovir and

Table 26.1 Herpesviruses Known to Cause Infections in Humans

Herpesvirus	Key clinical feature
Herpes simplex virus 1	Vesicles lips – oral cavity
Herpes simplex virus 2	Vesicles genitals – oral cavity
Varicella zoster virus	Varicella – herpes zoster
Cytomegalovirus	Infectious mononucleosis-like syndrome
Epstein-Barr virus	Infectious mononucleosis
Human herpes virus 6	Exanthema subitum
Human herpes virus 7	Exanthema subitum
Human herpes virus 8	Kaposi's sarcoma



Figure 26.2 Herpes simplex type 1.

Table 26.2 Recommended Dosages of Antiviral Medications for Treatment of Primary Herpes Simplex Virus Infections (Based on FDA Approved Treatment Recommendations for Genital Herpes and Standard Use of Famciclovir)

	Acyclovir	Valacyclovir	Famciclovir
Dose	200/400 mg	1000 mg	250 mg
Frequency	5 times a day/3 times a day	Twice a day	3 times a day
Duration	10 days	10 days	10 days

famciclovir; both drugs have a better bioavailability allowing fewer daily doses (Table 26.2)

Recurrent Herpes Simplex Infection

During the primary HSV-1 infection, the virus migrates to the sensory ganglion, where it is capable of remaining in a latent state. Approximately 30–40% of patients who have been exposed to HSV will develop recurrent infections [13]. Reactivation of virus typically follows exposure to cold, sunlight, stress, trauma, or immunosuppression. At least 70% of the population shed HSV-1 asymptomatically at least once a month, and many individuals appear to shed HSV-1 more than 2 times per month. Shedding of HSV-1 is present at many intraoral sites for short periods, at copy numbers sufficient to be transmitted [14]. Recurrent herpes labialis (RHL) is the common form of recurrent oral HSV infection that appears on the vermillion border of the skin of the lip and is referred to as a "cold sore" or "fever blister." Herpes can also recur as intraoral herpes (Fig. 26.1).



Figure 26.1 Intraoral HSV in oral mucosa of the inferior lip.

RHL begins with prodromal signs or symptoms such as burning, tingling, soreness or swelling at the site where the lesions will develop. Within hours, small vesicles develop in clusters along the vermilion border of the lips. The vesicles quickly rupture, resulting in erosions that can coalesce to form larger, irregular lesions with crusted surfaces (Fig. 26.2). In an otherwise healthy individual, the lesions heal without leaving scars within 7–14 days. Lesions of recurrent extraoral herpetic infections can develop anywhere along the affected sensory division of the trigeminal nerve. The diagnosis of RHL is usually based on the clinical appearance. Treatment of RHL is primarily symptomatic. Ice, chloroform, and rubbing alcohol have been used as topical agents with mixed results. Lysine, is antiviral in vitro, and has been used clinically with varying degrees of success. One study reported that the use of high doses of lysine resulted in milder episodes of RHL [15]. Topical medications have also been used for the treatment of RHL [16]. Topical penciclovir (Denavir®) reduces the duration and pain of RHL by 1–2 days. The recommended dose of topical penciclovir is application to the area every 2 hours for 4 days. Acyclovir, as well as N-Docosanol cream, is also available for topical use. Overall, the benefit of these topical medications (acyclovir and N-Docosanol) seems to be limited because the polyethylene glycol base prevents good penetration and does not significantly decrease the duration of lesions as compared with topical penciclovir. Systemic antiviral agents, such as acyclovir, have a better response than the topical medications (Table 26.3). In patients known to have RHL induced by exposure to sunlight, a prophylactic regimen of acyclovir (400 mg twice daily) and sunscreens may be used if prolonged actinic exposure is anticipated [17].

Although a majority of recurrent herpes occurs on the lips and heavily keratinized mucosa of the palate and gingiva, recurrent intraoral herpes (RIH) can occur on any intraoral mucosal surface, especially in immunocompromised patients. Patients at high risk for severe recurrences are those receiving cancer chemotherapy or immunosuppressive drugs to prevent graft rejection after transplantation and patients with advanced AIDS. Recurrent HSV lesions in immunocompromised patients appear

Table 26.3 Recommended Dosages of Antiviral Medications for the Treatment of Recurrent Herpes Simplex Virus Infections

	Acyclovir	Valacyclovir	Famciclovir
Dose	200/400 mg	2000 mg	1500 mg
Frequency	5 times a day/3 times a day	Twice a day	Once
Duration	5 days	1 day	1 day



Figure 26.3 Patient with immunosuppression secondary to chemotherapy. Herpes simplex type 1 developed in the inferior lip.

as progressively enlarging ulcers, which may involve large portions of the labial, intraoral, genital, or rectal mucosa if left untreated (Fig. 26.3). These lesions have the potential to disseminate, producing generalized infection. Therefore, it is critical for clinicians to rule out HSV-1 infection as the cause of oral vesicles or ulcers in immunosuppressed individuals.

Reactivation of HSV-1 can trigger episodes of erythema multiforme (EM) [18] (Fig. 26.4). EM is a mucocutaneous condition caused by hypersensitivity reaction with the appearance of cytotoxic T lymphocytes in the epithelium, which induce apoptosis in keratinocytes that leads to cell necrosis. In the oral cavity, EM presents as irregularly shaped large ulcers more often in the buccal mucosa, tongue and lips. Patients who experience severe recurring EM as a result of HSV-1 reactivation are commonly administered prophylactic doses of antiviral medication to prevent these recurrences.

Diagnosis

The majority of HSV-1 infections are diagnosed clinically. However, there are several conditions that mimic the lesions produced by HSV. Recurrent aphthous stomatitis (RAS) is commonly misdiagnosed as an HSV-1 infection. However, there are clinical characteristics that are unique to each disease. Primary HSV-1 infection typically has a prodrome of fever and malaise before vesicles and ulcer eruption. Primary HSV-1 infection usually presents with gingival erythema; RAS does not. HSV lesions can also be similar to coxsackie viral infection, the most common being herpangina and hand-foot-and-mouth disease (HFMD). Herpangina lesions are typically located in the posterior aspect of the oral cavity, including the soft palate, uvula, tonsils, and pharyngeal wall. Additionally, herpangina infections are typically milder than HSV-1 infections, generally occur in epidemics and do not cause an acute gingivitis. Laboratory tests may be necessary to diagnose atypical presentations of HSV infections. The diagnosis of herpesvirus infections can be made quickly and accurately by using culture and immunofluorescent techniques [19].

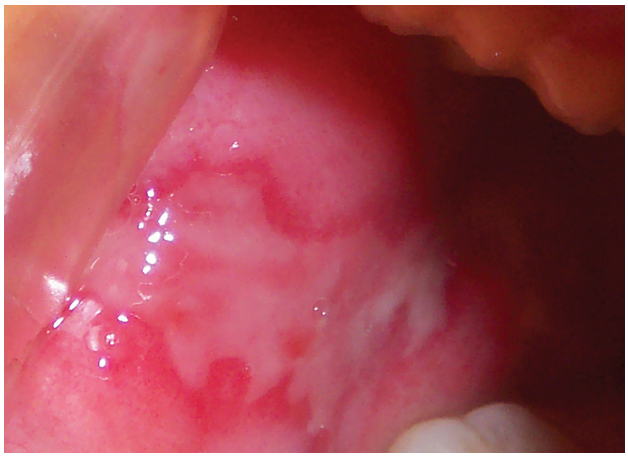


Figure 26.4 Ulcers in the oral cavity in a patient with diagnosis of erythema multiforme.

Varicella Zoster Virus

VZV is a highly infectious virus responsible for two major clinical infections: the primary type is chickenpox (varicella), and the recurrent type is shingles or herpes zoster (HZ).

Varicella

Chickenpox is an illness of children spread through the air or by direct contact with either the skin lesions or nasopharyngeal secretions of an infected patient. The incubation period is 10–21 days, and patients are infectious for approximately 1 week after symptoms begin. Skin lesions are characterized by maculopapular lesions that are pruritic. The lesions occur first on the trunk and face and rapidly develop into fluid-filled vesicles on an erythematous base. Oral lesions may be present, but are similar to the vesicles or ulcers seen in primary HSV-1.

Herpes Zoster

HZ or shingles is the result of reactivation from the VZV. HZ typically presents as unilateral rashes that can wrap around one side of the waist or torso. Annually, over 1,000,000 people in the USA experience a HZ outbreak [20]. Over 90% of the adult population has serological evidence of a prior VZV infection and is at risk for developing HZ [21]. The elderly and those immunocompromised (recent chemotherapy, patients who have undergone organ transplantation, or AIDS) are at greater risk for developing HZ. Between 10 and 20% of normal (immunocompetent) adults will get HZ during their lifetime [22].

VZV enters the host through the respiratory system, replicates at an undefined site (presumably the nasopharynx), infiltrates the reticuloendothelial system, and eventually makes its way into the bloodstream. After the primary infection (chickenpox), VZV retreats into the dorsal root ganglia where it can lie dormant for years until some excitatory factor triggers reactivation. VZV does not recur as frequently as other herpes viruses, such as HSV-1 or HSV-2, because some genes necessary for the reactivation are missing in VZV [23]. The classic presentation of HZ starts with a prodrome of mild-to-moderate burning or tingling (or in some cases numbness) in or under the skin of a given dermatome, often accompanied by fever, chills, headache, stomach upset, and malaise. Within 48–72 hours of the prodrome, an erythematous, maculopapular rash forms unilaterally along the dermatome that rapidly develops into vesicular lesions. The pain associated with HZ varies in intensity from mild to severe [22]. The lesions usually begin to dry and scab 7–10 days after appearing. Total duration of the mucocutaneous manifestations of the disease is generally



Figure 26.5 Extraoral herpes zoster affecting the maxillary branch of the trigeminal nerve.

between 3 and 4 weeks. However, it may take several weeks for the skin to return to normal. When HZ involves the trigeminal ganglion, the first division (ophthalmic) is most commonly involved, and eye involvement becomes a potentially serious complication.

Approximately 15–20% of the cases of HZ of the trigeminal nerves affect either the maxillary division or mandibular division, leading to pain, unilateral facial lesions, and intraoral lesions along the course of the affected nerve [24] (Fig. 26.5). Diagnosis of HZ is usually based on characteristic clinical signs and symptoms. Intraoral lesions caused by HZ usually demonstrate a unilateral distribution associated with intense pain (Fig. 26.6). When the presentation of the skin or oral lesions is not clear, as may be the case with immunocompromised patients, laboratory confirmation is recommended. The polymerase chain reaction (PCR) technique is the most sensitive and specific diagnostic test, as it can detect VZV DNA in fluid from infected vesicles. Use of direct immunofluorescence assay is a good alternative to PCR and is preferred over viral culture [21]. Immunocompromised patients with HZ are at risk for developing life-threatening infections including meningitis, encephalitis, VZV pneumonia, and hepatitis. Oral HZ in immunocompromised patients has been reported to cause necrosis of alveolar bone and exfoliation of teeth [25]. The most common complication associated with VZ is the development of postherpetic neuralgia, a condition where pain accompanying the rash persists long after the lesions have healed. The pain has been described as sharp, burning, stabbing, and capable



Figure 26.6 Intraoral herpes zoster (HZ) affecting the left side of the hard palate.

of affecting the quality of the patient's life. It is estimated that half the individuals aged over 50 years who develop HZ also develop postherpetic neuralgia [26]

Treatment of HZ is usually with antiviral agents, such as acyclovir, valacyclovir, or famciclovir (Table 26.4). The use of these medications has been shown to decrease the duration of the infection and the amount of pain. Clinical trials have yielded inconsistent results with the use of a short course of systemic corticosteroids to reduce the incidence of postherpetic neuralgia. One study, using a combination of prednisone and acyclovir, demonstrated a significant reduction in acute pain associated with HZ [27]. However, two double-blinded, randomized, controlled trials concluded that administration of corticosteroids for 21 days did not prevent the development of postherpetic neuralgia [27,28]. The use of nonsteroidal anti-inflammatory agents is indicated for the control of pain. In cases of severe pain, the use of narcotics may be indicated. Low doses of gabapentin, pregabalin, or tricyclic antidepressants have also been used for the treatment of postherpetic neuralgia. However, the positive effect on the pain requires at least 3 months of therapy [29].

Cytomegalovirus

Human CMV is a ubiquitous herpesvirus that infects humans early in life and is a frequent cause of asymptomatic infections [30]. However, CMV may cause significant clinical disease in immunosuppressed patients [31]. CMV is transmitted by contaminated blood and bodily secretions, including breast milk, saliva, and genital fluids [32]. CMV is a prevalent pathogen, with 40–100% of the general population showing prior exposure by serology [33].

Table 26.4 Recommended Dosages of Antiviral Medications for the Treatment of Varicella Zoster Infections

	Acyclovir	**Valacyclovir**	**Famciclovir**
Dose	800 mg	1000 mg	500 mg tablets
Frequency	5 tablets per day	Three times a day	Three times a day
Duration	7 days	7 days	7 days

Table 26.5 Recommended Dosages of Antiviral Medications for the Treatment of Acute Infections by CMV

	Ganciclovir	Valganciclovir
Dose	250, 500 mg	450 mg tablets
Frequency	1000 three times daily	Twice a day
Duration	21 days	21 days

Up to 20% of children in the USA will have contracted CMV before puberty. Infection is also common during adolescence, which directly corresponds to the start of sexual activity [34]. Primary infection is often asymptomatic. As with other herpes virus, CMV remains latent within the host and reactivates when the host's immune system is compromised.

CMV is not highly contagious. It is acquired from close personal contact with persons who excrete the virus in their body fluids (saliva, urine, blood, breast milk, semen, and even transplanted organ tissue). Initial infection in newborns and reactivation of the virus in immunocompromised persons can result in severe pathology. CMV produces a mononucleosis syndrome, very difficult to distinguish from Epstein-Barr-induced mononucleosis. The syndrome consists of an acute febrile illness with an increase of 50% or more in the number of lymphocytes. Patients may also present with nonspecific skin rashes, lymphadenopathy, splenomegaly, and pharyngeal erythema. However, these features are less common than in primary EBV infection [11]. The differential diagnosis of the infection caused by CMV is difficult as many of the clinical features overlap with other conditions such as mononucleosis by EBV, toxoplasmosis, acute viral hepatitis, HHV-6, and drug reactions [35]. Any febrile illness in which more than 10% of the patient's lymphocytes are atypical should raise the suspicion of mononucleosis. Although EBV is the causative agent in the majority of cases, the possibility of acute CMV infection should be explored if the antibody test and/or monospot rules out EBV. The best diagnostic test for establishing CMV mononucleosis is serology for CMV IgM antibodies that should be positive in the majority of the patients during the symptomatic phase of the disease. Complications of primary CMV infection may include myocarditis, pneumonitis, and septic meningitis.

CMV infection may produce serious disease and death in immunosuppressed patients. Patients at risk for developing life-threatening CMV are solid organ and bone marrow transplant recipients, as well as patients with advanced human immunodeficiency virus (HIV) infection. Forty percent of patients with HIV develop infection caused by CMV [31]. The widespread use of antiretroviral therapy has reduced the incidence of complications caused by CMV infection. However, a newly recognized syndrome consequent to the use of highly active antiretroviral therapy has been described [32]. This syndrome, immune recovery vitritis, has been reported in patients with inactive previously treated CMV retinitis, as the CD4 count reconstitutes on antiretroviral therapy [36]. There are reports of CMV-related oral lesions in AIDS patients. They have been described as slowly enlarging ulcers that mainly affect the buccal mucosa [37]. Co-infections of oral ulcers with both HSV and CMV are also possible.

The diagnosis of CMV disease is made by histologic evaluation of suspected lesions, viral culture, antigen detection, and CMV DNA detection [38]. Biopsy specimens of CMV demonstrate characteristic histopathologic changes, including enlarged cells with prominent intranucleolar and intracytoplasmic inclusions. Antiviral medications, such as ganciclovir and valganciclovir, have been shown to be effective in treating CMV infections [31] (Table 26.5).

Epstein-Barr Virus

EBV is a herpes virus that typically infects and replicates in B lymphocytes. EBV primary infection is usually asymptomatic or occasionally symptomatic in infectious mononucleosis (IM). Infection of humans with EBV usually occurs by contact with oral secretions. The virus replicates in cells of the oropharynx, and almost all seropositive persons actively shed virus in the saliva [39]. EBV is associated as an etiological factor with IM, different malignancies including nasopharyngeal carcinoma and Burkitt's lymphoma, and oral hairy leukoplakia. Several antiviral drugs inhibit replication of EBV in cell cultures, including acyclic nucleoside and nucleotide analogues, which inhibit the EBV DNA polymerase. Despite their potency in vitro, these drugs have limited use in vivo for treatment of acute primary EBV infection as well as EBV-associated malignancies for several reasons, including toxic side effects, poor oral bioavailability, and risk for emergence of drug-resistant virus strains [40].

Infectious Mononucleosis

IM is a clinical syndrome that is particularly common in adolescents and children. Typical features of IM include fever, pharyngitis, lymphadenopathy, malaise, and an atypical lymphocytosis. Splenomegaly, hepatomegaly, jaundice, and splenic rupture can occur in patients with IM, but these conditions are rare [41]. The infection is spread primarily by saliva, and the incubation period is 4–8 weeks. In an acute infection, antibodies that agglutinate sheep erythrocytes are produced. This process forms the basis for the monospot rapid latex agglutination test used in the diagnosis of IM. The majority of patients with IM present with sore throat, lymph node enlargement, fever, and tonsillar enlargement. Other common physical signs include pharyngeal inflammation and transient palatal petechiae [42]. The differential diagnosis of IM includes streptococcal pharyngitis or acute CMV infection. Both conditions share similar clinical signs of IM. The mainstay of treatment for IM is rest and good supportive care, including adequate hydration, nonsteroidal anti-inflammatory drugs or acetaminophen for fever and myalgias. Corticosteroids are recommended in patients with significant pharyngeal edema that causes or threatens respiratory compromise [42].

Malignancies Associated with Epstein-Barr Virus

A variety of head and neck malignancies are associated with EBV, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and lymphoproliferative disease [1] Burkitt's lymphoma is a high-grade malignant lymphoma of small, non-cleaved B cells. In Africa, tumors of Burkitt's lymphoma usually present in the jaw, and more than 90% of these cases are associated with EBV [39].

Oral Hairy Leukoplakia

Oral hairy leukoplakia is an EBV-induced white lesion that occurs on the lateral or ventral surfaces of the tongue in patients

with immunodeficiency [43]. Oral hairy leukoplakia is reported in about 25% of adults with HIV infection, but is not common in HIV-infected children [44]. The lesions are usually located on the lateral borders of the tongue, but may extend to the ventral or dorsal surfaces. Lesions are usually corrugated and mimic the lesions produced by tongue chewing. Histopathology examination of the lesions shows severe hyperkeratosis with an irregular surface, acanthosis with superficial edema, and numerous koilocytic cells (virally affected "balloon" cells) in the spinous layer and lack of inflammation. The definitive diagnosis can be established by demonstration of the presence of EBV through in situ hybridization or PCR [45]. The differential diagnosis of oral hairy leukoplakia includes hyperplastic candidiasis, leukoplakia induced by tongue chewing, lichen planus, lupus erythematosous, and verrucous leukoplakia. Since oral hairy leukoplakia is considered to be highly predictive for development of AIDS, differentiation from other lesions is important. No treatment is indicated. The condition usually disappears with antiviral medication used in the treatment of the HIV infection and its complicating viral infections. Topical application of podophyllin resin or tretinoin has led to short-term resolution of the lesions, but recurrence is often seen [46].

Human Herpes Virus 6

HHV-6 is a lymphotropic DNA virus with two documented variants, designated human herpesvirus 6 variant A (HHV-6A) and human herpesvirus variant B (HHV-6B). Current serologic methods cannot discriminate prior infection with one virus from prior infection with the other. Over 95% of the population older than 2 years of age is seropositive for either or both viruses. HHV-6A has not been associated with any human disease. HHV-6B is the etiologic agent of the common childhood illness exanthema subitum (ES), also known as roseola infantum or sixth disease, and related febrile illness and is frequently active in immunocompromised patients [47]. The classical presentation of ES in children includes fever (may exceed 40°C) and usually lasts for 3–5 days [48]. As the temperature normalizes, a macular or maculopapular rash develops, generally beginning on the trunk, and later spreading to the extremities and often to the neck, face, and oral cavity. Typical dermal lesions are 2–3 mm in diameter and fade with pressure. Cervical, postauricular, and/or occipital lymphadenopathy are also common findings. One study of Japanese children found small ulcers in the soft palate and uvula in 65% of the patients [49]. The virus can be isolated from saliva, and respiratory transmission is the major route of primary infection.

Human Herpes Virus 7

HHV-7 was first isolated in 1990 from a healthy HIV-negative donor whose cells were stimulated with antibody against CD3 and then incubated with interleukin-2 (IL-2) [50]. HHV-7 is very similar to HHV-6 and belongs to the same herpes virus subfamily; it uses CD4 cells as its cellular receptor and competes with HIV infection. HHV-7 is ubiquitous like HHV-6. In most cases, primary infection of HHV-7 occurs by the age of 12 years, and 90% of adults have antibodies to HHV-7 [50]. Transmissions seem to occur mainly through saliva. However, there is also evidence of transmission through breast milk [51]. Gingival tissues are also considered as a potential reservoir for HHV-7 [52]. When HHV-7 is present, it persists in a latent state in the majority of the cases [52].

Symptomatic clinical manifestations of primary infection are ES, like HHV-6. Clinically, it is difficult to distinguish between the two viruses, but primary HHV-7 infection generally occurs slightly later than HHV-6 infection. HHV-7 can cause reactivation of HHV-6. The clinical implications of primary HHV-7 infection are febrile seizure, liver dysfunction, and acute hemiplegia. Reactivation of HHV-7 in immunocompromised patients can lead to widespread multiorgan infection, including encephalitis, pneumonitis, and hepatitis [53]. Oral lesions are not commonly associated with HHV-7 infections.

Human Herpes Virus 8

In 1994, detection of a viral DNA fragment in KS tissue, consistent with a new herpesvirus was reported [54]. Since this first publication, additional work has been performed and has shown that the viral DNA belongs to a different member of the herpesviridae family called human herpesvirus 8 [55]. There are several diseases associated with herpesvirus 8 including KS, primary effusion lymphoma, and multicentric Castleman's disease. Only KS presents with oral lesions.

Kaposi's Sarcoma

Classic KS was originally described as an indolent tumor of the elderly man, prevalent in Mediterranean countries and the Near East. Epidemic KS, in conjunction with the AIDS epidemic, is one of the most frequently occurring tumors in Central Africa. In the Western world, KS became a hallmark of the AIDS epidemic and, in contrast to the classic form, shows a more aggressive course [56]. Finally, KS can be observed in patients with immunodeficiency not caused by HIV-infection, such as transplant patients [57]. Histology reveals a vascular type tumor evolving from a patch stage, showing small proliferating vessels with inflammatory infiltrate to nodular lesions. Intraoral KS lesions are most often found on the hard and soft palate with a typical clinical appearance of reddish-purple macules or nodules. Extrapalatal lesions may be seen on the gingiva and tongue; these lesions are associated with a more rapid progression of KS and with HIV disease [58]. Herpesvirus 8 can be detected in KS lesions by PCR.

Human Papilloma Virus

HPVs are small DNA tumor viruses with a double-stranded circular DNA genome enclosed in an icosahedron-shaped protein capsid. Over 100 types of HPV have been identified. HPV types are often designed as high risk (oncogenic) or low risk (nononcogenic). The high-risk types include those initially identified in cervical dysplasia and cancer, as well as those types whose DNA sequences are most closely related. These high-risk types are present in over 99% of cervical carcinomas [59]. The HPV low-risk types are found in mucosal and cutaneous sites and can cause benign lesions such as verrucae vulgaris or "warts" (HPV-2, HPV-4, and HPV-7), papillomas and condylomata (HPV-6 and HPV-11), and the lesions of focal epithelial hyperplasia (FEH) (HPV-13 and HPV-32) [60]. HPVs have been shown to be linked to a number of benign lesions of the oral mucosa, such as squamous cell papilloma (SCP), condyloma acuminatum (CA), verruca vulgaris (VV), and FEH (Table 26.6) [61]. HPV DNA has

Table 26.6 Human Papilloma Virus (HPV) Benign Oral Lesions

	Clinical characteristics	Histological characteristics
Squamous cell papilloma	Solitary, exophytic and pedunculated lesions	Koilocytes are uncommon
Verruca vulgaris	Solitary and exophytic	Koilocytes are common
Condyloma acuminatum	Cauliflower-like appearance, sessile base	Koilocytes are common
Focal epithelial hyperplasia	Limited to oral mucosa and perioral skin	Mild hyperparakeratosis and variable number of koilocytes

been detected in various premalignant and malignant oral lesions, e.g., larynx, tonsils, etc. [62]. Of the almost 100 known HPV types, at least 25 types have been detected in oral lesions [63].

Squamous Cell Papilloma

SCP is a common benign lesion of the oral mucosa associated with HPV types 6, 11, 13, 16, and 32 [64]. SCPs are usually solitary, exophytic, pedunculated growths that are composed of numerous finger-like projections of parakeratinized squamous epithelium surrounding a central connective tissue core (Fig. 26.7). SCP presents a papillomatous surface and a more pedunculated base. Histological features seen in SCP include cellular hyperplasia, papillomatosis, and hyperkeratosis. The fact that koilocytes are relatively uncommon in SCP distinguishes this condition from cutaneous warts [64]. The treatment of SCP is complete excision of the lesion including the base. Laser ablation of the lesion requires good evacuation to limit inhalation of the material, which can contain viral DNA. Intralesional injection of interferon-alpha (1 million of IU, 3 times a week for 3 weeks) has shown some promising results, especially in HIV patients with multiple lesions [70].

Verruca Vulgaris

VV or oral papilloma (common wart) is the most prevalent HPV lesion of the skin, but is also found in the oral mucosa. HPV types 2 and 4 have been associated with this lesion. The most common locations are keratinized mucosal areas of lip, hard palate, and gingiva. On clinical examination, VV is often very difficult to differentiate from SCP and condyloma. Histologically, the papillomatous projections have sharp borders with adjacent normal tissue and are formed by thickened layers of both orthokeratinizing and parakeratinizing cells covering thin connective tissue papillae. Koilocytes are common; they are limited to the upper spinous and granular cell layers in most cases [64]. To confirm the diagnosis, cutaneous HPV types should be identified in excised oral verruca.

Condyloma Acuminatum

CA or "venereal wart" is generally regarded as a sexually transmitted disease affecting the skin and mucous membranes of the anogenital tract. It is now accepted that oral condylomas can arise not only by oral sex but also by auto-inoculation or as a result of maternal transmission [61]. Oral lesions can occur without anogenital lesions. It may be difficult to differentiate between SCP, VV, and CA on the basis of histological criteria alone, but clinical features facilitate the diagnosis. Clinically, the surface of CA appears cauliflower-like, and its base is sessile. This cauliflower-like surface is the result of multiple, small, white or pink nodules that coalesce to produce a soft, nodular mass (Fig. 26.8). Treatment of CA is the complete excision of the lesion including the base.

Focal Epithelial Hyperplasia

FEH or Heck's disease, is a rare, benign epithelial hyperplasia that appears clinically as multiple, soft nodular elevations, most commonly affecting buccal mucosa, tongue, gingiva, and lips [65]. In distinction to SCP, VV, and CA, FEH is limited to oral mucosa and perioral skin. Perioral lesions are seen most commonly in the commissure and the lip vermillion. A genetic predisposition to this disease is suggested by the fact that FEH has an unusually high prevalence in selected geographic areas among some ethnic groups. FEH is more common among Native Americans and Eskimos from Greenland [64]. Histologically, FEH lesions are characterized by mild hyperkeratosis, increased cellular density, and acanthosis. There is a small number of koilocytes in the lesion. Greater than 90% of all FEH lesions have been found to harbor either HPV 13 or HPV 32 [66]. Treatment of FEH is complete excision of the lesion including the base.



Figure 26.7 Squamous cell papilloma (SCP) of the oral mucosa.



Figure 26.8 Condyloma acuminatum (CA) upper lip.

Oral Premalignant and Malignant Lesions Associated with Human Papillomavirus

Leukoplakia

Leukoplakia is defined clinically as a white plaque or patch that cannot be rubbed off and that is not classified clinically or microscopically as another condition [67]. Until recently, a possible role of HPV in oral leukoplakia has received little attention [68]. Malignant transformation of oral leukoplakia has been estimated to be 3–6% [64]. HPV types 6, 11, 16, and 18 were detected in the spinous layer of oral leukoplakia. These types of HPV have been detected in benign leukoplakia, as well as leukoplakic lesions demonstrating different degrees of dysplasia [69]. HPV has been detected in 15% of the benign leukoplakia specimens compared with 10% found in normal tissues. Although HPV has been detected in 15%, no known cause-effect has been established [71].

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) encompasses about 95% of all oral cancers. Its clinical aspects vary from a nodule to a chronic ulcer. Many researchers have shown HPV present in SCC [72]. Studies have shown the important role of HPV in head and neck cancers, and also suggest that HPV 16 and 18 may be involved in the development process of the SCC [73]. In a meta-analysis published in 2001, including data from 94 reports that analyzed 4680 samples, HPV was between 2 and 3 times more likely to be detected in precancer oral mucosa lesions, and 4.7 times more likely to be detected in SCC than in normal mucosa [74]. Recent data suggest HPV plays a significant role in oropharyngeal, tonsillar, and base of tongue SCC.

RNA VIRUS

Coxsackievirus Infections

Coxsackieviruses are RNA enteroviruses and are named for the city in upper New York State where they were first discovered. Coxsackieviruses have been separated into two groups, A and B. There are 24 known types of coxsackie group A and 6 types of coxsackie group B. These viruses cause hepatitis, meningitis, myocarditis, pericarditis, and acute respiratory disease. Three clinical types of infection of the oral region that have been described are usually caused by group A coxsackieviruses: herpangina, HFMD, and acute lymphonodular pharyngitis.

Herpangina

Herpangina is a systemic infection, common in childhood, that causes fever and sore throat usually lasting 2 days, followed by the appearance of lesions in the oropharynx. These are numerous small vesicles, 1–2 mm in diameter, found typically in the tonsillar pillars or fauces, uvula, palate, and tongue (Fig. 26.9). Unlike herpetic gingivostomatitis, the gingiva is not usually affected. Additionally, contrasting with recurrent herpes simplex infections that occur after exposure to triggers, herpangina frequently occurs in epidemics that have their highest incidence from June to October. The oral ulcerations will last for 3 or 4 days and typically do not recur. Coxsackievirus A4 has been shown to cause the majority of cases of herpangina, but types A1–A10 as well as types A16–A22 have also been implicated.

Herpangina is characterized by a 2- to 10-day incubation period, followed by generalized symptoms of chills, fever, and anorexia. The fever and other symptoms are generally milder than those experienced with primary HSV infection. The patient complains of sore throat, dysphagia, and occasionally sore mouth. Lesions start as punctuate macules, which in hours progress into papules and vesicles involving the posterior pharynx, tonsils, faucial pillars, and soft palate. Within 24–48 hours, the vesicles rupture, forming small ulcers. The disease is usually mild and heals without treatment in 1 week. Herpangina could be difficult to distinguish from herpes simplex infection. However, there are some important differences that help the clinician to establish the correct diagnosis: herpangina occurs in epidemics, it is milder than the infection for HSV, it is not usually associated with gingival lesions, and it produces lesions that are smaller than those of HSV [25]. The diagnosis of herpangina is based on the clinical presentation; a smear taken from the base of a fresh vesicle does not show ballooning degeneration or multinucleated giant cells. Treatment is supportive, including hydration and topical anesthesia. Specific antiviral treatment is not yet available.



Figure 26.9 Herpangina. Small ulcers in the soft palate.

Hand-Foot-and-Mouth Disease

This clinical entity was first reported by Robinson and Rhodes in 1958 [75]. They reported an exanthema with associated fever and oral lesions, noted in over 60 persons in June and July of 1957 in Toronto. Coxsackie virus A16 was isolated from two thirds of 27 stool specimens studied. HFMD is highly contagious, spread by oral-oral and fecal-oral routes. It typically affects children under 10 years old. Vertical spread from mother to fetus also occurs. In temperate climates, as in the USA, infection is more common during late summer and early fall [76].

HFMD is caused by enteroviruses, members of the picornavirus family (single-stranded RNA, unenveloped), and is most commonly associated with coxsackievirus A16 or enterovirus 71 [76]. Sporadic cases associated with coxsackievirus A 4–7, A9, A10, B1–3, and B5 have also been reported. Infections are usually sporadic, but epidemics regularly occur. Initial viral invasion is in the oral mucosa and ileal mucosa and is followed by rapid spread to regional lymph nodes. Viremia follows and virus spreads to the oral mucosa and skin. By day 7 after infection, serum antibody levels increase, and the virus disappears [77]. After an incubation period of 3–6 days, a brief 12–36 hour prodrome of low grade fever, malaise, cough, anorexia, abdominal pain, and sore mouth occurs. Painful ulcerative lesions occur anywhere in the oral cavity, but

are most commonly found on the hard palate, tongue, and buccal mucosa. Oral lesions resolve without treatment in 5–7 days. The exanthema, characterized by 2–3 mm erythematous macules or papules with a central gray vesicle, usually appears shortly after oral lesions, with the hands more commonly involved than the feet. The sides of the fingers and dorsal surfaces are more often involved than palms and soles. Lesions appear elliptical, with the long axis running parallel to skin lines, and may be asymptomatic or painful. They crust and gradually disappear over 5–10 days without scarring.

Although most cases resolve with no long-term complications, first trimester infection may lead to spontaneous abortion or intrauterine growth retardation. Other complications have been reported, including myocarditis, meningoencephalitis, pulmonary edema, and even death [78]. Recent epidemics of HFMD with enterovirus 71 have been associated with neurologic complications [79]. The most critical early sign of enterovirus 71 infection with central nervous system involvement was myoclonus with sleep disturbance [80]. Treatment of HFMD is symptomatic, aimed at providing relief of painful oral lesions with agents such as viscous lidocaine, dyclonine solution, diphenhydramine, magnesium hydroxide and sucralfate.

Acute Lymphonodular Pharyngitis

Acute lymphonodular pharyngitis is a variant of herpangina caused by coxsackievirus A10. The distribution pattern is similar to herpangina. However, the yellow-white nodules do not progress to vesicles or ulcers. The disease is self-limiting, and only supportive care is necessary.

Conclusion

A number of viral diseases present with oral manifestations, e.g., herpesviruses, papillomaviruses and coxsackieviruses. These manifestations include certain malignancies, especially with some papillomavirus infections. It is important to diagnose these lesions and initiate therapy early in the course.

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27 Ocular Manifestations of Viral Diseases

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Introduction

Viruses are obligate intracellular parasites that may damage tissue by direct invasion and proliferation or as a consequence of the host immune response. Many viruses, particularly the herpes viruses, have a predilection for retinal tissue, thus having enormous effects on visual function. Patients who are immunocompromised as a result of medication or disease (e.g., AIDS) are at greatest risk for retinal infection. Fortunately, advances in diagnosis and treatment of these diseases have substantially improved the outcome in many patients.

Virology

The term "herpes" stems from the Greek word "herpein," which means "to spread." Herpesviruses are widely disseminated in nature and can be found in nearly all animal species. About 100 different herpesviruses have been described so far, and eight of them are found in humans: herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), varicella-zoster virus (VZV), human cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesviruses 6, 7, and 8 (HHV-6, HHV-7, HHV-8) [1–3].

All herpesviruses share certain biologic properties. They all have a large number of enzymes that are involved in nucleic acid metabolism, DNA synthesis, and possibly the processing of proteins. The synthesis of DNA and the assembly of the capsid take place in the nucleus. The production of infectious virus particles in the cytoplasm leads to the destruction of the infected cell. All known herpesviruses establish latent or clinically silent infection in their natural hosts [3].

The status of latency is restricted to a small range of susceptible cells that vary among the different members of the herpesvirus family. During latency, the herpesvirus genomes form closed circular molecules, and only a small number of viral proteins are expressed, with no mature virus produced. After reactivation from latency, infectious viruses are transported to peripheral tissues, for example, by axonal transport. Whether reactivation takes a symptomatic or an asymptomatic course depends on the immune response of the host [3,4].

The family of Herpesviridae can be divided into three subfamilies according to differences in host range, reproduction rate, and cell tropism. HSV-1, HSV-2, and VZV belong to the subfamily of alpha herpesviruses; CMV, HHV-6 and HHV-7 to the beta herpesviruses; EBV and HHV-8 are in the family of gamma herpesviruses [3]. Table 27.1 summarizes the clinical characteristics of herpesviruses that are infectious for humans.

The two types of herpes simplex viruses described are HSV-1 and HSV-2. HSV-1 and HSV-2 are transmitted during close personal contact. HSV-1 causes labial infections (e.g., via transmission from mother to child), and HSV-2 is normally transmitted via sexual contact. The primary infection with HSV-1 is mostly asymptomatic, but may occur as gingivostomatitis or, less commonly, as conjunctivitis or keratitis. In most cases, infections with HSV-2 are acquired after infections with HSV-1 and can therefore be regarded as reinfections. This infection by HSV-2 remains asymptomatic in most cases because of the partial specific immune response already present. By contrast, primary infections with HSV-2 without previous contact with HSV-1 may cause apparent local and systemic symptoms.

The primary infection with HSV typically involves the mucosa. The virus replicates intracellularly and infects other cells in the mucosa. Lymphatic-hematogenous spread is rarely found. The virus penetrates the nerve ends in the mucosa and is transported retrograde via the axon into sensory ganglia. After a period of productive infection, replication decreases and a persistent and latent infection is established. A wide range of factors, e.g., exposure to ultraviolet (UV) light, fever, and stress, can cause a new period of viral replication, i.e., reactivation. This new period of viral replication can be asymptomatic or cause symptoms (e.g., orolabial lesions or the various ocular manifestations).

VZV causes two distinct diseases. Varicella, or chickenpox, is seen in primary infection. It is usually a mild, self-limited infection in children. Zoster occurs after reactivation of the persistent latent VZV infection in sensory ganglia.

Typical clinical pictures of intraocular inflammation induced by alpha herpesviruses include endothelitis, trabeculitis, iridocyclitis, acute retinal necrosis (ARN), and variants of necrotizing herpes retinopathy [5]. The clinical pictures of the various forms of intraocular inflammation caused by alpha herpesviruses share many similarities, therefore, in individual cases, it is often not possible to differentiate HSV from VZV. Nevertheless, the case history and clinical signs can sometimes point to the causative virus. In a few patients, HSV-1 forms typical blister-like skin eruptions [6,7] or zoster dermatitis may be present [8].

Varicella-zoster Retinitis

Varicella-zoster virus is the cause of varicella (chickenpox), an exanthematous rash that usually occurs in children. As with other herpesviruses, VZV establishes latency after primary infection; subsequent reaction of the virus in the sensory ganglionic neurons results in the painful, vesicular, unilateral dermatomal rash known as herpes zoster (shingles). Herpes zoster most commonly occurs in immunocompetent patients, but patients immunocompromised by malignancy, chemotherapy, or HIV infection are at increased risk. In our series of 1286 cases with AIDS, one of the most common presentations in young patients was herpes zoster ophthalmicus, seen in 7% of cases [9]. Involvement of the ophthalmic branch of the trigeminal nerve is second in frequency only to thoracic zoster [10]. Herpes zoster ophthalmicus is characterized by tender pre-auricular or submandibular lymphadenopathy with dermatomal vesicles (Figs. 27.1 and 27.2) and conjunctivitis; keratitis, uveitis, glaucoma, cranial nerve palsies, scleritis, and anterior segment ischemia can occur [11]. Treatment with oral acyclovir, valacyclovir, or famciclovir reduces viral shedding and

Table 27.1 Some Important Characteristics of Herpesviruses that are Infectious in Humans

Herpesvirus	Subfamily[1]	Site of latency	Primary infection	Symptomatic reactivation
Human herpesvirus 1 HSV-1	α	Sensory ganglia	Gingivostomatitis, keratoconjunctivitis, skin infection, genital disease, encephalitis	Herpes labialis, keratoconjunctivitis, skin infection, encephalitis
Human herpesvirus 2 HSV-2	α	Sensory ganglia	Genital disease, gingivostomatitis, encephalitis, neonatal infection	Genital disease, skin infection
Human herpesvirus 3 VZV	α	Sensory ganglia	Varicella	Zoster
Human herpesvirus 4 EBV	γ	Oropharyngeal epithelial sites, B lymphocytes, lymphoid tissues	Mononucleosis, hepatitis	Cofactor for "post-transplant" lymphomas
Human herpesvirus 5 CMV	β	Lymphoreticular cells, probably kidney and other tissues	Mononucleosis, hepatitis, neonatal infection	Pneumonia, retinitis, colitis
Human herpesvirus 6 HHV-6	β	Peripheral blood leukocytes	Exanthem subitum, lymphadenopathy	Post-transplant complications
Human herpesvirus 1 HHV-7	β		Pityriasis rosea possibly	
Human herpesvirus 1 HHV-8	γ		Kaposi's sarcoma	

the risk of keratitis and uveitis, but does not reduce the incidence, severity, or duration of postherpetic neuralgia [12].

Congenital VZV infection is a rare but devastating disease associated with a high mortality. Systemic features include limb atrophy, cerebral atrophy, seizures, hemiparesis, neuropathic bladder, atrophy of the limbs, bulbar palsies, cicatricial skin lesions, and learning disabilities [13]. Ocular findings may be subtle and include unilateral chorioretinal scars, chorioretinitis, atrophy and hypoplasia of the optic discs, microphthalmos, cataract, and Horner's syndrome [14]. The chorioretinal scars can mimic those seen in congenital toxoplasmosis and syphilis.

Acute Retinal Necrosis

During the past 2 decades, ARN syndrome has been a source of fear, frustration, and fascination for many ophthalmologists. Unfortunately, it is usually a visually devastating condition for the patient.

Definition

In 1971, Urayama and co-workers [15] first reported six cases of an apparently new syndrome characterized by acute necrotizing retinitis, vitreitis, retinal arteritis, choroiditis, and late-onset rhegmatogenous retinal detachment. Young and Bird [16], describing two similar cases in 1978, gave the syndrome the acronym BARN (bilateral acute necrosis syndrome). With the subsequent recognition of unilateral and asynchronous bilateral cases, the disease is simply known as acute retinal necrosis syndrome or ARN.

Patient Population

ARN syndrome occurs most commonly in otherwise healthy patients of either sex and of any age; in general, patients are not



Figure 27.1 Herpes zoster ophthalmicus.



Figure 27.2 Herpes zoster ophthalmicus.

immunocompromised or systemically ill. However, ARN patients may demonstrate subclinical immune dysfunction. In one review of 216 patients with ARN, impaired cellular immunity was noted in 16% [17]. Many authorities have broadened the diagnostic criteria to include immunocompromised hosts [18–21]. ARN was first described in immunocompromised patients in 1985 [22]; a case series described 26 cases of ARN in AIDS patients, noting a generally fulminant course. The cause of the retinitis in these immunocompromised patients may be particularly diverse or multifactorial. It is the evolution of clinical signs and symptoms, and not the specific pathogen or immune status of the patient, that serves as the sole basis by which ARN syndrome has been defined. Specific HLA haplotypes may increase the relative risk of developing ARN syndrome, such as the HLA-DQw7 antigen and phenotype Bw62, DR4 in Caucasian patients in the USA [23] and HLA-Aw33, B44, and DRw6 in Japanese patients [24].

Etiology

Considerable evidence points to one or more members of the herpesvirus family in the etiology of ARN syndrome. Varicella-zoster virus was isolated in tissue culture from the vitreous of a blind eye enucleated early in the course of the disease, and specific varicella-zoster antigens were identified in retinal tissue by immunocytologic staining [25]. Varicella-zoster virus was identified by electron microscopy in necrotic retinal tissue in two other cases of ARN [26]. Varicella-zoster DNA in intraocular fluids of ARN cases has been confirmed by polymerase chain reaction (PCR), and Winner quotients of paired serum to intraocular fluid antibody levels have been diagnostic of varicella zoster in numerous cases. Varicella-zoster antigens have been demonstrated in vitreous aspirates of patients with ARN syndrome [27].

Restriction endonuclease patterns of the ARN virus isolate were similar to those of typical varicella-zoster strains and showed similar sensitivities to a panel of antiviral drugs. Thus, these data do not support the notion that the ARN virus represents a mutant strain of varicella-zoster virus with significant alterations in either the viral thymidine kinase or DNA polymerase genes. Therefore, it remains enigmatic why an "old virus" should give rise to a "new" syndrome.

Some reports have suggested that other members of the herpesvirus family may cause ARN. In one study of a case of ARN, CMV was cultured and CMV antigens were demonstrated in retinal tissue, but megalic cells or electron-dense cytoplasmic inclusions, which have uniformly typified CMV infection of the retina, were not identified. In another case, the PCR yielded positive results for CMV in one immunocompetent individual whose vitreous was negative for varicella zoster and HSV types 1 and 2. Other studies have implicated HSV because of concurrent herpes simplex skin lesions, the detection of herpes simplex antigens on vitreous cells, the presence of immune complexes containing herpes simplex antigens in aqueous or serum, the documentation of intraocular antibody synthesis directed against HSV, diagnostic changes in serum antibody levels to herpes simplex, PCR detection of herpes simplex, or culture of herpes simplex from vitreous humor. Several cases have been described of ARN caused by reactivation of HSV type 2.

Clinical Features

The disease may affect one or both eyes; most cases begin with unilateral disease [28]. The second eye becomes involved in almost one third of cases, usually within 1–6 weeks; however, disease in the second eye has been reported to occur more than 10 years after disease in the first eye [29]. Most patients have a history of pain, redness, floaters, and blurred vision. An anterior uveitis with or without keratic precipitates often occurs early in the disease, and although a plasmoid aqueous has been described in these patients, hypopyon is rare. Occasionally, there is an associated herpes infection at another site [30,31], but most patients are healthy, immunocompetent, and without systemic symptoms.

With the onset of vitritis, patients report floaters and diminished visual acuity. Vitritis tends to worsen as cellular immunity to the virus occurs, and the infiltrating inflammatory cells are predominantly lymphocytes and plasma cells [32]. The earliest retinal lesions are small, patchy, white-yellow areas that tend to enlarge, increase in number, and coalesce over time. The lesions usually start in the midperiphery (Fig. 27.3); occasionally they occur in the posterior pole, but do not follow the architecture of the retinal vessels. After several weeks, the lesions begin to resolve with areas of clearing forming a Swiss cheese pattern. At this time, perturbation of the retinal pigment epithelium (RPE) also develops. Retinal vasculitis is another manifestation of ARN. Patients often demonstrate a severe retinal arteritis with vitritis (Fig. 27.4). Capillary

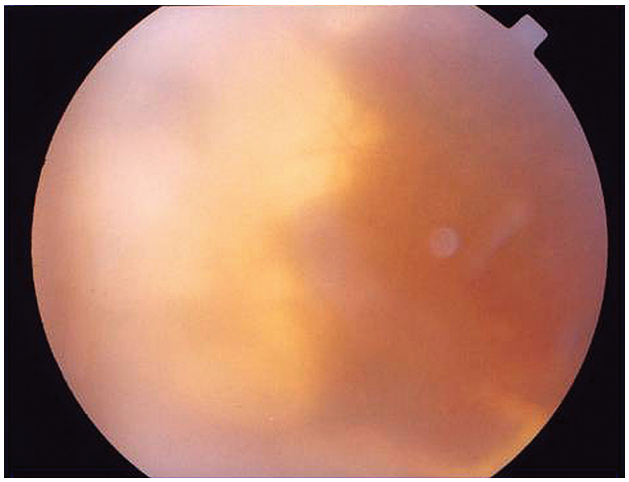


Figure 27.3 Acute retinal necrosis with peripheral necrotic retina.

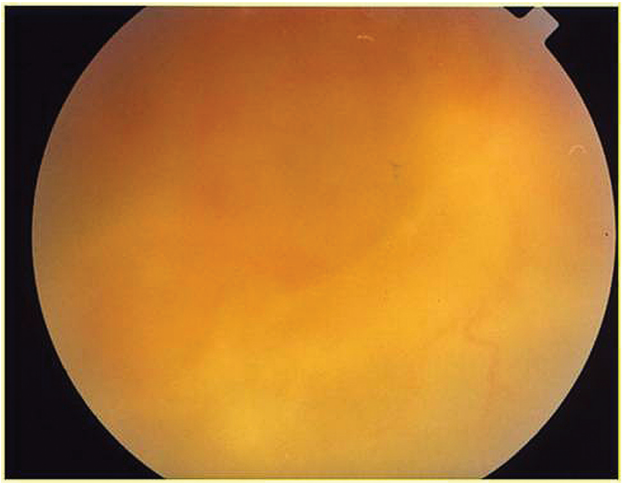


Figure 27.4 Acute retinal necrosis with vitritis.

nonperfusion can be documented on fluorescein angiography, and periphlebitis and venous occlusions have been described less commonly. Retinal hemorrhage can occur, especially in cases of venous occlusive disease. In contrast to other venous occlusive diseases, neovascularization of the iris or retina is uncommon, but has been reported [33,34]. The choroidal vasculature is also involved in this disease, and fluorescein angiography has shown areas of early hypofluorescence and late staining consistent with ischemia-induced inflammatory changes.

Optic neuropathy also occurs in patients with ARN. Disc edema is a common finding early in the course of the disease. Optic nerve involvement should be suspected in patients with an afferent pupillary defect and severe visual loss with few retinal findings.

The acute inflammatory disease tends to resolve with or without therapy in several months. In untreated patients, the acute phase of the disease usually resolves in 2–3 months, and this may be shortened by 4–6 weeks with acyclovir therapy, although this has not been shown in a well-controlled, masked, randomized clinical trial. The course of the disease can also be predicted by the number of hours of initial retinal involvement. Unfortunately, within the next several months, tractional and rhegmatogenous retinal detachments with many large breaks develop in up to 86% of patients [35]. Despite control of the active viral replication in the retina, cellular infiltration into the vitreous and the formation of vitreal membranes composed of RPE and fibroblasts develop and contribute to the tearing and detachment of an already thinned retina [36].

The Executive Committee of the American Uveitis Society published a set of standard diagnostic criteria for ARN syndrome [37] (Table 27.2). The criteria state that the designation of ARN syndrome should be based solely on clinical appearance and the course of infection.

Differential Diagnosis

Because ARN can often begin as an anterior uveitis, examination of the peripheral retina is important in all patients with a new onset of anterior inflammation. The differential diagnosis of ARN is listed in Box 1. In general, only Behcet's disease and endophthalmitis mimic the rapid progression and severity of ARN. The lesions of Behcet's disease rarely begin as uniformly in the periphery and are often associated with systemic symptoms and signs, such as arthritis, mouth and genital ulcers, and skin lesions. A vitrectomy may be needed to rule out endophthalmitis.

Box 1
Differential diagnosis of acute retinal necrosis syndrome
Exogenous bacterial endophthalmitis
Fungal endophthalmitis
Behcet's disease
Pars planitis
Toxoplasmosis
Syphilis
Cytomegalovirus retinitis
Sarcoidosis
Intraocular lymphoma
Progressive outer retinal necrosis (PORN) syndrome

Table 27.2 American Uveitis Society Criteria for Diagnosis of Acute Retinal Necrosis Syndrome

Required clinical criteria	Supporting clinical criteria
One or more foci of retinal necrosis with discrete borders, located in the peripheral retina	Optic neuropathy atrophy
Rapid progression of disease in the absence of therapy	Scleritis
Circumferential spread of disease	Pain
Evidence of occlusive vasculopathy and arteriolar involvement	
A prominent inflammatory reaction in the vitreous	

Lab Studies
ARN is a clinical diagnosis and laboratory tests may not be conclusive.
Viral titers may be helpful.
– Herpes simplex virus 1
– Herpes simplex virus 2
– Varicella-zoster virus
For baseline
– Complete blood count
– Renal function
– Liver function

Imaging Studies
Fluorescein angiography
Not diagnostic
Early decrease in choroidal perfusion
May show delayed arterial filling
Hypofluorescence in areas of active lesions
Ocular ultrasound
Can rule out retinal detachment in the presence of media opacity
May show enlarged optic nerve sheath
Computed tomography scan may show optic nerve sheath enlargement.
Magnetic resonance imaging may demonstrate concurrent lesions of the optic tract and the lateral geniculate body suggesting axonal spread.

Procedures
Lumbar puncture may show cerebrospinal fluid pleocytosis.

Staging
Stage 1: Necrotizing retinitis
Stage 1a: Discrete areas of peripheral retinitis
Stage 1b: Confluent areas of peripheral retinitis, papillitis, macular edema
Stage 2: Vitreous opacification or organization
Stage 3: Regression of retinal necrosis, secondary pigmentation of lesion with condensation of vitreous base
Stage 4: Retinal detachment

Stage 4a: Acute retinal tears or detachment with traction or proliferative vitreoretinopathy
Stage 4b: Chronic retinal detachment

Therapy

Many patients appear to benefit from treatment with acyclovir. Acyclovir has good activity against herpes simplex virus and, at slightly higher concentrations, is effective against herpes zoster. Although acyclovir is not as good a drug as ganciclovir or foscarnet for treating CMV infection, inasmuch as CMV is rarely a cause of ARN and acyclovir is an easier and a safer drug, acyclovir is the best initial therapy for the disease [38]. Our current therapeutic regimen is to treat patients with newly diagnosed ARN with a 10–14 day course of intravenously administered acyclovir, 500 mg/m^2 every 8 hours. Oral acyclovir, 800 mg five times a day, is then continued for an additional 6 weeks. The goal of therapy is to hasten the resolution of disease in the infected eye and to prevent contralateral spread. Severe side effects of acyclovir are relatively rare. A reversible rise in the serum creatinine level and elevation in liver function test results may occur. The most commonly reported side effects include nausea, vomiting, and headache, but most of these occur in fewer than 3% of patients. Recently, treatment with oral valganciclovir in doses of up to 1 g/day for 3 weeks has shown encouraging results.

Patients with severe and progressive disease despite acyclovir therapy may be treated with ganciclovir or foscarnet. Intravitreal ganciclovir, foscarnet, or cidofovir may also be given as a supplemental therapy. In addition, systemic corticosteroids, such as prednisone 0.5–1.0 mg/kg, can be added after the patient has received 24–48 hours of intravenous acyclovir. Steroids can be slowly tapered based on the amount of vitritis. Because of the extensive retinal arteritis and development of retinal vascular occlusions, some have suggested aspirin therapy [39], but again this therapy has not been scrutinized in a clinical trial.

Retinal detachment (RD) and optic neuropathy remain the causes of severe visual loss in this disease. Laser photocoagulation to demarcate a zone between involved and uninvolved retina has been tried as a prophylactic therapy to prevent retinal detachment. Others have suggested prophylactic vitrectomy, scleral buckling, and endolaser for eyes at high risk for detachment, but there are little data to support this therapy.

Clearly, surgery is warranted to repair retinal detachments in patients with ARN, although these detachments are difficult to repair and proliferative vitreoretinopathy is common [35]. Vitrectomy, fluid-gas exchange, and endolaser have been suggested for cases of complicated detachments [35]. Silicone oil is the usual choice due to the multiple necrotic/atrophic retinal holes (Swiss cheese appearance) (Fig. 27.5). Less well studied is the effect of therapy on optic nerve disease. Optic nerve fenestration and corticosteroids have been used for treating optic neuropathy in ARN, but no well-controlled data are available to support the effectiveness of these therapeutic interventions. With the discovery of the viral etiology of ARN, specific therapy has been employed for the treatment of this disease. Nevertheless, many questions about the disease remain. We still do not know why certain individuals are more susceptible to developing the disease, because ARN is relatively rare, but herpesvirus infection is quite common. Finally, although acyclovir and corticosteroids are used to treat patients with ARN, there are still no randomized, masked, clinical trials definitively showing the benefits of therapy.

Progressive Outer Retinal Necrosis

During the last several years, a syndrome characterized by rapid PORN has been described in immunocompromised patients. This syndrome seems to be different from the other cases of ARN in immunocompromised patients and carries an extremely poor prognosis. Unfortunately, it is thought to be the second most frequent opportunistic retinal infection in AIDS patients in North America [40]. In India, in our series of 1286 cases with AIDS, PORN was seen in 1.1% of cases [9].

Diagnosis

PORN is thought to be a variant of a necrotizing herpetic retinopathy in immunocompromised patients. The syndrome was described by Forster and colleagues in 1990 [41]. Margolis and coworkers [42] then described varicella-zoster virus retinitis in patients with AIDS and also noted a rapidly progressive necrotizing retinitis with early patchy choroidal and deep retinal lesions, which progressed relentlessly until patients were left with atrophic and necrotic retinas and pale optic nerves (Fig. 27.6). Unlike typical ARN, there is little or no



Figure 27.5 Silicone-oil filled-eye after RD surgery in ARN.

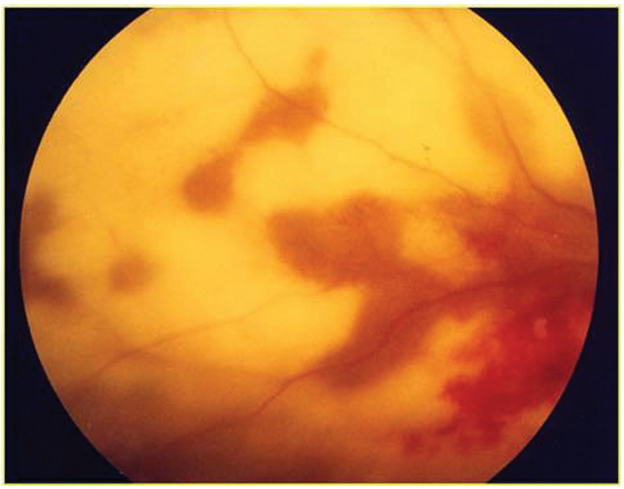


Figure 27.6 Progressive outer retinal necrosis.

Table 27.3 Differentiating Features of Three Types of Viral Retinitis in Acquired Immunodeficiency Syndrome

	Acute retinal necrosis	Progressive outer retinal necrosis	Cytomegalovirus retinitis
Immune status	Healthy	Immunosuppressed	Immunosuppressed
Laterality	Bilateral 30-80%	Bilateral 71%	Bilateral 30-50%
Visual loss	Severe	Early loss of vision	Only if it involves macula
Anterior uveitis	Mild to moderate	Mild	Mild
Vitreous reaction	Significant vitritis	Minimal/no vitritis	Minimum/no vitritis
Retinal involvement	Full thickness	Deep outer retinal involvement	Full thickness involvement with granular border
Classic appearance	Late Swiss-cheese	Cracked mud	Pizza-pie
Vasculitis	Common	Uncommon	Seen but not common
Retinal hemorrhages	Common	Uncommon	Common in active lesion
Retinal detachment	Common	Common	Less common
Progression	Rapid	Rapid	Slow

vasculitis and less vitritis, and in many cases, posterior pole involvement occurs early in the course of disease (Table 27.3).

Engstrom and colleagues [40] reviewed the cases of 38 AIDS patients with PORN. A definite history of cutaneous herpes zoster was documented in 22 of 33 (67%) patients. The median CD4 lymphocyte count in these patients was 21/mm^3 with a range of 0–130/mm^3. Most patients had a unilateral decrease in visual acuity, although about one fourth of the patients had a presenting complaint of decreased peripheral vision or constriction of visual field. Seven patients (11%) were symptom-free at the time of diagnosis. The median visual acuity at presentation was 20/30, but some patients had no light perception (NLP) vision at presentation. Anterior chamber and vitreous inflammation were minimal or absent in all patients. Multifocal, deep retinal lesions were typically found in the periphery; however, macular lesions were noted in 21 eyes (32%) at the time of diagnosis. Optic nerve involvement was present in 11 of 65 eyes (17%), and an afferent pupillary defect was noted in 11 of 29 patients (38%). Characteristic of this syndrome, the lesions rapidly progressed to confluence. Interestingly, although the syndrome is described as involving the outer retina, Rao has presented pathologic evidence that the disease causes substantial destruction of the inner retina.

Differential diagnosis

The differential diagnosis for PORN is similar to that of ARN, and a comparison of their diagnostic criteria is noted in Table 27.3. It is important to differentiate these two disorders. Retinal lesions in PORN appear to predominantly involve the deep retina, whereas lesions in ARN appear full-thickness. Posterior retinal lesions are more common in PORN, whereas anterior chamber inflammation and dense vitritis are characteristic of ARN but rare in PORN. Similarly, vascular inflammation is also rare in PORN, but common in ARN. Finally, lesions progress rapidly to confluence despite therapy in PORN, but are usually controlled with acyclovir therapy in ARN.

Therapy

High-dose intravenous acyclovir at a dosage of 10 mg/kg every 8 hours for 2 weeks has also been used with inconsistent success. Others have reported that initial intravenous antiviral therapy appeared to reduce disease activity in 17 of 32 eyes (53%), but final visual outcome was not altered by therapy (40). In this study, final visual acuity was NLP in 67% of eyes within 4 weeks after diagnosis. Complications of the disorder included RD in 70% of eyes, despite prophylactic laser retinopexy in some eyes. Unfortunately, the number of cases with this syndrome appears to be increasing, making the search of effective therapy critical.

Cytomegalovirus Infections of the Retina

Definition

CMV belongs to the group of herpesviruses. It is a ubiquitous pathogen in the general population, but rarely causes clinically apparent disease in an immunocompetent individual. In immunosuppressed patients, CMV can be pathogenic and cause gastrointestinal, central nervous system (CNS), and pulmonary disease. The most common manifestation, however, is CMV retinitis, which is the most frequent cause of blindness in patients with AIDS.

History

"Cytomegalia" was described in 1921 by Goodpasture [43] as the histopathologic finding of large mononuclear inclusions in various organs of a child. In the 1950s, the virus responsible for this disease was visualized by electron microscopy [44], isolated, and grown in culture [45].

CMV eye disease was described in a newborn child in 1947 [46] and in an adult under chemotherapy in 1964 [47]. In the pre-AIDS era, CMV retinitis was a rare disease, found in adults under medical immunosuppression. In the 1980s with the AIDS pandemic, CMV retinitis became the most common form of posterior uveitis in urban populations [48]. With the introduction of highly active antiretroviral therapy (HAART) in AIDS patients, the incidence of CMV retinitis has declined significantly [49,50].

Epidemiology

United States**:** CMV is ubiquitous, infecting 50–80% of the adult population. Clinically evident disease is found almost exclusively in immunosuppressed individuals. Prior to HAART, CMV occurred in 25–40% of all AIDS patients and was the most common opportunistic infection in AIDS patients with a CD4 count below 50 cells/ml. While HAART has decreased the incidence of CMV retinitis by 55–83%, the decline in AIDS-related mortality has led to an increase in the number of patients with CMV disease. CMV retinitis remains a leading cause of visual loss in patients

with AIDS and is increasing in organ transplant recipients as the number of those procedures performed each year increases.

International: The frequency of disease in other developed countries is equivalent. The incidence of CMV in developing countries mirrors the spread of the HIV virus and the availability of antiretroviral medications. In our series of 1286 cases of Indian origin, it was the most common opportunistic infection involving the posterior segment of the eye in cases with AIDS [9], with CMV retinitis being seen in 24% of 1286 cases who are taking HAART and 39% in those cases not using HAART.

Sex. Although the incidence of CMV retinitis is the same among men and women, the prevalence is higher in men than in women because of the higher prevalence of AIDS in men. The prevalence of CMV retinitis in the heterosexual community has been steadily increasing.

Age. The age of most individuals developing CMV retinitis is 20–50 years.

Pathophysiology, Immunology, Pathology, and Pathogenesis

After primary infection, CMV is disseminated by the blood stream, and replication can be found in multiple organ tissues, in polymorphonuclear leukocytes, monocytes, and T lymphocytes. Despite the fact that primary CMV infection is a systemic infection, healthy individuals commonly are without apparent symptoms. This suggests that the CMV-specific immune response must be protective. Both the humoral and cellular immune response, especially the T-cell response, contributes to this observation [51]. After primary infection, CMV remains in its host, establishing a latent infection typical for all herpesviruses. The viruses persist in latency in a large variety of tissues, in lymphoreticular cells, and in the secretory glands [52]. In patients with AIDS, CMV infection is one of the most important opportunistic infections. Of these patients, 90% develop CMV infections [53], generally representing reactivation from latency.

In most cases, the retina is infected via hematogenous spread during an episode of systemic CMV replication. An infection via the optic nerve by extension from the CNS or CMV papillitis is less common. There is experimental evidence that an impaired antiviral T-cell response is of particular importance for the development of retinitis [54,55]. The microangiopathy caused by HIV infection of capillary endothelial cells probably facilitates the passage of CMV-infected cells from the blood stream to the retina. The higher incidence of CMV retinitis in patients with AIDS in comparison to other patients under immunosuppression may be facilitated by this endothelial tropism [56].

Histopathologic examinations have revealed that CMV infects all layers of the retina, including the pigmented epithelium, but without choroidal involvement. It has been demonstrated that HIV accelerates the CMV replication in coinfected retinal cells. Nerve fiber infarcts, retinal hemorrhages, opacifications, and perivascular sheathing can be found [57].

Clinical Characteristics

CMV retinitis commonly begins in the peripheral retina. Symptoms of the early disease may therefore be minimal or initially even absent. Blurring and floaters may be experienced, as well as nonspecific visual disturbances. Symptomatic scotomas are usually noticed only if more central parts of the retina are involved. In patients at risk with CD4+ cells below 50 cells/mm^3 or if other organs have CMV disease, ophthalmologic screening with dilated pupils every 3–4 months is recommended [58]. It should be noted, however, that CMV retinitis may occur in patients under HAART who have CD4 counts of more than 100 cells/mm^3 [59]. Patients should be educated to pay attention to the symptoms and seek ophthalmologic care after the onset of visual disturbances. In selected motivated patients, entoptic perimetry can be helpful as a screening test for CMV retinitis [60]. In both forms, there are no sharply defined edges of the involved retina.

There are three clinical forms of CMV retinitis. The classical form (pizza pie retinopathy or cottage cheese with catsup) is characterized by confluent retinal necrosis with hemorrhage that develops mostly in the peripheral retina (Figs. 27.7 and 27.8). The advancing edge of these lesions is usually very sharp and spreads contiguously. Typically, over several weeks, untreated lesions progress to full-thickness necrosis with resultant retinal gliosis (Fig. 27.9) and pigment epithelial atrophy. Patients often have loss of visual field or visual acuity and scotoma. The affected area commonly has irregular borders and is surrounded by satellite

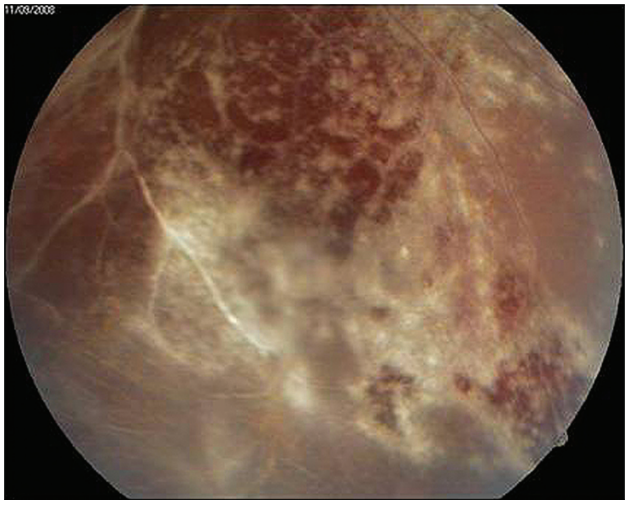


Figure 27.7 Classic CMV retinitis.

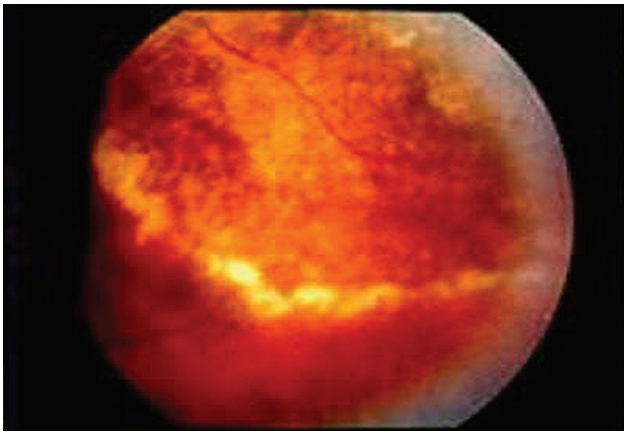


Figure 27.8 Classic CMV retinitis.



Figure 27.9 Gliosis after healed CMV retinitis.

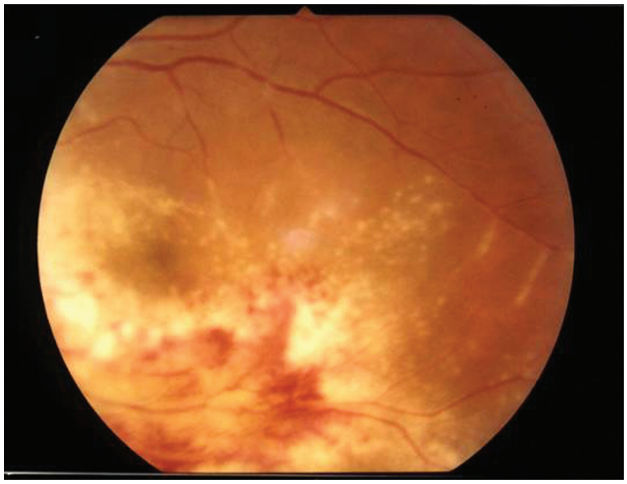


Figure 27.10 CMV retinitis of posterior pole.

infiltrates. The optic disc can be infiltrated as retinitis progresses toward the posterior pole (Fig. 27.10). Primary involvement of the optic disc is less common (Fig. 27.11). There is mostly a low-grade vitritis. Only a mild anterior chamber inflammatory reaction may be present. Fulminant courses with rapid progression rarely occur. Progression of the retinal infiltration without therapy is usually slow, at about 0.2 mm per week, leading to complete destruction of the entire retina in about 3–6 months [61]. The clinical course is probably dependent on the immune status of the patient. Complete necrosis of the involved retina develops and atrophic zones with stippling of the underlying RPE are usually left behind in the center of the lesion as the active lesions resolve. Only the active edges are edematous and opaque. By contrast, the indolent form is recognized as a granular lesion in the peripheral retina, often with little or no hemorrhage (Fig. 27.12). Patients may notice floaters, or they may be asymptomatic. A third uncommon presentation is frosted branch angiitis (Figs. 27.13 and 27.14). Because approximately 15% of patients with active CMV retinitis are asymptomatic, routine screening with dilated indirect ophthalmoscopy has been recommended at 3-month intervals in patients with CD4+ counts less than 50 cells/μl.

CMV retinitis may result in either serous or rhegmatogenous retinal detachment, although the latter is much more common. Rhegmatogenous RD has been reported in 13–29% of patients with CMV retinitis and may occur during the active or healed phase of the disease. However, since the advent of HAART, incidence of RD has decreased by approximately 60–77% in the western world [62]. By contrast, in our series, the incidence of CMV-related RD was found to have increased [9]. This may be due to a higher number of patients taking inappropriate HAART, or people taking HAART have larger areas of healed CMV retinitis that eventually develop necrotic holes leading to detachment (Fig. 27.15).

With anti-CMV treatment, the active lesions also become atrophic and the infiltration at the edges becomes less opaque. Remaining opacities do not necessarily represent active inflammation. If they do not progress, they can be caused by fibrosis or necrotic debris that has not cleared (Fig. 27.16). Progression under maintenance therapy is mostly slow and with only mild opacification

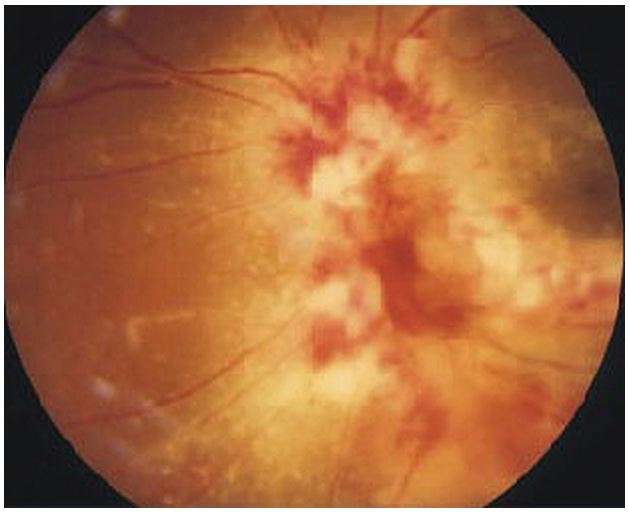


Figure 27.11 CMV retinitis of optic disc.

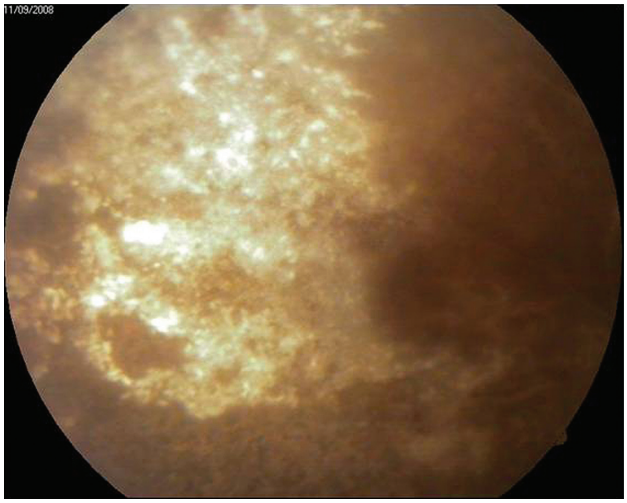


Figure 27.12 Granular variety of CMV retinitis.

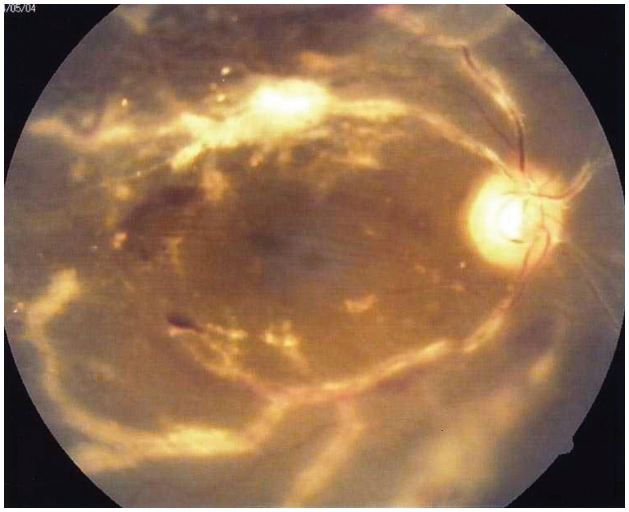


Figure 27.13 Frosted branch angiitis.

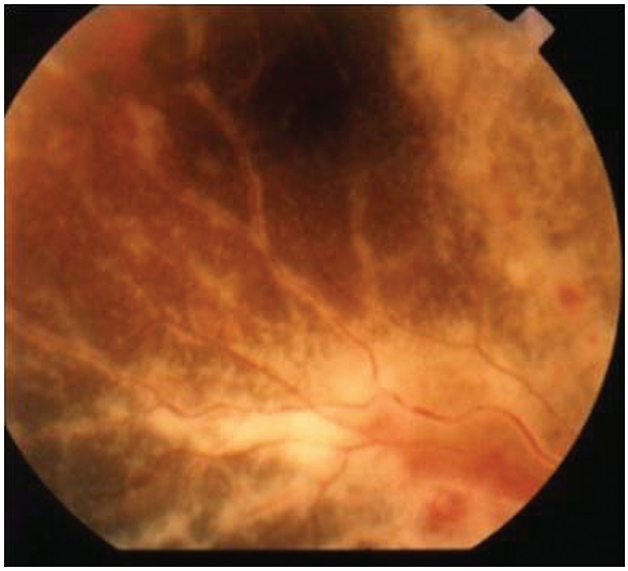


Figure 27.14 Frosted branch angiitis.

of the edges of the lesion. Serial photographs are much more sensitive than funduscopy or fundus drawings for the detection of relapsing CMV retinitis. Monthly follow-up of inactive lesions is recommended. Rarely, CMV infections of the retina may present as ARN in immunocompetent [63] and immunocompromised patients [64]. CMV has been detected in selected cases of conjunctivitis, iridocyclitis, or keratitis, but a causal relationship for CMV with ocular diseases other than retinitis is probably very rare.

The advent of potent antiretrovirals has had a profound impact on the ophthalmological manifestations of AIDS patients. As these drugs lead to improved immune function, patients have fewer opportunistic infections. There have been reports of dramatic decreases in the frequency of CMV retinitis in areas where three- and four-drug antiretroviral combination therapies are routinely being used. In addition to decreased incidence, there are improved outcomes in patients with CMV retinitis who received new active antiretroviral therapy in addition to anti-CMV therapy. In many patients with healed CMV retinitis who have responded to HAART, anti-CMV therapy has been discontinued without reactivation of the retinitis.

In our study where combination antiretroviral treatment was given to 12 patients with active CMV retinitis, all anti-CMV medications were omitted once the CD4 cell counts were >100/mm^3 for 3 months [65]. The median CD4 cell count increased from 36.5/mm^3 (range: 3–74/mm^3) at baseline to 175.5/mm^3 (range: 97–410/mm^3) at 3 months. No patient had reactivation of CMV retinitis or development of extraocular CMV during median follow-up of 16.7 months. Although, at present there are no standardized criteria for determining whether immunologic improvement is sufficient to allow withdrawal of therapy, a CD4+ cell count of at least 100 cells/mcL for at least 3–6 months, or a rise of at least 50 cells/mcL has been recommended. Reactivation of CMV retinitis has been reported in patients who discontinue or become intolerant to HAART. When maintenance therapy is discontinued, close observation is required.

Immune Recovery Uveitis

Immune recovery uveitis (IRU) is a noninfectious intraocular inflammation that develops in patients with inactive CMV retinitis

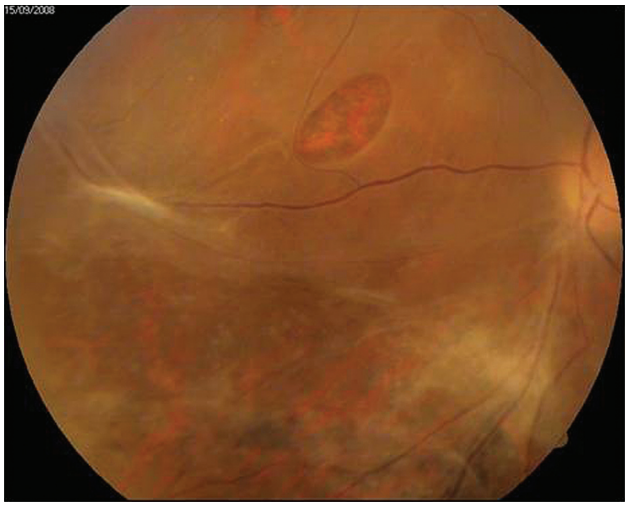


Figure 27.15 Retinal detachment in CMV retinitis with hole.

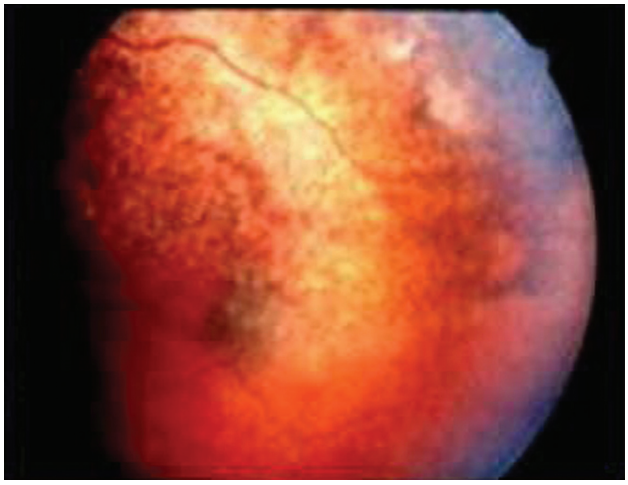


Figure 27.16 Healed CMV retinitis after intravitreal cidofovir injection.

who have had a substantial elevation in CD4+ count with HAART. IRU is the leading cause of new visual loss in persons with AIDS, seen in about 16–63% of HAART responders (9). The severity of the inflammation depends on the degree of immune reconstitution, extent of CMV retinitis, amount of intraocular CMV antigen, and previous treatment. Clinical findings include anterior chamber or vitreous reaction, panuveitis with hypopyon, optic disc and cystoid macular edema, epiretinal membrane formation, cataract, vitreomacular traction syndrome, and proliferative vitreoretinopathy (Fig. 27.17). Treatment with corticosteroids is effective in controlling inflammation and improving vision in some cases. However, surgery may be required in patients with vitreomacular traction syndrome.

Laboratory studies

The CD4 count: The CD4 count is a marker of immune dysfunction in patients infected with HIV. Patients may be asymptomatic with CMV retinitis; therefore, ophthalmic screening frequency is based on CD4 count.

CD4 >50 cells/ml – little risk; screening examination every 6 months if CD4 50–100 cells/ml; screen yearly if CD4 >100 cells/ml.

CD4 <50 cells/ml – up to 35% incidence of CMV retinitis; median time to diagnosis of CMV retinitis is 13 months; screen every 3 months.

The above screening regimen was used prior to the routine use of HAART. The frequency of examinations will probably be modified by assessing viral load, result of CMV DNA capture, CD4 count, and response to treatment.

CMV DNA capture: A PCR test can be qualitative or quantitative. Specimens can be obtained from blood buffy coat, semen, or urine. Detection of CMV in the blood by DNA PCR is most predictive of developing CMV disease. Patients with AIDS who test positive will have more than a 60% chance of developing CMV end-organ disease. Responders to ganciclovir prophylaxis convert to PCR negative with treatment. Compared to nonresponders, survival is increased 2.4 times at 12 months.

Viral load: Increased viral load can be a predictor of development of CMV end-organ disease.



Figure 27.17 Severe vitritis due to immune recovery uveitis.

HIV test: Complete blood count (CBC) with differential is important in evaluation for causes of immunosuppression and in assessment for side effects of ganciclovir use.

Blood urea nitrogen (BUN) and creatinine baseline assessment and serial measurements are used to evaluate for side effects of foscarnet or cidofovir use.

Imaging studies

1. Ultrasound is used for evaluation of retinal detachment, particularly if vitritis obscures adequate fundus visualization
2. Fluorescein angiogram – assessment for areas of ischemia
3. Chest radiography – assessment for concurrent Pneumocystis pneumonia

Other tests

1. Fluorescent treponemal antibody absorption (FTA-ABS) test or microhemagglutination *Treponema pallidum* (MHA-TP) – serologic testing for infection with syphilis, a differential diagnosis for CMV retinitis
2. Serum toxoplasma titer – differential diagnosis for retinitis with vitritis

Differential diagnosis

Toxoplasmic retinochoroiditis
Syphilitic retinochoroiditis
Tuberculous chorioretinitis
Sarcoid chorioretinitis
Bartonella henselae – associated retinitis
Herpes simplex virus retinitis
Varicella-zoster virus retinitis
Cryptococcal chorioretinitis
Candidal chorioretinitis
Chorioretinal metastasis
Intraocular lymphoma
Severe hypertensive or diabetic retinopathy
Retinal vein occlusion
Cotton-wool spots

Treatment

Medical care. An internist or infectious disease specialist coordinates medical care. Ophthalmic assessment is required on a regular basis, with frequency dependent on existence of CMV retinitis and on CD4 count. The immunosuppressed individual requires evaluation for other opportunistic infections and surveillance for side effects of prescribed medications.

Medication. A number of different antiviral medications are available for the treatment of CMV retinitis. Routes of delivery and adverse effect profiles vary significantly, so treatment programs are tailored to individual patients and their response to treatment. Current therapies use an induction dose to halt active disease followed by a lower maintenance dose that must be continued indefinitely unless immune recovery occurs. In recent years, several developments have drastically improved the quality of life for patients with CMV retinitis. Table 27.4 gives an overview of the medications for CMV retinitis (9). HAART therapy, as previously mentioned, has allowed immune recovery that, in turn, allows discontinuation of anti-CMV medication. This often obviates the need for multiple implant procedures or the

Table 27.4 Medications for Cytomegalovirus Retinitis

Medication	Route	Induction dose	Maintenance dose	Adverse effects
Ganciclovir	Intravenous	5 mg/kg bid for 2-3 weeks	5-10 mg/kg/day indefinitely	Neutropenia, anemia, thrombocytopenia, altered liver functions
	Oral	Not used	1 g tid indefinitely	Same as above
	Intravitreal	400-2000 μg twice/week	400-2000 μg once/week	Vitreous hemorrhage, retinal detachment
	Intraocular sustained-release Implant	6 mg pellet inserted surgically through pars-plana region	Replaced every 6-8 months	Vitreous hemorrhage, retinal detachment, cataract, endophthalmitis, extraocular CMV
Foscarnet	Intravenous	90 mg/kg bid for 2-3 weeks	90-120 mg/kg/d indefinitely	elavated creatinine, decreased Ca, Mg, K; tetany, perioral numbness, finger parasthesias
	Intravenous	2400 μg twice/week	2400 μg once/week	Vitreous hemorrhage, retinal detachment
Cidofovir	Intravenous	5 mg/kg weekly for 2 weeks	5 mg/kg every other week	Proteinuria, renal failure, Fanconi's syndrome, neutropenia, uveitis
	Intravenous	15 μg/0.1 ml	15 μg/0.1 ml every week	Uveitis, ocular hypotony, IRU, vitreous hemorrage, retinal detachment
Valganciclovir	Oral	900 mg bid for 3 weeks	900 mg/d	Neutropenia, anemia, thrombocytopenia, gastric disturbances
Fomivirsen	Intravitreal	330 μg on days 1 and 15	330 μg monthly	Vitreous hemorrhage, retinal detachment

bid - twice daily, tid - thrice daily, d - daily, IRU - Immune recovery uveitis

long-term dose-related adverse effects of anti-CMV medications. The following are the pros and cons of catheterless therapies:

Pros:

Less systemic toxicity

Better effect versus CMV in implanted/injected eye

Can use AZT concomitantly

No indwelling catheter

Implant/intravitreal injection is useful if intolerant of systemic ganciclovir or if progression continues despite intravenous treatment

Cons:

Sixty-seven percent developed CMV in the fellow eye versus 0–15% rate in the intravenous treatment group

No systemic effect for CMV organ disease

Intravitreal injection

Topical anesthesia

Short half-life – injection is required twice per week

Increased risk of endophthalmitis, retinal detachment, and vitreous hemorrhage

Complications

Untreated retinitis will progress to blindness from retinal necrosis, optic nerve involvement, or retinal detachment. CMV retinitis can relapse despite ongoing treatment. Drug levels need to be assessed. Reinduction, a change in medication, combination drug therapy, or an ocular implant are alternatives for management.

Drug resistance. Resistance to ganciclovir, foscarnet, or cidofovir can occur, since these drugs are administered long term (62). The chance of this occurring increases with time. In a study of 76 newly diagnosed patients treated for CMV retinitis with intravenous ganciclovir, resistant isolates were obtained from blood or urine samples in 5.4% of patients at 3 months, 11.4% of patients at 6 months, and 27.5% of patients at 9 months. Management of drug resistance leading to reactivation of CMV retinitis or occurrence in the other eye involves combination therapy. Ganciclovir and foscarnet are synergistic and may be combined in intravenous or intravitreal therapy. Cidofovir is also used for cases showing resistance to ganciclovir or foscarnet.

Highly active antiretroviral therapy. This treatment regimen has altered the long-term management of CMV retinitis (65–67). Because the antiviral medications used to treat CMV are virustatic, it was necessary for patients to continue their use for the rest of their lives. The advent of HAART with consequent recovery of immune function allows individuals to discontinue their CMV therapy if the process has resolved adequately with initial antiviral treatment. As long as the CD4 count remains elevated, there is little risk of disease recurrence. Intravenous or oral therapy can be discontinued, or a scheduled implant replacement can be delayed indefinitely. Careful monitoring of both immune status and ophthalmic findings are necessary to prevent retinal damage from an asymptomatic recurrence.

Surgical Care

Individuals with CMV retinitis commonly require surgical intervention, whether for repair of a RD or for intravitreal instillation of ganciclovir by injection or implantation. Various approaches, including pars plana vitrectomy (PPV) with gas or silicone oil tamponade (preferably high viscosity 5000 CS), scleral buckling, and laser demarcation, have been effective in the repair of retinal detachments related to CMV retinitis.

Mortality/Morbidity

CMV retinitis frequently results in considerable loss of visual acuity, and, without treatment, it almost universally leads to blindness. Severe visual loss primarily occurs from the direct spread of retinitis into the posterior pole, affecting central vision, or from RD secondary to multiple retinal breaks in the peripheral, necrotic retina.

Early and aggressive treatment with antiviral medication for both CMV and HIV, combined with improved surgical techniques

for RD repair, has helped to improve the visual outcomes in these patients (62). Untreated CMV leads to progressive visual loss and eventual blindness. RD occurs in up to 29% of cases. Retinitis permanently destroys the retina; lesions change appearance with treatment but do not become smaller. If the CD4 count is less than 100 cells/ml, CMV retinitis will develop in 20–30% of patients over a year, although retinitis typically develops if the CD4 count is reduced below 50 cells/ml. Of these patients, 5–10% develop other systemic infections (e.g., pneumonitis, colitis, esophagitis).

Prognosis

Untreated retinitis will progress to blindness from retinal necrosis, optic nerve involvement, or retinal detachment. Of treated patients, 80–95% will respond, with resolution of intraretinal hemorrhages and white infiltrates. If treatment is discontinued and the individual is still immunocompromised (i.e., CD4 <50), then the retinitis will recur in 100%. Prior to the advent of HAART, 50% of patients would experience recurrence within 6 months despite maintenance therapy. This rate is reduced if the CD4 count is elevated. If a RD occurs, repair with vitrectomy and silicone oil tamponade will result in at least a 70% reattachment rate.

Human Immunodeficiency Virus

Retinal microvasculopathy, also called AIDS retinopathy, is one of the most common ocular findings in human immunodeficiency virus (HIV) disease and manifests most frequently as cotton-wool spots (Fig. 27.18). In our series of 1286 cases with AIDS in Western India, the incidence of HIV retinopathy was 16–22% (9). The finding of cotton-wool spots in a patient with HIV infection suggests advanced immunosuppression. Although HIV, the causative virus of AIDS, has been identified in retinal vascular endothelium [68], it does not occur in amounts sufficient to account for the arteriolar occlusion that causes the cotton-wool spots [69]. Retinal infections in patients with AIDS are caused by opportunistic pathogens in the presence of severe host immune dysfunction, but not by HIV itself. No active treatment is required for this disease.

Rubella Virus Retinitis

Rubella virus is an enveloped, single-stranded RNA virus that causes both congenital [70] and, less frequently, acquired retinal infection. Congenital rubella syndrome consists of deafness, cardiac malformations, and mental retardation; ocular involvement includes cataracts, glaucoma, iritis, and a characteristic "salt-and-pepper" retinopathy caused by areas of hypopigmentation and hyperpigmentation. The retinopathy is most prominent in the macula; when it is peripheral, it may be monocular and may involve only one or two quadrants. Vision and visual fields are usually normal and stable over time in the absence of significant cataract or glaucoma. No treatment is indicated. Choroidal neovascular membranes can occur as a late complication, resulting in severe visual loss [71].

Other Viral Retinitides

A discussion of all the viruses reported to cause retinitis in humans is beyond the scope of this chapter. A number of other viruses have been associated with retinitis or retinal pigment epitheliopathy, although a causal relationship is frequently unproven. Some of these viruses include EBV, rubeola, coxsackievirus B, subacute sclerosing panencephalitis, Rift Valley fever virus, influenza A, and mumps. It is likely that evolving molecular biologic techniques will ultimately prove a viral cause in at least some other diseases of the eye and will spur efforts to find effective antiviral therapies.

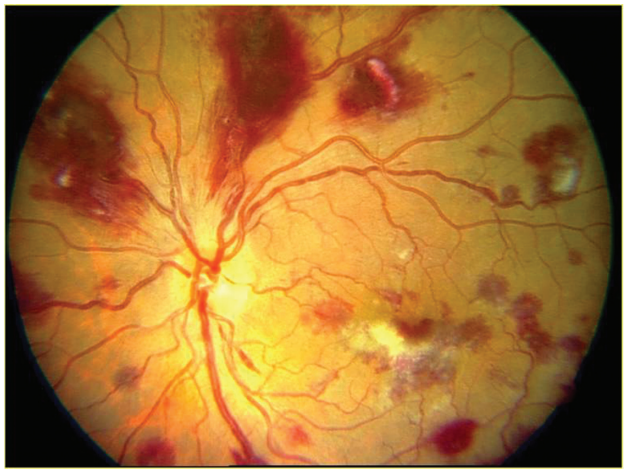


Figure 27.18 HIV retinopathy.

Conclusions

A number of viral diseases cause decreased vision, including blindness. The herpesvirus family includes some of the leading causes of loss of vision, as does HIV and its opportunistic infections. Prevention of loss of vision should include early detection and treatment of these diseases and prevention of the infection, when possible.

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