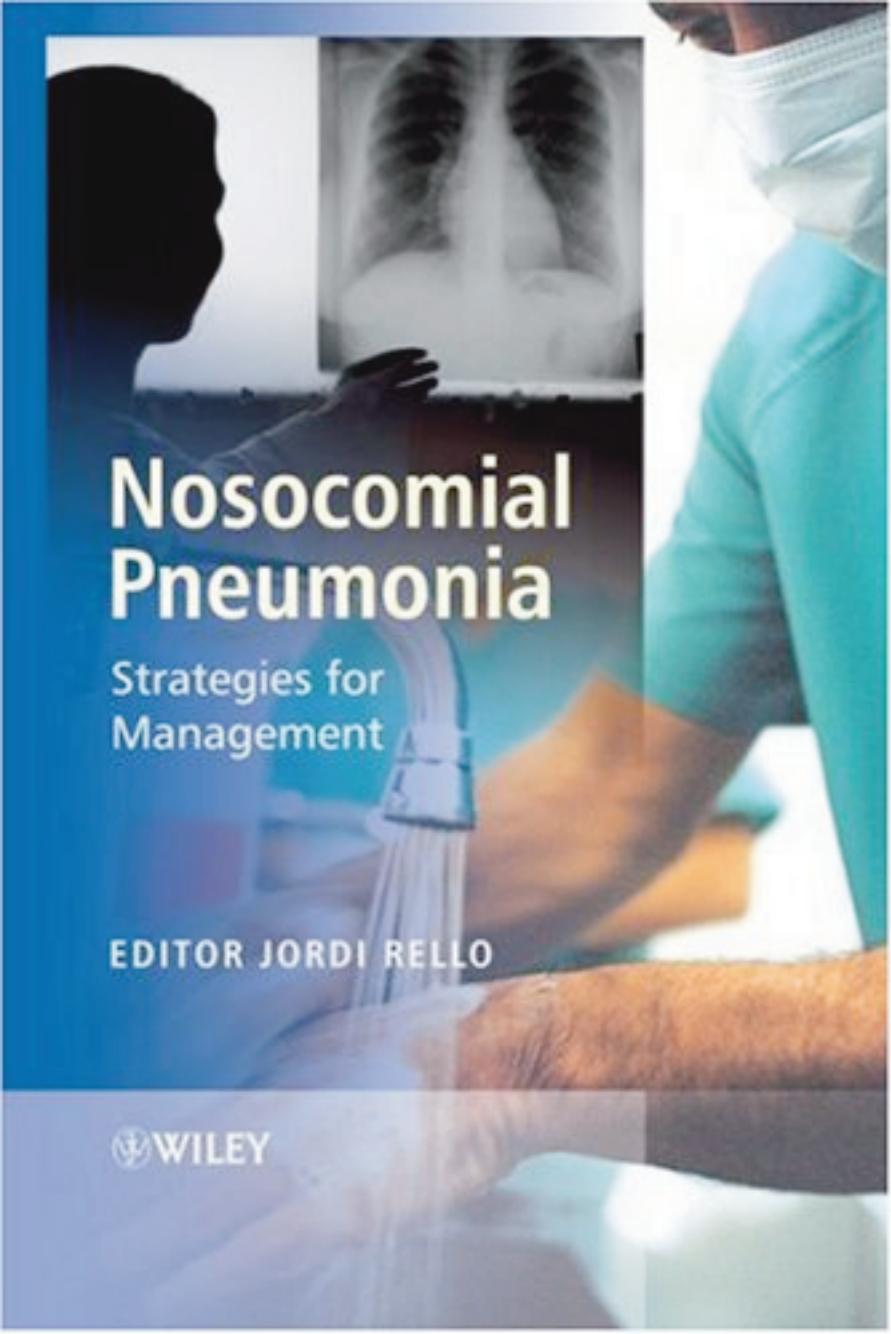
Nosocomial Pneumonia
Strategies for Management
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Nosocomial Pneumonia

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Nosocomial Pneumonia

Strategies for Management

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Contents

Preface

In the face of rapid developments in respiratory medicine, this book seeks to present the current knowledge on the pathophysiology, clinical presentation, diagnosis and treatment of nosocomial pneumonia. New considerations in the classification, such as healthcare-associated pneumonia, as well the importance of a patient-based approach, are discussed. A large part of the book consists of population-specific chapters, including an in-depth discussion of practical approaches to the management of pneumonia in immunocompromised patients. Other chapters address the importance of the inflammatory process and provide keys to the future improvement of nosocomial pneumonia management.

An outstanding panel of international experts have assumed the responsibility to focus particularly on the most recent developments. It has been an honour working with them, and thanks to their efforts, the bulk of the references are less than five years old. Ms. Rosi Luque, with the sponsorship of CIBERes, helped me in the coordination of the editorial workload, and I'm indebted to her for this. I also acknowledge the support that the authors have given to this project. With their contributions, and a multidisciplinary approach, this volume has been designed to become a valuable aid in the management of hospitalised patients who develop pneumonia as a complication.

Jordi Rello
September 2007

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Abbreviations

abbreviated injury score (AIS)
accessory group regulator (agr)
acute lung injury (ALI)
acute respiratory distress syndrome (ARDS)
allergic bronchopulmonary aspergillosis (ABPA)
alveolar macrophages (AM)
American Thoracic Society (ATS)
Infectious Disease Society of America (IDSA)
bone marrow transplant (BMT)
bronchoalveolar lavage (BAL)
bone marrow transplant (BMT)
Centers for Disease Control and Prevention (CDC)
central nervous system (CNS)
cerebro-spinal fluid (CSF)
chronic granulomatous disease (CGD)
chronic obstructive pulmonary disease (COPD)
clinical pulmonary infection score (CPIS)
compensatory anti-inflammatory response syndrome (CARS)
complicated intra-abdominal infections (cIAIs)
complicated skin and skin structure infections (cSSSIs)
computed tomography (CT)
confidence interval (CI)
continuous lateral rotation therapy (CLRT)
continuous subglottic suctioning (CSS)
cost-effectiveness analyses (CEAs)
C-reactive protein (CRP)
enzyme immunoassays (EIA)
enzyme-linked immunosorbent assay (ELISA)
epithelial lining fluid (ELF)
extended-spectrum beta-lactamase (ESBL)
fever of unknown origin (FUO)

fiberoptic bronchoscopy with bronchoalveolar lavage (FO–BAL)
Food & Drug Administration (FDA)
Glasgow Coma Scale (GCS)
glycopeptide intermediate-resistant *Staphylococcus aureus* (GISA)
graft-versus-host disease (GVHD)
granulocyte-colony stimulating factor (G-CSF)
granulocyte-macrophage colony stimulating factor (GM-CSF)
healthcare-associated (HCA)
healthcare-associated pneumonia (HCAP)
herpes simplex virus (HSV)
high-efficiency particulate air (HEPA)
high-resolution computed tomography (HRCT)
hospital-acquired pneumonia (HAP)
interferon gamma (IFN-γ)
injury severity score (ISS)
intensive care unit (ICU)
laminar air flow (LAF)
length of stay (LOS)
lipopolysaccharide (LPS)
loading doses (LD)
magnetic resonance imaging (MRI)
metallo-β-lactamases (MBLs)
methicillin-resistant *Staphylococcus aureus* (MRSA)
methicillin-susceptible (or methicillin-sensitive) *Staphylococcus aureus* (MSSA)
minimum bactericidal concentration (MBC)
minimum inhibitory concentration (MIC)
monoamino oxidase (MAO)
multidrug resistant MDR
multiple daily dosing (MDD)
National Nosocomial Infections Surveillance (NNIS)
non-invasive positive pressure ventilation (NPPV)
once daily dosing (ODD)
Panton–Valentine Leukocidin (PVL)
penicillin-binding proteins (PBPs)
peripheral blood mononuclear cells (PBMCs)
pharmacodynamics (PD)
pharmacokinetics (PK)
pharmacokinetic/pharmacodynamic (PK/PD)
platelet-aggregating factor (PAF)
pneumocystis pneumonia (PCP)
polymerase chain reaction (PCR)
polymorphonuclear cell (PMN)
polymorphous neutrophil leukocytes (PMNL)
post-antibiotic effect (PAE)

quality-adjusted life-year (QALY)
protected specimen brush (PSB)
receiver operating curve (ROC)
relative risk (RR)
selective digestive decontamination (SDD)
soluble triggering receptor expressed on myeloid cells (sTREM)
stem cell transplant (SCT)
subglottic suctioning (SS)
Therapeutic Interventions Severity System (TISS)
vancomycin-resistant *Enterococcus* (VRE)
ventilator-associated pneumonia (VAP)
volume of distribution (Vd)

1

Healthcare-Associated Pneumonia: Epidemiology, Microbiology and Clinical Outcomes

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Introduction

Pneumonia is one of the leading causes of hospitalisation and mortality in the United States [1]. Effective empiric treatment involves selecting an antibiotic with a spectrum of activity that includes the possible causative pathogen(s) [1]. Therefore, an evidence-based classification scheme that differentiates pneumonia based on the most likely causative organism(s) will help clinicians maximize the likelihood of providing the correct treatment and achieve favourable outcomes. Community-acquired pneumonia (CAP) is defined as signs, symptoms and radiographic evidence of pneumonia present in patients that come from the community which develop within 48 hours of hospital admission. In contrast, hospital-acquired pneumonia (HAP) is diagnosed as the presence of respiratory signs, symptoms and radiological evidence of pneumonia that begin after 48–72 hours of hospital admission. This classification is based in part due to differences in underlying etiologic pathogens, but despite the wide use of this dichotomous classification for pneumonia, data related to a variety of infectious processes indicate that these classifications may have significant limitations.

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Healthcare reflects a continuum of care with many of the traditional 'inpatient services' now provided in outpatient settings. Some of these services include intravenous therapy at home, dialysis units and residence in long-term care facilities. In addition, invasive medical therapies are now routinely administered in nursing homes, rehabilitation centres or extended care facilities. Many surgeries or minor procedures are regularly performed in outpatient-based surgical centres, or ambulatory inpatient surgical areas. Thus, many patients who reside in the community have a constant exposure to inpatient settings, such as those that need chemotherapy, radiation therapy or haemodialysis [2]. Additionally, patients can move from hospital to a subacute care facility, and return to hospital, without ever truly residing in the 'community'. Pneumonia that develops in these patients outside the hospital has been commonly categorized as CAP, even if those patients have been receiving healthcare in an outpatient facility or have a recent exposure to healthcare provided in facilities intimately related to inpatient care.

Thus, patients residing in long-term care facilities, individuals who have recently been hospitalised, and who have come in contact with the healthcare environment are an expanding part of the population. In these patients, infection is more common than in people residing in the community, and lower respiratory tract infection, including pneumonia, is the second most common infection [3]. In addition, nursing home-acquired pneumonia is the leading cause of mortality, hospitalisation and costs in older nursing home patients [4]. Muder reported that in the nursing home population the median rate of pneumonia is 365 per 1000 persons, compared to 34 per 1000 persons in those over 75 years of age who live in the community [5]. In addition, Vergis and colleagues [6] described a cohort of long-term care patients with pneumonia and compared them to patients without pneumonia closely matched for age, level of dependency and duration of institutionalisation. They found that an episode of pneumonia is associated with significant excess mortality that persists for up to two years. Other authors have demonstrated that pneumonia is the most common cause of infection when a resident of a long-term care facility has to be transferred to hospital for the treatment of infection [5]. These investigators showed that 10–18% of pneumonia related hospital admissions were nursing home residents [5].

All of these patients are commonly recognized in our traditional care model as subjects who develop infections in the 'community'. This traditional care model indicates that community infections are usually caused by 'community pathogens' and that limited antibiotic therapy should be used for these infections. However, recent data indicate that these healthcare-associated infections have a unique epidemiology. The pathogens causing these infections may resemble those seen in hospital-acquired infections and are associated with higher morbidity, mortality and costs [7–15]. Accumulating evidence from other infectious diseases suggests that healthcare associated infections are distinct from those that are truly community acquired [7–15]. This is why these infections are now considered 'healthcare-associated' infections. The epidemiology, etiology and clinical outcomes of a new entity called Healthcare-Associated Pneumonia (HCAP) are reviewed in this chapter. Clarifying the epidemiology of these healthcare-associated infections, and HCAP specifically,

is crucial in efforts to design appropriate empiric antimicrobial treatment guidelines and improve patient outcomes.

Healthcare-Associated Infections

Over the last several years, a number of investigators have documented that the pathogens responsible for healthcare-associated (HCA) infections are different from pathogens identified in patients from the community [7–15]. In fact, because of their contact with the healthcare environment, these patients may already be colonized with drug-resistant pathogens, bringing these organisms to the hospital at the time of admission. Tambyah and collaborators [9] showed, in one study of 383 patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infection, that 123 organisms (32 %) were isolated from patients who had been in the hospital less than 48 hours, while only one was a true community-acquired isolate. From the patients that were in the hospital for less than two days, the remainder of isolates were found in patients that came from long-term care facilities (21, 17 %); hospitalised or treated in an outpatient facility (94, 76 %); or received dialysis, visiting nurse care and had undergone day surgery (7, 6 %) [9]. Naimi and colleagues [8] showed, in a study of 1100 MRSA infections, that 85 % were healthcare related. The definition of healthcare-associated infection included history of hospitalisation, surgery, dialysis or residence in a long-term care facility within a year of contracting the infection; or presence of a permanent indwelling catheter or medical device (e.g. gastrostomy, tracheostomy; and/or Foley catheter) [8]. In this cohort of healthcare-associated infection, Gram-negative multidrug-resistant (MDR) pathogens were frequently isolated [8].

Pop-Vicas *et al.* [7] demonstrated that MDR Gram-negative organisms collected within the first 48 hours of hospital admission were frequently identified as *Escherichia coli, Klebsiella* species and *Enterobacter cloacae,* but not *Pseudomonas aeruginosa.* Fifty-three per cent of these isolates were resistant to three antimicrobial groups and 12 % were resistant to five antibiotic classes [7]. The risk factors for MDR pathogens included: elderly (>65 years of age), prior exposure to antibiotics and previous residence in a long-term care facility [7]. Thus, these data demonstrate that MDR pathogens such as, for example *P. aeruginosa* and *S. aureus,* are frequently found in healthcare-associated infections.

Healthcare-Associated Pneumonia

Definition

Healthcare-associated pneumonia (HCAP) was recently defined as a different infectious condition by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) HAP consensus statement [16]. HCAP is now recognized as

an important cause of morbidity and mortality despite advances in antimicrobial therapy and better supportive care modalities [17–19]. HCAP includes pneumonias in any patient who is hospitalised in an acute care facility if the subject has any of the following characteristics: resided in a nursing home or long-term care facility; received intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days; or attended a hospital or haemodialysis clinic [17–19]. In addition, these guidelines suggest that MDR pathogens should be considered in other nosocomial infections (current hospitalisation for more than five days and high frequency of antibiotic resistance in the community or in the specific hospital unit); or conditions not directly related to the hospitalisation, such as immunosuppressive disease and/or therapy (Table 1.1).

Table 1.1 Definitions of 'healthcare-associated' infections in recent literature

ATS/IDSA [16] HCA-pneumonia	Kollef *et al.* [20] HCA-pneumonia	Friedman *et al.* [2] HCA-bloodstream infections
Patients with pneumonia on admission or within 2 days of admission and any of the following: (1) resided in a nursing home or long-term care facility; (2) home infusion therapy (received intravenous antibiotic therapy, chemotherapy); (3)˜wound care within the past 30 days; (4) hospitalisation for >2 days in the preceding 3 months; (5) chronic dialysis within 30 days; (6) family member with multi-drug resistant pathogen.	Patients with a first positive bacterial respiratory culture finding within 2 days of admission and any of the following: (1) admission source indicates a transfer from another health-care facility; (2) receiving long-term haemodyalisis (ICD-9-CM codes); and (3)˜prior hospitalisation within 30 days who do not meet VAP definition.	Patients with positive blood culture obtained at the time of hospital admission or within 2 days of admission and any of the following: (1) received intravenous therapy at home; received wound care or specialized nursing care through a healthcare agency, family or friends; or had self-administered intravenous medical therapy in the 30 days before the bloodstream infection. Patients whose only home therapy was oxygen use were excluded; (2) attended a hospital or a haemodyalisis clinic or received intravenous chemotherapy in the 30 days before the bloodstream infection; (3) hospitalised in an acute care hospital for >2 days in the 90 days before the bloodstream infection; (4) resided in a nursing home or long-term care facility.

ATS – American Thoracic Society; IDSA – Infectious Diseases Society of America; HCA – healthcare-associated; VAP – ventilator-associated pneumonia

Clinical Characteristics

Limited information is available on the clinical characteristics of patients with HCAP. Kollef and colleagues [20] provided a comparison of patients with CAP, HCAP, HAP and ventilator-associated pneumonia (VAP). The reported data were from a retrospective cohort of 4543 patients with culture-positive pneumonia based on US inpatient databases. Of the 4543 patients, 2221 had CAP (48.9 %), 988 had HCAP (21.7 %), 835 had HAP (18.4 %) and 499 had VAP (11 %) [20]. Their definition of HCAP required patients to have positive bacterial respiratory tract cultures within two days of hospital admission and to have come from a healthcare facility, be receiving haemodialysis or have been hospitalised within the past 30 days. HCAP patients were significantly older than CAP patients (77 versus 65 years), but were similar in age to those with HAP. Half of the HCAP patients came from nursing homes, which was a far higher percentage than the percentage among patients with HAP and VAP residing in long-term care facilities. Illness severity was similar in both HCAP and VAP patients, but was higher than that seen in those patients with CAP and HAP [20].

Microbiology

Most of the current microbiological data available are from patients with nosocomial infections in non-ventilated (HAP) or ventilated patients (VAP). The data on the pathogens that are isolated in patients with HCAP infections are more limited. However, given the frequent transfer of patients and healthcare workers between long-term and outpatient facilities and hospitals, the pathogens in these facilities are more likely to closely resemble those seen in nosocomial infections. Another limitation is that in most nursing home patients with HCAP there is no identifiable etiology [21]. This occurs in part because many patients are unable to produce sputum specimens suitable for analysis, and the difficulty of distinguishing colonization and infection in patients with adequate samples [5, 6, 18, 21].

Muder *et al.* [5] reviewed published studies and found that the most commonly identified healthcare pathogens included *S. pneumoniae* (0−39 %), *S. aureus* (0−33 %) and Gram-negative bacteria (0−51 %). A potential relationship has been suggested between unrecognised aspiration of oral or gastric contents, the presence of dysphagia, increased oropharyngeal colonization and the subsequent development of pneumonia in older adults. In addition, isolation of *S aureus* and Gram-negative bacilli (*E. coli* and *K. pneumoniae*) in the oropharynx could potentially lead to aspiration pneumonia [22]. Leibovitz and colleagues [23] showed that *P. aeruginosa* has been isolated from 34 % of nasogastric tube fed older patients but from none of the orally fed control group. Other Gram-negative bacilli were isolated from 64 % of tube fed patients and only 8 % from the control group, suggesting that the oropharynx of tube fed patients could be a potential reservoir for *P. aeruginosa* and other Gram-negative bacilli [23]. In the study by Kollef *et al.* [20] *S. aureus* was a major pathogen in all pneumonia types, with its occurrence markedly higher in the non-CAP groups than in the CAP group. Kollef *et al.* [20], showed that the etiology of HCAP was different from HAP and VAP. However, HCAP differs from HAP or VAP to a lesser degree

than from CAP (e.g. more comparable *S. aureus* occurrences and mortality rates). These investigators also reported that *S. aureus* was a predominant pathogen in all types of pneumonia, including CAP.

There is a consensus in the literature that the most common pathogen for CAP is *S. pneumoniae* [24]. However, the results found by Kollef and collaborators [20] – that fewer patients admitted for CAP had *S. pneumoniae* infection than had *S. aureus* infection – probably reflected that the CAP patients were hospitalised [25, 26]. The high prevalence of *S. aureus* might be due to the relationship between this bacteria and severity of illness, in which the more severe CAP patients are the ones that tend to be hospitalised [1]. The occurrence of *S. aureus* in patients with HCAP was markedly higher than in patients with CAP. Compared with the HAP group, a greater proportion of patients in the HCAP group had *Pseudomonas* spp. and *S. pneumoniae* and a lower proportion had non-group *Streptococcus.* Compared with the VAP group, patients with HCAP were more likely to be infected by *S. pneumoniae* and less likely to have *Haemophilus* sp infection. Thus, HCAP is microbiologically different from CAP, HAP and VAP (Figure 1.1).

While most of the microbiology of healthcare-associated infections has not been focused strictly on pneumonia, data are available from pneumonia patients that were residents of long-term care facilities. El Solh *et al.* described, in a study of 95 elderly pneumonia patients, that those admitted from a nursing home had a higher frequency of enteric Gram-negative organisms and *S. aureus,* and a lower frequency of pneumococcus compared to those admitted from the community [27]. The same group of investigators showed, in a different study [28] of patients with severe pneumonia who had been admitted from a nursing home, that the frequency of MDR pathogens was increased in those who had recently received antibiotics and in those who also had a worse functional status (defined by the performance of activities of daily living).

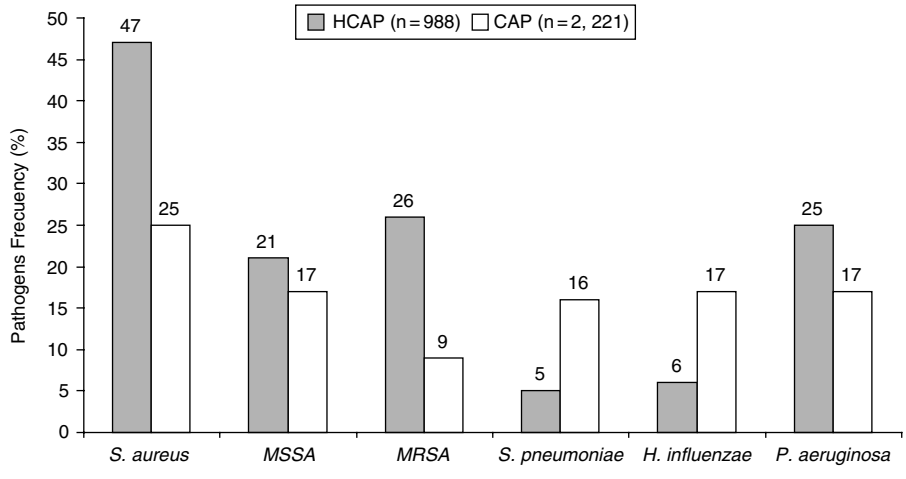

Figure 1.1
Most common pathogens identified in HCAP patients compared to CAP patients.
CAP – community-acquired pneumonia; HCAP – healthcare associated pneumonia; $p < 0.01$ for all comparisons with HCAP
Source: Adapted from Kollef *et al.* [20].

Recent data show that MRSA strains isolated from patients with healthcare-associated infections are distinct from those that are truly community acquired [8]. These bacteria isolates have different susceptibility to antibiotics [8]. In addition to the complexity introduced by evolving healthcare practices, the causative pathogens associated with CAP have also changed in prevalence in recent years. Although *S. pneumoniae* remains the most common causative pathogen, other pathogens (e.g. *Chlamydophila pneumoniae, Mycoplasma pneumoniae* and *Legionella* spp.) exist, and their prevalence changes over time and varies by geographic location [1]. Furthermore, the emerging antimicrobial resistance of respiratory pathogens has complicated the management of these infections. These changes necessitate an evolving treatment strategy based on the most recent microbiologic and epidemiologic data [29].

Outcomes

At the present time, a large proportion of hospitalised CAP patients may in fact have HCAP. Thus, our understanding of the outcome of this condition is not clearly defined. The recent data on HCAP strongly suggest that this is a new category of pneumonia with high mortality, length of stay and costs compared to CAP patients and even similar to HAP and VAP (Table 1.2). Kollef *et al.* [20] reported that mortality rates associated with HCAP (19.8 %) and HAP (18.8 %) were comparable ($p > 0.05$); and both were significantly higher than that for CAP (10 %, all $p < 0.0001$) and lower than that for VAP (29.3 %, all $p < 0.0001$). Mean length of stay varied significantly with pneumonia category (in order of ascending values: CAP, HCAP, HAP and VAP; all $p < 0.0001$). In addition, the length of hospital stay increased progressively for CAP, HCAP, HAP and VAP patients, and, in parallel with this, hospital costs increased for each of the four groups in the same order ($p < 0.0001$). If HCAP patients were included in the CAP category according to the traditional classification schemes, these would have accounted for 31 % of hospitalised CAP patients.

Multivariate analysis of the factors associated with pneumonia mortality indicated that *S. aureus* was the only pathogen that correlated with increased mortality. *S. aureus* not only increased mortality, but was also associated with increased length of hospital stay, and treatment costs observed in patients with HCAP, HAP and VAP. The clinical outcomes in patients with HCAP and HAP were comparable in terms of overall mortality. However, the mean length of hospital stay and treatment costs for HCAP patients was significantly lower in these groups of patients than in those with

Table 1.2 Clinical outcomes and costs in patients with HCAP compared to CAP

Outcomes	HCAP (n = 988)	CAP (n = 2221)	p value
Mortality	19.8 %	10.0 %	< 0.0001
Length of stay, mean (SD) days	8.8 (7.8)	7.5 (7.2)	< 0.0001
Cost, mean (SD), total charges, $	27 647 (37 974)	25 218 (40 577)	< 0.0001

* CAP – community acquired pneumonia; HCAP – healthcare-associated pneumonia; $p < 0.01$ for all comparisons with HCAP
Source: Adapted from Kollef *et* al. [20]

HAP. This might reflect a difference in treatment for HCAP among clinicians who do not distinguish HCAP from CAP. Moreover, since treatment guidelines often do not recommend coverage for *S. aureus* in CAP, the association between the presence of *S. aureus* and mortality may reflect that subjects with such infections were more likely to have received antibiotics not effective against MSSA or MRSA. In other words, recovery of *S. aureus* may be a surrogate marker for the prescription of inappropriate antimicrobial therapy, a known predictor of poor outcomes in pneumonia [13]. Although the data reported by Koleff *et al.* [20] did not allow the investigators to separate colonization from infection, or to tell whether the isolated pathogen was actually causing the respiratory infection, the epidemiologic, bacteriologic and outcomes data were interesting, and help to better define the entity of HCAP.

It is important to take into consideration that the inclusion of HCAP in the nosocomial pneumonia guidelines and algorithms may suggest that empiric therapy for HCAP patients will not routinely include coverage against atypical pathogens, as is the case in CAP patients. This recommendation requires close monitoring, since outbreaks of atypical pathogen pneumonia can occur among nursing home residents, mainly *Legionella* spp. Conflicting data from two recent meta-analyses in patients with mild and moderate CAP showed that atypical coverage did not have an impact on patient's outcomes [30, 31]. However, from the subgroup analysis, patients with Legionella infections tended to do worse if atypical coverage was not added [30, 31]. In addition, there may be some patients with HCAP (such as those with a risk factor of recent antibiotic therapy for a short time or dialysis) who may not be at high risk of infection with MDR pathogens. In these patients the use of broad-spectrum antibiotics may be not necessary. Thus, in HCAP patients broad-spectrum antibiotics should initially be started, but later adjust based on the culture results.

Summary

Healthcare-associated pneumonia is now identified as a unique entity that differs from CAP, and in many ways is similar to nosocomial pneumonia (either HAP or VAP). HCAP differs from CAP in both bacteriology and outcomes, and thus therapy for these two categories of pneumonia should be approached differently. This conclusion is based on the recently published American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for the treatment of nosocomial pneumonia, which included patients with HCAP [16]. These guidelines suggested that HCAP patients should be treated differently from CAP patients, but similarly to HAP and VAP patients [16]. The guideline definition for HCAP included the following: hospitalisation for two days in the preceding 90 days; residence in a nursing home or extended care facility; recipients of home infusion therapy; long-term dialysis within 30 days; home wound care; and exposure to family members infected with MDR pathogens. The pathogens isolated in HCAP share more similarity with HAP and VAP than with CAP [16]. In the guidelines it was recommended that patients with HCAP be treated for potential MDR pathogens, including resistant Gram-negative organisms and MRSA. *S aureus* was a major pathogen of all pneumonias with higher

rates in non-CAP pneumonias [16]. Compared to CAP, non-CAP was associated with more severe disease, higher mortality rate, greater length of stay and increased cost. The HCAP diagnosis implies that there is a need for confirmatory studies, and that future clinical practice guidelines and local critical pathways aimed at optimising and streamlining initial empiric antibiotic treatment for pneumonia would benefit from the separation of HCAP from CAP.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

References

1. Niederman, M.S., Mandell, L.A., Anzueto, A. *et al*. (2001) Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med*, **163**, 1730−1754.
2. Friedman, N.D., Kaye, K.S., Stout, J.E. *et al*. (2002) Healthcare-associated bloodstream infections in adults: a reason to change the accepted definition of Community-Acquired Infections. *Ann Intern Med*, **137**, 791−797.
3. Stevenson, K.B. (1999) Regional data set of infection rates for long-term care facilities: description of a valuable benchmarking tool. *Am J Infect Control*, **27**, 20−26.
4. Muder, R.R., Aghababian, R.V., Loeb, M.B., Solot, J.A. and Higbee, M. (2004) Nursing home-acquired pneumonia: an emergency department treatment algorithm. *Curr Med Res Opin*, **20**, 1309−1320.
5. Muder, R.R. (1998) Pneumonia in residents of long-term care facilities: epidemiology, etiology, management, and prevention. *Am J Med*, **105**, 319−330.
6. Vergis, E.N., Brennen, C., Wagener, M. and Muder, R.R. (2001) Pneumonia in long-term care: a prospective case-control study of risk factors and impact on survival. *Arch Intern Med*, **161**, 2378−2381.
7. Pop-Vicas, A.E. and D'Agata, E.M. (2005) The rising influx of multidrug resistant Gram-negative bacilli into a tertiary care hospital. *Clin Infect Dis*, **40**, 1792−1798.
8. Naimi, T.S., LeDell, K.H., Como-Sabetti, K. *et al*. (2003) Comparison of community- and healthcare-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA*, **290**, 2976−2984.
9. Tambyah, P.A., Habib, A.G., Ng, T.M., Goh, H. and Kumarasinghe, G. (2003) Community-acquired methicillin-resistant *Staphylococcus aureus* infection in Singapore is usually "healthcare associated". *Infect Control Hosp Epidemiol*, **24**, 436−438.
10. Shorr, A.F., Tabak, Y.P., Killian, A.D. *et al*. (2006) Healthcare-associated bloodstream infection: a distinct entity? Insights from a large U.S. database. *Crit Care Med*, **34**, 2588−2595.
11. Engelhart, S.T., Hanses-Derendorf, L., Exner, M. and Kramer, M.H. (2005) Prospective surveillance for healthcare-associated infections in German nursing home residents. *J Hosp Infect*, **60**, 46−50.
12. Lesens, O., Hansmann, Y., Brannigan, E. *et al*. (2005) Healthcare-associated *Staphylococcus aureus* bacteremia and the risk for methicillin resistance: is the Centers for Disease

Control and Prevention definition for community-acquired bacteremia still appropriate? *Infect Control Hosp Epidemiol*, **26**, 204−209.
13. McDonald, J.R., Friedman, N.D., Stout, J.E., Sexton, D.J. and Kaye, K.S. (2005) Risk factors for ineffective therapy in patients with bloodstream infection. *Arch Intern Med*, **165**, 308−313.
14. Siegman-Igra,Y., Fourer, B., Orni-Wasserlauf, R. *et al*. (2002) Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. *Clin Infect Dis*, **34**, 1431−1439.
15. Morin, C.A. and Hadler, J.L. (2001) Population-based incidence and characteristics of community onset *Staphylococcus aureus* infections with bacteremia in 4 metropolitan Connecticut areas, 1998. *J Infect Dis*, **184**, 1029−1034.
16. American Thoracic Society/Infectious Diseases Society of America (2005) Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med*, **171**, 388−416.
17. Mylotte, J.M. (2002) Nursing home-acquired pneumonia. *Clin Infect Dis*, **35**, 1205−1211.
18. Hutt, E. and Kramer, A.M. (2002) Evidence-based guidelines for management of nursing home-acquired pneumonia. *J Fam Pract*, **51**, 709−716.
19. Tablan, O.C., Anderson, L.J., Besser, R. *et al*. (2004) Healthcare infection control practices advisory C: Guidelines for preventing healthcare-associated pneumonia, 2003: recommendations of CDC and the healthcare infection control practices advisory committee. *MMWR Recomm Rep*, **53**, 1−36.
20. Kollef, M.H., Shorr, A., Tabak, Y.P. *et al*. (2005) Epidemiology and outcomes of healthcare-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*, **128**, 3854−3862.
21. Medina-Walpole, A.M. and Katz, P.R. (1999) Nursing home-acquired pneumonia. *J Am Geriatr Soc*, **47**, 1005−1015.
22. Marik, P.E. and Kaplan, D. (2003) Aspiration pneumonia and dysphagia in the elderly. *Chest*, **124**, 328−336.
23. Leibovitz, A., Dan, M., Zinger, J. *et al*. (2003) *Pseudomonas aeruginosa* and the oropharyngeal ecosystem of tube-fed patients. *Emerg Infect Dis*, **9**, 956−959.
24. Mandell, L.A., Bartlett, J.G., Dowell, S.F. *et al*. (2003) Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis*, **37**, 1405−1433.
25. Guest, J.F. and Morris, A. (1997) Community-acquired pneumonia: the annual cost to the national health service in the UK. *Eur Respir J*, **10**, 1530−1534.
26. Marrie, T.J. (1994) Community-acquired pneumonia. *Clin Infect Dis*, **18**, 501−13; quiz 514−505.
27. El-Solh, A.A., Sikka, P., Ramadan, F. and Davies, J. (2001) Etiology of severe pneumonia in the very elderly. *Am J Respir Crit Care Med*, **163**, 645−651.
28. El Solh, A.A.Pietrantoni, C., Bhat, A., Bhora, M. and Berbary, E. (2004) Indicators of potentially drug-resistant bacteria in severe nursing home-acquired pneumonia. *Clin Infect Dis*, **39**, 474−480.
29. Niederman, M.S. (2004) Review of treatment guidelines for community-acquired pneumonia. *Am J Med*, **117** (3A), 51S−57S.
30. Shefet, D., Robenshtok, E., Paul, M. and Leibovici, L. (2005) Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. *Arch Internal Med*, **165**, 1992−2000.
31. Mills, G.D., Oehley, M.R. and Arrol, B. (2005) Effectiveness of beta-lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. *BMJ*, **330**, 456.

2
Prevention of Hospital-Acquired Pneumonia

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Nosocomial infections constitute a major complication in hospitalised patients, particularly in those who are critically ill and need intensive care [1]. Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in the Intensive Care Unit (ICU) [2, 3] and complicates the illness course by increasing mortality rate, length of hospital stay [4] and costs for patients who acquire it.

Hospital-acquired pneumonia (HAP) can be defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission [5, 6].

Healthcare-associated pneumonia (HCAP) includes any patient who was hospitalised in an acute care hospital for two or more days within 90 days of the onset of infection; resided in a nursing home or long-term care facility; received intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of the current infection; or attended a hospital or haemodialysis clinic.

Because most reported data have been collected from studies of patients with VAP, and microbiologic data from nonintubated patients may be less accurate, the focus in this chapter is more on VAP, but most of the principles overlap with HAP and HCAP.

VAP is commonly defined as a pneumonia occurring more than 48 hours after the initiation of endotracheal intubation and mechanical ventilation. It is often difficult to define an incidence of VAP, because there may be an overlap with other respiratory tract infections, such as infectious tracheobronchitis, in mechanically ventilated patients. Besides, the incidence of VAP in patients diagnosed by qualitative or

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semi-quantitative secretion cultures may be up to two times greater than when quantitative cultures of lower respiratory tract secretions are used. VAP-related mortality has been estimated to be between 33 and 50 %. Therefore, VAP prevention is a major issue in ICU clinical practice since it may help improve clinical outcome and reduce costs.

Risk factors for the development of VAP can be differentiated into modifiable and nonmodifiable conditions [7]. These risk factors may be either patient-related (male/female, pre-existing pulmonary disease or multiple organ system failure) or treatment-related (intubation or enteral feeding). Modifiable risk factors for VAP (Table 2.1) are obvious targets for improved management and prophylaxis in several studies and in the comprehensive Guidelines for Preventing Healthcare-Associated Pneumonia, published by the Centers for Disease Control and Prevention, 2004.

The pathogenesis of VAP usually requires two important processes to happen: bacterial colonization of the aerodigestive tract, and aspiration of contaminated secretions into the lower airway. Therefore, strategies aimed at preventing VAP usually focus on reducing the burden of bacterial colonization in the aerodigestive tract, and in decreasing the incidence of aspiration. Besides, the presence of invasive devices is an important contributor to the pathogenesis and development of VAP (nasogastric tube, endotracheal tube, ventilator circuit and respiratory therapy equipment).

Several strategies, mostly evidence-based guidelines [5–10], have been developed for preventing VAP (Table 2.2). These preventive measures are aimed mainly at reducing either oropharyngeal colonization or gastric colonization, and avoiding aspiration of contaminated aerodigestive tract secretions, as well [7, 8].

Table 2.1 Risk factors for ventilator-associated pneumonia

– Age older than 60 years
– Duration of mechanical ventilation
– Previous administration of antibiotics
– Use of antacids or H_2 antagonists
– Chronic lung disease
– Supine position
– Nasal intubation (tracheal or gastric)
– Gastric distension
– Inadequate maintenance of endotracheal tube
– Ventilator circuit condensate
– Aspiration
– Coma
– Enteral nutrition
– Re-intubation
– Tracheotomy
– Patient's transport
– Brain injury
– Neurosurgery
– Neuromuscular diseases
– Acute respiratory distress syndrome

Table 2.2 Selected recommendations from the guidelines fo preventing heathcare-associated pneumonia of CDC and the HICPAC, 2003 [6]

Recommendation	Category
Staff Education and Involvement in Infection Prevention	
Educate healthcare workers for preventing hospital pneumonia.	IA
Infection and Microbiologic Surveillance	
Conduct surveillance for bacterial pneumonia in intensive care unit (ICU)	IB
Breathing circuits with humidifiers	
Do not change routinely. Change the circuit when it is visibly soiled or mechanically malfunctioning	IA
Periodically drain and discard any condensate that collects in the tubing of a mechanical ventilator, taking precautions not to allow condensate to drain toward the patient.	IB
Wear gloves to perform the previous procedure and/or when handling the fluid.	IB
Decontaminate hands with soap and water (if hands are visibly soiled) or with an alcohol-based hand rub after performing the procedure or handling the fluid.	IA
Ventilator breathing circuits with HMEs	
No recommendation can be made for the preferential use of either HMEs or heated humidifiers to prevent pneumonia in patients receiving mechanically assisted ventilation.	IB (Unresolved issue)
Hand hygiene	
Decontaminate hands by washing them with either antimicrobial soap and water or with nonantimicrobial soap and water or by using an alcohol-based waterless antiseptic agent.	IA
Gloving	
Wear gloves for handling respiratory secretions or objects contaminated with respiratory secretions of any patient.	IB
Change gloves and decontaminate hands between contacts with different patients.	IA
Care of patients with tracheostomy	
Perform tracheostomy under aseptic conditions.	II
When changing a tracheostomy tube, wear a gown, use aseptic technique	IB
No recommendation can be made for the daily application of topical antimicrobial agent(s) at the tracheostoma	Unresolved issue
Suctioning of respiratory tract secretions	
No recommendation can be made for the preferential use of either the multiuse closed-system suction catheter or the single-use open-system suction catheter for prevention of pneumonia	Unresolved issue
Use of noninvasive ventilation (NIV)	
Use of NIV to reduce the need for and duration of endotracheal intubation.	II
As much as possible, avoid repeat endotracheal intubation in patients who have received mechanically assisted ventilation.	II
Unless contraindicated by the patient' condition, perform orotracheal rather than nasotracheal intubation on patients.	IB
Use an endotracheal tube with a dorsal lumen above the endotracheal cuff to allow drainage of tracheal secretions that accumulate in the patient' subglottic area.	II

Table 2.2 (Continued)

Recommendation	Category
Before deflating the cuff of an endotracheal tube in preparation for tube removal, or before moving the tube, ensure that secretions are cleared from above the tube cuff.	II
Prevention of aspiration associated with enteral feeding	
In the absence of medical contraindication(s), elevate at an angle of 30°–45° degrees of the head of the bed of a patient at high risk for aspiration.	II
Routinely verify appropriate placement of the feeding tube.	IB
No recommendation can be made for the preferential use of small-bore tubes for enteral feeding.	Unresolved issue
No recommendation can be made for preferentially administering enteral feedings continuously or intermittently.	Unresolved issue
Prevention or modulation of oropharyngeal colonization	
Oropharyngeal cleaning and decontamination with an antiseptic agent: develop and implement a comprehensive oral hygiene program (that might include the use of an antiseptic agent) for patients in acute-care settings or residents in long-term care facilities who are at high risk for healthcare-associated pneumonia.	II
No recommendation can be made for the routine use of an oral chlorhexidine rinse for the prevention of healthcare-associated pneumonia in all postoperative or critically ill patients and/or other patients at high risk for pneumonia.	II (Unresolved issue)
Prevention of gastric colonization	
No recommendation can be made for the preferential use of sucralfate, H_2-antagonists and/or antacids for stress-bleeding prophylaxis in patients receiving mechanically assisted ventilation.	Unresolved issue
No recommendation can be made for the routine selective decontamination of the digestive tract (SDD) of all critically ill, mechanically ventilated or ICU patients.	Unresolved issue
Systemic antimicrobial prophylaxis	
No recommendation can be made about the routine administration of systemic antimicrobial agent(s) to prevent pneumonia in critically ill patients or in those receiving mechanically-assisted ventilation.	Unresolved issue
Scheduled changes in the class of antimicrobial agents used for empiric therapy.	Unresolved issue
Turning or rotational therapy	
No recommendation can be made for the routine use of turning or rotational therapy, either by 'kinetic' therapy or by continuous lateral rotational therapy.	Unresolved issue

Category IA. Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies.
Category IB. Strongly recommended for implementation and supported by certain clinical or epidemiologic studies and by strong theoretical rationale.
Category IC. Required for implementation, as mandated by federal or state regulation or standard.
Category II. Suggested for implementation and supported by suggestive clinical or epidemiologic studies or by strong theoretical rationale.
No recommendation; unresolved issue. Practices for which insufficient evidence or no consensus exists about efficacy.

Effective strategies include strict infection control, alcohol-based hand disinfection, the use of microbiologic surveillance with ready availability of data on local antibiotic-resistant pathogens, monitoring and early removal of invasive devices, and implementation of programs to reduce or alter antibiotic-prescribing practices. Antibiotic policy is a major issue in nosocomial infection control, and practice guidelines [11] for antimicrobial therapy that attempt to restrict antibiotic use are expected to help in preventing antibiotic-resistant infections. Furthermore, antibiotic use strategies, such as rotating antibiotic classes, have been recommended in some VAP prevention guidelines [8].

Another major issue related to the use of mechanical ventilation is the diagnosis of VAP. Adequate control and treatment of VAP requires an accurate definition of cases, which may help to reduce use of antibiotics. Some researchers [12] believe that implementation of bronchoscopic techniques for diagnosing VAP may reduce antibiotic use and improve patient outcome. In spite of there being increasing evidence-based clinical guidelines [13], their daily use appears to be variable and still limited. Some studies [9, 14, 15, 16] have documented the implementation of VAP prevention strategies and guidelines through surveys. Such surveys may serve to identify current practice related with VAP prevention and so detect ways to improve it.

Given the impact of VAP on healthcare outcome, infection control professionals and hospital epidemiologists should use the latest evidence to evaluate, manage and prevent this common safety problem. The 100 000 Lives Campaign of the Institute for Health Care Improvement has identified prevention of VAP as a priority area [17, 18].

Strategies for VAP prevention can be grouped into two classes: non-pharmacologic strategies, which are focused on preventing aspiration, and pharmacologic strategies, which are aimed at preventing colonization.

Non-Pharmacologic Strategies

Staff Education and Nursing Staffing Levels in the Intensive Care Unit

There is a considerable body of evidence that patients frequently do not receive optimal medical care [19]. This includes the failure to employ thrombolytics, beta-blockers, angiotensin-converting enzyme inhibitors and aspirin in acute myocardial infarction [20, 21], the use of the inappropriate beta-agonist monotherapy or inadequate doses of inhaled corticosteroids [22]; several treatments have also been shown to be over-used in some cases [21]. In Spain, France and the United States, variable national critical care practice patterns have been described in studies of mechanical ventilation [23], non-invasive ventilation [24] and weaning from mechanical ventilation [25], respectively.

Two important Franco–Canadian studies based on a survey of ventilator circuit and secretion management practices – two measures recognized as preventing VAP – have been performed [14, 26]. These studies showed considerable variability in practice between countries regarding humidification systems, intubation route,

endotracheal suction system, subglottic secretion drainage, kinetic therapy beds and body position. Recently, a survey on current practices in ICUs in southern Spain confirmed these findings; it concluded that clinical practice for preventing and diagnosing VAP is variable and many opportunities exist to improve the care of patients receiving mechanical ventilation [27].

Reasons why evidence-based recommendations for preventing VAP were not used were examined in three surveys [14, 16, 28]. Various barriers to adhering to VAP prevention recommendations were disclosed, including disagreement with the reported results of source studies, resource paucity, elevated costs, inconvenience for nurses, fear of potential adverse effects and patient discomfort [14, 16, 28]. Nurses appeared to have different levels of adherence than physicians for many nonpharmacological evidence-based guidelines [28].

Staff education, particularly targeting those clinicians and staff who manage patients receiving mechanical ventilation, is a cornerstone of efforts to reduce the incidence of VAP [29]. The power of educational initiatives and their potential to lead to significant reductions in VAP is striking. Zack *et al*. [30] described the impact of a self-study instructional module on VAP prevention strategies. This educational effort helped reduce VAP by 57.6%. Kollef *et al*. [31] reported the success of a VAP educational prevention program carried out in five ICUs. Rates of VAP dropped nearly 58%, to 5.7/1000 ventilator days, and cost savings were estimated to be between US$425 606 and $4 000 000. In another study, Babcock *et al*. [32] reported a 46% reduction in VAP over an 18-month period in four hospitals. However, not all guidelines or educational initiatives have achieved such success.

Staffing must be sufficient to allow patient care to be provided while ensuring that staff is able to comply with essential infection control practices and other prevention strategies [33, 34]. Decreased nursing staffing has been associated with significantly higher rates of respiratory and cardiac complications [35].

Nurse-to-patient ratios should be 1:1 for high-risk complicated ICU patients, and 2:1 for patients with lower disease acuity. Increased workload for nurses and less trained health care personnel result in greater rates of nosocomial infection.

Hand Hygiene

Microorganisms can be spread easily from patient to patient on the hands of healthcare workers. Moreover, wrist watches, bangles and other jewellery commonly act as reservoirs for organisms, and impede effective hand cleaning [36, 37, 38].

Hand hygiene is a general term that applies to hand washing, antiseptic handwash, antiseptic handrub, or surgical hand antisepsis [39].

Thus, basic hygiene principles of infection control (hand hygiene just before and after each contact with a patient, and barrier measures including the use of gloves and sterile equipment) have been widely recognized as an important but underused measure for the prevention of VAP. However, compliance of healthcare workers to hand hygiene is low (25−40%), and high workload decreases their compliance [40, 41, 42].

The use of alcohol-based foams and lotions facilitates more efficient hand disinfection [43]. Besides, hand antiseptics (alcohol-based handrub solution), easier access

to sinks and availability of washing equipment, decrease in workload, communication and education tools and feedback improve compliance and decrease the cross-transmission of nosocomial infection [39, 44, 45, 46].

Although the use of protective gowns and gloves has also been found to reduce acquired nosocomial infections in children, their routine use is not recommended for prevention of VAP. Use of protective gowns and gloves appears to be most effective when directed at specific antibiotic-resistant microorganisms, and when respiratory secretions or contaminated objects have to be handled [8].

Patient Positioning

Potentially pathogenic bacteria can often colonize both gastric contents and secretions from the upper aerodigestive tract. These secretions can be aspirated to the lower airway and cause pneumonia.

Aspiration from upper-airway secretions is common in the supine position, even in healthy adults. Supine positioning of patients has been shown to be independently associated with the development of ventilator-associated pneumonia, possibly because of an increased risk from gastroesophageal reflux and aspiration. Several studies using radio-labelled enteral feeding solutions in mechanically ventilated patients have reported that aspiration of gastric contents occurs to a greater degree when patients are in the supine position, compared with the semi-recumbent position [47, 48, 49]. In addition to the supine position, nasogastric tubes are a risk factor for aspiration because of increasing gastroesophageal reflux.

Semi-recumbent Position

Only two randomized studies have assessed the effect of the semi-recumbent position as a VAP-preventive measure. Drakulovic *et al*. [50], enrolled 86 intubated and mechanically ventilated patients, who were randomly assigned to a semi-recumbent or supine body position. The frequency of clinically suspected nosocomial pneumonia was lower in the semi-recumbent group than in the supine group (8 % vs. 34 %, $p = 0.003$). However, mortality was similar in both groups. Another recent study by Van Nieuwenhoven *et al*. [51], in which patients receiving mechanical ventilation were randomly assigned to backrest elevation of 45° vs the standard of 10°, did not demonstrate this relationship, perhaps because they found barriers to implementing this strategy.

Although the semi-recumbent position is theoretically useful for VAP prevention, and has been demonstrated in practice, several studies have shown a lack of adherence to this measure [51, 52, 53, 54].

Semi-recumbent positioning is a low cost and low-risk approach for preventing VAP.

Prone Position

Prone positioning has been shown to increase the PaO_2 in many patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). However, it has not been demonstrated that the prone position reduces mortality in ARDS patients.

Two studies have reported a significant reduction in VAP rates in patients in the prone rather than supine position, but mortality rate is not affected [55, 56]. However, the use of the prone position increases the risk of complications, including pressure sores, selective intubation and obstruction of endotracheal tube.

Therefore, the prone position cannot be recommended as a habitual measure in the prevention of the VAP.

Kinetic Beds

Healthy humans, even during sleep, change their position approximately every 11.6 minutes. This phenomenon has been named as the 'minimum physiologic mobility requirement' [57]. Critical patients often remain immobile in the supine position for a long time. In this position, the functional residual capacity is decreased because of alveolar closure in dependent lung zones and impaired mucociliary clearance. This leads to the accumulation of mucus, atelectasis onset and ensuing infection [58, 59, 60].

It has been suggested that the use of rotational therapy may improve some of these physiological changes. Rotational therapy includes kinetic bed therapy and continuous lateral rotation therapy (CLRT), which work with patients on beds that turn on their longitudinal axes intermittently or continuously.

Several studies have looked into the impact of rotational therapy on the incidence of VAP [61–74]. However, many of these studies have included relatively small sample sizes and have had poor methodological quality, with high heterogeneity. Recently, these studies have been analyzed in two meta-analyses [75, 76]. Both systematic reviews have found that kinetic therapy prevents VAP but does not modify either ventilator days or the stay in ICU. Furthermore, no reduction in either mortality rate or duration of hospital stay could be demonstrated [76].

Thus, rotational therapy diminishes VAP incidence, but due to high costs and the absence of impact on mortality, the duration of mechanical ventilation, or the length of stay in the ICU or hospital, its clinical use can still not be fully recommended.

Artificial Airway Management

Oral vs Nasal Intubation

Both nasogastric and nasotracheal tubes can cause oropharyngeal colonization and nosocomial sinusitis. In addition, the nasogastric tube, by impairing the function of the upper oesophagus sphincter, may facilitate gastroesophageal reflux. All this increases the risk of VAP [77, 78, 79, 80]. In a prospective study of sinusitis, Holzapfel *et al.* [78] found that bacterial paranasal sinusitis was associated with an almost three-fold increased risk of pneumonia. In another study of patients with sinusitis and VAP, Souweine *et al.* [81] recovered the same pathogens in cultures from both sites of infection.

Thus, use of the oral route for both endotracheal and gastric intubation should be considered to decrease the risk of VAP.

Subglottic Suctioning

Subglottic suctioning (SS) is performed through a special endotracheal tube with a separate lumen that opens on its dorsal side above the cuff and is connected to an evacuation system with a reservoir for secretions. This system can aspire continuously or intermittently [82]. The suction pressure must be set at a level of between 20 and 30 cm H_2O, and the system should be checked every four hours to assure lumen patency. The endotracheal tube cuff pressure should also monitored every four hours and maintained at a level of 25−30 cm H_2O.

The main pathogenic mechanism of VAP is the aspiration of contaminated secretions. Subglottic secretion drainage can prevent the development of VAP, since these secretions are pooled above the cuff of the endotracheal tube and may leak around it, entering the lower airway.

Six randomised trials have been performed to assess the role of SS in VAP prevention in both medical and surgical populations [83−86]. Four of these studies were performed in patients requiring more that 72 hours of mechanical ventilation. All the studies demonstrated a reduction in the relative risk of VAP in patients with subglottic secretion drainage. This reduction was statistically significant in all except the trial conducted by Kollef [85]. In the study by Vallés *et al*. [84], this decrease in VAP incidence was due to a reduction in episodes caused by Gram-positive cocci and *Haemophilus influenzae*. However, episodes caused by *Pseudomonas aeruginosa* and *Enterobacteriaceae* were not affected. Recently, Liu *et al*. [87] have observed something similar. The dominant bacteria cultured in the lower airway secretions were *P. aeruginosa* and *A. baumanii;* no significant difference between the use of SS and a standard endotracheal tube was revealed.

In a meta-analysis [88] of five of these studies, SS reduced the incidence of VAP by half, shortened ICU stay by three days and delayed the onset of VAP by 6.8 days.

Although these endotracheal tubes are more expensive, two analyses of cost-effectiveness have been carried out, by Shorr [89] and Dezfulian [88], with similar results. Use of SS resulted in savings of $4992 per case of VAP prevented.

No adverse events were reported with aspiration of subglottic secretions in a study done with more than 150 patients [85], although a study with animals conducted by Berra [90] demonstrated widespread injury to tracheal mucosa/submucosa from the use of continuous SS.

A tracheostomy tube capable of subglottic suction has recently become available, but there has been no report on its effectiveness [91].

Endotracheal Tube Cuff Pressure

The secretions that pool above inflated endotracheal tube cuffs may be a source of aspirated material and ensuing VAP. The endotracheal tube cuff pressure should be adequate to prevent leakage of colonized subglottic secretions into the lower airway, and to impede tracheal mucosa damage as well. Besides, the level of cuff pressure should be around of 25 cm H_2O (range, 25−30 cm H_2O).

The use of endotracheal tubes with low-pressure cuffs may increase the risk of VAP, whereas those with high-pressure cuffs may increase the risk of tracheal damage.

Persistent pressures into the tube cuff below 20 cm H_2O have been associated with the development of VAP [92]. On the other hand, tube cuff pressures over 30 cm H_2O may impair the blood flow of the tracheal mucosa layer, so damaging it [93].

Silver-Coated Endotracheal Tubes

A biofilm is defined as a microbial-derived sessile community – a 'city of microbes', and a real microbial 'bunker' as well [94] – characterized by cells that are irreversibly attached to a substratum, or interfaced with each other, are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription [95]. Biofilm formation on the distal third of an endotracheal tube occurs frequently and represents an important source of organisms that cause VAP [96]. Rates of bacterial biofilm formation increase over time as biofilms are protected from host humoral and cellular defences as well as antibiotics, and may contain high concentrations of bacteria.

Silver has interesting medical properties. It prevents biofilm formation, has bactericidal activity, reduces bacterial burden and also lessens the inflammatory response [97]. It has been shown that bacterial biofilm formation on urinary catheters has been reduced by the use of a silver coating [98].

A laboratory investigation demonstrated that by coating the endotracheal tube with silver, the bacterial load of the proximal tube was significantly reduced [99]. This use has been effective in preventing VAP in a dog model [100]. In dogs intubated with silver coated endotracheal tubes there was a delayed appearance of aerobic bacteria on the endotracheal tube surface, especially *Pseudomonas aeruginosa*, along with a lower bacterial burden in lung parenchyma. A prospective randomised study has recently evaluated the use of silver-coated endotracheal tubes [97]. In this study the proportion of patient days with quantitative endotracheal aspirates $>10^5$ CFU was greater among patients with uncoated endotracheal tubes. In another randomised study, silver-coated endotracheal tubes were associated with delayed colonization, reduced colonization rate by days on the tube, and in quantitative endotracheal aspirates compared with the control endotracheal tube [101].

Silver-coated endotracheal tubes appear to be safe, reduce bacterial biofilm and can delay airway colonization. However, further studies are needed to determine their efficacy in preventing VAP.

Suction Systems

Usual suctioning procedure includes hyperoxygenation, disconnection from the ventilator circuit and insertion of a sterile single-use catheter. Closed-circuit suctioning was introduced around 25 years ago to decrease the complications associated with traditional suctioning, allowing the patient to remain on positive-pressure ventilation and reducing environmental contamination by avoiding a 'break in the circuit'.

Although early studies demonstrated increased levels of catheter colonization in the closed system [102, 103], two prospective randomised trials of open versus closed suctioning systems have demonstrated no increase in VAP rates [104, 105]. However, other studies did find differences between both suctioning systems [106, 107]. Thus,

Combes *et al*. [106] reported a 3.5 times greater risk of VAP associated with the use of an open suctioning system than with that of a closed suctioning system; they also found that VAP increased the length of stay by 17 days. Recently, a prospective, randomised study did not find significant differences in either VAP development or number of VAP cases per 1000 mechanical ventilation days when both types of suction systems were compared [108].

Daily changes of these suction catheters are not needed for infection control, since a study on suction catheters did not find significant differences in VAP rates when daily changes were compared with no routine changes, which might reduce costs [109].

Centers for Disease Control and Prevention (CDC) have stated that 'no recommendation can be made for the preferential use of either the multi-use closed system suction catheter or the single-use open system suction catheter for prevention of pneumonia' [6].

Mechanical Ventilation Management

Ventilator Circuit Changes

Condensate collecting in the ventilator circuit can become contaminated from patient secretions or by opening the circuit and is a risk factor in VAP. Vigilance is needed to prevent accidental drainage of condensate into the lower airway and contamination of carers during ventilator disconnection.

Early use of mechanical ventilation was dominated by daily routine ventilator circuit changes. However, from 1982 this routine practice changed after a study comparing daily ventilator circuit changes to circuit changes every 48 hours reported that 30 % of ventilator circuits were colonized within 24 hours and 32 % by 48 hours [110]. Since then, several studies have evaluated the contribution of the ventilator circuits to VAP occurrence, focusing specifically on the frequency of circuit changes. These studies demonstrated that routine changing of ventilator circuits should be not recommended because no change in the incidence of VAP was observed [111−118]. Variable periods of change have been used in these trials, ranging from 48 hours to 2 weeks, and even monthly [117].

Two meta-analyses demonstrated that overwhelming evidence supports less frequent ventilator circuit changes [119, 120].

Thus, increasing the frequency of circuit changes does not prevent VAP, and it is an area for substantial cost saving. The maximum time that circuits can be left safely is still unknown.

The CDCs recommendation was 'do not change routinely, on basis of duration of use, the breathing circuit (i.e. ventilator tubing and exhalation valve and the attached humidifier) that is in use on an individual patient. Change the circuit when it is visibly soiled or mechanically malfunctioning' [6].

Humidification With Heat and Moisture Exchangers

Humidification of the inspired air is a major measure in ventilator management. The use of mechanical ventilation by an artificial airway requires the conditioning of inspired gas. Because medicinal gases are cold and dry, they need

heating and humidifying. Medicinal gases can be humidified using active humidifiers (heated humidifiers) or passive humidifiers (heat-moisture exchangers). In active or heated humidifiers (HH) inspired gas passes across a heated water bath. Passive humidifiers, known as artificial noses or heat moisture exchangers (HME), trap heat and humidity from air exhaled by the patient and return some of it to the patient on the subsequent inhalation. In humidification, formation of condensate in tubing and colonization of this condensate with microorganisms is an important risk factor for VAP.

Although the incidence of VAP has been analysed in many studies comparing HH use with HME use, these studies have included varied types of HME and HH, different types of suctioning, varied durations of mechanical ventilation and variable diagnostic criteria of VAP [121−129]. Several investigators reported lower rates of VAP in HME compared to HH groups [121, 124, 125, 130]. However, the effect of HME in preventing VAP is still controversial and recent studies have failed to show a significant difference in rates of infection [128, 129, 131].

Three meta-analyses have been carried out from many of these studies, comparing HME to HH with VAP incidence as the end point [119, 120, 132]. The most recent of these meta-analyses [132] showed a reduction in VAP rates in the HME group (relative risk [RR], 0.7), particularly in patients where the duration of mechanical ventilation was at least 7 days (RR, 0.57). However, as has happened in other meta-analyses, the pooled results were influenced by a single trial, the study by Kirton that showed a RR of 0.41. When this study was selectively removed from analysis, the trend towards a reduced VAP rate favoured HME use, but the differences were not statistically significant [133].

Contra-indications to HME use include the risk of airway occlusion from insufficient humidity, occlusion of the HME by blood or secretions, increased dead space ventilation, air leak (bronchopleural fistula, incompetent airway cuff) and hypothermia [134−137].

Duration of HME use has also been studied and it appears not to exhibit adverse effects for up to 96 hours [138, 139].

Thus, additional studies are needed to identify the benefits of HME to infection control of VAP. No recommendation can be made yet for the preferential use of either HME or HH to prevent VAP [6].

Non-Invasive Positive Pressure Ventilation (Tracheal Intubation Avoidance)

Endotracheal intubation is one of the most important risk factors contributing to the onset of VAP. Both intubation and mechanical ventilation increase the risk of VAP six- to 21-fold and therefore should be avoided whenever possible [6, 140−142]. Several factors can contribute to increased VAP risk, including: the presence of sinusitis and trauma to nasopharynx (nasotracheal tube), impaired swallowing of secretions, increased bacterial adherence and colonization of airways, presence of a foreign body that traumatizes the oropharyngeal epithelium, ischemia secondary to cuff pressure, impaired ciliary clearance and diminished cough, leakage of secretions around the cuff and repeated suctioning to remove secretions. VAP is often due to aspiration of pharyngeal secretions around the cuff of the endotracheal tube [143].

Moreover, several studies have identified an association between the duration of mechanical ventilation and the development of VAP [92, 144, 145, 146]. Cook *et al*. reported a cumulative increased risk of VAP across time (3 % per day in the first week, 2 % per day in the second week and 1 % per day en the third week) [147]. Specific strategies have been recommended to reduce the duration of mechanical ventilation, including optimised use of sedative and analgesic drugs and implementing clinical guides that facilitate and accelerate weaning.

Non-invasive positive pressure ventilation (NPPV) is an attractive alternative for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), or acute hypoxemic respiratory failure. The use of NPPV in selected groups of patients has been shown to be effective in preventing endotracheal intubation. NPPV decreases the rates of intubation and mortality, particularly when it is indicated for exacerbations of chronic obstructive pulmonary disease (the greater exacerbation the most benefit) [148−152].

The impact of NPPV on the development of VAP and clinical outcome has been studied in randomised trials which included a wide spectrum of diseases [153−165]. Nourdine *et al*. [157] conducted a prospective epidemiologic survey observing the pneumonia rate in patients receiving NPPV, comparing them with those receiving invasive ventilation support. Pneumonia occurred in none of the 129 patients who received only NPPV, four out of 25 (16 %) patients who received NPPV and were subsequently intubated, compared to 80 out of 607 (13 %) patients receiving only invasive ventilation support ($p < 0.01$). A meta-analysis [166] pooling 12 studies, showed a strong benefit of NPPV (RR, 0.31; 95 % confidence interval [CI], 0.16−0.57, $p = 0.0002$). Although a few studies were designed specifically to assess the effect of NPPV on pneumonia rate, in most of the studies pneumonia rate was a secondary outcome.

Burns *et al*. [167], in a recent Cochrane review, reported significant benefits of NPPV use, including: decreased mortality (RR, 0.41; 95 % CI, 0.22−0.76), lower rates of VAP (RR, 0.28; 95 % CI, 0.09−0.85), decreased length of ICU and hospital stay and lower duration of mechanical support. In addition, sub-group analyses suggested fewer weaning failures and a lower mortality associated with NPPV in COPD when compared to mixed populations.

However, NPPV use has been not recommended for respiratory failure after extubation. Two randomised, controlled trials examined the use of NPPV in patients with respiratory failure after extubation. Initially, Keenan *et al*. [162] enrolled 81 patients in a single-centre study and found that the use of non-invasive ventilation did not significantly alter the need for reintubation. Recently, Esteban *et al*. [168], in a multicentre study enrolled 221 patients (114 patients randomly assigned to NPPV and 107 patients to standard medical therapy), and reported that NPPV neither precluded reintubation nor reduced mortality in unselected patients who have respiratory failure after extubation. Mortality rates tended to be higher among the patients assigned to non-invasive ventilation than among those assigned to standard medical therapy. Therefore, these findings indicate that NPPV may not be a good strategy for avoiding reintubation after initial extubation.

Pharmacologic Strategies

Decolonization of the Aerodigestive Tract

The human upper airways (above the vocal cords) are usually heavily colonized, whereas the lower respiratory tract is sterile, in spite of most adults aspirating during sleep. Normal flora in the oropharynx includes *Streptococcus viridans*, *Haemophilus* sp and anaerobes. However, there is a predominance of aerobic Gram-negative bacilli and *Staphylococcus aureus* in the oral flora of critically ill patients [169, 170].

The oropharyx constitutes the endogenous source of microorganisms that colonize and infect the lower airways following microaspiration of saliva or migration of bacteria. Oropharyngeal colonization, either present on admission or acquired during ICU stay, has been identified as an independent risk factor for the development of VAP caused by enteric Gram-negative bacteria and *Pseudomonas aeruginosa* [171]. Up to 85 % of pneumonia cases that occur during mechanical ventilation are caused by microorganisms from the patient's own oropharyngeal flora. This is the endogenous mechanism in the pathogenesis of VAP [172].

Several factors have been involved in disturbing the host defence mechanisms of mechanically ventilated patients; reduced mucosal immunoglobulin A, elevated airway pH and an impaired cough reflex compromise mucociliary clearance and damage the tracheal epithelium. After a patient is intubated and mechanically ventilated, the airway loses sterility and becomes colonized within hours. The risk of subsequent VAP is greatest in the first week after intubation. Rates of 3 % per day in mechanical ventilation have been reported [147].

Modulation of Oropharyngeal Colonization

Chlorhexidine is an antiseptic solution that has been used since 1959 for the control of dental plaque. Several studies have evaluated the use of chlorhexidine antiseptic solution for oral care in prevention of VAP [173–177]. Oral care with chlorhexidine solution has been shown to reduce the incidence of oral microbial colonization and the occurrence of VAP. However, in several studies this prophylaxis measure was studied in a low risk population, namely cardiac-surgical patients.

In a recent multi-centre, randomised clinical trial, Koeman *et al.* [177] studied VAP outcomes of three groups of patients; those treated with 2 % chlorhexidine (CHX) paste (n = 127), those receiving 2 % chlorhexidine with 2 % colistin paste (CHX–COL) (n = 128), and a third group receiving a placebo (n = 130). The daily risk of VAP was significantly reduced (65 %) in the CHX group, and 55 % in the CHX–COL group but there was no reduction in placebo group. CHX–COL provided a significant reduction in oropharyngeal colonization by both Gram-negative and Gram-positive bacteria, whereas CHX mostly affected Gram-positive colonization. Endotracheal colonization was reduced in CHX–COL patients, and to lesser extent in CHX patients. No differences were noted in the duration of mechanical ventilation, ICU stay or survival rates among the different study groups.

Topical oral decontamination with CHX or CHX−COL appears to reduce VAP incidence and oral contamination. It is a cheap measure, but whether is it a safe one − it does not select resistant microorganisms − remains to be investigated.

Selective Decontamination of the Digestive Tract

Selective decontamination of the digestive tract (SDD) is the decontamination of potentially pathogenic microorganisms living in the mouth and stomach, whilst jointly attempting to preserve the indigenous anaerobic flora to prevent the overgrowth of resistant pathogens.

Different antibiotic combinations have been evaluated. The most common regimen uses a combination of three topical, nonabsorbent antibiotics: polymyxin E, tobramycin, and amphotericin B.

Selective decontamination of the digestive tract has three components: oral, gastric and intravenous, although the basic elements are the first two [178]. The oral component consists of the cleaning of the oropharynx with 0.1 % hexetidine and the application of a topical triple-antibiotic paste containing 2 % concentrations of polymyxin E, tobramycin (or gentamicin) and amphotericin B. The gastric component is achieved by administrating a solution containing 100 mg of polymyxin E, 80 mg of tobramicin (or gentamicin) and 500 mg of amphotericin B. These topical antibiotics are given at six-hour intervals daily through a gastric tube (oro or nasogastric), and also four times daily as 0.5 g of paste with methylcellulose, which is used as an adherent agent (so lengthening the contact time between antibiotics and microorganisms). Selective decontamination of the digestive tract can be supplemented by administration of intravenous antibiotics, normally for 3−4 days, using standard doses of either cefotaxime or ceftriaxone. In addition, polymyxin E or amphotericin B may be given by nebulisation in cases of persistent tracheal colonization, or the same paste may be applied around the tracheostomy [179].

Around 54 trials on SDD have been published during the last 20 years. It is difficult to assess their results since substantial methodological differences exist, including populations, study design and SDD regimens used. Several studies have been done with selected patients, such as pancreatitis or liver transplant patients. Reported benefits of SDD in these studies include decreased incidence of VAP [180−184], decreased mortality rate [181, 184, 185], decreased length of stay in ICU [185], along with cost savings [183, 185]. However, VAP rates differed in both study groups, reflecting differences in diagnostic criteria.

The results of many of these studies have been pooled and analysed in several meta-analyses [186−194]. Pooled results of meta-analyses have shown that SDD reduces VAP rates in mixed ICU populations (medical, trauma and surgical patients). This benefit appears to be greater in combined use of topical and systemic prophylaxis compared with topical prophylaxis alone [178].

In his review Liberati *et al*. [190] stated that the number needed to treat (NNT) was five patients to prevent one infection, whereas the number of patients who need to be treated to prevent one death was 21.

When evaluating mortality as an outcome variable, pooled results of meta-analyses have not shown a significant reduction in mortality rates (odds ratio [OR]

from 0.70 to 1.14). However, a recent meta-analysis [190] did find that SDD regimens which use combined topical and parenteral antibiotic regimens reduced mortality rates (OR, 0.60−0.81) compared to regimens that used topical antibiotics alone (OR, 0.86−1.14). Besides, SDD has been shown to have a protective effect on mortality rates in surgical patients receiving topical with parenteral antibiotic prophylaxis [186].

Selective decontamination of the digestive tract has been demonstrated to decrease both VAP rates and duration of stay in ICU in two large studies [180, 185].

The principal risk associated with SDD is the emergence of antibiotic-resistant flora, especially methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *enterococcus* (VRE), because SDD is not active against these pathogens [195]. Five studies have prospectively evaluated antibiotic resistance over a long period (between two and seven years), and no increase in the rate of super-infections due to resistant bacteria could be demonstrated [196−198]. Several trials conducted in ICUs where MRSA was endemic showed a trend towards higher MRSA infection rates in patients receiving SDD. However, three studies using vancomycin as oropharingeal or enteral components for SDD demonstrated the prevention and eradication of carriage and overgrowth of MRSA, and a reduction of severe infections by MRSA [199−201].

In summary, SDD is an effective and safe preventive measure in ICUs where incidence rates of MRSA and VRE are low, but in ICUs with high rates of multi-resistant microorganisms it is a measure that is effective but not safe. Since acceleration in the development of resistant bacteria is a substantial long-term risk, no evidence exists of its safety over a long time. There would be a potential long-term risk to public health. The routine use of SDD in ICUs cannot be recommended, and its indication should be decided according to the characteristics of the clinical population and ICU. Continued evaluation of delayed complications related to antibiotic resistance is warranted before SDD is widely implemented [179, 202, 203].

Stress Ulcer Prophylaxis

Evidence exists to implicate the stomach as a potential reservoir of bacteria causing VAP, because gastric contents can be aspired into the lower airways [204−206].

In humans, few bacteria entering the stomach survive in the presence of gastric acid. However, conditions that reduce the gastric pH, such as treatment with H_2 antagonists (histamine H_2 receptors antagonists) or proton-pump inhibitors, or enteral nutrition, predispose the stomach to bacterial proliferation. Studies have shown a powerful relationship between a high gastric pH and a massive overgrowth of gastric bacteria. Clinical evidence suggests that a gastric pH of 3.5 prevents bacterial colonization, whereas a pH >4.0 is associated with clinically important bacterial colonization and a higher incidence of nosocomial pneumonia [207, 208].

Critically ill patients with either respiratory failure requiring mechanical ventilation or coagulopathy are at increased risk from clinically important, stress-related gastrointestinal bleeding. This has been associated with a significantly higher mortality rate, compared to patients without evidence of bleeding [209].

Sucralfate, an agent often used for stress ulcer prophylaxis, has a limited effect on gastric pH, and has both cytoprotective and antibacterial properties, and thus may not increase the risk of pneumonia.

Seven meta-analyses of over 20 randomised trials have evaluated the risk of VAP associated with various methods of stress ulcer prophylaxis [210−216]. Four of the seven meta-analyses reported a significantly decreased incidence of VAP with sucralfate therapy compared with H_2 antagonists [211, 213, 214, 216]. Three of them reported a statistically significant mortality benefit with sucralfate [210, 211, 215]. In addition, three meta-analyses found similar trends in the reduction of VAP rates in patients give sucralfate [210, 212, 215].

However, a recent randomised trial compared sucralfate with ranitidine and found no effect on VAP occurrence, though it did show a significant increase in the risk of clinically important bleeding associated to sucralfate use. There was also a relative and nonsignificant increase in VAP rates among the patients treated with ranitidine. Mortality rates were similar in both groups [217].

Critically ill patients at risk from important gastrointestinal bleeding (shock, respiratory failure requiring mechanical ventilation or coagulopathy) should receive H_2 antagonists such as ranitidine rather than sucralfate.

Antibiotic Policy and Infection Control

Infection control programs have demonstrated efficacy in reducing nosocomial infection rates and restraining multidrug resistant (MDR) microorganism emergence [218, 31, 34]. All personnel involved, including clinicians and laboratory, pharmacy and infection control staff, should know and share microbiological results and infect rates.

Antibiotic policy is a major issue in nosocomial infection control. Practice guidelines [11] for antimicrobial therapy that attempt to restrict antibiotic use are expected to help prevent antibiotic-resistant infections. Antibiotic control programs serve not only to control infections but also to reduce the emergence of MDR microbes and reduce healthcare costs.

Establishing a rational antibiotic policy is a key issue for both better patient care and combating antimicrobial resistance [219]. The problem of rational antibiotic use is complex and requires coordination of the activities of healthcare authorities, institutions, and individual practitioners. The rational use of antibiotics should be established in both hospital and healthcare settings; and institutional, regional, national and global aspects of antibiotics policies should be considered [220].

A strategy using a scheduled switch of antibiotic class appears to minimize antimicrobial resistance [221, 222]. Such a strategy has been associated with decreases in VAP rate in cases of antibiotic-resistance emergence.

Controlling antibiotic use constitutes a crucial issue in preventive strategies. Development and colonization of resistant organisms have been associated with prolonged use or unnecessary use of broad-spectrum antibiotics. Reducing the use of broad-spectrum antibiotics and shortening the duration of antibiotic therapy have been shown to decrease colonization and VAP rates. Combining antibiotic restriction with

antibiotic rotation has proved to be an effective measure of controlling resistant organisms. Antibiotic rotation schemes and antibiotic class switches can reduce VAP rates, and prevalence of resistant organisms.

Shortening the duration of empirical antibiotic therapy may also be a strategy for reducing subsequent VAP caused by antibiotic-resistant bacteria [223−225]. Nevertheless, a randomized trial involving VAP patients, comparing 8 days of adequate antibiotic therapy with 15 days of treatment, gave evidence that despite similar efficacy the longer course of antibiotic therapy was associated with a significantly greater emergence of resistant bacteria [226].

Following initial empiric therapy, de-escalation means using microbiologic and clinical data to change from an initial broad-spectrum, multidrug empiric therapy regimen to a therapy with fewer antibiotics and agents of narrower spectrum [227]. De-escalation therapy is a relatively new concept that is currently used in the management of serious infections, particularly serious nosocomial pneumonias. Its practice is at the halfway between two controversial positions: the exclusive use of an empirical prescription of antibiotics following a clinical diagnosis and the approach that urges the use of bronchoscopic techniques to assure the diagnosis of VAP and to direct the antibiotic treatment [228].

Several recent studies have shown how the application of de-escalation therapy can lead to a high rate of initially appropriate empiric therapy of VAP, while still limiting the use of antibiotics, and thereby helping to control antimicrobial resistance [228−231].

Antibiotic rotation programs have yielded results that are more difficult to appraise, though this approach has also been recommended for lessening MDR pathogens [232, 233].

Transfusion Practice

Several studies have suggested that the use of red blood cell (RBC) transfusion heightens the risk of nosocomial infection in non-ICU patients. Similar data have been reported for VAP [234−236]. In a secondary analysis of data from a large study ($n = 4892$) on transfusion practices in critically ill patients, RBC transfusion was found to be an independent risk factor for VAP [237, 238].

Moreover, RBC transfusion clearly represents an easily modifiable risk factor. In a study performed by Levy *et al.* [239], patients receiving mechanical ventilation received RBC transfusions at higher pre-transfusion haemoglobin concentrations than those not receiving mechanical ventilation (8.7 ± 1.7 g/dL vs. 8.2 ± 1.7 g/dL, respectively; $p < 0.0001$). It was concluded that while longer ICU stays accounted for much of this risk, patients receiving mechanical ventilation also appeared to undergo transfusions at higher haemoglobin thresholds than patients who were not mechanically ventilated, at least early in the ICU stay. Justification of this relatively liberal transfusion practice in patients receiving mechanical ventilation will require further studies.

Recently, Taylor *et al*. [240] studied the effects of RBC transfusion in 2085 critically ill patients (21.5 % of those receiving RBC transfusions). Different outcomes were analysed including nosocomial infections, mortality rates and intensive care unit and length of hospital stay. Pneumonia was the most common of the infections not present on admission that occurred during the stay in the ICU, followed by sepsis and bacteraemia. The rate of nosocomial infections that occurred after transfusions was 14.3 %. This rate was significantly higher than that of non-transfused patients (5.8 %) ($p < 0.0001$). A multivariate analysis demonstrated that only the number of transfusions was independently associated with nosocomial infection (OR, 1.097; 95 % CI, 1.028−1.171).

Originally, the Transfusion Requirements in Critical Care (TRICC) trial had concluded [241] that a restrictive strategy of red cell transfusion is at least as effective as, and possibly superior to, a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.

Sedation and Duration of Mechanical Ventilation

There is evidence that the longer patients are intubated and receiving mechanical ventilation, the greater is the risk of VAP occurring [146].

Elevated doses and administration over long periods of sedative drugs should be prevented in order to reduce aspiration of oropharyngeal contents.

Using sedation protocols appears to be useful for reducing VAP risk and subsequent increased ICU stay [143]. By implementing such protocols reduces the number of episodes of unplanned extubation and self-extubation.

Daily interruption of sedative drugs, allowing patients to wake up, has been demonstrated to decrease the duration of mechanical ventilation and ICU stay [242].

A study recently compared the continuous infusion of sedative drugs with a regimen based on a daily interruption of sedative infusions. The group of patients whose sedative infusion was interrupted daily had a shorter ICU stay, shorter mechanical ventilation and a lower incidence of complications [243].

References

1. National Nosocomial Infections Surveillance System (2004) National nosocomial infections surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control*, **32**, 470−485.
2. Richards, M.J., Edwards, J.R., Culver, D.H. *et al.* (2000) Nosocomial infections in combined medical-surgical intensive care units in the united states. *Infect Control Hosp Epidemiol*, **21**, 510−15.
3. Vincent, J.L., Bihari, D.J., Suter, P.M. *et al*. (1995) The prevalence of nosocomial infection in intensive care units in Europe: Results of the European prevalence of infection in intensive care (EPIC) study. *EPIC International Advisory Committee JAMA*, **274**, 639−44.
4. Heyland, D.K., Cook, D.J., Griffith, L. *et al*. (1999) The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian critical trials group. *Am J Respir Crit Care Med*, **159**, 1249−56.

5. American Thoracic Society. (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*, **171**, 388−416.
6. Centers for Disease Control, and Prevention (2004)Tablan O.C., Anderson L.J., Besser R., Bridges C., Hajjeh R., C.D.C, healthcare infection control practices advisory committee (2004). Guidelines for preventing health-care--associated pneumonia, 2003: Recommendations of CDC and the healthcare infection control practices advisory committee. *MMWR Recomm Rep*, **53** (RR-3), 1−36.
7. Isakow, W. and Kollef, M. Preventing ventilator-associated pneumonia: An evidence-based approach of modifiable risk factors. (2006) *Semin Respir Crit Care Med*, **27**, 5−17.
8. Kollef, M.H. (1999) The prevention of ventilator associated pneumonia. *N Engl J Med*, **340**, 627−34.
9. Heyland, D.K., Cook, D.J., Dodek, P.M. *et al*. (2002) Prevention of ventilator-associated pneumonia: Current practice in Canadian intensive care units. *J Crit Care*, **17**, 161−7.
10. Collard, H.R., Saint, S. and Matthay, M.A. (2003) Prevention of ventilator-associated pneumonia: An evidence-based systematic review. *Ann Intern Med*, **138**, 494−501.
11. Kollef, M.H. and Fraser, V.J. (2001) Antibiotic resistance in the intensive care unit. *Ann Intern Med*, **134**, 298−314.
12. Fagon, J.Y., Chastre, J., Wolff, M. *et al*. (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia: A randomized trial. *Ann Intern Med*, **132**, 621−30.
13. Halm, E.A., Atlas, S.J., Borowsky, L.H. *et al*. (2000) Understanding physician adherence with a pneumonia practice guideline: Effects of patient, system, and physician factors. *Arch Intern Med*, **160**, 98−104.
14. Cook, D., Ricard, J.D., Reeve, B. *et al*. (2000) Ventilator circuit and secretion management strategies: A Franco−Canadian survey. *Crit Care Med*, **28**, 3547−54.
15. Manangan, L.P., Banerjee, S.N. and Jarvis, W.R. (2000) Association between implementation of CDC recommendations and ventilator-associated pneumonia at selected US hospitals. *Am J Infect Control*, **28**, 222−7.
16. Rello, J., Lorente, C., Bodi, M. *et al*. (2002) Why do physicians not follow evidence-based guidelines for preventing ventilator-associated pneumonia?: A survey based on the opinions of an international panel of intensivists. *Chest*, **122**, 656−61.
17. Berwick, D.M., Calkins, D.R., McCannon, C.J. *et al*. (2006) The 100 000 lives campaign setting a goal and a deadline for improving health care quality. *JAMA*, **295**, 324−7.
18. 100k Lives Campaign. Institute for Healthcare Improvement Web page. Available at: http://www.ihi.org/IHI/Programs/Campaign.
19. Rubenfeld, G.D. (2004) Implementing effective ventilator practice at the bedside. *Curr Opin Crit Care*, **10**, 33−9.
20. Chassin, M.R. (1997) Assessing strategies for quality improvement. *Health Aff*, **16**, 151−61.
21. Chassin, M.R. and Calvin, R.W. (1998) The urgent need to improve healthcare quality. Institute of medicine national roundtable on healthcare quality. *JAMA*, **280**, 1000−5.
22. Veninga, C.G., Lagerlow, P., Wahlstrom, R. *et al*. (1999) Evaluating an educational intervention to improve the treatment of asthma in four European countries. Drug education project group. *Am J Respir Crit Care Med*, **160**, 1254−62.
23. Esteban, A., Inmaculada, A. and Ibañez, J. *et al*. (1994) Modes of mechanical ventilation and weaning: A national survey of Spanish hospitals. *Chest*, **106**, 1188−93.

24. Richard, J.C., Carlucci, A., Wysocki, M. *et al*. (1999) French multicentre survey: Non-invasive versus conventional mechanical ventilation. *Am Rev Respir Crit Care Med*, **159**, A367.
25. Venus, B., Smith, R.A. and Mathru, M. (1987) National survey of methods and criteria used for weaning from mechanical ventilation. *Crit Care Med*, **15**, 530–3.
26. Ricard, J.D., Cook, D., Griffith, L. *et al*. (2002) Physicians' attitude to use heat and moisture exchangers or heated humidifiers: A Franco–Canadian survey. *Intensive Care Med*, **28**, 719–25.
27. Sierra, R., Benitez, E., Leon, C. *et al*. (2005) Prevention and diagnosis of ventilator-associated pneumonia. A survey on current practices in southern Spanish ICUs. *Chest*, **128**, 1667–73.
28. Ricart, M., Lorente, C., Diaz, E. *et al*. (2003) Nursing adherence with evidence-based guidelines for preventing ventilator-associated pneumonia. *Crit Care Med*, **31**, 2693–6.
29. Craven, D.E. (2006) Preventing ventilator-associated pneumonia in adults. *Chest*, **130**, 251–60.
30. Zack, J.E., Garrison, T., Trovillion, E. *et al*. (2002) Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. *Crit Care Med*, **30**, 2407–12.
31. Kollef, M.H. (2004) Prevention of hospital-associated pneumonia and ventilator associated pneumonia. *Crit Care Med*, **32**, 1396–405.
32. Babcock, H.M., Zack, J.E., Garrison, T. *et al*. (2004) An educational intervention to reduce ventilator-associated pneumonia in an integrated health system: A comparison of effects. *Chest*, **125**, 2224–31.
33. Rello, J., Ollendorf, D.A., Oster, G. *et al*. (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest*, **122**, 2115–21.
34. Crnich, C.J., Safdar, N. and Maki, D.G. (2005) The role of the intensive care unit environment in the pathogenesis and prevention of ventilator-associated pneumonia. *Respir Care*, **50**, 813–36.
35. Dang, D., Johanlgen, M.E., Prontovost, P. *et al*. (2002) Postoperative complications: Does intensive care unit staff and nursing make a difference. *Heart Lung*, **31**, 219–28.
36. Hoffman, P.N., Cooke, E.M., McCarville, M.R. *et al*. (1985) Microorganisms isolated from skin under wedding rings worn by hospital staff. *Br Med J*, **290**, 206–7.
37. Jacobson, G., Thiele, J.E., McCune, J.H. *et al*. (1985) Handwashing: Ring-wearing and number of microorganisms. *Nurs Res*, **34**, 186–8.
38. Salisbury, D.M., Hutfilz, P., Treen, L.M. *et al*. (1997) The effect of rings on microbial load of healthcare workers' hands. *Am J Infect Control*, **25**, 24–7.
39. Centers for Disease Control, and Prevention (2002)Boyce JM, Pittet D, Healthcare Infection Control Practices Advisory Committee, HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force (2002). Guideline for Hand Hygiene in Health-Care Settings. Recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Society for Healthcare Epidemiology of America/Association for Professionals in Infection Control/Infectious Diseases Society of America. *MMWR Recomm Rep*, **51** (RR-16), 1–45, quiz CE1–4.
40. Thompson, B.L., Dwyer, D.M., Ussery, X.T. *et al*. (1997) Handwashing and glove use in a long-term care facility. *Infect Control Hosp Epidemiol*, **18**, 97–103.
41. Pittet, D., Mourouga, P. and Pernerger, T.V. (1999) Compliance with handwashing in a teaching hospital. Infection control program. *Ann Intern Med*, **130**, 126–30.
42. Harris, A.D., Samore, M.H., Nafziger, R. *et al*. (2000) A survey on handwashing practices and opinions of healthcare workers. *J Hosp Infect*, **45**, 318–21.

43. Girou, E., Loyeau, S., Legrand, P. *et al*. (2002) Efficacy of handrubbing with alcohol based solution versus satandard handwashing with antiseptic soap: Randomized clinical trial. *BMJ*, **325**, 362.
44. Trick, W.E., Vernon, M.O., Hayes, R.A. *et al*. (2003) Impact of ring wearing on hand contamination and comparison of hand hygiene agents in a hospital. *Clin Infect Dis*, **36**, 1383–90.
45. Craven, D.E. and Steger, K.A. (1997) Hospital-acquired pneumonia: Perspectives for the healthcare epidemiologist. *Infect Control Hosp Epidemol*, **18**, 783–95.
46. Pittet, D., Hugonnet, S., Harbarth, S. *et al*. (2000) Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. *Lancet*, **356**, 1307–12.
47. Ibañez, J., Peñafiel, A., Raurich, J.M. *et al*. (1992) Gastroesophageal reflux in intubated patients receiving enteral nutrition: Effect of supine and semirecumbent positions. *J Parenter Enteral Nutr*, **16**, 419–22.
48. Torres, A., Serra-Battles, J., Ros, E. *et al*. (1992) Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: The effect of body position. *Ann Intern Med*, **116**, 540–3.
49. Orozco-Levi, M., Torres, A., Ferrer, M. *et al*. (1995) Semirecumbent position protects from pulmonary aspiration but no completely from gastroesophageal reflux in mechanical ventilation patients. *Am J Respir Crit Care Med*, **152**, 1387–90.
50. Drakulovic, M.B., Torres, A., Bauer, T.T. *et al*. (1999) Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A ramdomised trial. *Lancet*, **354**, 1851–8.
51. van Nieuwenhoven, C.A., Vandenbroucke-Grauls, C. and van Tiel, F.H. *et al*. (2006) Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A ramdomized study. *Crit Care*, **34**, 396–402.
52. Helman, D.L.Jr, Sherner, J.H.III.,Fitzpatrick, T.M. *et al*. (2003) Effect of standardized orders and provider education on head-of-bed positioning in mechanically ventilated patients. *Crit Care Med*, **31**, 2285–90.
53. Kollef, M.H. (1993) Ventilator-associated pneumonia: A multivariate analysis. *JAMA*, **270**, 1965–70.
54. Reeve, B.K. (1999) Semirecumbency among mechanically ventilated ICU patients: A multicentre observational study. *Clin Intensive Care*, **10**, 241–4.
55. Guerin, C., Gaillard, S., Lemasson, S. *et al*. (2004) Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA*, **292**, 2379–87.
56. Beuret, P., Carton, M., Nourdine, K. *et al*. (2002) Prone position as prevention of lung injury in comatose patients: A prospective, randomized, controlled study. *Intensive Care Med*, **28**, 564–9.
57. Keane, F.X. (1979) The minimum physiological mobility requirement for man supported on a soft surface. *Paraplegia*, **16**, 383–9.
58. Konrad, F., Schiener, R., Marx, T. *et al*. (1995) Ultrastructure and mucociliary transport of bronchial respiratory epithelium in intubated patients. *Intensive Care Med*, **21**, 482–9.
59. Dolovich, M., Rushbrook, J. and Churchill, E. (1998) Effect of continuous lateral rotational therapy on lung mucus transport in mechanically ventilated patients. *J Crit Care*, **13**, 119–25.
60. Marik, P.E. and Fink, M.P. (2002) One good turn deserves another. *Crit Care Med*, **30**, 2146–8.
61. Gentilello, L., Thompson, D.A., Tonnesen, A.S. *et al*. (1988) Effect of a rotating bed on the incidence of pulmonary complications in critically ill patients. *Crit Care Med*, **16**, 783–6.

62. Summer, W., Curry, P., Haponik, E.F. *et al*. (1989) Continuous mechanical turning of intensive care unit patients shortens length of stay in some diagnostic-related groups. *J Crit Care*, **4**, 45−53.
63. Demarest, G.B., Schmidt-Nowara, W.W., Vance, L.W. *et al*. (1989) Use of the kinetic treatment table to prevent the pulmonary complications of multiple trauma. *West J Med*, **150**, 35−8.
64. Fink, M., Helsmoortel, C.M., Stein, K.L. *et al*. (1990) The efficacy of an oscillating bed in the prevention of lower respiratory tract infection in critically ill victims of blunt trauma. A prospective study. *Chest*, **97**, 132−7.
65. Clemmer, T.P., Green, S., Ziegler, B. *et al*. (1990) Effectiveness of the kinetic treatment table for preventing and treating pulmonary complications in severely head-injured patients. *Crit Care Med*, **18**, 614−17.
66. Shapiro, M.J. and Keegan, M.J. (1992) Continuous oscillation therapy for the treatment of pulmonary contusion. *Am Surg*, **58**, 546−50.
67. Nelson, L.D. and Choi, S.C. (1992) Kinetic therapy in critically ill trauma patients. *Clinical Intensive Care*, **3**, 248−52.
68. deBoisblanc, B., Castro, M., Everret, B. *et al*. (1993) Effect of air-supported, continuous, postural oscillation on the risk of early ICU pneumonia in nontraumatic critical illness. *Chest*, **103**, 1543−7.
69. Whiteman, K., Nachtmann, L., Kramer, D. *et al*. (1995) Effects of continuous lateral rotation therapy on pulmonary complications in liver transplant patients. *Am J Crit Care*, **4**, 133−9.
70. Traver, G.A., Tyler, M.L., Hudson, L.D. *et al*. (1995) Continuous oscillation: Outcome in critically ill patients. *J Crit Care*, **10**, 97−103.
71. MacIntyre, N., Helms, M., Wunderink, R. *et al*. (1999) Automated rotational therapy for the prevention of respiratory complications during mechanical ventilation. *Respiratory Care*, **44**, 1447−51.
72. Kirschenbaum, L., Azzi, E., Sfeir, T. *et al*. (2002) Effect of continuous lateral rotational therapy on the prevalence of ventilator-associated pneumonia in patients requiring long-term ventilatory care. *Crit Care Med*, **30**, 1983−6.
73. Bhazad, M., Ross, J., Ciddock, D. *et al*. (2002) The effect of continual lateral rotation vs conventional critical care bed in the management of acute respiratory distress syndrome. *Chest*, **122**, 53S−4S.
74. Ahrens, T., Kollef, M., Stewart, J. *et al*. (2004) Effect of kinetic therapy on pulmonary complications. *Am J Crit Care*, **13**, 376−83.
75. Hess, D.R. (2005b) Patient positioning and ventilator-associated pneumonia. *Respir Care*, **50**, 892−8.
76. Delaney, A., Gray, H., Laupland, K.B. *et al*. (2006) Kinetic bed therapy to prevent nosocomial pneumonia in mechanical ventilated patients: A systematic review and meta-analysis. *Crit Care*, **10**, R70.
77. Holzapfel, L., Chevret, S., Madinier, G. *et al*. (1993) Influence of long-term oro or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: Results of a prospective, randomized, clinical trial. *Crit Care Med*, **21**, 1132−8.
78. Salord, F., Gaussorgues, P.Marti-Flich, J. *et al*. (1990) Nosocomial maxillary sinusitis during mechanical ventilation: A prospective comparison of orotracheal versus the nasotracheal route for intubation. *Intensive Care Med*, **16**, 390−3.
79. Bach, A., Boehrer, H., Schmidt, H. *et al*. (1992) Nosocomial sinusitis in ventilated patients. Nasotracheal versus orotracheal intubation. *Anaesthesia*, **47**, 335−9.
80. Rouby, J.L., Laurent, P. and Gosnach, M. *et al*. (1994) Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med*, **150**, 776−83.

81. Souweine, B., Mom, T., Traore, O. *et al*. (2000) Ventilator-associated sinusitis: Microbiological results of sinus aspirates in patients on antibiotics. *Anesthesiology*, **93**, 1255–60.
82. Smulders, K., Van der Hoeven, H. and Weers-Pothoff, I. *et al*. (2002) A randomized clinical trial of intermittent subglottic secretions drainage in patients receiving mechanical ventilation. *Chest*, **121**, 858–62.
83. Mahul, P., Auboyer, C., Jospe, R. *et al*. (1992) Prevention of nososcomial pneumonia in intubated patients: Respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intensive Care Med*, **18**, 20–5.
84. Vallés, J., Artigas, A., Rello, J. *et al*. (1995) Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann Intern Med*, **122**, 179–86.
85. Kollef, M.H., Skubas, N.J. and Sundt, T.N. (1999) A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. *Chest*, **116**, 1339–46.
86. Bo, H., He, L. and Qu, J. (2000) Influence of the subglottic secretion drainage on the morbidity of ventilator associated pneumonia in mechanically ventilated patients. *Zhonghua Jie He He Hu Xi Za Ahi*, **23**, 472–4.
87. Liu, S.H., Yan, X.X., Cao, S.Q. *et al*. (2006) The effect of subglottic secretion drainage on prevention of ventilator-associated lower airway infection. *Zhonghua Jie He He Hu Xi Za Zhi*, **29**, 19–22.
88. Dezfulian, C., Shojania, K., Collard, H.R. *et al*. (2005) Subglottic secretion drainage for preventing ventilator-associated pneumonia: A meta-analysis. *Am J Med*, **118**, 11–18.
89. Shorr, A.F. and O'Malley, P.G. (2001) Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia: Potential economic implications. *Chest*, **119**, 228–35.
90. Berra, L., De Marchi, L., Panigada, M. *et al*. (2004) Evaluation of continuous aspiration of subglottic secretion in an in vivo study. *Crit Care Med*, **32**, 2071–8.
91. Hess, D.R. (2005c) Tracheostomy tubes and related appliances. *Respir Care*, **50**, 497–510.
92. Rello, J., Soñora, R., Jubert, P. *et al*. (1996) Pneumonia in intubated patients: Role of respiratory care. *Am J Respir Crit Care Med*, **154**, 111–15.
93. Seegobin, R.D. and Van Hasselt, G.L. (1984) Endotracheal cuff pressure and tracheal mucosal blood flow: Endoscopic study of effects of four large volume cuffs. *Br Med J (Clin Res Ed)*, **288**, 965–8.
94. Morales, M., Mendez-Alvarez, S., Martin-Lopez, J.V. *et al*. (2004) Biofilm: The microbial 'bunker' for intravascular catheter-related infection. *Support Care Cancer*, **12**, 701–7.
95. Donlan, R.M. and Costerton, J.W. (2002) Biofilms: Survival mechanisms of clinically relevant microorganisms. *Clin Microbiol Rev*, **15**, 167–93.
96. Feldman, C., Kassel, M., Cantrell, J. *et al*. (1999) The presence and sequence of endotracheal tube colonitation in patients undergoing mechanical ventilation. *Eur Respir J*, **13**, 546–51.
97. Diaz, E., Rodrìguez, A.H. and Rello, J. (2005) Ventilator-associated pneumonia: Issues related to the artificial airway. *Respir Care*, **50**, 900–6.
98. Rupp, M.E., Fitzgerald, T., Marion, N. *et al*. (2004) Effect of silver-coated urinary catheters: Efficacy, cost-effectiveness, and antimicrobial resistance. *Am J Infect Control*, **32**, 445–50.
99. Hartmann, M., Guttmann, J. and Müller, B. *et al*. (1999) Reduction of the bacterial load by the silver-coated endotracheal tube (SCET): A laboratory investigation. *Technol Health Care*, **7**, 359–70.

100. Olson, M.E., Harmon, B.G. and Kollef, M.H. (2002) Silver-coated endotracheal tubes associated with reduced bacterial burden in the lungs of mechanically ventilated dogs. *Chest*, **121**, 863–70.
101. Rello, J., Kollef, M., Diaz, E. *et al*. (2006) Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal tube in a randomized multiple-centre feasibility study. *Crit Care Med*, **34**, 2766–72.
102. Ritz, R., Scott, L.R., Coyle, M.B. *et al*. (1986) Contamination of a multiple-use suction catheter in a closed-circuit system compared to contamination of a disposable, single-use suction catheter. *Respir Care*, **31**, 1086–91.
103. Freytag, C.C., Thies, F.L., Konig, W. *et al*. (2003) Prolonged application of closed in-line suction catheters increases microbial colonization of the lower respiratory tract and bacterial growth on catheter surface. *Infection*, **31**, 31–7.
104. Deppe, S.A., Kelly, J.W., Thoi, L.L. *et al*. (1990) Incidence of colonization, nosocomial pneumonia, and mortality in critically ill patients using a trach care closed-suction system versus an open-suction system: Prospective, randomised study. *Crit Care Med*, **18**, 1389–93.
105. Johnson, K.L., Kearney, P.A., Johnson, S.B. *et al*. (1994) Closed versus open endotracheal suctioning: Costs and physiologic consequences. *Crit Care Med*, **22**, 200–3.
106. Combes, P., Fauvage, B. and Oleyer, C. (2000) Nosocomial pneumonia in mechanically ventilated patients, a prospective randomised evaluation of the stercath closed suctioning system. Intensive Care Med, **26**, 878–82.
107. Zeitoun, S.S., de Barros, A.L. and Diccini, S. (2003) A prospective, randomized study of ventilator-associated pneumonia in patients using a closed vs open suction system. *J Clin Nurs*, **12**, 484–9.
108. Lorente, L., Lecuona, M., Martin, M.M. *et al*. (2005) Ventilator-associated pneumonia using a closed vs open tracheal suction system. *Crit Care Med*, **33** (1), 115–19.
109. Kollef, M.H., Prentice, D., Shapiro, S.D. *et al*. (1997) Mechanical ventilation with or without daily changes of in-line suction catheters. *Am J Respir Crit Care Med*, **156**, 466–72.
110. Craven, D.E., Connolly, M.G.Jr, Lichtenberg, D.A. *et al*. (1982) Contamination of mechanical ventilators with tubing changes every 24 or 48 hours. *N Engl J Med*, **306**, 1505–9.
111. Craven, D.E., Kunches, L.M., Kilinsky, V. *et al*. (1986) Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis*, **133**, 792–6.
112. Dreyfuss, D., Djedaini, K., Weber, P. *et al*. (1991) Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. *Am Rev Respir Dis*, **143**, 738–43.
113. Kollef, M.H., Shapiro, S.D., Fraser, V.J. *et al*. (1995) Mechanical ventilation with or without 7-day circuit changes: A randomized, controlled trial. *Ann Intern Med*, **123**, 168–74.
114. Long, M.N., Wickstrom, G., Grimes, A. *et al*. (1996) Prospective, randomized study of ventilator-associated pneumonia in patients with one versus three ventilator circuit changes per week. *Infect Control Hosp Epidemiol*, **17**, 14–19.
115. Hess, D., Burns, E., Romagnoli, D. *et al*. (1995) Weekly ventilator circuit changes: A strategy to reduce costs without affecting pneumonia rates. *Anesthesiology*, **82**, 903–11.
116. Thompson, R.E. (1996) Incidence of ventilator-associated pneumonia (VAP) with 14-day circuit change in a subacute environment. *Respir Care*, **41**, 601–6.
117. Fink, J.B., Krause, S.A., Barrett, L. *et al*. (1998) Extending ventilator circuit change interval beyond two days reduces the likelihood of ventilator-associated pneumonia. *Chest*, **113**, 405–11.

118. Han, J.N., Liu, Y.P., Ma, S. *et al*. (2001) Effects of decreasing the frequency of ventilator circuit changes to every seven days on the rate of ventilator-associated pneumonia in a Beijing hospital. *Respir Care*, **46**, 891−6.
119. Cook, D., De Jonghe, B., Brochard, L. *et al*. (1998a) Influence of airway management on ventilator-associated pneumonia: Evidence from randomized trials. *JAMA*, 279, 781−787. *Erratum in: JAMA* 1999, **281**, 2089.
120. Hess, D.R., Kallstrom, T.J., Mottram, C.D. *et al*. (2003) Care of the ventilator circuit and its relation to ventilator associated pneumonia. *Respir Care*, **48**, 869−79.
121. Martin, C., Perrin, G., Gevaudan, M.J. *et al*. (1990) Heat and moisture exchangers and vaporizing humidifiers in the intensive care unit. *Chest*, **97**, 144−9.
122. Misset, B., Escudier, B., Rivara, D. *et al*. (1991) Heat and moisture exchanger vs heated humidifier during long-term mechanical ventilation: A prospective randomized study. *Chest*, **100**, 160−3.
123. Roustan, J.P., Kienlen, J., Aubas, P. *et al*. (1992) Comparison of hydrophobic heat and moisture exchangers with heated humidifier during prolonged mechanical ventilation. *Intensive Care Med*, **18**, 97−100.
124. Dreyfuss, D., Djedaini, K., Gros, I. *et al*. (1995) Mechanical ventilation with heated humidifiers or heat and moisture exchangers: Effects on patient colonization and incidence of nosocomial pneumonia. *Am J Respir Crit Care Med*, **151**, 986−92.
125. Kirton, O.C., DeHaven, B., Morgan, J. *et al*. (1997) A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: Rates of ventilator-associated early onset (community-acquired) or late onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest*, **112**, 1055−9.
126. Boots, R.J., Howe, S., George, N. *et al*. (1997) Clinical utility of hygroscopic heat and moisture exchangers in intensive care patients. *Crit Care Med*, **25**, 1707−10.
127. Kollef, M.H., Shapiro, S.D., Boyd, V. *et al*. (1998) A randomized clinical trial comparing an extended-use hygroscopic condenser humidifier with heated water humidification in mechanically ventilated patients. *Chest*, **113**, 759−67.
128. Memish, Z.A., Oni, G.A., Djazmati, W. *et al*. (2001) A randomized clinical trial to compare the effects of a heat and moisture exchanger with a heated humidifying system on the occurrence rate of ventilator-associated pneumonia. *Am J Infect Control*, **29**, 301−5.
129. Lorente, L., Lecuon, M., Jiménez, A. *et al*. (2006) Ventilator-associated pneumonia using a heated humidifier or a heat and moisture exchanger − a randomized controlled trial. *Crit Care*, **10**, R116.
130. Hurni, J.M., Feihl, F., Lazor, R. *et al*. (1997) Safety of combined heat and moisture exchanger filters in long-term mechanical ventilation. *Chest*, **111**, 686−91.
131. Lacherade, J.C., Auburtin, M., Cerf, C. *et al*. (2005) Impact of humidification systems on ventilator-associated pneumonia: A randomized multicentre trial. *Am J Respir Crit Care*, **172**, 1276−82.
132. Kola, A., Eckmanns, T. and Gastmeier, P. (2005) Efficacy of heat and moisture exchangers in preventing ventilator-associated pneumonia: Meta-analysis of randomized controlled trials. *Intensive Care Med*, **31**, 5−11.
133. Branson, R.D. (2005) The ventilator circuit and ventilator-associated pneumonia. *Respir Care*, **50**, 774−85.
134. Iotti, G.A., Olivei, M.C. and Braschi, A. (1999) Mechanical effects of heat-moisture exchangers in ventilated patients. *Crit Care*, **3**, R77−82.
135. Campbell, R.S., Davis, K.Jr, Johannigman, J.A. *et al*. (2000) The effects of passive humidifier dead space on respiratory variables in paralyzed and spontaneously breathing patients. *Respir Care*, **45**, 306−12.

136. Prin, S., Chergui, K., Augarde, R. *et al*. (2002) Ability and safety of a heated humidifier to control hypercapnic acidosis in severe ARDS. *Intensive Care Med*, **28**, 1756–60.
137. Prat, G., Renault, A., Tonnelier, J.M. *et al*. (2003) Influence of the humidification device during acute respiratory distress syndrome. *Intensive Care Med*, **29**, 2211–15.
138. Boisson, C., Viviand, X., Arnaud, S. *et al*. (1999) Changing a hydrophobic heat and moisture exchanger after 48 hours rather than 24 hours: A clinical and microbiological evaluation. *Intensive Care Med*, **25**, 1237–43.
139. Markowicz, P., Ricard, J.D., Dreyfuss, D. *et al*. (2000) Safety, efficacy, and cost-effectiveness of mechanical ventilation with humidifying filters changed every 48 hours. A prospective, randomized study. *Crit Care Med*, **28**, 665–71.
140. Craven, D.E. and Steger, K.A. (1996) Nosocomial pneumonia in mechanically ventilated adult patients: Epidemiology and prevention in 1996. *Semin Respir Infect*, **11**, 32–53.
141. Weinstein, R.A. (1991) Epidemiology and control of nosocomial infections in adult intensive care units. *Am J Med*, **91**, 179–84.
142. Torres, A., Gatell, J.M., Aznar, E. *et al*. (1995) Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. *Am J Crit Care Med*, **152**, 137–41.
143. Rello, J. and Diaz, E. (2003) Pneumonia in the intensive care unit. *Crit Care Med*, **31**, 2544–51.
144. Ibrahim, E.H., Tracy, L., Hill, C. *et al*. (2001a) The occurrence of ventilator-associated pneumonia in a community hospital: Risk factors and clinical outcomes. *Chest*, **120**, 555–61.
145. Langer, M., Mosconi, P., Cigada, M. *et al*. (1989) Long-term respiratory support and risk of pneumonia in critically ill patients. Intensive care unit group of infection control. *Am Rev Respir Dis*, **140**, 302–5.
146. Rello, J., Diaz, E., Roque, M. *et al*. (1999) Risk factors for developing pneumonia within 48 hours of intubation. *Am J Respir Crit Care Med*, **159**, 1742–6.
147. Cook, D.J., Walter, S.D., Cook, R.J. *et al*. (1998c) Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med*, **129**, 433–40.
148. Keenan, S.P., Kernerman, P.D., Cook, D.J. *et al*. (1997) Effect of noninvasive positive pressure ventilation on mortality in patients admitted with acute respiratory failure: A meta-analysis. *Crit Care Med*, **25**, 1685–92.
149. Peter, J.V., Moran, J.L., Phillips-Hughes, J. *et al*. (2002) Noninvasive ventilation in acute respiratory failure: A meta-analysis update. *Crit Care Med*, **30**, 555–62.
150. Lightowler, J.V., Wedzicha, J.A., Elliott, M.W. *et al*. (2003) Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ*, **326**, 185–9.
151. Keenan, S.P., Sinuff, T., Cook, D.J. *et al*. (2003) Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med*, **138**, 861–70.
152. Hess, D.R. (2004) The evidence for noninvasive positive-pressure ventilation in the care of patients in acute respiratory failure: A systematic review of the literature. Respir Care, **49**, 810–29.
153. Brochard, L., Mancebo, J., Wysocki, M. *et al*. (1995) Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*, **333**, 817–22.
154. Guerin, C., Girard, R., Chemorin, C. *et al*. (1997) Facial mask noninvasive mechanical ventilation reduces the incidence of nosocomial pneumonia: A prospective epidemiological survey from a single ICU. *Intensive Care Med*, **23**, 1024–32.

155. Nava, S., Ambrosino, N., Clini, E. *et al*. (1998) Noninvasive mechanical ventilation in the weaning of patients with respiratory failure Due To chronic obstructive pulmonary disease: A randomized, controlled trial. *Ann Intern Med*, **128**, 721−8.
156. Antonelli, M., Conti, G., Rocco, M. *et al*. (1998) A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med*, **339**, 429−35.
157. Nourdine, K., Combes, P., Carton, M.J. *et al*. (1999) Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey. *Intensive Care Med*, **25**, 567−73.
158. Antonelli, M., Conti, G., Bufi, M. *et al*. (2000) Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: A randomized trial. *JAMA*, **283**, 235−41.
159. Antonelli, M. and Conti, G. (2000) Noninvasive positive pressure ventilation as treatment for acute respiratory failure in critically ill patients. *Crit Care*, **4**, 15−22.
160. Girou, E., Schortgen, F., Delclaux, C. *et al*. (2000) Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA*, **284**, 2361−7.
161. Hilbert, G., Gruson, D., Vargas, F. *et al*. (2000) Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Crit Care Med*, **28**, 3185−90.
162. Keenan, S.P., Powers, C., McCormack, D.G. *et al*. (2002) Noninvasive positive-pressure ventilation for post-extubation respiratory distress: A randomized controlled trial. *JAMA*, **287**, 3238−44.
163. Ferrer, M., Esquinas, A., Arancibia, F. *et al*. (2003) Noninvasive ventilation during persistent weaning failure: A randomized controlled trial. *Am J Respir Crit Care Med*, **168**, 70−6.
164. Hilbert, G., Gruson, D., Vargas, F. *et al*. (2001) Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med*, **344**, 481−7.
165. Carlucci, A., Richard, J.C., Wysocki, M. *et al*. (2001) Noninvasive versus conventional mechanical ventilation: An epidemiologic survey. *Am J Respir Crit Care Med*, **163**, 874−80.
166. Hess, D.R. (2005a) Noninvasive positive-pressure ventilation and ventilator-associated pneumonia. *Respir Care*, **50**, 924−31.
167. Burns, K.E.A., Adhikari, N.K. and Meade, M.O. (2003) Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane anaesthesia group. *Cochrane Database of Systematic Reviews*, 4, CD004127.
168. Esteban, A., Frutos-Vivar, F., Ferguson, N.D. *et al*. (2004) Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*, **350**, 2452−60.
169. Cardenosa, J.A., Sole-Violan, J., Bordes, A. *et al*. (1999) Role of different routes of tracheal colonization in the development of pneumonia in patients receiving mechanical ventilation. *Chest*, **116**, 462−70.
170. Niederman, M.S. (1990) Gram-negative colonization of the respiratory tract: Pathogenesis and clinical consequences. *Semin Respir Infect*, **5**, 173−84.
171. Bonten, M.J.M., Bergmans, D.C.J.J., Ambergen, A.W. *et al*. (1996) Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. *Am J Respir Crit Care Med*, **154**, 1339−46.
172. Kolak, J., Van Saene, H.K.F., De la Cal, M. *et al*. (2005) Control of bacterial pneumonia during mechanical ventilation. *Croat Med J*, **46**, 183−96.

173. De Riso, A.J., 2nd, Ladowski JS, Dillon TA. *et al*. (1996) Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. *Chest*, **109**, 1556–61.
174. Fourrier, F., Cau-Pottier, E., Boutigny, H. *et al*. (2000) Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. *Intensive Care*, **26**, 1239–47.
175. Houston, S., Hougland, P., Anderson, J.J. *et al*. (2002) Effectiveness of 0. 12% chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. *Am J Crit Care*, **11**, 567–70.
176. Grap, M.J., Munro, C.L. and Elswick, R.K.Jr. *et al*. (2004) Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: A pilot study. *Heart Lung*, **33**, 83–91.
177. Koeman, M., van der Ven, A.J.A.M., Hak, E. *et al*. (2006) Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **173**, 1348–55.
178. Kallet, R.H. and Quinn, T.E. (2005) The gastrointestinal tract and ventilator-associated pneumonia. *Respir Care*, **50**, 910–21.
179. de Jonge, E. (2005) Effects of selective decontamination of digestive tract on mortality and antibiotic resistance in the intensive-care unit. *Curr Opin Crit Care*, **11**, 144–9.
180. Sanchez, M., Cambronero, J.A., Lopez, J. *et al*. (1998) Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients. *Am J Respir Crit Care Med*, **158**, 908–16.
181. Kerver, A.J.H., Rommes, J.H., Mevissen-Verhage, E.A.E. *et al*. (1988) Prevention of colonization and infection in critically ill patients: A prospective randomized study. *Crit Care Med*, **16**, 1087–93.
182. Bergmans, D.C., Bonten, M.J., Gaillard, C.A. *et al*. (2001) Prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med*, **164**, 382–8.
183. Quinio, B., Albanese, J., Bues-Charbit, M., *et al*. (1996) Selective decontamination of the digestive tract in multiple trauma patients: A prospective double-blind, randomized, placebo-controlled study. *Chest*, **109**, 765–72.
184. Pugin, J., Auckenthaler, R., Lew, D.P. *et al*. (1991) Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. *JAMA*, **265**, 2704–10.
185. de Jonge, E., Schultz, M.J., Spanjaard, L. *et al*. (2003) Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: A randomized controlled trial. *Lancet*, **362** (9389), 1011–16.
186. Nathens, A.B. and Marshall, J.C. (1999) Selective decontamination of the digestive tract in surgical patients: A systematic review of the evidence. *Arch Surg*, **134**, 170–6.
187. Selective Decontamination of the Digestive Tract Trialists' Collaborative Group (1993) Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract. *BMJ*, **307**, 525–32.
188. D'Amico, R., Pifferi, S., Leonetti, C. *et al*. (1998) Effectiveness of antibiotic prophylaxis in critically ill adult patients: Systematic review of randomized controlled trials. *BMJ*, **316**, 1275–85.
189. Safdar, N., Said, A. and Lucey, M.R. (2004) The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: A systemic review and meta-analysis. *Liver Transpl*, **10**, 817–27.
190. Liberati, A., D'Amico, R., Pifferi, S. *et al*. (2004) Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *Cochrane Database Syst Rev*, (1), CD000022.

191. Vandenbroucke-Grauls, C.M. and Vandenbroucke, J.P. (1991) Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit. *Lancet*, **338**, 859–62.
192. Heyland, D.K., Cook, D.J., Jaeschke, R. *et al*. (1994) Selective decontamination of the digestive tract: An overview. *Chest*, **105**, 1221–9.
193. Kollef, M.H. (1994) The role of selective digestive tract decontamination on mortality and respiratory tract infections: A meta-analysis. *Chest*, **105**, 1101–8.
194. van Nieuwenhoven, C.A., Buskens, E., van Tiel, F.H. *et al*. (2001) Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *JAMA*, **286**, 335–40.
195. van Saene, H.K., Petros, A.J., Ramsay, G. *et al*. (2003) All created truths are iconoclastic: Selective decontamination of the digestive tract moves from heresy to level 1 truth. *Intensive Care Med*, **29**, 677–90.
196. Hammond, J.M. and Potgieter, P.D. (1995) Long-term effects of selective decontamination on antimicrobial resistance. *Crit Care Med*, **23**, 637–45.
197. Lingnau, W., Berger, J., Javorsky, F. *et al*. (1998) Changing bacterial ecology during a five-year period of selective intestinal decontamination. *J Hosp Infect*, **39**, 195–206.
198. Leone, M., Albanese, J., Antonini, F. *et al*. (2003) Long-term (six-year) effect of selective digestive decontamination on antimicrobial resistance in intensive care. *Crit Care Med*, **31**, 2090–5.
199. Silvestri, L., Milanese, M., Oblach, L. *et al*. (2002) Enteral vancomycin to control methicillin-resistant *Staphylococcus aureus* outbreak in mechanically ventilated patients. *Am J Infect Control*, **30**, 391–9.
200. de la Cal, M.A., Cerda, E., van Saene, H.K. *et al*. (2004) Effectiveness and safety of enteral vancomycin to control endemicity of methicillin-resistant *Staphylococcus aureus* in a medical/surgical intensive care unit. *J Hosp Infect*, **56**, 175–83.
201. Silvestri, L., van Saene, H.K., Milanese, M. *et al*. (2004) Prevention of MRSA pneumonia by oral vancomycin decontamination: A randomised trial. *Eur Respir J*, **23**, 921–6.
202. Bonten, M.J.M. (2006) Selective digestive tract decontamination - will it prevent infection with multidrug resistant Gram-negative pathogens but still be applicable in institutions where methicillin-resistant *Staphylococcus aureus* and vancomycin resistant enterococci are endemic. *Clin Infect Dis*, **43**, S70–4.
203. Flanders, S.A., Collard, H.R., Saint, S. *et al*. (2006) Nosocomial pneumonia: State of the science. *Am J Infect Control*, **34**, 84–93.
204. Heyland, D. and Mandell, L.A. (1992) Gastric colonization by Gram-negative bacilli and nosocomial pneumonia in the intensive care unit patient. Evidence for causation. *Chest*, **101**, 187–93.X
205. Torres, A., Ebiary, M., Gonzalez, J. *et al*. (1993) Gastric and pharyngeal flora in nosocomial pneumonia acquired during mechanical ventilation. *Am Rev Respir Dis*, **148**, 352–7.
206. Inglis, T.J., Sherratt, M.J., Sproat, L.J *et al*. (1993) Gastroduodenal dysfunction and bacterial colonisation of the ventilated lung. *Lancet*, **341**, 911–13.
207. Hillman, K.M., Riordan, T., O'Farrell, S.M. *et al*. (1982) Colonization of the gastric contents in critically-ill patients. *Crit Care Med*, **10**, 444–7.
208. Daschner, F., Kappstein, I., Engels, I. *et al*. (1988) Stress ulcer prophylaxis and ventilation pneumonia: prevention by antibacterial cytoprotective agents? *Infect Control Hospital Epidemiol*, **9**, 59–65.
209. Cook, D.J., Fuller, H.D., Guyatt, G.H. *et al*. (1994) Risk factors for gastrointestinal bleeding in critically-ill patients. Canadian critical care trials group. *N Engl J Med*, **330**, 377–81.

210. Tryba, M. (1991) Prophylaxis of stress ulcer bleeding. A meta-analysis. *J Clin Gastroenterol*, **13**, S44–55.
211. Tryba, M. (1991) Sucralfate versus antacids or H_2-antagonists for stress ulcer prophylaxis: A meta-analysis on efficacy and pneumonia rate. *Crit Care Med*, **19**, 942–9.
212. Cook, D.J., Laine, L.A., Guyatt, G.H. *et al*. (1991) Nosocomial pneumonia and the role of gastric pH. A meta-analysis. *Chest*, **100**, 7–13.
213. Tryba, M. and Cook, D.J. (1995) Gastric alkalinization, pneumonia, and systemic infections: The controversy. *Scand J Gastroenterol Suppl*, **210**, 53–9.
214. Cook, D.J. (1995) Stress ulcer prophylaxis: Gastrointestinal bleeding and nosocomial pneumonia. Best evidence synthesis. *Scand J Gastroenterol Suppl*, **210**, 48–52.
215. Cook, D.J., Reeve, B.K., Guyatt, G.H. *et al*. (1996) Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA*, **275**, 308–14.
216. Messori, A., Trippoli, S., Vaiani, M. *et al*. (2000) Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: Meta-analysis of randomised controlled trials. *BMJ*, **321**, 1103–6.
217. Cook, D., Guyatt, G., Marshall, J. *et al*. (1998) A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian critical care trials group. *N Engl J Med*, **338**, 791–7.
218. Safdar, N., Crnich, C.J. and Maki, D.G. (2005) The pathogenesis of ventilator-associated pneumonia: Its relevance to developing effective strategies for prevention. *Respir Care*, **50**, 725–39.
219. Gruson, D., Hilbert, G., Vargas, F. *et al*. (2000) Rotation and restricted use of antibiotics in a medical intensive care unit: Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant Gram-negative bacteria. *Am J Respir Crit Care Med*, **162**, 837–43.
220. Keuleyan, E. and Gould, I.M. (2001) Key issues in developing antibiotic polices: From an institutional level to Europe-wide. European study group on antibiotic policy (ESGAP), subgroup III. *Clin Microbiol Infect*, **7** (Suppl. 6), 16–21.
221. Kollef, M.H., Vlasnik, J.S.L., Sharpless, L. *et al*. (1997) Scheduled change of antibiotic classes: A strategy to decrease the incidence of VAP. *AM J Respir Crit Care Med*, **156**, 1040–8.
222. Kollef, M.H., Ward, S., Sherman, G. *et al*. (2000) Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choice. *Crit Care Med*, **28**, 3456–64.
223. Singh, N., Rogers, P., Atwood, C.W. *et al*. (2000) Short course empiric antibiotic therapy for pulmonary infiltrates in the intensive care unit: A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care*, **162**, 505–11.
224. Ibrahim, E.H., Ward, S., Sherman, G. *et al*. (2001) Experience with a clinical guideline for the treatment of ventilator associated-pneumonia. *Crit Care Med*, **29**, 1109–15.
225. Dennesen, PJ, van derVen, AJ., and Kessels, AG. *et al*. (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **163**, 1371–5.
226. Chastre, J., Wolff, M., Fagon, J.Y. *et al*. (2003) Comparison of 8 vs 15 days antibiotic therapy for ventilator-associated pneumonia in adults. *JAMA*, **290**, 2588–98.
227. Niederman, M.S. (2006) De-escalation therapy in ventilator-associated pneumonia. *Curr Opin Crit Care*, **12**, 452–7.
228. Rello, J., Vidaur, L., Sandiumenge, A. *et al*. (2004) De-escalation therapy in ventilator-associated pneumonia. *Crit Care Med*, **32**, 2183–90.
229. Micek, S.T., Ward, S., Fraser, V.J. *et al*. (2004) A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest*, **125**, 1791–9.

230. Soo Hoo, G.W., Wen, E., Nguyen, T.V. *et al*. (2005) Impact of clinical guidelines in the management of severe hospital-acquired pneumonia. *Chest*, **128**, 2778−87.
231. Kollef, M.H., Morrow, L.E., Niederman, M.S. *et al*. (2006) Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. *Chest*, **129**, 1210−18.
232. Gruson, D., Hilbert, G., Vargas, F. *et al*. (2003) Strategy of antibiotic rotation: Long-term effect on incidence and susceptibilities of Gram-negative bacilli responsible for ventilator-associated pneumonia. *Crit Care Med*, **31**, 1908−14.
233. Raymond, D.P., Pelletier, S.J., Crabtree, T.D. *et al*. (2001) Impact of rotating empiric antibiotic schedule on infections mortality in an intensive care unit. *Crit Care Med*, **29**, 1101−8.
234. Carson, J.L., Altman, D.G., Duff, A. *et al*. (1999) Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. *Transfusion*, **39**, 694−700.
235. Chang, H., Hall, G.A., Geerts, W.H. *et al*. (2000) Allogeneic red blood cell transfusion is an independent risk factor for the development of postoperative bacterial infection. *Vox Sang*, **78**, 13−18.
236. Hill, G.E., Frawley, W.H., Griffith, K.E. *et al*. (2003) Allogeneic blood transfusion increases the risk of postoperative bacterial infection: A meta-analysis. *J Trauma*, **54**, 908−14.
237. Shorr, A.F., Duh, M.S., Kelly, K.M., Kollef, M.H. and CRIT Study Group, (2004) Red blood cell transfusion and ventilator-associated pneumonia: A potential link. *Crit Care Med*, **32** (3), 666−674.
238. Corwin, H.L., Gettinger, A., Pearl, R.G. *et al*. (2004) The CRIT study: Anemia and blood transfusion in the critically ill: current clinical practice in the united states. *Crit Care Med*, **32**, 39−52.
239. Levy, M.M., Abraham, E., Zilberberg, M. *et al*. (2005) A descriptive evaluation of transfusion practices in mechanically ventilated patients. *Chest*, **127**, 928−35.
240. Taylor, R.W., O'Brien, J., Trottier, S.J. *et al*. (2006) Red blood cell transfusions and nosocomial infections in critically ill patients. *Crit Care Med*, **34**, 2302−8.
241. Hébert, P.C., Wells, G., Blajchman, M.A. *et al*. (1999) A multicentre, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med*, **340**, 409−17.
242. Kress, J.P., Pohlman, A.S., O'Connor, M.F. *et al*. (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New Engl J Med*, **342**, 1471−7.
243. Schweickert, W.D., Gehlbach, B.K., Pohlman, A.S. *et al*. (2004) Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Crit Care Med*, **32**, 1272−6.

3

Role of the Microbiology Laboratory in the Diagnosis of Ventilator-Associated Pneumonia

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Introduction

Nosocomial pneumonia (NP) is among the main causes of hospital infection and of death by infection in the healthcare setting [1–3]. Incorrect treatment of NP within the initial hours of infection has devastating consequences on its prognosis. The clinician is forced initially to apply broad-spectrum antibiotics to act against the largest number of pathogens possible [2, 4]. This management approach, however, has the shortcoming that excessive use of antibiotics in intensive care units leads to higher rates of morbidity and mortality [5, 6]. Moreover, it has been reported that for every 100 patients with clinically suspected ventilator-associated pneumonia (VAP), microbiological confirmation will only be obtained in 45 to 69 patients [7–14].

The microbiology laboratory thus has to offer timely information such that the empirical antimicrobial regimen is as short as possible to restrict and adjust, or reduce, the use of antimicrobial agents. To all effects, NP should be considered

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a microbiological emergency that demands the same level of diligence when handling laboratory samples as would, for instance, a suspicion of bacterial meningitis.

The main steps involved in the role played by the microbiology laboratory are summarized in this chapter, specifically focusing on the management of pneumonia associated with mechanical ventilation. Although many of the measures adopted for this form of pneumonia can be equally applied to other forms of NP, the specific details of nosocomial pneumonia not associated with mechanical ventilation, pneumonia in psychiatric hospitals or other healthcare institutions, and pneumonia in the immunocompromised patient, are not discussed.

Causal Microorganisms

Today, it is well accepted that the main cause of ventilator-associated pneumonia (VAP) is the aspiration of the bacteria that colonize the upper respiratory tract or upper digestive tract into the lower respiratory tract [15, 16]. Some of these bacteria are scarcely pathogenic for the lung, such as most species of the genus *Corynebacterium,* streptococci displaying green haemolysis, *Enterococcus* and *Bacillus* species and coagulase-negative staphylococci. Their isolation from the lower respiratory tract (LRT) in patients subjected to mechanical ventilation has generally no pathological significance. Some Gram-negative nonglucose-fermenting bacteria also fall into this category. In contrast, the microorganisms most frequently responsible for VAP are *Staphylococcus aureus,* most microorganisms of the *Enterobacteriaceae* family and some Gram-negative, nonglucose-fermenting bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter baumanii.* Hence, the search carried out by the microbiology laboratory is preferentially geared towards identifying these pathogens.

It should not be forgotten that, on many occasions, VAP is polymicrobial, although this in itself is not an aggravating factor [17]. The more resistant microorganisms appear in the so-called late onset form of VAP, which occurs 5−7 days into mechanical ventilation or hospital stay [18].

Over the last few years, *S. aureus* has increasingly been identified as a pneumonia-causing microorganism and is now as commonly implicated as *P. aeruginosa* [17]. Considering that between 50 % and 70 % of all *S. aureus* strains in some settings are methicillin-resistant (MRSA), the percentage of VAP episodes caused by this pathogen could be as high as 10−12 %. Antibiotic resistance can also be a trait of Gram-negative microorganisms. In a recent study, 15 % of *P. aeruginosa* strains were found to be resistant to carbapenems [18, 19] . However, given that resistance percentages vary from one hospital to the next and depend on the patient type and use of particular antibiotics, the resistance pattern of each health centre should be known before choosing the empirical antibiotic therapy to use.

There is also some evidence of anaerobic bacteria playing a major role as causal agents of VAP although, so far, this evidence can only be considered as anecdotal [20−23].

Fungi as the causal agents of VAP are rare, except in a small subgroup of patients with severe immunodeficiency associated mainly with neutropenia or the use of high doses of corticosteroids [24–27]. Isolates of the genus *Candida* obtained from LRT secretions can be mostly attributed to simple colonization and do not often indicate pneumonia [28–30]. The same may be said of *Aspergillus* and other filamentous fungi, whose appearance in LRT samples should be interpreted in the light of the patient's immune status. *Aspergillus* may cause VAP in patients under steroid treatment, with neutropenia or with other serious forms of immunodeficiency [25, 31].

Similarly, viruses are not a usual cause of VAP, yet some herpes viruses are often isolated from respiratory secretions in patients with and without VAP [32–34]. In a systematic, prospective study performed on mechanically ventilated patients, *Herpes simplex* was isolated from LRT specimen cultures in 6.8 % (28 patients) of patients without VAP and 13.4 % (19 patients) of patients with VAP [35]. Their presence seems to be an indicator of disease severity but to date there is insufficient data on the potential role of these viruses as a cause of VAP. Cytomegalovirus (CMV) has also been described as a cause of VAP in immunocompetent patients without haematological disease and it is possible that this entity is under-diagnosed and under-reported, since virus isolation techniques do not form part of the routine assessment of VAP [36].

The occurrence of influenza in patients subjected to mechanical ventilation is rare [32, 37].

Sampling Techniques

The best sampling method for a diagnosis of VAP is a subject of dispute and there is presently no consensus recommendation. It is, however, accepted that patient specimens for culture should be taken before administering the first dose of antibiotic treatment or before any change in treatment, so that the results interpreted are valid [38–41]. It is also clear that an approach based solely on clinical data will be deficient [7]. The latest recommendations of the American Thoracic Society and the Infectious Diseases Society of America include taking LRT specimens [42].

It is essential that the laboratory is informed of the type of sample submitted to adequately process the sample and interpret the results [42]. Nonetheless, in a survey of different sampling techniques Ruiz *et al*. [43] found no differences in rates of diagnoses, length of Intensive Care Unit (ICU) stay, days on mechanical ventilation and crude 30-day or adjusted mortality.

Routine Surveillance Cultures

Today, the main question to be addressed is whether the routine collection of LRT specimens for culture (known as surveillance cultures) in patients who do not yet have VAP could help identify patients at a greater risk of developing it. The problem to be tackled is the indiscriminate use of antibiotics involved in treating simple colonization

and not an established infection. When VAP occurs, a further question that arises is if the causal microorganism is the same as one of those isolated in previous surveillance cultures. Studies addressing this issue have been scarce and have only involved small patient series. In addition, different procedures have been used for surveillance cultures and for identifying pneumonia, so that it is difficult to draw solid conclusions [44–47]. In a prospective study performed by our research group in an Intensive Care Unit for heart surgery patients, samples for surveillance cultures were taken twice a week. The bacterial colonization of lower airway secretions was found to be an indicator of a worse prognosis, although this prognosis could also be inferred from many data other than positive cultures. In this study, the microorganism causing VAP was detected in previous surveillance cultures in only one case of VAP out of 28 [48]. Therefore, it is not recommended that routine LRT cultures (neither endotracheal aspirates nor protected specimen brush (PSB) samples) are taken in patients lacking criteria that could raise a suspicion of VAP. These cultures represent a large amount of work for the nursing staff and the microbiologist, often lead to clinical errors and take up time that the microbiologist could have devoted to more useful tasks related to this subject.

A recent study has, nevertheless, questioned the validity of this recommendation [44]. In this investigation, Michel *et al*. undertook surveillance cultures twice weekly in mechanically ventilated ICU patients. The results of these surveillance cultures were only revised when there was a suspicion of VAP in a patient, who was then also subjected to bronchoalveolar lavage (BAL) to confirm the diagnosis. Based on the surveillance data, an empirical antibiotic therapy regimen was established and compared to that indicated by the BAL results. Using this strategy, the proportion of patients in whom empirical antibiotic treatment was appropriate increased to 95 %.

Specimens to be Collected on the Suspicion of Pneumonia

The type of specimen that should be obtained for microbiologic processing as soon as VAP is suspected is another issue that has generated a large amount of medical literature. There is no doubt that the quickest, easiest and cheapest sample to obtain is the endotracheal aspirate. The doubt that arises is whether bronchoscope-directed sampling methods (plugged telescoping catheter or BAL, etc.) are sufficiently more efficient than simple endotracheal aspiration to warrant their higher cost and, mainly, the delay that these more complex procedures often entail [49].

Bronchoscopic versus Nonbronchoscopic Sampling Procedures

Undoubtedly, blind aspiration sampling can lead to errors but the use of the bronchoscope also carries risks, such as inducing cardiac arrhythmia, hypoxemia, bleeding, pneumothorax, along with greater costs both in terms of time and resources. The overall sensitivity provided by bronchoscopic and non-bronchoscopic sampling techniques is comparable [50, 51], although in some patients diagnosis could be missed by a blind technique, especially in the case of pneumonia involving the left lung [52].

In patients with diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest radiography, determining the correct airway to sample may be difficult. In these cases, sampling should be directed towards the area where endobronchial abnormalities are maximal. In case of doubt and since autopsy studies have revealed that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be sampled preferentially [52].

At present, there is no convincing evidence that taking multiple specimens is more accurate for diagnosing VAP than taking a single specimen, and the most reasonable conclusion to be drawn is that the potential diagnostic benefits of searching for the etiology of VAP using bronchoscopic methods do not justify their routine use [53, 54]. In three studies conducted in Spain, no differences in mortality or morbidity emerged when invasive techniques (BAL or plugged telescoping catheter) were compared with non-bronchoscopic methods (quantitative tracheal aspirate cultures). However, the number of cases examined was limited and there is a need for similar studies performed on larger patient series [13, 43, 55]. Non-bronchoscopic techniques, however, are limited to mechanically ventilated patients.

Owing to inevitable oropharyngeal bacterial contamination of all respiratory secretion samples, the use of techniques that quantify cultures is the *key issue* for a microbiology laboratory, despite this is not always undertaken in many hospitals today [56, 57]; some authors even disputing this approach [58]. The method that should be most recommended for etiologic diagnosis of VAP is that which can be undertaken most rapidly by each particular institution, and the one that the centre has most experience with. In the following section, the value of the methods most commonly employed are discussed; they are summarised in Table 3.1.

Table 3.1 Value of the different types of laboratory specimens used for the etiologic diagnosis of ventilator-associated pneumonia (VAP)

Sampling method	Cut-off	Sensitivity	Specificity	References
Bronchoscopic				
Endotracheal aspirate	10^5 cfu/mL	80 % (60–97)	62 % (41–74)	[50, 61, 63, 67]
Endotracheal aspirate	10^6 cfu/mL	66 % (38–82)	78 % (72–85)	[132–134]
BAL	10^4 cfu/mL	73 % (42–93)	82 % (45–100)	[91, 97, 135–139]
PSB	10^3 cfu/mL	66 % (33–100)	90 % (50–100)	[97, 135, 138, 139]
PTC	10^3 cfu/mL	72 % (54–100)	82 % (58–93)	[61, 73, 123]
Non Bronchoscopic				
Endotracheal aspirate	10^5 cfu/mL	94 %	50 %	[54]
Endobronchial aspirate	10^3-10^4 cfu/mL	74–97 %	74–100 %	[140]
Mini BAL	10^3-10^4 cfu/mL	63–100 %	66–100 %	[54, 140]
PSB	10^3 cfu/mL	66 % (54–98)	91 % (57–100)	[50, 78, 140]
PTC	10^3 cfu/mL	65 %	83 %	[54]

BAL – bronchoalveolar lavage; PSB – protected specimen brush; PTC – plugged telescoping catheter. Ranges given in parentheses.

Endotracheal Aspiration

Endotracheal aspiration is the simplest method of obtaining airway secretions in the mechanically ventilated patient. The aspirate obtained is undiluted or only slightly diluted and a bacterial count $\geq 10^5$ cfu/mL indicates a positive culture result.

Qualitatively treated at the microbiology laboratory, this type of specimen shows high sensitivity (80−100 %), although its specificity is unacceptably low (14−47 %) [59]. In contrast, the quantitative culture of endotracheal aspirates provides results that are comparable to those obtained using the plugged telescoping catheter or by BAL [50, 60−67].

Protected Specimen Brush (PSB)

The characteristics and description of the Protected Specimen Brush (PSB) method of obtaining LRT specimens can be found elsewhere [49, 68−72].

The cut-off value recommended for this method is 10^3 cfu/mL for a sample to be considered clinically significant. This is based on the assumption that the brush picks up between 0.001 and 0.01 mL of secretions, which are sent to the laboratory diluted in 1 mL of Ringer's solution. Thus, 10^3 cfu/mL corresponds to approximately 10^5 or 10^6 cfu/mL in undiluted respiratory secretions.

The use of PSB for the diagnosis of nosocomial pneumonia has been assessed in several studies involving both mechanically ventilated and non-ventilated patients. Its sensitivity ranges from 33 to 100 % and specificity from 50 to 100 %. The mean sensitivity of PSB is estimated at 73 ± 18 % (SD) and its mean specificity is 82 ± 19 % (SD) [69]. In general, it is accepted that the probability that a positive result reflects the presence of VAP is very high. On the contrary, the rate of false negatives runs from 0 to as much as 40 % [73−75]. According to some authors, repeating the method in the same patients and circumstances is not very reproducible [71, 76].

False negatives have been attributed to a lack of standardization of the technique, obtaining specimens too early, unilateral or blind sampling and to previous antibiotic treatment [38−40, 77].

The rate of false positives is around 30 % and can be ascribed to the contamination of samples with microorganisms from the upper respiratory tract or to the collection of microorganisms colonizing the lower tract, which could be promoted by accompanying diseases, such as chronic obstructive pulmonary disease.

Several authors value blind sampling as much as bronchoscope-guided sampling [78, 79] and consider its diagnostic value is comparable to that of endotracheal aspiration [80].

Bronchoalveolar Lavage (BAL)

Bronchoalveolar lavage is performed by advancing the bronchoscope as far as a subsegmental bronchus (generally a 3rd or 4th generation bronchus), until its lumen becomes occluded. The next step consists of distally installing 20−50 mL aliquots of sterile saline solution and resuctioning the contents of the distal bronchus. There is no defined consensus as to the specific volume to be installed and several authors have

reported the use of 100−240 mL of saline solution for the diagnosis of pneumonia. Although the volume recovered usually ranges from 5−70 % of the volume installed, 5 mL is generally sufficient for microbiological analysis. It should be admitted that a very small return from BAL may contain only diluted material from the bronchi rather than the alveoli and thus give rise to false-negatives, particularly in patients with very severe chronic obstructive pulmonary disease. In these patients, the diagnostic value of BAL techniques is greatly diminished and the PSB technique is preferential [81].

Bronchoalveolar lavage samples are then Giemsa or Gram stained and cell counts are undertaken. As a general rule, the presence of more than 1 % squamous endothelial cells is a sign of oropharangeal contamination. Quantitative bacterial cultures are essential to distinguish between colonization and infection and it is currently accepted that the differentiation threshold is 10^4-10^5 cfu/mL.

In twenty-one studies [39, 52, 65, 74, 82−98], the mean sensitivity of BAL was estimated at 69.3 ± 24 % (SD) and its mean specificity was 83.1 ± 18.5 % (SD). This variation detected in both sensitivity and specificity depends upon previous antibiotic treatment, the patient population examined and the method used as reference. The reasons for false positives and false negatives are the same as those mentioned for PSB.

A recently published study has examined the effect of the dilution factor used for the BAL culture on the bacterial count [99]. The authors compared the concentration of urea in serum and BAL to determine the dilution factor of the sample and established that 17 additional patients would have reached the cut-off level after correction for the dilution effect, which varied between 1.8- and 130-fold. These findings stress the implications of the dilutions used in cultures for the diagnosis and treatment of these patients.

Fagon has summarised the existing arguments for the use of BAL in the diagnosis of VAP as: (a) antibiotic therapy that is directed by quantitative cultures is more effective than empirical treatment [14, 100, 101]; (b) bronchoscopic techniques can reduce excessive antibiotic use, limiting the emergence of drug-resistant strains, the increased risks of superinfection and antibiotic-related toxicity [102]; (c) bronchoscopic techniques also reduce overall costs [8, 103, 104]; and (d) the major benefit of a negative BAL culture is to direct attention away from the lungs as the source of fever [105].

Both PSB and BAL samples very reliably identify, qualitatively and quantitatively, the microorganisms present in lung specimens with bacterial pneumonia, even if the infection develops as a superinfection in a patient that has already received antimicrobial treatment for several days [41]. These techniques should, nevertheless, be repeated in symptomatic patients with a negative result [106]. Moreover, borderline results should be interpreted cautiously and the clinical circumstances taken into consideration before drawing any therapeutic conclusion.

A further point to consider is that BAL cultures are unreliable in patients requiring prolonged mechanical ventilation (over sixty days). These patients have a large burden of bacteria in their distal airspaces, frequently exceeding the levels diagnostic for VAP in patients with acute respiratory failure. The distinction between colonization, tracheobronchitis and VAP is difficult in these patients. Despite the high burden of bacteria, these patients have a low daily incidence of VAP [107].

Blood Cultures

Blood cultures show low sensitivity and low specificity for diagnosing VAP. A positive result is obtained in only 10–30 % of cases. On the contrary, the lungs are not the source of bacteraemia in approximately half the patients with positive blood cultures [108–112]. Notwithstanding this, a positive blood culture is an indicator of the severity of infection and of the type of microorganism that grows in blood, and often guides the diagnosis in the critical patient to sources of infection other than the lower respiratory tract. In patients with borderline LRT specimen bacterial counts or counts lower than that of diagnostic significance, the presence of the same bacterium in the blood helps to establish a diagnosis of pneumonia. Despite the limitations, the lower cost of blood cultures and their low invasiveness justify their routine use in septic patients with suspected VAP.

Lung Biopsy as the Final Reference

A lung biopsy specimen is not routinely used to diagnose VAP due to obvious risks. This procedure is generally employed in post-mortem studies to validate other techniques and to gain knowledge on the physiopathology of VAP [97, 113]. The findings of such studies have indicated that the origin of VAP is bronchogenic; that it is a multifocal process; that blind methods using telescoping catheters or lavages are as effective as bronchoscope-guided methods and that previous antibiotic treatment modifies the diagnostic precision of quantitative cultures irrespective of the sampling method. The best diagnostic method for VAP is probably a combined histological and quantitative culture approach, which is not feasible in clinical practice. Therefore, BAL is left as the technique that best reflects the histology (cytology) and bacteriology of the lung [59, 114].

Transport to the Laboratory

Collected specimens should ideally be transported to the microbiology laboratory in under 30 minutes for immediate processing to avoid bacterial overgrowth [115]. Few studies have explored the microbiological consequences of refrigerating specimens for processing hours or days after their collection [116]. In a recent study, the impact of refrigerating BAL specimens for 24 hours before processing was assessed [83]. At 24 hours, the sensitivity, specificity, positive and negative predictive values were 77, 100, 100 and 93 % when compared to cultures performed instantly. Thus, this delay can cause a reduction in the sensitivity of the technique of over 20 %, which is clearly unacceptable. Even if no substantial losses in the qualitative or quantitative recovery of microorganisms are assumed, the delay in providing information will have clinically devastating consequences.

Rello *et al*. suggested that the use of a thioglycolate medium for the transport of protected specimen brushes could be associated with an improved performance of the Gram stain in a limited series of cases. In their work, VAP etiology was anticipated by direct Gram staining and permitted a more targeted initial empirical treatment in

75 % of samples transported in thioglycolate, compared with only 37.5 % of samples transported in saline solution ($p < 0.05$) [117].

Rapid Information Provided by the Gram Stain

There is still much dispute over the value of the Gram stain when trying to pre-empt a microbiological diagnosis of VAP (Table 3.2) The reasons for this controversy could stem from the different methods used in studies assessing this issue. These studies differ in the type of specimen evaluated, the way the specimen is treated in the laboratory before Gram staining, the gold standard used and the interpretation of the impact that this information has on treatment.

In our experience, Gram staining LRT secretions obtained by endotracheal aspiration in patients with suspected VAP, followed by the immediate reporting of the results to the medical staff responsible for the patient, is of extraordinary value for the etiologic diagnosis of VAP and as a guide for its timely treatment.

The medical literature, however, is full of variable data regarding the sensitivity (Sens) (57−95 %), specificity (Sp) (48−87 %), positive predictive value (PPV) (47−78 %), negative predictive value (NPV) (69−96 %) and precision (P) (60−88 %) of the Gram stain in the management of a patient with VAP [118−121] (Table 3.2).

Blot *et al*. [121] assessed the value of the Gram stain in patients with suspected VAP, on respiratory secretions obtained by endotracheal aspiration and the plugged telescoping catheter. They found a high microbiologically proven sensitivity in the

Table 3.2 Data on the sensitivity and specificity of the Gram stain on different specimens to predict VAP

Ref. No.	Sample type	Endotracheal aspirate	
	First author	Sensitivity	Specificity
[141]	Marquette	50 %	75 %
[121]	Blot	89 %	62 %
[121]	Blot	91 %	64 %
		Bronchoscopic aspirate (BAS)	
[98]	Papazian	62 %	73 %
[121]	Blot	70 %	96 %
		Protected specimen brush (PSB)	
[122]	Marquette	47 %	88 %
[121]	Blot	67 %	95 %
		Bronchoalveolar lavage (BAL)	
[97]	Marquette	47 %	87 %
[98]	Papazian	54 %	100 %
[52]	Meduri	54 %	87 %
[118]	Davis[†]	73–87 %	49–59 %

[†] Gram-negative organisms not reliably identified by Gram's stain.

use of endotracheal aspirates for the diagnosis of VAP (91 %) and a high NPV in the test (94 %) in patients not undergoing recent changes in antibiotic treatment. When secretions were obtained by plugged telescoping catheters, the Gram stain showed high specificity (95 %) but lower sensitivity (67 %). Blot *et al.* argued that a negative Gram stain in an endotracheal aspirate has high negative predictive value for a diagnosis of VAP and justifies the decision to not start antibiotic treatment. A positive Gram stain on a plugged telescoping catheter sample indicates VAP is highly probable and treatment should be promptly started. In patients with a positive endotracheal aspirate but negative plugged telescoping catheter sample, the treatment decision is less clear, although the best option is probably to start antibiotic treatment with subsequent modification of the empirical therapy regimen based on culture results.

These findings are supported by others [122] but not all authors share this optimistic viewpoint, especially when trying to rule out VAP caused by Gram-negative bacilli [118]. The low sensitivity values (20 %) for the Gram stain recorded in a study by Pham *et al.* may be related to the use of very diluted samples that required cytocentrifugation techniques [123].

The latest published report on the value of the Gram stain is that by Laupland *et al.* [124]. They evaluated the utility of the Gram stain along with determining bacterial adenosine triphosphate in BAL specimens from patients with suspected VAP and obtained Sens, Sp, PPV, NPV and P values of 95.3, 54.9, 37.9 97.6 and 63.9 %, respectively, comparable to those of Blot *et al.* mentioned above.

Other Quick Procedures

At present, there is no rapid procedure that has demonstrated unquestionable performance in the management of VAP other than those already mentioned. Rapidly expanding molecular techniques, which enable the detection of one or several microorganisms and the rapid determination of specific resistance mechanisms using direct clinical specimens, have yet to be explored in the specific area of VAP.

Preemptive Rapid Cultures

With the traditional laboratory processing of a respiratory secretion specimen for bacterial isolation it usually takes between three and four days to provide the clinician with a result. After plating the sample and incubating for 24−48 hours, bacterial counts have to be performed and strains isolated and grown in pure culture. This is followed by microorganism identification and antimicrobial sensitivity testing, which takes a further 24 hours. To this, must be added the time taken to transmit information, write reports and make therapeutic decisions. This late information, at least in other areas such as blood cultures, clearly helps to improve the prescription of drugs, optimises their consumption and reduces costs but it has not yet been possible to establish its impacts on shortening hospital stay or decreasing mortality [125].

Antibiogram procedures require a standardized inoculum and usually start with isolated bacteria in culture. It is known, however, that antibiograms performed directly on clinical specimens – that is, omitting the bacterial isolation step – can provide preliminary information, which generally correlates well with that offered by standard procedures. This is presently undertaken on blood cultures and urine or CSF samples in circumstances that demand urgency. A procedure that is not affected by the inoculum is the so-called E-test. This method uses a strip impregnated with increasing concentrations of an antibiotic. After its diffusion in agar, the strip provides a minimum inhibitory concentration (MIC) for the particular bacterium and antimicrobial agent tested. The results of a direct E-test antibiogram including six antimicrobials commonly used in VAP patients have been compared with sensitivities obtained by the usual procedure. The six antibiotics included in the rapid test were: oxacilin, cefepime, imipenem, piperacillin-tazobactam, amikacin and ciprofloxacin. Sensitivity data were comparable to those obtained by the standard procedure in 98 % of cases [126]. The impact of this method in improving and reducing the use of antimicrobials in patients with VAP has already been demonstrated [127]. Patients with information provided by direct E-test differed significantly from the second group in terms of the factors: more days of adequate antibiotic treatment, smaller defined daily doses (DDD) of antibiotics, less days of fever, less episodes of diarrhea associated with *C. difficile* and less money spent on antibiotics.

Conventional Cultures

Conventional cultures, despite being slow, allow confirmation of the clinical picture and enable the modification or de-escalation of the initially applied treatment. The fact that the different laboratory specimens have different bacterial count thresholds assigned to them is related to the dilution of the respiratory secretions with which the microbiologist has to work (Table 3.1). It must be admitted, however, that these different figures can be very confusing and that a standard procedure needs to be agreed upon, which refers to counts in undiluted secretions to give a common generally accepted value. It is evident that lower values will translate to improved sensitivity at the expense of a loss in specificity [65, 128, 129] and that increasing these values will result in the opposite problem.

Although the serial dilution technique for the quantitative culture of bronchoalveolar fluid is considered to be the gold standard for the diagnosis of ventilator-associated pneumonia, the calibrated loop technique is equally effective [130].

It should also be stressed that although the results of a positive culture, including bacterial identification and antibiotic sensitivity, are usually available after 48–72 hours, a negative result, which provides information that is equally useful and reliable for the clinician, can be obtained much quicker, after some 18–24 hours of incubation. This issue was recently addressed in a study by Kollef *et al*. In a series of 101 patients with suspected VAP in whom BAL results were negative, the authors suspended antibiotic treatment after three days, provided the patient's condition was clinically stable or improving. No increased mortality was observed in this subset of patients

suggesting that a negative culture result can be useful clinical information. Other authors have noted that this measure achieves a substantial reduction in antibiotic costs [79] with no negative secondary effects [11, 131].

Transmitting Information and its Clinical Interpretation

A clear aspect for improvement is communication among microbiologists and clinicians during the care of patients with VAP. It is important that microbiologists understand that this entity is not yet another of the many nosocomial infections confronted every day but, rather, it is among the most common causes of hospital-acquired infection, and undoubtedly the most serious of these. In addition, VAP is perhaps among the clinical pictures whose timely management has been most clearly shown to save lives. The intensive care specialist should share the responsibility with other specialists in trying to reduce the incidence and improve the prognosis of VAP.

References

1. Rello, J. (2005) Bench-to-bedside review: therapeutic options and issues in the management of ventilator-associated bacterial pneumonia. *Crit Care*, **9** (3), 259–65.
2. Kollef, M.H. (2005) What is ventilator-associated pneumonia and why is it important. *Respir Care*, **50** (6), 714–21; discussion 721–724.
3. Chastre, J. (2005) Conference summary: ventilator-associated pneumonia. *Respir Care*, **50** (7), 975–83.
4. Park, D.R. (2005) Antimicrobial treatment of ventilator-associated pneumonia. *Respir Care*, **50** (7), 932–52; discussion 952–955.
5. Kollef, M. and Niederman, M. (2001) Antimicrobial resistance in the ICU: the time for action is now. *Crit Care Med*, **29** (4 Suppl), N63.
6. Kollef, M.H. and Fraser, V.J. (2001) Antibiotic resistance in the intensive care unit. *Ann Intern Med*, **134** (4), 298–314.
7. Fagon, J.Y., Chastre, J., Hance, A.J. *et al*. (1993) Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest*, **103** (2), 547–53.
8. Croce, M.A., Fabian, T.C., Shaw, B. *et al*. (1994) Analysis of charges associated with diagnosis of nosocomial pneumonia: can routine bronchoscopy be justified? *J Trauma*, **37** (5), 721–7.
9. Rodriguez deCastro, F., Solé, J. and Elcuaz, R. (1994) Quantitative cultures of protected brush specimens and bronchoalveolar lavage in ventilated patients without suspected pneumonia. *Am J Respir Crit Care Med*, **149** (2 Pt 1), 320–3.
10. Luna, C.M., Vujacich, P., Niederman, M.S. *et al*. (1997) Impact of BAL data on the therapy and outcome of ventilator- associated pneumonia. *Chest*, **111** (3), 676–85.
11. Bonten, M.J., Bergmans, D.C., Stobberingh, E.E. *et al*. (1997) Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use. *Am J Respir Crit Care Med*, **156** (6), 1820–4.
12. Kollef, M.H. and Ward, S. (1998) The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator- associated pneumonia. *Chest*, **113** (2), 412–20.

13. Sanchez-Nieto, J.M., Torres, A., Garcia-Cordoba, F. *et al*. (1998) Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. *Am J Respir Crit Care Med*, **157** (2), 371–6.
14. Shorr, A.F., Sherner, J.H., Jackson, W.L. and Kollef, M.H. (2005) Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. *Crit Care Med*, **33** (1), 46–53.
15. Park, D.R. (2005) The microbiology of ventilator-associated pneumonia. *Respir Care*, **50** (6), 742–63; discussion 763–765.
16. Chastre, J. and Fagon, J.Y. (2002) Ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **165** (7), 867–903.
17. Combes, A., Figliolini, C., Trouillet, J.L. *et al*. (2002) Incidence and outcome of polymicrobial ventilator-associated pneumonia. *Chest*, **121** (5), 1618–23.
18. Ibrahim, E.H., Ward, S., Sherman, G. and Kollef, M.H. (2000) A comparative analysis of patients with early onset *vs*. late onset nosocomial pneumonia in the ICU setting. *Chest*, **117** (5), 1434–42.
19. Neuhauser, M.M., Weinstein, R.A., Rydman, R. *et al*. (2003) Antibiotic resistance among Gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *Jama*, **289** (7), 885–8.
20. Dore, P., Robert, R., Grollier, G. *et al*. (1996) Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. *Am J Respir Crit Care Med*, **153** (4 Pt 1), 1292–8.
21. Grollier, G., Dore, P., Robert, R. *et al*. (1996) Antibody response to *Prevotella* spp. in patients with ventilator-associated pneumonia. *Clin Diagn Lab Immunol*, **3**(1), 61–5.
22. Robert, R., Grollier, G., Dore, P. *et al*. (1999) Nosocomial pneumonia with isolation of anaerobic bacteria in ICU patients: therapeutic considerations and outcome. *J Crit Care*, **14** (3), 114–19.
23. Marik, P.E. and Careau, P. (1999) The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: a prospective study [see comments]. *Chest*, **115** (1), 178–83.
24. Crnich, C.J., Safdar, N. and Maki, D.G. (2005) The role of the intensive care unit environment in the pathogenesis and prevention of ventilator-associated pneumonia. *Respir Care*, **50** (6), 813–36; discussion 836–838.
25. Bouza, E., Guinea, J., Pelaez, T. *et al*. (2005) Workload Due To *Aspergillus fumigatus* and significance of the organism in the microbiology laboratory of a general hospital. *J Clin Microbiol*, **43** (5), 2075–9.
26. Munoz P, Alcala, L., SanchezConde, M. *et al*. (2003) The isolation of *Aspergillus fumigatus* from respiratory tract specimens in heart transplant recipients is highly predictive of invasive aspergillosis. *Transplantation*, **75** (3), 326–9.
27. Chen, K.Y., Ko, S.C., Hsueh, P.R., Luh, K.T. and Yang, P.C. (2001) Pulmonary fungal infection: emphasis on microbiological spectra, patient outcome, and prognostic factors. *Chest*, **120** (1), 177–84.
28. el-Ebiary, M., Torres, A., Fabregas, N. *et al*. (1997) Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. *Am J Respir Crit Care Med*, **156** (2 Pt 1), 583–90.
29. Rello, J., Esandi, M.E., Diaz, E. *et al*. (1998) The role of *Candida* sp isolated from bronchoscopic samples in non-neutropenic patients. *Chest*, **114** (1), 146–9.
30. Azoulay, E., Cohen, Y., Zahar, J.R. *et al*. (2004) Practices in non-neutropenic ICU patients with *Candida*-positive airway specimens. *Intensive Care Med*, **30** (7), 1384–9.
31. Safdar, N., Crnich, C.J. and Maki, D.G. (2005) The pathogenesis of ventilator-associated pneumonia: its relevance to developing effective strategies for prevention. *Respir Care*, **50**(6), 725–39; discussion 739–741.

32. Daubin, C., Vincent, S., Vabret, A. *et al*. (2005) Nosocomial viral ventilator-associated pneumonia in the intensive care unit: a prospective cohort study. *Intensive Care Med*, **31** (8), 1116–22.
33. Bruynseels, P., Jorens, P.G., Demey, H.E. *et al*. (2003) Herpes simplex virus in the respiratory tract of critical care patients: a prospective study. *Lancet*, **362** (9395), 1536–41.
34. Simoons-Smit, A.M., Kraan, E.M., Beishuizen, A., Strack van Schijndel, R.J. and Vandenbroucke-Grauls, C.M. (2006) Herpes simplex virus type 1 and respiratory disease in critically-ill patients: real pathogen or innocent bystander? *Clin Microbiol Infect*, **12** (11), 1050–9.
35. Bouza, E., Torres, M., Catalán, P. *et al*. (2005) Incidence And Significance of Herpes Simplex Virus (HSV) in Bacterial Ventilator-Associated Pneumonia (Vap): A Prospective Study. In:ASM, editor. 45 th ICAAC, Washington, D.C.
36. Papazian, L., Fraisse, A., Garbe, L. *et al*. (1996) Cytomegalovirus. An unexpected cause of ventilator-associated pneumonia. *Anesthesiology*, **84** (2), 280–7.
37. Stott, D.J., Kerr, G. and Carman, W.F. (2002) Nosocomial transmission of influenza. *Occup Med (Lond)*, **52** (5), 249–53.
38. Prats, E., Dorca, J., Pujol, M. *et al*. (2002) Effects of antibiotics on protected specimen brush sampling in ventilator-associated pneumonia. *Eur Respir J*, **19** (5), 944–51.
39. Souweine, B., Veber, B., Bedos, J.P. *et al*. (1998) Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: impact of previous antimicrobial treatments [see comments]. *Crit Care Med*, **26** (2), 236–44.
40. Montravers, P., Fagon, J.Y., Chastre, J. *et al*. (1993) Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. *Am Rev Respir Dis*, **147** (1), 38–44.
41. Fagon, J.Y. (2006) Diagnosis and treatment of ventilator-associated pneumonia: fiberoptic bronchoscopy with bronchoalveolar lavage is essential. *Semin Respir Crit Care Med*, **27** (1), 34–44.
42. American Thoracic Society/Infectious Diseases Society of America(2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, healthcare-associated pneumonia. *Am J Respir Crit Care Med*, **171** (4), 388–416.
43. Ruiz, M., Torres, A., Ewig, S. *et al*. (2000) Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. *Am J Respir Crit Care Med*, **162** (1), 119–25.
44. Michel, F., Franceschini, B., Berger, P. *et al*. (2005) Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: a role for routine endotracheal aspirate cultures. *Chest*, **127** (2), 589–97.
45. Hayon, J., Figliolini, C., Combes, A. *et al*. (2002) Role of serial routine microbiologic culture results in the initial management of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **165** (1), 41–6.
46. Delclaux, C., Roupie, E., Blot, F. *et al*. (1997) Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: incidence and diagnosis. *Am J Respir Crit Care Med*, **156** (4 Pt 1), 1092–8.
47. Nopmaneejumruslers, C. and Chan, C.K. (2005) Is there a role for routine surveillance endotracheal aspirate cultures in the treatment of BAL-confirmed ventilator-associated pneumonia. *Chest*, **127** (2), 425–7.
48. Bouza, E., Perez, A., Munoz, P, *et al*. (2003) Ventilator-associated pneumonia after heart surgery: a prospective analysis and the value of surveillance. *Crit Care Med*, **31** (7), 1964–70.
49. Chastre, J., Combes, A. and Luyt, C.E. (2005) The invasive (quantitative) diagnosis of ventilator-associated pneumonia. *Respir Care*, **50** (6), 797–807; discussion 807–812.

50. Wood, A.Y., Davit, A.J., 2nd, Ciraulo, D.L. *et al*. (2003) A prospective assessment of diagnostic efficacy of blind protective bronchial brushings compared to bronchoscope-assisted lavage, bronchoscope-directed brushings, and blind endotracheal aspirates in ventilator-associated pneumonia. *J Trauma*, **55** (5), 825−34.
51. Brun-Buisson, C., Fartoukh, M., Lechapt, E. *et al*. (2005) Contribution of blinded, protected quantitative specimens to the diagnostic and therapeutic management of ventilator-associated pneumonia. *Chest*, **128** (2), 533−44.
52. Meduri, G.U., Reddy, R.C., Stanley, T. and El-Zeky, F. (1998) Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. *Am J Respir Crit Care Med*, **158** (3), 870−5.
53. Flanagan, P.G., Findlay, G.P., Magee, J.T. *et al*. (2000) The diagnosis of ventilator-associated pneumonia using non-bronchoscopic, non-directed lung lavages. *Intensive Care Med*, **26** (1), 20−30.
54. Mentec, H., May-Michelangeli, L., Rabbat, A. *et al*. (2004) Blind and bronchoscopic sampling methods in suspected ventilator-associated pneumonia. A multicentre prospective study. *Intensive Care Med*, **30** (7), 1319−26.
55. SoleViolan, J., Fernandez, J.A., Benitez, A.B., CardenosaCendrero, J.A. and Rodriguez deCastro, F. (2000) Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. *Crit Care Med*, **28** (8), 2737−41.
56. Sierra, R., Benitez, E., Leon, C. and Rello, J. (2005) Prevention and diagnosis of ventilator-associated pneumonia: a survey on current practices in southern Spanish ICUs. *Chest*, **128** (3), 1667−73.
57. Bouza, E., Hortal, J., Munoz P, *et al*. (2006) Infections following major heart surgery in European intensive care units: there is room for improvement (ESGNI 007 study). *J Hosp Infect*, **63** (4), 399−405.
58. Fujitani, S. and Yu, V.L. (2006) Quantitative cultures for diagnosing ventilator-associated pneumonia: a critique. *Clin Infect Dis*, **43** (Suppl 2), S106−113.
59. Kirtland, S.H., Corley, D.E., Winterbauer, R.H. *et al*. (1997) The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. *Chest*, **112** (2), 445−57.
60. Elatrous, S., Boukef, R., OuanesBesbes, L. *et al*. (2004) Diagnosis of ventilator-associated pneumonia: agreement between quantitative cultures of endotracheal aspiration and plugged telescoping catheter. *Intensive Care Med*, **30** (5), 853−8.
61. Valencia Arango, M., Torres Marti, A., Insausti Ordenana, J. *et al*. (2003) [Diagnostic value of quantitative cultures of endotracheal aspirate in ventilator-associated pneumonia: a multicenter study]. *Arch Bronconeumol*, **39** (9), 394−9.
62. Wu, C.L., Yang, D., Wang, N.Y., Kuo, H.T. and Chen, P.Z. (2002) Quantitative culture of endotracheal aspirates in the diagnosis of ventilator-associated pneumonia in patients with treatment failure. *Chest*, **122** (2), 662−8.
63. Fangio, P., Rouquette-Vincenti, I., Rousseau, J.M., Soullie, B. and Brinquin, L. (2002⟩) [Diagnosis of ventilator-associated pneumonia: a prospective comparison of the telescoping plugged catheter with the endotracheal aspirate]. *Ann Fr Anesth Reanim*, **21** (3), 184−92.
64. Bergmans, D.C., Bonten, M.J., DeLeeuw, P.W. and Stobberingh, E.E. (1997) Reproducibility of quantitative cultures of endotracheal aspirates from mechanically ventilated patients. *J Clin Microbiol*, **35** (3), 796−8.
65. Torres, A., Martos, A., Puig de laBellacasa, J.*et al*. (1993) Specificity of endotracheal aspiration, protected specimen brush, and bronchoalveolar lavage in mechanically ventilated patients. *Am Rev Respir Dis*, **147** (4), 952−7.

66. Sauaia, A., Moore, F.A., Moore, E.E. *et al*. (1993) Diagnosing pneumonia in mechanically ventilated trauma patients: endotracheal aspirate versus bronchoalveolar lavage. *J Trauma*, **35** (4), 512–17.
67. Woske, H.J., Roding, T., Schulz, I. and Lode, H. (2001) Ventilator-associated pneumonia in a surgical intensive care unit: epidemiology, etiology and comparison of three bronchoscopic methods for microbiological specimen sampling. *Crit Care*, **5** (3), 167–73.
68. Wimberley, N.W., Bass, J.B.Jr, Boyd, B.W. *et al*. (1982) Use of a bronchoscopic protected catheter brush for the diagnosis of pulmonary infections. *Chest*, **81** (5), 556–62.
69. Baughman, R.P. (2000) Protected-specimen brush technique in the diagnosis of ventilator-associated pneumonia. *Chest*, **117** (4 Suppl 2), 203S–6S.
70. deJaeger, A., Litalien, C., Lacroix, J., Guertin, M.C. and InfanteRivard, C. (1999) Protected specimen brush or bronchoalveolar lavage to diagnose bacterial nosocomial pneumonia in ventilated adults: a meta-analysis [see comments]. *Crit Care Med*, **27** (11), 2548–60.
71. Timsit, J.F., Misset, B., Francoual, S. *et al*. (1993) Is protected specimen brush a reproducible method to diagnose ICU-acquired pneumonia? *Chest*, **104** (1), 104–8.
72. Marquette, C.H., Herengt, F., Saulnier, F. *et al*. (1993) Protected specimen brush in the assessment of ventilator- associated pneumonia. Selection of a certain lung segment for bronchoscopic sampling is unnecessary. *Chest*, **103** (1), 243–7.
73. Casetta, M., Blot, F., Antoun, S. *et al*. (1999) Diagnosis of nosocomial pneumonia in cancer patients undergoing mechanical ventilation: a prospective comparison of the plugged telescoping catheter with the protected specimen brush. *Chest*, **115** (6), 1641–5.
74. Barret, J.P., Ramzy, P.I., Wolf, S.E. and Herndon, D.N. (1999) Sensitivity and specificity of bronchoalveolar lavage and protected bronchial brush in the diagnosis of pneumonia in paediatric burn patients. *Arch Surg*, **134** (11), 1243–6.
75. Rodríguez de Castro, F., Solé Violán, J., Lafarga Capuz, B. *et al*. (1991) Reliability of the bronchoscopic protected catheter brush in the diagnosis of pneumonia in mechanically ventilated patients. *Crit Care Med*, **19** (2), 171–5.
76. Herer, B., Fuhrman, C., Demontrond, D. *et al*. (2001) Diagnosis of nosocomial pneumonia in medical ward: repeatability of the protected specimen brush. *Eur Respir J*, **18** (1), 157–63.
77. Butler, K.L., Best, I.M., Oster, R.A. *et al*. (2004) Is bilateral protected specimen brush sampling necessary for the accurate diagnosis of ventilator-associated pneumonia. *J Trauma*, **57** (2), 316–22.
78. Bello, S., Tajada, A., Chacón, E. *et al*. (1996) "Blind" protected specimen brushing versus bronchoscopic techniques in the aetiolological diagnosis of ventilator- associated pneumonia [see comments]. *Eur Respir J*, **9** (7), 1494–9.
79. Marik, P.E. and Brown, W.J. (1995) A comparison of bronchoscopic *vs*. blind protected specimen brush sampling in patients with suspected ventilator-associated pneumonia. *Chest*, **108** (1), 203–7.
80. Rumbak, M.J. and Bass, R.L. (1994) Tracheal aspirate correlates with protected specimen brush in long-term ventilated patients who have clinical pneumonia. *Chest*, **106** (2), 531–4.
81. Baselski, V.S. and Wunderink, R.G. (1994) Bronchoscopic diagnosis of pneumonia. *Clin Microbiol Rev*, **7** (4), 533–58.
82. Wahl, W.L., Ahrns, K.S., Brandt, M.M. *et al*. (2005) Bronchoalveolar lavage in diagnosis of ventilator-associated pneumonia in patients with burns. *J Burn Care Rehabil*, **26** (1), 57–61.

83. deLassence, A., Joly-Guillou, M.L., Salah, A. *et al*. (2004) Accuracy of delayed (24 hours) processing of bronchoalveolar lavage for diagnosing bacterial pneumonia. *Crit Care Med*, **32** (3), 680−5.
84. Mueller, E.W., Wood, G.C., Kelley, M.S. *et al*. (2003) The predictive value of preliminary bacterial colony counts from bronchoalveolar lavage in critically ill trauma patients. *Am Surg*, **69** (9), 749−55; discussion 755−756.
85. Balthazar, A.B., VonNowakonski, A., DeCapitani, E.M. *et al*. (2001) Diagnostic investigation of ventilator-associated pneumonia using bronchoalveolar lavage: comparative study with a postmortem lung biopsy. *Braz J Med Biol Res*, **34** (8), 993−1001.
86. Vazquez-Garcia, J.C., Morales-Gomez, J., Rivera-Martinez, E., Serna-Secundino, I. and Sansores-Martinez, R. (1998) [Diagnostic usefulness of bronchoalveolar lavage in nosocomial pneumonia associated with mechanical ventilation in patients undergoing antibiotic treatment]. *Gac Med Mex*, **134** (6), 651−9.
87. Speich, R., Hauser, M., Hess, T. *et al*. (1998) Low specificity of the bacterial index for the diagnosis of bacterial pneumonia by bronchoalveolar lavage. *Eur J Clin Microbiol Infect Dis*, **17** (2), 78−84.
88. Schreiber, T., Heroldt, J., Gottschall, R. and Klein, U. (1998) [Value of aspiration of tracheal secretions and bronchoalveolar lavage in diagnosis of nosocomial pneumonia in ventilated patients]. *Anaesthesiol Reanim*, **23** (4), 93−8.
89. Djamin, R.S., Drent, M., Schreurs, A.J., Groen, E.A. and. Wagenaar, S.S. (1998) Diagnosis of *Pneumocystis carinii* pneumonia in HIV-positive patients. Bronchoalveolar lavage *vs*. Bronchial brushing. *Acta Cytol*, **42** (4), 933−8.
90. Prekates, A., Nanas, S., Nakos, G. *et al*. (1997) Conditional evaluation of bronchoalveolar lavage in mechanically ventilated patients with suspected unilateral lobar pneumonia. *S Afr Med J*, **87** (5 Suppl), 643−8.
91. Jourdain, B., Joly-Guillou, M.L., Dombret, M.C. *et al*. (1997) Usefulness of quantitative cultures of BAL fluid for diagnosing nosocomial pneumonia in ventilated patients. *Chest*, **111** (2), 411−18.
92. Saldias, F., Blacutt, M. and Moreno, R. (1996⟩) [Management of patients with severe pneumonia in mechanical ventilation: usefulness of bronchoalveolar lavage]. *Rev Med Chil*, **124** (8), 950−8.
93. Cadranel, J., GilletJuvin, K., Antoine, M. *et al*. (1995) Site-directed bronchoalveolar lavage and transbronchial biopsy in HIV-infected patients with pneumonia. *Am J Respir Crit Care Med*, **152** (3), 1103−6.
94. Cook, D.J., Brun-Buisson, C., Guyatt, G.H. and Sibbald, W.J. (1994) Evaluation of new diagnostic technologies: bronchoalveolar lavage and the diagnosis of ventilator-associated pneumonia. *Crit Care Med*, **22** (8), 1314−22.
95. Vallés, J., Rello, J., Fernández, R. *et al*. (1994) Role of bronchoalveolar lavage in mechanically ventilated patients with suspected pneumonia. *Eur J Clin Microbiol Infect Dis*, **13** (7), 549−58.
96. Solé Violán, J., Rodríguez de Castro, F., Caminero Luna, J., Bordes Benítez, A. and Manzano Alonso, J.L. (1993) Comparative efficacy of bronchoalveolar lavage and telescoping plugged catheter in the diagnosis of pneumonia in mechanically ventilated patients. *Chest*, **103** (2), 386−90.
97. Marquette, C.H., Copin, M.C., Wallet, F. *et al*. (1995) Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. *Am J Respir Crit Care Med*, **151** (6), 1878−88.
98. Papazian, L., Autillo Touati, A., Thomas, P. *et al*. (1997) Diagnosis of ventilator-associated pneumonia: an evaluation of direct examination and presence of intracellular organisms. *Anesthesiology*, **87** (2), 268−76.

99. Zedtwitz-Liebenstein, K., Schenk, P., Apfalter, P. *et al*. (2005) Ventilator-associated pneumonia: increased bacterial counts in bronchoalveolar lavage by using urea as an endogenous marker of dilution. *Crit Care Med*, **33** (4), 756–9.
100. Rello, J., Gallego, M., Mariscal, D., Sonora, R. and Valles, J. (1997) The value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **156** (1), 196–200.
101. Kollef, M.H. (1993) Ventilator-associated pneumonia. A multivariate analysis. *Jama*, **270** (16), 1965–70.
102. Kollef, M.H. and Kollef, K.E. (2005) Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. *Chest*, **128** (4), 2706–13.
103. Ost, D.E., Hall, C.S., Joseph, G. *et al*. (2003) Decision analysis of antibiotic and diagnostic strategies in ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **168** (9), 1060–7.
104. Chastre, J., Luyt, C.E., Combes, A. and Trouillet, J.L. (2006) Use of quantitative cultures and reduced duration of antibiotic regimens for patients with ventilator-associated pneumonia to decrease resistance in the intensive care unit. *Clin Infect Dis*, **43** (Suppl 2), S75–81.
105. Fagon, J.Y., Chastre, J., Wolff, M. *et al*. (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med*, **132** (8), 621–30.
106. Dreyfuss, D., Mier, L., LeBourdelles, G. *et al*. (1993) Clinical significance of borderline quantitative protected specimen brush culture results. *Am Rev Respir Dis*, **147**, 941–51.
107. Baram, D., Hulse, G. and Palmer, L.B. (2005) Stable patients receiving prolonged mechanical ventilation have a high alveolar burden of bacteria. *Chest*, **127** (4), 1353–7.
108. Luna, C.M., Videla, A., Mattera, J. *et al*. (1999) Blood cultures have limited value in predicting severity of illness and as a diagnostic tool in ventilator-associated pneumonia. *Chest*, **116** (4), 1075–84.
109. Bryan, C.S. (1999) Nosocomial pneumonia: blood cultures remain useful [editorial; comment]. *Chest*, **116** (4), 859–60.
110. Chendrasekhar, A. (1996) Are routine blood cultures effective in the evaluation of patients clinically diagnosed to have nosocomial pneumonia. *Am Surg*, **62** (5), 373–6.
111. Taylor, G.D., Buchanan-Chell, M., Kirkland, T., McKenzie, M. and Wiens, R. (1995) Bacteremic nosocomial pneumonia. A 7-year experience in one institution. *Chest*, **108** (3), 786–8.
112. Rello, J., Mirelis, B., Alonso, C. and Prats, G. (1991) Lack of usefulness of blood cultures to diagnose ventilator- associated pneumonia. *Eur Respir J*, **4** (8), 1020.
113. Chastre, J., Viau, F., Brun, P. *et al*. (1984) Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. *Am Rev Respir Dis*, **130** (5), 924–9.
114. Chastre, J., Fagon, J.Y., Bornet-Lecso, M. *et al*. (1995) Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*, **152** (1), 231–40.
115. Baselski, V.S., el-Torky, M., Coalson, J.J. and Griffin, J.P. (1992) The standardization of criteria for processing and interpreting laboratory specimens in patients with suspected ventilator- associated pneumonia. *Chest*, **102** (5 Suppl 1), 571S–9S.
116. Georges, H., Santre, C., Leroy, O. *et al*. (1996) Reliability of quantitative cultures of protected specimen brush after freezing. *Am J Respir Crit Care Med*, **153** (2), 855–7.

117. Rello, J., Mariscal, D., Gallego, M. and Valles, J. (2002) Effect of enriched thioglycolate on direct examination of respiratory specimens and guiding initial empirical therapy in intubated patients with pneumonia: a prospective, randomized study. *Crit Care Med*, **30** (2), 311–14.
118. Davis, K.A., Eckert, M.J., Reed, R.L. *et al*. (2005) Ventilator-associated pneumonia in injured patients: do you trust your gram's stain. *J Trauma*, **58** (3), 462–6; discussion 466–467.
119. Croce, M.A., Fabian, T.C., Waddle-Smith, L. *et al*. (1998) Utility of Gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: a prospective study. *Ann Surg*, **227** (5), 743–51; discussion 751–755.
120. Prekates, A., Nanas, S., Argyropoulou, A. *et al*. (1998) The diagnostic value of gram stain of bronchoalveolar lavage samples in patients with suspected ventilator-associated pneumonia. *Scand J Infect Dis*, **30** (1), 43–7.
121. Blot, F., Raynard, B., Chachaty, E. *et al*. (2000) Value of gram stain examination of lower respiratory tract secretions for early diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*, **162** (5), 1731–7.
122. Marquette, C.H., Wallet, F., Nevière, R. *et al*. (1994) Diagnostic value of direct examination of the protected specimen brush in ventilator-associated pneumonia. *Eur Respir J*, **7** (1), 105–13.
123. Pham, L.H., Brun-Buisson, C., Legrand, P. *et al*. (1991) Diagnosis of nosocomial pneumonia in mechanically ventilated patients. Comparison of a plugged telescoping catheter with the protected specimen brush. *Am Rev Respir Dis*, **143** (5 Pt 1), 1055–61.
124. Laupland, K.B., Church, D.L. and Gregson, D.B. (2005) Validation of a rapid diagnostic strategy for determination of significant bacterial counts in bronchoalveolar lavage samples. *Arch Pathol Lab Med*, **129** (1), 78–81.
125. Bouza, E., Sousa, D., Munoz P, *et al*. (2004) Bloodstream infections: a trial of the impact of different methods of reporting positive blood culture results. *Clin Infect Dis*, **39** (8), 1161–9.
126. Cercenado, E., Cercenado, S., Marín, M. *et al*. (2007) Comparison of rapid antimicrobial susceptibility testing (E-test) performed directly on lower respiratory tract samples with conventional antimicrobial susceptibility of isolated bacteria. Diagn Microbiol Infect Dis, **58** (2), 211–16.
127. Bouza, E., Torres, M.V., Radice, C. *et al*. (2007) Direct E-test on lower respiratory tract samples improves antimicrobial use in ventilator-associated pneumonia. *Clin Infect Dis*, **44** (3), 382–7
128. Miller, P.R., Meredith, J.W. and Chang, M.C. (2003) Optimal threshold for diagnosis of ventilator-associated pneumonia using bronchoalveolar lavage. *J Trauma*, **55** (2), 263–7; discussion 267–268.
129. Croce, M.A., Fabian, T.C., Mueller, E.W. *et al*. (2004) The appropriate diagnostic threshold for ventilator-associated pneumonia using quantitative cultures. *J Trauma*, **56** (5), 931–4; discussion 934–936.
130. Afessa, B., Hubmayr, R.D., Vetter, E.A. *et al*. (2006) Bronchoscopy in ventilator-associated pneumonia: agreement of calibrated loop and serial dilution. *Am J Respir Crit Care Med*, **173** (11), 1229–32.
131. Croce, M.A., Fabian, T.C., Schurr, M.J. *et al*. (1995) Using bronchoalveolar lavage to distinguish nosocomial pneumonia from systemic inflammatory response syndrome: a prospective analysis. *J Trauma*, **39** (6), 1134–9; discussion 1139–1140.
132. Aucar, J.A., Bongera, M., Phillips, J.O., Kamath, R. and Metzler, M.H. (2003) Quantitative tracheal lavage versus bronchoscopic protected specimen brush for the diagnosis of nosocomial pneumonia in mechanically ventilated patients. *Am J Surg*, **186** (6), 591–6.

133. Cook, D. and Mandell, L. (2000) Endotracheal aspiration in the diagnosis of ventilator-associated pneumonia. *Chest*, **117** (4 Suppl 2), 195S−7S.
134. Jourdain, B., Novara, A., JolyGuillou, M.L. *et al*. (1995) Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*, **152** (1), 241−6.
135. Torres, A. and El-Ebiary, M. (2000) Bronchoscopic BAL in the diagnosis of ventilator-associated pneumonia. *Chest*, **117** (4 Suppl 2), 198S−202S.
136. Sole-Violan, J., Rodriguez de Castro, F., Rey, A., Martin-Gonzalez, J.C. and Cabrera-Navarro, P. (1994) Usefulness of microscopic examination of intracellular organisms in lavage fluid in ventilator-associated pneumonia. *Chest*, **106** (3), 889−94.
137. Timsit, J.F., Misset, B., Goldstein, F.W., Vaury, P. and Carlet, J. (1995) Reappraisal of distal diagnostic testing in the diagnosis of ICU-acquired pneumonia [see comments]. *Chest*, **108** (6), 1632−9.
138. Chastre, J., Fagon, J.Y. and Trouillet, J.L. (1995) Diagnosis and treatment of nosocomial pneumonia in patients in intensive care units. *Clin Infect Dis*, **21** (Suppl 3), S226−237.
139. Papazian, L., Thomas, P., Garbe, L. *et al*. (1995) Bronchoscopic or blind sampling techniques for the diagnosis of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **152** (6 Pt 1), 1982−91.
140. Campbell, G.D. (2000) Blinded invasive diagnostic procedures in ventilator-associated pneumonia. *Chest*, **117** (4 Suppl 2), 207S−11S.
141. Marquette, C.H., Georges, H., Wallet, F. *et al*. (1993) Diagnostic efficiency of endotracheal aspirates with quantitative bacterial cultures in intubated patients with suspected pneumonia. Comparison with the protected specimen brush [see comments]. *Am Rev Respir Dis*, **148** (1), 138−44.

4

Pathophysiology of Pneumonia

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Introduction

Pneumonia is an infectious process caused by the invasion and overgrowth of microorganisms in lung parenchyma that break down defences and provoke intra alveolar exudates.

The term 'community pneumonia' is used when the infection appears in a nonhospitalised population. The term 'hospital-acquired pneumonia' or nosocomial pneumonia is used when there is no evidence that the infection was present or incubating at the time of admission to hospital. Nosocomial pneumonia is most frequently found in mechanically ventilated patients and, therefore, is commonly known as ventilator-associated pneumonia (VAP). With the development of non-invasive ventilation, a new term must be found when Intensive Care Unit (ICU), nonintubated patients develop pneumonia; then, VAP must be related to 'intubation-associated pneumonia'.

Within the pathogenesis of nosocomial pneumonia several ways of accessing the lung parenchyma have already been described. The development of pneumonia requires the pathogen to reach the alveoli and host defences to be overwhelmed,

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either by microorganism virulence or due to the inoculums‘ size. Intrusion of bacteria into the lower respiratory tract is usually the result of the aspiration of organisms from the upper respiratory tract. Underlying disease, loss of mechanical respiratory defences with the use of sedatives, tracheal intubation and antibiotic treatment are determinant factors for change in the normal flora of the upper respiratory tract.

Nasal, oropharynx, biofilm and respiratory tract colonization have been related to the risk of developing pneumonia, especially in ‘late onset pneumonia’. Aspiration of normal oropharynx flora in comatose patients and during intubation seems to be the pathogenesis of ‘early onset pneumonia’. Less frequently, bacteraemia, contaminated aerosols, tracheal aspiration manoeuvres or fibrobronchoscopes can introduce microorganisms directly to the lung parenchyma. The relationship of the gastric chamber, as the only source of colonization, with VAP is more debatable.

Post-mortem studies showed the complexity of the histology findings, and that quantitative cultures of lung samples could not easily discriminate the presence or absence of histological pneumonia.

Nasal Colonization

The upper airway is usually colonized. In a study by Campbell *et al.* [1] of 776 trauma victims, 18.7 % of nasal cultures were positive for *S. aureus* on the day of admission.

The extent and risk factors for nasal methicillin-resistant *S. aureus* (MRSA) carriage within the community have been determined [2]. Anterior nares cultures were obtained within 48 hours of admission during a one-month period. A total of 53 (7.3 %) of 726 patients had a nares culture positive for MRSA. In multivariate analysis, risk factors for MRSA colonization included antibiotic use within three months prior to admission (odds ratio [OR], 2.5; 95 % confidence interval [CI], 1.2−5.0), hospitalisation during the past 12 months (OR, 4.0; 95 % CI, 2.0−8.2), diagnosis of skin or soft-tissue infection at admission (OR, 3.4; 95 % CI, 1.5−7.9) and HIV infection. These results highlight the importance of surveillance cultures; Scudeller *et al.* [3] studied 7640 consecutive patients admitted to their Italian Hospital, and the overall incidence of MRSA nasal carriers was 1.12 %.

Oropharyngeal and Gastric Colonization

The colonization of the oral cavity is an important precursor for development of VAP [4]. The normal ecology of the oropharynx may vary in some situations. Johanson [5] assessed oral colonization of Gram-negative bacilli (GNB) in five groups of individuals with varying degrees of illness, including nonhospitalised healthy people, healthy hospital employees, physically healthy hospitalised patients, moderately ill hospitalised patients and critically ill hospitalised patients. The oral ecology was tested by oropharyngeal culture. GNB were rarely cultured in the healthy individuals (0−2 %), but were found more frequently in the moderately and critically ill

patients (16 and 57 %). Several studies have explored the association between oral and lung bacteria in patients with VAP. Of interest is that the same bacterial species were isolated from oral cavity cultures and from fiberoptic bronchoscopy of the lungs in a wide range (0–97 %) of cases [6].

Fibronectin, a component of whole saliva, provides binding sites for the adhesion of oral streptococci while inhibiting adhesion of aerobic Gram-negative bacilli (AGNB). The reduction of normal inhibitory flora promotes the colonization of respiratory pathogens and in hospitalised patients the oropharynx becomes a reservoir of infected secretions.

Gastric pH <4 prevents bacterial growth in the gastric chamber. In hospitalised patients, treatment with antacid drugs or ranitidine is frequent to prevent the appearance of stress ulcers. These drugs give rise to an increase in the pH of the gastric juice. De la Torre *et al.* [7] found that in 80 patients under mechanical ventilation who were studied serially during the first two weeks of admission, only 10 showed no microorganisms in gastric cultures. These patients had a lower mean gastric pH (3.3) than patients with gastric colonization (mean gastric pH of 4.6). In a 1991 meta-analysis Tryba found [8] that antacids and H_2-antagonists were significantly superior to untreated patients in preventing stress bleeding. Sucralfate was superior to H_2-antagonists. Patients treated with antacids or H_2-antagonists showed a significantly higher risk of developing nosocomial pneumonia. Later, Cook *et al.* [9] demonstrated the trend towards less clinically important bleeding with H_2-antagonists and antacids than with sucralfate. There was a trend towards an increased risk of pneumonia associated with H_2-antagonists when compared with no prophylaxis and a significantly higher risk when compared with sucralfate. Finally, the last meta-analysis [10] concluded that ranitidine is ineffective in preventing gastrointestinal bleeding and might increase the risk of pneumonia. Studies on sucralfate do not provide conclusive results. Currently, there are insufficient data to to conclude anything one way or the other but the rate of clinically significant bleeding due to stress ulcers is low.

The type of microorganism that colonizes the stomach is determined by the germs present in the saliva or in the duodenum. In non-hospitalised patients being treated with H_2-blockers, Gram-positive bacteria dominate the gastric flora, while in hospitalised patients AGNB are predominant [11], reflecting the presence of these microorganisms in the duodenum or in the oropharyngeal saliva.

Oropharyngeal and Gastric Aspiration

Normal adults frequently aspirate oropharyngeal secretions during sleep, but host defences prevent lung infections and the type of microorganisms aspirated are less virulent. However, for ill patients conditions are different. Firstly, there is colonization of dental plaque and the oropharynx by AGNB. Secondly, a nasogastric tube (NGT) that gives rise to lower oesophageal sphincter incompetence is frequently present. Ferrer *et al*. [12] demonstrated that small-bore nasogastric tubes in intubated patients do not reduce gastroesophageal reflux (GOR) or microaspiration. Thirdly, the supine position is important. Torres *et al*. [13] recognized the importance of body position

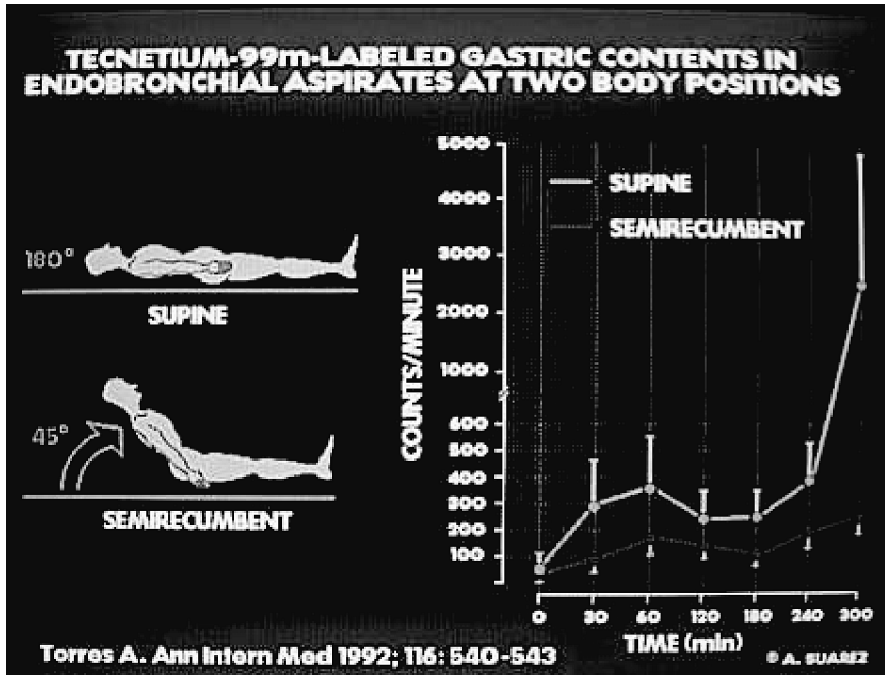

Figure 4.1
Semi-recumbent position protects from aspiration of gastric contents to lower airways, as demonstrated using a radio-labelled technetium marker.

in gastric reflux and tracheal aspiration. Instilling a colloid with technetium via nasogastric tube and placing patients in a recumbent position significantly reduced the radioactivity in tracheal secretions in comparison with patients in a supine position (Figure 4.1). In the same way, a study was aimed at evaluating the effect of a NGT incorporating a low-pressure oesophageal balloon on GOR and bronchoaspiration in patients receiving mechanical ventilation [14]. Fourteen patients were studied in a semi-recumbent position for two consecutive days. Samples of blood, gastric content and oropharyngeal and bronchial secretions were taken every two hours over a period of eight hours. A radioactively labelled nutritional solution was continuously administered through the NGT. The magnitudes of both the GOR and bronchoaspiration were measured by radioactivity counting of oropharyngeal and bronchial secretion samples, respectively. Inflation of the oesophageal balloon resulted in a significant decrease in both GOR and bronchoaspiration of gastric content. This protective effect was statistically significant from four hours following inflation throughout the duration of the study. This study demonstrates that an inflated oesophageal balloon delays and decreases gastro-oesophageal and bronchial aspiration of gastric content in patients carrying a nasogastric tube and receiving enteral nutrition during mechanical ventilation.

However, recently, Girou *et al*. [15] in a randomised study, found no significant differences in the daily bacterial count in the oropharynx and in the trachea between

patients placed in a semi-recumbent position with continuous subglottic suctioning and patients who were in a supine position.

It has not, however, been possible to demonstrate the responsibility of gastric colonization as the initial source of microorganisms and the later development of VAP [16].

Lower Airway Colonization

Lower airways can be colonized in chronic obstructive pulmonary disease (COPD) patients and in hospitalised patients. Early tracheal colonization (within the first 24 hours of mechanical ventilation) has been described in intubated and mechanically ventilated patients. In this short time of intubation, 80 % of the patients were colonized [7].

The composition of the tracheal colonizing flora is worthy of special mention, and the pattern of tracheal colonization changes over time among hospitalised and ventilated patients.

An important factor to take into account is that healthy patients may be chronically colonized. In a study by Ewig *et al*. [17], the initial colonization rate at any site (nasal and pharyngeal, tracheobronchial, gastric juice and protected specimen brush sample) on ICU admission following brain injury was 83 %. *S. pneumoniae, H. influenzae* and *S. aureus* were the predominant microorganisms on the upper airways. In a study by Sirvent *et al*. [18] including 100 head injury patients, 68 % of the endotracheal aspirates (EA) samples taken within 24 hours of intubation were colonized: *S. aureus* in 22 % of patients, *H. influenzae* in 20 % patients, *S. pneumoniae* in 6 % and Gram-negative bacilli in 20 % of patients. These microorganisms are responsible for the majority of 'early onset pneumonia', suggesting that aspiration of oropharynx secretions, when the patient becomes unconscious or at the moment of intubation, can play a role in the development of pneumonia.

Pseudomonas spp. have increased affinity to ciliated tracheal epithelial cells, and these microorganisms are not usually present in the oropharynx. *Pseudomonas* spp. are probably not present in subglottic secretions. The adherence of *Pseudomonas* increases to desquamated epithelium, following influenza virus infection, tracheostomy or repeated tracheal suctions in intubated patients [19]. In this way, tracheal colonization could be classified as pre-cuff and post-cuff with two different behaviours.

Colonization of Artificial Airways

Condensates of ventilator circuits can be a potential source of microorganisms. Craven *et al*. [20] demonstrated that the inner parts of the ventilator circuit closest to the patient have the highest rates of contamination and the highest bacterial counts. After 24 hours in use, 80 % of the ventilator circuits and the condensates were colonized, predominantly by aerobic Gram-negative bacilli (76 %), Gram-positive cocci (21 %) and by yeast (3 %). These microorganisms had frequently been isolated from sputum cultures on previous occasions.

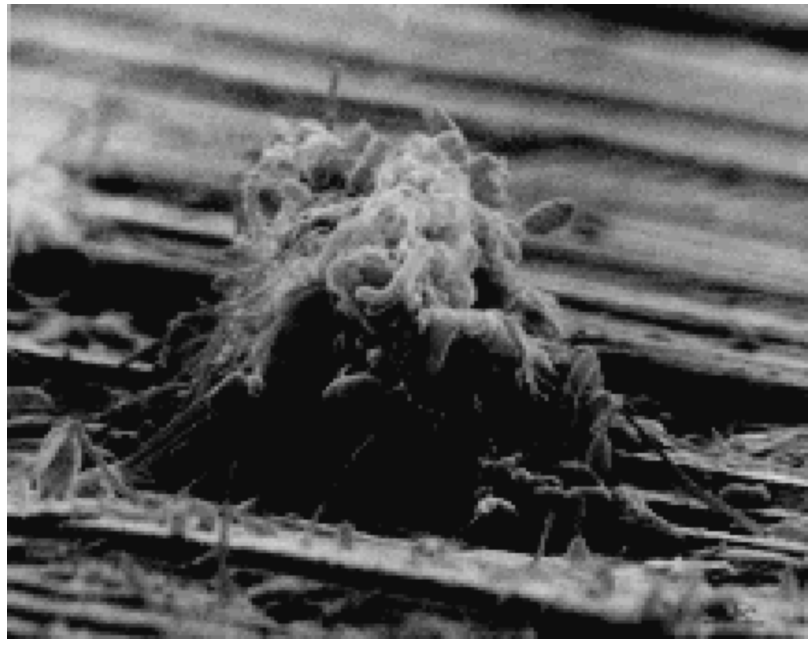

Figure 4.2
Microscopic electronic demonstration of biofilm formation in an endotracheal tube.

The endotracheal tube has been described as a reservoir for microorganisms that can adhere to the surface of the foreign body. This biofilm is relatively insensitive to the effects of antibiotics and host defences, and fragments of endotracheal tube biofilm can be dislodged by suction catheter or by ventilator gas flow (Figure 4.2). It has been proposed that bacteria from the biofilm lining of the endotracheal tube might be scattered into the lungs during ventilation gas flow, since dissemination of bacteria from the tube has been demonstrated *in vitro* [21]. Dynamic studies simulating the scattering of tracheal tube biofilm have shown that bacteria can be disseminated many centimetres from the orifice of the endotracheal tube, far into the lung [22]. In 1999, Adair CG *et al*. [23] carried out a study on 20 patients with VAP and 20 patients as control. Endotracheal tubes were examined for the presence of biofilm, after extubation, and the relation with microorganisms that caused VAP. It was found that 70 % of patients with VAP had identical pathogens isolated from both endotracheal biofilm and tracheal secretions (electrophoresis, polymerase chain reaction technique and susceptibility testing). No pairing of pathogens was observed in the control patients ($p < 0.005$).

Feldman *et al*. [24] described the sequence of endotracheal tube colonization very well. They studied 10 patients, who on admission showed no evidence of any infection, and cultured the oropharynx, gastric content, interior of the airway tube (throat swab) and end tracheal secretions twice a day, for five days. Nine patients became colonized. The oropharynx was the first site (at 36 hours), followed by the stomach (36−60 hours) and, thereafter, the lower respiratory tract (60−84 hours).

Isolation of organisms from the endotracheal tube began at 48 hours but occurred in significant amounts later (60−96 hours). No Gram-positive isolates were found to colonize the endotracheal tube in significant amounts. Nosocomial pneumonia was diagnosed in three of the ten patients. In two cases, *Acinetobacter anitratus,* the pathogen considered to be responsible for VAP was first isolated from tracheal aspirates and from the interior of the endotracheal tube (between 60 and 84 hours) and clinical evidence of nosocomial pneumonia developed later (at 96 hours). When colonization changes to infection depends on many factors and is a topic of debate.

Relationship between Colonization and Infection

Performing a multivariate logistic regression analysis Sirvent *et al*. [18] found out that tracheal colonization by S. *aureus, H. influenzae* or *S. pneumoniae* within 24 hours of intubation in head injury patients was an independent risk factor for developing 'early onset' pneumonia (OR, 28.9; 95 % CI, 1.59−52.5).

Berrouane *et al*. [25] investigated early onset pneumonia in a neurosurgical intensive care unit. A cohort of patients was studied over a 13-month period and neurotrauma patients were compared with non-neurotrauma patients. Five hundred and sixty five adults were included, 57.9 % had trauma and 129 patients developed 152 episodes of pneumonia. In both groups the distribution of risk stratified by hospital days was bimodal, being highest during the first three days. However, the risk peaked again at days 5 and 6, and thereafter remained low. Pneumonia occurring during the first three days was associated with trauma ($p = 0.036$). It has been shown that head injury may induce immunosuppression, which could explain in part why neurotrauma patients are at higher risk of developing early onset pneumonia. In the Berrouane *et al*. study [25], early VAP was caused by S. *aureus* (33 %), *Haemophilus* spp. (23 %), other Gram-positive cocci (22 %) and other Gram-negative bacilli (19 %); whereas after the third day Gram-negative bacilli other than *Haemophilus* spp. accounted for 45.4 % of isolates, methicillin-resistant *S. aureus* were 13 % before the fourth day and 32 % afterwards. This change in causative organisms, in 'late onset' VAP, was confirmed in the Ewig *et al*. study [17]. In the follow up cultures of respiratory samples, colonization rates with Gram-negative bacilli and *Pseudomonas* spp. increased significantly, with previous short-term antibiotics representing a risk factor.

Is there a Relationship between Sinusitis and Pneumonia?

Nosocomial sinusitis is a complication of endotracheal intubation and mechanical ventilation in critically ill patients. Its incidence is often underestimated because of a lack of clinical signs. It is suspected in patients with nasal discharge or unexplained fever. Its diagnosis is based on radiological examination, by radiograph or computed tomography scan, and microbiological cultures of maxillary sinus aspirate [26].

Several authors have tried to demonstrate the relationship between sinusitis and the development of pneumonia. Holzapfel *et al*. [27] demonstrated with multivariate

analysis that sinusitis increased the risk of nosocomial pneumonia by a factor of 3.8. However, it is still not clear if they are concomitant infections or if one favours the development of the other. The same authors [28] tried to demonstrate the relationship between pneumonia and sinusitis by researching and treating sinusitis in 199 patients against the control group (200 patients). VAP was observed in 88 patients, 37 of whom were in the study group and 51 in the control group ($p = 0.02$). In 80 patients with nosocomial sinusitis in the study group, 10 patients from 23 that developed VAP had the same organism isolated in both the lung and sinus. These findings, however, are of limited value, as the microorganisms that cause sinusitis and VAP are similar (*Pseudomonas, S. aureus, Strepcoccus*). Chromosomal identification of microorganisms was not used.

The incidence of infectious maxillary sinusitis (IMS) and its clinical relevance was prospectively studied in 162 consecutive critically ill patients who were mechanically ventilated for a period longer than seven days. All had a paranasal computed tomography (CT) scan within 48 hours of admission and were divided into three groups according to the radiological aspect of their maxillary sinuses. During the study period, a total of 133 patients had evidence of radiological sinusitis. After bacteriological analysis of the sinus aspirate, 51 patients (38 %) were considered to have true IMS.

The incidence of nosocomial bronchopneumonia occurring within seven days of the initial paranasal CT scan was evaluated in 96 patients with initial radiological maxillary sinusitis. 67 % of patients with IMS versus 43 % of patients with non-infectious sinusitis subsequently developed a nosocomial bronchopneumonia ($p < 0.02$). In 38 % of the patients with IMS who secondarily developed nosocomial bronchopneumonia, identical pathogens were isolated in sinus aspirate and in the protected mini-BAL. This study confirms that IMS and nosocomial bronchopneumonia are significantly associated in terms of incidence and causative microorganisms.

However, the nature of the link between both infections cannot be established with certainty [29]. The drawbacks of the studies about the relationship between sinusitis and VAP are: the different criteria and procedures used to diagnose sinusitis in intubated patients (image procedures or endoscopic sampling), the population studied and the use of genetic typing of the pathogens isolated from sinuses and lower airways.

Is there a Relationship between Bacteraemia and Pneumonia?

Bacteraemia is not frequently considered a source of microorganisms producing VAP. Blood cultures in patients with VAP are clearly useful if there is a suspicion of another probable infectious condition, but the isolation of a microorganism in the blood does not confirm that microorganism as the pathogen causing VAP. The ways in which microorganisms enter the lung, divided into endogenous and external sources, are shown in Figure 4.3.

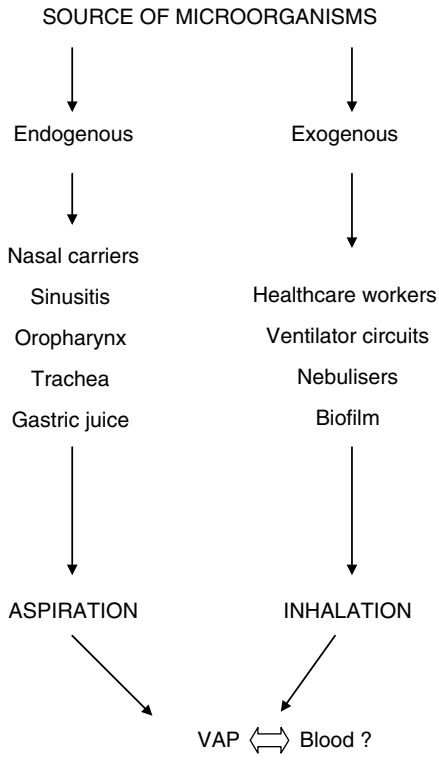

Figure 4.3
Pathogenesis of ventilator-associated pneumonia. Microorganisms can reach lung parenchyma from different reservoirs.

VAP Histological Characteristics

The histology of VAP has only been known in recent years mainly through immediate post-mortem studies. These studies have investigated extensively the lungs of patients who have been mechanically ventilated for several days and along with experimental models of pneumonia have allowed the peculiar histological and microbiological characteristics and interactions of human VAP to be described. From this information important clinical implications have been concluded.

Histological Findings in VAP

The histological presence of VAP has classically been accepted as the presence of foci of consolidation with intense leukocyte accumulation in bronchioles and adjacent alveoli. This definition is very simplistic since it does not take into account severity and distribution of lesions.

In a post-mortem study with bilateral multiple biopsy sampling [30] our evolution stages of pneumonia are described (Figure 4.4):

(A) *Early phase* (0–2 days of evolution), which shows the presence of capillary congestion with increased number of polymorphous neutrophil leukocytes (PMNL) at this level; the alveolar spaces usually showed a fibrinous exudate (Figure 4.1).
(B) *Intermediate phase* (3–4 days of evolution) characterized by the presence of fibrin, few erythrocytes and several PMNL within the alveoli.
(C) *Advanced phase* (5–7 days of evolution) showing PMNL filling up most of the alveoli and macrophages incorporating cellular debris in the cytoplasm.
(D) *Resolution phase* (>7 days of evolution) when the inflammatory exudate is eliminated due to phagocytic activity of mononuclear cells.

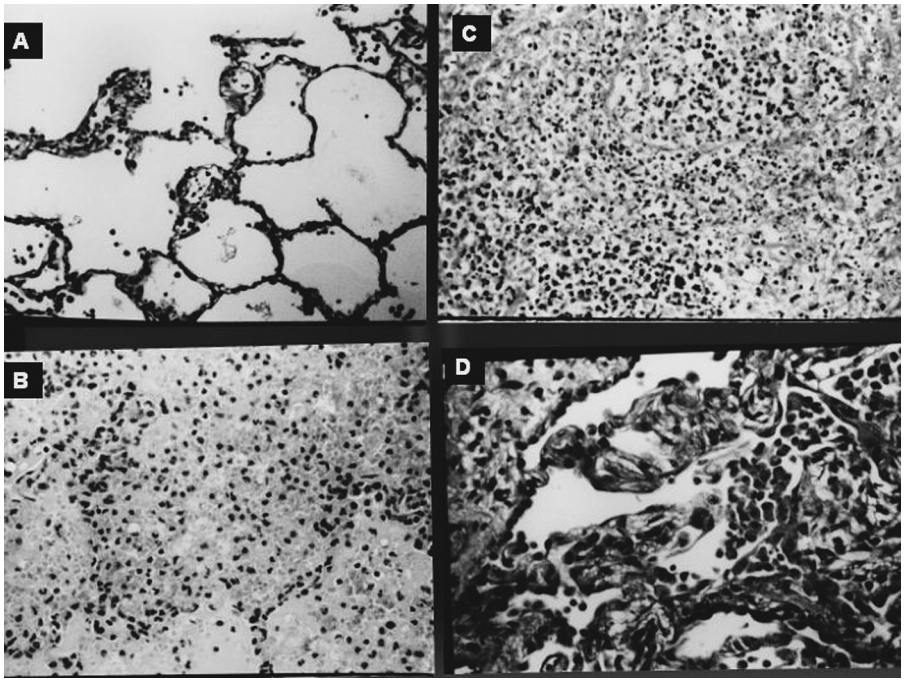

Figure 4.4
Histopathology phases of VAP (haematoxylin and eosin, x200) [15] (A) Early phase (0–2 days of VAP evolution). Capillary congestion with increased number of PMNL. Alvoelar spaces with fibrinous exudates. (B) Intermediate phase (3–4 days of VAP evolution). Presence of fibrin, eritrocytes and several PMNL within the alveoli. (C) Advanced phase (5–7 days of VAP evolution). PMNL filling up most of the alveoli and macrophages incorporating cellular debris in the cytoplasm. (D) Resolution phase (>7 days). Inflammatory exudates eliminated due to phagocytic activity of mononuclear cells.

Two degrees of severity in relation to the lung extension of the lesion have also been defined: mild and severe.

Human and Experimental Post-Mortem Histological and Microbiological Studies on VAP

Chastre and colleagues [31] were the first to develop a post-mortem human model upon critically ill patients. In the immediate post-mortem period (within 30 minutes) a left thoracotomy was performed, under surgical aseptic conditions, and six superficial small specimens from the anterior segment of the left lower lobe obtained for culture. In addition a 1 cm^3 specimen was obtained for histological analysis. A good association between histological and bacteriological findings (quantitative cultures) was found.

Rouby and colleagues [32] performed a more extensive approach and analysed histologically two small lung specimens obtained from an area of consolidation of the lower lobe. Another small specimen was cut from the same area and bacteriologically examined. Then the entire lung was surgically removed and a complete lung autopsy was done. They were the first in describing that pneumonia in ventilated patients is a multifocal process disseminated within each pulmonary lobe. These foci of pneumonia were predominantly distributed to lower lobes and in dependent zones of the lung. The histological lesions of bronchopneumonia were always located within large zones of altered lung parenchyma. It was demonstrated that a single lung specimen misses the histological pneumonia in around 30 % of cases. The latter finding must be taken into account when interpreting the results of earlier studies that limited histological examination to a single sample.

Marquette *et al*. [33] studied the histological characteristics of the entire fixed lung and confirmed the findings of the previous studies. Pneumonia was found in 50 % of the dependent segments and in 37 % of the nondependent segments. One of the major characteristics of the lesions was their typically scattered pattern of distribution within normal or damaged lung parenchyma. Only 14 of 83 examined lobes (16.8 %) had all of their segments involved by the infectious process. The scattering of the lesions was even more prominent at the segmental level, where the infectious alveolar damage ranged from limited foci of pneumonia to large areas of confluent pneumonia. A distinctive finding in several cases was the absence of pneumonia from the peripheral lung samples, while more central areas of the same segment displayed typical foci.

Quantitative cultures of lung samples could not easily discriminate the presence or absence of histological pneumonia. In the previous mentioned post-mortem study [30] patients were included with and without antibiotic treatment (48 hours at least free of antibiotic treatment). Several specimens from each lobe of the two lungs were aseptically obtained (an average of 16 samples per patient). Applying the evolution classification of VAP described above, the disseminated multifocal heterogeneous pattern of VAP predominantly involving lower lobes was confirmed. Interestingly, it was observed that all the phases alluded to above coexisted in the same patient and in the same lung exhibiting a pleomorphic histological pattern. Overall, intermediate

phase and advanced phase were the most common stages of pneumonia observed in this study. As in other studies, nonspecific alveolar damage and bronchiolitis were also frequently found.

Papazian and co-workers [34] analysed one entire lung of 38 patients. No sign of bronchopneumonia was found in 20 cases. Conversely, in the remaining 18 cases bronchopneumonia was confirmed histologically. There was no relationship between the results of the various cultures and the pathology results. Bronchiolitis was noted in eight patients, out of whom five had concomitant histological signs of pneumonia. The remaining three patients had negative lung cultures. Additional histological findings were fibrosis in nine cases and diffuse alveolar damage in seven cases. These authors examined the significance of the isolation of *Candida* spp. in their samples. Despite frequent lung colonization by *Candida,* only two patients exhibited histological signs of *Candida* pneumonia. Lung tissue cultures were positive for *Candida albicans* in these two patients. This agrees with the results of the study by El-Ebiary *et al*. [35] in which the incidence of *Candida* pneumonia was found to be 8 %. Nevertheless, in this study, the incidence of *Candida* isolation from pulmonary biopsies in critically ill mechanically ventilated, non-neutropenic patients that die is high (40 %), indicating that *Candida* is a frequent colonizing agent in very critically ill patients.

To avoid confounding factors such as antibiotic presence or lung injury described in other studies, Marquette *et al*. [36] induced pneumonia in pigs free from antibiotics and previous concomitant lung disease secondary to tracheobronchial stenosis. It was found that the histological lesions of pneumonia, as well as the lung bacterial burden, were unequally distributed within the lungs and even within the lung segments. Moreover, specimens showing histological evidence of pneumonia had significantly higher bacterial burden than specimens with bronchial infections and specimens with neither bronchial nor lung infection. However, the authors could not define a clear threshold for quantitative cultures to discriminate the presence or absence of pneumonia. This study, which provides experimental insights into the relationship between microbiological and histological features in bacterial pneumonia, confirms previous findings in humans.

In humans there is now compelling evidence that quantitative biopsy cultures cannot reliably discriminate between patients with and without evidence of histological pneumonia. The use of a specific threshold to define the presence of pneumonia does not take into account that lung infection occurs along a bacteriologic continuum. Thus, when pneumonia begins or if infectious bronchiolitis is present, the diagnostic threshold may not be met. The same occurs when a prior antibiotic has been given. Another explanation for low qualitative lung cultures in the presence of histological pneumonia is the normal functioning of antibacterial lung defences, which clear lung bacterial burden. On the other hand, the specificity of lung cultures is low with a high rate of false-positive cultures. In post-mortem studies false-positive lung cultures (without pneumonia) may be due to bacterial colonization and bronchiolitis. It has been suggested that close to death, in critically ill patients, the lung could suffer from massive bacterial colonization, which could explain the frequent presence of bacteria in distal airways without histological pneumonia. From all these findings it is clear, owing to the poor relationship between quantitative lung cultures and histological

examination, that quantitative lung biopsy cultures alone cannot be used to validate *in vivo* diagnostic techniques used to investigate VAP microbiologically.

Clinical Implications of Histological and Microbiological Findings in Post-Mortem VAP Studies

The histological findings of human post-mortem studies have the following clinical implications:

(1) Initial phases of VAP that probably need to be treated with antibiotics cannot be detected by portable chest X-ray.

(2) Since VAP is a multifocal process, the techniques that explore broad lung regions, such as bronchoalveolar lavage, are clearly preferred to those that only explore a segment (protected specimen brush).

(3) Blind diagnostic methods that can sample lung dependent zones are probably as accurate as visually guided methods.

The microbiological findings have the following clinical implications:

(1) As mentioned above, quantitative post-mortem lung cultures cannot be used as gold standard to validate microbiological diagnostic techniques.

(2) When interpreting quantitative bacteriology at the bedside, the clinician should weigh a number of factors that can modify bronchial and alveolar bacterial burden: presumed stage of bronchopneumonia, administration of antibiotics, technique of distal sampling, natural host bacterial defences, duration of mechanical ventilation and presence of acute lung injury.

The microbiological complexity of VAP does not support the concept of a standard threshold for the diagnosis of pneumonia. Thus, treatment algorithms based upon definite thresholds of quantitative cultures may lead to the under-treatment of patients. Since early and adequate initial antibiotic treatment is one of the major factors related to prognosis of VAP, the strict execution of treatment based upon quantitative thresholds without clinical judgment may be hazardous to patients.

Summary

Healthy patients may be chronically colonized – it is known that more than 50 % of patients admitted to intensive care units have already been colonized at the time of admission – with the microorganisms responsible for the subsequent infection.

The development of pneumonia requires the pathogen to reach the alveoli and the host defences to be overwhelmed, either by microorganism virulence or by

the size of the inoculum. The endogenous sources of microorganisms are: nasal carriers, sinusitis, oropharynx, gastric or tracheal colonization and haematogenous spread. Other external sources of contamination, such as ICU workers, aerosols or fibrobronchoscopy, must be considered as accidental.

Histological findings in post-mortem studies show the complexity and the heterogeneity of the distribution of VAP. Quantitative biopsy cultures cannot reliably discriminate between patients with and without evidence of histological pneumonia.

References

1. Campbell, W., Hendrix, E., Schwalbe, R. *et al.* (1999) Head-injured patients who are nasal carriers of *Staphylococcus aureus* are at risk for *Staphylococcus aureus* pneumonia. *Crit Care Med*, **27**, 798–801.
2. Hidron, A.I., Kourbatova, E.V., Halvosa, J.S. *et al.* (2005) Risk factors for colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) in patients admitted to an urban hospital: Emergence of community-associated MRSA nasal carriage. *Clin Infect Dis*, **41**, 159–66.
3. Scudeller, L., Leoncini, O., Boni, S. *et al.* (2000) MRSA carriage: The relationship between community and healthcare setting. A study in an Italian hospital. *J Hosp Infect*, 222–9.
4. Brennan, M.T., Bahrani-Mugeot, F., Fox, P.C. *et al.* (2004) The role oral microbial colonization in ventilator-associated pneumonia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, **98**, 665–72.
5. Johanson, W.G., Pierce, A.K. and Sanford, J.P. (1969) Changing pharyngeal bacterial flora of hospitalised patients. Emergence of Gram-negative bacilli. *N Engl J Med*, **281**, 1137–40.
6. Garrouste-Orgeas, M., Chevret, S., Arlet, G. *et al.* (1997) Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. *Am J Respir Crit Care Med*, **156**, 1647–55.
7. De la Torre, F.J., Pont, T., Ferrer, A. *et al.* (1995) Pattern of tracheal colonization during mechanical ventilation. *Am J Respir Crit Care Med*, **152**, 1028–33.
8. Tryba, M. (2003) Prophylaxis of stress ulcer bleeding. A meta-analysis. *J Clin Gastroenterol*, **13** (Suppl 2), S44–55.
9. Cook, D.J., Reeve, B., Guyatt, G.H. *et al.* (2003) Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA*, **275** (4), 308–14.
10. Messori, A., Tripoli, S., Vaiani, M., Gorini, M. and Corrado, A. (2003) Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: Meta-analysis of randomised controlled trials. *BMJ*, **321** (7269), 1103–6.
11. Driks, M.R., Craven, D.E., Celli, B.R. *et al.* (1987) Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonization. *N Engl J Med*, **317**, 1376–82.
12. Ferrer, M., Bauer, T.T., Torres, A. *et al.* (1999) Effect of nasogastric tube size on gastroesophageal reflux and microaspiration in intubated patients. *Ann Intern Med*, **130**, 991–4.
13. Torres, A., Serra-Batlles, J., Ros, E. *et al.* (1992) Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: The effect of body position. *Ann Intern Med*, **116**, 540–3.

14. Orozco-Levi, M., Félez, M., Martínez-Miralles, E. *et al*. (2003) Gastro-oesophageal reflux in mechanically ventilated patients: Effects of an oesophageal balloon. *Eur Respir J*, **22**, 348–53.
15. Girou, E., Buu-Hoy, A., Stephan, F. *et al.* (2004) Airway colonization in long-term mechanically ventilated patients. *Intensive Care Med*, **30**, 225–33.
16. Cardeñosa, J.A., Sole-Violan, J., Bordes, A. *et al*. (1999) Role of different routes of tracheal colonization in the development of pneumonia receiving mechanical ventilation. *Chest*, **116**, 462–70.
17. Ewig, S., Torres, A., El-Ebiary, M. *et al*. (1999) Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **159**, 188–98.
18. Sirvent, J.M., Torres, A., Vidaur, L. *et al.* (2000) Tracheal colonisation within 24 hours of intubation in patients with head trauma: Risk factors for developing early onset ventilator-associated pneumonia. *Intensive Care Med*, **26**, 1369–72.
19. Estes, R.J. and Meduri, G.U. (1995) The pathogenesis of ventilator-associated pneumonia., I: mechanisms of bacterial transcolonization and airway inoculation. *Intensive Care Med*, **21**, 365–83.
20. Craven, D.E., Goularte, T.A. and Make, B.J. (1984) Contaminated condensate in mechanical ventilator circuits. A risk factor for nosocomial pneumonia. *Am Rev Respir Dis*, **129**, 625–8.
21. Inglis, T.J., Millar, M.R., Jones, J.G. *et al*. (1989) Tracheal tube biofilm as a source of bacterial colonization of the lung. *J Clin Microbiol*, **27**, 2014–18.
22. Inglis, T.J. (1993) Evidence for dynamic phenomena in residual tracheal tube biofilm. *Br J Anaesthesiology*, **70**, 22–4.
23. Adair, C.G., Gorman, S.P., Feron, B.M. *et al.* (1999) Implications of endotracheal tube biofilm for ventilator-associated pneumonia. *Intensive Care Med*, **25**, 1072–6.
24. Feldman, C., Kassel, M., Cantrell, J. *et al.* (1999) The presence and sequence of endotracheal tube colonization in patients undergoing mechanical ventilation. *Eur Respir J*, **13**, 546–51.
25. Berrouane, Y., Daudenthun, I., Riegel, B. *et al.* (1998) Early onset pneumonia in neurosurgical intensive care unit patients. *J Hosp Infect*, **40**, 275–80.
26. Bert, F. and Lambert-Zechovsky, N. (1996 Jul) Sinusitis in mechanically ventilated patients and its role in the pathogenesis of nosocomial pneumonia. *Eur J Clin Microbiol Infect Dis*, **15** (7), 533–44.
27. Holzapfel, L., Chevret, S., Madinier, G. *et al.* (1993) Influence of long-term oro- or nasotracheal intubation on nosocomial maxillary sinusitis and pneumonia: Results of a prospective, randomised, clinical trial. *Crit Care Med*, **21**, 1132–1138.
28. Holzapfel, L., Chastang, C., Demingeon, G. *et al.* (1999) A randomised study assessing the systemic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Influence of nosocomial maxillary sinusitis on the occurrence of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **159**, 695–701.
29. Rouby, J.J., Laurent, P., Gosnach, M. *et al.* (1994) Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med*, **150**, 776–83.
30. Fábregas, N., Torres, A. and El-Ebiary, M. *et al*. (1996) Histopathologic and microbiologic aspects of ventilator-associated pneumonia. *Anesthesiology*, **84**, 757–9.
31. Chastre, J., Viau, F., Brun, P. *et al.* (1984) Prospective evaluation of the protected catheter brush for the diagnosis of pulmonary infections in ventilated patients. *Am Rev Respir Dis*, **130**, 924–39.

32. Rouby, J.J., Rossignon, M.D., Nicolas, M.H. *et al.* (1989) A prospective study of protected bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. *Anesthesiology*, **71**, 679–85.
33. Marquette, C.H., Copin, M.C., Wallet, F. *et al.* (1995) Diagnostic tests for pneumonia in ventilated patients: Prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. *Am J Respir Crit Care Med*, **151**, 1878–88.
34. Papazian, L., Thomas, P., Garbe, L. *et al.* (1995) Bronchoscopic or blind sampling techniques for the diagnosis of ventilator associated pneumonia. *Am J Respir Crit Care Med*, **152**, 1982–91.
35. El-Ebiary, M., Torres, A. and Fàbregas, N. *et al*. (1997) Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. An immediate post-mortem histologic study. *Am J Crit Care Med*, **156**, 583–90.
36. Marquette, C.H., Wallet, F., Copin, M.C. *et al.* (1996) Relationship between microbiologic and histologic features in bacterial pneumonia. *Am J Respir Crit Care Med*, **154**, 1784–7.

5

Clinical Approach to the Patient with Hospital-Acquired Pneumonia

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Introduction

Pneumonia represents a spectrum of disease that ranges from community-acquired pneumonia (CAP) to hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). HAP is defined as pneumonia that occurs 48 hours after hospital admission and VAP as pneumonia occurring more than 48 hours after intubation. Compared to patients with CAP, those with HAP and VAP are at greater risk of colonization and infection with a spectrum of multidrug-resistant (MDR) bacterial pathogens, and often have higher morbidity and mortality [1]. Though difficult to determine the exact incidence of HAP and VAP, it ranges between 5 and 15 cases per 1000 hospital admissions depending on the case definition and study population; the incidence of VAP is 6- to 20-fold greater than in nonventilated patients [2–4].

Ventilator-associated pneumonia is the leading nosocomial infection in the intensive care unit (ICU) [5]. The true attributable mortality of VAP episodes in critically

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ill patients has been debated [6]. However, well designed, matched cohort studies have demonstrated the association between late onset VAP and higher mortality, particularly when caused by virulent bacteria, such as *Pseudomonas aeruginosa* producing type III secretory proteins [7].

Moreover, associated mortality and morbidity in VAP is increased in patients with wrong or delayed initial antibiotic treatment, which is frequently associated with the presence of resistant strains [8, 9].

Most epidemiological and etiological data have been obtained from patients with suspected VAP, due to the simplicity of collecting respiratory samples and identifying a causative agent. Despite this, a similar approach should be used in both. Risk factors for colonization and infection by MDR pathogens are shared by HAP and VAP. They include prior hospitalisation, residence in a chronic care facility and previous exposure to antibiotics [1].

When a HAP episode is suspected the attending physician needs to answer three questions [10, 11]. Firstly, does this patient actually have pneumonia? Secondly, are microbiologic studies indicated? Thirdly, which antibiotic regimen is the best option? Once these questions have been answered, the attending physician should follow the evolution of these patients in order to evaluate the response to therapy and optimise antibiotic treatment, and thus limit the emergence of MDR bacteria.

Clinical Suspicion

The diagnoses of HAP and VAP are usually made using clinical criteria: fever, cough, purulent sputum, suggestive Gram-stain, change in oxygenation, elevated or low leukocyte count with a shift toward bands and polymorphonuclear leukocytes. In the elderly, signs and symptoms may be more subtle, such as change in mental status, anorexia, lethargy or hypothermia [1]. Although tachypnea is frequent, confusion may be the only presenting symptom [12]. This approach is sensitive but non-specific, especially in diagnosing VAP [13]. Fever and leukocytosis may be related to non-infectious origins, such as drug-related fever, pulmonary edema or infarction and non-pulmonary infections, such as vascular catheter infection, gastrointestinal infection, urinary tract infection, postoperative fever, sinusitis or wound infection. Meduri *et al*. [14] confirmed the presence of lung infection in only 42% of patients with clinically suspected VAP and the frequent occurrence of multiple infectious or non-infectious processes.

Once a patient develops fever and leukocytosis, the physicians must promptly identify the source of infection in order to: (i) start adequate antibiotic therapy for sepsis and (ii) control the source of infection if needed, as has been previously described [15].

The pathophysiology of HAP includes the spread of infecting organisms to the lower respiratory tract, overwhelming the local respiratory defences. A local inflammatory response develops in the respiratory tract, manifested as respiratory purulent secretions. In fact, the absence of purulent secretion in the respiratory tract makes the diagnosis of VAP unlikely [16], but their presence may be due to other conditions,

frequently it is due to tracheobronchitis. The differential diagnosis between tracheobronchitis and VAP should be based on radiographic tools, usually chest X-ray in spite of its known limitations in the ICU. For definite diagnosis of VAP, radiological opacity with alveolar condensation has to be present. Although never evaluated, chest X-ray infiltrates in non-ventilated patients seems to be more specific than in ventilated patients.

To improve the sensitivity of the clinical approach, the probability of developing pneumonia can be evaluated using the Clinical Pulmonary Infection Score (CPIS) in intubated patients [17]. The CPIS considers the degree of fever, volume and appearance/characteristics of tracheal secretions, chest radiograph, white blood cell count, oxygenation and tracheal aspirate culture. The score establishes the likelihood of having VAP. Serial versions have been used to establish clinical resolution of VAP [18]. Singh *et al*. used a modification of the CPIS and reported that low-risk patients (CPIS <6) with suspected VAP could be treated with antibiotics for three days and had better clinical outcomes and fewer antibiotic-resistant superinfections than those receiving 10−21 days of therapy [19]. Unfortunately, some variables are subjective and the value given to each element of the score is arbitrary. So, clinical suspicion of HAP has to be established when otherwise unexplained pulmonary infiltrates (new or persistent) develop in chest X-ray in conjunction with purulent respiratory secretions and clinical signs of sepsis (fever and/or leukocytosis).

Diagnostic Approach

The choice of empirical antibiotic treatment can be improved if the decision is based on direct staining of respiratory samples. Gram stains are available for protected specimen brush samples [20], bronchoalveolar lavage [21] or tracheal aspirates [22]. Unfortunately, the use of these techniques is limited in non-ventilated populations because of the invasiveness of bronchoscopic procedures. The quality of the lower respiratory tract samples is also crucial in the interpretation of the microorganisms involved in the etiology of HAP [23]. The presence of $>1\%$ of epithelial cells in bronchoscopic samples suggests heavy orophayngeal contamination [24], as does a proportion of $>10\%$ of epithelial cells if tracheal aspirate has been performed [22]. The microbiologic information is of vital importance to ensure that the antibiotic therapy is appropriate and to optimise therapy from a broad to a narrow spectrum if the patient is responding to therapy. Direct staining of respiratory secretions is a simple procedure and can give valuable information (in less than an hour) to guide initial therapy. Moreover, Gram staining is useful for determining the quality of the respiratory sample. On this issue some important problems are detected; for example, the use of previous antibiotic therapy, steroids or the presence of *Pseudomonas aeruginosa* has been associated with negative direct staining [25]. In an international consensus conference [26] on the diagnosis and treatment of VAP, several experts agreed that microbiological findings are useful and that the presence of intracellular bacteria and a positive Gram stain (or other direct tests) may be of great help in selecting the initial antibiotic regimen but not in making the diagnosis of pneumonia. The diagnostic

technique used (bronchoscopic or tracheal aspirate with quantitative cultures) did not influence either the rate of de-escalation or mortality in a recent report [27].

Indeed, it is often forgotten that early modification of antibiotic therapy based on early diagnosis bronchoscopic techniques performed in the hours immediately after the onset of pneumonia has been associated with the resolution of 63 % of episodes [8]. Performing e-test sensitivity analysis in respiratory samples before microorganism identification provides important information for the day following pneumonia onset, with a significant reduction in the period of inadequate therapy [28]. Indeed, the rapid initiation of antibiotic therapy avoiding delay in microbiologic sampling has more impact on outcome than the type of semiquantitative or quantitative technique used [27, 29, 30]. All patients with suspected HAP or VAP should have two blood cultures drawn and, if possible, sputum collected from the lower respiratory tract for Gram-staining and cultures before antibiotics are initiated; in VAP at least a quantitative tracheal aspirate should be obtained. Despite this recommendation account must be made of the low sensitivity of blood cultures, especially in VAP [8, 31]. Rather, the importance of the blood cultures may be in that they point the physician to a possible alternative source for infection.

Best Initial Management of HAP

Cardiovascular support and supportive measures to improve haemodynamics and oxygenation are critical to overcoming a severe infection. Likewise, early implementation of adequate antibiotics, as soon as there is clinical suspicion of VAP, should increase the likelihood of early reduction of bacterial burden of the pathogens responsible, thus minimizing the risks and the potential consequences of delayed therapy [30]. In addition, information regarding risk factors/co-morbidities, previous antibiotic exposure and length of hospitalisation can provide useful assistance in selecting the initial antibiotic agent. The use of broad-spectrum antibiotics should be quickly narrowed based on microbiologic information whenever possible. In this way, initial use of narrow-spectrum antibiotics may increase the probability of death due to inadequate therapy if resistant pathogens are involved.

Second, quantitative microbiological findings can enable physicians to change, adjust, or reduce the administration of antibiotics in certain patients. The majority of experts agree that the use of broad-spectrum antibiotics for less than 48 hours would not induce significant risk of multiresistance [26].

Classifying patients according to prior duration of mechanical ventilation or prior exposure to antibiotics provides a basis for anticipating the pathogens [32]. Considerable information is available on the influence of certain co-morbidities or risk factors such as steroids, head trauma, lung structural disease and immunocompromise on the spectrum of the pathogens responsible for an infectious event [33]. However, the causes of VAP vary across different ICUs [34, 35], as indicated in Figure 5.1. These differences can be explained by differences in patients´ demographics, strategies for prophylaxis and methods of diagnosis and local patterns of resistant organisms [35]. Table 5.1 summarises the points that determine the management of VAP in the Joan

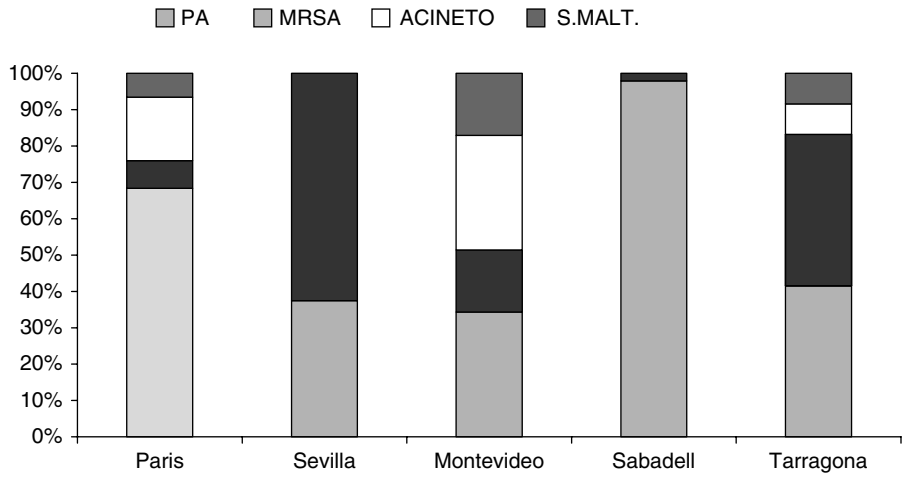

Figure 5.1
Distribution of pathogens for late onset VAP and antibiotic exposure subset across five different institutions (modified from reference 35)
(PA: *P. Aeruginosa;* MRSA: methicillin-resistant *S. Aureus;* ACINETO: *A. Baumannii;* S.MALT: *S. maltophilia*).

Table 5.1 Tarragona strategy for therapy of VAP (modified from reference 10)

1. Antibiotic therapy should be started immediately.
2. Antibiotic choice can be targeted, in same cases, based on direct staining.
3. The prescription should be modified in the light of microbiologic findings.
4. Prolonging antibiotic treatment does not prevent recurrences.
5. Patients with chronic obstructive pulmonary disease or 1 week of intubation should receive combination therapy, due to the risk of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*.
6. Methicillin-resistant *Staphylococcus aureus* is not expected in the absence of antibiotic exposure, whereas methicillin sensitive *S. Aureus* should be strongly suspected in comatose patients.
7. Therapy against yeast is not required, even in presence of *Candida* species colonization.
8. Vancomycin administration for Gram-positive pneumonia is associated with a very poor outcome.
9. The specific choice of agent should avoid any regimen to which a patient has been exposed previously.
10. Guidelines should be regularly updated and customized to local patterns.

XXXIII University Hospital, Spain. Knowledge of the local microbial epidemiology and susceptibility patterns is crucial for initial choice of antibiotics [10].

Overall, some patients (those who develop their infection within five days of hospitalisation, those without recent antibiotic exposure and those who have not been hospitalised in the past three months) are at low risk of infection by resistant organisms. In this subset, adequate initial selection would be a non-pseudomonal third

generation cephalosporin, since the antibiotics should target common community-acquired organisms in addition to some *Enterobacteriaceae* and methicillin-sensitive *Staphylococcus aureus* (MSSA). The presence of MSSA should be strongly suspected in comatose patients. Several reports have demonstrated a higher incidence of MSSA in patients with an altered level of consciousness [36]. Drugs effective against *S. aureus* should be included in the empirical regimen for treating nosocomial pneumonia in patients in coma.

Methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonias are common in patients with prolonged intubation periods and prior use of antibiotics. MRSA is the second most frequently isolated pathogen from patients who die of pneumonia. The treatment options for this pathogen are limited. A high mortality rate (around 50 %) among patients treated with vancomycin for pneumonia caused by MRSA or MSSA has been consistently reported [37]. This may be due to the poor lung penetration of vancomycin that results from prescribing label doses (1 g/12 hours) [38]. In addition under-dosing of glycopeptides is frequent in ventilated septic patients with renal failure who have an increase in the volume of distribution. Achieving adequate steady state levels usually takes four days with teicoplanin [39]. This evidence suggests that current glycopeptides are suboptimal for MRSA pneumonia [37, 40].

Alternative treatment choices are restricted, currently to daptomycin, quinupristin/dalfopristin or linezolid therapy. Daptomycin has limited penetration into pulmonary epithelial fluid, and its activity is inhibited by pulmonary surfactants. In a randomised trial, patients with nosocomial MRSA pneumonia [41] who received quinupristin/dalfopristin had a clinical response rate of 19.4 % compared with 40 % in vancomycin recipients. The potential superiority of linezolid therapy over vancomycin therapy in treating nosocomial pneumonia (and VAP) due to MRSA has been noted [42, 43].

Pseudomonas aeruginosa are frequent in patients with severe chronic obstructive pulmonary disease, one week of prior hospitalisation, prolonged periods of intubation (> 8 days) and prior exposure to antibiotics. Pneumonia caused by *P. aeruginosa* is associated with increased mortality rates and prolonged ICU stays [44]. Empirical treatment in patients meeting these criteria should include combination therapy with drugs with antipseudomonal activity until a microbiological diagnosis is established; for example those patients require initial use of a combination of piperacilin/tazobactam and ciprofloxacin, or amikacin plus imipenem, meropenem or an antipseudomonal cephalosporines. On the other hand, carbapenems are the drug of choice for patients with suspected *P. aeruginosa* infection who are receiving beta-lactam agents. If the patient is receiving a carbapenem, an antipseudomonal fluoroquinolone is a reasonable option. Finally, if a patient with VAP is receiving a quinolone, combination therapy based on piperacillin−tazobactam should be considered [45].

Acinetobacter baumannii has specific risk factors that differs from *P. aeruginosa* or other nonfermenters. Baraibar *et al.* [46] identified the following risk factors for VAP caused by *A. baumannii*: neurosurgery, acute respiratory distress syndrome (ARDS), head trauma and large-volume pulmonary aspiration. Resistance is increasing, and carbapenems, sulbactam and colistin are the most sensitive agents. Sulbactam is bacteriostatic and it is suitable for mild infections at a dose of 8 g/day. Colistin, like

Table 5.2 Etiology of HAP in non-ICU patients

Microorganisms	Vallés *et al.* (2003) N %	Sopena *et al.* (2005) N %	Barreiro *et al.* (2005) N %
Unknown	29 (30 %)	107 (65 %)	53 (80 %)
P. aeruginosa	18 (19 %)	7 (4.2 %)	2 (3 %)
Enterobacteriacea	8 (8 %)	8 (5 %)	4 (6 %)
L. Pneumophila	9 (9 %)	7 (4.2 %)	
S. pneumoniae	11 (11.5 %)	16 (10 %)	7 (10 %)
S. aureus	9 (9 %)	4 (3 %)	1 (1 %)
Aspergillus spp.	13 (13.5 %)	—	—
Others	—	14 (8, 6 %)	—

*Late onset pneumonia in 96 % of episodes
Data from references 48,49,58

aminoglycosides or vancomycin, has extremely poor lung penetration. Tygecicline may be a reliable alternative in the future. *A. baumannii* tends to cause polymicrobial infections colonizing the respiratory tract of patients with artificial airways rather than cause invasive disease. If risk of *Acinetobacter baumannii* exists, experimental models confirm that antimicrobial therapy should include a carbapenem, alone or associated to rifampin or tobramycin [47].

The same considerations that apply in VAP have to be applied in non-ventilated patients suffering from pneumonia. Data from some institutions that include hospital-wide surveillance suggest that the bacteriology of nosocomial pneumonia in non-ventilated patients is similar to that in ventilated patients, especially when severe HAP is considered [1,48]. That may not be the case when ICU patients are excluded. A recent study of HAP in non-ICU patients found that *Streptococcus pneumoniae* and *Legionella pneumophilia* were the most commonly isolated organisms; however, methodological problems with this study limit how far its results can be generalised [49]. Additionally, the incidence of resistant organisms varies widely between institutions and even on different wards within an institution (Table 5.2).

Evaluation of the Clinical Resolution in HAP

Once a patient has been diagnosed with HAP and empirical broad-spectrum antibiotic has been started, the evaluation of resolution of different clinical parameters is a useful tool for tailoring the response to treatment. According to standard clinical practice, the clinical response to therapy is evaluated on the third day of HAP onset, but at present there is no definition of treatment failure. No absolute consensus has been achieved regarding the 'gold standard' to monitor response to treatment in HAP. The most widely used variables for evaluating the response to treatment in HAP have been the resolution of the local or systemic inflammatory variables involved. Resolution of hypoxemia or improvement of the PaO_2/FiO_2 ratio, resolution of radiological infiltrates and clearance of purulent secretions as local inflammatory markers, evolution

of core temperature and white blood cell count as systemic inflammatory markers, or microbiological follow up cultures have been used in different studies evaluating clinical resolution or failure to improve in VAP [42, 43, 46].

Denessen *et al*. [50] prospectively studied a cohort of patients with clinical diagnosis of VAP and evaluated the response to treatment based on three clinical variables (highest daily body temperature, highest daily leukocyte count and daily PaO_2/FiO_2 ratio) and microbiologic variables measured as semi-quantitative cultures of endotracheal secretions. Clinical resolution of pneumonia was defined when fever was $<38°C$, leukocyte count was $\leq 10\,000$, PaO_2/FiO_2 was ≥ 25 kPa and there was 0 or +1 growth on endotracheal cultures. The time up to resolution of VAP for clinical parameters was six days and was delayed to nine days when a microbiological variable was added, even though all patients had appropriate antibiotic treatment. The earliest resolution parameter was the improvement of hypoxemia.

The CPIS has also been evaluated for tailoring the response to treatment [18, 51]. This score has also been used to evaluate the response to treatment in patients with VAP [51, 52], with a fall in this score to <6 achieved after the fifth day of treatment interpreted as a complete resolution of VAP.

Patterns of clinical resolution in patients with clinical suspicion of VAP, with or without ARDS, have been evaluated [53]. 95 episodes of VAP with appropriate initial antibiotic treatment were prospectively evaluated, 20 of them with ARDS and 75 without. The clinical variables used to evaluate response to treatment were measured daily, starting at the time of VAP onset and followed for 15 days or until discharge from ICU or death. The five main parameters analysed were: the evolution of core temperature, oxygenation, white blood cell count, clearance of purulent secretions and chest X-ray infiltrates. In the group of patients without ARDS, it was found that $>70\,\%$ of the patients resolved fever and PaO_2/FiO_2 ratio within the first 48 hours of antibiotic treatment, in contrast with white blood cell count, clearance of purulent respiratory secretions and chest X-ray infiltrates, which resolved later. The presence of ARDS delayed significantly the clinical response to treatment in critically ill patients with VAP, although temperature remained the earliest parameter to be resolved in this group of patients. Radiological resolution was an extremely poor indicator being only present in $10\,\%$ of ARDS patients after 15 days of follow up. Indeed, quick radiological resolution excludes the diagnosis of pneumonia.

In conclusion, when evaluating response to therapy in patients with VAP, the interpretation of parameters of resolution should bear in mind the presence of ARDS. To evaluate clinical response to antibiotic therapy, fever and hypoxemia are two clinical parameters that can be easily monitored at the bedside of the patient simply by physical examination.

Optimising Antibiotic Therapy

The main goal in the treatment of HAP in critically ill patients is to deliver appropriate initial antibiotic therapy as early as possible in order to diminish mortality [9, 54, 55]. The initial antibiotic therapy has to cover all the responsible pathogens involved, as

described in reports on management of HAP. However, the overuse of antibiotics is associated with the emergence of resistant bacteria [56].

De-Escalation of Antibiotic Therapy

An approach to the treatment of HAP based on de-escalation of antimicrobial therapy, once the microorganism responsible for HAP is isolated, diminishes the overuse of antibiotics and the emergence of resistant bacteria [57].

An evaluation of the practice of de-escalation in a cohort of critically ill patients with clinical suspicion of VAP has been reported [27]. De-escalation requires the implementation of initial broad-spectrum empirical antibiotic therapy and aims to avoid the overuse of antibiotics. The first stage involves administering broad-spectrum antibiotics and the second stage focuses on simplifying the antibiotic therapy. This approach to managing VAP involves:

(a) Changing the focus from multiple agents to a single agent if *Pseudomonas aeruginosa* is not present.
(b) Shortening the therapy to >5 days if the culture is negative and >48 hours of defervescence.
(c) Changing from a broad to narrow agent in the light of culture data.

In the study, patients receiving carbapenems were de-escalated to piperacillin–tazobactam and patients receiving piperacillin–tazobactam were de-escalated to an antipseudomonal cephalosporin in presence of *Pseudomonas aeruginosa,* if possible. In the absence of *P. aeruginosa,* patients with combination therapy were switched to monotherapy after discontinuation of ciprofloxacin or amikacyn. Similarly, the second agent was changed to a nonantipseudomonal betalactam in accordance with susceptibilities.

The etiology was known in 111 of 121 episodes, and initial inadequate antibiotic therapy was reported in 9 %. The microbiological results allowed a narrowing of the antibacterial spectrum in about one-third of the patients. Interestingly, the mortality of patients with de-escalation was lower than that observed in the group with unchanged initial antibiotic therapy (18 % vs. 43 %, $p < 0.05$).

The rate of de-escalation was significantly lower in episodes caused by potentially resistant Gram-negative bacilli. In conclusion, de-escalation avoids the overuse of antibiotics in the attempt to reduce the emergence of resistant bacteria. However, in non-ICU patients this approach can be difficult to achieve due to the low ratio of etiological diagnoses [49, 58].

Shorten Antibiotic Therapy

The duration of antibiotic therapy is still a controversial issue. In recent years a course of antibiotic treatment of 14 to 21 days has been advocated for treating HAP [59], but the length of antibiotic treatment is crucial if the overuse of antibiotic treatment and the emergence of multiresistant bacteria is to be avoid. Longer courses

of antibiotics can increase costs, side effects and resistant phenotypes and do not necessarily prevent recurrences [60]. Shorter antibiotic regimens have been used to reduce antimicrobial costs, adverse events and the emergence of antibiotic-resistant pathogens [19]. Recently, a shorter course of antibiotic regimen has been proposed. In a prospective randomised clinical trial, Chastre *et al*. [61] demonstrated that an 8-day antibiotic regimen is comparable to a 15-day one in terms of mortality, superinfections or relapses of VAP.

As reported elsewhere [10], a patient-based approach is recommended. The duration of antibiotic therapy has to be on an individual basis on clinical resolution of VAP and the response to treatment. Resolution patterns can help to optimise the duration of antibiotic therapy. After 48 hours of defervescence and resolution of hypoxemia the antibiotic therapy can be withdrawn. In the subset of patients with ARDS, the main clinical parameter useful for evaluating response to therapy is fever.

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References

1. (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*, **171**, 388−416.
2. Chastre, J. and Fagon, J.Y. (2002) Ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **165**, 867−903.
3. Celis, R., Torres, A., Gatell, J.M. *et al*. (1988) Nosocomial pneumonia: A multivariate analysis of risk and prognosis. *Chest*, **93**, 318−24.
4. Torres, A., Aznar, R., Gatell, J.M. *et al*. (1990) Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respi Dis*, **142**, 523−8.
5. Vincent, J.L., Bihari, D.J., Suter, P.M. *et al*. (1995) The prevalence of nosocomial infection in intensive care units in Europe: Results of the European prevalence of infection in intensive care (EPIC study). *JAMA*, **274**, 639−44.
6. Rello, J. (1999) Impact of nosocomial infections on outcome: Myths and evidence. *Infect Control Hosp Epidemiol*, **20**, 392−4.
7. Hauser, A.R., Cobb, E., Bodi, M. *et al*. (2002) Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by *pseudomonas aeruginosa*. *Crit Care Med*, **30**, 521−28.
8. Rello, J., Gallego, M., Mariscal, D. *et al*. (1997) The value of routine microbiological investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **156**, 196−200.
9. Luna, C.M., Vujacich, P., Niederman, M.S. *et al*. (1997) Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest*, **111**, 676−85.
10. Sandiumenge, A., Diaz, E., Bodi, M. and Rello, J. (2003) Therapy of ventilator-associated pneumonia. A patient based approach based on the ten rules of "the Tarragona Strategy." *Intensive Care Med*, **29**, 876−83.
11. Rello J. and Diaz, E. (2003) Pneumonia in the intensive care unit. *Crit Care Med*, **31**, 2544−51.
12. Janssens, J.P. and Krause, K.H. (2004) Pneumonia in the very old. *Lancet Infect Dis*, **4**, 112−24.

13. Wunderink, R.G. (2000) Clinical criteria in the diagnosis of ventilator-associated pneumonia. *Chest*, **117**, 191S−4S.
14. Meduri, G.U., Mauldin, G.L., Wunderink, R.G. *et al*. (1994) Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest*, **106**, 221−35.
15. Vidaur, L., Rodriguez, A. and Rello, J. (2004) *Antibiotic Therapy for Sepsis, Severe Sepsis and Septic Shock: the "Tarragona Strategy". In Yearbook of Intensive Care and Emergency Medicine*, Springer, Berlin. pp. 229-41.
16. Gallego, M. and Rello, J. (1999) Diagnostic testing for ventilator-associated pneumonia. *Clin Chest Med*, **20**, 671−79.
17. Pugin, J., Auckentaler, R. and Mili, N. (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis*, **143**, 1121−9.
18. Luna, C., Blanzaco, D., Niederman, M. *et al*. (2003) Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med*, **31**, 676−82.
19. Singh, N., Rogers, P., Atwood, C.W., Wagener, M.M. and Yu, V.L. (2000) Short course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. *Am J Respir Crit Care Med*, **162**, 505−11.
20. Rello, J., Mariscal, D., Gallego, M. and Vallés, J. (2002) Effect of thioglycolate as transport medium in the direct examination of respiratory samples and guiding initial antibiotic treatment in intubated patients with pneumonia. *Crit Care Med*, **30**, 311−14.
21. Chastre, J., Fagon, J.Y. and Soler, P. (1998) Diagnosis of nosocomial bacterial pneumonia in intubated patients undergoing ventilation: Comparison of the usefulness of bronchoalveolar lavage and the protected specimen brush. *Am J Med*, **84**, 499−506.
22. Morris, A.J., David, C.T. and Reller, L.B. (1993) Rejection criteria for endotracheal aspirates from adults. *J Clin Microbiol*, **31**, 1027−9.
23. Mertens, A.H., Nagler, J.M., Galdermans, D.I.*et al*. (1998) Quality assessment of protected specimen brush samples by microscopic cell count. *Am J Respir Crit Care Med*, 1240−3.
24. Salata, R.A., Lederman, M.M. and Shlaes, D.M.. (1987) Diagnosis of nosocomial pneumonia in intubated intensive care unit patients. *Am Rev Respir Dis*, **135**, 426−32.
25. Valles, J., Rello, J., Fernández, R. *et al*. (1994) Role of bronchoalveolar lavage in mechanically ventilated patients with suspected pneumonia. *Eur J Microbiol Infect Dis*, **13**, 549−8.
26. Rello, J., Paiva, A., Baraibar, J. *et al*. (2001) International conference for the development of consensus on the diagnosis and treatment of ventilator-associated pneumonia. *Chest*, **120**, 955−70.
27. Rello, J., Vidaur, L., Sandiumenge, A. *et al*. (2004) De-escalation therapy in ventilator-associated pneumonia. *Crit Care Med*, **32**, 2183−90.
28. Bouza, E., Torres, M.V., Radice, C. *et al*. (2007) Direct E-test on lower respiratory tract samples importes antimicrobial use in ventilator-associated pneumonia. *Clin Infect Dis*, **44**, 382−7.
29. Gallego, M., Valles, J. and Rello, J. (1997) New perspectives in the diagnosis of ventilator-associated pneumonia. *Curr Opin Pulm Med*, **23**, 116−19.
30. Iregui, M., Ward, S., Sherman, G. *et al*. (2002) Clinical importance of delays in initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest*, **122**, 262−8.
31. Taylor, G.D., Buchanan-Chell, M., Kirkland, T. *et al*. (1995) Bacteremic nosocomial pneumonia: A 7-year experience in one institution. *Chest*, **107**, 786−8.

32. Trouillet, J.L., Chastre, J., Vuagnat, A. *et al*. (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med*, **157**, 531–39.
33. Rello, J., Ausina, V., Ricart, M. *et al*. (1994) Risk factors for infection by *Pseudomonas aeruginosa* in patients with ventilator-associated pneumonia. *Intensive Care Med*, **20**, 193–8.
34. Namias, N., Samiian, L., Nino, D. *et al*. (2000) Incidence and susceptibility of pathogenic bacteria vary between intensive care unit within a single hospital: Implications for empiric antibiotic strategies. *J Trauma*, **49**, 638–45.
35. Rello, J., Sa-Borges, M., Correa, H. *et al*. (1999) Variations in etiology of ventilator-associated pneumonia across four treatment sites: Implications for antimicrobial prescribing practices. *Am J Respir Crit Care Med*, **160**, 608–13.
36. Rello, J., Ausina, V., Castella, J. *et al*. (1992) Nosocomial respiratory tract infections in multiple trauma patients. Influence of level of consciousness with implications for therapy. *Chest*, **102**, 525–9.
37. Gonzalez, C., Rubio, M., Romero-Vivas, J. *et al*. (1999) Bacteremic pneumonia due to *Staphylococcus aureus*: A comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin Infect Dis*, **29**, 1171–7.
38. Lamer, C., de Beco, V., Soler, P. *et al*. (1993) Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. *Antimicrob Agents Chemother*, **37**, 281–6.
39. Pea, F., Brollo, L., Viale, P. *et al*. (2003) Teicoplanin therapeutic drug monitoring in critically ill patients: A retrospective study emphasising the importance of a loading dose. *J Antimicrob Chemother*, **51**, 971–5.
40. Rello, J., Torres, A., Ricart, M. *et al*. (1994) Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes. *Am J Respir Crit Care Med*, **150**, 1545–49.
41. Fagon, J-Y., Patrick, H., Haas, D.W. *et al*. (2001) Nosocomial Pneumonia Group. Treatment of Gram-positive nosocomial pneumonia: prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. *Am J Respir Crit Care Med*, **163**, 1759–60.
42. Kollef, M.H., Rello, J., Cammarata, S.K. *et al*. (2004) Retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Med*, **30**, 388–94.
43. Wunderink, R., Rello, J., Cammarata, S.K. *et al*. (2003) Linezolid vs vancomycin. Analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*, **124**, 1789–97.
44. Rello, J., Jubert, P., Valles, J. *et al*. (1996) Evaluation of outcome for intubated patients with pneumonia due to *Pseudomonas aeruginosa*. *Clin Infect Dis*, **23**, 973–8.
45. Rello, J. and Diaz, E. (2001) Optimal use of antibiotics for intubation-associated pneumonia. *Intensive Care Med*, **27**, 337–9.
46. Baraibar, J., Correa, H., Mariscal, D. *et al*. (1997) Risk factors for infection by A*cinetobacter baumannii* in intubated patients with nosocomial pneumonia. *Chest*, **112**, 1050–4.
47. Montero, A., Ariza, J., Corbella, X. *et al*. (2004) Antibiotic combinations for serious infections caused by carbapenem-resistant *Acinetobacter baumannii* in a mouse pneumonia model. *J Antimicrob Chemother*, **54**, 1085–91.
48. Vallés, J., Mesalles, E., Mariscal, D. *et al*. (2003) A 7-year study of severe hospital-acquired pneumonia requiring ICU admission. *Intensive Care Med*, **29**, 1981–8.
49. Sopena, N., Sabria, M. and Neumos,. (2005) 2000 Study group. Multicentre study of hospital-acquired pneumonia in non-ICU patients. *Chest*, **127**, 213–9.

50. Denessen, P.J.W., van derVen, A.I.A.M., Kessels, A.G.H. *et al*. (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **163**, 1371−75.
51. Ioanas, M., Ferrer, M., Calvacanti, M. *et al*. (2004) Causes and predictors of nonresponse to treatment of intensive care unit-acquired pneumonia. *Crit Care Med*, **32**, 938−45.
52. Ioanas, M., Ewig, S. and Torres, A. (2003) Treatment failure in patients with ventilator-associated pneumonia. *Infect Dis Clin North Am*, **17**, 753−1.
53. Vidaur, L., Gualis, B., Rodrìguez, A. *et al*. (2005) Clinical resolution in patients with suspicion of VAP: A cohort study comparing patients with and without ARDS. *Crit Care Med*, **33**, 1248−53.
54. Kollef, M.H. (2000) Inadequate antimicrobial treatment an important determinant of outcome for hospitalised patients. *Clin Infect Dis*, **31**, S131−8.
55. Wunderinck R.G. (2003) Tif a gift to be simple. *Chest*, **124**, 777−8.
56. Hoffken, G. and Niederman, M.S. (2002) Nosocomial pneumonia: The importance of a de-escalation strategy for antibiotic treatment of pneumonia in the ICU. *Chest*, **122**, 2183−96.
57. Lisboa, T. and Rello, J. (2006) De-escalation in lower respiratory tract infection. *Curr Opin pulmMed*, **12**(5), 364−8.
58. Barreiro, B., Tricas, J.M., Mauri, E. *et al*. (2005) Factores de riesgo y pronósticos de la neumonìa en pacientes no ingresados en las unidades de cuidados intensivos. *Enf Infect Med Clin*, **23**, 529−34.
59. American Thoracic Society: A hospital-pneumonia in adults: Diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies.(1995) A consensus statements. *Am J Respir Crit Care Med*, **153**, 1711−25.
60. Rello, J., Mariscal, D., March, F. *et al*. (1998) Recurrent *Pseudomonas aeruginosa* pneumonia in ventilated patients. Relapse or reinfection. *Am J Respir Crit Care Med*, **157**, 912−16.
61. Chastre, J., Wolff, M., Fagon, J.Y. *et al*. (2003) PneumA trial group. Comparison of 8 to 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: A randomised trial. *JAMA*, **290**, 2588−98.

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Pneumonia Due to *Pseudomonas aeruginosa*

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Summary

Pseudomonas aeruginosa is one of the main Gram-negative bacilli that cause, with most frequency, nosocomial pneumonia. It is, also, the more common pathogen causing ventilator-associated pneumonia and the one that is associated with a higher mortality among hospital-acquired infections. *P. aeruginosa* produces a high number of toxins and in its surface has diverse components that make it especially virulent compared with other microorganisms. Some of these components are fimbriae (N-methyl-phenylalanine pili), flagella, lipopolysaccharide and other products excreted as exotoxin A, exoenzyme S and U, elastase, alkaline protease, cytotoxins and phospholipase. The main route of entry of these organisms into the lungs is the aspiration of previously colonized oropharyngeal secretions due to the manipulation of the endotracheal tube or via the polluted hands of healthcare personnel. There is a growing recognition of the importance of early antibiotic treatment in front of *P. aeruginosa* when ventilator-associated pneumonia is suspected or confirmed. Empiric therapy for nosocomial pneumonia should include drugs active against *P. aeruginosa*, especially in patients who have received previous antibiotics or present late onset pneumonia since they have a higher probability of infection due to this pathogen.

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Introduction

Pseudomonas aeruginosa (PA) is a glucose-nonfermenting Gram-negative bacilli (GNB). Since it affects mainly patients with local or general alterations to their defence mechanisms, it can be considered an opportunistic pathogen. It is the main pathogen responsible for hospital-acquired infections and causes serious infections in mechanically ventilated patients, individuals who are immunocompromised, burn patients and patients with malignancies or HIV infection. Among these risk groups, the most vulnerable hosts are neutropenic and patients in an intensive care unit (ICU) who are mechanically ventilated. PA also frequently infects patients with chronic lung disease and those affected of chronic obstructive pulmonary disease (COPD), bronchiectasies or cystic fibrosis.

Ventilator-associated pneumonia (VAP) is the most frequent infection among patients supported with mechanical ventilation (MV) [1]. VAP and bacteremia are the nosocomial infections associated with greater morbidity and mortality among critical patients [2].

Depending on the time the first symptoms appeared and the type of microorganism responsible, VAP has been classified in early onset pneumonia or primary endogenous (habitually in the first week of MV), late onset pneumonia or secondary endogenous (generally after the first week of MV) and exogenous. Early onset pneumonia is caused by microorganisms carried in the throat or gut on admission to the ICU, such as *S. pneumoniae*, *H. influe*nzae, *M. catharralis* and methicillin sensitive *S. aureus* (MSSA). VAP is classified as secondary endogenous when caused by microorganisms not carried on admission but acquired in the throat and gut later during the stay in the ICU, such as *Enterobacteriaceae* (*E. coli*, *Klebsiella* spp, *Proteus* spp) and nonfermenting Gram-negative rods, like PA. VAP is considered of exogenous origin when caused by microorganisms as PA, *Acinetobacter* spp, and methicillin-resistant *S. aureus* (MRSA) that enter the low respiratory tract directly without previous colonization, and generally are transmitted through the healthcare worker's hands or through the respirator external circuits [3].

Although it is a rather arbitrary classification, since the causative microorganisms of VAP are influenced by factors other than time of MV (like underlying diseases or prior antibiotic use), it is a generally accepted and useful classification for targeting empiric antibiotic treatment. So, PA is rarely responsible for early onset VAP except in patients with cystic fibrosis or bronchiectasies because the respiratory tract of these individuals is frequently colonized by PA [4].

Pneumonia caused by PA is one of the most frequent and, generally also, more serious nosocomial pneumonias, especially in mechanically ventilated patients [5–8]. In patients with severe nosocomial pneumonia admitted to ICUs, 42% of VAP microbial etiology is due to GNB, and PA is the causative microorganism in 60% of cases [9].

The incidence of VAP ranges from 8–70% [5–7], and this great variability is attributed to the population studied, the duration of ICU stay and the diagnostic criteria approach, especially the microbiological diagnostic method(s) used. Among the studies published, those in which diagnostic methods of great specificity – like

Table 6.1 Etiology of ventilator-associated pneumonia

Microorganisms	Rello *et al.* [5] (%)	Torres *et al.* [7] (%)	Fagon *et al.* [6] (%)
Gram-positive			
S. aureus	24.7	8.6	20.2
S. pneumoniae	4.4	–	3.5
Enterococcus sp	1.7	4.3	–
Other	1.7	4.3	5.9
Gram-negative			
H. influenzae	17.6	–	5.9
P. aeruginosa	21.2	21.7	19.0
Acinetobacter sp	3.5	39.1	9.5
Proteus sp	3.5	4.3	9.5
Serratia sp	4.4	4.3	NN
Klebsiella sp	NN	–	2.3
E. coli	2.6	–	4.7
Other	7.0	8.5	9.5
Anaerobic flora	3.5	NN	1.1
Fungi	3.5	4.3	–

NN = Not notified

protected specimen brush or bronchoalveolar lavage – have been used, Gram-positive microorganisms are the causative agents in nearly 30 % of VAP, while GNB are responsible for 60 % of pneumonias, with PA responsible for 20–25 % of all the cases [5–7] (Table 6.1).

Pathogenesis

The microorganisms responsible for a lung infection can basically reach the low respiratory tract in one of three ways:

1. Aspiration of secretions from the oropharyngeal airways.
2. Haematogenous spread.
3. Inhalation.

The majority of nosocomial pneumonias appear to result from aspiration of potential pathogens that have previously colonized the upper respiratory airways [10]. Oropharyngeal colonization takes place quickly (in the first 4–5 days of hospital stay) and mainly by GNB coming from the stomach (endogenous) or healthcare worker's hands (exogenous).

There are diverse risk factors for oropharyngeal colonization with GNB that favour their adherence to respiratory epithelial cells. Among other factors, underlying diseases (diabetes, alcoholism, neutropenia), prior or concomitant antimicrobial

therapy, malnutrition, coma, intubation, surgery and the neutralization of gastric secretions can be highlighted [11].

In mechanically ventilated patients, the aspiration of secretions through the space between the endotracheal cuff and the trachea is the main way that microorganisms enter the lung; in addition, in these patients the microorganisms can also reach the lower airways directly through the endotracheal tube, without previously colonizing the oropharynx [11, 12]. Once the pathogens reach to lower airways, the balance between the inoculum and the local lung defences will be the factor that determines whether these microorganisms cause pneumonia or be simply colonizers. According to this, pneumonia is the result of the three main factors: an overwhelming bacterial inoculum, the virulence of the microorganisms and the local host defences.

The relationship between the previous colonization of the airway and the subsequent infection has been broadly demonstrated in the case of nosocomial pneumonia in critical patients and, concretely, in pneumonia due to PA [13, 14]. However, the main way of entry into the airways and whether the origin is endogenous or exogenous has not still been well established in the case of PA.

Globally, 4–24 % of the microorganisms that colonize the respiratory tract of critical patients, and 0–15 % of those that causes VAP, come from the stomach (gastropulmonary route) [13, 15, 14]. However, in the case of PA,the origin in the stomach seems to be smaller. Bonten *et al*. [16] carried out a study in which sequential cultures from oropharynx, rectum and gastric juice were made; it was demonstrated that only in two of 28 cases of VAP caused by PA, had the microorganism been isolated previously in the stomach.

Other studies, such as that of Latorre *et al*. [17], have established that the trachea of mechanically ventilated patients becomes colonized by PA before VAP appears in most of the cases, and the oropharynx is the place of origin of the microorganism in most cases of VAP.

However, bacterial adherence studies of Niederman *et al*. [18] have suggested that PA has a special tropism toward the tracheal epithelium. It was observed that *Enterobacteriaceae* usually appear in the oropharynx first, whereas PA more often appears first in the trachea. For this reason a pattern of colonization has been proposed that is different for PA that for other GNB.

When tracheal colonization does not occur before oropharynx colonization, it is admitted that the pathway of PA to the tracheobronchial tract is by direct inoculation: tube manipulation or respiratory therapy equipment (exogenous route of colonization), the hands of healthcare personnel being responsible for microorganism transmission (cross infection).

More recent studies on pathogenesis of VAP due to PA have demonstrated that an important policlonality exists amongst the strains of PA isolated in ICUs, not only those isolated in patients but also PA isolated in inanimate surfaces and tap water outlets [19–21, 9]. This suggests that endogenous paths as much as exogenous paths are important in PA lung colonization/infection.

In summary, these studies have proved that the origin of strains that will colonize and infect the lung is preferably the oropharynx but, in some cases, a primary respiratory colonization will take place. The gastric origin of the strains that will

colonize the respiratory tract later on is not very important in the case of PA, compared with other pathogens.

It depends on the balance between the inoculum, the virulence of the pathogens and the host's local lung defences; the pneumonia will develop or the host's defenses will be able to avoid the infection. PA is characterized as having a great number of virulence factors (Table 6.2) that alter the balance and favour the initial colonization of the lower respiratory tract and the later infection.

Cell-associated virulence factors of PA intervene mainly in the initial colonization of respiratory epithelial cells. Adherence of PA to epithelium is mediated by pili and flagella; several other nonpilus adhesions responsible for the binding to mucin have been described, but their role in the infection process remains unclear. PA colonization/infection requires a substantial break in first-line defenses. Such a break is caused mainly by tracheal intubation, MV, trauma, indwelling devices or chronic lung pathology [22].

Later on PA has the capacity to excrete several extracellular products that will participate in the development and spread of the infection by direct tissue destruction or by recruitment of inflammatory cells that will promote the lung damage. The most-studied extracellular virulence factors associated with PA infection are type I, II and III secretion protein systems, and the quorum sensing or cell-to-cell signaling.

Type I and II secretion protein systems liberate proteases and toxins to the cell surface and, later on, these hydrolytic enzymes will produce their prejudicial action directly on the host's cells or activating inflammatory mediators. Alkaline protease is one of the virulence factors excreted by the type I system and exercises its action: inactivating the complement system and other inhibitors of proteases. Type II system secreted elastase, exotoxin A, phospholipase, and alkaline phosphatase act by injuring the structure of the lung tissue directly and activating apoptosis [22].

Type III secretion systems (TTSS) are characterized by their injection of effector proteins (virulence factors) directly into the cytosol of target eukaryotic cells (host cytoskeleton and innate immune response pathways of macrophages and epithelial cells). The main TTSS effector proteins identified for PA are ExoS, ExoT, ExoU and ExoY. These are responsible for disruption of the actin cytoskeleton in host cells, inhibition of DNA synthesis, interference with cell matrix adherence, production of epithelial cell injury, inhibition of internalization and induction of apoptosis.

Table 6.2 Virulence factors of *P. aeruginosa*

1.	– Surface factors
	– Lipopolysaccharide (LPS), polysaccharide slime (alginate), flagella, pili
2.	– Protein secretion systems
	– Type I
	– Type II
	– Type III
	ExoS, ExoT, ExoU, and ExoY
3.	– Quorum sensing system
4.	– Other virulence factors
	– Iron captators, catalase, proteases, exotoxin A, pyocyanin

In an experimental mouse model of pneumonia due to PA, the lung instillation of a noncytotoxic, isogenic mutant strain (PA103Δ*UT*), which is defective for the production of type III secreted toxins, did not cause either systemic inflammatory response or septic shock, despite a potent inflammatory response in the lung. [23]. Likewise, the analysis of PA strains isolated from patients with VAP proved that TTSS was detected in 81 % of the isolates associated with serious sepsis or septic shock while it was only detected in 38 % of the less serious cases of pneumonia [24].

Diverse GNB communicate with each other using the quorum sensing system. They produce and secrete certain signalling compounds (called autoinducers or pheromones). When the cell-population density is sufficient that it produces a threshold accumulation of a secreted autoinducer, there is an activation of transcription in certain genes, including those that regulate the production and excretion of virulence factors. In PA, the quorum-sensing signal autoinducers are *N*-acyl homoserine lactones (AHLs), which regulate the production and excretion of virulence factors, or substances that take part in the formation of the biofilm (Figure 6.1).

Until now, two quorum sensing systems have been described: (i) the lasR/lasI system, that participates in the production of elastases A and B, alkaline protease, exotoxin A and proteins of the excretory tract, and also participates in the formation of the biofilm; and (ii) the rhlR/rhlI system, that is also involved in the production of elastases, proteases, pyocyanin and haemolysin. The quorum sensing system also has immunomodulatory activity on the host's immune responses before infection. PA quorum sensing molecule 3O-C12-HSL is a potent inducer of cyclooxygenase-2 (Cox-2) production in human lung fibroblasts. The Cox-2 enzyme is important for the conversion of arachidonic acid to prostaglandins and is associated with edema, inflammatory infiltrate, fever and pain. 3O-C12-HSL also activates T cells to produce

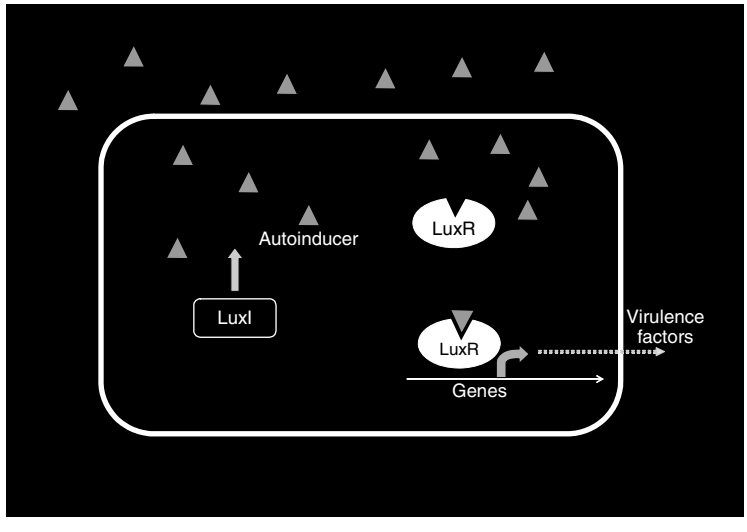

Figure 6.1
Quorum sensing system of Gram-negative bacilli

the inflammatory cytokine gamma interferon and therefore potentially promotes a Th1 environment. Therefore, the quorum-sensing systems of PA contribute to its pathogenesis both by regulating expression of virulence factors (exoenzymes and toxins) and by inducing inflammation [25, 26].

In experimental models in which quorum-sensing mutant strains of PA have been used, the loss of virulence and the incapacity of developing infection of these strains has been demonstrated [27]: the mutant strain could colonize the lung, but it does not achieve high densities and it does not cause pneumonia, bacteraemia or death. The mutant does not have a growth defect under laboratory conditions, it could invade the lung and survive but it could not cause disease.

Because quorum sensing is required for virulence of PA, in the future it is hoped that it will be possible to identify general or specific inhibitors of that system (e.g. azythromycin, furanones etc.), inhibitors of TTSS, or inhibitors of the virulence factors excreted, and to test their effectiveness in preventing and treating infections, particularly persistent biofilm infections [26].

Risk Factors

Most critical patients present underlying diseases; monitoring use and invasive treatments that, together with the severity of the current illness causing admission to an intensive care unit, mean that the patient is predisposed to acquiring a nosocomial pneumonia caused by multiresistant microorganisms, such as PA. Pathologies that are predisposed to the development of a nosocomial pneumonia due to PA are cystic fibrosis (although they don't present a lung infection at admission, they have a high probability of developing it during a stay in hospital), chronic obstructive pulmonary disease (COPD) and also patients considered immunocompromised, so much for effect of the treatment received as for their own underlying disease [4, 19].

However, even patients admitted to intensive care units without previous underlying diseases, mainly those that require prolonged MV, are considered at high risk of acquiring lung infection due to PA. In patients with acute respiratory distress syndrome (ARDS), the main supportive treatment of the failing respiratory system is continued MV until the patient is well enough to breathe on their own. Many patients with ARDS are young, with major trauma and without important underlying conditions. Most clinical studies have found that the microorganism most frequently isolated from patients with ARDS and VAP was PA [28, 10, 29, 30].

Other authors have analysed the risk factors for infection caused by PA in patients with VAP. Rello *et al*. [19], using a model of multiple logistic regression, described that independent factors associated with the development of VAP due to PA were the presence of COPD (relative risk [RR], 29.9; 95% confidence interval [CI], 4.86−184.53), more than eight days of MV (RR, 8.1; 95% CI, 1.01−65.40) and previous use of antibiotics (RR, 5.5; 95% CI, 0.88−35.01). Niederman *et al*. [18], in a study about routes of colonization of the lower airway in mechanically ventilated patients, suggested that patients with COPD or malnutrition were predisposed to

present lung infections caused by *Pseudomonas* spp; this is related to changes in bacterial adhesiveness to the tracheal epithelium. Torres *et al*. [7] also consider that the patients with COPD and bronchiectasies are at high risk of developing a VAP by PA. Peacock and Garrad [4] also describe that when VAP presents in patients that have received antibiotics during their stay in the ICU for at least 5 days, the responsible microorganism is invariably PA. In this sense, Rello and Ricart [31] also indicate that, in their experience, when patients with severe community-acquired pneumonia that requires MV or patients that have suffered some previous episode of nosocomial pneumonia present a respiratory superinfection, it is highly probable that this is produced by PA.

These risk factors must be considered especially when it is necessary to begin an empiric antibiotic treatment. In this sense, patients in MV for more than eight days, COPD, immunocompromised or with ARDS and those treated previously with antibiotics for several days have a high risk of being infected by PA. Once a diagnosis of ventilator-associated pneumonia is suspected, early broad-spectrum antibiotic administration (active in front of PA) should be started.

Clinical Manifestations

Pneumonia caused by PA does not present special clinical characteristics that can distinguish it from pneumonias caused by other GNB. Generally, it causes a necrotizing pneumonia, which is associated with deterioration of the patient's general condition and a torpid course; many times there are relapses and approximately 10 % of episodes are bacteremia [31, 32].

Pneumonia is generally diffuse and bilateral, with minimum pleural effusion, although sometimes empyema can be developed. Generally, the findings in the chest X-ray are non-specific, but a few differences exist. The major distinguishing radiographic factor is development of a lung abscess. Some enzymes of PA have vase-invasive properties, causing thrombosis of pulmonary vessels and pulmonary infarction; this produces nodular bilateral lesions, predominantly in inferior lobes, and it is such a characteristic image that it should make the presence of PA suspected. After an episode of pneumonia by *Pseudomonas* spp., the lung architecture is not normalized and there are cicatrisation areas [32, 31].

Pneumonia due to *Pseudomonas* spp. in MV patients appears late, generally after the first week of ventilation, affects patients with a high grade of organic dysfunction before the development of the pneumonia, and those that have received antibiotic previously in more than 85 % of cases [32, 29].

One of the characteristics of PA pneumonia is its recurrence in 3−50 % of cases, depending on the diagnostic approaches and the specificity of the diagnostic techniques used [31]. In our experience, most recurrent episodes of PA pneumonia in ventilated patients occur due to persistence of strains present in a prior infection [33].

Pronostic Factors

PA pneumonia is associated with a high morbidity and mortality. In a prospective study of patients with VAP due to PA, the overall case fatality rate was 42.3 %, mortality attributable to VAP 13.5 % (95 % CI, 1.95−25.04) and the risk ratio for death was 1.46 (95 % CI, 0.79−2.73) [34]. Fagon *et al.* [35], in a retrospective study of pneumonias caused by *Pseudomonas* spp or *Acinetobacter* spp in MV patients, described a crude mortality of 71.4 % and an attributable mortality of 42.8 %. There are differences between both studies because in the former, all the episodes of pneumonia evaluated had received combined empirical antibiotic treatment with agents active against the causal microorganisms. On the other hand, in the study of Fagon, included patients that had received inadequate antibiotic treatment or treatment that had been delayed until the result of microbiologic cultures were known.

Antibiotic Treatment: General Considerations

Crude mortality of VAP caused by PA is high, mostly related to the severity of the underlying disease itself, and the virulence of PA makes adequate initial antibiotic treatment difficult.

As well as the respiratory and haemodynamic support required by the systemic alterations caused by VAP due to PA, appropriate antibiotic treatment will be of critical importance to the recovery of these patients, since the balance between the virulence of the microorganism and the patient's defences is very narrow, contrary to other less virulent microorganisms, more susceptible to many antibiotics [32].

Brewer *et al.* [36], in a retrospective study of 38 cases of VAP caused by PA found that, in 67 % of the cases, the empiric antibiotic treatment was inadequate and that this therapeutic failure was associated with a higher mortality (79 % vs. 42 %) in comparison to patients with an early, adequate antibiotic treatment. In this same study, the presence of multiorganic failure on the day of the diagnosis of VAP is associated independently with a bad presage (odds ratio [OR], 1.73; 95 % CI, 1.02−2.92); inadequate antibiotic treatment is one of the factors significantly ($p = 0.02$) associated with the presence of multiorganic failure. In a study by Rello *et al.* [34] the progression of the multiorganic dysfunction during the 72 hours following the diagnosis of the pneumonia was a sign of bad presage and is associated to a bigger mortality. This fact highlights the importance in the final prognosis of the illness's evolution in the first hours after pneumonia due to PA has been diagnosed and the importance of starting an early and adequate antibiotic treatment.

Election of the Empirical Antibiotic Treatment

Parenteral antibiotic therapy with two antibiotics is accepted as standard treatment of pneumonia due to PA. The use of a ß-lactam with antipseudomonic activity associated to an aminoglycoside is the treatment habitually recommended by Hilf *et al.* [37].

He demonstrated that this therapeutic combination is associated with a better prognosis for the treatment of *Pseudomonas* spp. bacteraemias; among those, 28 pneumonia episodes were included.

There are currently new antimicrobials such as carbapenems, ß-lactams associated with ß-lactam inhibitors and fluoroquinolones (ciprofloxacin, levofloxacin) that allow more variability in treatment. But in all cases of pneumonia by PA, with or without bacteraemia, therapeutic combination is recommended, contrary to infections by *Pseudomonas* spp in other localizations. Combined treatment seems to be safer and to avoid the appearance of resistances during the treatment. Indeed, in a study where the utility of monotherapy with ciprofloxacin was compared to that of imipenem in lung infections, there was a 34 % rate of therapeutic failure due mainly to the development of resistances during the treatment in cases of infection by *Pseudomonas* spp [38].

Alternative treatments to aminoglycosides – to avoid toxicity problems associated with their use – are ß-lactams with an antipseudomonal spectrum associated with fluoroquinolones such as ciprofloxacin, although comparative studies have still not been published. The combination of two ß-lactams in the treatment of pneumonia by PA is not advisable owing to the resistance that can take place – induction of ß-lactamases – and the secondary effects.

Since pneumonia due to *Pseudomonas* spp is generally developed in critical patients that have received multiple antibiotic treatments previously, it is very probable that at the moment of the diagnosis there already exists a high resistance to different antibiotics or that it is developed during the treatment. To improve the effectiveness of empiric antibiotic treatment, it is important to know what the pattern of resistance is in each hospital and also to follow some rules concerning sequential use of antimicrobials.

In our experience and in accordance with the recommendations of Dunn and Wunderink [32], before choosing an empiric treatment it is necessary to remember:

1. If the patient has not received antibiotics previously, the combination of an antipseudomonal ß-lactam (ceftazidime, cefepime, piperacillin etc.) plus an aminoglycoside would be the combination of first line.

2. ß-lactam antibiotics can induce in Pseudomonas spp the production of ß-lactamases. For this reason, if the patient develops pneumonia during the stay, it is very probable that the strain of PA would be resistant to ß-lactams. In this case it is preferable to use a carbapenem associated to an aminoglycoside because carbapenem is resistant to ß-lactamases produced by *Pseudomonas* spp. This is the most frequent situation in the clinical practice in intensive care, since a high percentage of patients that develop pneumonia due to PA are receiving ß-lactams for other reasons.

3. Although resistance to fluoroquinolones is due mainly to alterations in the DNA girase, in the case of *Pseudomonas* spp the main mechanism of resistance is due to a decrease in the permeability of the cellular wall to the antibiotic. Due to this mechanism of resistance, strains with resistance to fluoroquinolones can induce crossed resistance toward other antibiotics such as the carbapenems.

On the contrary, the resistance acquired by alteration of the permeability to carbapenems is not usually transmittable to fluoroquinolones. For this reason, in the de-escalating therapy, fluoroquinolonas should be located later on from the election of the carbapenem. If a patient treated with a fluorquinolone develops a pneumonia due to PA, the empiric treatment will be based on the combination of a ß-lactam plus an aminoglycoside.

4. The resistance to aminoglycoside is generally due to a modification of the antibiotic mediated enzymatically. Different enzymes that act on different aminoglycosides exist. As well as knowing the endemic pattern of resistance in front of aminoglycosides, it is necessary to keep in mind that if the patient has received gentamicin or tobramicin previously, it is wise to begin empirically with a ß-lactam plus amikacin. If the patient has already received amikacin, it would be necessary to look for an alternative to antibiotic treatment with an aminoglycoside (it could be a fluoroquinolone). In this case, there is possibility of cross transmission of resistances from fluoroquinolones to carbapenems, so they should never be used in combination, a good alternative being the combination of imipenem with aztreonam.

Once the antibiogram is known, treatment will be modified if necessary and, although there are no data based on evidence about the duration of treatment in *Pseudomonas* spp pneumonia, at the moment it is habitual practice to maintain it for a minimum of 15 days.

In our experience, prognosis is conditioned by the evolution during the first three days [34]. Due to the severity of this infection, it is advisable to repeat a culture of lung secretions after 72 hours of appropriate antibiotic treatment to verify that the bacterial load is lower, and to confirm the absence of changes in PA antibiotic susceptibility with respect to the strain isolated in first cultures.

References

1. Vincent, J.L, Bihari, D.J., Suter, P.M. *et al*. (1995) The prevalence of nosocomial infection in intensive care units in Europe. *JAMA*, **274**, 639−44.
2. Bueno-Cavanillas, A, Delgado-Rodriguez, M., López-Luque, A. *et al*. (1994) Influence of nosocomial infection on mortality rate in an intensive care unit. *Critical Care Medicine*, **22**, 55−60.
3. Stoutenbeeck, C. and vanSaene, H.K.F. (1992) Prevention of pneumonia by selective decontamination of the digestive tract. *Intensive Care Medicine*, **18**, S18−23.
4. Peacock, S.J. and Garrad, C.S. (1997) The challenge of *Pseudomonas aeruginosa* pneumonia. InVincent, J.L. (ed) *Yearbook of Intensive Care and Emergency Medicine*, Berlin, Springer, 617−24.
5. Rello, J., Quintana, E., Ausina, V. *et al*. (1991) Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. *Chest*, **100**, 439−44.
6. Fagon, J.Y., Chastre, J., Hance, A.J. *et al*. (1989) Nosocomial pneumonia in patients receiving continuous mechanical ventilation: Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture technique. *The American Review of Respiratory Disease*, **139**, 877−84.

7. Torres, A., Aznar, R., Gatell, J.M. *et al*. (1990) Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *The American Review of Respiratory Disease*, **142**, 523–8.
8. Rello, J., Ausina, V., Ricart, M. *et al*. (1993) Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. *Chest*, **104**, 1230–5.
9. Vallés, J., Mesalles, E., Mariscal, D. *et al*. (2003) A 7-year study of severe hospital-acquired pneumonia requiring ICU admission. *Intensive Care Medicine*, **29**, 981–8.
10. Delclaux, C., Roupie, E., Blot, F. *et al*. (1997) Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **156**, 1092–8.
11. Craven, D.E., Steger, K.A., Barat, L.M. and Duncan, R.A. (1992) Nosocomial pneumonia: Epidemiology and infection control. *Intensive Care Medicine*, **18**, S3–9.
12. Tobin, M.J. and Grenvik, A. (1984) Nosocomial lung infection and its diagnosis. *Critical Care Medicine*, **12**, 191–9.
13. Bonten, M.J.M., Bergmans, D.C.J.J., Ambergen, A.W. *et al*. (1996) Risk factors for pneumonia, and colonization of respiratory tract and stomach in mechanically ventilated ICU patients. *American Journal of Respiratory and Critical Care Medicine*, **154**, 1339–46.
14. Bergmans, D. and Bonten, M. (1999) Colonization and infection with pseudomonas aeruginosa in intensive care: Endogenous or exogenous origin? InVincent, J.L(ed) *Yearbook of Intensive Care and Emergency Medicine*, Springer, Berlin, 131–40.
15. Bonten, M.J.M., Gaillard, C.A., deLeeuw, P.W. and Stobberingh, E.E. *et al*. (1997) Role of colonization of the upper intestinal tract in the pathogenesis of ventilator-associated pneumonia. *Clinical Infectious Diseases*, **24**, 309–19.
16. Bonten, M.J.M., Gaillard, C.A., vanTiel, F.H. *et al*. (1994) The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. *Chest*, **105**, 878–84.
17. Latorre, F.J., Pont, T., Ferrer, A. *et al*. (1995) Pattern of tracheal colonization during mechanical ventilation. *American Journal of Respiratory and Critical Care Medicine*, **152**, 1028–33.
18. Niederman, M.S., Mantovani, R., Schock, P. *et al*. (1989) Patterns and routes of tracheobronchial colonization in mechanically ventilated patients: The role of nutritional status in colonization of the lower airway by *Pseudomonas* species. *Chest*, **95**, 155–61.
19. Rello, J., Ausina, V., Ricart, M. *et al*. (1994) Risk factors for infection by *Pseudomonas aeruginosa* in patients with ventilator-associated pneumonia. *Intensive Care Medicine*, **20**, 193–8.
20. Foca, M., Jacob, K., Whittier, S. *et al*. (2000) Endemic *Pseudomonas aeruginosa* infection in a neonatal intensive care unit. *New England Journal of Medicine*, **343**, 695–700.
21. Reuter, S., Sigge, A., Wiedeck, H. and Trautmann, M. (2002) Analysis of transmission pathways of *Pseudomonas aeruginosa* between patients and tap water outlets. *Critical Care Medicine*, **30**, 2222–8.
22. Sadikot, R.T., Blackwell, T.S., Christman, J.W. and Prince, A.S. (2005) Pathogen-host interactions in *Pseudomonas aeruginosa* pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **171**, 1209–23.
23. Kurahashi, K., Kajikawa, O., Sawa, T. *et al*. (1999) Pathogenesis of septic shock in *Pseudomonas aeruginosa* pneumonia. *Journal of Clinical Investigation*, **104**, 743–50.
24. Hauser, A. Cobb, E., Bodi, M. *et al*. (2002) Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by pseudomonas aeruginosa. *Critical Care Medicine*, **30**, 521–8.

25. Smith, R.S., Harris, S.G., Phipps, R. and Iglewski, B.H. (2002) The *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-oxododecanoyl)homoserine lactone contributes to virulence and induces inflammation in vivo. *Journal of Bacteriology*, **184**, 1132–9.
26. Smith, R.S. and Iglewski, B.H. (2003) *Pseudomonas aeruginosa* quorum-sensing as a potential antimicrobial target. *Journal of Clinical Investigation*, **112**, 1460–5.
27. Lesprit, P., Faurisson, F., Joint-Lambert, O. *et al*. (2003) Role of the quorum-sensing system in experimental pneumonia due to *Pseudomonas aeruginosa* in rats. *American Journal of Respiratory and Critical Care Medicine*, **167**, 1478–82.
28. Sutherland, K.R., Steinberg, K.P., Maunder, R.J. *et al*. (1995) Pulmonary infection during the acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **152**, 550–6.
29. Chastre, J., Trouillet, J.L., Vaugnat, A. *et al*. (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, **157**, 1165–72.
30. Meduri, G.U., Reddy, R.C., Stanley, T. and El-Zeky, F. (1998) Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. *American Journal of Respiratory and Critical Care Medicine*, **158**, 870–5.
31. Rello, J. and Ricart, M. (1998) Infecciones del tracto respiratorio en pacientes intubados causadas por *Pseudomona aeruginosa*. *Revista Clìnica Española*, **198**, 17–20.
32. Dunn, M. and Wunderink, R.G. (1995) Ventilator-associated pneumonia caused by *Pseudomonas* infection. *Clinics Chest Medicine*, **16**, 95–109.
33. Rello, J., Mariscal, D., March, F. *et al*. (1998) Recurrent pseudomonas aeruginosa pneumonia in ventilated patients: Relapse or reinfection. *American Journal of Respiratory and Critical Care Medicine*, **157**, 912–16.
34. Rello, J., Jubert, P., Vallés, J. *et al*. (1996) Evaluation of outcome in intubated patients with pneumonia caused by *Pseudomonas aeruginosa*. *Clinical Infectious Diseases*, **23**, 973–8.
35. Fagon, J.Y., Chastre, J., Hance, A.J. *et al*. (1993) Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. *American Journal of Medicine*, **94**, 281–8.
36. Brewer, S.C., Wunderink, R.G., Jones, C.B. and Leeper, K.V. (1996) Ventilator-associated pneumonia Due To *Pseudomonas aeruginosa*. *Chest*, **109**, 1019–29.
37. Hilf, M., Yu, V.L., Sharp, J. *et al*. (1989) Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: Outcome correlations in a prospective study of 200 patients. *American Journal of Medicine*, **87**, 540–6.
38. Fink, M.P., Snydman, D.R., Niederman, M.S. *et al*. (1994) Treatment of severe pneumonia in hospitalised patients: Results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. *Antimicrobial Agents and Chemotherapy*, **38**, 547–57.
39. Coalson, J.J. (1995) The pathology of nosocomial pneumonia. *Clinics Chest Medicine*, **16**, 13–28.

7

Hospital-Acquired Pneumonia Caused by *Staphylococcus aureus*

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Introduction

Nosocomial pneumonia or hospital-acquired pneumonia (HAP) causes considerable morbidity and mortality. It is the second most common nosocomial infection and the leading cause of death from hospital-acquired infections [1]. According to data from the National Nosocomial Infections Surveillance (NNIS) System, 83 % of HAP was associated with mechanical ventilation (MV) [2].

The etiology of HAP varies, mostly depending on prior antibiotic exposure, length of stay (LOS) in hospital and duration of MV. In early onset pneumonia, endogenous microorganisms of the oropharyngeal flora are usually the cause, with methicillin-sensitive *Staphylococcus aureus* (MSSA) being the leading pathogen. In the presence of exposure to antibiotics or in the setting of prolonged hospital stay the frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) increases [3]. *S. aureus* is at present the most common cause of ventilator-associated pneumonia (VAP) in Europe, as frequent as *Pseudomonas aeruginosa* in the United States [4], and the most prevalent organism isolated in the blood culture of patients with bacteremic nosocomial pneumonia [5].

MSSA is a member of endogenous flora, whereas MRSA is an exogenous organism. MRSA can also be isolated from the nasal mucosa of normal hosts, but

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Table 7.1 Major differences between MSSA and nosocomial-acquired MRSA strains

	MSSA	HA-MRSA
Source	Endogenous	Exogenous
PBP2a production	no	yes
mecA gene	no	yes
Coresistance to non beta-lactam antimicrobial drugs	rare	95 %
Early pneumonia onset	Usually	In the presence of risk factors
Risk factors for pneumonia	Cranial trauma, Coma, Younger age	Recent antibiotic exposure, Prior or prolonged hospitalisation, COPD, Chronic steroid use, Nasal carriage, Poor infection control practices
Association with bacteremic pneumonia episode	10–20 %	40–50 %

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *S. aureus*

it should be always considered as a potential pathogen [6] Pneumonia caused by susceptible *S. aureus* strains has several differences compared to pneumonia caused by resistant strains in terms of epidemiological characteristics, clinical course, treatment modalities and resolution patterns (Table 7.1) [7].

Microbiology

S. aureus is an aerobic Gram-positive coccus that in microscopic examination appears in clusters resembling grapes (grape = staphylos in ancient Greek). It is catalase-positive, oxidase-negative, facultative anaerobe that grows by aerobic respiration or by fermentation. Nearly all strains of *S. aureus* produce the enzyme coagulase and can be distinguished by this feature from other staphylococcal species [8].

The staphylococcal genome is a circular chromosome that consists of plasmids, transposons and prophages. Genes that govern virulence and antibiotic resistance may be found on the chromosome or extrachromosomal elements. These genes can be transferred between staphylococcal strains and species and also between other Gram-positive bacterial species through extrachromosomal elements [9]. The organism contains cell wall, capsule, surface proteins, toxins, enzymes and other bacterial components. Some of these constituents are potential virulence factors and are major cause of HAP. Preliminary animal studies indicate that expression of many of these virulence factors is regulated by the *agr* and s*arA* locuses that are complex global regulators [10, 11] and only *S. aureus* strains with intact *agr* and *sarA* are able to cause invasive diseases, while mutant microorganisms have the ability to elicit inflammatory responses [12]. The *sarA* locus is important for genes encoding hemolysins and fibronectin binding proteins [11]. Interaction between fibronectin

binding protein of the *S. aureus* and the host's fibronectin plays a key role in the pathogenesis of invasive diseases [13, 14].

A particularly ominous development in staphylococcal microbiology has been the emerging incidence of strains bearing the Panton−Valentine leukocidin gene that has been associated with necrotizing pneumonia and aggressive soft tissue infections [15]. The role of the Panton-Valentine leukocidin gene in HAP is not significant, yet; however, increasing hospital admissions due to community-acquired MRSA pneumonia should not be ignored [16].

Epidemiology

The prevalence of microorganisms leading to HAP may vary according to the hospital population characteristics, LOS and the specific diagnostic methods that were applied [2]. *S. aureus* and *P. aeruginosa* now are the most common causes of VAP both in Europe and the United States. It was reported that *S. aureus* was responsible for 20.4 % of the VAP episodes, being the second most frequent isolate following *P. aeruginosa* (24.4 %), and that 55.7 % of the strains were methicillin-resistant [17].

Several studies reported differences in epidemiology of methicillin susceptible and methicillin-resistant strains. MSSA VAP is associated with coma, trauma and young age, whereas MRSA VAP is associated with prior antibiotic exposure, steroid use, prior hospitalisation, prolonged MV (>6 days), age >25 years, chronic obstructive pulmonary disease, poor infection control practices and nasal carriage (Table 7.1) [7, 18, 19]. Temporal trends show an increasing proportion of methicillin resistance in the last two decades [20].

Although many studies suggest that MRSA bacteraemia is associated with worse outcome [21, 22], recent studies report similar outcomes for MSSA and MRSA bacteraemia after adjusting for early initiation of appropriate antibiotic treatment [19, 23]. A recent study that compared MSSA pneumonia with MRSA pneumonia (both groups having received appropriate initial therapy) reported that age and Day-1 organ dysfunctions or infection score were associated with 28-day mortality, but methicillin resistance was not associated [19]. Nonetheless, another study that compared patients with MRSA VAP to patients with MSSA VAP demonstrated that MRSA VAP independently prolongs the duration of Intensive Care Unit (ICU) hospitalisation and, in turn, increases overall costs, even for patients initially given appropriate antibiotic treatment [24]. Infection with MRSA as opposed to MSSA doubled the probability of needing continued ICU care (hazard ratio, 2.08; 95 % CI: 1.09−3.95; p = 0.025] [24]. The PaO_2/FIO_2 ratio at the time pneumonia was diagnosed, ventilation duration prior to VAP onset, prolonged ventilation after the diagnosis and the reason for MV were associated with ICU LOS [24].

Risk Factors Associated with MSSA HAP

Head Trauma and Coma: Cranial trauma, neurologic and neurosurgical admissions and accompanying coma are associated with tracheal colonization and pneumonia due

to MSSA [20, 25−27]. A prospective, large-cohort study of mechanically ventilated patients demonstrated that in 7% of the patients, MSSA already had colonized the trachea at ICU admission; acquired tracheal colonization occurred in 10% of the patients and was less frequent in those previously hospitalised for more than >48 hours before admission to the ICU compared to patients admitted directly to the ICU (6% vs. 15%). It was also demonstrated that colonization was acquired more frequently among trauma and neurological/neurosurgical patients (22%) when compared to surgical and medical patients (7%) [28]. 4% developed *S. aureus* VAP, the incidence being higher in patients with MSSA colonization of the trachea compared to those without colonization (21% vs. 1%) [28]. *S. aureus* VAP developed more often in trauma and neurological/neurosurgical patients when compared to surgical and medical patients (8% vs. 3%) [28]. Another study has reported similar findings [29].

Risk Factors Associated With MRSA HAP

Prior Antibiotic Therapy: Prior antibiotic exposure is the major predisposing factor for nosocomial MRSA pneumonia [7]. Based upon a large retrospective cohort, a study investigated clinical and epidemiological characteristics of mechanically ventilated patients with MRSA pneumonia. All the patients with MRSA pneumonia had previously received at least one antibiotic and 75.6% had previously received two or more antibiotics, whereas only 25.5% with MSSA pneumonia had previously received at least one antibiotic and only 12.7% two or more [18]. Antibiotic class may also play a role. However, studies specifically focusing on this issue are needed.

Prolonged Mechanical Ventilation: Prolonged mechanical ventilation is an independent risk factor for MRSA pneumonia [30−32]. Typically MRSA develops after five days of MV. A retrospective cohort study which investigated epidemiology, treatment and outcomes of nosocomial bacteraemic *S. aureus* pneumonia reported that 70% of *S. aureus* was MRSA, that 29% of the patients with *S. aureus* bacteraemia had staphylococcal pneumonia and that the median length of stay on MV prior to the diagnosis of pneumonia was three days for MSSA and nine days for MRSA [33].

Colonization: *Staphylococcus* is mainly found on the skin, the axillae, the perineal area and the anterior nares. In the past colonization was mainly by MSSA, but recently community-acquired MRSA colonization has increased significantly and still increases. The incidence of MRSA infections, especially in ICU patients, is growing at an alarming rate, with an associated increase in morbidity and mortality and the cost of care [34]. Colonization by MRSA may be transient or persistent, at single or multiple body sites. Furthermore, patients may be colonized by multiple strains, although one strain is always predominant [35]. Different strains have different abilities to colonize, invade and infect specific sites [35]. MRSA colonizes transiently up to 30−70% of healthy adults [36], and the persistent carriage rate is 11−32% among healthy adults and 25% among hospital personnel. Rates of colonization are high among patients with Type-1 diabetes, intravenous drug users, patients undergoing dialysis, surgical

patients, individuals with dermatological diseases and chronically ill patients with long-term indwelling catheters and patients with acquired immune deficiency syndrome [37]. It seems that nasal carriage is more important than skin colonization for the development of invasive diseases [6].

Older age: Based upon the data from the National Hospital Discharge Survey (NHDS), it can be estimated that the incidence of MRSA pneumonia and MRSA bacteremia both gradually increase with age and peaks in the geriatric population. In the United States, from 1990 to 2000 there were 29 823 patients hospitalised with MRSA pneumonia, of which 24 276 (81 %) were $\geq$65 years old. In this descriptive study it was also reported that the methicillin resistance rate gradually increases with age. The proportion of methicillin-resistant isolates from lower respiratory cultures was 19 % in the $\leq$14 age group and 59 % in $\geq$65 age group [20].

Prevention

Prevention is achieved with: the optimised use of antibiotics and a decrease in horizontal transmission of MRSA between patients. Evidence based antimicrobial treatment guidelines, a restrictive policy for certain antibiotics and the rotation of antibiotics over time may lead to the prevention of colonization/infection with MRSA [34]. The effort to decrease horizontal transmission of MRSA focuses on routine surveillance cultures to identify and isolate patients colonized/infected with MRSA, on handwashing guidelines for staff/visitors (with alcoholic handrub solution), and on the prevention of environmental cross-contamination [38, 39].

The most useful cultures for detecting cases of MRSA seem to be from wound, tracheostomy site and sputum from intubated patients. Rectal or perineal colonization has been suggested as an important, and perhaps more difficult to eradicate, reservoir of MRSA.

The transmission rate from patients in contact isolation is significantly lower than in patients not in isolation [40]. Contact precautions recommended by the Centers for Disease Control and Prevention for hospitalised patients with MRSA include the use of a private room, wearing gloves on entering the room, wearing a gown if contact with the patient or items in the room is anticipated, and hand washing on removal of the gloves. For patients with MRSA pneumonia contact precautions should be combined with droplet precautions. Despite these guidelines, nosocomial MRSA has been increasing in frequency [41]. It is not clear if these guidelines are effective in controlling MRSA and well-designed, randomised controlled studies are needed [42, 43]. Moreover, adherence to the guidelines has been suboptimal, and hand washing, in particular, inadequate.

To eradicate MRSA in colonized individuals, topical application of mupirocin into the nares or systemic use of co-trimoxazole has been used. This strategy was associated with different success rates and with resistance development and is not recommended as a general measure [40]. However, given the increased morbidity and mortality from MRSA infections, it is indicated in selected patients, including

individuals with recurrent skin abscesses despite appropriate antimicrobial treatment and their contacts with positive nasal cultures.

On the other hand, not only did selective decontamination of the digestive tract not reduce the overall incidence of ICU acquired pneumonia, but it also increased oropharyngeal colonization with staphylococci [40, 44]. Attempts to combine topical mupirocin with antibacterial baths (e.g. in chlorhexidine, povidone–iodine or systemic agents) deserve further study. Lysostaphin, a glycylglycine endopeptidase that specifically cleaves the cross-linking pentaglycine bridges in the cell walls of staphylococci, has also been used to eradicate MRSA colonization in animal models with promising results (lysostaphin cream locally applied to the nares) [45].

Pathogenesis, Pathophysiology and Mechanisms of Resistance

For microorganisms to cause pneumonia, they must first gain access to the normally sterile lower respiratory tract, where they can adhere to the mucosa and produce sustained infection [3]. Microorganisms gain access by one of the following mechanisms: (i) by aspiration or leaking around the endotracheal tube cuff of microbe-laden secretions, either from the oropharynx directly or, secondarily, by reflux from the stomach into the oropharynx and then into the lower respiratory tract; (ii) by direct extension of a contiguous infection; (iii) through inhalation of contaminated air or medical aerosols; or (iv) by haematogenous carriage of microorganisms to the lung from remote sites of local infection, such as infected vascular or urinary catheters or right-sided endocarditis [46, 47]. Of these mechanisms, the most important one for the development of MRSA VAP is the aspiration of colonized oropharyngeal secretions. Intubation is one of the factors known to facilitate microaspiration [48]. Pneumonia occurs depending on the inoculum and the host defences. The stomach and/or the intestine may play a secondary role as a reservoir of nosocomial organisms; however, the digestive tract does not appear to be the initial site of colonization in most cases [47]. Endotracheal tube biofilm may contribute to sustaining colonization, creating an increased risk of infection, but further studies are needed to determine its exact role in facilitating and sustaining infection [46]. (More details about the pathophysiology of HAP are given in Chapter 4).

There are two basic mechanisms responsible for the resistance of *S. aureus* to β-lactams: antimicrobial agents: Production of β-lactamase, a serine protease that destroys the β-lactam ring; and an alteration in membrane-bound enzymes called penicillin-binding proteins (PBPs). *S. aureus* with *mec A* gene produce modified low-affinity PBPs which are primarily responsible for resistance to antistaphylococcal penicillins, the so-called 'methicillin resistance'. Resistance to methicillin confers resistance to all penicillinase-resistant penicillins and cephalosporins [8]. All strains of MRSA produce a unique PBP (PBP2a) that confers resistance ranging from a few cells (heterogeneous resistance) to a majority of cells of a population (homogeneous resistance) [49]. The *fem* (factor essential for methicillin resistance) and *aux* (auxiliary) factors are required for full phenotypic expression of methicillin resistance

[50, 51]. The *vanA* gene, encoded by a transposon, has been identified as playing a major role in vancomycin resistance. Although vancomycin intermediate *S. aureus* (VISA) has been isolated from clinical samples, to date none was responsible for pneumonia. Moreover, all of them have been susceptible to linezolid [52].

The relative virulence of MRSA when compared with MSSA remains to be elucidated. Although a plethora of studies have demonstrated the virulence of MRSA, it has been suggested that many strains are neither highly contagious nor possess virulence determinants [34]. However, several *in vitro* studies have failed to show that increasing antibiotic resistance is associated with decreasing virulence. MRSA strains did not differ from MSSA strains in intraleukocyte survival or phagocytic destruction, animal lethality studies or the production of intracellular haemolysins, enzymes or toxins. On the other hand, it has been shown that persistent MRSA nasal carriage in patients in long-term care facilities was significantly more likely to result in serious staphylococcal infection than MSSA carriage, but this association may have been due to underlying host factors rather than to differences in the virulence of the organisms [49].

Clinical Features, Course and Prognosis

Pneumonia caused by *S. aureus* does not have distinctive clinical features that differentiate it from other types of nosocomial pneumonia. The common presentation of the disease is with cough, fever and purulent sputum. Nevertheless, patients with MRSA infection tend to present with more severe disease and the percentage of patients developing acute respiratory distress syndrome is significantly higher for patients with MRSA infection [19]. Chest radiographs in nonembolic nosocomial setting staphylococcal pneumonia show a bronchopneumonic pattern. Lobar consolidation is relatively rare, multilobar involvement is frequent (50%) and cavitation, contrary to popular opinion, is also a relatively unusual complication (2%). Empyema was once reported as a complication in 8–30% of cases but is now less frequent [53]. Patients under appropriate therapy who do not show improvement need to be evaluated with Computed Tomography of the chest for pulmonary abscess or empyema. If empyema is diagnosed, chest tube drainage is required [34].

Early onset pneumonia is frequent in head trauma patients and, as has been already mentioned, the majority is caused by MSSA. A prospective observational study that was undertaken to assess the consequences of early onset pneumonia in neuro-trauma patients confirmed *S. aureus* as the leading cause of early onset VAP and showed that patients with early onset pneumonia had a worse PaO_2/FiO_2 ratio, more fever, more arterial hypotension and more intracranial hypertension, factors known to worsen the neurological prognosis and that may lead to secondary neurological injuries [25].

MRSA is the second leading cause of death in patients with VAP. The question of whether MRSA pneumonia is related to a more immediate deterioration or a more severe outcome is under debate. According to the underlying pathology, excess mortality caused MRSA pneumonia ranges between 14 and 47% and is significantly lower among patients receiving appropriate initial antibiotic treatment

compared with patients requiring a change in treatment [54]. Patients with MRSA infections may have a median hospital LOS 4.5 days longer than matched control patients with MSSA infection, as a result of complications related to MRSA infection [55]. A study designed for control of endemic MRSA has reported a four-day increase in overall LOS. Increase in ICU LOS was even higher at 8.5 days in survivors, but lower than previous reports. Another study demonstrated that MRSA VAP treated with early appropriate initial antibiotic therapy is not significantly associated with infection recurrence, super-infection or 28-day mortality compared with MSSA VAP [19]. Regarding co-colonization and co-infection, it was reported that co-colonization/infection with vancomycin-resistant *Enterococcus* (VRE) and MRSA was common among medical patients requiring intensive care, occurring in 9.5 % of the admissions [56]. Increasing age, hospitalisation during the preceding six months and admission to a long-term care facility were independently associated with co-colonization or co-infection with VRE and MRSA [56]. (For the diagnosis of HAP see Chapter 4.)

Treatment

In choosing the correct antibiotic regimen for HAP, not only should the susceptibilities (appropriate therapy) be taken into account, but so too should the pharmacokinetic and pharmacodynamic properties of the antibiotics (adequate therapy). The efficacy of an antibiotic against a susceptible pathogen depends on both the concentrations that can be achieved and maintained in the blood and at the infection site (pharmacokinetics [PK]) and its antimicrobial activity at that concentration−time profile against a given pathogen (pharmacodynamics [PD]) [57, 58]. The dose and the dose interval depend on the PK/PD properties of the antibiotics. Details on PK/PD for pneumonia can be found in Chapter 12. Considering all these factors when deciding the concordant antibiotic regimen, may substantially improve outcome [59].

For MSSA HAP the best antibiotic choice is a beta-lactam. In intubated patients with pneumonia caused by MSSA treated with cloxacillin, a mortality rate of 2.6 % was reported compared with 54.5 % mortality in VAP due to MRSA treated by intermittent administration of vancomycin with serum level monitoring [7]. In another study of patients with bacteremic pneumonia caused by *S. aureus* the infection-associated mortality among patients with MSSA pneumonia was significantly greater for those treated with vancomycin than for those treated with cloxacillin [47 % vs 0 %; $p < 0.01$], vancomycin treatment was independently associated with mortality from the infection and the risk of death was 14 times greater (OR, 14.5) for vancomycin treated patients than for those who had received other treatments [60].

In this chapter the focus is on the treatment of MRSA HAP, which is more complicated due to the limited availability of antibiotics with proven *in vivo* activity. Many antibiotics have *in vitro* activity against MRSA but *in vivo* work suboptimally [34]. The available agents that are active against MRSA include the glycopeptides vancomycin and teicoplanin, linezolid, the first oxazolidinone in clinical use, the streptogramines quinupristin/dalfopristin, daptomycin, which is the first lipopeptide in clinical use,

and tigecycline, a recently approved newer broad-spectrum intravenous tetracycline. However, not all are effective in MRSA HAP. Agents currently in clinical development include ceftobiprole and ceftaroline, which are broad-spectrum cephalosporins, dalbavancin, oritavancin and telavancin, which are newer semi-synthetic glycopeptides, iclaprim, which is a diaminopyrimidine, and newer quinolones [61].

Currently Available Anti-MRSA Agents

Vancomycin: Vancomycin is a glycopeptide that exerts (mostly) bactericidal action by inhibiting bacterial cell wall synthesis. It is active against Gram-positive pathogens, such as *S. aureus* (MRSA included), *S. epidermidis,* Streptococcus, Enterococcus and Gram-positive anaerobes. However, vancomycin-resistant *enterococcus* (VRE) and VISA/VRSA [Vancomycin Intermediate Minimal Inhibitory Concentration (MIC): 8−16 μg/mL or Vancomycin Resistant MIC: 32−1024 μg/mL or more] have emerged. 10−55 % of the substance is protein-bound in serum and the drug is eliminated by glomerular filtration (dose adjustment is needed in renal insufficiency). Vancomycin is only available as intravenous (iv) formulation; the label adult dose is 15 mg/kg every 12 hours iv. Side effects associated with vancomycin include the 'Red man syndrome', which may be avoided by infusing vancomycin for at least 60 minutes, ototoxicity (when elevated peak levels) and nephrotoxity. Nephrotoxicity is not so common if vancomycin is used alone, but it potentiates aminoglycoside nephrotoxicity when the two drugs are used in combination [34].

The usual 1g dose of vancomycin results in serum levels above 20 μg/mL, while the common sensitivity of MRSA to vancomycin is 2−5 μg/ml. However, a significant percentage of patients will have a peak level less than 20 with the standard one gramme dose. In addition, a few MRSA microorganisms have a minimal bactericidal concentration that is eight times higher than the MIC. Vancomycin has a half-life of approximately six hours but no post-antibiotic effect (PAE). Therefore, the usual dosing interval (every 12 hours or longer) results in a prolonged period without bacterial killing or even inhibition [62]. Continuous infusion of vancomycin should be preferred for the treatment of MRSA pneumonia, because this agent exhibits time-dependent bactericidal activity [63−65]. It has been demonstrated that for vancomycin the ratio of Area Under the Curve (AUC) to MIC best predicts success of treatment [66], and that AUC/MIC values for vancomycin predict time-related clinical and bacteriological outcomes in patients with MRSA pneumonia [67]. Maintaining constant concentrations in serum of four to five times the MIC may be the ideal way to deliver this antibiotic for severe infections [68].

Although vancomycin has been the standard therapy for blood stream infections due to MRSA for many years, several studies have demonstrated its poor effectiveness in HAP/VAP caused by *S. aureus* [18, 33, 60, 69]. It has several pharmacokinetic properties that may adversely affect its ability to effectively treat MRSA pneumonia, mainly poor penetration into the alveolar space. The ratio between pulmonary epithelial lining fluid (ELF) levels and serum levels is approximately 0.09−0.19 [70]. It was proposed by many physicians that high serum levels (of >20 μg/mL) should be maintained to ensure adequate therapeutic ELF concentrations [71].

Linezolid: Linezolid is the first of a new class of antibiotics, the oxazolidinones, and acts by inhibiting protein synthesis at 70 S ribosomal initiation complex. It is active against a broad spectrum of Gram-positive bacteria (MRSA, MSSA, VRE and penicillin resistant *S. pneumoniae*). Its intravenous and oral formulations have the same pharmacokinetic profile. The usual adult dose is 600 mg (iv or p.o.) every 12 hours. Peak plasma levels are achieved 1−2 hours after administration. Linezolid is a time-dependent drug with a post-antibiotic effect. It has an ELF:Plasma ratio of ~3.2, ELF ~31 μg/mL at eight hours and mean ELF >4 μg/mL at 24 hours [72]. No dose adjustment is recommended for renal or hepatic insufficiency. However, linezolid metabolites may accumulate; dialysis removes linezolid and its metabolites. Bone marrow suppression (transient/reversible), especially thrombocytopenia, is limited to patients on linezolid for longer than two weeks and discontinuation of the drug should be considered.

Caution is recommended with regard to monoamino oxidase (MAO) inhibitory effect of Linezolid. Linezolid resistant *S. aureus* has emerged, but it is currently rare [73]. The American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recommend the use of linezolid as the initial therapy in MRSA HAP/VAP (Type II evidence) [3]. A study that analysed data from two previous double-blind studies of patients with suspected Gram-positive VAP showed that clinical cure rates assessed 12−28 days after the end of therapy significantly favoured linezolid in the Gram-positive and MRSA subsets compared to vancomycin. Linezolid was an independent predictor of clinical cure with an OR of 1.8 for all patients, 2.4 for Gram-positive VAP, and 20.0 for MRSA VAP and Kaplan−Meier survival rates favoured linezolid in the MRSA subset [74]. Patients with renal failure or with prior exposure to vancomycin have additional benefits with linezolid's administration. Another retrospective study that analysed the efficacy of linezolid vs vancomycin in the treatment of patients with MRSA HAP reported that survival rates for the linezolid group were 80.0 % vs 63.5 % for the vancomycin group ($p = 0.03$) and clinical cure rates 59.0 % vs 35.5 % respectively ($p < 0.01$) [69].

It should also be highlighted that the expression of virulence factors of *S. aureus* are especially sensitive to the inhibition of protein synthesis by linezolid, even in subinhibitory concentrations, which is considered an advantage in the treatment of infections with toxin-producing *S. aureus* [75]. Further studies are needed to elucidate the immunomodulatory mechanisms of linezolid and of other protein synthesis inhibitors in order to optimize antimicrobial treatment [76]. Regarding the cost of care, a study that compared the cost-effectiveness of linezolid and vancomycin in the treatment of patients with MRSA HAP demonstrated that the higher acquisition cost of linezolid was almost completely offset by improved survival and a reduction in healthcare costs associated with improved survival (Table 7.2) [77].

Teicoplanin: Teicoplanin is a glycopeptide, with a longer elimination half life (40−70 hours) and a slower release from tissues than vancomycin. It is administered once a day at 6−10 mg/kg. There are no published data about its lung concentrations. It is suboptimal for acute infections and even with double loading dose the steady-state concentrations above MIC for MRSA can be achieved only after

Table 7.2 Comparison of linezolid vs vancomycin for MRSA HAP

- Linezolid reported to have significantly better clinical cure (59.0 % vs 35.5 %) and survival rates (80.0 % vs 63.5 %) compared to vancomycin in MRSA HAP.
- A pooled analysis of five randomized studies comparing the outcomes of patients with secondary *S. aureus* bacteraemia treated with linezolid with the outcomes of vancomycin-treated patients, demonstrated that linezolid was associated with outcomes that were not inferior to those of vancomycin.
- The expression of virulence factors of *S. aureus* and GAS is especially sensitive to the inhibition of protein synthesis by linezolid, even in sub-inhibitory concentrations, a characteristic that may give an advantage to linezolid in the treatment of infections with toxin-producing Gram-positive bacteria.
- Regarding the cost of care, linezolid has been reported almost cost-neutral compared with vancomycin in the treatment of MRSA HAP.

four days of treatment [78]. It is used in many countries, including European but is not approved by the US Food and Drug Administration (FDA).

Quinupristin/dalfopristin: Quinupristin/dalfopristin (30:70) is a synergistic drug derived from macrolactones that acts by inhibiting protein synthesis. It was reported that patients with MRSA pneumonia treated with quinupristin/dalfopristin had clinical cure rates of only 19.4 % compared to 40.0 % when treated with vancomycin [79].

Tigecycline: Tigecycline is a broad-spectrum glycylcycline (a novel drug of the tetracycline family) with activity against a broad range of Gram-positive, Gram-negative, atypical, anaerobic and antibiotic-resistant bacteria [80]. Potent action against MRSA, VRE and penicillin-resistant *Streptococcus pneumoniae* is included. Whilst exhibiting antibacterial activities typical of earlier tetracyclines, it has more potent activity against tetracycline resistant organisms. Tigecycline is available as a parenteral agent only, exhibits linear pharmacokinetics, has a long terminal half-life and is extensively distributed into the tissues.

The pharmacokinetics of tigecycline appear unaffected by age, renal disease and food [81]. It is administered twice daily, although its long half-life and post-antibiotic effect make once daily dosing possible, appears to have good tissue penetration (e.g. skin) and does not require adjustment in the presence of renal or hepatic diseases [80]. It is efficacious in complicated skin and skin structure infections (cSSSIs) and in complicated intra-abdominal infections (cIAIs). In a randomized comparison study, clinical cure rates were 67 and 74 % in patients with cSSSIs who received 25 mg and 50 mg daily, respectively [82]. Clinical trials have shown that tigecycline (a loading dose of 100 mg and then 50 mg iv every 12 hours) in adults is safe and generally well tolerated for up to 11.5 days despite the increased frequency of mild to moderate nausea and vomiting (of limited duration) [81]. It has recently been approved by the FDA for cIAIs and cSSSIs. Randomized controlled trials on pneumonia continue [83].

Daptomycin: Although it has a good *in vitro* activity for *S. aureus,* it is not recommended in pneumonia due to inactivation by pulmonary surfactant [84].

Future Therapeutic Options for S. aureus HAP

Ceftobiprole: Ceftobiprole medocaril [BAL 5788] is the water-soluble prodrug of the pyrrolidinone cephalosporin ceftobiprole [BAL 9141] [85]. It has excellent activity against MRSA (with MICs at which 50 and 90% of the isolates tested are inhibited in the range of 2−4 μg/mL) [83, 86, 87].Its activity against MRSA is due to potent inhibition of PBP2a and stability with respect to beta-lactamase hydrolysis [85].Also, it has a broad spectrum of activity against Gram-positive and Gram-negative bacteria such as *Streptococcus* spp., *Haemophilus influenzae, Moraxella catarrhalis, Neisseria* spp., *Enterobacteriaceae* and anaerobes, but only modest activity against non-fermentative Gram-negative species and extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* or *Klebsiella pneumoniae* [88].It has not shown resistance development *in vitro* or in stringent animal models.

Ceftobiprole has completed Phase III clinical trials for cSSSIs, resulting in >90% clinical cure rates for infections caused by MRSA and has demonstrated non-inferiority compared to vancomycin. In the trials, it was well tolerated with only mild adverse events (including nausea, taste disturbance, diarrhoea and vomiting). In May 2007 a New Drug Application (NDA) was submitted to the FDA for the treatment of cSSSIs [89]. Also, Phase III trials in patients with HAP (including VAP) and hospitalised patients with CAP are underway with anticipated completion in the second half of 2007 [89].

Iclaprim: Iclaprim is a newer selective dihydrofolate reductase (DHFR) inhibitor (diaminopyrimidine), which shows marked differences in activity when compared with older ones (e.g. trimethoprim [TMP]) [90]. Iclaprim, like TMP, specifically and selectively inhibits dihydrofolate reductase of the microorganisms at submicromolar concentrations with little or no inhibition of the human enzyme even at over five orders of magnitude higher concentrations. It is a broad-spectrum antibiotic (for Gram-positive and Gram-negative pathogens), exhibiting potent activity even against Gram-positive pathogens resistant not only to TMP, but also to methicillin (MRSA), macrolides, quinolones and glycopeptides. It is rapidly bactericidal against Gram-positive pathogens at concentrations close to their MICs and exhibits a significant PAE of up to several hours. Moreover, it shows important *in vitro* synergy with sulfonamides but, based on its potent bactericidal activity, it is currently in development as monotherapy. In addition to the *in vitro* activity of iclaprim, it has also been documented as efficacious in animal models with septicaemia, peritonitis and pneumonia [91].

It was reported that iclaprim [0.8 mg/kg bid) in cSSSIs exhibited similar cure rates with vancomycin (92.9%), but the eradication rates of Gram-positives were higher than vancomycin (90% vs 70%) [92]. A Phase I clinical study reported that iclaprim has good lung penetration, having ELF and alveolar macrophage concentrations 20 and 40 times higher than plasma levels respectively [93]. These data suggest that iclaprim could be efficacious for Gram-positive pneumonia, for example for staphylococcal pneumonia. Iclaprim is well tolerated with no significant adverse effects. It is currently in Phase III clinical development and was recently granted fast track status by FDA as iv therapy for cSSSIs. Oral preparation of iclaprim is

currently in Phase I clinical trial. Iclaprim could, in the future, offer the advantage of switching from intravenous to oral therapy [91].

Dalbavancin: Dalbavancin is a newer semisynthetic glycopeptide (lipoglycopeptide) that exerts action by binding to the peptidoglycan precursors, thus blocking enzymes involved in the final stages of peptidoglycan synthesis and bacterial cell wall formation. It is bactericidal with activity against Gram-positive pathogens including MRSA and VRE. Peak concentrations of dalbavancin occur immediately following infusion and increase in proportion to the dose given. After infusion, there is a rapid decline in plasma concentrations due to distribution of the drug into the body's tissues and fluids; the initial rapid decline in plasma concentration is followed by a slower terminal, log-linear elimination phase, in which dalbavancin exhibits an elimination half-life ranging from 9−12 days. Due to the long elimination half-life of dalbavancin, once-weekly dosing may be an option. A total of two doses given one week apart for SSSIs resulted in a 94 % cure rate, compared with 76.2 % cure rate in those randomised to receive the standard care [94]. A Phase III non-inferiority study reported that two doses of dalbavancin (1 g given on Day 1 followed by 0.5 g given on Day 8) were as well tolerated and as effective for the treatment of patients with cSSSIs, including those infected by MRSA, as linezolid given twice daily for 14 days [95]. Current data suggest that dalbavancin is well tolerated by patients, with most adverse events being described as mild. It is currently in Phase III trials and it is under review by the FDA for use in cSSTIs (Fast Track designation).

Oritavancin: Oritavancin is a newer semisynthetic glycopeptide (lipoglycopeptide), with long plasma half-life (151±39 hours). It exerts potent action against Gram-positive pathogens and has the advantage that it is insensitive to widespread glycopeptide resistance mechanisms in staphylococci and enterococci that undermine the utility of vancomycin. Preclinical pharmacodynamic studies have shown oritavancin to possess concentration-dependent bactericidal activity, a prolonged PAE, synergy with both beta-lactams and aminoglycosides and good lung penetration. As the pharmacokinetics and pharmacodynamics of oritavancin appear to be favourable, once-daily dosing is likely [96]. Two large multicenter Phase III clinical trials with oritavancin have been completed and demonstrated the drug to be safe and effective in treating cSSSIs. Clinical studies and NDA are planned for additional indications, including catheter-related bacteremia and nosocomial pneumonia [97].

Telavancin: Telavancin is a newer semisynthetic glycopeptide (lipoglycoptide), rapidly bactericidal for Gram-positive pathogens, including MRSA, with a plasma half-life of ≅ 7 hours [98]. Telavancin has multiple actions that inhibit the formation of the bacterial cell wall and disrupt bacterial cell membrane integrity. In a murine model of pneumonia that compared the efficacy of telavancin to that of vancomycin and linezolid against MRSA, telavancin produced a greater reduction in lung bacterial titer and mortality than vancomycin and linezolid, suggesting a potential use of telavancin for treating MRSA pneumonia [99]. Furthermore, in an immunocompromised murine model of bacteremia that compared the efficacy of telavancin with the efficacy of vancomycin against MRSA it was demonstrated that the *in vivo* bactericidal activity of telavancin was superior to that of vancomycin against a single strain of

MRSA and resulted in successful infection resolution and, consequently, improved survival [100]. Currently, it is in Phase III trials for cSSSIs and pneumonia [101].

In conclusion, the optimal treatment for MRSA pneumonia is not easily achieved, because of the limited number of antibiotics that combine potent anti-MRSA activity and favourable pharmacokinetics/pharmacodynamics that permit adequate concentrations in the lungs. Efforts in the future should focus in developing alternative agents to glycopeptides, rather than investigating the best dosing scheme for glycopeptides [59]. (Tables 7.3 and 7.4).

Table 7.3 Newer antibiotics for the management of MRSA

ANTIBIOTIC	
Linezolid (Zyvox)	• Belongs to a new class of antibiotics, the oxazolidinones • Bacteriostatic agent • Acts at 70 S ribosomal initiation complex • Active against a broad spectrum of Gram-positive bacteria (MRSA, MSSA, VRE and penicillin resistant *S. pneumoniae*) • Intravenously and orally available • Oral bioavailability 100 % • Peak plasma level is achieved within 1–2 hours after administration • Post-antibiotic effect • Good lung penetration: ELF: Plasma ratio ~ 3.2, ELF ~ 31 μg/L at 8 hours and mean ELF > 4 μg/L at 24 hours • No dose adjustment is recommended for renal or hepatic insufficiency • Linezolid metabolites may accumulate; dialysis removes linezolid and its metabolites • Adults dose: 600 mg every 12 hours (iv or p.o.) • Side-effects: Bone marrow suppression (transient/reversible), especially thrombocytopenia limited to patients on linezolid for > 2 weeks • Interactions: Caution is recommended with regard to linezolid's MAO inhibitory effect
Quinupristin/ dalfopristin (Synercid)	• Streptogramin derivative • Bactericidal (bacteriostatic if monotherapy) • Inhibition of protein synthesis • Spectrum: broad range of gram-positive bacteria, including MRSA, VREF (poor activity against *E. faecalis*), *Streptococcus pneumoniae* (including multidrug resistant), *Clostridium perfringens* and *Peptostreptococcus* spp, and against selected Gram-negative respiratory tract pathogens including *Moraxella catarrhalis, Legioniella pneumophila* and *Mycoplasma pneumoniae* • Adults dose: 7.5 mg/kg iv every 8 hours • Side effects: mainly painful myalgias and thrombocytopenia • **MRSA pneumonia treated with quinupristin/dalfopristin had clinical cure rates of only 19.4 % compared to 40.0 % for vancomycin**
Tigecycline (Tygacil)	• Glycylcycline (tetracycline derivative); the first in the glycylcycline class to undergo clinical development • Bacteriostatic *in vitro*

	• Not affected by either specific efflux pump or ribosomal protection mechanisms of resistance: active against bacterial pathogens that have acquired mechanisms of resistance to older congeners (tetracycline, minocycline and doxycycline) • Spectrum: active against a broad range of Gram-positive, Gram-negative, atypical and anaerobic bacteria, including: **MRSA**, VRE and resistant *S.pneumoniae*; active *in vitro* against imipenem-resistant *Acinetobacter baumannii* and ESBL-producing *Enterobacteraceae*; modest activity ($MIC_{90} \geq 8$ mg/L) against *P. aeruginosa* • **MIC_{90} for MRSA significantly lower than vancomycin, linezolid and quinapristin/dalfopristin** • Only iv formulation; a loading dose of 100 mg and then 50 mg/12 hours • Long half-life; PAE; Good tissue penetration (e.g. skin) • No adjustment for renal or hepatic dysfunction • Well tolerated (only increased frequency of nausea/ vomiting) • FDA approved (2005) for complicated intra-abdominal (cIAIs) and complicated skin/skin-structures infections (cSSSIs)
Daptomycin (Cubicin)	• Cyclic lipopeptide • Concentration dependent bactericidal activity; binds to the bacterial cell membrane • Spectrum: active against Gram-positive cocci including **MSSA**, **MRSA** and **VRSA** • Adult dose: 4 kg iv every 24 hours • Renal excretion • Generally well tolerated; dose-dependent myopathy – CPK should be monitored • FDA approved for skin and soft tissue infections (cSSSIs) • Ongoing phase III trials with 6 mg/kg/day for bacteremia and endocarditis • Limited penetration to bones/CNS • Limited penetration to ELF – Inhibited by pulmonary surfactant • **FAILED in a trial involving patients with community-acquired pneumonia**

ELF: (pulmonary) epithelial lining fluid, VISA: vancomycin intermediate S. aureus, MRSA: methicillin-resistant Staphylococcus aureus, VRSA: vancomycin resistant S. aureus, VREF: vancomycin-resistant Enterococcus faecium, cSSSIs: complicated skin and skin structures infections, PAE: post-antibiotic effect, VAP: ventilator-associated pneumonia, HAP: hospital-acquired pneumonia, CAP: community-acquired pneumonia

Table 7.4 Investigational antibiotics for the management of MRSA

ANTIBIOTIC	
Ceftobiprole medocaril (BAL5788)	• New parenteral cephalosporin (pyrrolidinone-3-ylidenemethyl cephalosporin) • Ceftobiprole medocaril is the water-soluble prodrug of the pyrrolidinone cephalosporin, ceftobiprole [BAL 9141]; readily converted to ceftobiprole • Bactericidal; has not shown resistance development in vitro or in stringent animal models

Table 7.4 (Continued)

ANTIBIOTIC	
	• Spectrum: broad-spectrum; **excellent activity against MRSA** (beta-lactamase stable, with high affinity for PBP_{2a})-MICs at which 50 % and 90 % of MRSA isolates tested are inhibited in the range of 2 to 4 μg/L; notable activity against *Streptococcus* spp., *Haemophilus influenzae, Moraxella catarrhalis, Neisseria* spp., *Enterobacteriaceae*, nonfermentative gram-negative bacilli, anaerobes; modest activity against nonfermentative Gram-negative species and ESBL-producing *Escherichia coli* or *Klebsiella pneumoniae* • For IV administration • Phase III trails for cSSSIs due to MRSA completed (NDA submitted); Ongoing phase III trials of **HAP** (including VAP) and hospitalized **CAP** due to suspected or proven MRSA; fast-track status by the FDA for these two indications.
CB-181963 (CAB-175)	• Novel investigational cephalosporins (azomethine subgroup) • May have a role in the treatment of staphylococcal infections, including those caused by MRSA and in the prophylaxis of biofilm-associated MSSA and MRSA infections • Short PAE, may have to be administered more frequently than other beta-lactam antibiotics, or given via prolonged infusion
Ceftaroline (PPI-0903M)	• The water-soluble prodrug form of the bactericidal compound PPI-0903M • High affinity for penicillin-binding protein (PBP) • IV administration • Active against both gram-positive and gram-negative bacteria; excellent **anti-MRSA** activity; • Phase II clinical trial of ceftaroline for the treatment of cSSSI reported clinical cure rate was 96.8 % for subjects treated with ceftaroline and 88.9 % for those treated with standard therapy of vancomycin. • Two phase III trials of ceftaroline in cSSSIs initiated in early 2007 • Fast tract designation by FDA
Dalbavancin	• Lipoglycopeptide (semisynthetic glycopeptide) • Plasma half-life 9–12 days; highly protein bound (>90 %) • Spectrum: activity against a variety of Gram-positive pathogens; against **MSSA** and **MRSA** it has demonstrated favorable MICs compared with those of currently available agents • A total of two doses given 1 week apart (1 g iv Day 1 and 0.5 g iv on Day 8) • Clinical success and safety have been shown in Phase II and III trials for cSSSIs and a phase II trial for catheter-related bloodstream infections; in these trials comparable results with vancomycin, linezolid and various beta-lactams • In clinical trials – Under review by FDA for use in cSSTIs (Fast Track designation)
Telavancin	• Lipoglycopeptide (semisynthetic glycopeptide) • Concentration-dependent, rapid bactericidal activity • Plasma half-life 7 hours • Spectrum: highly active against Gram-positive bacteria, including **MRSA**, **VISA**, **VRSA**

	• In phase III clinical trials – Under review by FDA for use in HAP and in cSSSIs (Fast Track designation)
Everninomycin	• Oligosaccharide • Good **anti-MRSA** activity • Its clinical application hampered by toxicity
Iclaprim	• New selective bacterial dihydrofolate reductase inhibitor (diaminopyrimidine) • Potent activity against Gram-positive and Gram-negative clinical isolates. • Rapidly bactericidal against Gram-positive: **active against methicillin, TMP and vancomycin resistant *S. aureus*** • Important *in vitro* synergy with sulfonamides but, based on its potent bactericidal activity, it is currently in development as monotherapy • Significant PAE • **Good lung penetration**: ELF and alveolar macrophage concentration 20 and 40 times respectively higher than plasma (Phase I clinical trial) • Well tolerated, no significant adverse effects. • In Phase III clinical trials for intravenous use in cSSSIs – Under revision by FDA • Oral formulation in Phase I clinical trials
DX 619	• des-fluoro[6] quinolone; in Phase I clinical trials • **Particularly potent against staphylococci**, including ciprofloxacin and methicillin-resistant strains; MIC_{90}: 0.5 μg/mL. Also active against Gram-negative bacteria • Intracellular concentration in human polymorphonuclear leukocytes 10 times higher than the extracellular; intracellular activity against *S. aureus* • Its potency was emhasided by the results of a study that compared the effectiveness of DX-619 and vancomycin in murine model with haematogenous lung infection caused by MRSA and VISA
WCK 771	• The arginine salt of S-(-)-nadifloxacin; in Phase II clinical trails • Several studies demonstrated effectiveness (oral and parenteral administration) for the treatment of diverse staphylococcal infections in mice, including those caused by quinolone resistant strains, **MRSA** and **VISA**
Lysostaphin	• A glycylglycine endopeptidase (antibacterial enzyme) • Specifically cleaves the cross-linking pentaglycine bridges in the cell walls of Staphylococcus • Extremely staphylocidal; MIC_{90}: 0.001-0.064 μg/mL; rapidly lyses both actively growing and quiescent *S. aureus;* **MRSA** and **VISA** included • Effectiveness in vitro and in various animal models • Effective for nasal carriage eradication in mouse models • Disrupts staphylococcal biofilm formation in artificial surfaces

ELF: (pulmonary) epithelial lining fluid, VISA: vancomycin intermediate S. aureus, MRSA: methicillin-resistant Staphylococcus aureus, VRSA: vancomycin-resistant S. aureus, VREF: vancomycin-resistant Enterococcus faecium, cSSSIs: complicated skin and skin structures infections, PAE: post-antibiotic effect, VAP: ventilator-associated pneumonia, HAP: hospital-acquired pneumonia, CAP: community-acquired pneumonia

References

1. Richards, M.J., Edwards, J.R., Culver, D.H. and Gaynes, R.P. (1999) Nosocomial infections in medical intensive care units in the United States. National nosocomial infections surveillance system. *Critical Care Medicine*, **27**, 887–92.
2. National Nosocomial Infections Surveillance (NNIS). (2000) System report, data summary from January 1992–April 2000, issued June 2000. *American Journal of Infection Control*, **28**, 429–48.
3. American Thoracic Society/Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **171**, 388–416.
4. Schramm, G.E., Johnson, J.A., Doherty, J.A. *et al*. (2006) Methicillin-resistant *Staphylococcus aureus* sterile-site infection: The importance of appropriate initial antimicrobial treatment. *Critical Care Medicine*, **34**, 2069–74.
5. Taylor, G.D., Buchanan-Chell, M., Kirkland, T. *et al*. (1995) Bacteremic nosocomial pneumonia. A 7-year experience in one institution. *Chest*, **108**, 786–8.
6. von Eiff, C., Becker, K., Machka, K. *et al*. (2001) Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study group. *The New England Journal of Medicine*, **344**, 11–16.
7. Rello, J., Torres, A., Ricart, M. *et al*. (1994) Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes. *American Journal of Respiratory and Critical Care Medicine*, **150**, 1545–9.
8. Lowy, F.D. (1998) *Staphylococcus aureus* infections. *The New England Journal of Medicine*, **339**, 520–32.
9. Schaberg, D.R. and Zervos, M.J. (1986) Intergeneric and interspecies gene exchange in Gram-positive cocci. *Antimicrobial Agents and Chemotherapy*, **30**, 817–22.
10. Coulter, S.N., Schwan, W.R., Ng, E.Y. *et al*. (1998) *Staphylococcus aureus* genetic loci impacting growth and survival in multiple infection environments. *Molecular Microbiology*, **30**, 393–404.
11. Wolz, C., Pohlmann-Dietze, P., Steinhuber, A. *et al*. (2000) Agr-independent regulation of fibronectin-binding protein(s) by the regulatory locus *sar* in *Staphylococcus aureus*. *Molecular Microbiology*, **36**, 230–43.
12. Heyer, G., Saba, S., Adamo, R. *et al*. (2002) *Staphylococcus aureus* agr and sara functions are required for invasive infection but not inflammatory responses in the lung. *Infection and Immunity*, **70**, 127–33.
13. Hauck, C.R. and Ohlsen, K. (2006) Sticky connections: Extracellular matrix protein recognition and integrin-mediated cellular invasion by *Staphylococcus aureus*. *Current Opinion in Microbiology*, **9**, 5–11.
14. O'Brien, L., Kerrigan, S.W., Kaw, G. *et al*. (2002) Multiple mechanisms for the activation of human platelet aggregation by *Staphylococcus aureus*: Roles for the clumping factors clfa and clfb, the serine-aspartate repeat protein sdre and protein A. *Molecular Microbiology*, **44**, 1033–44.
15. Lina, G., Piemont, Y., Godail-Gamot, F. *et al*. (1999) Involvement of panton–valentine leukocidin producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clin Infect Dis*, **29**, 1128–32.
16. Maltezou, H.C. and Giamarellou, H. (2006) Community-acquired methicillin-resistant *Staphylococcus aureus* infections. *International Journal of Antimicrobial Agents*, **27**, 87–96.
17. Chastre, J. and Fagon, J.Y. (2002) Ventilator-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **165**, 867–903.

18. Pujol, M., Corbella, X., Pena, C. *et al*. (1998) Clinical and epidemiological findings in mechanically-ventilated patients with methicillin-resistant *Staphylococcus aureus* pneumonia. *Eur J Clin Microbiol Infect Dis*, **17**, 622–8.
19. Combes, A., Luyt, C.E., Fagon, J.Y. *et al*. (2004) Impact of methicillin resistance on outcome of *Staphylococcus aureus* ventilator-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine*, **170**, 786–92.
20. Kuehnert, M.J., Hill, H.A., Kupronis, B.A. *et al*. (2005) Methicillin-resistant *Staphylococcus aureus* hospitalisations, United States. *Emerging Infectious Diseases*, **11**, 868–72.
21. Romero-Vivas, J., Rubio, M., Fernandez, C. and Picazo, J.J. (1995) Mortality associated with nosocomial bacteremia due to methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*, **21**, 1417–23.
22. Conterno, L.O., Wey, S.B. and Castelo, A. (1998) Risk factors for mortality in *Staphylococcus aureus* bacteremia. *Infect Control Hosp Epidemiol*, **19**, 32–7.
23. Zahar, J.R., Clec'h, C., Tafflet, M. *et al*. (2005) Is methicillin resistance associated with a worse prognosis in *Staphylococcus aureus* ventilator-associated pneumonia. *Clin Infect Dis*, **41**, 1224–31.
24. Shorr, A.F., Combes, A., Kollef, M.H. and Chastre, J. (2006) Methicillin-resistant *Staphylococcus aureus* prolongs intensive care unit stay in ventilator-associated pneumonia, despite initially appropriate antibiotic therapy. *Critical Care Medicine*, **34**, 700–6.
25. Bronchard, R., Albaladejo, P., Brezac, G. *et al*. (2004) Early onset pneumonia: Risk factors and consequences in head trauma patients. *Anesthesiology*, **100**, 234–9.
26. Rello, J., Ausina, V., Castella, J. *et al*. (1992) Nosocomial respiratory tract infections in multiple trauma patients. Influence of level of consciousness with implications for therapy. *Chest*, **102**, 525–9.
27. Espersen, F. and Gabrielsen, J. (1981) Pneumonia due to *Staphylococcus aureus* during mechanical ventilation. *The Journal of Infectious Diseases*, **144**, 19–23.
28. Bergmans, D., Bonten, M., Gaillard, C. *et al*. (1996) Clinical spectrum of ventilator-associated pneumonia caused by methicillin sensitive *Staphylococcus aureus*. *Eur J Clin Microbiol Infect Dis*, **15**, 437–45.
29. Sirvent, J.M., Torres, A., Vidaur, L. *et al*. (2000) Tracheal colonisation within 24 hours of intubation in patients with head trauma: Risk factor for developing early onset ventilator-associated pneumonia. *Intensive Care Medicine*, **26**, 1369–72.
30. Giantsou, E., Liratzopoulos, N., Efraimidou, E. *et al*. (2005) Both early onset and late onset ventilator-associated pneumonia are caused mainly by potentially multiresistant bacteria. *Intensive Care Medicine*, **31**, 1488–94.
31. Gastmeier, P., Sohr, D., Geffers, C. *et al*. (2005) Mortality risk factors with nosocomial *Staphylococcus aureus* infections in intensive care units: Results from the German nosocomial infection surveillance system (KISS). *Infection*, **33**, 50–5.
32. Trouillet, J.L., Chastre, J., Vuagnat, A. *et al*. (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *American Journal of Respiratory and Critical Care Medicine*, **157**, 531–9.
33. DeRyke, C.A., Lodise, T.P.Jr, Rybak, M.J. and McKinnon, P.S. (2005) Epidemiology, treatment, and outcomes of nosocomial bacteremic *Staphylococcus aureus* pneumonia. *Chest*, **128**, 1414–22.
34. Koulenti, D., Myrianthefs, P., Dimopoulos, G. and Baltopoulos, G. (2005) Hospital-acquired pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Enfermedades Infecciosas Y Microbiologia Clinica*, **23** Suppl 3, 37–45.
35. Haddadin, A.S., Fappiano, S.A. and Lipsett, P.A. (2002) Methicillin-resistant *Staphylococcus aureus* (MRSA) in the intensive care unit. *Postgraduate Medical Journal*, **78**, 385–92.

36. Foster, T.J. (2004) The *Staphylococcus aureus* 'superbug' *The Journal of Clinical Investigation*, **114**, 1693–6.
37. Lam, A.P., Wunderink R.G. (2006) Methicillin-resistant *S. aureus* ventilator-associated pneumonia: Strategies to prevent and treat. *Seminars in Respiratory and Critical Care Medicine*, **27**, 92–103.
38. Haroche, J., Morvan, A., Davi, M. *et al*. (2003) Clonal diversity among streptogramin A-resistant *Staphylococcus aureus* isolates collected in French hospitals. *Journal of Clinical Microbiology*, **41**, 586–91.
39. Lucet, J.C., Paoletti, X., Lolom, I. *et al*. (2005) Successful long-term program for controlling methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intensive Care Medicine*, **31**, 1051–7.
40. Petti, C.A. and Fowler, V.G. Jr. (2003) *Staphylococcus aureus* bacteremia and endocarditis. *Cardiology Clinics*, **21**, 219–33, vii.
41. National Nosocomial Infections Surveillance (NNIS), (2004) System report, data summary from January 1992 through June 2004, issued October 2004. *American Journal of Infection Control*, **32**, 470–85.
42. Cepeda, J.A., Whitehouse, T., Cooper, B. *et al*. (2005) Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: Prospective two-centre study. *Lancet*, **365**, 295–304.
43. Cooper, B.S., Stone, S.P., Kibbler, C.C. *et al*. (2004) Isolation measures in the hospital management of methicillin-resistant *Staphylococcus aureus* (MRSA): Systematic review of the literature. *BMJ* (Clinical research ed), **329**, 533.
44. Laupland, K.B. and Conly, J.M. (2003) Treatment of *Staphylococcus aureus* colonization and prophylaxis for infection with topical intranasal mupirocin: An evidence-based review. *Clin Infect Dis*, **37**, 933–8.
45. Kokai-Kun, J.F., Walsh, S.M., Chanturiya, T. and Mond, J.J. (2003) Lysostaphin cream eradicates *Staphylococcus aureus* nasal colonization in a cotton rat model. *Antimicrobial Agents and Chemotherapy*, **47**, 1589–97.
46. Safdar, N., Crnich, C.J. and Maki, D.G. (2005) The pathogenesis of ventilator-associated pneumonia: Its relevance to developing effective strategies for prevention. *Respiratory Care*, **50**, 725–39, discussion, 739–741.
47. al-Ujayli, B., Nafziger, D.A. and Saravolatz, L. (1995) Pneumonia due to *Staphylococcus aureus* infection. *Clinics in Chest Medicine*, **16**, 111–20.
48. Craven, D.E. and Steger, K.A. (1996) Nosocomial pneumonia in mechanically ventilated adult patients: Epidemiology and prevention in 1996. *Seminars in Respiratory Infections*, **11**, 32–53.
49. Mulligan, M.E., Murray-Leisure, K.A., Ribner, B.S. *et al*. (1993) Methicillin-resistant *Staphylococcus aureus*: A consensus review of the microbiology, pathogenesis, and epidemiology with implications for prevention and management. *The American Journal of Medicine*, **94**, 313–28.
50. deLencastre, H., deJonge, B.L., Matthews, P.R. and Tomasz, A. (1994) Molecular aspects of methicillin resistance in *Staphylococcus aureus*. *The Journal of Antimicrobial Chemotherapy*, **33**, 7–24.
51. Chambers, H.F. (1997) Methicillin resistance in staphylococci: Molecular and biochemical basis and clinical implications. *Clinical Microbiology Reviews*, **10**, 781–91.
52. Chang, S., Sievert, D.M., Hageman, J.C. *et al*. (2003) Infection with vancomycin-resistant *Staphylococcus aureus* containing the vana resistance gene. *The New England Journal of Medicine*, **348**, 1342–7.
53. Kaye, M.G., Fox, M.J., Bartlett, J.G. *et al*. (1990) The clinical spectrum of *Staphylococcus aureus* pulmonary infection. *Chest*, **97**, 788–92.

54. Theaker, C., Ormond-Walshe, S., Azadian, B. and Soni, N. (2001) MRSA in the critically ill. *The Journal of Hospital Infection*, **48**, 98−102.
55. Kopp, B.J., Nix, D.E. and Armstrong, E.P. (2004) Clinical and economic analysis of methicillin susceptible and resistant *Staphylococcus aureus* infections.*The Annals of Pharmacotherapy*, **38**, 1377−82.
56. Warren, D.K., Nitin, A., Hill, C. *et al*. (2004) Occurrence of co-colonization or co-infection with vancomycin resistant enterococci and methicillin-resistant *Staphylococcus aureus* in a medical intensive care unit. *Infect Control Hosp Epidemiol*, **25**, 99−104.
57. Craig, W.A. (1998) Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. *Clin Infect Dis*, **26**, 1−10, quiz 11−12.
58. Zhanel, G.G. (2001) Influence of pharmacokinetic and pharmacodynamic principles on antibiotic selection. *Curr Infect Dis Rep*, **3**, 29−34.
59. Rello, J. and Mallol, J. (2006) Optimal therapy for methicillin-resistant *Staphylococcus aureus* pneumonia: What is the best dosing regimen. *Chest*, **130**, 938−40.
60. Gonzalez, C., Rubio, M., Romero-Vivas, J. *et al*. (1999) Bacteremic pneumonia due to *Staphylococcus aureus*: A comparison of disease caused by methicillin-resistant and methicillin susceptible organisms. *Clin Infect Dis*, **29**, 1171−7.
61. Koulenti, D. and Rello, J. (2006) Therapy of methicillin-resistant *Staphylococcus aureus* infections. *Future Directions in Surgery*, Touch Briefings, 42−47.
62. Lundstrom, T.S. and Sobel, J.D. (2000) Antibiotics for Gram-positive bacterial infections. Vancomycin, teicoplanin, quinupristin/dalfopristin, and linezolid. *Infectious Disease Clinics of North America*, **14**, 463−74.
63. Rello, J., Sole-Violan, J., Sa-Borges, M. *et al*. (2005) Pneumonia caused by oxacillin-resistant *Staphylococcus aureus* treated with glycopeptides. *Critical Care Medicine*, **33**, 1983−7.
64. Wysocki, M., Thomas, F., Wolff, M.A. *et al*. (1995) Comparison of continuous with discontinuous intravenous infusion of vancomycin in severe MRSA infections. *The Journal of Antimicrobial Chemotherapy*, **35**, 352−4.
65. James, J.K., Palmer, S.M., Levine, D.P. and Rybak, M.J. (1996) Comparison of conventional dosing versus continuous-infusion vancomycin therapy for patients with suspected or documented Gram-positive infections. *Antimicrobial Agents and Chemotherapy*, **40**, 696−700.
66. Craig, W.A. (2003) Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. *Infectious Disease Clinics of North America*, **17**, 479−501.
67. Moise-Broder, P.A., Forrest, A., Birmingham, M.C. and Schentag, J.J. (2004) Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clinical Pharmacokinetics*, **43**, 925−42.
68. Koulenti, D. and Rello, J. (2006) Hospital-acquired pneumonia in the 21st century: A review of existing treatment options and their impact on patient care. *Expert Opinion on Pharmacotherapy*, **7**, 1555−69.
69. Wunderink, R.G., Rello, J., Cammarata, S.K. *et al*. (2003) Linezolid vs vancomycin: Analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*, **124**, 1789−97.
70. Lamer, C., de Beco, V., Soler, P. *et al*. (1993) Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. *Antimicrobial Agents and Chemotherapy*, **37**, 281−6.
71. Nathwani, D. and Tillotson, G.S. (2003) Vancomycin for *Staphylococcus aureus* therapy of respiratory tract infections: The end of an era. *International Journal of Antimicrobial Agents*, **21**, 521−4.

72. Conte, J.E. Jr, Golden, J.A., Kipps, J. and Zurlinden, E. (2002) Intrapulmonary pharmacokinetics of linezolid. *Antimicrobial Agents and Chemotherapy*, **46**, 1475–80.
73. Tsiodras, S., Gold, H.S., Sakoulas, G. *et al*. (2001) Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. *Lancet*, **358**, 207–8.
74. Kollef, M.H., Rello, J., Cammarata, S.K., Croos-Dabrera, R.V. and Wunderink, R.G. (2004) Clinical cure and survival in Gram-positive ventilator-associated pneumonia: Retrospective analysis of two double-blind studies comparing linezolid with vancomycin. *Intensive Care Medicine*, **30**, 388–94.
75. Bernardo, K., Pakulat, N., Fleer, S. *et al*. (2004) Subinhibitory concentrations of linezolid reduce *Staphylococcus aureus* virulence factor expression. *Antimicrobial Agents and Chemotherapy*, **48**, 546–444.
76. Coyle, E.A. (2003) Targeting bacterial virulence: The role of protein synthesis inhibitors in severe infections. Insights from the society of infectious diseases pharmacists. *Pharmacotherapy*, **23**, 638–42.
77. Mullins, C.D., Kuznik, A., Shaya, F.T. *et al*. (2006) Cost-effectiveness analysis of linezolid compared with vancomycin for the treatment of nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clinical Therapeutics*, **28**, 1184–98.
78. Pea, F., Brollo, L., Viale, P. *et al*. (2003) Teicoplanin therapeutic drug monitoring in critically ill patients: A retrospective study emphasizing the importance of a loading dose. *The Journal of Antimicrobial Chemotherapy*, **51**, 971–5.
79. Fagon, J., Patrick, H., Haas, D.W. *et al*. (2000) Treatment of Gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial pneumonia group. *American Journal of Respiratory and Critical Care Medicine*, **161**, 753–62.
80. Nathwani, D. (2005) Tigecycline: Clinical evidence and formulary positioning. *International Journal of Antimicrobial Agents*, **25**, 185–92.
81. Rello, J. (2005) Pharmacokinetics, pharmacodynamics, safety and tolerability of tigecycline. *Journal of Chemotherapy (Florence, Italy)*, 17 Suppl, **1**, 12–22.
82. Postier, R.G., Green, S.L., Klein, S.R. *et al*. (2004) Results of a multicentre, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalised patients. *Clinical Therapeutics*, **26**, 704–14.
83. Schmidt-Ioanas, M., de Roux, A. and Lode, H. (2005) New antibiotics for the treatment of severe staphylococcal infection in the critically ill patient. *Current Opinion in Critical Care*, **11**, 481–6.
84. Paterson, D.L. (2006) Clinical experience with recently approved antibiotics. *Current Opinion in Pharmacology*, **6**, 486–90.
85. (2006) Ceftobiprole BAL5788, JNJ 30982081, JNJ30982081, RO 65–5788, RO 655788. *Drugs in R& D*, **7**, 305–11.
86. Jones, R.N., Deshpande, L.M., Mutnick, A.H. and Biedenbach, D.J. (2002) In vitro evaluation of BAL9141, a novel parenteral cephalosporin active against oxacillin-resistant staphylococci. *The Journal of Antimicrobial Chemotherapy*, **50**, 915–32.
87. Bogdanovich, T., Ednie, L.M., Shapiro, S. and Appelbaum, P.C. (2005) Antistaphylococcal activity of ceftobiprole, a new broad-spectrum cephalosporin. *Antimicrobial Agents and Chemotherapy*, **49**, 4210–19.
88. Deshpande, L., Rhomberg, P.R., Fritsche, T.R. *et al*. (2004) Bactericidal activity of BAL9141, a novel parenteral cephalosporin against contemporary Gram-positive and Gram-negative isolates. *Diagnostic Microbiology and Infectious Disease*, **50**, 73–5.
89. www.jnj.com.
90. Schneider, P., Hawser, S. and Islam, K. (2003) Iclaprim, a novel diaminopyrimidine with potent activity on trimethoprim sensitive and resistant bacteria. *Bioorganic & Medicinal Chemistry Letters*, **13**, 4217–21.

91. http://iclaprim.com.
92. Krievens D., Leighton A., Brandt R., *et al*. "Efficacy, safety of intravenous Iclaprim in complicated skin, skin-structures infections: results of a phase II study", In: Proceedings of the 44th Interscience Conference on Antimicrobial Agents, Chemotherapy (2005), Washington, DC. American Society for Chemotherapy, (abstract L-1579).
93. Andrews, J.M., Honeyboune, D.,Ashby, J.P. *et al*. (2005) "Concentration of Iclaprim in plasma, epithelial lining fluid (ELF) alveoalar macrophages (AM), bronchial mucosa (BM) following a single 1.6 mg/kg intravenous infusion in healthy subjects", In: Proceedings of the 44th Interscience Conference on Antimicrobial Agents, *Chemotherapy*, Washington, DC, American Society for Chemotherapy, (abstract A-9).
94. Seltzer, E., Dorr, M.B., Goldstein, B.P. *et al*. (2003) Once-weekly dalbavancin versus standard-of-care antimicrobial regimens for treatment of skin and soft-tissue infections. *Clin Infect Dis*, **37**, 1298−303.
95. Jauregui, L.E., Babazadeh, S., Seltzer, E. *et al*. (2005) Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis*, **41**, 1407−15.
96. Ward, K.E., Mersfelder, T.L. and LaPlante, K.L. (2006) Oritavancin--an investigational glycopeptide antibiotic. *Expert Opinion on Investigational Drugs*, **15**, 417−29.
97. http://www.targanta.com/pipeline/oritavancin.html.
98. Pace, J.L. and Judice, J.K. (2005) Telavancin (theravance). *Curr Opin Investig Drugs*, **6**, 216−25.
99. Reyes, N., Skinner, R.Kaniga, K. *et al*. (2005) Efficacy of telavancin (TD-6424), a rapidly bactericidal lipoglycopeptide with multiple mechanisms of action, in a murine model of pneumonia induced by methicillin-resistant Staphylococcus aureus. *Antimicrobial Agents and Chemotherapy*, **49**, 4344−6.
100. Reyes, N., Skinner, R. Benton, B.M. *et al*. (2006) Efficacy of telavancin in a murine model of bacteraemia induced by methicillin-resistant Staphylococcus aureus. *The Journal of Antimicrobial Chemotherapy*, **58**, 462−5.
101. Van Bambeke, F. (2006) Glycopeptides and glycodepsipeptides in clinical development: A comparative review of their antibacterial spectrum, pharmacokinetics and clinical efficacy. *Curr Opin Investig Drugs*, **7**, 740−9.

8

Nosocomial Pneumonia by *Acinetobacter baumannii*

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Introduction

Acinetobacter baumannii is a major cause of nosocomial pneumonia that causes especially late ventilator-associated pneumonia. In Spain, *A. baumannii* is the third leading pathogen after *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Invasive techniques with quantitative cultures are of value in differentiating true infections from simple colonizations. Crude mortality of patients with *A. baumannii* pneumonia is high although the attributable mortality seems to be marginal.

Adequate empirical antimicrobial therapy of *A. baumannii* pneumonia is a protective factor even though therapeutic options are often limited. Control measures are essential to erradicate this multidrug resistant pathogen in outbreaks and reduce the number of episodes in endemic situations. These measures should be implemented in the hospital and particularly in high-risk areas such as intensive care units.

Microbiological Characteristics of A*cinetobacter baumannii*

Acinetobacter baumannii is a non fermenting Gram-negative bacillus, able to grow at a temperature of 44 °C, unlike the other 20 genospecies of the genus *Acinetobacter*, which over the past two decades has become an important nosocomial pathogen that

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is difficult to control and treat [1,2]. According to data provided by the Centers for Disease Control and Prevention (CDC) and the National Nosocomial Infection Surveillance (NNIS) *Acinetobacter* spp., caused 1% of all episodes of bacteraemia and 3% of all episodes of pneumonia in US hospitals [3].

The increase of *A. baumannii* infections is due to its great resistance to the environment which enables it to spread, its limited virulence and its extraordinary ability to develop resistance to all antimicrobials.

The simplicity of the nutritional requirements of *A. baumannii*, the variety of sources of carbohydrates that it uses and its ability to grow in different temperatures and pH values, explain its prolonged survival in inert environmental elements, which is similar to *Staphylococcus aureus* and much greater than other Gram-negative bacteria. These qualities facilitate the intense contamination of hospital equipment, which is typical of outbreaks caused by this pathogen.

The virulence factors of *A. baumannii*, epithelial cell adhesion, the production of lipolytic enzymes and lipopolysaccharide of the cell wall are scarce compared to other Gram-negative bacteria. Consequently, it is considered an opportunist pathogen that frequently simply colonizes patients and only very rarely causes community-acquired infections. In a study of *A. baumannii* clinical epidemiology carried out in 28 centers in Spain by the Hospital Infection Study Group (GEIH), 47% of the 221 clinical samples of *A. baumannii* were considered as mere colonization [4].

The mechanisms of its resistance to antimicrobials are principally acquired through its ability to exchange genetic material, and include the presence of different β-lactamases (TEM-1, TEM-2, OXA 23, CARB-5, pI 8.5 cephalosporinases and ceftazidimases), aminoglycoside-inactivating enzymes of (aminoglycoside-3'-phosphotransferase VI), changes in porin of the outer membrane, mutations of the gyrA and parC genes and alterations in the penicillin-binding proteins (PBPs). The ease with which *A. baumannii* develops resistance to antimicrobials has been so quick and efficient that at the beginning of the 1990s the first strains resistant to carbapenems were described and in 1998 the first pan-resistant strain was described, defined as resistant to all antimicrobials with the exception of colistin [5].

A. baumannii has now successfully developed resistance against all common antibiotics, including colistin (polymyxin E), the last universally active drug against this pathogen.

Susceptibility of *A. baumannii* to antimicrobials can be different even within different areas of the same hospital. This variability can be explained by the coexistence of various epidemic and endemic clones in the same centre that result in different epidemiological situations. In vitro antimicrobial activity for the 221 *A. baumannii* clinical strains collected in the GEIH study is shown in Table 8.1. It must be highlighted that 41% of the strains were resistant to imipenem [6]. These rates of resistance are much higher that those described in other countries; thus while the minimum inhibitory concentration $(MIC)_{90}$ of imipenem was 128 mg/L, in a similar study carried out in 49 hospitals in the United States, it was 1 mg/L[7]. The distribution of *A. baumannii* strains resistant to imipenem in Spain is widespread, to such an extent that they are isolated in 39% of the hospitals, reaching alarming proportions in some centres[8]. The principal risk factors for acquiring *A. baumannii*

Table 8.1 *In vitro* antimicrobial activity against 221 isolates of *A. baumannii* in 25 Spanish hospitals [Fernández]

Antimicrobial	IMC_{90} (mg/L)	Resistance (%)
Colistin	2	0
Rifampicin	8	4.9
Sulbactam	64	33.3
Imipenem	128	41.2
Meropenem	> 128	49.8
Amikacin	256	54.2
Tobramycin	128	56.5
Doxycicline	64	64.9
Cefepime	256	73.4
Ceftazidime	> 256	80
TMP–SMX	64	87.6
Piperacillin	> 512	88.4
Ciprofloxacin	> 64	90.3
Ampicillin	> 256	93

resistant to imipenem are: being admitted to large hospitals with over 500 beds; being admitted to intensive care units (ICUs); surgery; urinary catheter and previous antimicrobial treatment including third generation cephalosporins and imipenem [8, 9]. In recent years, *A. baumannii* strains resistant to imipenem and generally multiresistant have been described in other countries [10, 11]. The resistance of *A. baumannii* to carbapenems is of such significance that the International Network for the Study and Prevention of Emerging Antimicrobial Resistance has defined it as a 'sentinel event', which requires an urgent, coordinated response to control this multiresistant pathogen [12]. Unfortunately, *A. baumannii* strains resistant to colistin have also been isolated in different Institutions [13].

Epidemiological Characteristics

A. baumannii is one of the most common etiologies of hospital-acquired pneumonia (HAP), especially in late onset ventilator-associated pneumonia (VAP). There are huge geographical differences, however [14, 15]. In Europe, it was the third most common pathogen after *Staphylococcus aureus* and *Pseudomonas aeruginosa* according to a prevalence study of nosocomial infections in ICUs in 1992 [16]. In Spain, according to data from 2002, *A. baumannii* is also the third most common cause of pneumonia in ICUs after *P. aeruginosa* and *S. aureus* [17] and, in some centres, *A. baumannii* even ranks first [18]. In Latin America, *Acinetobacter* spp. is the fourth most common cause of nosocomial pneumonia, with 10 % of the cases, following *P. aeruginosa* (26 %), *S. aureus* (23 %) and *Klebsiella pneumoniae* (10 %) [19].

Identified risk factors for developing *A. baumannii* ventilator-associated pneumonia are cranial trauma, neurosurgery, acute respiratory distress syndrome, aspiration and previous antimicrobial treatment [20, 21]. Treatment with a carbapenem is an independent risk factor for developing imipenem resistant ventilator-associated *A. baumannii* pneumonia [18].

Clinical Characteristics

A. baumannii ventilator-associated pneumonia usually has a late onset, affecting patients after 10–14 days on mechanical ventilation [22]. The colonization of *A. baumannii* prior to pneumonia is a common fact [23]. Approximately, half of the cases develop septic shock. Bacteremia occurs in approximately 20% of the cases of pneumonia and the most common source of *A. baumannii* bacteremia is the lung [24, 25]. The X-ray pattern is not specific; in half of the cases it causes lung infiltration and a diffuse bilateral pattern is seen in the other half of the cases [21].

For a definitive diagnosis, respiratory samples must be taken using invasive techniques and quantitative cultures should be performed in order to differentiate a real infection from common colonization. Adequately evaluating the diagnosis of the *A. baumannii* isolations avoids unnecessary antimicrobial treatment that may induce resistance and is of prognostic interest as mortality amongst colonized patients is significantly lower than amongst infected patients [26].

Crude mortality for patients with ventilator-associated *A. baumannii* pneumonia is high, ranging from 33–70% [18, 21, 27]. However, mortality attributable to *A. baumannii* pneumonia is a matter of debate. Infections caused by other multiresistant pathogens, such as *P. aeruginosa* or methicillin-resistant *S. aureus*, are associated with an excess of mortality in critically ill patients [28, 29]. Controversy still exists regarding attributable mortality due to *A. baumannii*. In some studies the rate of mortality was found to be higher in infected patients than in the control group [26, 30], even though the French study included patients with *P. aeruginosa* and *A. baumannii* pneumonia. Conversely, a recent matched case-control study found that mortality attributable to *A. baumannii* pneumonia is marginal although a trend towards significance was observed in episodes caused by imipenem resistant strains [22]. It must be highlighted that adequate antimicrobial treatment is an independent predictor of survival in patients with ventilator-associated pneumonia *A. baumannii* [18].

Treatment

No well-designed, randomized controlled trials have been conducted to comprehensively evaluate the effectiveness and safety of different antibiotics for the treatment of *A. baumannii* pneumonia and to elucidate their clinical indications. Therefore, the scientific evidence for treating this lung infection is based on *in vitro* data, the results of experimental models and clinical series. In recent years, interesting data have been obtained regarding the treatment of this infection; they are analyzed in the following

section. Therapeutic options for *A. baumannii* infections are limited, as shown in Table 8.1.

Treatment of Carbapenem Susceptible *A. baumannii* Pneumonia

Carbapenems

Owing to their wide spectrum, carbapenems are recommended as the first line of empiric treatment for patients suspected of having *A. baumannii* pneumonia [31]. It is supported by their *in vitro* activity, the experimental data and the extensive clinical experience. Moreover, imipenem exhibits *in vivo* a prolonged post-antibiotic effect on the lungs in a lung model of *A. baumannii* pneumonia [32]. The cure rate from using imipenem ranges from 57−83 % in two series with 14 and 63 cases of *A. baumannii* pneumonia [33, 34].

Sulbactam

Sulbactam is a penicillanic acid sulfone which, as well as being a β-lactamases inhibitor, acts as a bactericide against *A. baumannii* and has demonstrated its *in vivo* efficiency in a murine model of pneumonia [35]. In a small series, clinical results using sulbactam to treat *A. baumannii* pneumonia can be compared with those obtained when using imipenem [36, 37]. In both studies, sulbactam was used together with ampicillin. However, this association is not necessary given that the ampicillin/sulbactam activity against *A. baumannii* is exclusively due to sulbactam [38].

Sulbactam is considered an alternative to carbapenems even in serious infections, including *A. baumannii* bloodstream infections [39]. Sulbactam is an attractive option due to its specific antibacterial activity profile compared with imipenem. Its use can contribute to reduced carbapenem use, the principal risk factor for the occurrence of infections due to imipenem resistant *A. baumannii* strains [9, 18].

Aminoglycosides

Aminoglycosides combined with β-lactams are recommended for treating *A. baumannii* pneumonia, although it has not been proven that the combination is more effective than the use of a β-lactamic in monotherapy. In contrast, in an *A. baumannii* pneumonia experimental model on immunocompetent mice, it has been proven that combining amikacin with imipenem is not more effective than monotherapy with imipenem [40]. Similarly, in an experimental model carried out on guinea pigs, combining amikacin with imipenem negatively affected the efficiency of imipenem in monotherapy, which is related to pharmacokinetic/pharmacodynamic alterations of both drugs when administered together [41]. Therefore, and without more recent data, there is no reason to recommend combined treatment using imipenem and an aminoglycoside for an *A. baumannii* pneumonia.

Treatment of Carbapenem Resistant *A. baumannii* Pneumonia

The treatment available for carbapenem resistant *A. baumannii* pneumonia is extremely limited. In the study carried out by the GEIH, active antimicrobials against imipenem resistant *A. baumannii* strains were polymyxins (100 % susceptible strains), sulbactam (14 %), ceftazidime (7.5 %), amikacin (18 %) and doxycycline (13 %). It is necessary to highlight that imipenem is active *in vivo* against *A. baumannii* with a low level of resistance ($MIC_{90} = 8$ mg/L), whilst it is inactive against strains with a high resistance level ($MIC_{90} = 512$ mg/L) [42]. Consequently, it is highly recommended that the MIC of imipenem is determined in order to optimise the antimicrobial therapy for this difficult-to-treat pathogen.

Colistin

Polymyxins are a group of polypeptide cationic antibiotics. Two forms of colistin, or polymyxin E, are commercially available for clinical use: colistin sulfate, which is usually used topically or orally for selective bowel decontamination, and colistimethate sodium, which is used parenterally. Nowadays, colistin is the antimicrobial with the greatest level of *in vitro* activity against *A. baumannii* strains. Colistin showed excellent potency and spectrum against 2621 *Acinetobacter* spp. isolates MIC_{50}, $<$ or $=$ 1 mg/L and MIC_{90} 2 mg/L. Polymyxin B resistance rates were slightly higher for carbapenem resistant *Acinetobacter* spp. (2.8 %), or multidrug resistant *Acinetobacter* spp. (3.2 %). Among *Acinetobacter* spp. polymyxin B resistance rates varied from 2.7 % in Europe to 1.7 % in North America and Latin America [43]. However, the *A. baumannii* endocarditis experimental model failed to eradicate bacteria from the vegetations although it was effective in reducing bacteraemia [44]. Furthermore, in an experimental model of pneumonia caused by three *A. baumannii* strains with varying imipenem susceptibilities, colistin was not effective in reducing mortality or the concentration of bacteria in the lungs or blood [45].

The clinical results of *A. baumannii* pneumonia treated with colistin have been considered poor in comparison with other localisations [46], which may be explained by the poor penetration of this antimicrobial into the lung tissue [47]. Notwithstanding, colistin was as effective as imipenem in a prospective study that enrolled 14 cases of *A. baumannii* ventilator-associated pneumonia susceptible to imipenem that were treated with this antibiotic and 21 patients with ventilator-associated pneumonia caused by *A. baumannii* sensitive only to colistin that were treated with this antimicrobial exclusively by an intravenous route [33]. These findings have been confirmed by a prospective cohort study in which the most frequent infection was ventilator-associated pneumonia [48]. It has been demonstrated that there may be colistin resistant subpopulations in clinical isolations considered equally susceptible based on MIC, which may explain certain therapeutic failures [49].

Therefore, it seems judicious to use colistin only to treat *A. baumannii* infections without other therapeutic alternatives. There is extensive experience with administering colistin in an aerosol to patients with cystic fibrosis, in whom this type of

treatment is used to treat lung infections with *P. aeruginosa* strains. The use of colistin in aerosol form as adjunctive therapy for *A. baumannii* pneumonia may be beneficial but always as an adjunct to intravenous colistin [47, 50]. Treatment with colistin in aerosol form may be complicated by bronchoconstriction.

Nephrotoxicity and neurotoxicity are the main adverse affects reported with the use of colistin. The basic molecular mechanism by which polymyxin B induces nephrotoxicity is by increasing membrane permeability, resulting in an increased influx of cations, anions and water, leading to cell swelling and lysis [51]. Renal toxicity associated with the use of polymyxins is now considered less frequent compared with series published in the 1970s. Nowadays, neuromuscular disturbances induced by colistin are very uncommon [33].

Sulbactam

For reasons mentioned earlier, sulbactam is the chosen treatment for uncommon cases of carbapenem resistant and sulbactam susceptible *A. baumannii* pneumonia.

Tetracyclines

The combination of doxycycline and amikacin was synergic *in vitro* against *A. baumannii* susceptible to both antimicrobials and was as effective as imipenem in a murine model of pneumonia [52]. Clinical experiments using tetracyclines was limited to seven cases of pneumonia, six of which were cured [53]. Therefore, doxycycline combined with amikacin may be an option when treating the uncommon type of pneumonia that is susceptible to tetracycline and resistant to β-lactams and sulbactam.

Rifampicin

Rifampicin maintains a high level of activity both *in vitro* and *in vivo* against *A. baumannii* even in carbapenem resistant strains. In an experimental model of *A. baumannii* pneumonia caused by strains susceptible, intermediate or resistant to imipenem, monotherapy with rifampicin was more effective in reducing bacteria in the lungs than any of the other antimicrobials (imipenem, sulbactam, tobramycin and colistin). However, rifampicin should not be used in monotherapy because it induces the occurrence of *A. baumannii* resistant to this antimicrobial both *in vitro* and *in vivo* [54].

Combined Treatments

The combination of imipenem plus sulbactam is synergic *in vitro* against strains resistant to both antimicrobials [55]. The combination of rifampicin with imipenem or tobramycin was effective in *A. baumannii* pneumonia with a high level of resistance to imipenem and moderate resistance to rifampicin, whilst the combination of sulbactam and meropenem is greater than monotherapy with these drugs in a multiresistant *A. baumannii* pneumonia experimental model [56].

Clinical information regarding the use of combined treatments for pan-resistant *A. baumannii* is reduced to a series of 69 patients with different infections caused by this microorganism and treated with sulbactam plus carbapenem (n = 39) or with another β-lactam or fluorquinolones plus an aminoglycoside (n = 30). The cure rates were 42 and 40 %, respectively [57]. A recent study evaluated the combination of imipenem plus rifampicin in the treatment of 10 patients with carbapenem resistant *A. baumannii* infections (4 cases were ventilator-associated pneumonia). The results obtained were discrete and the authors themselves do not recommend this therapeutic regimen [58].

Therefore, further investigations are warranted to confirm whether the combinations of rifampicin with a carbapenem or sulbactam with a carbapenem are a therapeutic option and an alternative to colistin in treating multi resistant *A. baumannii* pneumonia caused by a low level of resistance to imipenem (MIC_{90} = 8 mg/L).

The recommendations outlined above for the treatment of *A. baumannii* pneumonia are summarized in Table 8.2.

New Antimicrobials

Tigecycline, a minocycline derivative, is active against *A. baumannii*, including strains resistant to imipenem [59], and a synthetic peptide derived from human lactoferrin, which is effective both *in vitro* and *in vivo* in an experimental model [60], are potential therapeutic options. Tigecycline will shortly be available in Europe and a successful treatment with tigecycline in a critically ill patient has been reported even though it was used in combination with other antimicrobials [61].

Table 8.2 Antimicrobials options for the treatment of *A. baumannii* pneumonia

Non-multiresistant *A. baumannii* pneumonia
- First choice: β-lactam active following antibiogram results (the one with the narrowest spectrum)
- Alternative: Sulbactam 1 g/iv/6 h.

Multiresistant *A. baumannii* pneumonia
- First choice:
  - Imipenem 500 mg/iv/6 h.
  - Sulbactam 1 g/iv/6 h

Panresistant *A. baumannii* pneumonia
- First choice: colistin 2.5–5 mg/kg/ day (in two–three doses)
  - Alternatives:
  - Rifampicin 600 mg/iv. plus Imipenem 500 mg/iv/6 h.
  - Rifampicin 600 mg/iv. plus Sulbactam 1 g/iv/6 h.
  - Imipenem 500 mg/iv./6 h. plus Sulbactam 1 g/iv. cada 6 h.
  - Aerosolized colistin (in conjuntion with intravenous colistin): 40 mg (500 000 IU) every 12 hours for patients with body weight $\leq$ 40 kg, and 80 mg (1 million IU) every 12 hours for patients with a body weight >40 kg

Prevention

Acinetobacter spp. is a normal commensal flora in the skin of patients and hospital staff that converts them into a reservoir of infection in hospitals in epidemic and endemic situations. Many parts of the patient's body but, in particular, the skin, pharynx and humid areas such as the axils, the groins or the perineum, may be colonized with this Gram-negative bacillus. It should be pointed out that, in a critically ill patient, the digestive tract can be colonized with *A. baumannii*, so becoming a reservoir in endemic situations, which is very relevant given that *Acinetobacter* spp. is not part of the gastrointestinal flora.

The main form of *A. baumannii* transmission is through direct contact; the hospital staff is the main transmission vector of this pathogen [62, 63]. In addition, it has also been recorded that it can be spread by air transmission and it has been demonstrated that *A. baumannii* can be isolated more than four metres away from patients with respiratory colonization [64]. For this reason, open aspirations in patients with colonization or respiratory infection with this pathogen can infect other patients at a significant distance and, therefore, should be avoided.

Given that the main transmission mechanism is by direct contact, measures such as hand washing and barrier protections should be used to avoid the spread of this pathogen. Strict control measures should be implemented including the use of gowns, gloves and masks. Additionally, patients colonized or infected with *A. baumannii* should be isolated from other patients in individual rooms [65].

Multidrug resistant *A. baumannii* isolation requires a rapid, coordinated, multidiscipline response to avoid its spread and eliminate the reservoirs. It is clear that a correct antibiotic policy would help to mitigate this growing problem [66].

References

1. Bergogne-Bérézin, E. and Towner, K.J. (2006) *Acinetobacter* spp. As nosocomial pathogens: Microbiological, clinical and epidemiological features. *Clin Microbiol Rev*, **9**, 148–65.
2. Allen D.M. and Hartman B.J., (2005). *Acinetobacter species*. (In: Eds Mandell G.L., Douglas R.G., Bennett J.E. Principles and Practices of Infectious Diseases). Elsevier INC. Philadelphia, pp. 2632–2636.
3. Gales, A.C., Jones, R.N., Forward, K.R. *et al*. (2001) Emerging importance of multidrug resistant *Acinetobacter* species and stenotrophomonas maltophilia as pathogens in seriously ill patients: Geographic patterns, epidemiological features, and trends in the SENTRY antimicrobial surveillance program (1997–1999). *Clin Infect Dis*, **32** (Suppl 2), 104–13.
4. Rodríguez-Baño, J., Cisneros, J.M., Fernández Cuenca, F. *et al*. (2004) Clinical Features and Epidemiology of *Acinetobacter baumannii* Colonization and Infection in Spanish Hospital. *Infect Control Hosp Epidemiol*, **25**, 819–24.
5. Hsueh, P.R., Teng, L.J., Chen, C.Y. *et al*. (2002) Pandrug-resistant *Acinetobacter baumannii* causing nosocomial infections in a university hospital, Taiwan. *Emerging Infect Dis*, **8**, 827–32.
6. Fernández, F., Pascual, A., Ribera, A. *et al*. (2004) Diversidad Clonal y Sensibilidad a los Antimicrobianos de *Acinetobacter baumannii* Aislados en Hospitales espa ñoles.

Estudio multic Éntrico nacional: Proyecto GEIH-ab 2000. *Enferm Infecc Microbiol Clin*, **22**, 267−71.
7. Wisplinghoff, H., Edmond, M.B., Pfaller, M.A. *et al*. (2000) Nosocomial bloodstream infections caused by *Acinetobacter* species in United States hospitals: Clinical features, molecular epidemiology, and antimicrobial susceptibility. *Clin Infect Dis*, **31**, 690−7.
8. Cisneros, J.M., Rodríguez-Baño, J., Fernández-Cuenca, F. *et al*. (2005) Risk Factor for the Acquisition of Imipenem Resistant *Acinetobacter baumannii* in Spain: A Nationwide Study. *Clin Microbiol Infect*, **11**, 874−9.
9. Lee Kim, S.O.N.J., Choi, S.H., Hyong Kim, T. *et al*. (2004) Risk Factors for Acquisition of Imipenem Resistant *Acinetobacter baumannii*: a Case-Control Study. Antimicrob. *Agents Chemother*, **48**, 224−8.
10. Fierobe, L., Lucet, J.C., Decré, D. *et al*. (2001) An Outbreak of Imipenem Resistant *Acinetobacter baumannii* in Critically Ill Surgical Patients. *Infect Control Hosp Epidemiol*, **22**, 35−40.
11. Manikal, V.M., Landman, D., Saurina, G. *et al*. (2000) Endemic carbapenem resistant *Acinetobacter* species in Brooklyn, New York: Citywide prevalence, interinstitutional spread and relation to antibiotic usage. *Clin Infect Dis*, **31**, 101−6.
12. Richet, H.M., Mohammed, J., McDonald, L.C.and Jarvis, W.R. (2001) Building communication networks: International network for the study of emerging antimicrobial resistance. *Emerging Infect Dis*, **7**, 319−22.
13. Arroyo, L.A., Garcia-Curiel, A., Pachón-Ibañez, M.E. *et al*. (2005) Reliability of the E-test Method in the Detection of Colistin Resistance in Clinical Isolates of *Acinetobacter baumannii*. *J Clin Microbiol*, **43**, 903−5.
14. Rello, J., Sa-Borges, M., Correa, H., Leal, S.R. and Baraibar, J. (1999) Variations in Etiology of Ventilator-Associated Pneumonia Across Four Treatment Sites. *Am J Resp Crit Care Med*, **160**, 608−13.
15. Trouillet, J.L., Chastre, J., Vaugnat, A. *et al*. (1998) Ventilator-Associated Pneumonia Caused by Potentially Drug-Resistant Bacteria. *Am J Resp Crit Care Med*, **157**, 531−9.
16. Spencer, R.C. (1996) Predominant pathogens found in the European prevalence of infection in intensive care study. *Eur J Clin Microbiol Infect Dis*, **15**, 281−5.
17. Álvarez-Lerma, F., Palomar-Martínez, M., Olaechea-Astigarraga, P. *et al*. (2005) Estudio Nacional de Vigilancia de infección Nosocomial en Unidades de Cuidados Intensivos. Informe del año 2002. *Med Intensiva*, **29**, 1−12.
18. Garnacho-Montero, J., Ortiz-Leyba, C., Fernandez-Hinojosa, E. *et al*. (2005) *Acinetobacter baumannii* Ventilator-Associated Pneumonia: Epidemiological and Clinical Findings. *Intensive Care Med*, **31**, 649−55.
19. Gales, A.C., Sader, H.H.S. and Jones, R.N. (2002) Respiratory tract pathogens isolated from patients hospitalised with suspected pneumonia in Latin America: Frequency of occurrence and antimicrobial susceptibility profile: results from the SENTRY antimicrobial surveillance program (1997-2000). *Diagn Microbiol Infect Dis*, **44**, 301−11.
20. Baraibar, J., Correa, H., Mariscal, D. *et al*. (1997) Risk Factors for Infection by A. *baumannii* in Intubated Patients with Pneumonia. *Chest*, **112**, 1050−4.
21. Husni, R.N., Goldstein, L.S., Arroliga, A.C. *et al*. (1999) Risk factors for an outbreak of multidrug resistant *Acinetobacter* nosocomial pneumonia among intubated patients. *Chest*, **115**, 1378−82.
22. Garnacho-Montero, J., Sole-Violan, J., Sa-Borges, M. *et al*. (2003) Clinical Impact of Pneumonia caused by *A. baumannii* in Intubated Patients: A Matched Cohort Study. *Crit Care Med*, **31**, 2478−82.
23. Corbella, X., Pujol, M., Ayats, J. *et al*. (1996) Relevance of digestive tract colonization in the epidemiology of nosocomial infections due to multiresistant *A. baumannii*. *Clin Infect Dis*, **23**, 329−34.

24. García Garmendia, J.L., Ortiz Leyba, C., Garnacho-Montero, J. *et al*. (2001) Risk Factors for *A. baumannii* Nosocomial Bacteremia in Critically Ill Patients: a Cohort Study. *Clin Infect Dis*, **33**, 939–46.
25. Cisneros, J.M., Reyes, M.J., Pachón, J. *et al*. (1996) Bacteremia due to *Acinetobacter baumannii*: Epidemiology, Clinical and Prognostic Features. *Clin Infect Dis*, **22**, 1026–32.
26. García-Garmendia, J.L., Ortiz-Leyba, C., Garnacho-Montero, J. *et al*. (1999) Mortality and the Increase in Length of Stay due to the Acquisition of *Acinetobacter* in Critically Ill Patients. *Crit Care Med*, **27**, 1794–9.
27. Fagon, J.Y., Chastre, J., Domart, Y. *et al*. (1996) Mortality Due To ventilator-associated pneumonia or colonization with Pseudomonas or *Acinetobacter* species: Assessment by quantitative culture of samples obtained by a protected specimen brush. *Clin Infect Dis*, **23**, 538–42.
28. Rello, J., Jubert, P. and Vallés, J. *et al*. (1996) Evaluation of outcome in intubated patients with pneumonia caused by Pseudomonas aeruginosa. *Clin Infect Dis*, **23**, 973–8.
29. Rello, J., Sole-Violan, J., Sa-Borges, M. *et al*. (2005) Pneumonia caused by Oxacillin-Resistant Staphylococcus aureusTreated with Glycopeptides. *Crit Care Med*, **33**, 1983–7.
30. Fagon, J.Y., Chastre, J., Hance, A.J. *et al*. (1993) Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. *Am J Med*, **94**, 281–8.
31. Jordá, J., Torres, A., Ariza, F.J. *et al*. (2004) Recomendaciones para el Tratamiento de la neumonía Intrahospitalaria Grave. Documento de Consenso. *Enferm Infecc Microbiol Clin*, **22**, 471–85.
32. Joly-Guillou, M.L., Wolf, M., Pocidalo, J.J. *et al*. (1997) Use of a new mouse model of *A. baumannii* pneumonia to evaluate the postantibiotic effect of imipenem. Antimicrob. *Agents Chemother*, **41**, 345–51.
33. Garnacho-Montero, J., Ortiz-Leyba, C., Jimenez-Jimenez Barrero-Almodovar, F.J.A.E. *et al*. (2003) Treatment of multiresistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: A comparison with imipenem susceptible VAP. *Clin Infect Dis*, **36**, 1111–18.
34. Wood, G.C., Hanes, S.D., Croce, M.A. *et al*. (2002) Comparison of ampicillin–sulbactam and imipenem–cilastatin for the treatment of *Acinetobacter* ventilator-associated pneumonia. *Clin Infect Dis*, **34**, 1425–30.
35. Rodriguez-Hernandez, M.J., Cuberos, L., Pichardo, C. *et al*. (2001) J. Sulbactam Efficacy in Experimental Models caused by Susceptible and Intermediate *Acinetobacter baumannii* Strains. *J Antimicrob Chemother*, **47**, 479–82.
36. Urban C., Go, E., Mariano, N. *et al*. (1993) Effect of Sulbactam on Infections caused by Imipenem Resistant *Acinetobacter* Calcoaceticus Biotype Anitratus. *J Infect Dis*, **167**, 448–451.
37. Levin, A.S.S., Levy, C.E., Manrique, A.E. *et al*. (2003) Severe nosocomial infections with imipenem resistant *Acinetobacter baumannii* treated with ampicillin/sulbactam. *Int J Antimicrob Agents*, **21**, 58–62.
38. Brauers, J., Frank, U., Kresken, M. *et al*. (2005) Activities of various beta-lactams and beta-lactam/beta–lactamase inhibitor combinations against *Acinetobacter baumannii* and *Acinetobacter* DNA group 3 strains. *Clin Microbiol Infect*, **11**, 24–30.
39. Cisneros, J.M. and Rodríguez-Baño, J. (2002) Nosocomial bacteremia due to *Acinetobacter baumannii*: Epidemiology, clinical features and treatment. *Clin Microbiol Infect*, **8**, 687–93.

40. Rodríguez-Hernández, M.J., Pachón, J., Pichardo, C. *et al*. (2000) Imipenem Doxycycline and Amikacin in Monotherapy and in Combination in *Acinetobacter baumannii* Experimental Pneumonia. *J Antimicrob Chemother*, **45**, 493–501.
41. Bernabeu-Wittel, M., Pichardo, C., Garcia-Curiel, A. *et al*. (2005) Pharmacokinetic/pharmacodynamic assessment of the in-vivo efficacy of imipenem alone or in combination with amikacin for the treatment of experimental multiresistant *Acinetobacter baumannii* pneumonia. *Clin Microbiol Infect*, **11**, 319–25.
42. Montero, A., Ariza, J., Corbella, X. *et al*. (2004) Antibiotic combinations for serious infections caused by carbapenem resistant *Acinetobacter baumannii* in a mouse pneumonia model. *J Antimicrob Chemother*, **54**, 1085–91.
43. Gales, A.C., Jones, R.N. and Sader, H.S. (2006) Global assessment of the antimicrobial activity of polymyxin B against 54 731 clinical isolates of Gram-negative bacilli: Report from the SENTRY antimicrobial surveillance programme (2001–2004). *Clin Microbiol Infect*, **12**, 315–21.
44. Rodriguez-Hernandez, M.J., Jiménez-Mejias, M.E., Pichardo, C. *et al*. (2004) Colistin Efficacy in an Experimental Model of *Acinetobacter baumannii* Endocarditis. *Clin Microbiol Infect*, **10**, 581–4.
45. Montero, A., Ariza, J., Corbella, X. *et al*. (2002) Efficacy of colistin versus β-lactams, aminoglucosides, and rifampin as monotherapy in a mouse model of pneumonia caused by multiresistant *A. baumannii*. Antimicrob. *Agents Chemother*, **46**, 1946–52.
46. Levin, A.S.S., Barone, A.A., Penço Santos MV. *et al*. (1999) Intravenous colistin as therapy for nosocomial infections caused by multidrug resistant Pseudomonas aeruginosa and *Acinetobacter baumannii*. *Clin Infect Dis*, **28**, 1008–1.
47. Falagas, M.E., Kasiakou, S.K., Tsiodras, S. and Michalopoulos, A. (2006) The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: A review of the recent literature. *Clin Med Res*, **4**, 138–46.
48. Reina, R., Estenssoro, E., Saenz, G. *et al*. (2005) Safety and Efficacy of Colistin in *Acinetobacter* and Pseudomonas Infections: a Prospective Cohort Study. *Intensive Care Med*, **31**, 1058–65.
49. Li, J., Rayner, C.R., Nation R.L. *et al*. (2006) Heteroresistance to Colistin in Multi-Drug Resistance *Acinetobacter baumannii*. Antimicrob. *Agents Chemother*, **50**, 2946–450.
50. Michalopoulos, A., Kasiakou, S.K., Pastora, Z. *et al*. (2005) Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug resistant Gram-negative bacteria in patients without cystic fibrosis. *Critical Care*, **9**, R53–9.
51. Berg, J.R., Spilker, C.M. and Lewis, S.A. (1996) Effects of polymyxin B on mammalian urinary bladder. *J Membr Biol*, **154**, 119–30.
52. Rodriguez-Hernandez, M.J., Pachón, J., Pichardo, C. *et al*. (2000) Imipenem Doxycycline and Amikacin in Monotherapy and in Combination in *Acinetobacter baumannii* Experimental Pneumonia. *J Antimicrob Chemother*, **45**, 493–501.
53. Wood, G.C., Hanes, S.D., Boucher, B.A., Croce, M.A. and Fabian, T.C. (2003) Tetracyclines for treating multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *Intensive Care Med*, **29**, 2072–6.
54. Pachón-Ibañez, M.E., Fernández-Cuenca, F., Docobo-Pérez, F. *et al*. (2006) Prevention of rifampicin resistance in *Acinetobacter baumannii* in an experimental pneumonia murine model, using rifampicin associated with imipenem or sulbactam. *J Antimicrob Chemother*, **58**, 689–92.
55. Choi, J.Y., Park, Y.S., Cho, C.H. *et al*. (2004) Synergic in-vitro Activity of Imipenem and Sulbactam against *Acinetobacter baumannii*. *Clin Microbiol Infect*, **10**, 1098–1.
56. Ko, W.C., Lee, H.C., Chiang, S.R. *et al*. (2004) *in vitro* and *in vivo* activity of meropenem and sulbactam against a multidrug resistant *Acinetobacter baumannii* strain. *J Antimicrob Chemother*, **53**, 393–5.

57. Lee, C.M., Lim, H.K., Liu, C.P. and Tseng, H.K. (2005) Treatment of Pan-drug Resistant *Acinetobacter baumannii*. *Scand J Infect Dis*, **37**, 195−9.
58. Saballs, M., Pujol, M., Tuban, F. *et al*. (2006) Rifampicin/imipenem combination in the treatment of carbapenem-resistant *Acinetobacter baumannii* infections. *J Antimicrob Chemother*, **58**, 697−700.
59. Pachón-Ibáñez, M.E., Jiménez-Mejias, M.E., Pichardo, C. *et al*. (2004) Activity of Tigeciclyne (GAR-936) against *Acinetobacter baumannii* Strains, Including those Resistant to Imipenem. Antimicrob. *Agents Chemother*, **48**, 4479−81.
60. Dijkshoorn, L., Brouwer, C.P., Bogaards, S.J. *et al*. (2004) The synthetic N-terminal peptide of human lactoferrin, hLF(1−11), is highly effective against experimental infection caused by multidrug resistant *Acinetobacter baumannii*. Antimicrob. *Agents Chemother*, **48**, 4919−21.
61. Taccone, F.S., Rodríguez-Villalobos, H., DeBacker, D. *et al*. (2006) Successful treatment of septic shock due to pan-resistant *Acinetobacter baumannii* using combined antimicrobial therapy including tigecycline. *Eur J Clin Microbiol Infect Dis*, **25**, 257−60.
62. Wagenvoort, J.H. (2002) Epidemic *Acinetobacter baumannii* strain with MRSA-like behaviour carried by healthcare staff. *Eur J Clin Microbiol Infect Dis*, **21**, 326−7.
63. El Shafie, S.S., Alishaq, M. and Leni Garcia, M. (2004) Investigation of an outbreak of multidrug-resistant *Acinetobacter baumannii* in trauma intensive care unit. *J Hosp Infect*, **56**, 101−5.
64. Brooks, S.E., Walczak, M.A. and Rizwanullah, H. (2000) Are we doing enough to contain *Acinetobacter* infections. *Infect Control Hosp Epidemiol*, **21**, 304.
65. Rello J. (1999) *Acinetobacter baumannii* infections in the I.C.U. Customization is the key. *Chest*, **115**, 1226−9.
66. Cisneros, J.M. and Pachón, J. (2003) *Acinetobacter baumannii*: un patógeno Nosocomial de difícil Control. *Enferm Infecc Microbiol Clin*, **21**, 221−3.

9
Fungal Pneumonia

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Introduction

Fungal infections represent a severe cause of morbidity and mortality (20–60%) in high risk patients (ICU patients, immunocompromised, transplant and HIV seropositive patients). Yeasts like the *Candida* species are the fourth or fifth most frequent pathogen isolated from bloodstream infections [1]. *Candida* albicans remains the commonest species associated with deep infection but in the last decade a 'shifting epidemiology' has been confirmed towards nonalbicans species because of a significant increase in the use of fluconazole, both as prophylaxis or long-term suppressive therapy in high risk patients and as first-line and empiric therapy in non-neutropenic patients. Moulds, like *Aspergillus* species, are of particular interest in immunocompromised patients or in surgical patients after severe peritonitis.

The diagnosis of a systemic fungal infection is difficult because of the lack of a laboratory method able to distinguish colonization from infection, often confirmed only by autopsy procedure [2]. However, histologically proven invasive fungal growth in a biopsy of sterile tissues and blood cultures (although their sensitivity is just 70%) ensures the diagnosis. *Candida* pneumonia is very rare in non-neutropenic patients, most commonly caused by haematogenous dissemination rather than by primary invasion. *Candida* pneumonia requires histopathological confirmation because the benign colonization of the airway with *Candida* species is much more common than invasive candidiasis [3]. Invasive aspergillosis and other endemic mycoses are characterized by unknown incubation period (acquired either outside or inside hospital), difficult

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and delayed diagnosis, delayed treatment that is often initiated empirically and a high mortality rate of more than 50 %. [4].

Candida Pneumonia

Candida spp. is a normal inhabitant of the gastrointestinal and the upper respiratory tracts, and can be recovered from sputum in 20−55 % of normal subjects [5]. Therefore, the predictive value of sputum, endotracheal aspirate or even bronchoalveolar lavage (BAL) cultures for true lung infection is far from ideal and a practical and precise method of establishing the diagnosis remains to be developed. However, *Candida* pneumonia does exist and various investigators have proposed its classification in two forms: primary *Candida* pneumonia following aspiration of oropharyngeal secretions [6, 7]; or, more commonly, secondary *Candida* pneumonia complicating haematogenous spread in the setting of disseminated candidiasis [8].

Epidemiology

The true incidence of primary *Candida* pneumonia is unknown and certainly depends on the population under study and the method used to establish its diagnosis. In two autopsy studies looking at a total number of 61 episodes of primary *Candida* pneumonia in cancer patients, the reported incidence was 0.2 and 0.4 %, respectively [9, 6]. More recently, Grossi *et al*. [10] studied 1963 patients who had undergone thoracic organ transplant (1852 heart and 111 lung (35 heart−lung, 30 double-lung, 46 single-lung)) in 12 Italian centres between November 1985 and January 1997; only 12 patients (22.6 % of the 51 patients with invasive fungal infection) were reported with candidiasis. There were seven episodes (58.3 %) of candidemia, two (16.7 %) of esophagitis, two (16.7 %) episodes of gastritis and one (8.3 %) episode of tracheobronchitis. Interestingly, there was no case of *Candida* pneumonia.

Similar findings were reported by Sharma *et al*. [11] in a study of the pulmonary autopsy findings from 71 deceased adult bone marrow transplant (BMT) recipients; only one case of *Candida* bronchopneumonia was found. On the contrary, the lung is very frequently involved in the setting of invasive candidiasis [8, 12−14]. For example, an autopsy study of 720 patients with haematological malignancies who received fluconazole prophylaxis, showed that approximately 13 % of patients (94/720) had post-mortem evidence of candidiasis; in 67 % of these (63/94) histological evidence of tissue invasion by pseudohyphae was noted [15]

Candida Pneumonia and *Candida* Species

Based on the data from Masur *et al*. [9] and Haron *et al*. [6], *C. albicans* is responsible for the majority of cases of primary pneumonia, while *Candida tropicalis*, *Candida glabrata* and *Candida parapsilosis* are the most frequent non*albicans* species implicated in cases of primary and secondary pneumonia. It seems that non*albicans* species are isolated with increased frequency at some medical centres [16, 17].

Clinical Manifestations

Patients with primary *Candida* pneumonia are usually severely ill, presenting with fever, dyspnea, tachypnea and chest pain. Secondary *Candida* pneumonia may be asymptomatic or its symptoms may be overshadowed by the intense manifestations of the episode of invasive candidiasis. Since most cases remain undiagnosed or are treated empirically, reliable mortality data are not available.

Diagnostic strategies

Candida pneumonia is exceedingly difficult to diagnose because colonization of the airway and/or contamination of the respiratory secretions by oropharyngeal material are very common. Histologic confirmation of tissue invasion is mandatory to establish the diagnosis. El Ebiary *et al*. [18] undertook a study on 25 non-neutropenic, mechanically ventilated Intensive Care Unit (ICU) patients who died in their ICU; the aim was to assess the incidence and significance of the isolation of *Candida* species from quantitative cultures of immediate *post-mortem* lung biopsies and different respiratory sampling techniques. Ten (40 %) patients had at least one pulmonary biopsy yielding *Candida* spp. but only two of them (8 % of the total population) had definite pulmonary candidiasis. Using the presence of confirmed pulmonary candidiasis as the gold standard (histology or pleural fluid culture), the sensitivity of the different diagnostic methods were: 100, 50, 50, 75 and 100 % for endotracheal aspirates, Protected Specimen Brush (PSB), BAL, guided lung biopsies and blind biopsies, respectively; the specificities were: 67, 55, 70, 33 and 20 %, respectively. It was concluded that 'the presence of *Candida* in respiratory samples, independently of quantitative cultures, is not a good marker of *Candida* pneumonia'.

The development of molecular techniques will hopefully provide a fast, accurate and noninvasive way to establish the diagnosis of candidiasis, but the results have not always been optimistic so far. For example, Ljungman *et al*. [19] prospectively studied 20 acute leukaemia and 15 autologous stem cell transplant (SCT) patients. Blood samples were examined for fungal DNA by polymerase chain reaction PCR. Six samples were positive for *Candida* DNA. *Candida* PCR was positive in two patients with fever of unknown origin (FUO), one patient with a bacterial infection, one patient with fungemia and in one afebrile patient. Three patients had confirmed *Candida* infections; one was PCR positive and two were negative. *Candida* PCR conferred no diagnostic benefit in this study.

Moreover, and despite the development of sophisticated radiological techniques, no radiological pattern can be considered characteristic of either primary or secondary *Candida* pneumonia [20]. Some patients may even have normal chest X-rays [9]. Abnormal reported findings include bilateral or unilateral, lobar or nonlobar infiltrates [21, 9]. However, pleural effusions [21] and cavitating lesions [22, 23] have also been described. In a recent study comparing the high-resolution computed tomography (HRCT) findings of pulmonary invasive aspergillosis and candidiasis in immunocompromised patients, the presence of cavitation, ground glass opacities and the computed tomography (CT) halo sign were similar in both groups [24].

Histopathology

As mentioned previously, the diagnosis of *Candida* pneumonia can only be established solidly with a histopathological sample. In the setting of primary *Candida* pneumonia, there are clusters of pseudohyphae and/or yeasts around the bronchioles with an associated acute inflammatory cell infiltrate with bronchopneumonia and abscess formation. The hallmark findings of secondary *Candida* pneumonia are miliary microabscesses (2−4 mm) randomly distributed in the pulmonary parenchyma with central necrosis and varying amounts of pseudohyphae, budding yeasts and acute inflammation.

Treatment

The Infectious Diseases Society of America (IDSA) guidelines [3] suggest that deoxycholate amphotericin B (0.7−1.0 mg/kg/day) is the treatment of choice and oral or intravenous fluconazole, with caspofungin or liposomal amphotericin B (LAmB) are suitable alternatives. In cases of secondary pneumonia associated with haematogenous disseminated infection, therapy should be directed to disseminated candidiasis, and include clearing local sites of infection (i.e. replacement of central venous catheters) along with any associated sites of systemic infection. An exciting therapeutic progress seems to find its way to clinical practice after a recent double-blind, randomised study showed that the combination of lipid-associated amphotericin B with mycograb, a human recombinant monoclonal antibody against heat shock protein 90, was superior to lipid-associated amphotericin B plus placebo in patients with culture-confirmed invasive candidiasis, in terms of clinical response, mycological response, *Candida*-attributable mortality and rate of culture-confirmed clearance of the infection [25].

The Significance of *Candida* Isolation from the Respiratory Tract of ICU Patients

Recovery of *Candida* spp. from the respiratory tract of an otherwise immunocompetent critically ill patient receiving mechanical ventilation (MV) is common. For example, in a recently published multicentre study of 803 immunocompetent critically ill patients receiving MV for ≥ 2 days, 214 patients (26.6%) had respiratory tract *Candida* colonization [26]. However, the clinical relevance of 'positive' unprotected or protected, proximal or distal, specimens from ICU patients after $\geq 2-3$ days of MV has remained a 'hot' and controversial topic for the last two decades.

In one of the first studies in the field, Rello *et al*. [27] performed a retrospective chart review in all non-neutropenic adult patients with *Candida* spp. isolates from respiratory secretions obtained by bronchoscopy over a five-year period (1991−1995) in a 16-bed mixed ICU of a 600-bed teaching hospital. Potential risk factors, therapeutic decisions and outcome were recorded. Microbiological findings, chest radiograph reports and pathologic material were reviewed. Thirty-seven consecutive patients with positive respiratory cultures for *Candida* were analysed. Thirty-two of these 37 patients (86.5%) received antibiotic therapy prior to sampling and 23 (62.2%) were intubated. Contamination was classified as definite in three patients

(8.1 %), probable in 30 (81.0 %) and indeterminate in two cases (5.4 %). Two additional patients (5.4 %) received antifungal agents for systemic candidiasis. No cases of pulmonary candidiasis could be demonstrated, although 24 of 28 patients showed PSB cultures $\geq 10^3$ cfu/mL. Very recently, in a retrospective study in a trauma ICU of 1077 BAL cultures, Wood *et al*. [28] found 85 (8 %) *Candida* spp., representing 64 episodes of possible *Candida* ventilator-associated pneumonia (VAP). No colony counts exceeded the diagnostic threshold for bacterial VAP ($\geq 10^5$ cfu/ml). Only two of 64 episodes (3 %) were treated with systemic antifungals and three other episodes (5 %) were treated because of concomitant therapy for *Candida* at other sites. The majority of episodes were not treated with antifungals and were considered contaminants (59/64, 92 %). No patients developed subsequent candidemia and most follow-up BALs (74 %) were negative for *Candida*. Overall mortality (17 %) was similar to previous patients with a similar severity of injury at the study centre (18 %). The authors' conclusion was that '*Candida* isolation from BAL in quantities below the diagnostic threshold for VAP in this population does not require antifungal therapy'.

Despite the almost unanimous conclusion by experts that mere respiratory isolation of *Candida* spp. has little prognostic value as far as true lung invasion is concerned, specialists in intensive care medicine have not adopted a clear-cut diagnostic or therapeutic approach. Azoulay *et al*. [29] presented a clinical vignette ('a mechanically ventilated patient with an acute exacerbation of chronic obstructive lung disease and a positive tracheal aspirate for *Candida*') to 198 French intensive care medical specialists with a special interest in infectious diseases. The respondents recommended BAL (62 of respondents), protected distal sampling and PSB (59 %), transbronchial biopsy (39 %) and tracheal aspiration (12 %) for the diagnosis of *Candida* pneumonia. A positive airway specimen was felt by most respondents (83 %) to indicate colonization; 67 % of respondents recommended tests for systemic candidiasis in this situation and 56 % serial sampling to compute the colonization index. Responses varied widely, with 38 % of respondents diagnosing clinically insignificant colonization, but 24 % recommending antifungal treatment and 62 % serial testing to assess the *Candida* colonization index. Intensive care medical specialists with greater experience with severely immunocompromised patients were more aggressive in their diagnostic management.

In a similar study, Eggimann *et al*. [30] presented case scenarios of candidiasis during interactive sessions at national specialty meetings to 65 infectious disease and 51 critical care physicians in Switzerland. It is noteworthy that in mechanically ventilated patients the isolation of 104 *Candida* spp. from BAL was considered a colonizer by 95 % of the infectious disease specialists, compared to 47 % of critical care specialists, with a marked difference in the use of antifungal agents (5 vs 50 %). These data highlight differences between management approaches for candidiasis in two groups of specialists, particularly in the reported use of antifungals.

A hypothesis-generating study [26] found that mechanically ventilated patients with *Candida* spp. respiratory tract colonization had longer stays in ICU and hospital but similar mortality to unexposed (not colonized) patients. This matched exposed/unexposed nested cohort study identified bronchial *Candida* colonization as

an independent risk factor for pneumonia (24.1 vs 17.6%; adjusted odds ratio [OR], 1.58; 95% confidence interval [CI], 0.94 to 2.68; p = 0.0860); the risk was greatest for *Pseudomonas* pneumonia (9 vs 4.8%; adjusted OR, 2.22; 95% CI, 1.00 to 4.92; p = 0.049). Since it has been previously shown that in mechanically ventilated patients *Pseudomonas* can form a dense biofilm on *Candida* filaments [31], a causal relationship between respiratory tract *Candida* colonization and subsequent *Pseudomonas* ventilator-associated pneumonia is biologically plausible. If this finding is confirmed in future studies, identification of *Candida* spp. in the respiratory tract may no longer be considered an innocuous finding in critically ill patients.

As noted by El-Ebiary *et al*. [18] in the ultimate paragraph of their seminal autopsy study, there is clearly a need 'for more research on markers of *Candida* pneumonia, the significance of ante-mortem isolation of *Candida* in respiratory samples and the investigation of the pathogenesis of this fungal pneumonia in mechanically ventilated patients'.

Aspergillus Pneumonia

Aspergillus is a ubiquitous fungal pathogen, found in soil, water, air and in decaying vegetation, where it is particularly common. Hosts with normal pulmonary host defences very rarely develop disease despite routine exposure to the organism during normal daily life. In contrast, patients with reduced pulmonary host defences have an increased susceptibility to the organism and rather frequently develop invasive disease. Depending on the immune status of the host, *Aspergillus* infection causes a spectrum of illnesses, ranging from allergic reactions (allergic bronchopulmonary aspergillosis, ABPA), colonization of pre-existent lung pathology without invasion (aspergilloma) or with invasion (chronic necrotizing aspergillosis) to invasive disease (invasive aspergillosis) (Table 9.1). Acute invasive pulmonary disease, the major form of nosocomial pulmonary disease caused by *Aspergillus*, is the focus here.

Epidemiology

Deficiencies in host defences that render a patient susceptible to invasive aspergillosis are quite complex but can be broadly divided into three major categories: neutropenia; qualitative defects in phagocyte function; and deficits in cell-mediated immunity [32]. Therefore, the major predisposing factors for the development of *Aspergillus* infections are:

Neutropenia. The profound (< 100 neutrophils/μL) and prolonged (> 10 days) neutropenia pose high risks for invasive aspergillosis, usually in haematology patients receiving multiple cycles of potent cytotoxic chemotherapy or myeloablative haematopoietic stem cell transplantation (HSCT).

Haematopoietic stem cell transplantation. The temporal distribution of risk in this patient population is typically bimodal: in the early stage, the major risk factor is neutropenia after the conditioning regimen. However, the increasing use of non-myeloablative transplantation procedures and neutrophil growth factors shorten this period. Today, most cases of invasive disease occur after neutrophil recovery in

Table 9.1 Clinical syndromes caused by *Aspergillus*.

Clearance of microorganism.	Most common outcome in normal host
Colonization	Persistence of *Aspergillus* in airways or sinuses without causing disease
Allergic reactions	Allergic bronchopulmonary aspergillosis (ABPA). Extrinsic allergic alveolitis. Maybe involved in allergic asthma and/or rhinosinusitis
Invasive disease	Acute (<1 month). Subacute (1–3 months). Chronic (<3 months)
Aspergilloma	Fungal mass, in the lung or sinus, usually in pre-existing cavitary lesions (tuberculosis, cancer, etc.); non-invasive
Airway involvement	Obstructing tracheobronchitis – *mucus impaction, non-invasive*. *Aspergillus* tracheobronchitis – *superficially invasive*. Ulcerative tracheobronchitis – *locally invasive; typically at lung transplant anastomosis* – Pseudomembranous trachobronchitis – *extensive disease, locally invasive; associated with IPA*

the setting of potent immunosuppressive therapy for graft-versus-host disease [33]. Allogeneic HSCT recipients have a much higher risk of invasive aspergillosis than autologous HSCT recipients because of the greater intensity of immunosuppression. Factors associated with an increased risk include receipt of T-cell depleted or CD34-selected stem cell products, receipt of corticosteroids or TNF-alpha antagonists, neutropenia, lymphopenia, cytomegalovirus disease and graft-versus-host disease (GVHD), which greatly prolongs the period of risk for invasive infection [34]. Corticosteroids seem to have an interesting role; besides their well-known immunosuppressive effects, they seem to directly stimulate growth of *Aspergillus* fumigatus, at least in vitro, possibly via sterol binding in the fungus [35]. The incidence of invasive aspergillosis in allogeneic HSCT is about 8−15 % and is associated with high mortality.

Solid Organ Transplantation (SOT). The period of risk is usually the first year post-transplant, especially in the setting of potent immunosuppression to treat allograft rejection. Among SOT recipients, lung or heart−lung recipients are at higher risk. Anastomotic infection is rather common, but disease ranges from ulcerative tracheobronchitis to disseminated infection. *Aspergillus* colonization within the first six months of transplant seems to be predictive of subsequent invasive disease [36].

Other patients receiving potent immunosuppressive therapy. High-dose systemic steroids (e.g. prednisone equivalent > 20 mg/day for > 3 weeks), calcineurin inhibitors, anti-lymphocyte immunoglobulin preparations, anti-TNF-alpha agents and combinations of the above with cytotoxic agents, such as those used in the treatment of autoimmune disease, are the most important risk factors in this patient group.

Aids. Invasive aspergillosis is relatively uncommon in AIDS today because of the use of highly potent antiretroviral therapy. It usually occurs in CD4 depleted patients (< 100 per μL), commonly with co-existent neutropenia or corticosteroid use, and has an ominous prognosis.

Chronic granulomatous disease (CGD). Invasive aspergillosis is the most important cause of mortality in this patient group. Despite the routine use of Interferon-gamma for prophylaxis, fungal infection is a persistent problem with an incidence of 0.1 fungal infections per patient-year [37]. Itraconazole use seems safe and effective in preventing fungal disease in CGD patients [38].

Critically ill patients. Recently, invasive aspergillosis cases have been described with increasing frequency in critically ill patients without malignancy [39]. Two at-risk patient groups seem to stand out: chronic obstructive pulmonary disease patients, especially with concomitant corticosteroid use, and patients in severe hepatic failure. Inhalation of spores is believed to be the usual mode of transmission. In the community spores are widely distributed in soil, air or water, but they are also present in hospital, especially during periods of construction work. Other sources have been also implicated in the hospital environment, for example contaminated water aerosols [40]. It is commonly hypothesized that infections occur in immunocompromised patients after endogenous reactivation of prior colonizing aspergilli acquired before hospital admission. However, there are well-documented hospital epidemics due to exposure to an extremely high environmental load, usually the result of construction or renovation work in or near the hospital. In an interesting review of the epidemiology of invasive aspergillosis, Manuel and Kibbler [41] conclude that up to half of the cases could be acquired in hospital. There exists a significant positive link between the incidence of nosocomial aspergillosis and the degree of environmental fungal contamination [42].

In a recent systematic review [43] of nosocomial *Aspergillus* outbreaks, 53 outbreaks and 458 patients were analysed. Patients with haematology malignancy were most common (65.3 %), followed by solid organ transplant (renal and lung) or other immunocompromised patients (high-dose steroids, neonates, cancer, chronic lung disease) and surgical patients with no severe immunodeficiency (thoracic surgery, cataract surgery, ICU patients). The major site of primary infection was the lower respiratory tract (77.7 %). Species identified most often from clinical samples were *Aspergillus* fumigatus (50 %) and *Aspergillus* flavus (28.8 %). Airborne transmission was documented in all cases but one. Among 41 outbreaks where the source was tracked down, 63 % were attributed to construction or renovation work in the hospital or surrounding area and 22 % to a contaminated or defective air supply system. Mortality was greater (57.6 %) among patients with haematologic malignancies; this was significantly higher compared to the mortality of patients without any known immunodeficiency.

Pathogenesis

The usual route of infection is through airborne inhalation of conidia into the lungs. Intact ciliary clearance mechanisms are the first line of defence. Alveolar

access depends on conidial size and *Aspergillus* fumigatus owes part of its increased pathogenicity for humans to the suitable size of its spores [44].

At the alveolar level, the pulmonary macrophage is responsible for ingesting and killing conidia, which when not scavenged by alveolar macrophages enlarge and germinate, transforming into hyphae with subsequent vascular invasion and dissemination. The incubation period for conidial germination in pulmonary tissue is variable, ranging from two days to months and may even vary for different species. After cells germinate, polymorphonuclear cells act to extracellularly kill both swollen conidia and hyphae. Efficacy may be enhanced by opsonisation of conidia with complement or other molecules, such as mannose-binding protein or surfactant proteins. Antibodies develop but they are neither protective nor diagnostic. The role of cellular immunity is not well established, but experiments on a murine model of invasive pulmonary aspergillosis suggest that an IL4-induced Th1 response was associated with favourable outcome. Toll-like receptors appear to be crucial for the recognition of *Aspergillus* fumigatus by human cells; recognition by TLR2 and TLR4 result in intracellular activation and cytokine production. A variety of toxins are produced by aspergilli, including aflatoxins, ochratoxin A, fumagillin, gliotoxin and various proteases and phospholipases, although their role as virulence factors is not well established [44].

Corticosteroids seem to have an interesting mediating role in the pathogenesis of the disease, explaining its major role as a risk factor; they decrease oxidative killing of the organism by macrophages but they also seem able to increase the linear growth rate of the hyphae by 30−40% and fungal cell synthesis by more than 150% [35].

Clinical Manifestations

Invasive aspergillar disease most frequently begins in the lung following inhalation; invasion of hyphae in the pulmonary vasculature occurs in as many as a third of patients with invasive pulmonary aspergillosis and is the hallmark of disseminated disease occurring through haematogenous spread to the brain, thyroid, liver, spleen, kidney, bone, heart and skin. Disease can also spread by contiguous extension from the lungs to the pleura, vertebrae or pericardium.

Invasive pulmonary aspergillosis rarely manifests before 10−12 days of profound neutropenia, and a significant number of patients have manifestations of invasive pulmonary disease either on admission or within the first two weeks of hospital admission. The clinical picture is characterized by progressive dry cough, dyspnea, pleuritic chest pain, fever despite broad-spectrum antibiotics and nodular pulmonary infiltrates. Symptoms may be reduced if the patient is profoundly neutropenic or on high-dose steroids. Less often, hemoptysis, pleural effusion and pneumothorax can occur. Laboratory signs are notoriously non-specific and may include elevated bilirubin or lactate dehydrogenase, coagulation abnormalities or C-reactive protein (CRP) elevation. In some patients, typically in lung transplant and AIDS patients, aspergillar tracheobronchitis develops. In lung transplants it is usually the suture line of the lung allograft that is affected, occasionally leading to dehiscence of the anastomotic site. It is followed by non-specific symptoms such as dyspnea, cough,

chest pain, fever or haemoptysis, unilateral wheeze or stridor and an obstructive flow pattern in pulmonary function testing. Bronchoscopically it is characterized by extensive pseudomembranous or ulcerative lesions and may resemble a rejection reaction. Chest X-ray is normal and diagnosis depends on clinical suspicion and bronchoscopy with biopsies.

Often enough, especially in severely immunocompromised patients, invasive pulmonary disease is followed by dissemination to other sites, providing clues to an elusive pulmonary diagnosis and, potentially, tissue more amenable to biopsy (e.g. skin). It is thus important to seek out signs of disseminated disease on suspicion of invasive pulmonary disease.

The paranasal sinuses are a frequent concurrent infection site with fever, cough, epistaxis, sinus discharge and headaches the most common symptoms. An ulcerated nasal lesion with an eschar or nonsensitive area are useful clinical signs. Contiguous progression to other paranasal sinuses, palate, orbit or brain can occur. Sinus CT imaging can be helpful and biopsy is diagnostic. Focal neurologic signs, alteration in mental status and headache point to cerebral aspergillosis. Concomitant pulmonary infection is usually but not always present. CT or Magnetic Resonance Imaging (MRI) of the brain is characteristic showing a brain abscess with peripheral ring enhancement along with surrounding edema and may be hemorrhagic. Biopsy is needed for diagnosis, although in cases of documented disseminated disease the diagnosis is often presumed. Cutaneous infection is an interesting sign of disseminated disease, manifesting as an area of rapidly increasing erythema with a necrotic, often ulcerated, centre, resembling pyoderma gangrenosum. It can serve as easily-accessible tissue for a diagnostic biopsy. Other uncommon sites of disease extension are bone, most commonly the vertebral column, heart, kidney and intestine.

Diagnosis

Diagnosis of invasive pulmonary aspergillosis is challenging because clinical and radiological signs are very insensitive or non-specific. Tissue biopsy is invasive and often not possible. On the other hand, early diagnosis leading to prompt institution of appropriate therapy may result in improved patient outcomes.

A definite diagnosis of invasive aspergillosis requires a tissue biopsy demonstrating invasion with hyphae and a positive culture for *Aspergillus* [45]. Angioinvasion of hyphae leading to vascular thrombosis, tissue infarction and coagulative necrosis is characteristic in neutropenic patients as well as in non-neutropenic allogeneic HSCT recipients with GVHD [46]. Definite diagnosis can also be established with positive cultures from a normally sterile site such as CSF; blood cultures are very rarely positive. In biopsies, hyphae can be visualized by common fungal stains such as Gomori methenamine silver (GMS) or periodic acid−Schiff (PAS). *Aspergillus* hyphae are hyaline, septate, acute-angle branched and 3−6 μm in width. These features generally differentiate *Aspergillus* from agents of zygomycosis but not from other opportunistic moulds, including *Scedosporium*, *Fusarium* and others, so that species identification in positive cultures is also needed to confirm the diagnosis [44]. A positive culture of respiratory specimens for *Aspergillus* is not uncommon and merits cautious

interpretation. In series of cases of invasive aspergillosis the sensitivity of a positive respiratory culture ranged from 15 to 69%; higher values were obtained with bronchoalveolar lavage specimens [47]. However, only 12% of patients with positive cultures are diagnosed with invasive disease. The predictive value of a positive culture for invasive aspergillosis is thus best evaluated in the context of a compatible clinical picture and the presence of risk factors [48]. A high-risk patient (allogeneic BMT, neutropenia, haematological cancer) with a positive respiratory culture and compatible clinical picture with new pulmonary infiltrates is defined as a probable case of invasive pulmonary aspergillosis (70–80% positive predictive value). On the other hand, a positive culture in a low-risk patient (e.g. cystic fibrosis) very rarely represents invasive disease. In intermediate risk patients (autologous BMT, malnutrition, corticosteroids, HIV, solid-organ transplants) the culture result has lower predictive value (20–50%) and the clinician must aggressively determine the relevance of an *Aspergillus* isolate with regard to disease by other means (histopathology, radiology and/or serology) [49].

Plain chest radiographs are of limited diagnostic value because they are insensitive and nonspecific. One or more nodules is the most common finding in chest CT in early invasive aspergillosis in neutropenic patients and HSCT recipients [50]. In extensive infection, multiple diffuse nodular pulmonary infiltrates carry an extremely poor prognosis (Figure 9.1). Pleural effusions can occur and may be more common than previously considered [51]. The presence of a 'halo' sign of low attenuation surrounding a nodular lesion is highly suggestive of invasive pulmonary aspergillosis in patients with prolonged neutropenia. However. it is also characteristic of other angioinvasive organisms, such as *Zygomycetes*, *Fusarium*, *Scedosporium* as well as *P. aeruginosa* and *Nocardia*. It has been used in patients with neutropenic fever as a marker for initiating early antifungal therapy, which may have improved outcome [52]. The incidence of the 'halo' sign progressively decreases during the first week of therapy as the frequency of the 'air-crescent' sign increases, denoting cavitation of the lesion, usually coinciding with neutrophil count recovery (Figure 9.1). It is notable that the median volume of lesions increases during the first week of therapy and remains stable during the second, without predicting a negative response to therapy [53]. It should also be noted that the diagnostic accuracy of radiographic findings has not been as well validated in groups other than neutropenic and bone marrow transplant patients.

Recently, testing for *Aspergillus* cell-wall antigens has been introduced in clinical practice, mainly as surveillance tools in high risk patients (e.g. allogeneic HSCT recipients) to detect early aspergillosis before clinically overt disease.

Galactomannan is a polysaccharide component of the cell wall that is released by *Aspergillus* during growth. A double sandwich enzyme-linked immunosorbent assay (ELISA) for its detection has been approved by the US Food & Drug Administration (FDA) and serial measurements are made, usually twice weekly, but results are not always straightforward to interpret. In a recent meta-analysis, including 27 studies in high-risk patients (haematologic malignancy and transplant patients) where galactomannan testing was used as a surveillance tool, results for assay performance were reported [54]. The overall sensitivity was 61–71%, specificity

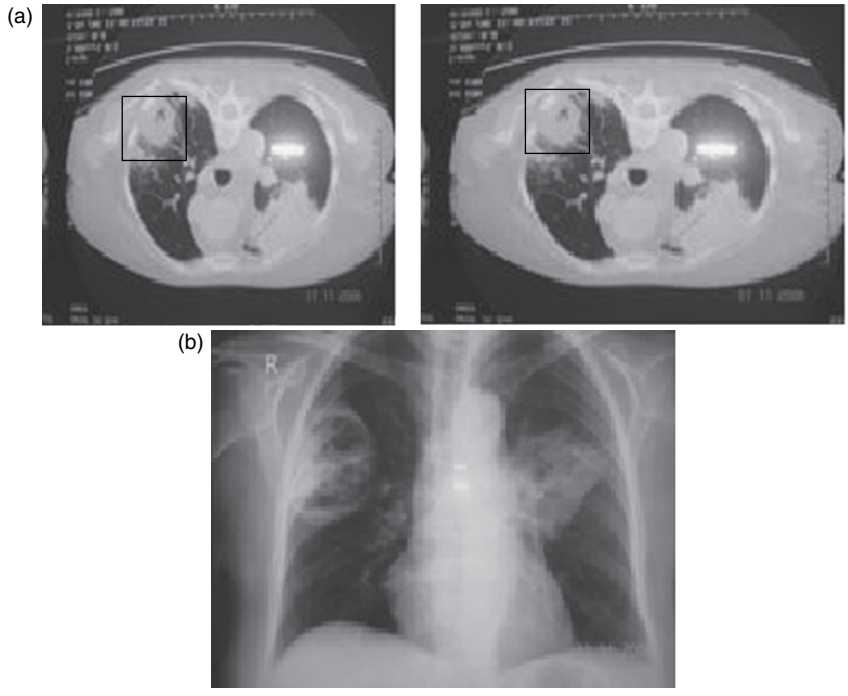

Figure 9.1
Specific (a) and non-specific (b) indicators of probable invasive aspergillosis in patients at high risk.*

* (a) Air-crescent sign – crescent of gas surmounting a retracting soft tissue sequestrum of necrotic tissue within a nodular or cavity lesion; (b) Cavitary lesions in the chest-x-ray.

89–93% with a significant negative (95–98%) but low positive predictive value (26–53%), suggesting that the assay is valuable in ruling out the diagnosis but less so in confirming it. The test performed differently in different patient subgroups, for example it had much less diagnostic accuracy in solid organ transplant recipients. Lowering the cut-off limit for a positive result seemed to increase test accuracy at the expense of sensitivity. Antifungal therapy reduced dramatically the sensitivity of the assay, a relevant finding for patients at risk receiving prophylaxis. There have also been reported false positive results with concomitant use of beta-lactams (e.g. piperacillin–tazobactam), even five days after the cessation of treatment [55]. The galactomannan assay should be used only in high-risk patients. The combination of a high-risk patient with compatible clinical syndrome and chest imaging plus two consecutive positive serum galactomannan assays has been defined as 'probable' invasive aspergillosis [45].

The diagnostic role of galactomannan measurement or quantitative PCR in bronchoalveolar lavage fluid is unknown. An interesting study [56] compared galactomannan assay, quantitative real-time PCR and quantitative cultures in an experimental model of invasive aspergillosis. Galactomannan performed slightly better than qPCR and both were better than BAL cultures. All techniques lowered impressively their diagnostic yield when antifungal therapy was used. Published

studies in humans support the view that use of the galactomannan assay and quantitative PCR analysis in BAL fluid could increase the diagnostic sensitivity for invasive aspergillosis in high-risk patients [57].

Detection of serum beta-glucan, another cell wall constituent, has also been recently approved for use by the FDA. It has been shown to be highly sensitive and specific in detecting early invasive fungal infections in immunocompromised patients [58]; However, more research is needed to establish its role in invasive aspergillosis.

Treatment

The efficacy of antifungal therapy in invasive aspergillosis is generally poor. In general, therapeutic outcome depends on the extent of the disease and the degree of immunosuppression of the patient, with worse outcome in disseminated and/or central nervous system (CNS) disease and in allogeneic bone marrow transplants. Favourable responses were reported to be less than 40 % and overall case fatality rate about 60 % [59, 60]. However, these numbers may have changed since the introduction of voriconazole and echinocandin use; bearing in mind that published trials show significantly improved prognosis for patients receiving newer drugs, it might be expected that changes in outcome will be mirrored in future observational studies [108].

Amphotericin B deoxycholate has traditionally been standard therapy for invasive aspergillosis. However, its limited efficacy has been well documented in several studies, with overall response rates ranging between 10−25 % [61]. Also, renal toxicity is common, evident in about 30 % of patients, with an associated six-fold increase in mortality and augmentation of hospitalisation costs [62]. Primary therapy of invasive aspergillosis with amphotericin B is no longer recommended. Furthermore, there are few randomised studies evaluating lipid amphotericin formulations, suggesting less toxicity but not significantly better efficacy than the deoxycholate salt. Lipid preparations of amphotericin are not suitable alternatives for primary invasive aspergillosis treatment and are approved for use only as salvage therapy.

Voriconazole is now a standard primary therapy for invasive aspergillosis. This recommendation is based on a landmark study [61] involving 391, mostly haematological, patients with definite or probable aspergillosis randomised to receive either voriconazole or amphotericin B deoxycholate treatment. Successful outcome at three months, defined as complete or partial response to treatment, was significantly better in the voriconazole group (52.8 %) versus standard treatment (31.6 %). Survival at three months was better in the voriconazole group (70.8 %) compared to the amphotericin group (57.9 %). Voriconazole seems to be the best initial therapy choice and results in fewer switches to salvage antifungal therapy because of drug intolerance or insufficient response [63]. It has also demonstrated favourable activity in paediatric patients, as well as in difficult to treat conditions such as central nervous system infections and osteomyelitis. In clinical trials, voriconazole has been well tolerated. It has, however, significant drug interactions, especially with immunosuppressive drugs, because of p450 isoenzyme inhibition. Intravenous formulations should be used with caution in patients with pre-existing significant renal impairment because

of the potential of the cyclodextrin vehicle to accumulate in serum and worsen renal function. The most common adverse effect is visual disturbance (up to 45 %) described as blurred vision, altered visual or colour perception and photophobia; it is dose related, usually transient and resolves without intervention. Other adverse events include liver abnormalities in 10–15 %, skin rashes in 6 %, nausea and vomiting in 2 % and anorexia in 1 %.

Among the newer triazoles, posaconazole has been effective (43 % response rate), when studied as salvage therapy [64] in patients with refractory invasive fungal infection in a multicentre, open-label study. It has also been shown to be effective in chronic granulomatous disease patients [65]. Itraconazole has a documented efficacy (about 40 %) against invasive aspergillosis, but has been mainly used for prophylaxis [66]. It is approved for empiric antifungal therapy in febrile neutropenia patients. It has negative cardiac inotropic effects and the intravenous formulation should be used with caution in renal failure patients because of potential cyclodextrin vehicle toxicity.

Caspofungin has not been evaluated as initial monotherapy for invasive aspergillosis in clinical trials. Its use as salvage therapy in patients refractory or intolerant to either voriconazole or amphotericin had acceptable efficacy (45 % favorable response) and safety profile [67, 68]. It is approved as salvage therapy for patients refractory or intolerant of standard therapies.

The idea of combination therapy with an echinocandin with either a triazole or an amphotericin B preparation is appealing, based on the rationale that echinocandins target the β-glucan constituent of the fungal cell wall while polyenes and azoles target distinct sites on the cell membrane. The combination in *vitro* seems to have neutral to synergistic activity, but results from animal models have been conflicting. In a clinical trial [69] comparing voriconazole alone versus voriconazole and caspofungin as salvage therapy after failure of initial amphotericin B treatment, the combination fared better in three-month survival rate (32 vs 63 %, respectively). The combination of caspofungin and amphotericin B has not been studied in a controlled design, but it has been shown to have a 42 % response rate when used as salvage therapy after liposomal amphotericin B monotherapy failure [70]. It is clear that a randomised, prospective study is needed to define the benefit of combination therapy in invasive aspergillosis.

A prompt diagnosis and aggressive initial therapy are both critical in improving the outcome of this infection, maybe with the use of chest CT and galactomannan enzyme immunoassay. Voriconazole is the primary therapy of choice; if the patient does not respond or tolerate it, caspofungin, another triazole or a lipid formulation of amphotericin B is the next choice. The use of combination therapy in a salvage setting seems to be justified because of the poor outcomes of a single agent in progressive infection [32].

Because of the bad prognosis of invasive aspergillosis, several immune augmentation interventions have been tried, showing promising results at an experimental level, with few however reaching clinical significance [32]. Recombinant interferon gamma is licensed as a prophylactic agent in patients with chronic granulomatous disease, as it has been shown to reduce the number and severity of (mostly bacterial) infections by 70 % [71]. Colony-stimulating factors have also several theoretical advantages and

positive results from experimental studies. However, the clinical database for CSFs as adjunctive therapy for fungal infections is inadequate for assessing efficacy. The American Society of Clinical Oncology appropriately advises that a CSF should be considered as adjuvant therapy in febrile neutropenic patients during serious infections, such as invasive fungal disease[72].

Prophylaxis

Preventive measures include reducing the environmental exposure of patients to sources of infection and antifungal prophylaxis.

High-risk patients are usually placed in protective isolation rooms in which positive pressure is maintained. (Air pressure in such rooms is higher than that in surrounding areas, thus preventing the ingress of potentially contaminated air). These sealed rooms are provided with high-efficiency particulate air (HEPA) filters and frequent air changes, significantly reducing the concentration of fungal spores and the incidence of invasive aspergillosis [73]. In addition, horizontal laminar air flow (LAF) is provided in some facilities, where air is swept across the room parallel to the floor driving contaminants out through the ducts, involving many more air changes per unit time [74].

There have been no randomised clinical trials evaluating positive pressure ventilation rooms as a prevention measure and it is not clear whether the beneficial outcomes reported in some of the studies represent a positive result of the specific intervention or occur as part of the natural history of the outbreak [75]. There are studies supporting the value of HEPA filtering of the air in reducing the incidence of invasive aspergillosis [76], although it is sometimes overwhelmed during building renovation, when LAF may be required. The use of high-efficiency filtration masks (filtering to a particle size of 0.1 μg) when transporting an at-risk patient outside the positive pressure room (operating theater, X-ray department) decreased significantly the incidence of invasive aspergillosis [77] during a period of hospital construction.

Several measures have been proposed for preventing nosocomial invasive aspergillosis, including [78, 75]: avoiding non-emergency admissions during heavy construction periods; locating high-risk patients as far as possible from areas of demolition or construction; sealing off patient care areas with adequate and impermeable barriers, keeping doors and windows closed; verifying that HEPA filtration is sufficient and proper air exchange rates are maintained; aiming for positive pressure in patient rooms and for negative pressure in in-house construction areas; wet-cleaning wards thoroughly without raising dust; performing infection surveillance in patients that are at increased risk of invasive aspergillosis.

Targeted primary antifungal prophylaxis for haematopoietic stem cell transplantation or haematological patients who are at high risk of developing invasive fungal infections is not currently recommended [79]. Agents evaluated with no conclusive results include a low-dose of amphotericin B or its lipid preparations, aerosol forms of amphotericin B, fluconazole, itraconazole and caspofungin. In a interesting review and meta-analysis, Glasmacher and Prentice [80] concluded that itraconazole is effective and superior to fluconazole as an antifungal prophylaxis in neutropenic patients with haematological malignancies and in patients after allogeneic stem cell

transplantation, reducing the incidence and mortality of invasive fungal infection, suggesting that an evidence-based recommendation be made.

Itraconazole appears to be helpful in reducing the incidence of serious fungal infections in chronic granulomatous disease patients [38].

After recovery from an episode of invasive aspergillosis, patients are at high risk of recurrence during subsequent immunosuppression [81]. Secondary prophylaxis with an agent active against filamentous fungi is advised for the entire period of immunosuppression.

Endemic Mycoses

Endemic mycoses are dimorphic fungi that grow in mycelial form in the environment (25°C), but in yeast form in the body (37°C). The major causative agents of endemic mycoses are: *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Penicillium marneffei, Paracoccidioides brasiliensis* and *Sporothrix schenkii*. Each has a distinct geographic distribution (Table 9.2). These fungi are

Table 9.2 Summary of the main characteristics of the endemic mycoses.

Endemic mycoses	Areas of endemicity	Clinical presentations	Diagnostic tests	Treatment
Histoplasmosis	Ohio and Mississippi River valleys. Eastern half of the United States. Latin America. Tropical Africa	Asymptomatic. Acute and chronic pulmonary. Acute disseminated	Cultures of blood, bone marrow, BAL, etc. Antigen detection. Skin testing not useful for diagnosis	Amphotericin B. Itraconazole after clinical stability
Blastomycosis	South central and southeastern United States. Ohio and Mississippi River valleys. Canadian provinces, Great Lakes and areas of Canada and New York, along the St. Lawrence River. Africa	Subclinical. Acute pneumonia. Subacute or chronic respiratory illness. Disseminated	Culture or direct visualization of the fungus. No serologic, skin test or antigen detection method are useful	Amphotericin B. Itraconazole after clinical stability

Coccidioidomycosis	Southwestern United States (Arizona, California and parts of New Mexico, Nevada, Utah, Texas). Central America (Mexico, Guatemala, Honduras, Nicaragua). South America (Argentina, Colombia, Paraguay, Venezuela)	Acute pulmonary. Persistent pneumonia, nodule or cavity. Chronic progressive pneumonia. Disseminated	Serologic testing. Culture, especially of skin and bones, and histopathology. Skin testing has limited diagnostic utility	Amphotericin B. Itraconazole or fluconazole after clinical stability
Paracoccidioidomycosis	Latin America	Primary, benign pulmonary infection.	Smear or histological section or culture of	Amphotericin B. Azoles Sulfonamides (sulfadiazine, etc.)
	Disseminated form	clinical specimen. Serologic testing		
Penicilliosis	Southeast Asia	Reticulonodular or diffuse alveolar infiltrates	Smear, culture or histopathological sections	Amphotericin B. Fluconazole, itraconazole
Sporotrichosis	Midwestern River valleys (especially the Mississippi and Missouri River valleys)	Primary pulmonary. Lymphocutaneous	Culture or biopsy	Amphotericin B. Itraconazole

usually present in the soil and inhalation of conidia leads to infection. Manifestation of disease may occur during primary exposure or through reactivation.

Histoplasmosis

Two varieties of *Histoplasma* may cause disease in humans, *H. capsulatum var. capsulatum* (endemic in Ohio and Mississippi River valleys, the eastern half of the United States and most of Latin America) and *H. capsulatum var. duboisii* (endemic in tropical Africa).

The infection usually remains asymptomatic or it might cause a slowly progressive disorder. However, immunocompromised patients (e.g. those with leukaemia, lymphoma or acquired immunodeficiency syndrome or those on immunosuppressants) may develop symptoms after primary infection [82]. Acute self-limited pulmonary histoplasmosis, progressive pulmonary histoplasmosis and progressive disseminated histoplasmosis are among the clinical presentations. The origin of most infections in endemic areas seems to be primary acquisition. Almost all patients with primary acquisition have pulmonary involvement and the rate of dissemination is high. The disseminated form usually occurs after a large inoculum of infectious particles of *H. capsulatum* reaches the alveolar spaces of an immunocompromised host followed by dissemination to other organs. It is noteworthy that transmission of *H. capsulatum* with a donor organ has also been reported, after the transplant of two kidneys harvested from a resident of Kansas [83].

Constitutional symptoms (fever, weight loss and malaise) along with pulmonary symptoms (dyspnea, cough, pleuritic pain) are the presenting features. The presence of pancytopenia and the laboratory evidence of hepatic involvement may raise suspicion of histoplasmosis [84]. Chest X-rays usually reveal bilateral, reticulonodular or interstitial infiltrates. The isolation of the organism from body fluids (BAL) or tissues is required to establish the diagnosis [85]. In patients with the disseminated form of the disease, bone marrow biopsy/culture and/or blood cultures may establish the diagnosis in more than 50% of cases. Urinary and serum antigen testing may also be used to make the diagnosis of disseminated histoplasmosis and monitor the response to treatment. In fact, urine Histoplasma antigen is the most sensitive test, being positive in approximately 90% of patients with disseminated disease [84].

The IDSA guidelines [86] suggest the use of deoxycholate amphotericin B, 0.7 mg/kg/day (or one of the lipid preparations at a dose of 3 mg/kg/day for patients with renal impairment) in immunocompetent patients with severe, diffuse pulmonary histoplasmosis requiring ventilation support. They also propose the use of prednisone at a daily dose of 60 mg for two weeks to ameliorate the inflammatory response that may contribute to the pathogenesis of the respiratory compromise following the institution of the antifungal therapy. After clinical stability is achieved, itraconazole, 200 mg once or twice daily, should be used to complete a 12-week course.

Blastomycosis

Blastomycosis is usually considered a similar disease to histoplasmosis but differences do exist. For example, it extends further north than histoplasmosis, being endemic not only in the south central and southeastern United States and areas bordering the Mississippi and Ohio River basins, but also in the Canadian provinces, the Great Lakes and areas of Canada and New York along the St. Lawrence River [87]. It is 5–10 times less common than histoplasmosis [88]. It is also endemic in Africa. Initial infection usually results from inhalation of conidia into the lungs. Clinical presentation of pulmonary blastomycosis spans a spectrum from subclinical illness or just a flu-like syndrome to acute pneumonia, subacute or chronic respiratory illness and

fulminant acute respiratory distress syndrome [89]. Cases of blastomycosis have been reported in transplant recipients [90]. Radiographic imaging reveals interstitial infiltrates, reticulonodular infiltrates, nodules and cavitary lung lesions [91]. Definitive diagnosis requires the growth of *Blastomyces dermatitidis* from a clinical specimen. Visualization of the characteristic budding yeast form in clinical specimens supports the diagnosis of blastomycosis and in the appropriate clinical setting may prompt the initiation of antifungal therapy. Serological tests are generally not helpful because they lack sensitivity and specificity. Therefore, a negative serological test should never be used to rule out disease, nor should a positive titre be considered indicative of infection.

The IDSA guidelines [92] suggest that all immunocompromised patients and patients with progressive pulmonary disease or extrapulmonary disease should be treated. Treatment options include amphotericin B (0.7−1 mg/kg/day; total dose, 1.5−2.5 g), ketoconazole, itraconazole and fluconazole, although no comparative trials of these agents has been performed. Rapidly progressing pulmonary disease with worsening oxygen saturation should be treated with amphotericin B. Therapy for some patients may be switched to itraconazole (200−400 mg/day) after clinical stabilization with an initial course of amphotericin B treatment. Lipid preparations of amphotericin B may provide an alternative for selected patients unable to tolerate standard amphotericin B because of toxicity. Surgery has only a limited role in the treatment of blastomycosis.

Coccidioidomycosis

Coccidioides immitis is endemic in the southwestern United States (Arizona, California and parts of New Mexico, Nevada, Utah, Texas) and areas of Mexico (near the US border and in the southwest), Central America (Guatemala, Honduras, Nicaragua) and South America (Argentina, Colombia, Paraguay, Venezuela). It is caused by inhalation of the infectious conidia of *Coccidioides immitis* or *Coccidioides posadii*, the two genetically distinct species of *Coccidioides* that cannot be distinguished phenotypically or clinically. Inhalation results in symptomatic illness in approximately 30 % of those infected and clinical manifestations range from a mild flu-like illness to pneumonia to dissemination. It is actually considered a common cause of community-acquired pneumonia after exposure in a disease-endemic region [93]. Person-to-person transmission does not occur. Older age, smoking and diabetes mellitus are associated with severe pulmonary coccidioidomycosis, while black race and pregnancy are identified risk factors for disseminated disease. Virtually any organ may be involved. However, extrapulmonary dissemination most frequently involves the skin, the skeletal system and the meninges.

The most common form of symptomatic *C. immitis* infection is a subacute pulmonary syndrome, which resolves spontaneously over weeks to months. Rarely, coccidioidomycosis may present with respiratory failure [94]. Radiological imaging usually reveals an air-space consolidation; other presentations include effusions and hilar adenopathy, pulmonary nodules, cavitary lesions with or without an air-fluid level, pneumothorax (0.9 %) and so on. Approximately 5−10 % of infections result in

residual pulmonary sequelae, usually nodules or peripheral thin-walled cavities. Serologic testing by means of enzyme immunoassays (EIA), complement−fixation (CF) titers and immunodiffusion is helpful in supporting the diagnosis. EIA are the easiest and least expensive to perform, but have far from ideal sensitivity and specificity, and can be falsely negative early in the disease course. Even though CF testing becomes positive after EIA testing, it has the advantages of a higher specificity and being a marker to follow disease activity, as rising titres are usually indicative of disease relapse. Cultures, especially of the skin and bone, have a high yield. Histopathology is extremely helpful, as detection of a *C. immitis* spherule is pathognomonic for coccidioidomycosis [95].

Practice guidelines for the treatment of coccidioidomycosis endorsed by the IDSA [96] recommend antifungal therapy if a patient develops progressive pulmonary or disseminated disease. Specific antifungals include: amphotericin B (0.5−0.7 mg/kg/day iv), ketoconazole (400 mg/day per os), fluconazole (400−800 mg/day per os or iv) and itraconazole (200 mg twice a day per os). If itraconazole is used, measurement of its serum concentrations after two weeks may determine if absorption is satisfactory. In severe and life-threatening cases, amphotericin B is probably the treatment of choice. Several weeks of therapy are often required to produce clear evidence of improvement. After this time, amphotericin B may be replaced with oral azole antifungal therapy. The total length of therapy should be at least one year, and for patients with severe immunodeficiency oral azole therapy should be continued as secondary prophylaxis. The new triazole posaconazole appears to have excellent activity even in cases refractory to standard therapies [97]. Because diffuse pneumonia due to *C. immitis* is usually a manifestation of fungemia, patients should be evaluated for other extrapulmonary lesions that may also require attention.

Penicilliosis

Penicillium marneffei, the only *Penicillium* species that is dimorphic, is endemic in Southeast Asia. The mode of transmission is not well understood but is probably via ingestion or inhalation of conidia. Reports of infection in Europe, Australia and the United States have been limited primarily to HIV-infected travellers returning home from endemic regions [98, 99]. The disease has also been detected in children, adults without immunodeficiency and in renal transplant recipients. Pulmonary lesions can appear as reticulonodular or diffuse alveolar infiltrate; cavitary lesions and haemoptysis have also been described [100]. Diagnosis of penicilliosis is usually made by identifying the organism from smear, culture or histopathologic sections. Rapid diagnosis can be obtained by microscopic examination of bone marrow aspirate, lymph node or skin biopsy smear. Microscopic examination reveals yeast forms both within phagocytes and extracellularly. This organism may appear morphologically similar to *Histoplasma capsulatum* when found intracellularly. In the extracellular environment in vivo, the fungal cell elongates, becomes slightly curved and forms an intercellular septum. The demonstration of characteristic central septations and elongated sausage-shaped forms, by methenamine silver stain, clearly distinguish

P. marneffei from *H. capsulatum*. *P. marneffei* is usually susceptible to both amphotericin B and the azoles [101]. Treatment with amphotericin B has been successful in the majority of cases. Fluconazole and itraconazole should also be considered for mild to moderate cases of penicilliosis. Lifelong suppressive therapy with itraconazole is recommended in HIV-patients with penicilliosis.

Paracoccidioidomycosis

Paracoccidioides brasiliensis is endemic in Latin America [102]. The disease is acquired through airways by aspiration of infecting conidia, with a pathogenesis similar to that of tuberculosis. As in tuberculosis, the cell immunity is of great importance in the host defense from *P. brasiliensis*infection. Primary pulmonary infection occurs commonly in the first and second decades of life and usually has a benign, self-limited course, but the organism has the ability to remain dormant for long periods and cause clinical disease when the immune system is compromised, for example in patients receiving immunosuppressive treatment for a solid organ transplant [102−104]. Presenting symptoms include fever, cough, malaise, anorexia and weight loss. Radiographic images show predominantly multiple nodules. Diagnosis should be based on the identification of *P. brasil iensis* in a direct microscopic examination of a clinical specimen, complemented by its isolation in culture for subsequent identification. Smears of sputum or BAL may be very helpful in establishing the diagnosis. Serologic tests such as the double immunodiffusion in agar gel, the complement−fixation, the indirect immunofluorescence, immunoelectrophoresis and enzyme-linked immunosorbent assay (ELISA) are also available [102]. The treatment of paracoccidioidomycosis includes amphotericin B, the azoles and the sulfonamides. Traditionally, short-acting sulfadiazine (a dose of up to 4 g per os every 4−6 hours; maintenance = half dose up to two years) is considered the sulfonamide of choice. Trimethoprim/sulfamethoxazole (attack dose = 800 mg/160 mg twice a day; maintenance = half dose up to two years) and sulfadiazine and trimethoprim (attack dose = 820 mg/180 mg twice a day; maintenance = half dose up to two years) can be used with good results in localized disease, untreated mild-to-moderate disseminated disease, supportive therapy after amphotericin B treatment and in cases with concurrent central nervous system involvement. The treatment should be carried out for long periods (two years) because shorter treatment periods carry a great risk of relapse. Itraconazole is the best azole for the treatment of paracoccidioidomycosis in a 100 or 200 mg/day single dose. A recently published systematic review highlighted the lack of adequate studies comparing sulfa drugs with azoles for the treatment of paracoccidioidomycosis [105]. Amphotericin B (up to 1.0 mg/kg/day) should be used only in severe cases or when there is allergy or resistance to sulfonamides or azoles.

Sporotrichosis

Sporotrichosis is caused by the dimorphic fungus *Sporothrix schenckii*, which is found worldwide in decaying vegetation and soil [106]. While the usual mode of

infection is by cutaneous inoculation, pulmonary and disseminated forms of infection can occur when *S. schenckii* conidia are inhaled. Infections are most often sporadic and usually associated with trauma during the course of outdoor work. Infection can also be related to zoonotic spread from infected cats or scratches from digging animals [109]. Outbreaks have been reported in association with activities (e.g. gardening) that involve contaminated sphagnum moss, hay or wood [106].

Pulmonary sporotrichosis has been reported in middle-aged men with structural lung disease (such as chronic obstructive pulmonary disease) and relative immunocompromised states, most commonly chronic alcohol abuse, chronic steroid use and diabetes mellitus [106, 107], and most commonly presents as chronic cavitary fibronodular lesion [106].

The practice guidelines for the management of patients with sporotrichosis endorsed by the Mycoses Study Group [106] recommend the use of amphotericin B (at a total dose of 1−2 g) for patients with life-threatening or extensive pulmonary sporotrichosis, followed, if feasible, by surgical resection of the lung lesion. If pulmonary sporotrichosis is not life-threatening, itraconazole at a dosage of 200 mg twice daily can be used as initial therapy. It should be noted that the guidelines make a firm statement against the use of saturated solution of potassium iodide (SSKI), ketoconazole and fluconazole for treating pulmonary sporotrichosis.

References

1. Blumberg, H.M., Jarvis, W.R., Soucie, J.M. *et al*. (2001) Risk factors for *Candida*l bloodstream infections in surgical intensive care unit patients: The NEMIS prospective multicentre study. The national epidemiology of mycosis survey. *Clin Infect Dis*, Jul 15, **33** (2), 177−86.
2. Dimopoulos, G., Piagnerelli, M., Berré Salmon, J.I. *et al*. (2004) Post mortem examination in the intensive care unit: Still useful. *Intensive Care Med*, **30** (11), 2080−5.
3. Pappas, P.G., Rex, J.H., Sobel, J.D. *et al*. (2004) Guidelines for treatment of candidiasis. *Clinical Infectious Diseases*, **38**, 161−89.
4. Dimopoulos, G., Piagnerelli, M., Berre, J. *et al*. (2003) Disseminated aspergillosis in intensive care unit patients: An autopsy study. *J Chemotherap*, **15** (1), 71−5.
5. Baum, G.L. (1960) The significance of *Candida* albicans in human sputum. *New England Journal of Medicine*, **263**, 70−3.
6. Haron, E., Vartivarian, S., Anaissie, E. *et al*. (1993) Primary *Candida* pneumonia. *Medicine*, **72**, 137−42.
7. Yamamoto, T., Ueta, E., Kamatani, T. *et al*. (2005) DNA identification of the pathogen of *Candida*l aspiration pneumonia induced in the course of oral cancer therapy. *Journal of Medical Microbiology*, **54**, 493−6.
8. Bodey, G., Bueltmann, B., Duguid, W. *et al*. (1992) Fungal infections in cancer patients: An international autopsy survey. *European Journal of Clinical Microbiology and Infectious Diseases*, **11**, 99−109.
9. Masur, H., Rosen, P.P. and Armstrong, D. (1977) Pulmonary disease caused by *Candida* species. *American Journal of Medicine*, **63**, 914−25.
10. Grossi, P., Farina, C., Fiocchi, R. and DallaGasperina, D. (2000) Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients:

A multicentre retrospective study. Italian study group of fungal infections in thoracic organ transplant recipients. *Transplantation*, **70**, 112−16.
11. Sharma, S., Nadrous, H.F., Peters, S.G. *et al*. (2005) Pulmonary complications in adult blood and marrow transplant recipients: Autopsy findings. *Chest*, **128**, 1385−92.
12. Hughes, W.T. (1982) Systemic candidiasis: A study of 109 fatal cases. *Pediatric Infectious Diseases Journal*, **1**, 11−18.
13. Kontoyiannis, D.P., Reddy, B.T., Torres, H.A. *et al*. (2002) Pulmonary candidiasis in patients with cancer: An autopsy study. *Clinical Infectious Diseases*, **34**, 400−3.
14. Maksymiuk, A.W., Thonprasert, S., Hopfer, R. *et al*. (1984) Systemic candidiasis in cancer patients. *American Journal of Medicine*, **77**, 20−7.
15. Kami, M., Machida, U., Okuzumi, K. *et al*. (2002) And. *British Journal of Haematology*, **117**, 40−6.
16. Kobayashi, T., Miyazaki, Y., Yanagihara, K. *et al*. (2005) A probable case of aspiration pneumonia caused by *Candida* glabrata in a non-neutropenic patient with candidemia. *Internal Medicine*, **44**, 1191−4.
17. Petrocheilou-Paschou, V., Georgilis, K., Kontoyannis, D. *et al*. (2002) Pneumonia due to *Candida* krusei. *Clinical Microbiology and Infection*, **8**, 806−9.
18. El-Ebiary, M., Torres, A., Fabrega, N. *et al*. (1997) Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. *American Journal of Respiratory and Critical Care Medicine*, **156**, 583−90.
19. Ljungman, P., von Dobeln, L., Ringholm, L. *et al*. (2005) The value of CMV and fungal PCR for monitoring for acute leukaemia and autologous stem cell transplant patients. *Scandinavian Journal of Infectious Diseases*, **37**, 121−7.
20. Dubois, P.J., Myerowitz, R.L. and Allen, C.M. (1977) Pathoradiologic correlation of pulmonary candidiasis in immunosuppressed patients. *Cancer*, **40**, 1026−36.
21. Buff, S.J., McLelland, R., Gallis, H.A. *et al*. (1982) *Candida* albicans pneumonia: Radiographic appearance. *American Journal of Roentgenology*, **138**, 645−8.
22. Kassner, E.G., Kauffman, S.L., Yoon, J.J. *et al*. (1981) Pulmonary candidiasis in infants: Clinical, radiologic and pathologic features. *American Journal of Roentgenology*, **137**, 707−16.
23. Watanakunakorn, C. (1983) Acute pulmonary mycetoma due to *Candida* albicans with complete resolution. *Journal of Infectious Diseases*, **6**, 1131.
24. Althoff Souza, C., Muller, N.L., Marchiori, E. *et al*. (2006) Pulmonary invasive aspergillosis and candidiasis in immunocompromised patients: A comparative study of the high-resolution CT findings. *Journal of Thoracic Imaging*, **21**, 184−9.
25. Pachl, J., Svoboda, P., Jacobs, F. *et al*. (2006) A randomized, blinded, multicentre trial of lipid-associated amphotericin B alone versus in combination with an antibody-based inhibitor of heat shock protein 90 in patients with invasive candidiasis. *Clinical Infectious Diseases*, **42**, 1404−13.
26. Azoulay, E., Timsit, J.F., Tafflet, M. *et al*. (2006) *Candida* colonization of the respiratory tract and subsequent Pseudomonas ventilator-associated pneumonia. *Chest*, **129**, 110−17.
27. Rello, J., Esandi, M.E., Diaz, E. *et al*. (1998) The role of *Candida* sp isolated from bronchoscopic samples in non-neutropenic patients. *Chest*, **114**, 146−9.
28. Wood, G.C., Mueller, E.W., Croce, M.A. *et al*. (2006) *Candida* sp. Isolated from bronchoalveolar lavage: Clinical significance in critically ill trauma patients. *Intensive Care Medicine*, **32**, 599−603.
29. Azoulay, E., Cohen, Y., Zahar, J.R. *et al*. (2004) Practices in non-neutropenic ICU patients with *Candida*-positive airway specimens. *Intensive Care Medicine*, **30**, 1384−9.

30. Eggimann, P., Calandra, T., Fluckiger, U. *et al*. (2005) Invasive candidiasis: Comparison of management choices by infectious disease and critical care specialists. *Intensive Care Medicine*, **31**, 1514–21.
31. El-Azizi, M.A., Starks, S.E. and Khardori, N. (2004) Interactions of *Candida* albicans with other *Candida* spp. and bacteria in the biofilms. *Journal of Applied Microbiology*, **96**, 1067–73.
32. Segal, B.H. and Walsh, T.J. (2006) Current approaches to diagnosis and treatment of invasive aspergillosis. *Am J Respir Crit Care Med*, **173**, 707–17.
33. Baddley, J.W., Stroud, T.P., Salzman, D. and Pappas, P.G. (2001) Invasive mould infections in allogeneic bone marrow transplant recipients. *Clin Infect Dis*, **32**, 1319–24.
34. Marr, K.A., Carter, R.A., Boeckh, M. *et al*. (2002) Invasive aspergillosis in allogeneic stem cell transplant recipients: Changes in epidemiology and risk factors. *Blood*, **100**, 4358–66.
35. Ng, T.T., Robson, G.D. and Denning, D.W. (1994) Hydrocortisone-enhanced growth of *Aspergillus* spp.: Implications for pathogenesis. *Microbiol*, **140**, 2475–9.
36. Cahill, B.C., Hibbs, J.R., Savik, K. *et al*. (1997) *Aspergillus* airway colonization and invasive disease after lung transplantation. *Chest*, **112**, 1160–4.
37. Almyroudis, N.G., Holland, S.M. and Segal, B.H. (2005) Invasive aspergillosis in primary immunodeficiencies. *Med Mycol Suppl*, **43**, S247–59.
38. Gallin, J.I., Alling, D.W., Malech, H.L. *et al*. (2003) Itraconazole to prevent fungal infections in chronic granulomatous disease. *N Engl J Med*, **348**, 2416–22.
39. Meersseman, W., Vandecasteele, S.J., Wilmer, A. *et al*. (2004) Invasive aspergillosis in critically ill patients without malignancy. *Am J Respir Crit Care Med*, **170**, 621–5.
40. Annaissie, E.J., Stratton, S.L., Dignani, M.C. *et al*. (2003) Pathogenic molds (including *Aspergillus* species) in hospital water distribution systems: A 3-year prospective study and clinical implications for patients with haematologic malignancies. *Blood*, **101**, 2542–6.
41. Manuel, R.J. and Kibbler, C.C. (1998) The epidemiology and prevention of invasive aspergillosis. *J Hosp Infect*, **39**, 95–109
42. Alberti, C., Bouakline, A., Ribaud, P. *et al*. (2001) Relationship between environmental fungal contamination and the incidence of invasive aspergillosis in haematology patients. *J Hosp Infect*, **48**, 198–206.
43. Vonberg, R.P. and Gastmeier, P. (2006) Nosocomial aspergillosis in outbreak settings. *J Hosp Infect*, **63**, 246–54.
44. Patterson, T.F. (2005) *Aspergillus* species, In Mandell, G.L., Bennett, J.F. and Dolin, R. (eds) *Principles and Practice of Infectious Diseases*, Churchill Livingstone, pp. 2958–73.
45. Ascioglu, S., Rex, J.H., Pauwde, Bennett J.E. *et al*. (2002) Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and haematopoietic stem cell transplants: An international consensus. *Clin Infect Dis*, **34**, 7–14.
46. Shaukat, A., Bakri, F., Youn P. *et al*. (2005) Invasive filamentous fungal infections in allogeneic haematopoietic stem cell transplant recipients after recovery from neutropenia: Clinical, radiologic and pathologic characteristics. *Mycopathologia*, **159**, 181–8.
47. Horvath, J.A. and Dummer, S. (1996) The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. *Am J Clin Pathol*, **100**, 171–8.
48. Yu, V.L., Muder, R.R. and Poorsattar, A. (1986) Significance of isolation of *Aspergillus* from the respiratory tract in diagnosis of invasive pulmonary aspergillosis. Results from a three-year prospective study. *Am J Med*, **81**, 249–54.

49. Perfect, J.R., Cox, G.M., Lee, J.Y. *et al*. (2001) The impact of culture isolation of *Aspergillus* species: A hospital-based survey of aspergillosis. *Clin Infect Dis*, **33**, 1824−33.
50. Kuhlman, J.E., Fishman, E.K., Burch, P.A. *et al*. (1987) Invasive pulmonary aspergillosis in acute leukemia: The contribution of CT to early diagnosis and aggressive management. *Chest*, **92**, 95−9.
51. Denning, D.W. (1998) Invasive aspergillosis. *Clin Infect Dis*, **26**, 781−803.
52. Caillot, D., Casasnovas, O., Bernard, A. *et al*. (1997) Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*, **15**, 139−47.
53. Caillot, D., Couaillier, J.F., Bernard, A. *et al*. (2001) Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol*, **19**, 253−9.
54. Pfeiffer, C.D., Fine, J.P. and Safdar, N. (2006) Diagnosis of invasive aspergillosis using a galactomannan assay: A meta-analysis. *Clin Infect Dis*, **42**, 1417−27.
55. Adam, O., Auperin, A., Wilquin, F. *et al*. (2004) Treatment with piperacillin−tazobactam and false-positive *Aspergillus* galactomannan antigen test results for patients with haematological malignancies. *Clin Infect Dis*, **38**, 917−20.
56. Francesconi, A., Kasai, M., Petraitiene, R. *et al*. (2006) Characterization and comparison of galactomannan enzyme immunoassay and quantitative real-time PCR assay for detection of *Aspergillus* fumigatus in bronchoalveolar lavage fluid from experimental invasive aspergillosis. *J Clin Microbiol*, **44**, 2475−80.
57. Musher, B., Fredricks, D., Leisenring, W. *et al*. (2004) *Aspergillus* galactomannan enzyme immunoassay and quantitative PCR for diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. *J Clin Microbiol*, **42**, 5517−22.
58. Ostrosky-Zeichener, L., Alexander, B.D., Kett, D.H. *et al*. (2005) Multicenter clinical evaluation of the (1−>3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. *Clin Infect Dis*, **41**, 654−9.
59. Patterson, T.F., Kirkpatrick, W.R., White, M. *et al*. (2000) Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 *Aspergillus* study group. *Medicine (Baltimore)*, **79**, 250−60.
60. Lin, S.J., Schranz, J. and Teutsch, S. (2001) Aspergillosis case-fatality rate: Systematic review of the literature. *Clin Infect Dis*, **32**, 358−66.
61. Herbrecht, R., Denning, D., Patterson, T. *et al*. (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*, **347**, 408−15.
62. Wingard, J.R., Kubilis, P., Lee, L. *et al*. (1999) Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis*, **29**, 1402−7.
63. Patterson, T.F., Boucher, H.W., Herbrecht, R. *et al*. (2005) Strategy of following voriconazole versus amphotericin B therapy with other licensed antifungal therapy for primary treatment of invasive aspergillosis: Impact of other therapies on outcome. *Clin Infect Dis*, **41**, 1448−52.
64. Ullmann, A.J., Cornely, O.A., Burchardt, A. *et al*. (2006) Pharmacokinetics, safety and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. *Antimicrob Agents Chemother*, **50**, 658−66.
65. Segal, B.H., Barnhart, L.A., Anderson, V.L. *et al*. (2005) Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection. *Clin Infect Dis*, **40**, 1684−8.
66. Potter, M. (2005) Strategies for managing systemic fungal infection and the place of itraconazole. *J Antimicrob Chemother*, **56** (Suppl 1), i49−54.

67. Maertens, J., Raad, I., Petrikkos, G. *et al*. (2004) Efficacy and safety of caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis*, **39**, 1563–71.
68. Glasmacher, A., Cornely, O.A., Orlopp, K. *et al*. (2006) Caspofungin treatment in severely ill, immunocompromised patients: A case-documentation study of 118 patients. *J Antimicrob Chemother*, **57**, 127–34.
69. Marr, K.A., Boeckh, M., Carter, R.A. *et al*. (2004) Combination antifungal therapy for invasive aspergillosis. *Clin Infect Dis*, **39**, 797–802.
70. Kontoyiannis, D.P., Hachem, R., Lewis, R.E. *et al*. (2003) Efficacy and toxicity of caspofungin in combination with liposomal amphotericin B as primary or salvage treatment of invasive aspergillosis in patients with haematological malignancies. *Cancer*, **98**, 292–9.
71. International Chronic Granulomatous Disease Cooperative Study Group, (1991) A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease: The international chronic granulomatous disease cooperative study group. *N Engl J Med*, **324**, 509–16.
72. Smith, T.J., Khatcheressian, J., Lyman, G.H. *et al*. (2006) 2006 Update of recommendations for the use of blood cell growth factors: An evidence-based clinical practice guideline. *J Clin Oncol*, **24**, 3187–205.
73. Cornet, M., Levy, V., Fleury, L. *et al*. (1999) Efficacy of prevention by high-efficiency particulate air filtration or laminar airflow against *Aspergillus* airborne contamination during hospital renovation. *Infect Control Hosp Epidemiol*, **20**, 508–13.
74. Barnes, R.A. and Rogers, T.R. (1989) Control of an outbreak of nosocomial aspergillosis by laminar air-flow isolation. *J Hosp Infect*, **14**, 11–18.
75. Humphreys, H. (2004) Positive-pressure ventilation and the prevention of invasive aspergillosis. What is the evidence. *J Hosp Infect*, **56**, 93–100.
76. Sherertz, R.J., Belani, A., Kramer, B.S. *et al*. (1987) Impact of air filtration on nosocomial *Aspergillus* infections. Unique risk of bone marrow transplant recipients. *Am J Med*, **83**, 709–18.
77. Raad, I., Hanna, H., Osting, C. *et al*. (2002) Masking of neutropenic patients on transport from hospital rooms is associated with a decrease in nosocomial aspergillosis during construction. *Infect Control Hosp Epidemiol*, **23**, 41–3.
78. Bartley, J.M. (2000) APIC state-of-the-art report: The role of infection control during construction in health care facilities. *Am J Infect Control*, **28**, 156–69.
79. Dykewicz, C.A., Jaffe, H.W. and Kaplan, J.E. (2000) Guidelines for preventing opportunistic infections among haematopoietic stem cell transplant recipients. Recommendations of CDC, the Infectious Diseases Society of America, and the American Society of Blood and Bone Marrow Transplantation. *Biol Blood Marrow Transplant*,**6**, 659–727.
80. Glasmacher, A. and Prentice, A.G. (2005) Evidence-based review of antifungal prophylaxis in neutropenic patients with haematological malignancies. *J Antimicrob Chemother*, **56** (Suppl S1), i23–32.
81. Fukuda, T., Boeckh, M., Guthrie, K.A. *et al*. (2004) Invasive aspergillosis before allogeneic haematopoietic stem cell transplantation: 10-Year experience at a single transplant center. *Biol Blood Marrow Transplant*, **10**, 494–503.
82. Gangat, N., Lin, Y. and Elkin, P.L. (2005) 68-Year-old man with fatigue, fever, and weight loss. *Mayo Clinic Proceedings*, **80**, 939–42.
83. Limaye, A.P., Connolly, P.A., Sagar, M. *et al*. (2000) Transmission of Histoplasma capsulatum by organ transplantation. *New England Journal of Medicine*, **343**, 1163–6.
84. Wheat, L.J. and Kauffman, C.A. (2003) Histoplasmosis. *Infectious Disease Clinics of North America*, **17**, 1–19.

85. Wheat, L.J. (2006) Histoplasmosis: A review for clinicians from non-endemic areas. *Mycoses*, **49**, 274−82.
86. Wheat, J., Sarosi, G., McKinsey, D. *et al*. (2000) Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. *Clinical Infectious Diseases*, **30**, 688−95.
87. Bradsher, R.W., Chapman, S.W. and Pappas, P.G. (2003) Blastomycosis. *Infectious Disease Clinics of North America*, **17**, 21−40.
88. Chu, J.H., Feudtner, C., Heydon, K. *et al*. (2006) Hospitalisations for endemic mycoses: A population-based national study. *Clinical Infectious Diseases*, **42**, 822−5.
89. Lemos, L.B., Baliga, M. and Guo, M. (2001) Acute respiratory distress syndrome and blastomycosis: Presentation of nine cases and review of the literature. *Annals of Diagnostic Pathology*, **5**, 1−9.
90. Winkler, S., Stanek, G., Hubsch, P. *et al*. (1996) Pneumonia Due To Blastomyces dermatitidis in a European renal transplant recipient. *Nephrology, Dialysis, Transplantation*, **11**, 1376−9.
91. Winer-Muram, H.T. and Rubin, S.A. (1992) Pulmonary blastomycosis. *Journal of Thoracic Imaging*, **7**, 23−8.
92. Chapman, S.W., Bradsher, R.W. Jr, Campbell, G.D. *et al*. (2000) Practice guidelines for the management of patients with blastomycosis. Infectious Diseases Society of America. *Clinical Infectious Diseases*, **30**, 679−83.
93. Valdivia, L., Nix, D., Wright, M. *et al*. (2006) Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerging Infectious Diseases*, **12**, 958−62
94. Larsen, R.A., Jacobson, J.A., Morris, A.H. and Benowitz, B.A. (1985) Acute respiratory failure caused by primary pulmonary coccidioidomycosis. Two case reports and a review of the literature. *The American Review of Respiratory Disease*, **131**, 797−9.
95. Stevens, D.A. (1995) Coccidioidomycosis. *New England Journal of Medicine*, **332**, 1077−82.
96. Galgiani, J.N., Ampel, N.M., Catanzaro, A. *et al*. (2000) Practice guidelines for the treatment of coccidioidomycosis. *Clinical Infectious Diseases*, **30**, 658−61.
97. Anstead, G.M., Corcoran, G., Lewis, J. *et al*. (2006) Refractory coccidioidomycosis treated with posaconazole. *Clinical Infectious Diseases*, **40**, 1770−6.
98. Sirisanthana, T. and Supparatpinyo, K. (1998) Epidemiology and management of penicilliosis in human immunodeficiency virus-infected patients. *International Journal of Infectious Diseases*, **3**, 48−53.
99. Supparatpinyo, K., Khamwan, C., Baosoung, V. *et al*. (1994) Disseminated Penicillium marneffei infection in southeast Asia. *Lancet*, **344**, 110−13.
100. Cheng, N.C., Wong, W.W., Fung, C.P. *et al*. (1998) Unusual pulmonary manifestations of disseminated Penicillium marneffei infection in three AIDS patients. *Medical Mycology*, **36**, 429−32.
101. Imwidthaya, P., Thipsuvan, K., Chaiprasert, A. *et al*. (2001) Penicillium marneffei: Types and drug susceptibility. *Mycopathologia*, **149**, 109−15.
102. Bethlem, E.P., Capone, D., Maranhao, B. *et al*. (1999) Paracoccidioidomycosis. *Current Opinion in Pulmonary Medicine*, **5**, 319−25.
103. Shikanai-Yasuda, M.A., Duarte, M.I., Nunes, D.F. *et al*. (1995) Paracoccidioidomycosis in a renal transplant recipient. *Journal of Medical and Veterinary Mycology*, **33**, 411−14.
104. Sugar, A.M., Restrepo, A. and Stevens, D.A. (1984) Paracoccidioidomycosis in the immunosuppressed host: Report of a case and review of the literature. *The American Review of Respiratory Disease*, **129**, 340−2.
105. Menezes, V.M., Soares, B.G. and Fontes, C.J. (2006) Drugs for treating paracoccidioidomycosis. *Cochrane Database of Systematic Reviews*, 2, CD004967.

106. Kauffman, C.A., Hajjeh, R. and Chapman, S.W. (2000) Practice guidelines for the management of patients with sporotrichosis. *Clinical Infectious Diseases*, **30**, 684–7.
107. Zhou, C., Asuncion, A. and Love, G. (2003) Laryngeal and respiratory tract sporotrichosis and steroid inhaler use. *Archives of Pathology and Laboratory Medicine*, **127**, 893–8.
108. Centers for Disease Control and Prevention, (2000) Guidelines for preventing opportunistic infections among haematopoietic stem cell transplant recipients. *MMWR Recomm Rep*, **49**, 1–128.
109. Reed, K.D., Moore, F.M., Geiger, G.E. *et al*. (1993) Zoonotic transmission of sporotrichosis: Case report and review. *Clinical Infectious Diseases*, **16**, 384–7.

10

Nosocomial Pneumonia: Strategies for Management

General pharmacological considerations and dose adjustment in antibiotic therapy for HAP

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Introduction

One of the pivotal principles of the management of severe infections is that early, appropriate broad-spectrum antibiotic therapy is associated with more favourable clinical outcome. In the last ten years, several studies have confirmed the clinical role of de-escalation therapy as a suitable tool for reducing the risk of incorrect first-line therapy [1].

The concept of 'inappropriate therapy', even among the most recent medical literature, is almost exclusively based on the pattern of microbiological coverage of the chosen regimen, so that the relevance of the studies on this issue is limited. In fact, this literature usually refers to fixed dosing regimens, regardless of the infection site and of the patients' pathophysiological conditions (apart from impairment of emunctory functions), which conversely should definitively be taken into account with the intent of ensuring maximized antimicrobial pharmacodynamic exposure.

Although identification of the causative organism, or even a reliable estimate, coupled with its resistance profile represent essential information upon which to base

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therapeutic choices, they are by no means the only variable entering the decision process. Once drugs with an adequate pattern of antimicrobial coverage have been correctly chosen on the basis of microbiological and epidemiological data, three additional issues need to be appropriately addressed to optimise therapy outcome.

These issues, which are covered in this present chapter, are aimed at guaranteeing effective drug exposure against the causative microorganism at the infection site while, at the same time, minimizing the spread of resistant strains.

The first aspect is to consider, on the basis of the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of each molecule, is which is the most suitable drug dosage schedule with the intent of ensuring effective plasma levels (Figure 10.1). Secondly, it is necessary to ensure that these effective concentrations can be achieved at the infection site as well; this may vary greatly among the different compounds according to their physicochemical properties and/or even to the eventual presence of anatomical barriers. Lastly, it must be remembered that drug disposition in the body can be substantially altered by the patient's pathophysiological conditions, which may sometimes cause overexposure (with potential toxicity risks) or conversely underexposure (with the risk of therapeutic failure). The net result of this is that in the treatment of critically ill patients the daily dosages of several antibiotics could be very much different from the daily dosages used for patients presenting with normal and stable clinical conditions.

Indeed, the antimicrobial therapy of a severe infection such as hospital-acquired pneumonia (HAP), which often represents the archetypal nosocomial acquired severe

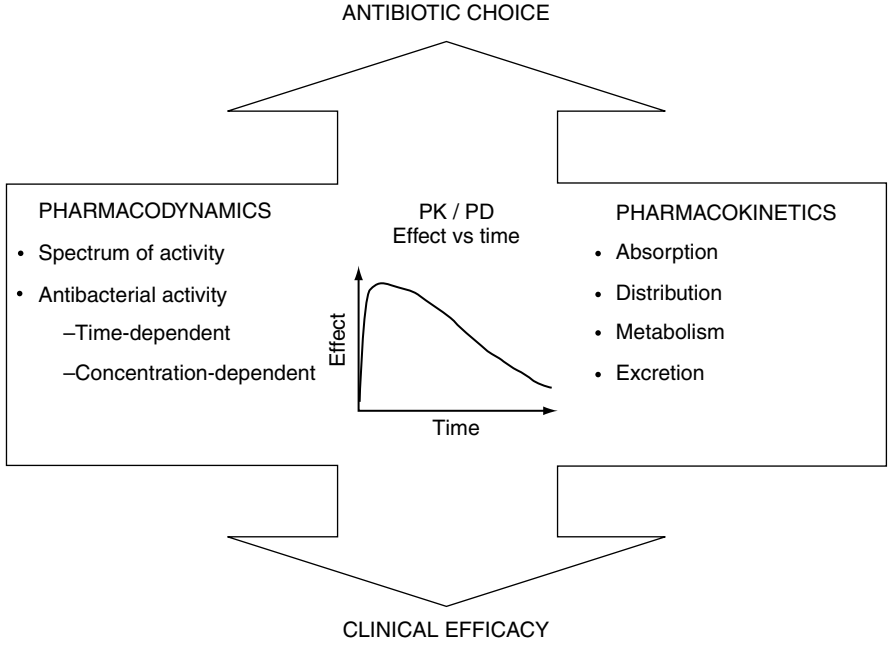

Figure 10.1
Relevant pharmacological factors for clinical efficacy of antimicrobial agents.

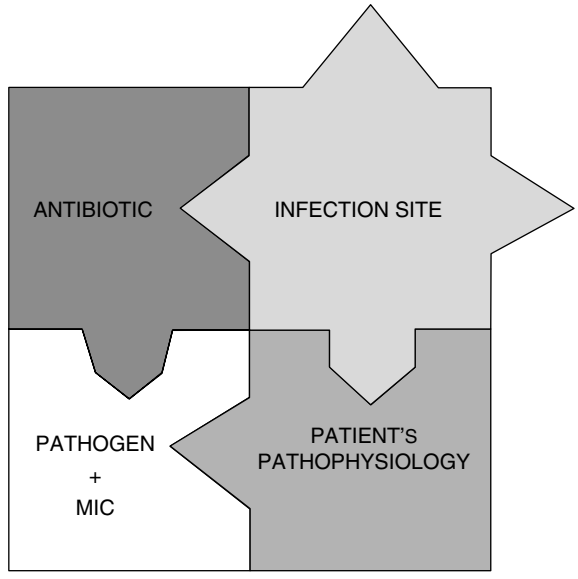

Figure 10.2
The antimicrobial therapy puzzle [2] The antimicrobial therapy puzzle. Reprinted with permission from F. Pea, P. Viale The antimicrobial therapy puzzle: could pharmacokinetic- pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? Clin Infect Dis. 2006 Jun 15;42(12):1764-71.

infection, may be likened to a puzzle composed of several different pieces that need to be merged together to obtaining the appropriate solution, namely to ensure both clinical cure and prevention of resistance. These pieces are represented by the antibiotic with its PK/PD characteristics, the microorganism involved with its *in vitro* susceptibility, the infection site and the patient's pathophysiological conditions (Figure 10.2) [2]. Once antimicrobial therapy is optimised according to these criteria, the classification of antimicrobials into bactericidal (killing microbial populations) and bacteriostatic (blocking microbial growth) may become obsolete, being valid only in *in vitro* standardized conditions, but often seeming arbitrary *in vivo* where drug exposure achievable at the site of infection has probably a higher therapeutic relevance than the intrinsic activity of the molecule itself [3].

Towards Clinically Useful Classifications of Antimicrobials

Among the many existing classifications of antibiotics, besides those based on spectrum of activity and cellular mechanism of action, that based on PK/PD principles of antimicrobial activity appears extremely useful for both drug choice and daily schedule planning.

Such classification splits antimicrobial agents in two major categories, namely time-dependent or concentration-dependent agents. In the former category, which includes beta-lactams, glycopeptides, oxazolidinones and macrolides (especially those of natural origin), the most relevant pharmacodynamic determinant of efficacy is the time during which plasma drug concentration persists above the pathogen's Minimum Inhibitory Concentration (t > MIC) [4,5] (Figure 10.3).

Although a t > MIC of 50% of the dosing interval may be sufficient for valid efficacy with time-dependent agents in the immunocompetent host [4,5], the most suitable situation to always ensure clinical effectiveness with these agents is probably represented by the maintenance of plasma concentration above the pathogen's MIC for the entire dosing interval, as it occurs when trough plasma level is still above the MIC (C_{min} > MIC) [2]. In fact, the efficacy of time-dependent compounds may only improve slightly in the presence of very high levels, the maximum effect usually being observed at concentrations four- to five-fold the MIC [6]. The importance of C_{min} > MIC becomes extremely relevant, other than in immunocompromised patients, in the presence of severe Gram-negative infections treated with beta-lactams as well. In fact, due to the poor post-antibiotic effect (PAE) (except for carbapenems) [7], very low trough levels of beta-lactams, falling below the pathogens' MIC for Gram-negative microorganisms, should be avoided to prevent bacterial regrowth and breakthrough resistance.

Despite concentration-independent *in vitro* antimicrobial activity, in some *in vivo* studies the AUC/MIC ratio (AUC: Area Under plasma concentration time Curve) was found to be a better predictor of efficacy for some time-dependent agents, as for example in the case of vancomycin [8,9]. It should be pointed out that the AUC_{24h}/MIC ratio was also found to be a relevant surrogate marker of efficacy

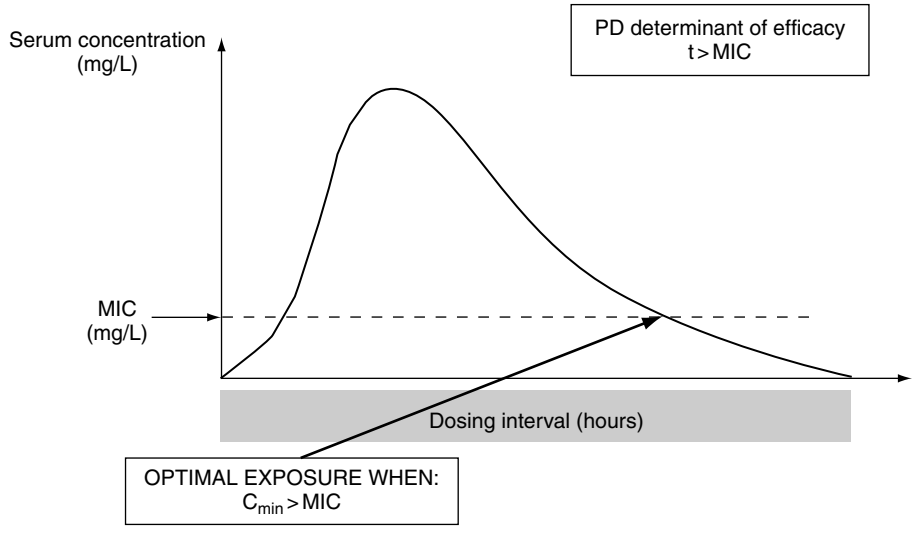

Figure 10.3
Pharmacodynamic determinants of efficacy for time-dependent antimicrobial agents.

for several concentration-dependent agents, so that this parameter, when considered alone, might not be completely predictive of the type of antibacterial activity. This is consistent with the fact that in each single patient the daily drug exposure (AUC_{24h}) is a function of the total daily drug amount ($AUC_{24h} = dose_{24h}/clearance$) only, so that the same daily dose is expected to be providing equal AUC_{24h} irrespective of dose fractioning. In other words, if AUC_{24h}/MIC was the only relevant predictor of an agent's activity, dose fractioning should not influence efficacy, as administering the same total daily dose either as a single pulse or as a continuous infusion will provide the same AUC_{24h}/MIC ratio. On the contrary, a recent observation seems to confirm the clinical and epidemiological relevance of optimising the PK/PD characteristics of the antibiotic schedule in preventing the development of resistance with time-dependent drugs. In a patient treated with vancomycin for nine months for several subsequent episodes of catheter-related methicillin-resistant *S. aureus* (MRSA) bacteraemia, despite the long-term use, the steady maintenance of a trough drug plasma level >10 mg/L was shown both to ensure persistent clinical efficacy and to avoid the selection of Glycopeptide Intermediate-Resistant *Staphylococcus aureus* (GISA) [10].

The most suitable daily schedule regimen to persistently ensure high C_{min} is represented by the multiple fractioning of the daily dosage, the frequency of which should be inversely proportional to the length of the drug elimination half-life. For time-dependent agents with a very short or short half-life (< 6–8 hours), there is growing experimental and clinical evidence to indicate that the application of intravenous (iv) continuous infusion may be beneficial in maximizing pharmacodynamic exposure [11]. This is not surprising considering that, under the same total daily dose and therefore the same AUC_{24h}/MIC value, continuous infusion may ensure the highest C_{min} >MIC (Figure 10.4).

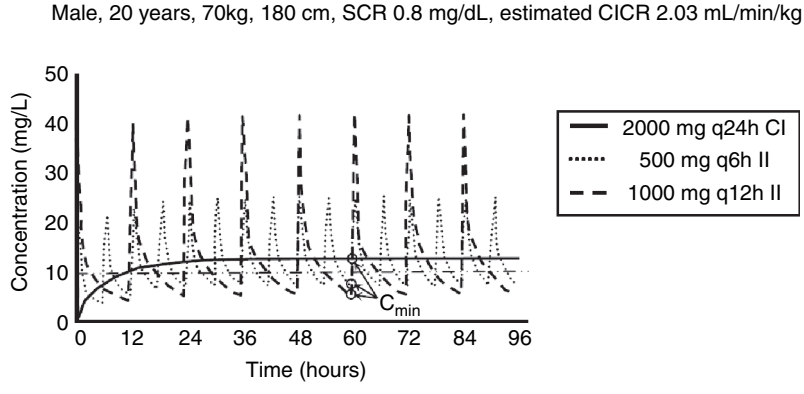

Figure 10.4
Simulation of the serum pharmacodynamic exposure achievable with standard vanomycin dosages (2000 mg/daily) according to different administration schedules in a young patient with normal renal function.
Dash and dot line represents the suggested trough level (C_{MIN}) for optimal treatment (10 mg/L). CI, continuous infusion; II, intermittent infusion.

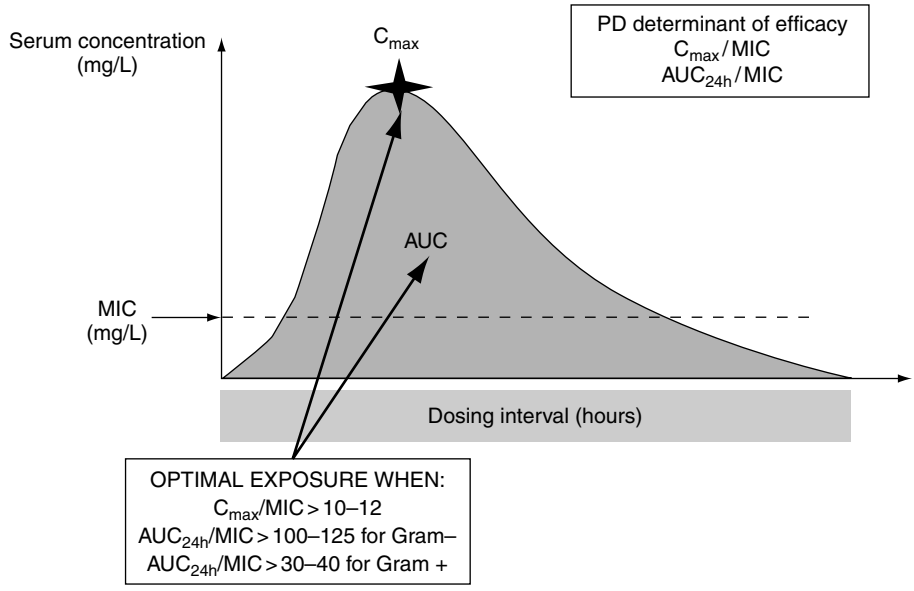

Figure 10.5
Pharmacodynamic determinants of efficacy for concentration-dependent antimicrobial agents.

Antimicrobials with concentration-dependent activity, which includes aminoglycosides and fluoroquinolones, exhibit a progressive increase in their antibacterial potency and rapidity of action with increasing concentrations, theoretically never reaching a *plateau*. The major pharmacodynamic determinants of efficacy are the maximum plasma concentration to MIC ratio (C_{max}/MIC) and the area under the plasma concentration versus time curve (AUC) to the MIC ratio (AUC/MIC) (Figure 10.5).

Fluoroquinolones were among the first antimicrobial agents for which the clinical value of the AUC/MIC ratio was well documented. In patients treated with different ciprofloxacin regimens for lower respiratory tract infections, the probability of both clinical cure and bacterial eradication was shown to become relevant when the AUC/MIC $>100-125$ [12]. More recently, it has been postulated that whereas this threshold has to be considered mandatory against Gram-negative pathogens [13, 14], a value of $30-40$ might be sufficient against Gram-positive bacteria [15, 16]. Additionally, several more recent studies have shown that a C_{max}/MIC ratio of $10-12$ may ensure clinical cure and prevent the spreading of resistance with these antimicrobials [17–20].

Accordingly, although the AUC/MIC ratio depends only on the amount of the total daily dose regardless of dose fractioning, the C_{max}/MIC ratio, on the other hand, obviously depends on dose fractioning as well; to maximize the C_{max}/MIC ratio, concentration-dependent drugs need to be administered less frequently (once or twice daily, depending on their pharmacokinetic characteristics and tolerability) [2]. Despite short plasma elimination half-life, aminoglycosides may be administered once daily, thanks to their valid PAE, and this may significantly increase their clinical efficacy. Interestingly, the administration of the entire daily dose of aminoglycosides all at once was not shown to increase the nephrotoxicity

risk. In a study assessing the effect of once daily dosing (ODD) versus multiple daily dosing (MDD) of tobramycin on enzyme markers of nephrotoxicity, it was shown that patients receiving ODD, despite higher plasma exposure, had a lower increase of enzymuria [21]. These findings may be explained when it is considered that aminoglycosides are hydrophilic agents whose penetration into renal tubular cells may occur only through carriers. Since the carrier-mediated transport kinetics rapidly undergoes saturation when the entire daily dose is administered all at once, this approach may enable renal excretion of these drugs before that the carrier becomes available once again.

On the contrary, fluoroquinolones, being lipophilic agents, may passively diffuse through cellular membranes, and even through some anatomical barriers. Therefore, their tolerability, especially for neurotoxicity, might significantly decrease if exceedingly high maximum concentrations are achieved. For this reason, when it is necessary to increase their effectiveness over the standard, it is preferable to avoid exceedingly high single doses by increasing the frequency of administration (i.e. 500 mg every 12 hours for levofloxacin); this approach enables both an increase in the total daily AUC/MIC ratio and, at the same time, the effective C_{max}/MIC ratio to be achieved twice per day.

Indeed, the distinction of antimicrobial agents according to their physicochemical characteristics in hydrophilic and lipophilic compounds represents another interesting example of a new clinically useful classification of antibiotics (Figure 10.6).

From a pharmacokinetic point of view, hydrophilic antimicrobials, which include beta-lactams, aminoglycosides and glycopeptides, are characterized either by low

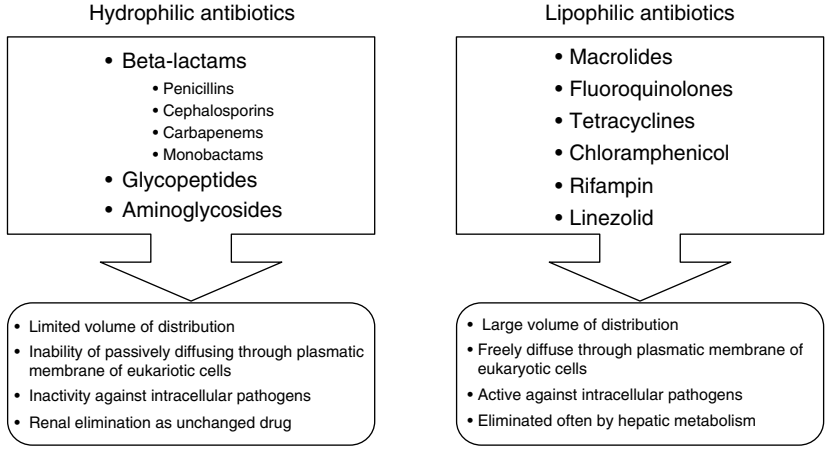

Figure 10.6
Classification of antimicrobials according to their solubility and pharmacokinetic/pharmacodynamic properties (Modified from [2, 26]) Classification of antimicrobials according to their solubility and pharmacokinetic/pharmacodynamic properties. Modified from Pea F, Furlanut M,. Viale P. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet. 2005;44(10):1009–34) and F. Pea, P. Viale Clin Infect Dis. 2006 Jun 15;42(12):1764–71.

volume of distribution (Vd), limited at the extracellular space, and by major renal elimination as unchanged drug. Because of their inability to passively diffuse through the plasmatic membrane of eukaryotic cells they are fully inactive against intracellular pathogens (i.e. *Legionella pneumophila*).

Conversely, lipophilic antimicrobials, which include macrolides, fluoroquinolones and oxazolidinones amongst others, are highly active against intracellular pathogens thanks to their ability to freely cross the plasmatic membrane of eukaryotic cells, often exhibit wide Vd due to intracellular accumulation and, whenever presenting low enough molecular weight, extensive diffusion through anatomical barriers (for example the blood–brain barrier). Due to their lipophilic nature they often have to be metabolised through different pathways, mainly by the liver.

There are some notable exceptions to these rules. Oxacillin and ceftriaxone, although hydrophilic, are mainly eliminated through hepatic metabolisation and biliary excretion, respectively, so that no dosage adjustment is usually needed in presence of renal impairment. Conversely, levofloxacin and gatifloxacin, which are moderately lipophilic fluoroquinolones, are mainly eliminated by renal excretion as antimicrobially active unchanged drugs (>75 %), so that dosage reduction must be applied according to the degree of renal function. Of note, ciprofloxacin presents multiple clearance pathways, with the renal route accounting for about 50–60 %, hepatic metabolisation for about 20–30 % and transintestinal secretion for the remaining proportion. Interestingly, when there is renal impairment, the other mechanisms of clearance may prevent drug accumulation, so that dosage reduction is often unnecessary for ciprofloxacin in patients with renal insufficiency [22]. Likewise, azithromycin, despite its high lipophilicity, is almost completely eliminated unchanged in the faeces through biliary excretion.

Principles for Appropriate Antibiotic Exposure in HAP

The correct application of these PK/PD principles focused at maximizing plasma drug exposure may really improve antimicrobial use in daily clinical practice, but indeed it may not be sufficient for optimal cure of pneumonia if appropriate exposure at the infection site is not ensured as well.

Physicochemical properties, molecular weight and degree of plasma protein binding are among the most important intrinsic characteristics that influence the disposition of a given drug at different body sites.

A methodologically correct approach for investigating drug exposure in the different lung compartments after systemic administration of an antimicrobial agent is to detect drug levels by means of bronchoalveolar lavage (BAL), in the epithelial lining fluid (ELF) for extracellular respiratory pathogens (the most frequent bacterial aetiological agents of nosocomial pneumonia), or in alveolar macrophages (AM) for intracellular respiratory pathogens such as *Legionella pneumophila* (a well known agent of nosocomial pneumonia).

According to their hydro or lipophilicity, antimicrobial agents are expected to achieve different amounts of exposure in the ELF and/or in AM. As a general rule, lipophilic compounds may achieve much higher levels in the ELF in comparison

with hydrophilic ones, and are the only compounds able to significantly accumulate in AM (Table 10.1). Therefore, when using hydrophilic compounds, applying the most suitable dosing schedule according to the PK/PD principles must always be considered mandatory to avoid a significant risk of underexposure in the ELF.

A good example of the relative weakness of the penetration rate of hydrophilic antibiotics in the lung is represented by the glycopeptides, one of the most frequently used classes of antimicrobial, in HAP due to the high incidence of MRSA in the hospital setting. In a recent paper, Shorr and coworkers demonstrated that MRSA ventilator-associated pneumonia (VAP) may independently prolong the duration of Intensive Care Unit (ICU) hospitalisation even in patients initially given appropriate antibiotic treatment, defined as iv vancomycin at 15 mg/kg every 12 hours, and postulates that the adverse impact of MRSA may reflect concerns related to vancomycin [23].

Although concerns about vancomycin efficacy in MRSA VAP might be well founded, defining the twice daily regimen of vancomycin as 'correct' for VAP therapy is questionable, considering that only 5–25 % of simultaneous serum concentrations may diffuse in the ELF [24]. The conventionally recommended every 12 hour regimen might cause subtherapeutic trough levels (Figure 10.4), especially in patients with normal renal function [25] or in those presenting with pathophysiological conditions that enhance the volume of distribution or renal clearance of hydrophilic antibiotics [2, 26]. Conversely, a more frequent dose fractioning up to continuous infusion should be considered more appropriate in these situations; a recent retrospective study carried out on patients treated with vancomycin because of oxacillin-resistant VAP showing that the application of continuous infusion resulted in lower mortality rate versus intermittent infusion seems to confirm this hypothesis [27].

This issue is particularly relevant because the MIC distribution of vancomycin against *S. aureus* isolates is rapidly changing, with several studies detecting a significant incidence of strains with intermediate susceptibility (vancomycin intermediate *S. aureus*, VISA), whose real incidence is probably underestimated by routine automated systems of antibiotic susceptibility [28, 29].

Although no clinical study has determined definitely to what extent patient outcome may be predicted according to *in vitro* MIC values for vancomycin, some relevant experiences noted either an inverse relationship between MIC values for vancomycin and clinical response or a significantly higher proportion of therapeutic failures with vancomycin in the treatment of infections caused by VISA [30, 9, 29, 31].

Likewise, similar penetration rates in the ELF during VAP treatment were recently documented for another glycopeptide as well, namely teicoplanin. In thirteen adult patients with VAP treated with twice the standard dosages of teicoplanin (daily maintenance dose of 12 mg/kg after a 48 hours loading period with 12 mg/kg every 12 hours), on day 4–6 the median ELF concentration was 4.9 mg/L with an ELF-to-plasma ratio of about 0.30 [32].

On the basis of these findings, when deciding upon the use of glycopeptides in HAP, two concepts must be kept in mind. Firstly, going beyond the well-established distinction between methicillin sensitive *Staphylococcus aureus* (MSSA) and MRSA by taking into consideration the relevance of the punctual MIC value for vancomycin (or teicoplanin) as well; and, secondly, pursuing more aggressive dosing strategies

Table 10.1 Pulmonary disposition of some antimicrobial agents [2]. Reprinted with permission from F. Pea, P. Viale The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? Clin Infect Dis. 2006 Jun 15;42(12):1764–71.

	C_{ELF} (mg/L) at hour									C_{ELF}/C_P ratio at hour									C_{AM} (mg/L) at hour				C_A
	0.5	1	2	4	6	8	12	24	48	0.5	1	2	4	6	8	12	24	48	4	8	12	24	4
HYDROPHILIC AGENTS																							
Ceftazidime (4g/die CI) [37]	8.2§	8.2§	8.2§	8.2§	8.2§	8.2§	8.2§	8.2§	8.2§	0.21§	0.21§	0.21§	0.21§	0.21§	0.21§	0.21§	0.21§	0.21§					
Meropenem (1g) [36]	5.04	7.07	3.86	2.20	0.59					0.19	0.51	0.33	1.04	0.82									
Vancomycin (15 mg/kg)* [24]	4.5§	4.5§	4.5§	4.5§	4.5§	4.5§	4.5§	4.5§	4.5§	0.19§	0.19§	0.19§	0.19§	0.19§	0.19§	0.19§	0.19§	0.19§					
LIPOPHILIC AGENTS																							
Linezolid (600 mg every 12 h) [33]				64.3	31.4	24.3	7.60	0.7					4.15		3.53	2.38	4.22	3.5					
Linezolid (600 mg every 12 h) [34]		14.4				2.6					1.05					1.04							
Levofloxacin (500 mg every 12 h) [39]		17.8**									1.27												
Levofloxacin (500 mg every 24 h) [39]		11.9**									1.31												
Levofloxacin (500 mg every 24 h) [47]				11.01			2.50	1.24					2.32			1.53	2.58			83.9		18.3	5.6
Azithromycin (500 mg LD, 250 mg every) [48]				1.01		2.18	0.95	1.22					12.62		24.22	23.75	24.4			42.7	57.2	40.4	41.7
Clarithromycin (500 mg every12 h) [48]				34.5		26.1	15.1	4.60					17.25		16.84	12.38	20.0			480	220	181	99.4

finalized to rapidly achieve and subsequently maintain trough plasma levels of 15−20 mg/L for vancomycin and 25−30 mg/L for teicoplanin.

An attractive therapeutic alternative to glycopeptides in MRSA HAP may surely be represented by linezolid. This lipophilic compound exhibits time-dependent antibacterial activity and was shown to achieve very high ELF levels, approaching plasma levels, either in healthy volunteers or in patients [33, 34]. Additionally, in a retrospective assessment of two comparative trials with vancomycin in the treatment of HAP, a significant improvement in survival of patients with MRSA infections receiving linezolid at the standard 600 mg every 12 hour dosage was reported (80 vs 64 %) [35]. These data seem to confirm that the better pharmacokinetic performance of linezolid may be associated with better clinical outcome. Indeed, it should not be overlooked that these studies presented some bias concerning sample size and administration schedule for vancomycin, so a prospective comparative trial definitively confirming the eventual superiority of linezolid versus glycopeptides in the treatment of MRSA pneumonia is necessary.

Similar PK/PD considerations may be applied as well to antimicrobials used to treat pneumonia due to Gram-negative pathogens. After a single one-gramme intravenous dose, meropenem concentrations in the ELF of healthy volunteers dropped significantly below the MIC_{90} for both *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* just 6 hours after administration [36], thus supporting the redosing every 6 hours rather than every 8 hours with the intent of maximizing pharmacodynamic exposure during pneumonia treatment.

In patients receiving intravenous continuous infusion of ceftazidime at 4 g per day for the treatment of severe nosocomial pneumonia, ELF concentrations at steady state in more than half of the patients were lower than 8 mg/L with mean ELF-to-plasma ratio of 0.21 [37]. These findings suggest that ceftazidime, despite its very low plasma protein binding, may only partially diffuse in the ELF, so that higher dosages (i.e. 6 g iv continuous infusion) should be administered to maximize efficacy in the empirical or targeted treatment of pneumonia due to susceptible strains of *P. aeruginosa.*

Similar findings were documented for piperacillin−tazobactam (P/T) as well [38]. In ten adult patients with severe nosocomial pneumonia receiving a 30-minute iv intermittent infusion of P/T at the rate of 4 g/0.5 g every 8 hours, the mean ELF-to-plasma ratio was 0.57 for piperacillin and 0.91 for tazobactam. Average intermediate steady-state ELF concentrations were 13.6 and 2.1 mg/L for piperacillin and tazobactam, respectively, providing suboptimal concentrations into lung tissue to exceed the MIC of many Gram-negative rods, especially *Pseudomonas aeruginosa* and *Acinetobacter* spp. Accordingly, more frequent dosing (i.e. 4.5 g q6 h) was advocated for adequate treatment of VAP with P/T in critically ill patients.

In critically ill patients with severe community-acquired pneumonia (CAP) levofloxacin, a moderately lipophilic drug, showed high penetration rates in the ELF, the steady-state ELF-to-plasma ratios one hour after 500 mg iv always being >1 whether the dosage was given either every 24 hours or every 12 hours [39]. Interestingly, mean C_{max} in the ELF were 11.9 and 17.8 mg/L with the dosages every 24 hours and every 12 hours, respectively; but whereas the threshold of 10 mg/L (necessary to ensure C_{max}ELF/MIC ratio ≥ 10 considering that the MIC_{90} against

S. pneumoniae and the MIC_{50} against *P. aeruginosa* are of 1 mg/L) was always exceeded by the dosage every 12 hours, this was not the case when the dosage was every 24 hours. This suggests that in critically ill patients with severe pneumonia a dosage every 12 hours might ensure more appropriate exposure.

Overall, the lower ELF concentrations and ELF-to-plasma ratios exhibited by the hydrophilic antimicrobials seem to support the hypothesis that dosages higher than needed for the treatment of bacteriemia are advisable when treating pneumonia with these agents to ensure optimal pharmacodynamic exposure at the infection site.

Principles for Dose Adjustment in Critically Ill Patients

The differences in physicochemical properties among the various classes of antibiotics may explain the variable influence that the patient's underlying pathophysiological conditions may have on antimicrobial disposition in critically ill patients. Fluctuations in extracellular fluid content and/or in renal clearance represent the two principal pathogenetic mechanisms of interindividual pharmacokinetic variability, especially for hydrophilic antibiotics [26], explaining why critically ill patients frequently need very different daily dosages towards the standard of care (Figure 10.7).

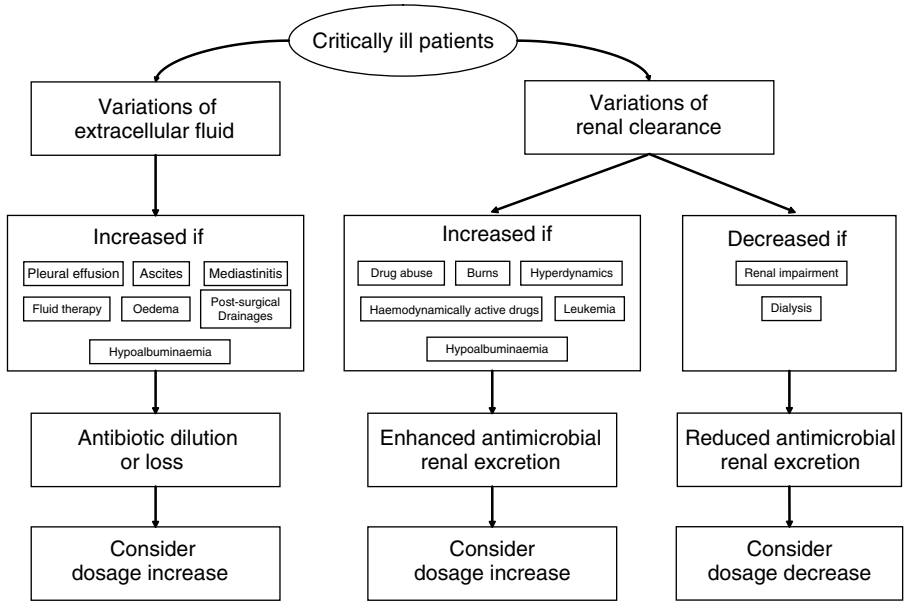

Figure 10.7
Pathophysiological or iatrogenic conditions affecting the distribution and elimination of antimicrobials, and clinical recommendations in such conditions [2, 26] Pathophysiological or iatrogenic conditions affecting the distribution and elimination of antimicrobials, and clinical recommendations in such conditions. Reproduced with permission from Pea F, Furlanut M,. Viale P. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet. 2005;44(10):1009–34) and F. Pea, P. Viale Clin Infect Dis. 2006 Jun 15;42(12):1764–71.

As far as volume of distribution is concerned, an extra volume in the interstitial fluids will have different consequences according to hydro- or lipophilicity. Drug concentration in the extracellular space will significantly decrease when considering hydrophilic agents, whose distribution is limited to plasma and interstitial fluids, whereas only minimal drug dilution will be expected for lipophilic agents, since a drug redistribution from the intracellular space, which acts as a reservoir, to the extracellular space will occur. This means that in patients with different extracellular fluid content (e.g. in the presence of post-septic or post-traumatic oedema, ascites, other relevant trasudates or exudates, fluid overload) when commencing therapy with hydrophilic antibiotics higher than standard loading doses should be considered to promptly achieve therapeutically relevant concentrations, so avoiding the risk of initial under-exposure.

Another important pharmacological issue concerning Vd, pivotal in ensuring rapid and early achievement of therapeutically relevant concentrations, is represented by the mandatory administration of loading doses (LD) at the beginning of treatment when in the presence of drugs with long elimination half-life (e.g. teicoplanin) or when continuous infusion is preferred. Since time to steady-state is equal to 4−5 times the drug elimination half-life, it is clear that the longer the half-life, the longer it will take to reach the steady-state effective concentration (C_{ss}). Under these circumstances loading represents a useful tool in rapidly achieving therapeutically active concentrations similar to the C_{ss}.

Importantly, LD depends only on the volume of distribution (Vd) of the drug and on the target plasma level (C_T); it is completely independent of drug clearance and, therefore, from the patient's hepatic or renal emunctory function ($LD = Vd \times C_T$). Accordingly, whenever necessary at the commencement of therapy, LD must be always administered irrespective of the patient's renal or hepatic function.

In a personal experience retrospectively assessing trough levels of teicoplanin in 202 critically ill patients, target plasma value for efficacy ($C_{min} \geq 10$ mg/L) was reached in most of the patients only 4−5 days after starting therapy, the proportion of patients with $C_{min} \geq 10$ mg/L being less than 10 % during the first 48 hours and 35 % after 96 hours of therapy [40]. The main reason for these disappointing findings was the absence of appropriate loading (defined as 6 mg/kg q12 hours for 3 to 4 doses) in almost two-thirds of patients. After reviewing the patients by renal function, appropriate loading was observed in about 60 % of patients with normal renal function (estimated creatinine clearance (CL_{Cr}) > 50 mL/min), but in a much lower percentage of patients with renal impairment (26.8 % if CL_{Cr} of 20−50 mL/min; 5.4 % if CL_{Cr} < 20 mL/min).

Interestingly, a subsequent triennial prospective study, focused on improving the appropriate use of antibiotics in a hospital setting by means of a multidisciplinary educational intervention, documented a significant increase in the correct application of loading among the 605 patients receiving teicoplanin and undergoing therapeutic drug monitoring (66 vs 36 %), especially in those with impaired renal function (59.8 vs 29.8 % with CL_{Cr} 20−50 mL/min; 27.7 vs 5.4 % with CL_{Cr} < 20 mL/min) [41].

These findings highlight once again the importance of rectifying cultural errors about PK/PD principles with the intent of preventing antibiotic failure.

Likewise, all those pathophysiological conditions that promote an increase of renal blood flow, such as the use of haemodynamically active drugs, intravenous drug abuse, extensive burns, leukaemia and hyperdynamic sepsis, will increase total body clearance of renally excreted drugs, so that higher maintenance doses should be administered.

Interestingly, hypoalbuminemia can cause either increased volume of distribution of hydrophilic compounds, by promoting fluid extravasation, or increased clearance of highly protein bound hydrophilic drugs, namely teicoplanin and ceftriaxone, by favouring an increase in the unbound moiety.

Conversely, whenever renal impairment occurs, the subsequent reduction of renal clearance will necessitate the appropriate reduction in dosage of renally eliminated drugs to prevent potential toxicity.

As an example, the findings (from two personal experiences) about the impact of some of the above variables on plasma exposure to teicoplanin in a cohort of patients with acute leukaemia and febrile neutropenia can be reported. Patients with acute leukaemia represent an excellent example of how the simultaneous presence of several pathophysiological conditions may significantly alter drug disposition. In fact, at least three situations frequently occur in this context: fluid overload (due to complex parenteral therapy), which may increase the extracellular water content; the leukaemic disease itself, which may be responsible for increased renal blood flow [42, 43]; hypoalbuminaemia, which may affect both volume of distribution and clearance of highly protein bound drugs. In the first study, patients with acute leukemia were treated with two different dosages of teicoplanin. Those undergoing standard daily dosage (400 mg every 12 hours for three doses followed by 400 mg once daily) were significantly underexposed when compared to those treated with high dosages (800 mg plus 400 mg 12 hours apart on Day 1, 600 mg plus 400 mg 12 hours apart on Day 2 and 400 mg q12 hours subsequently). In particular, whereas no patient had the recommended teicoplanin C_{min} of 10 mg/L within the first 72 hours in the group receiving the standard dosage, in the group receiving the high dosage this therapeutically effective level was achieved within 24 hours in about half of the patients, and within 48 hours in all but one patient. Of note, no patients in the high dosage group complained of side effects and none presented nephrotoxicity [44].

Subsequently, the PK/PD profile of ceftazidime was studied during continuous intravenous infusion at fixed 6 g/24 hours in 20 patients with acute myeloid leukaemia. Although continuous infusion was found to be an useful tool for maximizing pharmacodynamic exposure (defined as steady−state concentrations of 40 mg/L) in most of the patients, when assessing the decay of plasma concentrations 8 hours after stopping ceftazidime infusion (namely, at the time of redosing when considering intermittent regimens), an amazing inter−patient variability (>1 log) was observed [45].

These findings suggest that when multiple pathophysiological conditions simultaneously coexist in the same patient, the risk of under-dosing with standard fixed dosages of hydrophilic antimicrobials may be very high, so that careful assessment of patient's clinical conditions may become fundamental for appropriate antibiotic treatment.

It is worth noting that therapeutic drug monitoring (TDM), by tailoring drug dosages in each single patient, may be considered a very useful tool in optimizing drug exposure in critically ill patients [46, 26]. This is especially true for patients showing rapidly changing pathophysiological situations, even in a matter of hours. The modern approach to TDM of antimicrobials, in fact, is related not only to toxicological reasons, as originally happened for aminoglycosides and vancomycin in the recent past, but to the need of maximizing the pharmacodynamic effectiveness of antibiotics to ensure clinical cure while preventing resistance spread.

References

1. Niederman, M.S. (2006) Use of broad-spectrum antimicrobials for the treatment of pneumonia in seriously ill patients: Maximizing clinical outcomes and minimizing selection of resistant organisms. *Clin Infect Dis*, **42** (Suppl2), S72−81.
2. Pea, F. and Viale, P. (2006) The antimicrobial therapy puzzle: Could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients. *Clin Infect Dis*, **42**, 1764−71.
3. Pankey, G.A. and Sabath, L.D. (2004) Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. *Clin Infect Dis*, **38**, 864−70.
4. Craig, W.A. (1998a) Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. *Clin Infect Dis*, **26**, 1−10.
5. Craig, W.A. (1998b) Choosing an antibiotic on the basis of pharmacodynamics. *Ear Nose Throat J*, **77**, 7−11. discussion 11−12.
6. Mouton, J.W. and Vinks, A.A. (1996) Is continuous infusion of beta-lactam antibiotics worthwhile? Efficacy and pharmacokinetic considerations. *J Antimicrob Chemother*, **38**, 5−15.
7. MacKenzie, F.M. and Gould, I.M. (1993) The post-antibiotic effect. *J Antimicrob Chemother*, **32**, 519−37.
8. Knudsen, J.D., Fuursted, K., Raber, S. *et al*. (2000) Pharmacodynamics of glycopeptides in the mouse peritonitis model of *Streptococcus pneumoniae* or *Staphylococcus aureus* infection. *Antimicrob Agents Chemother*, **44**, 1247−54.
9. Moise-Broder, P.A., Forrest, A., Birmingham, M.C *et al*. (2004) Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet*, **43**, 925−42.
10. Sakoulas, G., Gold, H.S., Cohen, R.A. *et al*. (2006b) Effects of prolonged vancomycin administration on methicillin-resistant *Staphylococcus aureus* (MRSA) in a patient with recurrent bacteraemia. *J Antimicrob Chemother*, **57**, 699−704.
11. Kasiakou, S.K., Sermaides, G.J., Michalopoulos, A. *et al*. (2005) Continuous versus intermittent intravenous administration of antibiotics: A meta-analysis of randomised controlled trials. *Lancet Infect Dis*, **5**, 581−9.
12. Forrest, A., Nix, D.E., Ballow, C.H. *et al*. (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother*, **37**, 1073−81.
13. Hyatt, J.M. and Schentag, J.J. (2000) Potential role of pharmacokinetics, pharmacodynamics and computerized databases in controlling bacterial resistance. *Infect Control Hosp Epidemiol*, **21**, S18−21.
14. Schentag, J.J. (2000) Clinical pharmacology of the fluoroquinolones: Studies in human dynamic/kinetic models. *Clin Infect Dis*, **31**, S40−44.

15. Ambrose, P.G., Grasela, D.M., Grasela, T.H. *et al*. (2001) Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in patients with community-acquired respiratory tract infections. *Antimicrob Agents Chemother*, **45**, 2793−7.
16. Nightingale, C.H., Grant, E.M. and Quintiliani, R. (2000) Pharmacodynamics and pharmacokinetics of levofloxacin. *Chemotherapy*, **46**, 6−14.
17. Aminimanizani, A., Beringer, P. and Jelliffe, R. (2001) Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet*, **40**, 169−87.
18. Preston, S.L., Drusano, G.L., Berman, A.L. *et al*. (1998) Pharmacodynamics of levofloxacin: A new paradigm for early clinical trials. *Jama*, **279**, 125−9.
19. Rodvold, K.A. (2001) Pharmacodynamics of antiinfective therapy: Taking what we know to the patient's bedside. *Pharmacotherapy*, **21**, 319S−30S.
20. Turnidge, J. (1999) Pharmacokinetics and pharmacodynamics of fluoroquinolones. *Drugs*, **58**, 29−36.
21. Olsen, K.M., Rudis, M.I., Rebuck, J.R. *et al*. (2004) Effect of once-daily dosing vs. Multiple daily dosing of tobramycin on enzyme markers of nephrotoxicity. *Crit Care Med*, **32**, 1678−82.
22. Pea, F., Poz, D., Viale, P., Pavan, F. *et al*. (2006a) Which reliable pharmacodynamic breakpoint should be advised for ciprofloxacin monotherapy in the hospital setting? A TDM-based retrospective perspective. *J Antimicrob Chemother*, **58**, 380−6.
23. Shorr, A.F., Combes, A., Kollef, M.H. *et al*. (2006) Methicillin-resistant *Staphylococcus aureus* prolongs intensive care unit stay in ventilator-associated pneumonia, despite initially appropriate antibiotic therapy. *Crit Care Med*, **34**, 700−6.
24. Lamer, C., de Beco, V., Soler, P. *et al*. (1993) Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. *Antimicrob Agents Chemother*, **37**, 281−6.
25. Sakoulas, G., Moellering, R.C. Jr and Eliopoulos, G.M. (2006a) Adaptation of methicillin-resistant *Staphylococcus aureus* in the face of vancomycin therapy. *Clin Infect Dis*, **42** (Suppl 1), S40−50.
26. Pea, F., Viale, P. and Furlanut, M. (2005a) Antimicrobial therapy in critically ill patients: A review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. *Clin Pharmacokinet*, **44**, 1009−34.
27. Rello, J., Sole-Violan, J., Sa-Borges, M. *et al*. (2005) Pneumonia caused by oxacillin resistant *Staphylococcus aureus* treated with glycopeptides. *Crit Care Med*, **33**, 1983−7.
28. Jones, R.N. (2006) Microbiological features of vancomycin in the 21st century: Minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. *Clin Infect Dis*, **42** (Suppl 1), S13−24.
29. Sakoulas, G., Moise-Broder, P.A., Schentag, J. *et al*. (2004) Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol*, **42**, 2398−402.
30. Howden, B.P., Ward, P.B., Charles, P.G. *et al*. (2004) Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. *Clin Infect Dis*, **38**, 521−8.
31. Verdier, I., Reverdy, M.E., Etienne, J. *et al*. (2004) *Staphylococcus aureus* isolates with reduced susceptibility to glycopeptides belong to accessory gene regulator group I or II. *Antimicrob Agents Chemother*, **48**, 1024−7 .
32. Mimoz, O., Rolland, D., Adoun, M. *et al*. (2006) Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia. *Intensive Care Med*, **32**, 775−9.
33. Conte, J.E. Jr, Golden, J.A., Kipps, J. *et al*. (2002) Intrapulmonary pharmacokinetics of linezolid. *Antimicrob Agents Chemother*, **46**, 1475−80.

34. Boselli, E., Breilh, D., Rimmele, T. *et al*. (2005b) Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med*, **33**, 1529−33.
35. Wunderink, R.G., Rello, J., Cammarata, S.K. *et al*. (2003) Linezolid vs vancomycin: Analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*, **124**, 1789−97.
36. Allegranzi, B., Cazzadori, A., Di Perri, G. *et al*. (2000) Concentrations of single-dose meropenem (1 g iv) in bronchoalveolar lavage and epithelial lining fluid. *J Antimicrob Chemother*, **46**, 319−22.
37. Boselli, E., Breilh, D., Rimmele, T. *et al*. (2004a) Plasma and lung concentrations of ceftazidime administered in continuous infusion to critically ill patients with severe nosocomial pneumonia. *Intensive Care Med*, **30**, 989−91.
38. Boselli, E., Breilh, D., Cannesson, M. *et al*. (2004b) Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 g/0.5 g administered to critically ill patients with severe nosocomial pneumonia. *Intensive Care Med*, **30**, 976−9.
39. Boselli, E., Breilh, D., Rimmele, T. *et al*. (2005a) Pharmacokinetics and intrapulmonary diffusion of levofloxacin in critically ill patients with severe community-acquired pneumonia. *Crit Care Med*, **33**, 104−9.
40. Pea, F., Brollo, L., Viale, P., Pavan, F. *et al*. (2003) Teicoplanin therapeutic drug monitoring in critically ill patients: A retrospective study emphasizing the importance of a loading dose. *J Antimicrob Chemother*, **51**, 971−5.
41. Pea, F., Viale, P., Pavan, F. *et al*. (2006b) The effect of multifactorial, multidisciplinary educational interventions on appropriate use of teicoplanin. *Int J Antimicrob Agents*, **27**, 344−50.
42. Fernandez deGatta, M.M., Fruns, I., Hernandez, J.M. *et al*. (1993) Vancomycin pharmacokinetics and dosage requirements in haematologic malignancies. *Clin Pharm*, **12**, 515−20.
43. Lortholary, O., Tod, M., Rizzo, N. *et al*. (1996) Population pharmacokinetic study of teicoplanin in severely neutropenic patients. *Antimicrob Agents Chemother*, **40**, 1242−7.
44. Pea, F., Viale, P., Candoni, A. *et al*. (2004) Teicoplanin in patients with acute leukaemia and febrile neutropenia: A special population benefiting from higher dosages. *Clin Pharmacokinet*, **43**, 405−15.
45. Pea, F., Viale, P., Damiani, D. *et al*. (2005b) Ceftazidime in patients with febrile neutropenia during acute myeloid leukaemia: Helpfulness of intravenous continuous infusion in maximizing pharmacodynamic exposure. *Antimicrob Agents Chemother*, **49**.
46. Pea, F., Bertolissi, M., Di Silvestre, A. *et al*. (2002) TDM coupled with bayesian forecasting should be considered an invaluable tool for optimizing vancomycin daily exposure in unstable critically ill patients. *Int J Antimicrob Agents*, **20**, 326−32.
47. Rodvold, K.A., Danziger, L.H. and Gotfried, M.H. (2003) Steady-state plasma and bronchopulmonary concentrations of intravenous levofloxacin and azithromycin in healthy adults. *Antimicrob Agents Chemother*, **47**, 2450−7.
48. Rodvold, K.A., Gotfried, M.H., Danziger, L.H. *et al*. (1997) Intrapulmonary steady-state concentrations of clarithromycin and azithromycin in healthy adult volunteers. *Antimicrob Agents Chemother*, **41**, 1399−402.

11

Minimally Invasive Diagnostic Strategy in Immunocompromized Patients with Pulmonary Infiltrates

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Introduction

Physicians in most medical specialties are seeing a growing number of patients with solid tumours and haematological malignancies. Routine screening policies have been implemented to ensure that cancer is diagnosed early, and treatment advances have been achieved with the result that many patients have prolonged survival or recover completely. Intensive and prolonged treatment regimens introduced over the last decade have increased the overall survival rates amongst patients with various types of malignancy [1]. For instance, intensified and shortened cyclical chemotherapy for acute lymphoblastic leukaemia in adults has been associated with increased survival [2], advances in the understanding of multiple myeloma have led to the development of new drugs [3], targeted therapies have proved useful in patients with lymphoma and chronic myeloid leukaemia [4, 5] and growth factors that hasten neutropenia recovery have allowed higher-dose chemotherapy regimens which increase the chances of a cure [6]. However, treatment-related toxic and infectious complications have increased in tandem with the expanding use of aggressive cancer treatments.

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Pulmonary events are the leading complications in patients treated for cancer. These events are frequently severe, with diffuse pulmonary infiltrates, hypoxemia and secondary dysfunction of other organs (i.e. shock and kidney injury) [7]. Acute respiratory failure is the most common reason for admission of cancer patients to the intensive care unit (ICU) [8–10] and carries a mortality rate of about 50 % overall, 60–70 % when invasive mechanical ventilation is needed and 80–90 % in recipients of allogeneic bone marrow or stem cell transplants who require mechanical ventilation [11]. Noninvasive mechanical ventilation has improved survival in cancer patients requiring ventilation by reducing the need for endotracheal intubation [12–15].

A vast array of conditions can manifest as pulmonary infiltrates in patients with cancer (Table 11.1). Although the need for early treatment, most notably with antimicrobials, is universally recognized, debate continues about the best diagnostic

Table 11.1 Causes of pulmonary infiltrates in patients with solid tumors or haematological malignancies. Adapted from [16]

Infections
Bactrerial infections
Common pyogenic bacteria
Streptococcus pneumoniae
Staphylococcus aureus
Haemophilus influenzae
Pseudomonas aeruginosa and Enterobacteriaceae
Intracellualr bacteria
Legionella pneomophilia
Chlamydia and Mycoplasma pneumoniae
Other bacteria
Actinomyces israeli
Nocardia spp.
Pneumocystis jirovecii
Invasive fungal Infections
Molds
Aspergillosis
Emerging mycotic infections: trichosporosis, fusariosis, zygomycetes
Yeasts
Lung involvement during candidemia
Endemic fungal infections
Histoplasmosis, coccidioidomycosise, blastomycosis
Viral infections (primary infections or reactivations)
Seasonal respiratory viruses
Influenzae, parainfluenzae, rhinovirus
Respiratory syncytial virus
Herpes virus
Cytomegalovirus, herpes virus, zoster virus and HHV6
Other viruses: adenovirus
Mycobacterial infections
Tuberculosis and atypical mycobacteria

Noninfectious causes
Cardiogenic pulmonary edema
Capillary leak syndrome
Lung infiltration
Drug-induced toxicity
Alveolar hemorrhage
Transfusion-related acute lung injury
Radiation-induced lung damage
Alveolar proteinosis
Diffuse alveolar damage
Bronchiolitis
Cryptogenic organized pneumonia
Second malignancy

strategy in cancer patients with pulmonary infiltrates [16]. Suggested diagnostic strategies cover an extensive spectrum ranging from empirical treatment without diagnostic investigation to diagnostic lung biopsy. However, most groups recommend diagnostic investigation. The main difference across strategies is whether fiberoptic bronchoscopy with bronchoalveolar lavage (FO−BAL) is performed (Table 11.2) [16].

Table 11.2 The diagnostic strategy without bronchoscopy in cancer patients with pulmonary infiltrates. Adapted from [16]

Radiography
Chest radiography
Thin-section high-resolution computed tomography
Echocardiography or pleural ultrasonography
Sputum
Bacteria
Tubercle bacillus
Fungi (aspergillus)
Tests for *Pneumocystis jirovecii* (MGG staining and immuno-fluorescence)
PCR for *Pneumocystis jirovecii*
Blood cultures
Serum tests
Serology: Chlamydia, Mycoplasma, Legionella
Herpes consensus PCR test
Circulating aspergillus antigen
Circulating cytomegalovirus antigen
Nasopharyngeal aspiration
Tests for viruses (PCR and immunofluorescence)
Urine tests
Cytology, bacteriology
Legionella antigen
Biological markers
Brain natriuretic peptide (BNP) or ProBNP
C reactive protein
Fibrin
Procalcitonin

Delay since malignancy onset or BMT
Patterns of Immune deficiency
Radiographic appearence
Clinical Experience and knowledge of the literature
Clinical Picture
Findings by the high resolution computed Tomodensitometry (HRCT)

Figure 11.1
The DIRECT approach for selecting the initial antimicrobial treatment
Source: Adapted from [16]; this approach does not obviate the need for diagnostic investigations.

The debate about whether FO−BAL is appropriate is particularly relevant in patients with hypoxemic acute respiratory failure, among whom 40% experience respiratory status deterioration when FO−BAL is performed [17−19]. This risk must be weighed against the increased risk of death that is independently associated with failure to identify the cause of pulmonary infiltrates in patients with cancer [11, 20−22].

This review focuses on the diagnostic strategy for cancer patients with pulmonary infiltrates. Initially our DIRECT approach is reviewed briefly; this is designed to increase the likelihood of appropriate anti-infectious therapy being given within two hours of admission to the ICU (Figure 11.1). A strategy based solely on the DIRECT approach is not recommended, because identifying the cause of the pulmonary infiltrates increases the chances of survival. The two main strategies for identifying the cause of pulmonary infiltrates are described, with and without FO−BAL. Because the diagnostic efficiency of FO−BAL was evaluated recently, [16] the focus is on the strategy that does not include FO−BAL. In our ICU experience, although FO−BAL combined with other investigations fails to identify the cause in 10−15% of patients, [11, 23] the severe hypoxemia and associated organ dysfunctions limit the feasibility of lung biopsy. However, studies have found lung biopsy to be highly efficient, and this point is raised in the last section, which highlights areas for research that may help to improve the management of these very vulnerable patients.

The DIRECT Approach: A Guide for Selecting Initial Antimicrobial Treatment and Investigations

A clinical approach was recently proposed designed to help clinicians make hypotheses about the cause of pulmonary infiltrates in patients with haematological malignancies or solid tumours (Figure 11.1) [16]. This empiric approach is being evaluated prospectively. In the next paragraphs, this approach is described and one or two examples are provided for each situation. The main goal of the

DIRECT approach is to target diagnostic and therapeutic efforts toward those conditions that are most likely to be present in the individual patient, instead of running through the entire list of causes of pulmonary infiltrates in cancer patients. By identifying the two or three diagnoses that are plausible in a given patient, the DIRECT approach may help to initiate appropriate treatment within a few hours of admission.

D stands for Delay and refers to three time intervals that should be taken into account: (i) time from the diagnosis of malignancy; (ii) time from respiratory symptom onset; and (iii), where relevant, time from allogeneic bone marrow transplant (BMT). For example, pulmonary leukaemic infiltration or leukostasis occurs in patients with high circulating blast cell counts, that is at the earliest stage of acute leukaemia or during relapses [24]. Gradually worsening dyspnea over the last four weeks is more likely to indicate pulmonary infiltration by the malignancy or congestive heart failure and pulmonary edema than bacterial infection or pneumocystis pneumonia (PCP). In allogeneic BMT recipients, cytomegalovirus pneumonia may occur during graft-versus-host disease (GVHD) but is unlikely to explain pulmonary infiltrates during the first 30 days after transplantation [25].

I indicates the type of Immune deficiency. This information is crucial when making hypotheses about the type of infection responsible for pulmonary infiltrates. Patients with lymphocyte abnormalities (e.g. acute or chronic lymphocytic leukaemia or lymphoma) are at risk of viral or fungal infections (e.g. herpes simplex virus [HSV], PCP and emerging fungal infections); diseases affecting monocytes and macrophages (e.g. hairy cell leukaemia, chronic myelomonocytic leukaemia and chronic myeloid leukaemia) are associated with intracellular bacterial infections (e.g. *Legionella, Mycoplasma and tuberculosis*); and neutrophil abnormalities (e.g. absolute or relative neutropenia, myelodysplastic syndrome and chronic myeloid leukaemia) increase the risk of bacterial and fungal infections. In addition, hypogammaglobulinemia in patients with chronic lymphocytic leukaemia or myeloma is specifically associated with infection by encapsulated bacteria. However, all these patterns need to be re-evaluated using new technologies to assess the cellular defects. In addition, the increasing use of intensive and prolonged cancer chemotherapy regimens and of targeted therapies (e.g. rituximab and alemtuzumab) can be expected to change the patterns of immune deficiency seen in cancer patients and suggest that qualitative studies are needed.

R indicates the chest radiograph findings. These are detailed in the section on the diagnostic strategy without FO−BAL.

E refers to Experience and knowledge of the literature. For example, although diffuse alveolar haemorrhage can theoretically cause pulmonary infiltrates in immunosuppressed patients, this complication seems to be virtually confined to BMT recipients [26, 27]. Similarly, pulmonary aspergillosis, although possible in every cancer patient, occurs chiefly in patients with prolonged neutropenia (e.g. acute leukaemia patients) and in BMT recipients [28].

T refers to findings by high-resolution computed tomography (HRCT). These findings are detailed in the section on the diagnostic strategy without FO−BAL.

Bronchoscopy and Bronchoalveolar Lavage (FO–BAL) in Cancer Patients with Pulmonary Infiltrates

In the late 1980s, FO−BAL became the most widely used investigation for identifying the cause of pulmonary infiltrates in immunosuppressed patients [29−34]. It superseded lung biopsy, as it was easier, simpler and less invasive. These advantages were reported to be particularly helpful in patients at very high risk of death if treated with mechanical ventilation [35]. The results of 18 studies (in 1537 patients) indicated that FO−BAL provided the diagnosis in about half the patients and led to modification of treatment in one third (Table 11.3). Data from 764 BMT recipients in 15 studies showed that FO−BAL supplied the diagnosis in 55 % of cases but caused the respiratory status to deteriorate in up to 40 % (Table 11.4) [17−19].

The limited diagnostic efficiency of FO−BAL in immunocompromised patients may be related to several factors. Firstly, most patients are already on antimicrobial therapy at the time of FO−BAL. Therefore, bacterial pneumonia is usually documented clinically, but not bacteriologically, although FO−BAL may detect resistant pathogens that require adjustment of the antimicrobial regimen. Secondly, BAL fluid analysis is often confined to tests for infections and most studies fail to report the appearance of the alveolar cells, which may suggest drug toxicity, or the presence of malignant cells, indicating pulmonary infiltration. Thirdly, most studies were conducted in the 1990s, before the introduction of new tools for diagnosing infections

Table 11.3 Studies of fiberoptic bronchoscopy with bronchoalveolar lavage in patients with malignancies and pulmonary infiltrates. Adapted from [16]

Reference	n	Diagnosis	Diagnostic impact	Therapeutic impact
Stover *et al.*	97	HM	66	–
Martin *et al.*	100	HM	30	–
Xaubet *et al.*	96	HM	49	31
Campbell *et al.*	22	HM	55	–
Pisani *et al.*	150	HM	39	–
Maschmeyer *et al.*	46	Neutropenia	30	–
Cordonnier *et al.*	56	Neutropenia	53	24
Cazzadori *et al.*	142	HM	36	–
Von Eiff *et al.*	90	HM	66	65
White *et al.*	68	HM	31	24
Ewig *et al.*	49	HM	31	16
Gruson *et al.*	41	Neutropenia	63	28
Hilbert *et al.*	24/46	HM	62	71
Murray *et al.*	27	HM	33	28
Azuolary *et al.*	203	HM	49.5	45.1
Pagano *et al.*	127	HM	53	14
Jain *et al.*	104	HM	56	–
Hohenadel *et al.*	95	HM	30	–
Total	1537		46.2	34.6

Table 11.4 Studies of fiberoptic bronchoscopy with bronchoalveolar lavage in bone marrow transplant recipients with pulmonary infiltrates. Adapted from [16]

Author	n	Type of patients	Diagnostic impact	Therapeutic impact	Complications
Springmeyer *et al.*	22	Auto-allo	58	–	13
Cordonnier *et al.*	52	Allo	50	–	0
Cordonnier *et al.*	69	Allo	66	–	–
Milburn *et al.*	40	Allo	80	76	0
Springmeyer	15	Auto-allo	89	–	40
Heurlin *et al.*	18	Auto-allo	61	–	–
Weiss *et al.*	47	Auto-allo	47	–	12
Campbell *et al.*	27	-	74	63	11
AbuFarsakh *et al.*	77	Auto-allo	42	–	–
White *et al.*	68	Auto-allo	31	24	15(7 % MV)
Dunagan[a] *et al.*	71	Auto-allo	38	42	27(4 % MV)
Glazer *et al.*	79	Auto-allo	67	62	–
Gruson *et al.*	38	Auto-allo	42	–	–
Gruson *et al.*	52	Auto-allo	38	28	17
Huaringa *et al*	89	Auto-allo	42	–	–
Total	764	Auto-allo	55	49	0 to 40 %

[a] 32 % mechanical ventilation

with viruses, parasites and fungi [36]. However, the diagnostic yield of FO−BAL was not better in recent studies [11, 37]. Lastly, FO−BAL may be less efficient in patients with cancer than in those with AIDS because of pathophysiological differences in the development of pulmonary invasion by *Aspergillus* or *Pneumocystis* [28, 38−42]. For instance, a study of PCP in cancer patients showed marked inflammation and scarce *Pneumocystis* bodies, indicating that negative BAL fluid findings did not rule out PCP [40].

Diagnostic Strategy without Bronchoscopy

The investigations used in the diagnostic strategy without FO−BAL are listed in Table 11.2. Routinely performing all these tests may be an alternative to FO−BAL in most cancer patients with pulmonary infiltrates (Figure 11.2). Available data on the use of each of these investigations in cancer patients are reviewed here.

Chest Radiograph

Chest radiography is fast, widely available and inexpensive. Image quality may be suboptimal, as the radiograph is usually taken in the supine position, at the bedside, for these fragile patients who often require isolation precautions. Routine chest radiography was recommended when studies showed that a substantial proportion of

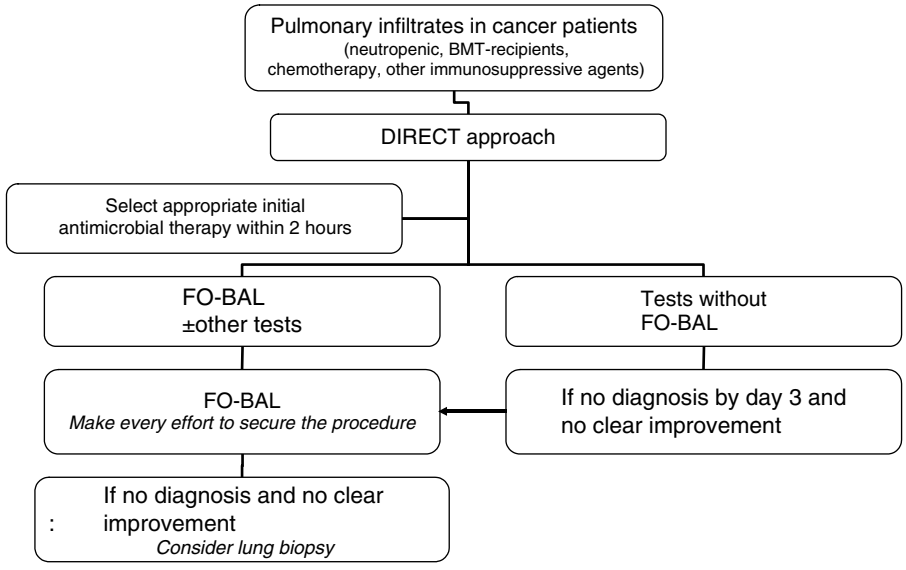

Figure 11.2
Diagnostic strategy for cancer patients with pulmonary infiltrates

febrile neutropenic patients with pneumonia had normal physical findings [43–45]. The assumption was that identifying chest radiograph abnormalities would improve patient management. However, conventional radiography has shown limited sensitivity in detecting pneumonia in neutropenic patients, in whom the blunted and delayed inflammatory response may fail to produce readily visible radiographic alterations.[46] Moreover, chest radiography findings lack specificity (Figure 11.3) [47].

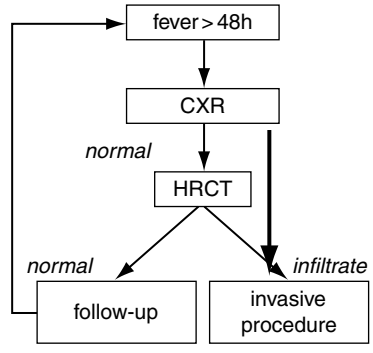

Figure 11.3
Radiographic patterns and causes of lung infiltrates in immunocompromised patients (from [47])

Table 5—Radiographic patterns and Etiologies of Infiltrates in the Immunosuppressed patients

Pattern of Infiltrate	Potential Etiologies	
	Infectious	Noninfectious
Focal infiltrate	Any type of organism	BOOP, DAH, disease progression, drug toxicity, GVHD, PAP, PTLD, radiation toxicity
Diffuse infiltrates	Legionella, mycobacterial (tuberculous and nontuberculous), *P carinii*, viruses	DAH, disease progression (particularly leukemic infiltrates or lymphangitic spread of tumor), drug toxicity, engraftment syndrome, GVHD, IPS, PAP, PTLD, radiation toxicity
Cavitary infiltrates and/or nodules	Bacteria, fungi, mycobacteria, *P carinii*, viruses (small nodules)	Disease progression, drug toxicity

Figure 11.4
Recommendations from the infectious diseases working party of the German Society of Haematology and Oncology (adapted from [45])

In one study, half of the patients with febrile neutropenia and normal chest radiograph findings had evidence of pneumonia by thin-section CT [48]. Moreover, among 109 episodes of febrile neutropenia without clinical evidence of lung infection in ambulatory patients receiving cancer chemotherapy, only two had chest radiographs that showed consolidation consistent with pneumonia, and this finding did not require a change in antibiotic therapy [49]. In a retrospective review of 195 febrile episodes in 127 patients with neutropenia, only 17% of episodes with signs and symptoms suggesting lung disease had abnormal chest radiographs, and the radiographic findings had no impact on treatment [50]. Thus, chest radiography may be of marginal value for investigating febrile episodes. Similar results have been found in recipients of autologous [51] or allogeneic BMT [52].

These data indicate that chest radiography is not sufficiently sensitive or specific to be performed routinely in cancer patients with fever, and that a normal chest radiograph should lead to CT before the diagnosis of pneumonia is ruled out (Figure 11.4) [44].

High-Resolution Computed Tomography (HRCT)

HRCT is the investigative technique of choice for accurately evaluating the lung parenchyma, most notably in patients with interstitial pneumonia. Contrast enhancement is not required to detect or to characterize pneumonia, except in specific situations such as pulmonary embolism or haemoptysis due to vessel erosion in aspergillosis. In long-term allogeneic BMT recipients, bronchiolitis obliterans should be sought by obtaining an expiratory CT scan to detect air trapping.

Repeated thoracic HRCT has been reported to detect abnormalities earlier, provide diagnostic guidance, help evaluate treatment responses and improve survival

[42, 48, 53]. As mentioned above, chest radiography lacks sensitivity, particularly in neutropenic patients, who are often found to have pulmonary infiltrates by HRCT despite normal chest radiographs (Figure 11.3). HRCT was evaluated for the early diagnosis of pneumonia in neutropenic patients with an unknown site of infection and normal or non-specific chest radiograph findings [53]. Of the 146 chest radiographs in 87 patients, 20 showed nonspecific abnormalities, which were consistently associated with evidence of pneumonia by HRCT. Of the 126 normal radiographs, 70 coincided with HRCT evidence of pneumonia. In addition, HRCT suggested pneumonia about five days earlier than chest radiography [53]. In a more recent study by the same group, up to 60 % of patients with normal chest radiographs had pneumonia indicated by HRCT.

HRCT is useful not only for early detection of pneumonia, but also for ruling out pneumonia in neutropenic patients and BMT recipients. A negative predictive value of 88 % has been reported [48]. Therefore, normal HRCT findings indicate that every effort should be made to detect infection at nonpulmonary sites, such as the gastrointestinal tract or an intravascular catheter.

Based on these data, HRCT has been added to the investigations recommended in febrile neutropenic patients. Early identification of lung infiltrates by HRCT significantly improves the prognosis. Conventional chest radiographs show lung infiltrates in less than 10 % of patients who remain febrile despite antibacterial therapy, whereas HRCT shows abnormalities in about 50 % of these patients. HRCT is recommended for the early detection or exclusion of pneumonia [43, 44, 54]. However, HRCT findings are not specific. They may fail to distinguish infectious from noninfectious infiltrates or to separate the different patterns of infection [48]. Nevertheless, in long-term BMT recipients, HRCT was efficient in diagnosing fungal and bacterial infections subsequently documented by FO−BAL [52].

High-Resolution Computed Tomography Findings in Common Conditions

Considerable overlap occurs in the HRCT manifestations of viral, bacterial and fungal pneumonia in neutropenic patients and BMT recipients. Findings in various situations are listed in Table 11.5.

In bacterial pneumonia, several radiographic patterns occur more frequently in immunocompromised patients. For instance, as well as consolidation and a positive pneumobronchogram, ground-glass opacities are more common [55]. In addition, because aspiration pneumonia or lung seeding from an infected catheter is more common in immunocompromised patients, the radiographic appearance of bacterial pneumonia may differ from the patterns seen in other patients [56].

Febrile neutropenia is associated with invasive fungal infection, mainly by *Aspergillus spp*. Mucormycosis is being increasingly found and produces similar radiographic abnormalities to those seen in aspergillosis [57]. The pathogenic potential of *Candida* spp. isolated from respiratory samples is still debated [58]. Invasive pulmonary aspergillosis may lead to typical ill-defined nodules with a halo sign (decreased attenuation surrounding a pulmonary mass) at the early phase and to a

Table 11.5 Radiological findings in various lung diseases in neutropenic patients and in bone marrow or stem cell recipients

Diagnosis	Radiological findings
Bacterial	*Consolidation, Pneumonia pneumobronchogram, Ground-glass opacities*
Fungal	*Ill-defined nodules, Cavitations (late phase)*
Pneumocystis	*Ground-glass opacities, Subpleural space spared, Intralobular septa (late phase)*
Tuberculosis	*Small ill-defined nodules/cavitations, tree-in-bud, homogeneous consolidation*
Viral	*Ground-glass opacities/mosaic pattern centrilobular nodules, branching opacities (tree-in-bud pattern), large nodules*
Graft vs. host	*Ground-glass opacities/mosaic pattern, Intralobular septa, Tree-in-bud, Air trapping*
Radiation toxicity	*Ground-glass opacities/paramediastinal distribution Intralobular septa*
Drug toxicity	*Ground-glass opacities/mosaic pattern Intralobular septa*
Pulmonary congestion	*Ground-glass opacities, Thickened interlobular septa*
Leukemic infiltration	*Thickened bronchovascular bundles, Thickened interlobular septa, Ground glass opacities*
Pulmonary hemorrhage	*Ground-glass opacities/sedimentation phenomenon*

nonspecific air-crescent sign with cavitation later on. HRCT has become an essential tool for the diagnosis of invasive pulmonary aspergillosis. In a study of 37 patients with documented or strongly suspected invasive pulmonary aspergillosis, HRCT showed suggestive halo signs in 34 (92 %) patients, compared to five (13 %) by chest radiography [59]. HRCT reduced the mean time to diagnosis from seven to 1.9 days [59]. In a study of repeated HRCTs, halo signs were found in 68, 22 and 19 % of cases on Day 3, Day 7 and Day 14, respectively; and air-crescent signs were found in 8, 28 and 63 % of cases on the same days [42]. The halo sign is relatively specific of invasive pulmonary aspergillosis in neutropenic patients with haematological malignancies. However, it may occur in other fungal infections (e.g. candidiasis and mucormycosis) and in organizing pneumonia, pulmonary haemorrhage, bronchiolitis obliterans with organizing pneumonia, cytomegalovirus pneumonia, pulmonary tuberculosis and *Candida pneumonia* [60]. Complicated nodules by HRCT strongly suggest fungal infection in febrile BMT recipients, whereas normal HRCT findings suggest bacteraemia or nonpulmonary infection with nonfilamentous fungi [61]. Studies are needed to evaluate the performance of chest radiography and HRCT using new definitions for interpreting imaging findings in invasive fungal infections. These definitions, which are intended for clinical and epidemiological research in neutropenic patients, were developed by the European Organization for Research and Treatment of Cancer, the Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group. Major criteria for fungal pneumonia include new infiltrates showing a halo sign, air-crescent

sign or cavity within an area of consolidation. New infiltrates that do not show these features are minor criteria for fungal pneumonia [41].

PCP can develop in transplant recipients and in patients treated with steroids. Trimethoprim/sulfamethoxazole prophylaxis substantially reduces the risk of PCP in these patients. Widespread ground-glass opacification with a mosaic pattern, typically in a perihilar distribution with areas of affected lung interspersed with normal lung parenchyma, is common and highly characteristic. The subpleural space is typically spared. Occasionally, reticulation or septal thickening may be seen within ground-glass opacities, presumably reflecting the presence of fluid and cells within the alveolar space, as well as thickening of the alveolar septa. Centrilobular opacities or Y-shaped branching structures may be present, indicating bronchiolitis and bronchioles impacted with inflammatory material.

Diffuse ground-glass opacification typically develops in the early phase of infection, whereas consolidation occurs when the course is fulminant. The predominance of intralobular linear patterns occurs later on during treatment for PCP. A combination of ground-glass opacities and intralobular septa sparing the subpleural space is highly suggestive of PCP [54, 62].

Tuberculosis should always be considered. The presentation may be unusual in immunocompromised patients [63], with widespread lymphogenic and haematogenous dissemination, and occasionally with a fulminant course. Small, ill-defined and at times cavitated nodules in a peribronchial distribution ('tree-in-bud' sign) may indicate miliary dissemination, but with bronchogenic spread (not haematogeneous spread). Gangliopulmonary tuberculous manifests as inhomogeneous consolidation and necrotic mediastinal and hilar lymphadenopathy [64]. Compared to immunocompetent patients with tuberculosis, HIV-negative immunocompromised patients were more likely to have a fever (84.1 vs 40 %), disseminated tuberculosis (23.8 vs 3.8 %), lobar or segmental consolidation (20.6 vs 0 %), miliary lesions (17.5 vs 3.8 %) and hilar and/or mediastinal lymphadenopathy (14.3 vs 2.5 %) [65].

Atypical pneumonia in neutropenic patients and BMT recipients may be caused by viral infections. The most frequently suspected viruses are cytomegalovirus, respiratory syncytial virus, HSV, influenza, para-influenza and adenovirus. There are no virus-specific radiological patterns. Viral pneumonia typically produces a combination of small centrilobular nodules, ground-glass opacification and air-space consolidation [66]. Bronchial thickening may occur in respiratory syncytial virus pneumonia. Interlobular septal thickening, bronchial dilatation and pleural effusion may develop in adenovirus pneumonia [67].

Pulmonary manifestations occur in up to 10 % of patients with chronic graft-versus-host disease, usually nine months after allogeneic transplantation. Bronchiolitis obliterans is among these manifestations. The most common abnormalities are decreased lung attenuation, segmental and subsegmental bronchial dilatation, centrilobular nodules and branching linear structures. Expiratory air trapping is consistently noted. Expiratory CT should be performed when bronchiolitis obliterans is suspected in a BMT recipient [54, 62].

Radiation therapy not only causes lung damage, but also potentiates the toxicity of cancer chemotherapy drugs. One problem in detecting radiation-induced toxicity

is that the time to clinical symptoms is about three weeks in most cases but may be as long as several months. HRCT shows ground-glass opacities with transition to consolidations. The key finding is that the abnormalities are confined to the radiation field. The paramediastinal and apical regions are particularly susceptible to radiation toxicity.

Pulmonary complications related to cytotoxic drugs are common, most notably with the high-dose chemotherapy regimens used for conditioning. Commonly used agents include bleomycin, methotrexate, cytarabine (Ara-C), carmustine (BCNU) and many other drugs. Drug-induced pneumonitis encompasses diffuse alveolar damage, non-specific interstitial pneumonia and bronchiolitis obliterans organizing pneumonia. HRCT shows ground-glass opacities with transition to consolidations, intralobular septa, air trapping and at times the nonspecific 'crazy paving' pattern. Although these abnormalities are similar to those induced by radiation, they are not confined to the radiation field. Pulmonary infiltration by blast cells occurs in a minority of patients with leukaemia [24] The infiltration predominates in the perilymphatic pulmonary interstitium. CT discloses thickening of the bronchovascular bundles and interlobular septa, as well as multiple small parenchymal nodules located along the bronchovascular bundles or in a centrilobular distribution. Confluence of poorly defined centrilobular nodules may produce a focus of consolidation. Nonlobular and nonsegmental ground-glass opacifications may be seen. The pattern sometimes mimics pulmonary congestion [69–71].

Laboratory Tests for Diagnosing Infectious

Bacterial Infections

Bacterial pneumonia in immunocompromised patients is usually due to Gram-negative bacilli or *Staphylococcus aureus*. Selection pressure due to the use of broad-spectrum antibiotics explains the emergence of resistant Gram-negative organisms. As discussed above, FO–BAL often fails to establish the diagnosis. Moreover, identified organisms may indicate colonization rather than infection. In a population of allogeneic BMT recipients, no pathogen was isolated in 70% of the patients, and some of the isolated microorganisms (such as *Candida* spp., coagulase-negative staphylococci and enterococci) were probably mere contaminants [72].

As shown in studies of FO–BAL, conventional microbiological testing may fail to identify the cause of lower respiratory tract infection. In patients on broad-spectrum antibiotics at the time of sample collection, Gram staining and culturing have low sensitivity, and cultures require time. Furthermore, these methods fail to distinguish colonization from infection. Serological testing is slow and often lacks both sensitivity and specificity. In most cases, the causative pathogen is not identified, despite optimal investigations. Methods that rapidly indicate the causative pathogen would help physicians select the best treatment decision. Such methods are already available for *Legionella pneumophila or Streptococus pneumoniae* and are being developed for other bacteria.

Legionella pneumophila. antibodies to *Legionella pneumophila* were first detected using indirect immunofluorescence or microagglutination tests. Since then, numerous

enzyme-linked immunosorbent assays (ELISAs) based on different antigen-extraction methods have been developed. The reported sensitivities of these assays vary substantially, from 41−75 % [73, 74]. Low titres of antibodies against *Legionella* spp. have been found in healthy volunteers, blood donors, outpatients and hospitalised patients [75, 76]. These low titers seem to indicate previous exposure to *Legionella* spp. The urinary antigen test produced positive results 1−3 days after the clinical onset and remained positive for almost one year in a small proportion of patients [77, 78]. Importantly, the urinary antigen test showed greater than 99 % specificity [79]. Sensitivity for *L. pneumophila* infections ranged from 56−99 % [80]. Low sensitivity of urinary antigen assays for serogroups other than *L. pneumophila* serogroup 1 has been reported, the range being 14−69 % [81, 82]. In the future, an easy-to-perform polymerase chain reaction (PCR) test with high sensitivity and greater than 99 % specificity will probably become available on a wider scale [83].

Streptococcus pneumoniae. the diagnosis of pneumococcal infection requires recovery of the microorganism from an uncontaminated specimen (e.g. blood or pleural fluid). Blood culture results are positive in only about one-quarter of cases, and prior antibiotic therapy significantly reduces the proportion of positive blood culture results. Bacteraemia may be absent in 70−80 % of cases of *S. pneumoniae* pneumonia. Sputum cultures provide only a probable diagnosis, since *S. pneumoniae* carriage in the nasopharynx is common. PCR assays for *S. pneumoniae* have shown inadequate sensitivity when used on blood or urine and inadequate specificity for infection when used on respiratory samples. Several publications have described antigen detection assays. Good sensitivity and specificity have been reported with commercial kits for urinary C polysaccharide detection in adults. For example, the Binax NOW *S. pneumoniae* urinary antigen test was 82 % sensitive and 97 % specific when positive blood cultures were used as the reference standard. The test is simple to perform, detects the C polysaccharide cell wall antigen common to all *S. pneumoniae* strains, and provides results within 15 minutes. Urinary antigen was still detected in 83 % of patients who were re-tested on treatment Day 3 and persisted for at least seven days in many patients [84]. Additional studies produced similar results (Table 11.6) [85−87]. A nested PCR assay targeting the pneumolysin gene was used to detect *S. pneumoniae* DNA in multiple sample types from 474 adults with community-acquired pneumonia and 183 control patients without pneumonia. The assay added little to information from existing diagnostic tests for *S. pneumoniae* and was unable to distinguish colonization from infection when used on respiratory samples [85, 87]. Studies of *S. pneumoniae* antigen tests involving latex agglutination or counter-current immunoelectrophoresis showed detection rates ranging from 0−88 %, and specificity was often poorly defined.

Mycoplasma pneumoniae. the diagnosis of hard-to-culture pathogens such as *Mycoplasma pneumoniae* classically relies on tests in paired sera to demonstrate a rise in the antibody titre. This method is of uncertain value in immunocompromised patients, most notably those with impaired cell-mediated immunity. Culturing is relatively insensitive and time-consuming, requiring up to three weeks for pathogen detection [88]. A number of PCR assays for *M. pneumoniae* have been evaluated in various respiratory specimens and patient populations, with promising results. PCR

Table 11.6 Binax NOW *S.pneumoniae* urinary antigen test: sensitivity and specificity

	Type of infection	Number of patients	Sensitivity (%)	Specificity (%)
Smith, *J Clin Microbiol*. 2003	Pneumococcal bacteremia	107	82	97
Murdoch, *J Clin 'Microbiol* 2001	Community-acquired pneumonia	420	80	100
Dominguez, *Chest* 2001	Bacteremic and nonbacteremic pneumonia	51	82	97

is more sensitive and considerably faster than culturing. In general, PCR results correlate well with serological results [89]. Both upper and lower respiratory tract samples are suitable for PCR testing. Upper respiratory tract samples (throat swabs and nasopharyngeal samples) may be the preferred sample types, as they are easy to obtain and ensure high sensitivity [85]. PCR on throat swabs may be the best existing diagnostic test for *M. pneumoniae*. However, standardized protocols will have to be developed before this test is recommended for widespread use [90].

Chlamydia pneumoniae detection are technically demanding and time-consuming, and their yield is generally low. Therefore, the diagnosis of *C. pneumoniae* infection relies largely on serological testing, whose value in immunocompromised patients is uncertain. Furthermore, both acute and convalescent phase sera must be tested, which can only provide a retrospective diagnosis. These major limitations have prompted many studies of PCR for diagnosing *C. pneumoniae* infection. Unfortunately, the results have been conflicting. Overall, PCR was at least as sensitive as culturing, but its specificity was difficult to assess given the absence of an appropriate reference standard [85]. *C. pneumoniae* DNA can be detected in both upper and lower respiratory tract samples, but it is unclear which sampling site is better. Highly sensitive PCR techniques may increase the ability to detect *C. pneumoniae* carriage, the clinical relevance of which is unclear.

Diagnosis of Viral Respiratory Infections using Nasopharyngeal Aspirates

In the past, viral cultures were the reference standard for the laboratory diagnosis of respiratory viral infections. However, 2−10 days were usually needed to obtain the results. To overcome this major limitation, faster diagnostic techniques such as viral antigen detection were introduced. These faster techniques are generally considered to be less sensitive and less specific than cell cultures. Moreover, viral antigen detection is not feasible for all respiratory viruses. PCR has proven extremely specific and sensitive for detecting respiratory viruses; it is now the reference standard for diagnosing respiratory viral infections and the only method available for detecting some viruses [36]. PCR was not only more sensitive than viral culture or antigen or

antibody tests for detecting respiratory viruses in patients with haematological malignancies but also decreased the time to diagnosis [91, 92]. Para-influenza viruses 1–3, respiratory syncytial virus, rhinovirus, influenza viruses A and B, enteroviruses and coronaviruses were reliably detected by PCR [93–95]. Nose–throat swabs yielded the same results with PCR as did BAL samples [36]. In a recent study of patients with haematological malignancies and respiratory viral infections, PCR on nasopharyngeal aspirates usually provided the diagnosis [96].

Cytomegalovirus frequently causes severe disease after stem cell transplantation. The cytomegalovirus antigen assay is a rapid quantitative tool for monitoring cytomegalovirus infection. However, this method is tedious, as it requires counting the cells in the samples. In addition, the results may be influenced by factors such as storage and fixation methods. PCR assays have been used to diagnose cytomegalovirus infection. Real-time PCR provides a qualitative assessment of viral load. However, although the antigenemia cut-off has been determined, the cut-off for viral load is unknown [36, 97].

BMT recipients and patients with haematological malignancies who have severe impairments of cell-mediated immunity are at risk for HSV pneumonia. Although HSV Type 1 accounts for most cases, other herpes viruses such as cytomegalovirus, varicella zoster virus, Epstein–Barr virus, HHV-6 and HHV-8 are also common causes of pneumonia in this population. Advances in diagnostic techniques and the use of preventive or pre-emptive treatments have altered the epidemiology of some of the herpes virus infections. However, herpes viruses continue to cause significant morbidity and mortality in stem cell recipients [98]. A multiplex PCR assay designed to amplify herpes virus DNA in a diverse range of clinical specimens yielded higher detection rates for the viruses represented in the assay than did virus isolation and immunofluorescence-based antigen detection [99]. The turnaround time was far less than for the other techniques. Overall, the multiplex PCR detected substantially more herpes viruses, in some cases in specimens or at body sites where these viruses were rarely or never found using conventional methods. Multiplex PCR has not yet been evaluated as a tool for diagnosing herpes virus pneumonia in patients with cancer. However, Multiplex PCR may help to assess the pathogenic role for herpes viruses found in respiratory samples. An oligonucleotide microarray for herpes virus detection in clinical samples has been developed and needs to be evaluated in clinical practice.

Noninvasive Diagnostic Strategy for Diagnosing Pneumocystis Pneumonia (PCP)

The standard method for diagnosing PCP pneumonia is microscopic identification of the organism using stains (methenamine silver, Giemsa or toluidine blue O) or antibodies in BAL or induced sputum samples [100]. Several studies confirmed that PCR was more sensitive than microscopy for detecting *P. jiroveci* [101]. PCR may be helpful in HIV-negative immunocompromised patients, who often have lower parasite counts than AIDS patients [40]. Nested PCR methods tend to have low specificity with high false-positive rates, whereas real-time PCR seems more specific [36, 102–104]. Samples similar to those used for microscopy can serve for PCR [101].

BAL specimens have the best yield; induced sputum samples, which are commonly used for HIV-infected patients, may be diagnostic but have not been evaluated in patients with other causes of immunodeficiency [103]. Oral washes may be used as alternative noninvasive samples, despite the lower sensitivity of PCR compared to lower respiratory tract samples [39, 105]. Given its excellent negative predictive value, PCR is recommended as the leading method for excluding PCP in cancer patients with pulmonary infiltrates. Negative PCR results on BAL fluid or induced sputum seem to indicate that PCP treatment can be safely discontinued [106].

Diagnosis of Fungal Infection

The diagnosis of invasive aspergillosis in immunocompromised patients is often challenging. Specimens from normally sterile sites are considered necessary for the definitive diagnosis of invasive fungal infections. Specimens from sites that may be colonized (e.g. sputum, BAL fluid or sinus aspirate) are rarely diagnostic. BAL fluid cultures positive for *Aspergillus* spp. may indicate colonization instead of invasive infection. Cultures may require days or weeks. The reference standard is histologically proven hyphal invasion in tissue specimens obtained by invasive procedures, but these may be deemed unsafe in patients with cytopenia [41, 107]. The first prospective, pathology-verified evaluation of a sandwich ELISA using a monoclonal antibody to galactomannan (GM) showed that serial monitoring was 92.6% sensitive and 95.4% specific [108]. The positive predictive value was 93% and the negative predictive value was 95% [108]. In more than half the cases, antigenemia was detected before invasive aspergillosis was suspected clinically [109, 110]. Based on this study and others, the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group convened a consensus panel to develop standard definitions for invasive fungal infections, introducing *Aspergillus* antigenemia testing as an important diagnostic tool. The panel recommended that *Aspergillus* antigenemia testing be used to support a probable diagnosis [41]. Finally, PCR has been used to detect *Aspergillus* spp., but false-positive results were noted and no standardized commercial method is available [111–113].

Conclusion and Avenues for Future Research

The diagnostic and therapeutic impact of FO–BAL has been evaluated in several studies and other diagnostic investigations have been evaluated individually. However, routine use of all the available investigations except FO–BAL has not been assessed. Neither have the diagnostic strategy and outcomes been compared in cancer patients managed with or without FO–BAL. The number of patients in whom FO–BAL can be avoided thanks to other investigations may also deserve to be determined.

The development of new tools will contribute to improved diagnosis of bacterial pneumonia (16S RNA) and viral pneumonia (oligonucleotide microarray). These

new tools can be expected to improve the diagnostic yield of BAL analysis, and nonbronchoscopic lavage may cause less respiratory deterioration than FO−BAL [114]. Markers for heart failure (brain natriuretic peptide) or bacterial infection (procalcitonin) need to be evaluated in cancer patients.

It is predicted that advances in diagnostic tools will decrease the role of FO−BAL, just as in the past FO−BAL decreased the role of lung biopsy [115]. When the diagnosis remains uncertain despite extensive investigations including FO−BAL, the feasibility, safety and diagnostic yield of lung biopsy should be evaluated, since identifying the cause of pulmonary infiltrates is known to reduce mortality [11, 16].

References

1. Brenner, H. (2002) Long-term survival rates of cancer patients achieved by the end of the 20th Century: a period analysis. *Lancet*, **360** (9340), 1131−35.
2. Linker, C., Damon, L., Ries, C. and Navarro, W. (2002) Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukaemia. *J Clin Oncol*, **20** (10), 2464−71.
3. Richardson, P.G., Sonneveld, P., Schuster, M.W. *et al*. (2005) Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*, **352** (24), 2487−98.
4. O'Brien, S.G., Guilhot, F., Larson, R.A. *et al*. (2003) Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukaemia. *N Engl J Med*, **348** (11), 994−1004.
5. Coiffier, B., Lepage, E., Briere, J. *et al*. (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*, **346** (4), 235−42.
6. Bergh, J., Wiklund, T., Erikstein, B. *et al*. (2000) Tailored fluorouracil, epirubicin and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. Scandinavian breast group 9401 study. *Lancet*, **356** (9239), 1384−91.
7. Chaoui, D., Legrand, O., Roche, N. *et al*. (2004) Incidence and prognostic value of respiratory events in acute leukemia. *Leukemia*, **18** (4), 670−75.
8. Azoulay, E., Recher, C., Alberti, C. *et al*. (1999) Changing use of intensive care for haematological patients: the example of multiple myeloma. *Intensive Care Med*, **25** (12), 1395−1401.
9. Kress, J.P., Christenson, J., Pohlman, A.S., Linkin, D.R. and Hall, J.B. (1999) Outcomes of critically ill cancer patients in a university hospital setting. *Am J Respir Crit Care Med*, **160** (6), 1957−61.
10. Soares, M., Fontes, F., Dantas, J. *et al*. (2004) Performance of six severity-of-illness scores in cancer patients requiring admission to the intensive care unit: a prospective observational study. *Crit Care*, **8** (4), R194−203, Epub 2004 May 24.
11. Azoulay, E., Thiery, G., Chevret, S. *et al*. (2004) The prognosis of acute respiratory failure in critically ill cancer patients. *Medicine (Baltimore)*, **83** (6), 360−70.
12. Azoulay, E., Alberti, C., Bornstain, C. *et al*. (2001) Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. *Crit Care Med*, **29** (3), 519−25.
13. Meert, A.P., Close, L., Hardy, M. *et al*. (2003) Noninvasive ventilation: application to the cancer patient admitted in the intensive care unit. *Support Care Cancer*, **11** (1), 56−59, Epub 2002 Jul 19.

14. Rabbat, A., Chaoui, D., Montani, D. *et al*. (2005) Prognosis of patients with acute myeloid leukaemia admitted to intensive care. *Br J Haematol*, **129** (3), 350–57.
15. Hilbert, G., Gruson, D., Vargas, F. *et al*. (2001) Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med*, **344** (7), 481–87.
16. Azoulay, E. and Schlemmer, B. (2006) Diagnostic strategy in cancer patients with acute respiratory failure. *Intensive Care Med*, **32** (6), 808–22, Epub 2006 Apr 29.
17. Dunagan, D.P., Baker, A.M., Hurd, D.D. and Haponik, E.F. (1997) Bronchoscopic evaluation of pulmonary infiltrates following bone marrow transplantation. *Chest*, **111** (1), 135–141.
18. White, P., Bonacum, J.T. and Miller, C.B. (1997) Utility of fibreoptic bronchoscopy in bone marrow transplant patients. *Bone Marrow Transplant*, **20** (8), 681–87.
19. Murray, P.V., O'Brien, M.E., Padhani, A.R. *et al*. (2001) Use of first line bronchoalveolar lavage in the immunosuppressed oncology patient. *Bone Marrow Transplant*, **27** (9), 967–71.
20. Stover, D.E., Zaman, M.B., Hajdu, S.I. *et al*. (1984) Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. *Ann Intern Med*, **101** (1), 1–7.
21. Gruson, D., Hilbert, G., Portel, L. *et al*. (1999) Severe respiratory failure requiring ICU admission in bone marrow transplant recipients. *Eur Respir J*, **13** (4), 883–87.
22. Gruson, D., Hilbert, G., Valentino, R. *et al*. (2000) Utility of fiberoptic bronchoscopy in neutropenic patients admitted to the intensive care unit with pulmonary infiltrates. *Crit Care Med*, **28** (7), 2224–30.
23. Rano, A., Agusti, C., Jimenez, P. *et al*. (2001) Pulmonary infiltrates in non-HIV immunocompromised patients: a diagnostic approach using non-invasive and bronchoscopic procedures. *Thorax*, **56** (5), 379–87.
24. Azoulay, E., Fieux, F., Moreau, D. *et al*. (2003) Acute monocytic leukemia presenting as acute respiratory failure. *Am J Respir Crit Care Med*, **167** (10), 1329–33.
25. Cordonnier, C., Escudier, E., Nicolas, J.C. *et al*. (1987) Evaluation of three assays on alveolar lavage fluid in the diagnosis of cytomegalovirus pneumonitis after bone marrow transplantation. *J Infect Dis*, **155** (3), 495–500.
26. Agusti, C., Ramirez, J., Picado, C. *et al*. (1995) Diffuse alveolar haemorrhage in allogeneic bone marrow transplantation. A post-mortem study. *Am J Respir Crit Care Med*, **151** (4), 1006–10.
27. Afessa, B., Tefferi, A., Litzow, M.R. *et al*. (2002) Diffuse alveolar haemorrhage in haematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med*, **166** (5), 641–45.
28. Patterson, T.F., Kirkpatrick, W.R., White, M. *et al*. (2000) Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. I3 aspergillus study group. *Medicine (Baltimore)*, **79** (4), 250–60.
29. Cordonnier, C., Bernaudin, J.F., Bierling, P. *et al*. (1986) Pulmonary complications occurring after allogeneic bone marrow transplantation. A study of 130 consecutive transplanted patients. *Cancer*, **58** (5), 1047–54.
30. Springmeyer, S.C. (1987) The clinical use of bronchoalveolar lavage. *Chest*, **92** (5), 771–72.
31. Milburn, H.J., Prentice, H.G. and du Bois, R.M. (1987) Role of bronchoalveolar lavage in the evaluation of interstitial pneumonitis in recipients of bone marrow transplants. *Thorax*, **42** (10), 766–62.
32. Cordonnier, C., Bernaudin, J.F., Fleury, J. *et al*. (1985) Diagnostic yield of bronchoalveolar lavage in pneumonitis occurring after allogeneic bone marrow transplantation. *Am Rev Respir Dis*, **132**(5), 1118–23.

33. Akoun, G.M., Milleron, B.J. and Mayaud, C.M. (1985) Diagnosis by bronchoalveolar lavage of cause of pulmonary infiltrates in haematological malignancies. *Br Med J (Clin Res Ed)*, **290** (6481), 1589−90.
34. White, D.A., Gellene, R.A., Gupta, S. *et al*. (1985) Pulmonary cell populations in the immunosuppressed patient. Bronchoalveolar lavage findings during episodes of pneumonitis. *Chest*, **88** (3), 352−59.
35. Rubenfeld, G.D. and Crawford, S.W. (1996) Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. *Ann Intern Med*, **125** (8), 625−33.
36. Murdoch, D.R. (2005) Impact of rapid microbiological testing on the management of lower respiratory tract infection. *Clin Infect Dis*, **41** (10), 1445−47, Epub 2005 Oct 13.
37. Jain, P., Sandur, S., Meli, Y. *et al*. (2004) Role of flexible bronchoscopy in immunocompromised patients with lung infiltrates. *Chest*, **125** (2), 712−22.
38. Azoulay, E., Parrot, A., Flahault, A. *et al*. (1999) AIDS-related Pneumocystis carinii pneumonia in the era of adjunctive steroids: implication of bal neutrophilia. *Am J Respir Crit Care Med*, **160** (2), 493−99.
39. Kovacs, J.A., Gill, V.J., Meshnick, S. and Masur, H. (2001) New insights into transmission, diagnosis, and drug treatment of Pneumocystis carinii pneumonia. *Jama*, **286** (19), 2450−60.
40. Kovacs, J.A., Hiemenz, J.W., Macher, A.M. *et al*. (1984)Pneumocystis carinii pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med*, **100** (5), 663−71.
41. Ascioglu, S., Rex, J.H. and de Pauw, B. *et al*. (2002) Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and haematopoietic stem cell transplants: an international consensus. *Clin Infect Dis*, **34** (1), 7−14, Epub 2001 Nov 26.
42. Caillot, D., Mannone, L., Cuisenier, B. and Couaillier, J.F. (2001) Role of early diagnosis and aggressive surgery in the management of invasive pulmonary aspergillosis in neutropenic patients. *Clin Microbiol Infect*, **7** (Suppl 2), 54−61.
43. Pizzo, P.A. (1993) Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med*, **328** (18), 1323−32.
44. Maschmeyer, G. (2001) Pneumonia in febrile neutropenic patients: radiologic diagnosis. *Curr Opin Oncol*, **13** (4), 229−35.
45. Maschmeyer, G., Beinert, T., Buchheidt, D. *et al*. (2003) Diagnosis and antimicrobial therapy of pulmonary infiltrates in febrile neutropenic patients--guidelines of the infectious diseases working party (AGIHO) of the German Society of Haematology and Oncology (DGHO). *Ann HAEMAtol*, **82** (Suppl 2), S118−26, Epub 2003 Sep 9.
46. Barloon, T.J., Galvin, J.R., Mori, M., Stanford, W. and Gingrich, R.D. (1991) High-resolution ultrafast chest CT in the clinical management of febrile bone marrow transplant patients with normal or nonspecific chest roentgenograms. *Chest*, **99** (4), 928−33.
47. Shorr, A.F., Susla, G.M. and O'Grady, N.P. (2004) Pulmonary infiltrates in the non-HIV-infected immunocompromised patient: etiologies, diagnostic strategies, and outcomes. *Chest*, **125** (1), 260−71.
48. Heussel, C.P., Kauczor, H.U., Heussel, G.E. *et al*. (1999) Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. *J Clin Oncol*, **17** (3), 796−805.
49. Oude Nijhuis, C.S., Gietema, J.A., Vellenga, E. *et al*. (2003) Routine radiography does not have a role in the diagnostic evaluation of ambulatory adult febrile neutropenic cancer patients. *Eur J Cancer*, **39** (17), 2495−98.
50. Donowitz, G.R., Harman, C., Pope, T. and Stewart, F.M. (1991) The role of the chest roentgenogram in febrile neutropenic patients. *Arch Intern Med*, **151** (4), 701−04.

51. Roy, V., Ali, L.I. and Selby, G.B. (2000) Routine chest radiography for the evaluation of febrile neutropenic patients after autologous stem cell transplantation. *Am J Hematol*, **64** (3), 170–74.
52. Schueller, G., Matzek, W., Kalhs, P. and Schaefer-Prokop, C. (2005) Pulmonary infections in the late period after allogeneic bone marrow transplantation: chest radiography versus computed tomography. *Eur J Radiol*, **53** (3), 489–94.
53. Heussel, C.P., Kauczor, H.U., Heussel, G. *et al*. (1997) Early detection of pneumonia in febrile neutropenic patients: use of thin-section CT. *AJR Am J Roentgenol*, **169** (5), 1347–53.
54. Heussel, C.P., Kauczor, H.U. and Ullmann, A.J. (2004) Pneumonia in neutropenic patients. *Eur Radiol*, **14** (2), 256–71, Epub 2003 Jul 24.
55. Reittner, P., Ward, S., Heyneman, L. *et al*. (2003) Pneumonia: high-resolution CT findings in 114 patients. *Eur Radiol*, **13** (3), 515–21, Epub 2002 Aug 3.
56. Conces, D.J. Jr. (1998) Bacterial pneumonia in immunocompromised patients. *J Thorac Imaging*, **13** (4), 261–70.
57. McAdams, H.P., Rosado de Christenson, M., Strollo, D.C. and Patz, E.F. Jr (1997) Pulmonary mucormycosis: radiologic findings in 32 cases. *AJR Am J Roentgenol*, **168** (6), 1541–48.
58. Azoulay, E. and Mayaud, C. (1999) [Candida pneumopathy: fact or fiction?]. *Rev Pneumol Clin*, **55** (6), 349–51.
59. Caillot, D., Casasnovas, O., Bernard, A. *et al*. (1997) Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol*, **15**(1), 139–47.
60. Kim, K., Lee, M.H., Kim, J. *et al*. (2002) Importance of open lung biopsy in the diagnosis of invasive pulmonary aspergillosis in patients with hematologic malignancies. *Am J Hematol*, **71** (2), 75–79.
61. Mori, M., Galvin, J.R., Barloon, T.J., Gingrich, R.D. and Stanford, W. (1991) Fungal pulmonary infections after bone marrow transplantation: evaluation with radiography and CT. *Radiology*, **178** (3), 721–26.
62. Tanaka, N., Matsumoto, T., Miura, G. *et al*. (2002) CT findings of leukaemic pulmonary infiltration with pathologic correlation. *Eur Radiol*, **12** (1), 166–74.
63. Ikezoe, J., Takeuchi, N., Johkoh, T. *et al*. (1992) CT appearance of pulmonary tuberculosis in diabetic and immunocompromised patients: Comparison with patients who had no underlying disease. *Ajr Am J Roentgenol*, **159** (6), 1175–79.
64. Van Dyck, P., Vanhoenacker, F.M., Van den Brande, P. and De Schepper, A.M. (2003) Imaging of pulmonary tuberculosis. *Eur Radiol*, **13** (8), 1771–85, Epub 2002 Aug 10.
65. Kiyan, E., Kilicaslan, Z., Gurgan, M. *et al*. (2003) Clinical and radiographic features of pulmonary tuberculosis in non-AIDS immunocompromised patients. *Int J Tuberc Lung Dis*, **7** (8), 764–70.
66. Escuissato, D.L., Gasparetto, E.L., Marchiori, E. *et al*. (2005) Pulmonary infections after bone marrow transplantation: high-resolution CT findings in 111 patients. *AJR Am J Roentgenol*, **185** (3), 608–15.
67. Chong, S., Lee, K.S., Kim, T.S. *et al*. (2006) Adenovirus pneumonia in adults: radiographic and high-resolution CT findings in five patients. *AJR Am J Roentgenol*, **186** (5), 1288–93.
68. Worthy, S.A., Flint, J.D. and Muller, N.L. (1997) Pulmonary complications after bone marrow transplantation: high-resolution CT and pathologic findings. *Radiographics*, **17** (6), 1359–71.
69. Tanaka, N., Matsumoto, T., Miura, G. *et al*. (2002) HRCT findings of chest complications in patients with leukaemia. *Eur Radiol*, **12** (6), 1512–22, Epub 2002 Feb 2.

70. Koh, T.T., Colby, T.V. and Muller, N.L. (2005) Myeloid leukaemias and lung involvement. *Semin Respir Crit Care Med*, **26** (5), 514–19.
71. Heyneman, L.E., Johkoh, T., Ward, S. *et al*. (2000) Pulmonary leukemic infiltrates: high-resolution CT findings in 10 patients. *AJR Am J Roentgenol*, **174** (2), 517–21.
72. Dettenkofer, M., Wenzler-Rottele, S., Babikir, R. *et al*. (2005) Surveillance of nosocomial sepsis and pneumonia in patients with a bone marrow or peripheral blood stem cell transplant: a multicentre project. *Clin Infect Dis*, **40** (7), 926–31, Epub 2005 Mar 4.
73. Blazquez, R.M., Espinosa, F.J., Martinez-Toldos, C.M. *et al*. (2005) Sensitivity of urinary antigen test in relation to clinical severity in a large outbreak of Legionella pneumonia in Spain. *Eur J Clin Microbiol Infect Dis*, **24** (7), 488–91.
74. Dominguez, J., Gali, N., Matas, L. *et al*. (1999) Evaluation of a rapid immunochromatographic assay for the detection of Legionella antigen in urine samples. *Eur J Clin Microbiol Infect Dis*, **18** (12), 896–8.
75. Waterer, G.W., Baselski, V.S. and Wunderink, R.G. (2001) Legionella and community-acquired pneumonia: a review of current diagnostic tests from a clinician's viewpoint. *Am J Med*, **110** (1), 41–48.
76. Deforges, L., Legrand, P., Tankovic, J. *et al*. (1999) Case of false-positive results of the urinary antigen test for Legionella pneumophila. *Clin Infect Dis*, **29** (4), 953–54.
77. Mykietiuk, A., Carratala, J. and Fernandez-Sabe, N. *et al*. (2005) Clinical outcomes for hospitalised patients with Legionella pneumonia in the antigenuria era: the influence of levofloxacin therapy. *Clin Infect Dis*, **40** (6), 794–99, Epub 2005 Feb 17.
78. Dominguez, J.A., Gali, N., Pedroso, P. *et al*. (1998) Comparison of the binax Legionella urinary antigen enzyme immunoassay (EIA) with the biotest Legionella urin antigen EIA for detection of Legionella antigen in both concentrated and nonconcentrated urine samples. *J Clin Microbiol*, **36** (9), 2718–22.
79. Wever, P.C., Yzerman, E.P., Kuijper, E.J. *et al*. (2000) Rapid diagnosis of Legionnaires' disease using an immunochromatographic assay for Legionella pneumophila serogroup 1 antigen in urine during an outbreak in The Netherlands. *J Clin Microbiol*, **38** (7), 2738–39.
80. Yzerman, E.P., den Boer, J.W., Lettinga, K.D. *et al*. (2002) Sensitivity of three urinary antigen tests associated with clinical severity in a large outbreak of Legionnaires' disease in The Netherlands. *J Clin Microbiol*, **40** (9), 3232–36.
81. Helbig, J.H., Uldum, S.A., Bernander, S. *et al*. (2003) Clinical utility of urinary antigen detection for diagnosis of community-acquired, travel-associated, and nosocomial Legionnaires' disease. *J Clin Microbiol*, **41** (2), 838–40.
82. Benson, R.F., Tang, P.W. and Fields, B.S. (2000) Evaluation of the binax and biotest urinary antigen kits for detection of Legionnaires' disease due to multiple serogroups and species of Legionella. *J Clin Microbiol*, **38** (7), 2763–65.
83. Den Boer, J.W. and Yzerman, E.P. (2004) Diagnosis of Legionella infection in Legionnaires' disease. *Eur J Clin Microbiol Infect Dis*, **23** (12), 871–8.
84. Smith, M.D., Derrington, P., Evans, R. *et al*. (2003) Rapid diagnosis of bacteremic pneumococcal infections in adults by using the binax NOW Streptococcus pneumoniae urinary antigen test: a prospective, controlled clinical evaluation. *J Clin Microbiol*, **41** (7), 2810–13.
85. Murdoch, D.R. (2003) Nucleic acid amplification tests for the diagnosis of pneumonia. *Clin Infect Dis*, **36** (9), 1162–70, Epub 2003 Apr 22.
86. Dominguez, J., Gali, N., Blanco, S. *et al*. (2001) Detection of Streptococcus pneumoniae antigen by a rapid immunochromatographic assay in urine samples. *Chest*, **119** (1), 243–49.
87. Murdoch, D.R., Laing, R.T., Mills, G.D. *et al*. (2001) Evaluation of a rapid immunochromatographic test for detection of Streptococcus pneumoniae antigen in urine

samples from adults with community-acquired pneumonia. *J Clin Microbiol*, **39** (10), 3495−98.
88. Jacobs, E., Bennewitz, A. and Bredt, W. (1986) Reaction pattern of human anti-mycoplasma pneumoniae antibodies in enzyme-linked immunosorbent assays and immunoblotting. *J Clin Microbiol*, **23** (3), 517−22.
89. Abele-Horn, M., Busch, U., Nitschko, H. *et al*. (1998) Molecular approaches to diagnosis of pulmonary diseases due to mycoplasma pneumoniae. *J Clin Microbiol*, **36** (2), 548−51.
90. Dorigo-Zetsma, J.W., Verkooyen, R.P., van Helden, H.P., Van der Nat, II and van den Bosch, J.M. (2001) Molecular detection of mycoplasma pneumoniae in adults with community-acquired pneumonia requiring hospitalisation. *J Clin Microbiol*, **39** (3), 1184−86.
91. van Elden, L.J., van Kraaij, M.G., Nijhuis, M. *et al*. (2002) Polymerase chain reaction is more sensitive than viral culture and antigen testing for the detection of respiratory viruses in adults with haematological cancer and pneumonia. *Clin Infect Dis*, **34** (2), 177−83, Epub 2001 Dec 4.
92. Templeton, K.E., Scheltinga, S.A., van den Eeden, W.C. *et al*. (2005) Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis*, **41** (3), 345−51, Epub 2005 Jun 22.
93. van Elden, L.J., van Loon, A.M. and van der Beek, A. *et al*. (2003) Applicability of a real-time quantitative PCR assay for diagnosis of respiratory syncytial virus infection in immunocompromised adults. *J Clin Microbiol*, **41** (9), 4378−81.
94. van Elden, L.J., van Loon, A.M. and van Alphen, F. *et al*. (2004) Frequent detection of human coronaviruses in clinical specimens from patients with respiratory tract infection by use of a novel real-time reverse-transcriptase polymerase chain reaction. *J Infect Dis*, **189** (4), 652−57, Epub 2004 Jan 28.
95. van Kraaij, M.G., van Elden, L.J. and van Loon, A.M. *et al*. (2005) Frequent detection of respiratory viruses in adult recipients of stem cell transplants with the use of real-time polymerase chain reaction, compared with viral culture. *Clin Infect Dis*, **40** (5), 662−69, Epub 2005 Feb 7.
96. Martino, R., Ramila, E., Rabella, N. *et al*. (2003) Respiratory virus infections in adults with haematologic malignancies: a prospective study. *Clin Infect Dis*, **36** (1), 1−8, Epub 2002 Dec 9.
97. Tanaka, Y., Kanda, Y., Kami, M. *et al*. (2002) Monitoring cytomegalovirus infection by antigenemia assay and two distinct plasma real-time PCR methods after haematopoietic stem cell transplantation. *Bone Marrow Transplant*, **30** (5), 315−19.
98. Taplitz, R.A. and Jordan, M.C. (2002) Pneumonia caused by herpes viruses in recipients of haematopoietic cell transplants. *Semin Respir Infect*, **17** (2), 121−29.
99. Druce, J., Catton, M., Chibo, D. *et al*. (2002) Utility of a multiplex PCR assay for detecting herpes virus DNA in clinical samples. *J Clin Microbiol*, **40** (5), 1728−32.
100. Thomas, C.F. Jr and Limper, A.H. (2004) Pneumocystis pneumonia. *N Engl J Med*, **350** (24), 2487−98.
101. Wakefield, A.E., Guiver, L., Miller, R.F. and Hopkin, J.M. (1991) DNA amplification on induced sputum samples for diagnosis of Pneumocystis carinii pneumonia. *Lancet*, **337** (8754), 1378−79.
102. Arcenas, R.C., Uhl, J.R., Buckwalter, S.P. *et al*. (2006) A real-time polymerase chain reaction assay for detection of Pneumocystis from bronchoalveolar lavage fluid. *Diagn Microbiol Infect Dis*, **54** (3), 169−75, Epub 2006 Jan 19.
103. Durand-Joly, I., Chabe, M., Soula, F. *et al*. (2005) Molecular diagnosis of Pneumocystis pneumonia. *FEMS Immunol Med Microbiol*, **45** (3), 405−10.

104. Alvarez-Martinez, M.J., Miro, J.M., Valls, M.E. *et al*. (2006) Sensitivity and specificity of nested and real-time PCR for the detection of Pneumocystis jiroveci in clinical specimens. *Diagn Microbiol Infect Dis*, **56** (2), 153−60, Epub 2006 May 4.
105. Fischer, S., Gill, V.J., Kovacs, J. *et al*. (2001) The use of oral washes to diagnose Pneumocystis carinii pneumonia: a blinded prospective study using a polymerase chain reaction-based detection system. *J Infect Dis*, **184** (11), 1485−88, Epub 2001 Nov 13.
106. Ribes, J.A., Limper, A.H., Espy, M.J. and Smith, T.F. (1997) PCR detection of Pneumocystis carinii in bronchoalveolar lavage specimens: analysis of sensitivity and specificity. *J Clin Microbiol*, **35** (4), 830−35.
107. Maertens, J., Verhaegen, J., Demuynck, H. *et al*. (1999) Autopsy-controlled prospective evaluation of serial screening for circulating galactomannan by a sandwich enzyme-linked immunosorbent assay for haematological patients at risk for invasive aspergillosis. *J Clin Microbiol*, **37** (10), 3223−28.
108. Maertens, J., Verhaegen, J., Lagrou, K. *et al*. (2001) Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. *Blood*, **97** (6), 1604−10.
109. Maertens, J., Van Eldere, J., Verhaegen, J. *et al*. (2002) Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. *J Infect Dis*, **186** (9), 1297−06, Epub 2002 Oct 8.
110. Maertens, J., Theunissen, K., Verhoef, G. *et al*. (2005) Galactomannan and computed tomography-based pre-emptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis*, **41** (9), 1242−50, Epub 2005 Sep 29.
111. Hohenthal, U., Itala, M., Salonen, J. *et al*. (2005) Bronchoalveolar lavage in immunocompromised patients with haematological malignancy − value of new microbiological methods. *Eur J Haematol*, **74** (3), 203−11.
112. Musher, B., Fredricks, D., Leisenring, W. *et al*. (2004) Aspergillus galactomannan enzyme immunoassay and quantitative PCR for diagnosis of invasive aspergillosis with bronchoalveolar lavage fluid. *J Clin Microbiol*, **42** (12), 5517−22.
113. Francesconi, A., Kasai, M., Petraitiene, R. *et al*. (2006) Characterization and comparison of galactomannan enzyme immunoassay and quantitative real-time PCR assay for detection of Aspergillus fumigatus in bronchoalveolar lavage fluid from experimental invasive pulmonary aspergillosis. *J Clin Microbiol*, **44** (7), 2475−80.
114. Perkins, G.D., Chatterjee, S., Giles, S. *et al*. (2005) Safety and tolerability of nonbronchoscopic lavage in ards. *Chest*, **127** (4), 1358−63.
115. Sharma, S., Nadrous, H.F., Peters, S.G. *et al*. (2005) Pulmonary complications in adult blood and marrow transplant recipients: autopsy findings. *Chest*, **128** (3), 1385−92.

12
Pneumonia in Trauma Patients

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Patients with severe trauma are at high risk of infections, especially of pneumonias [1]. Various risk factors have been identified and the pathogenesis is complex. Owing to associated injuries and organ damage, common preventative measures for ventilator-associated pneumonia (VAP) can often not be applied in a timely fashion. Likewise, the diagnosis of pneumonia can be difficult in patients with multiple traumas and the choice of antibiotic treatment must be guided by the underlying risks and organ dysfunctions.

This chapter is intended to help clinicians in approaching trauma patients who are at high risk of pneumonia and focuses on the special aspects in risk factors, pathogenesis, prevention, diagnosis and treatment. For further illustration of these aspects, brief case reports are also added.

Risk Factors

Intubation outside of the hospital has repeatedly been described as a risk factor [1]. Without doubt, endotracheal intubation of severely traumatized patients as soon as possible is state-of-the-art to prevent (further) aspiration and to allow adequate oxygenation, ventilation and administration of opioids for relief of pain. Thus, field intubation should be interpreted not as a risk factor per se, but as a marker that reflects both the severity of injury and depressed consciousness in such patients. Likewise, patients with severe head injury with a Glasgow Coma Scale (GCS) below nine

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(which mandates endotracheal intubation) are at high risk of pneumonia. Hypotension on admission – reflecting the amount of blood loss or haemorrhagic shock – as well as the severity of injury itself and an age above 55 years are associated with an increased risk of pneumonia [2, 3]. Furthermore, trauma-associated risks such as chronic consumption of alcohol and the associated deterioration in general health status and liver cirrhosis must be considered. Special risks in patients with alcoholism are bad dental status, which adds to the abnormal colonization of the oral cavity and of the pharynx with Gram-negative rods, which in turn is a special risk for pneumonia caused by such bacteria [4]. In patients with head trauma, nasal carriage of *S. aureus* on admission was found to be an independent risk factor of early onset pneumonia [5, 6].

The use of barbiturates in patients with head trauma has also been described as a risk factor for pneumonia. Numerous studies *in vitro* and some clinical investigations point to the immunosuppressive effects of barbiturates, increasing the risk for infectious complications [7–12]. However, the clinical studies are mostly flawed due to the fact that barbiturates were predominantly used in patients with more severe head trauma and increased intracranial pressures irresponsive to conventional treatment. Recent investigations using refined techniques with viable *Staphylococcus aureus* and a whole-blood *in vitro* model confirm the inhibitory effects of barbiturates, but not of propofol on granulocyte recruitment and phagocytosis capacity [6]. However, the inhibitory concentrations *in vitro* by far exceed the barbiturate concentrations found in clinical settings in patients receiving long-term barbiturate sedation monitored by burst-suppression-pattern in the electroencephalography. Thus, it remains unclear whether the immunosuppressive effects of barbiturates impose an independent risk for pneumonia and the fear of such effects should not preclude the use of barbiturates for treatment of increased intracranial pressure.

Croce and colleagues developed an empirical equation to predict the risk of ventilator-associated pneumonia (VAP) in trauma patients. The equation includes different factors, like mechanism of injury (higher risk after blunt injury versus penetrating injury), Glasgow Coma Scale, presence of spinal cord injury, need for emergent laparotomy, injury score for chest injury, units of blood transfused in the resuscitation area, injury severity score (ISS) and intubation in the field or resuscitation area. According to this formula variables, such as GCS, spinal cord injury, chest Abbreviated Injury Score (AIS), emergent laparotomy, blood transfusion, ISS and emergent intubation, are independent risk factors for pneumonia. This formula was concordant in 95 % and discordant in 5 % of the study population (Table 12.1) [13].

Other factors, like haematogenous spread from extrapulmonary sites of infection may less frequently be the cause of pneumonia in trauma patients [14]. Furthermore, VAP is a common complication in patients with acute lung injury and Acute Respiratory Distress Syndrome (ARDS), which in turn may be complications of severe trauma and haemorrhagic shock [14–18]. In addition, all other general risk factors for patients receiving long-term mechanical ventilation also apply to trauma patients, with the cumulative risk for VAP increasing by 3 % per day of mechanical ventilation within the first week after intubation [2]. A special reference may be made to the risk

Table 12.1 Risk factors for pneumonia in trauma patients [13]

Blunt injury	
Haemorrhagic shock	
Severity of injury	GCS
	ISS
Emergent intubation	
Injury pattern	Spinal cord injury
	Severe brain injury

factor 'transport within the hospital,' since trauma patients need frequent 'transports' to the Operating Room or for repeated CT-scans [19].

Pathogenesis

Loss of consciousness followed by gross aspiration is a common event that predisposes trauma patients for pneumonia. Lung contusion followed by infection of non-aerated, atelectatic lung tissue is another important mechanism. The complex interplay of the various factors is illustrated in Figure 12.1.

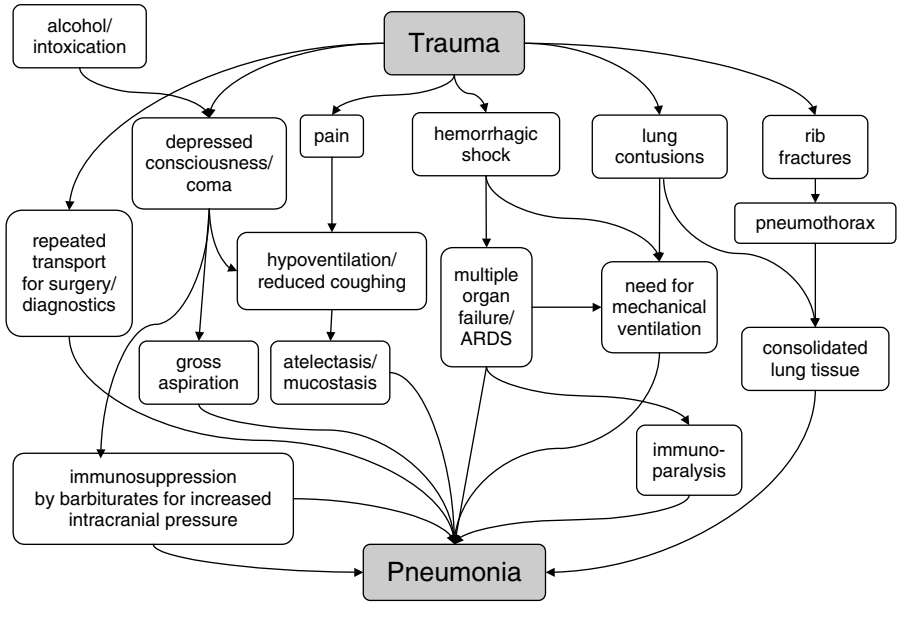

Figure 12.1
Schematic description of various factors leading to pneumonia in trauma patients

Causative Pathogens

Several studies in small numbers of patients with head injury report typical pathogens of early onset pneumonias, such as *S. aureus* and, less frequently, *Haemophilus influenzae* and *Streptococcus pneumoniae* as etiological agents. *S. aureus* is a typical pathogen for younger patients with head and brain trauma [6]. Tracheal colonization by *S. aureus, H. influenzae* or *S. pneumoniae* within 24 hours of intubation are independent risk factors for developing early onset pneumonia in patients with head trauma [20]. While the incidence of *S. aureus* VAP is increased in patients with coma, aerobic Gram-negative pathogens appear to be predominant in patients without coma [21]. Especially in older patients, Gram-negative rods of the family *Enterobacteriaceae* like *Escherichia coli* and *Klebsiella pneumoniae, Enterobacter* species, *Proteus* species and *Serratia marcescens* may also be causative for early onset pneumonia. This reflects the fact that older patients and patients with underlying diseases, such as diabetes or alcohol consumption, are more frequently colonized with Gram-negative rods in the oral cavity and in the pharynx [22]. However, in nonrisk patients no multidrug resistant pathogens are expected [23, 24].

As in all patients, colonization of the upper airways and of the trachea with Gram-negative enteric bacilli and with non-fermentative Gram-negative rods like *Pseudomonas* spp. increases with the longer the duration of mechanical ventilation [25]. Consequently, factors associated with late onset VAP include tracheobronchial colonization with Gram-negative enteric bacilli or *Pseudomonas* spp., duration of mechanical ventilation and prolonged antibiotic treatment [25]. In case of late onset pneumonia (>5 days after admission) or in patients who have been hospitalised before, multidrug resistant pathogens and local resistance patterns have to be considered for empirical therapy. Previous use of antibiotics increases the risk of colonization with Gram-negative enteric bacilli or *P. aeruginosa* but protects against infections with *S. aureus, H. influenzae* or *S. pneumonia* [25]. Inappropriate initial empiric antimicrobial therapy in patients at risk may lead to infection due *to P. aeruginosa, Acinetobacter* spp., *K. pneumoniae* and *Enterobacter* spp. as well as methicillin-resistant *S. aureus* (MRSA) or extended beta-lactamase producing pathogens. Therefore, in patients with ARDS, who frequently received prior antibiotic therapy, MRSA, *Enterobacteriaceae* and non-fermenting Gram-negative rods, such as *Acinetobacter* and *P. aeruginosa,* are frequently detected in bronchoalveolar lavage (BAL) samples [15, 17].

Patients with head trauma are at higher risk of *Acinetobacter* infection [26]. *Acinetobacter* spp. are particular important as a cause of outbreaks, possibly due to their ability to survive on surfaces and hands but also because of their intrinsic resistance to many common antibiotics [27]. *Legionella pneumophila* and other atypical pathogens are not particularly found in trauma patients but the incidence is increased in immunocompromised patients, as well as in patients with diabetes mellitus, underlying lung disease or end-stage renal disease [24, 28].

Candida spp. are found frequently in endotracheal aspirates or bronchoalveolar lavage fluid and mostly reflect colonization or contamination. Recently Wood and colleagues demonstrated the clinical relevance of *Candida* spp. isolated in BAL in a

retrospective study. Their results confirm the fact that the isolation of *Candida* spp. in BAL samples below 10^5 cfu/mL do not require antifungal therapy [29].

The role of anaerobic bacteria is not clear but they should be suspected in cases of lung abscesses and in empyemas following penetrating trauma of the thorax, but here also *S. aureus* and *Enterobacteriaceae* are the most common pathogens.

Prevention Strategies

Whenever aspiration is suspected in a patient, diagnostic bronchoscopy and lavage should be performed as soon as possible. Aspirated material should be removed to avoid further damage to the airways. Although no comparative studies exist, blind lavage is not recommended as it is thought to carry the risk of distributing aspirated gastric acid, which may extend the area of cellular damage.

Especially in patients without the need for mechanical ventilation and with painful rib fractures, use of thoracic epidural anesthesia catheters is recommended. This allows for early mobilization of the patient, for taking deep breaths and general physiotherapeutic measures. The aim is to avoid pain and opioid related hyperventilation, which may contribute to infection of atelectatic lung tissue [30, 31]. Furthermore, other risks associated with immobilization, such as phlebothrombosis and pulmonary emboli, should be avoided.

Although most patients with severe trauma require mechanical ventilation, strategies to reduce the duration of mechanical ventilation are recommended. Weaning protocols and regimens with daily stoppage of sedation (excluding patients with increased intracranial pressure) have proven to shorten the length of mechanical ventilation [32] and may thus decrease the incidence of VAP in such patients. However, reintubation has also been identified as risk factor for VAP [33]. Again, it is not the fact of reintubation per se that increases the risk, but the fact that patients that need reintubation suffer from depressed consciousness, muscular fatigue, hypoventilation, insufficient coughing reflex and other conditions that predispose for aspiration. These symptoms may already be the first manifestation of incubating pneumonia.

Since aspiration and microaspiration are major risk factors for the development of VAP, endotracheal cuff pressure should be controlled thoroughly and kept greater than 20 cm H_2O; following well-established guidelines for preventing pneumonia in mechanically ventilated patients is strongly recommended [24, 34]. However, some special issues exist in trauma patients that may not allow all preventative measures to be applied. Although difficult to establish [35], placing mechanically ventilated patients in a semi-recumbent position reduces the risk of microaspiration [36], augments functional residual capacity of the lung and reduces the incidence of pneumonia [37]. Subglottic suctioning through the use of specific endotracheal tubes with a dorsal lumen has been beneficial at least in some studies [38, 39]. However, trauma victims are usually intubated outside the hospital, where these tubes are not available and where it is difficult to estimate whether the patient will finally need long-term ventilation. Since reintubation carries an increased risk of pneumonia, it is not recommended that a regular intubation tube is replaced with a special tube just

for the purpose of subglottic suctioning. On the one hand, reintubation clearly carries the risk of aspiration and pneumonia [40]. Furthermore, patients that have initially been intubated without problems may present with a difficult airway on reintubation, due to bleeding and swelling of the upper airways.

Selective Digestive Decontamination (SDD) for Trauma Patients

Selective decontamination of the digestive tract (SDD) is a strategy for preventing infections in mechanically ventilated patients. Its rationale is based on the clinical observation of abnormal oral colonization that occurs in severely ill patients. This phenomenon was described more than thirty years ago by Waldemar Johanson [41,42]. The abnormal oropharyngeal colonization with Gram-negative bacteria increases the risk of nosocomial pneumonia. Therefore, modulation of colonization by using topically administered antibiotics is an intriguing concept, but also an everlasting matter of debate among medical microbiologists, infectious disease specialists and intensive care physicians. Recent trials have added substantially to the understanding of the potential benefits, but also of the limitations of the SDD concept. Here, the focus is especially on SDD studies performed in trauma patients, even though most of the trials included a mixed surgical and trauma intensive care unit (ICU) population.

Oral and intestinal (gastric) administration of non-absorbable antibiotics, in combination with IV antimicrobial prophylaxis among critically ill patients, was introduced by Stoutenbeek and coworkers [43]. Since then, SDD has been tested in many different variations and in a large variety of patients. In general, SDD is strongly associated with a reduction in ICU-acquired pneumonia, but the magnitude of the reduction is inversely related to the methodological quality of the study [44] and may even be absent in settings with high levels of antibiotic resistant bacteria [45,46]. As far as the individual components of SDD are concerned, oropharyngeal decontamination appears to be the most effective for preventing late onset pneumonia. This has been demonstrated by Bergmans and coworkers [47], who exclusively applied oropharyngeal decontamination with colistin, gentamicin, and vanomycin. This prophylaxis was associated with a relative risk reduction of pneumonia of 60%.

The role of intestinal decontamination (or decolonization) with respect to the prevention of infection is much less obvious. Indeed, in experimental settings translocation of enterococci across the intestinal barrier into mesenterial lymph nodes occurs more frequently when competing intestinal bacterial flora has been eradicated [48]. This phenomenon had been referred to as ‘colonization resistance’ of the gut in early trials investigating the influence of the indigenous microflora on the prevention of colonization by other pathogens [49]. However, only few data are available where exclusive intestinal decontamination has been investigated in patients. This method was used successfully to eradicate an intestinal reservoir of resistant bacteria but it had no influence on overall infection rates [50,51].

Since the topical administration of antibiotics aims at preventing abnormal colonization, it cannot be expected that there is an influence on early onset infections.

Therefore, the topically administered drugs are combined with a short course of intravenous antibiotic prophylaxis. Exclusive intravenous administration, however, has so far not been tested in comparison to the combined topical and intravenous regimen in any of the SDD studies. On the other hand, there are data from other trials that show the efficacy of intravenous antibiotics on the incidence of pneumonia. Sirvent and coworkers randomised mechanically ventilated comatose patients to two dosages of cefuroxim or placebo around intubation [52]. Patients receiving cefuroxim were less likely to develop ICU-acquired pneumonia. Similar results were achieved with a 3-day antibiotic prophylaxis in comatose patients with ampicillin−sulbactam [53].

The first evidence that SDD improves patient survival came from meta-analyses. Even though the analyses were based − with some exceptions − on the same sets of studies, the setup of these analyses was different [44, 54, 55]. Taken together, these analyses showed that only the full SDD regimen (systemic and topical prophylaxis) reduced ICU-mortality significantly and that surgical patients benefited more than medical patients [54, 55]. The results of these meta-analyses have again fostered the discussion of whether SDD should be applied as a method for preventing infections and for improving survival in all ICU-patients [56, 57]. Recently published individual trials gave new insights into which groups of patients may definitely derive benefits from the concept.

The first study used a stratified randomised double-blind design in which 546 surgical and trauma patients received systemic ciprofloxacin (or placebo) during the first days of ventilation in combination with oropharyngeal and gastro-intestinal application of gentamicin and polymyxin B [58]. Intravenous ciprofloxacin was chosen due to its pharmacokinetic properties: the levels of intravenously administered ciprofloxacin rapidly exceed the MICs of intestinal Gram-negative rods, thereby adding to the effect of depleting potentially pathogenic bacteria from the gastrointestinal tract [58, 59]. The patients in the SDD trial were stratified upon APACHE II score on admission in three groups (group I: scores < 20; group II: 20−29; and group III: > 29). Patients receiving SDD had significantly reduced infection rates and also a lower risk of organ failure. There was a trend toward reduced mortality but this was significant only in the pre-defined group II, which consisted of 122 SDD versus 115 placebo patients, where the mortality was 50 % lower (16 % compared to 33 %, risk ratio (RR) 0.508, 95 % confidence interval (CI) 0.295−0.875).

In the second trial, a mixed patient population was randomised in an open, prospective trial to one of two ICU-wards [60]. SDD consisted of cefotaxim intravenously for four days and of colistin, tobramycin, and amphotericin B applied topically. A total of 934 patients were evaluated. ICU mortality and hospital mortality were significantly lower among patients treated in the SDD ward, 35 and 28 % respectively.

In the third, and most recently published trial, the same SDD regimen was tested in 107 burn wound patients [61]. A 75 % relative reduction of mortality was achieved (from 27.8 % among the control to 9.4 %).

Several points of critique may be raised against the three studies but overall they confirm the results of the meta-analyses published before. Most importantly, all of

these trials were carried out in an environment of relatively low resistance rates, especially for MRSA.

The most critical question concerning the use of SDD is whether it promotes the emergence of resistance. There have been several SDD trials that showed increased selection pressure in an environment of pre-existent resistant microorganisms [46, 62]. On the other hand, in an environment with low endemicity of resistant bacteria – most importantly MRSA – SDD contributed to lower colonization rates with antibiotic resistant Gram-negative bacilli [60]. When SDD was used in an ICU in France over a six-year period, exclusively in patients with multiple trauma, a relative overgrowth of Gram-positive bacteria was observed but the overall impact on microbial resistance rates was low [63]. The most recently published data come from a 24-bed ICU in a tertiary care University Hospital in Germany, where SDD was used routinely over five years in a surgical and trauma population. Extensive surveillance cultures were used to detect antimicrobial resistance. The incidence densities of resistant Gram-negative bacteria were comparable or even lower than those in 33 other ICUs in Germany and MRSA rates remained below the German average [64]. Taken together, theses studies show that SDD does not automatically lead to increased resistance but it seems wise to monitor resistance rates, especially in ICUs where SDD is applied. There is, however, a lack of data for SDD applied in an environment with high baseline resistance rates.

Diagnosis

The complex issues related to the diagnosis of pneumonia in ventilated patients are covered elsewhere in this book. Here only those aspects that are particularly important in trauma patients are highlighted. Especially in patients with chest trauma, the interpretation of a chest radiograph may be difficult in regard to new infiltrates (see Figures 12.2–12.9). Lung contusions, atelectasis or early ARDS in combination with infections emerging in traumatized tissue at other body sites may mimic pneumonia or may be present simultaneously. In some cases, no information about patient history is available and it is unknown whether there are factors predisposing for pneumonia caused by multidrug resistant pathogens. Therefore, accurate diagnostic measurements are of paramount importance. Samples from the lower respiratory tract should be obtained as soon as possible and the bronchial system should be explored thoroughly for aspiration of blood, stomach contents or foreign bodies, such as teeth or dental prostheses. However, in patients with concomitant brain oedema, a rise in intracranial pressure due to stress or hypoventilation during the bronchoscopic procedure must be avoided. In such conditions, bronchoscopy should be performed only after a probe to measure intracranial pressure has been placed and the patient has been deeply sedated. In conditions with increased intracranial pressure, an individual decision has to be made and in some patients bronchoscopy cannot be performed.

Patients at risk from communities with a high frequency of antibiotic resistance, such as residents in nursing homes, patients undergoing chronic dialysis, home wound care or home infusion therapy, should be further screened for multidrug resistant pathogen colonization on admission. In addition, blood cultures should be collected

Table 12.2 Clinical pulmonary infection score (CPIS) [73]

Variables	Points
Temperature (°C) [at time of evaluation of pulmonary infiltrate]	
≥36.5 and ≤38.4 °C	0
≥38.5 and ≤38.9 °C	1
≥39.0 and ≤36.0 °C	2
Blood leukocyte count	
≥4000 and ≤11 000	0
≥4000 or <11 000 (add 1 point if band forms ≥50 %)	1
Tracheal Secretions	
Absence of tracheal secretion	0
Nonpurulent tracheal secretion	1
Purulent tracheal secretion	2
Oxygenation Pa_{O2}/Fi_{O2}, mmHg	
> 240 or ARDS (ARDS: $PaO_2/FiO_2 \leq 200$ or PCWP < 18 mmHg and acute bilateral infiltrates)	0
≤ 240 and no ARDS	2
Pulmonary radiography	
No infiltrate	0
Diffuse or patchy infiltrates	1
Localized infiltrate	2
Progression of pulmonary infiltrate	
No radiographical progression	0
Radiographical progression (excluding congestive heart disease and ARDS)	2
Culture of tracheal aspirate	
Pathogenic bacteria cultured in rare or light quantity or no growth	0
Pathogenic bacteria cultured in moderate or heavy quantity	1
Same pathogenic bacteria seen in Gram stain add 1 point	

to ensure the diagnosis of pneumonia and to exclude extrapulmonary infections (Table 12.2).

Therapy

Treatment of suspected pneumonia should begin early with empiric therapy based on the knowledge of the predominant pathogens in the clinical setting and with respect to the local pattern of antibiotic susceptibility. Most importantly, it has to be evaluated whether the patient is at risk of infection with multidrug resistant pathogens (Table 12.3). Inappropriate or delayed therapy increases mortality [65, 66] and several investigations point to an independent risk for increased mortality in trauma patients suffering from VAP [67].

Methicillin-susceptible *S. aureus*, pneumococci and *H. influenza* are common pathogens in comatose trauma patients. In such situations, short courses of cefuroxime [52] or of ampicillin−sulbactam [53] have been shown to reduce the incidence of pneumonia. Therefore, excluding risk factors for multidrug resistance and excluding late onset pneumonia, a cephalosporin-based therapy, either second generation (such

Table 12.3 Risk factors for multidrug resistant pathogens causing pneumonia [24]

Antimicrobial therapy in preceding 90 days
Current hospitalisation for >5 days
High incidence of antibiotic resistance in the community, or hospital unit
Hospitalisation for >2 days in preceding 90 days
Residence in a nursing home or care facility
Chronic dialysis
Home wound care
Family member with multidrug resistant pathogen
Immunosuppression

as cefuroxime) or third generation (such as ceftriaxone) seems appropriate for treating pneumonia in trauma patients. The third generation cephalosporin ceftazidime usually covers *Pseudomonas aeruginosa* but lacks sufficient activity against staphylococci and is therefore not recommended in early onset pneumonia in trauma patients. Alternatively, an aminopenicillin plus a beta-lactamase inhibitor (such as ampicillin plus sulbactam) may be used to treat early onset pneumonia in trauma patients and may be preferred in patients with gross aspiration due to the anaerobic activity. For a cephalosporin-based therapy, combination with metronidazole is necessary to cover enteric anaerobic bacteria.

It has, however, been questioned whether anaerobic coverage is really necessary for aspiration pneumonia, since the clinical significance of anaerobes is unclear and most cases of aspiration pneumonia resolve without anaerobic coverage [68]. This issue is difficult to answer, since anaerobes are often not retrieved in routine microbiological cultures, as these organisms rapidly die after contact with oxygen during transport to the laboratory. On the other hand, anaerobic bacteria were frequently described as co-pathogens in studies using specific laboratory methods [69, 70]. Thus, the importance of anaerobic bacteria is not completely clear and it is our personal practice to add metronidazole to a second generation cephalosporin for patients with documented gross aspiration. Such practice is also supported by large surveys on antibiotic prescribing patterns in intensive care units [71]. In case of allergies to beta-lactam antibiotics, treatment with fluoroquinolones, such as levofloxacin [72] and moxiflocacin, is recommended, with the latter also having anaerobic activity [23, 24]. The American Thoracic Society also recommends treatment with ertapenem for early onset pneumonia in ventilated patients [24]. This carbapenem antibiotic has even broader anaerobic activity than moxifloxacin.

In cases of suspected infection by multidrug resistant pathogens or in cases of late onset pneumonia, therapy should follow the guidelines given by the American Thoracic Society and the Infectious Diseases Society of America, which must be adapted to the local patterns of resistance (Table 12.4) [24].

Finally it has to be emphasised that the therapy should be narrowed down as soon as possible to reduce selection pressure for multidrug resistant pathogens.

Table 12.4 Initial empiric antibiotic therapy

	Potential Pathogen	Antibiotic	Dosage* (examples)
No Risk factors	Streptococcus pneumoniae	Cephalosporin (second or third generation)	Cefuroxime 3 × 1, 5 g/d Cefriaxone 1 × 2 g/d
	Haemophilus influenzae	or	
	MSSA[+]	Aminopenicillin + betalactamase inhibitor	Ampicillin–sulbactam 4 × 3 g/d
		or	
	Antibiotic-sensitive enteric Gram-negative bacilli *Escherichiaa coli* *Klebsiella* spp. Enterobacter species Proteus species *Serratia marcescens*	Fluoroquinolone or Non-pseudomonal carbapenem	Levofloxacin: 2 x 500 mg/d (or 1 x 750 mg/d) Ertapanem 1 × 1 g/d
Late Onset or risk factors for MDR[#]	*Pseudomonas aeruginosa* Klebsiella pneumoniae *Acinetobacter* species	Antipseudomonal cephalosporin (cefepime, ceftazidime)	Cefepime: 2 × 2 g/d Ceftazidime: 3–4 ×2 g/d
		or	
		Antipseudomonal carbapenem	Imipenem: 3 × 1 g/d
		or	Meropenem: 3 × 1 g/d
		ureidopenicillin + betalactamase-inhibitor	Piperacillin/tazobactam: 3–4 x 4, 5 g/d
		plus	
		Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin)	Ciprofloxacin: 3 × 400 mg/d
		or	Gentamicin: 7 mg/kg/d^
		Aminoglycoside (amikacin, gentamicin or tobramycin)	Tobramycin: 7 mg/kg/d^ Amikacin: 20 mg/kg/d[&]
		plus	Vancomycin: 2 x 15 mg/kg/d (or continuous infusion to achieve 15–25 mg/l)
	MRSA[x]	Linezolid or vancomycin	Linezolid: 2 × 600 mg/d

* based on normal renal and hepatic function; # MDR: Multidrug resistant pathogen;
+ MSSA: Methicillin sensitive *Staphylococcus aureus*; x: MRSA: Methicillin resistant *Staphylococcus aureus*; ^ trough levels of gentamicin and tobramycin should be < 1 μg/mL; &: amikacin level should be < 4–5 μg/mL; according to [24] and [23]

Case Reports

A 49-year-old, previously healthy patient was hit by a horse hoof on his right thorax. The chest radiograph showed several rib fractures as well as soft tissue emphysema (Figure 12.2). Despite immediate drainage of the right thorax, the emphysema proceeded. Since lung contusion is frequently associated with atelectases followed by infection, empirical treatment with cefuroxime was started at admission after bronchoscopy was carried out. The patient underwent repeated bronchoscopy due to atelectasis. Despite atelectasis, gas exchange remained stable with nasal O_2-insufflation, he was not intubated and was treated with thoracic epidural analgesia and vigorous respiratory therapy. In BAL samples, *S. aureus* was identified as pathogen. Antibiotic treatment was stopped after seven days and dystelectasis and infiltrates improved in follow-up chest radiographs (Figure 12.3).

A 43-year-old female patient was admitted to ICU after a tumbling down a stairway following ethanol intoxication. She was found with a GCS of six and was intubated immediately. A CT scan showed traumatic subarachnoidal haemorrhage, contusion of the brain and generalized brain oedema. Furthermore, she had lung contusions and right-sided fractures of the 10th and 11th ribs causing a tension pneumothorax with mediastinal shift to the left side. She also had older serial rib fractures on the left side (ribs 3 through 10; Figure 12.4). Due to the high risk of pneumonia (comatose patient with possible aspiration and lung contusion), the patient underwent bronchoscopy and empirical treatment was begun with cefotaxime to cover pneumococci as well

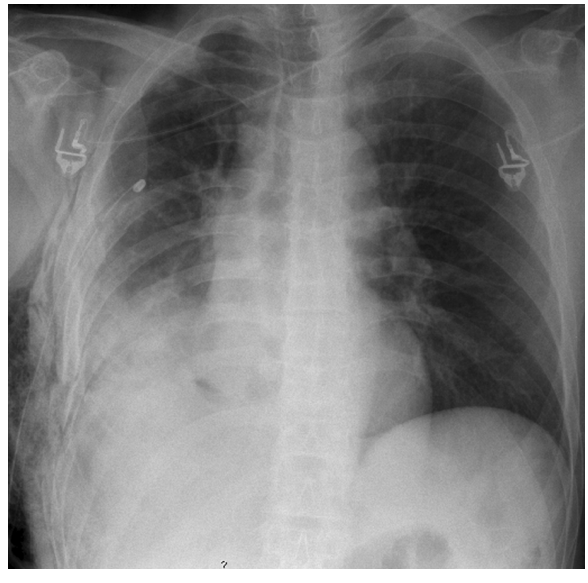

Figure 12.2
Chest radiograph of a 49-year-old patient, who was hit by a horse hoof (patient 1) at admission showing lung contusion and rib fractures at the right thorax and soft tissue emphysema with drainage

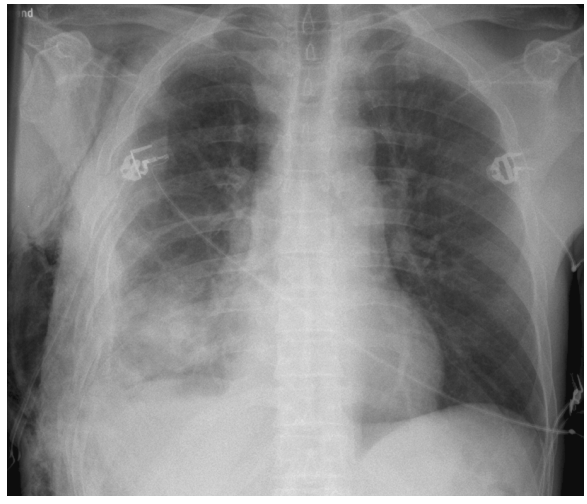

Figure 12.3
Chest radiograph of patient 1 after treatment with cefuroxim for 5 days

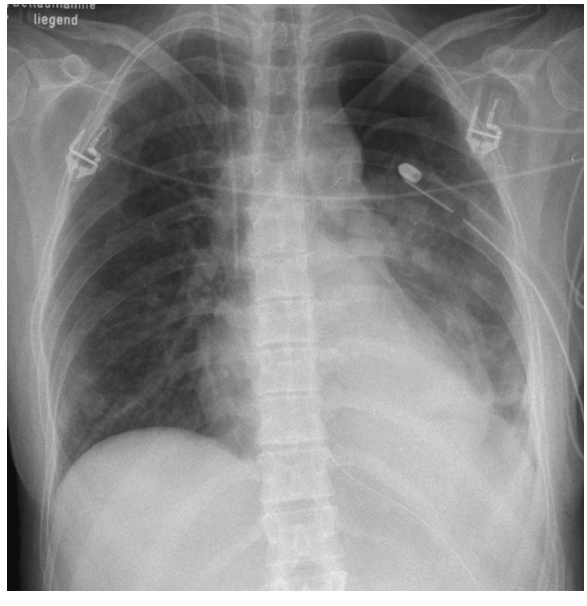

Figure 12.4
Chest radiograph of a 43-year-old patient with subarachnoidal bleeding after tumbling down a stairway (patient 2) at admission, showing lung contusions on the left side; Pneumothorax was drained immediately after admission

as Gram-negative bacteria, which are more commonly found in patients with chronic alcoholism. She suffered from recurrent atelectasis due to pneumothorax ex vacuo, which could only be treated after repeated bronchoscopies for removal of blood clots obturating the left bronchial system (Figure 12.5). BAL samples were sterile and cefotaxime was stopped accordingly on Day 3. Five days after admission, a chest radiograph did not show any signs of pneumonia or atelectasis (Figure 12.6).

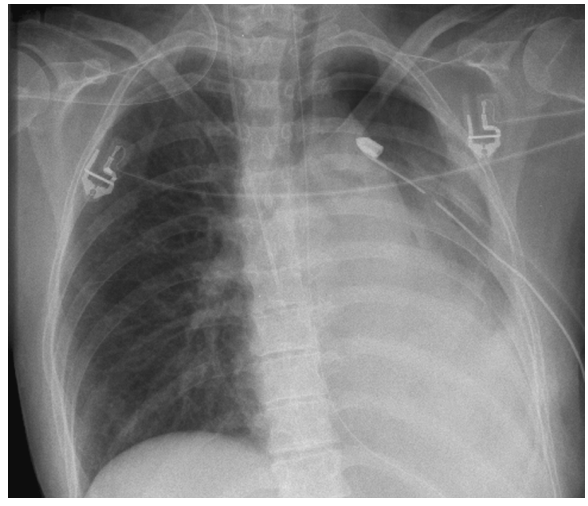

Figure 12.5
Patient 2 suffered from recurrent atelectasis due to pneumothorax e vacuo

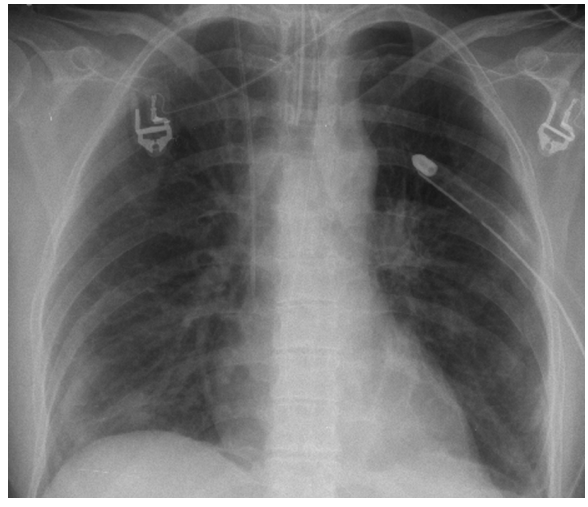

Figure 12.6
Five days after admission of patient 2, chest radiograph was without any signs for atelectasis or infiltrations

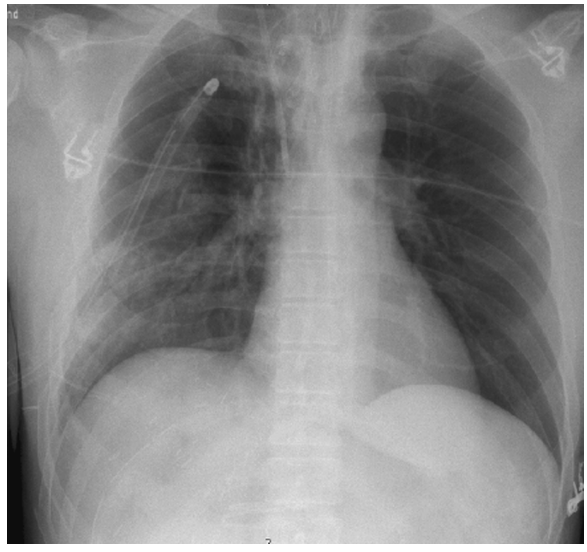

Figure 12.7
Chest radiograph of a 43-year-old patient with a haemorrhagic shock and hyperventilation after a motorcycle accident. Rib fractures at the right thoracic apperature are seen. Pneumothorax has been treated by a drainage on the right side

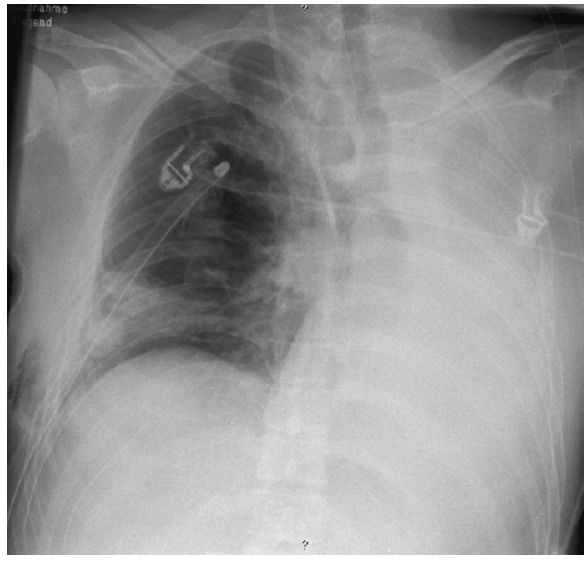

Figure 12.8
The chest radiograph of patient 3 show left-sided atelectasis due to bronchial obstruction by blood clots

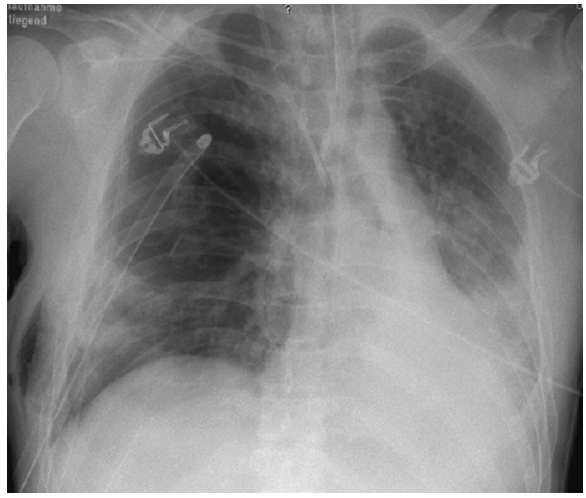

Figure 12.9
Chest radiograph of patient 3 after blood and purulent secretion has been removed by repeated bronchoscopies

The patient was extubated one week after the event and referred to a neurological rehabilitation center on Day 14.

A previously healthy 43-year-old man was found with a GSC of 13, but with haemorrhagic shock and hyperventilation after a motorcycle accident. He was intubated on the street and a chest tube was immediately placed into the right hemithorax, where crepitations suggested rib fractures, which were confirmed by radiology later (Figure 12.7). After transfer to our hospital, liver lacerations were diagnosed as well without need for surgical intervention. Bronchoscopy was carried out to remove blood clots in the bronchial system. Epidural analgesia was not placed due to coagulation abnormalities after liver trauma. The patient was extubated two days later, but suffered from repeated left-sided atelectasis due to bronchial obstruction and was re-intubated on Day 4 (Figure 12.8). Repeated bronchoscopy was carried out to remove blood and highly viscous, purulent secretions (Figure 12.9). The patient had received antibiotic prophylaxis on admission with cefuroxime and metronidazole due to soft tissue lacerations. Cefuroxime was continued for a total of seven days, after the initial BAL-samples yielded *S. aureus* as pathogen and the patient was extubated on Day 6 and transferred to a general ward on Day 8.

References

1. Eckert, M.J., Davis, K.A., Reed, R.L. *et al*. (2006) Ventilator-associated pneumonia, like real estate: Location really matters. *J.Trauma*, **60**, 104–10.
2. Rodriguez, J.L., Gibbons, K.J., Bitzer, L.G. *et al*. (1991) Pneumonia: Incidence, risk factors, and outcome in injured patients. *J.Trauma*, **31**, 907–12.

3. Wallace, W.C., Cinat, M., Gornick, W.B. *et al*. (1999) Nosocomial infections in the surgical intensive care unit: A difference between trauma and surgical patients. *Am.Surg*, **65**, 987–90.
4. Krueger, W.A. and Unertl., K.E. (2002) Selective decontamination of the digestive tract. *Curr.Opin.Crit Care*, **8**, 139–44.
5. Bronchard, R., Albaladejo, P., Brezac, G. *et al*. (2004) Early onset pneumonia: Risk factors and consequences in head trauma patients. *Anesthesiology*, **100**, 234–9.
6. Campbell, W., Hendrix, E., Schwalbe, R. *et al*. (1999) Head-injured patients who are nasal carriers of *Staphylococcus aureus* are at high risk for *Staphylococcus aureus* pneumonia. *Crit Care Med*, **27**, 798–801.
7. Ploppa, A., Kiefer, R.T., Nohe, B. *et al*. (2006) Dose-dependent influence of barbiturates but not of propofol on human leukocyte phagocytosis of viable *Staphylococcus aureus*. *Crit Care Med*, **34**, 478–83.
8. Eberhardt, K.E., Thimm, B.M., Spring, A. and Maskos, W.R. (1992) Dose-dependent rate of nosocomial pulmonary infection in mechanically ventilated patients with brain oedema receiving barbiturates: A prospective case study. *Infection*, **20**, 12–18.
9. Stover, J.F. and Stocker, R. (1998) Barbiturate coma MAY promote reversible bone marrow suppression in patients with severe isolated traumatic brain injury. *Eur.J.Clin.Pharmacol*, **54**, 529–34.
10. Nadal, P., Nicolas, J.M., Font, C. *et al*. (1995) Pneumonia in ventilated head trauma patients: The role of thiopental therapy. *Eur.J.Emerg.Med*, **2**, 14–16.
11. Davidson, J.A., Boom, S.J., Pearsall, F.J., Zhang, P. and Ramsay, G. (1995) Comparison of the effects of four anaesthetic agents on polymorphonuclear leukocyte function. *Br.J.Anaesth*, **74**, 315–18.
12. Galley, H.F., DiMatteo, M.A. and Webster, N.R. (2000) Immunomodulation by anaesthetic, sedative and analgesic agents: Does it matter. *Intensive Care Med*, **26**, 267–74.
13. Croce, M.A., Tolley, E.A. and Fabian, T.C. (2003) A formula for prediction of posttraumatic pneumonia based on early anatomic and physiologic parameters. *J.Trauma*, **54**, 724–9.
14. Eckert, M.J., Wade, T.E., Davis, K.A. *et al*. (2006) Ventilator-associated pneumonia after combined burn and trauma is caused by associated injuries and not the burn wound. *J.Burn Care Res*, **27**, 457–62.
15. Chastre, J., Trouillet, J.L., Vuagnat, A. *et al*. (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. *Am.J.Respir.Crit Care Med*, **157**, 1165–72.
16. Delclaux, C., Roupie, E., Blot, F. *et al*. (1997) Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: Incidence and diagnosis. *Am.J.Respir.Crit Care Med*, **156**, 1092–8.
17. Markowicz, P., Wolff, M., Djedaini, K. *et al*. (2000) Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS study group. *Am.J.Respir.Crit Care Med*, **161**, 1942–8.
18. Meduri, G.U., Reddy, R.C., Stanley, T. and El Zeky, F. (1998) Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. *Am.J.Respir.Crit Care Med*, **158**, 870–5.
19. Bercault, N., WolfRunge, M.I., Fleury, J.C. and Boulain, T. (2005) Intrahospital transport of critically ill ventilated patients: A risk factor for ventilator-associated pneumonia – a matched cohort study. *Crit Care Med*, **33**, 2471–8.
20. Sirvent, J.M., Torres, A., Vidaur, L. *et al*. (2000) Tracheal colonisation within 24 hours of intubation in patients with head trauma: Risk factor for developing early onset ventilator-associated pneumonia. *Intensive Care Med*, **26**, 1369–72.

21. Rello, J., Ausina, V., Castella, J., Net, A. and Prats, G. (1992) Nosocomial respiratory tract infections in multiple trauma patients. Influence of level of consciousness with implications for therapy. *Chest*, **102**, 525–9.
22. Johanson, W.G., Pierce, A.K. and Sanford, J.P. (1970) Oropharyngeal ecology. *N.Engl.J.Med*, **282**, 815.
23. Krueger, W.A. and Daschner, F.D. (2003) Pneumonias associated with artificial respiration. Diagnosis and therapy. *Anaesthesist*, **52**, 265–90.
24. Niederman, M.S., Craven, D.E., Bonten, M.J.M. *et al*. (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, healthcare-associated pneumonia. *Am.J.Respir.Crit Care Med*, **171**, 388–416.
25. Ewig, S., Torres, A., ElEbiary, M. *et al*. (1999) Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. *Am.J.Respir.Crit Care Med*, **159**, 188–98.
26. Baraibar, J., Correa, H., Mariscal, D. *et al*. (1997) Risk factors for infection by *Acinetobacter baumannii* in intubated patients with nosocomial pneumonia. *Chest*, **112**, 1050–4.
27. Corbella, X., Montero, A., Pujol, M. *et al*. (2000) Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant *Acinetobacter baumannii*. *J.Clin.Microbiol*, **38**, 4086–95.
28. ElEbiary, M., Sarmiento, X., Torres, A. *et al*. (1997) Prognostic factors of severe Legionella pneumonia requiring admission to ICU. *Am.J.Respir.Crit Care Med*, **156**, 1467–72.
29. Wood, G.C., Mueller, E.W., Croce, M.A. *et al*. (2006) *Candida* sp. Isolated from bronchoalveolar lavage: Clinical significance in critically ill trauma patients. *Intensive Care Med*, **32**, 599–603.
30. Bulger, E.M., Edwards, T., Klotz, P. and Jurkovich, G.J. (2004) Epidural analgesia improves outcome after multiple rib fractures. *Surgery*, **136**, 426–30.
31. Bulger, E.M., Arneson, M.A., Mock, C.N. and Jurkovich, G.J. (2000) Rib fractures in the elderly. *J.Trauma*, **48**, 1040–6.
32. Ely, E.W., Baker, A.M., Dunagan, D.P. *et al*. (1996) Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N.Engl.J.Med*, **335**, 1864–9.
33. Pawar, M., Mehta, Y., Khurana, P. *et al*. (2003) Ventilator-associated pneumonia: Incidence, risk factors, outcome, and microbiology. *J.Cardiothorac.Vasc.Anesth*, **17**, 22–8.
34. Tablan, O.C., Anderson, L.J., Besser, R. *et al*. (2004) Guidelines for preventing healthcare-associated pneumonia, 2003: Recommendations of CDC and the healthcare infection control practices advisory committee. *MMWR Recomm.Rep*, **53**, 1–36.
35. Bonten, M.J., and Weinstein, R.A. (2006) Antibiotic cycling in intensive care units: The value of organized chaos. *Crit Care Med*, **34**, 549–51.
36. Torres, A., Serra-Batlles, J., Ros, E. *et al*. (1992) Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: The effect of body position. *Ann.Intern.Med*, **116**, 540–3.
37. Drakulovic, M.B., Torres, A., Bauer, T.T. *et al*. (1999) Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. *Lancet*, **354**, 1851–8.
38. Smulders, K., van der, H.H., Weers-Pothoff, I. and Vandenbroucke-Grauls, C. (2002) A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. *Chest*, **121**, 858–62.
39. Valles, J., Artigas, A., Rello, J. *et al*. (1995) Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann.Intern.Med*, **122**, 179–86.

40. Torres, A., Gatell, J.M., Aznar, E. *et al*. (1995) Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. *Am.J.Respir.Crit Care Med*, **152**, 137–41.
41. Johanson, W.G., Pierce, A.K., and Sanford, J.P. (1969) Changing pharyngeal bacterial flora of hospitalised patients. Emergence of Gram-negative bacilli. *N.Engl.J.Med*, **281**, 1137–40.
42. Johanson, W.G., Jr, Pierce, A.K., Sanford, J.P. and Thomas, G.D. (1972) Nosocomial respiratory infections with Gram-negative bacilli. The significance of colonization of the respiratory tract. *Ann.Intern.Med*, **77**, 701–6.
43. Stoutenbeek, C.P., vanSaene, H.K., Miranda, D.R. and Zandstra, D.F. (1984) The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intensive Care Med*, **10**, 185–92.
44. van Nieuwenhoven, C.A., Buskens, E., vanTiel, F.H. and Bonten, M.J. (2001) Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *JAMA*, **286**, 335–40.
45. Gastinne, H., Wolff, M., Delatour, F. *et al*. (1992) A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. The French study group on selective decontamination of the digestive tract. *N.Engl.J.Med*, **326**, 594–9.
46. Verwaest, C., Verhaegen, J., Ferdinande, P. *et al*. (1997) Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. *Crit Care Med*, **25**, 63–71.
47. Bergmans, D.C., Bonten, M.J., Gaillard, C.A. *et al*. (2001) Prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double-blind, placebo-controlled study. *Am. J. Respir. Crit Care Med*, **164**, 382–8.
48. Krueger, W.A., Krueger-Rameck, S., Koch, S. *et al*. (2004) Assessment of the role of antibiotics and enterococcal virulence factors in a mouse model of extraintestinal translocation. *Crit Care Med*, **32**, 467–71.
49. van der Waaij, D. (1982) Colonization resistance of the digestive tract: Clinical consequences and implications. *J.Antimicrob.Chemother*, **10**, 263–70.
50. Agusti, C., Pujol, M., Argerich, M.J. *et al*. (2002) Short-term effect of the application of selective decontamination of the digestive tract on different body site reservoir ICU patients colonized by multi-resistant *Acinetobacter baumannii*. *J.Antimicrob.Chemother*, **49**, 205–8.
51. Brun-Buisson, C., Legrand, P., Rauss, A. *et al*. (1989) Intestinal decontamination for control of nosocomial multiresistant Gram-negative bacilli. Study of an outbreak in an intensive care unit. *Ann.Intern.Med*, **110**, 873–81.
52. Sirvent, J.M., Torres, A., ElEbiary, M. *et al*. (1997) Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am.J.Respir.Crit Care Med*, **155**, 1729–34.
53. Acquarolo, A., Urli, T., Perone, G. *et al*. (2005) Antibiotic prophylaxis of early onset pneumonia in critically ill comatose patients. A randomized study. *Intensive Care Med*, **31**, 510–16.
54. D'Amico, R., Pifferi, S., Leonetti, C. *et al*. (1998) Effectiveness of antibiotic prophylaxis in critically ill adult patients: Systematic review of randomised controlled trials. *BMJ*, **316**, 1275–85.
55. Nathens, A.B. and Marshall, J.C. (1999) Selective decontamination of the digestive tract in surgical patients: A systematic review of the evidence. *Arch.Surg*, **134**, 170–6.
56. Bonten, M.J., Brun-Buisson, C. and Weinstein, R.A. (2003) Selective decontamination of the digestive tract: To stimulate or stifle. *Intensive Care Med*, **29**, 672–6.

57. vanSaene, H.K., Petros, A.J., Ramsay, G. and Baxby, D. (2003) All great truths are iconoclastic: Selective decontamination of the digestive tract moves from heresy to level 1 truth. *Intensive Care Med*, **29**, 677–90.
58. Krueger, W.A., Lenhart, F.P., Neeser, G. *et al*. (2002) Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: A prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. *Am.J.Respir.Crit Care Med*, **166**, 1029–37.
59. Krueger, W.A., Ruckdeschel, G., and Unertl, K. (1999) Elimination of fecal enterobacteriaceae by intravenous ciprofloxacin is not inhibited by concomitant sucralfate – a microbiological and pharmacokinetic study in patients. *Infection*, **27**, 335–40.
60. deJonge, E., Schultz, M.J., Spanjaard, L. *et al*. (2003) Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: A randomised controlled trial. *Lancet*, **362**, 1011–16.
61. de laCal, M.A., Cerda, E., Garcia-Hierro, P. *et al*. (2005) Survival benefit in critically ill burned patients receiving selective decontamination of the digestive tract: A randomized, placebo-controlled, double-blind trial. *Ann.Surg*, **241**, 424–30.
62. Lingnau, W., Berger, J., Javorsky, F. *et al*. (1998) Changing bacterial ecology during a five-year period of selective intestinal decontamination. *J.Hosp.Infect*, **39**, 195–206.
63. Leone, M., Albanese, J., Antonini, F. *et al*. (2003) Long-term (6-year) effect of selective digestive decontamination on antimicrobial resistance in intensive care, multiple-trauma patients. *Crit Care Med*, **31**, 2090–5.
64. Heininger, A., Meyer, E., Schwab, F. *et al*. (2006) Effects of long-term routine use of selective digestive decontamination on antimicrobial resistance. *Intensive Care Med*, **32**, 1569–76.
65. Luna, C.M., Aruj, P., Niederman, M.S. *et al*. (2006) Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. *Eur.Respir.J*, **27**, 158–64.
66. Rello, J., Ollendorf, D.A., Oster, G. *et al*. (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest*, **122**, 2115–21.
67. Magnotti, L.J., Croce, M.A., and Fabian, T.C. (2004) Is ventilator-associated pneumonia in trauma patients an epiphenomenon or a cause of death. *Surg.Infect.(Larchmt.)*, **5**, 237–42.
68. Marik, P.E. and Careau, P. (1999) The role of anaerobes in patients with ventilator-associated pneumonia and aspiration pneumonia: A prospective study. *Chest*, **115**, 178–83.
69. Dore, P., Robert, R., Grollier, G. *et al*. (1996) Incidence of anaerobes in ventilator-associated pneumonia with use of a protected specimen brush. *Am.J.Respir.Crit Care Med*, **153**, 1292–8.
70. Robert, R., Grollier, G., Frat, J.P. *et al*. (2003) Colonization of lower respiratory tract with anaerobic bacteria in mechanically ventilated patients. *Intensive Care Med*, **29**, 1062–8.
71. Rebuck, J.A., Rasmussen, J.R. and Olsen, K.M. (2001) Clinical aspiration-related practice patterns in the intensive care unit: A physician survey. *Crit Care Med*, **29**, 2239–44.
72. Alvarez-Lerma, F., Grau, S. and Alvarez-Beltran, M. (2006) Levofloxacin in the treatment of ventilator-associated pneumonia. *Clin.Microbiol.Infect*, **12** (Suppl 3), 81–92.
73. Singh, N., Rogers, P., Atwood, C.W. *et al*. (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am.J.Respir.Crit Care Med*, **162**, 505–11.

13

Acute Respiratory Distress Syndrome and Pneumonia

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Pulmonary infection is a common complication of acute respiratory distress syndrome(ARDS) and one of the most challenging diagnostic and treatment dilemmas in critical care medicine. Previous clinical and histological studies have found that ventilator-associated pneumonia (VAP) can affect between 30 and 75 % of patients dying of ARDS [1–5]. Although the impact of nosocomial pneumonia on the outcome of mechanically ventilated patients remains controversial, it may play a key role in patients requiring mechanical ventilation (7) for ARDS by worsening hypoxemia and causing sepsis, multiple organ failure and death [1, 6]. The diagnosis of pulmonary infection in such patients, however, is often difficult [4, 7]. The systemic signs of infection, such as fever, tachycardia and leukocytosis, are nonspecific findings in patients with ARDS; a variety of causes other than pneumonia can explain asymmetric consolidation and marked asymmetry of radiographic abnormalities has also been reported in patients with uncomplicated ARDS [8].

The clinical characteristics of pulmonary infection in such a setting, based on personal experience and major additions to the literature that have appeared in recent years, are reviewed in this chapter.

Diagnosis and Incidence of VAP in Patients with ARDS

Accurate data on the epidemiology of VAP in ARDS patients are limited by the lack of standardized criteria for its diagnosis. Conceptually, VAP is defined as an

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inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time mechanical ventilation was started. Despite the clarity of this conception, the past three decades have witnessed the appearance of numerous operational definitions, none of which is universally accepted [9]. Even definitions based on histopathological findings at autopsy may fail to find consensus or provide certainty. Pneumonia in focal areas of a lobe may be missed, microbiological studies may be negative despite of presence of inflammation in the lung and pathologists may disagree on the findings [10]. The absence of a 'gold standard' continues to fuel controversy about the adequacy and relevance of many studies in this field.

When the lungs of patients who died of ARDS were examined histologically at autopsy, pneumonia could be demonstrated in as many as 73% [1,7]. However, VAP is difficult to detect clinically and is often unsuspected during ARDS. Several studies have clearly demonstrated the inability of physicians to accurately diagnose nosocomial pneumonia in this setting based on clinical criteria alone [4,7,8,11]. In the study by Delclaux and colleagues, new respiratory signs (increase in sputum, new infiltrate, or worsening of hypoxemia) were noted in less than 50% of VAP episodes (Figure 13.1). A new radiographic infiltrate was observed in seven out of 30 patients with ARDS, of which only four were associated with a microbiologically confirmed VAP; other episodes of new radiographic infiltrates were attributed to the occurrence of segmental atelectasis. Thus, the positive predictive value of a new radiographic infiltrate for diagnosing pneumonia was only 0.57. Similarly, a sustained decrease in the PaO_2/FIO_2 ratio was recorded 15 times, of which nine were associated with the occurrence of VAP; thus, the worsening of hypoxemia had a positive predictive value of only 0.60 in this series. Although the predictive value of individual signs was rather low, all VAP episodes were associated with at least one worsening clinical sign or symptom. Consequently, suspicion for VAP in the setting of ARDS should be high. The presence of even only one of the three classical clinical criteria for

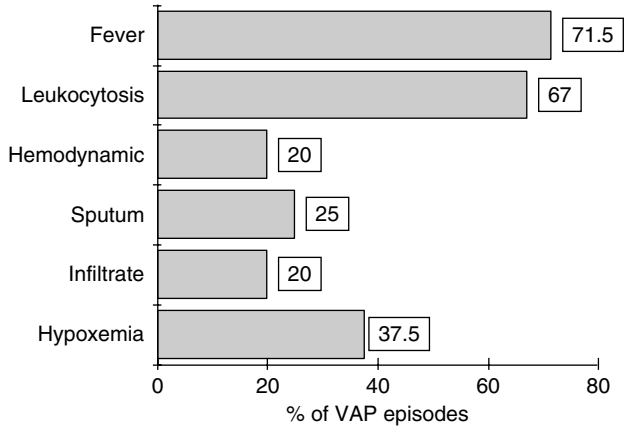

Figure 13.1
Clinical features of lower respiratory tract infection during ARDS (adapted from Delclaux *et al.* [4]).

VAP (i.e. fever, purulent secretions and leukocytosis), unexplained haemodynamic instability or an unexplained deterioration in arterial blood gases should prompt consideration of further diagnostic testing, even if these criteria are nonspecific and can be observed in many patients with ARDS in the absence of any bacterial infection [4].

Using bronchoalveolar lavage (BAL) and the protected specimen brush (PSB) technique at predetermined times from Day 3 to Day 21 after the onset of the syndrome in a series of 105 patients with ARDS, Sutherland *et al.* concluded that VAP may occur far less frequently than expected in this group of patients [2]. Only 16 (15.2%) of the 105 patients met the quantitative criteria for pneumonia (PSB $> 10^3$ cfu/mL or BAL $> 10^4$ cfu/mL); no correlations were found between total colony counts in BAL fluid or PSB cultures and the severity of ARDS, as judged by PaO_2/FIO_2 ratios, days on mechanical ventilation, static lung compliance and/or survival. Unfortunately, most patients included in the study were assessed while receiving antibiotics and at predetermined times during the course of ARDS, rather than at the time of clinically suspected infection. It is therefore likely that a number of occult pulmonary infections went undetected because of the lack of samples and/or because of concurrent changes in antibiotic therapy.

Several other studies have indeed demonstrated that VAP was a common complication in patients with ARDS when strict bronchoscopic criteria were applied for diagnosing pneumonia, taking great care to obtain specimens of distal pulmonary secretions before any modifications to the existing antimicrobial treatment [3–5, 12]. In a prospective study on 243 consecutive intensive care unit (ICU) patients who required MV for ≥48 hours, of whom 56 developed ARDS as defined by a Murray lung injury score >2.5, bronchoscopic samples were obtained for all enrolled patients and specifically for those with ARDS as soon as they became febrile and/or deteriorated clinically, even when no progression of the lung infiltrates could be ascertained [3]. Because each of the bronchoscopic techniques used may give rise to a few false-negative results when used alone, diagnostic classification was based on a protocol combining the results of direct microscopic examination of cells recovered by BAL with those obtained using quantitative culture of both PSB and BAL specimens. Logically, combining the three techniques should improve and strengthen overall diagnostic accuracy, because such false-negative results would probably not concern the three assays for the same patient. Results indicate that the incidence of microbiologically provable nosocomial pneumonia was particularly high in patients with ARDS; it was nearly two-fold higher than in other ventilated patients, but occurred later in the course of the syndrome, usually after the first week of MV (Figure 13.2).

According to three other studies that also used a very strict protocol to diagnose bacterial pulmonary infection, the VAP rate was also higher in ARDS patients than in other mechanically ventilated patients [4, 5, 12]. In one study on 30 ARDS patients for whom repeated quantitative culture results of specimens obtained with a plugged catheter were available and in 94 ARDS patients with suspected VAP who underwent 172 bronchoscopies, VAP incidences were 60% (incidence density, 4.2/100 ventilator-days) and 43%, respectively [4, 12]. In another prospective multicentre

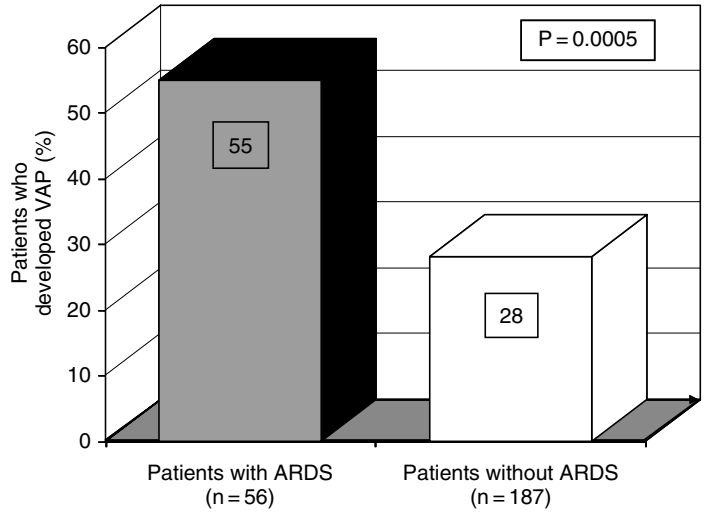

Figure 13.2
Incidence of VAP in 243 ICU patients with or without ARDS (adapted from Chastre *et al.* [3]).

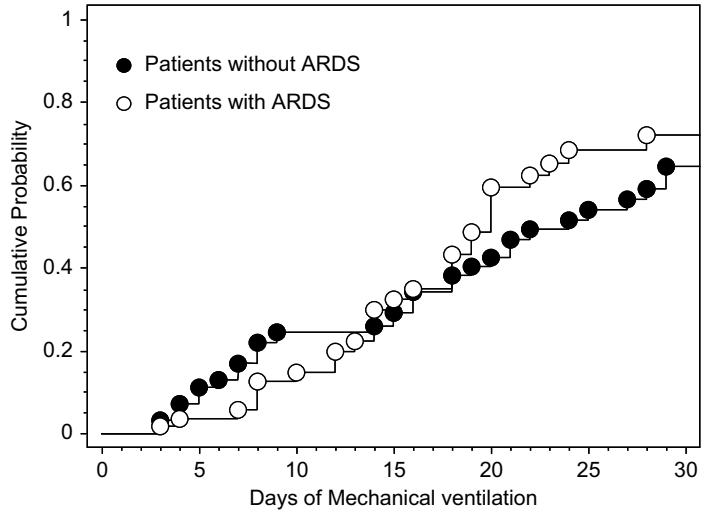

Figure 13.3
Kaplan–Meier estimates of the probability of developing VAP for patients with or without ARDS (modified with permission from Chastre *et al.* [3]).

study, VAP was bacteriologically confirmed in 49 (37%) out of 134 ARDS patients, versus 23% of ventilated non-ARDS patients ($p < 0.002$) [5].

A higher incidence of microbiologically probable VAP in patients with ARDS than in other populations of mechanically ventilated patients is not unexpected. Several studies have clearly demonstrated that alveolar macrophages and polymorphonuclear

cells retrieved from the lungs of patients with ARDS have an impaired phagocytic function and/or a lower capacity to express maximal activity after *ex vivo* stimulation by bacterial products, which could explain why these patients are at high risk of developing pulmonary infection [13–19]. Injurious mechanical ventilation with high tidal volume might also augment lung inflammation and injury, with impairment of bacterial clearance [20]. However, the actuarial risk of pneumonia after 30 days of MV did not differ significantly between patients with and without ARDS (Figure 13.3) [3]. Therefore, the higher incidence of VAP observed in ARDS patients could essentially be the result of their need for a much longer duration of MV than other patients, thereby increasing the time during which they are at risk of developing VAP.

Causative Microorganisms of VAP in ARDS Patients

It is noteworthy that a large proportion of all VAP episodes in patients with ARDS is caused by or include at least one methicillin-resistant *Staphylococcus aureus* (MRSA) and/or a non-fermenting Gram-negative bacillus, such as *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* or *Acinetobacter baumannii* (Figure 13.4) [3–5]. Indeed, ARDS patients who develop microbiologically probable VAP frequently accumulate predisposing factors for an increased risk of infection caused by multiresistant pathogens, as demonstrated by several previous studies: most infections occur after the first week of mechanical ventilation, nearly all patients are receiving antimicrobial therapy (mostly broad-spectrum antibiotics) during the 15 days preceding the onset of VAP [21, 22]. In fact, the distribution pattern of microorganisms responsible for infection in ARDS patients is the same as that observed for non-ARDS patients who require prolonged (>7 days) mechanical ventilation and have been receiving antibiotics before the onset of infection, thereby further highlighting the observation

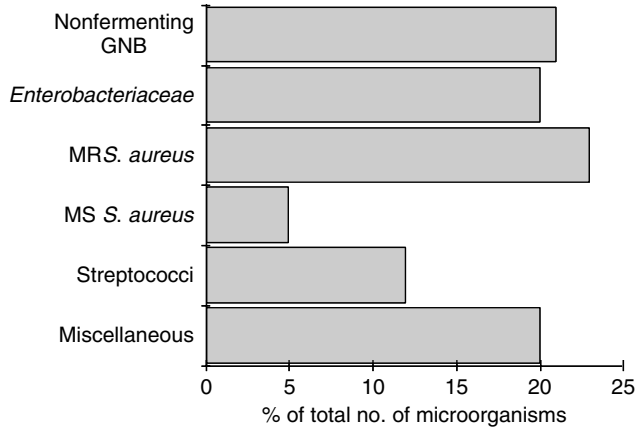

Figure 13.4
Bacteriology of infection in ARDS patients with nosocomial pneumonia (adapted from Chastre *et al.* [3]).

that the high incidence of multiresistant pathogens observed in ARDS patients is not so much the consequence of the peculiar type of the lung disease but probably more a reflection of the different kinetics of infection and different use of antimicrobial agents in the two populations. Clearly, the early administration of broad-spectrum antibiotics to ARDS patient could delay the onset of VAP by preventing early onset episodes and favoring the occurrence of late onset episodes due to multiresistant pathogens [9].

Mortality and Morbidity Owing to VAP in ARDS Patients

Patients without ARDS who develop microbiologically probable VAP have nearly a two-fold higher mortality rate when compared to non-pneumonia patients [9, 23]. Interestingly, in most studies of ARDS patients, investigators were unable to document the same increase in mortality, although many cases of VAP in this group of patients were due to multiresistant, difficult-to-treat pathogens. For example, in the study by Markowicz and colleagues, mortality rates were identical in ARDS patients with (28 of 49 patients, 57 %) and without (50 of 85 patients, 59 %) pulmonary infection ($p = 0.8$) [5]. Similar results were observed in other prospective cohort studies, as reported by Delclaux and colleagues, Meduri and colleagues and Chastre and colleagues [3, 4, 12]. One explanation for this paradoxical absence of VAP attributable mortality in patients with ARDS is that many patients die early, mostly because they have intractable shock with multiple organ failure and, therefore, have little opportunity to develop nosocomial pneumonia, rendering difficult the demonstration of an increase in VAP attributable mortality in ARDS patients.

In all studies, however, the total duration of MV was significantly longer for ARDS patients with microbiologically provable VAP than for other patients who did not acquire VAP, underlining the excess morbidity associated with this complication, as previously reported [3–5, 12]. For example, in the multicentre study reported by Markowicz and colleagues, the mean duration of mechanical ventilation for ARDS patients who did not develop pneumonia (11.3 ± 9.1 d) was the same as the mean duration of mechanical ventilation before the first episode of VAP for the patients who did develop pneumonia (11.7 ± 11.9 d; $p = 0.8$) [5]. However, the total time on mechanical ventilation was much longer for the patients with VAP (33 ± 21 d; $p < 0.0001$) (Figure 13.5). Similar findings were obtained when the analysis was restricted to the 56 patients who survived: the average total time on mechanical ventilation was 17 ± 12 d for surviving patients without pneumonia and 34 ± 15 d for surviving patients with VAP ($p < 0.001$).

Early recognition of factors predicting VAP treatment failure in patients with ARDS is of utmost importance, as they might contribute to improving outcomes of VAP. Among these factors, emphasis was recently shifted onto the role of appropriate initial empiric antibiotics [24, 25]. Nevertheless, improving the rates of appropriate initial antibiotics might be only one of the elements among a bundle of measures that might dramatically decrease adverse outcomes. Recent studies have attempted

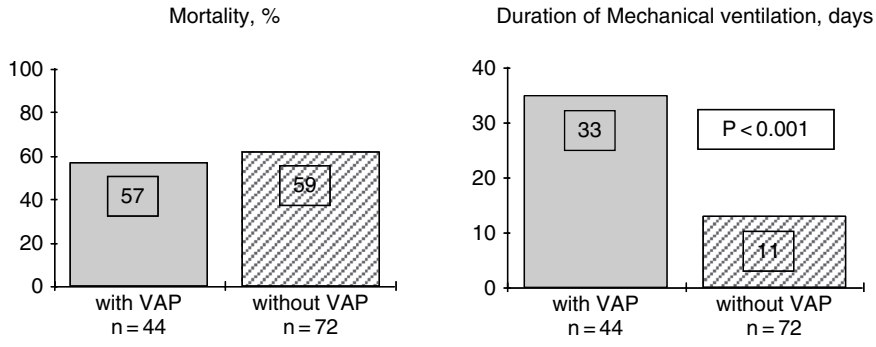

Figure 13.5
Overall mortality and duration of mechanical ventilation according to the presence or absence of VAP in 116 patints with ARDS (adapted from Markowicz *et al.* [5]).

to define the resolution pattern of VAP infectious parameters and to identify early factors predicting failure of VAP treatment in patients with or without ARDS [26, 27]. For example, Luna *et al.* [28] compared the evolution of the clinical pulmonary infection score (CPIS) and its components between survivors and nonsurvivors of 63 VAP episodes. After the development of VAP, the CPIS was significantly improved on Days 3 and 5 for survivors but not for nonsurvivors. Among the individual CPIS components, only PaO_2/FIO_2 distinguished between survivors and nonsurvivors. However, improved PaO_2/FIO_2 might be less useful for predicting outcomes of patients with severe lung damage. Indeed, when comparing the evolution of VAP episodes in patients with and without ARDS, Vidaur *et al.* [29] showed that VAP patients with ARDS took twice as long to become afebrile than those without, while hypoxemia and radiologic infiltrates persisted in both situations for a very long time.

The value of procalcitonin kinetics as a prognostic marker during VAP was recently investigated in a prospective, observational study [30]. Sixty-three consecutive patients with microbiologically proven VAP who survived three days after its diagnosis were included and grouped according to clinical outcome: favourable, or unfavourable, defined as death, VAP recurrence or extrapulmonary infection requiring antibiotics before Day 28. Serum procalcitonin and C-reactive protein concentrations decreased between Days 1 and 7 in both groups, but were significantly higher in patients whose outcomes would be unfavourable than in those with subsequent favourable outcome. To predict unfavourable outcome, a procalcitonin cut-off value of 0.5 ng/mL on Day 7 had a sensitivity of 90 % (95 % CI, 80–96 %) and a specificity of 88 % (95 % CI, 77–94 %), confirming data obtained in patients with severe sepsis [31]. Thus, serum procalcitonin level may provide an opportunity to change the treatment strategy early in the course of patients having developed VAP: either to intensify treatment when procalcitonin levels stay 'high', or to avoid unnecessary prolonged course of antibiotics when procalcitonin levels decrease rapidly.

In summary, results of the most studies indicate that microbiologically probable nosocomial pneumonia, as diagnosed by invasive bronchoscopy techniques, is really a common complication of ARDS and occurs far more frequently in this group of

patients than in other ventilated patients. The most probable explanation for this high incidence of VAP in this population is their need for a much longer period of mechanical ventilation, since the actuarial rate of pneumonia is similar for patients with and without the syndrome. Because ARDS patients are often treated very early with broad-spectrum antibiotics, infection is frequently delayed in time after the first week of mechanical ventilation and then mostly caused by methicillin-resistant *S. aureus* and other multiresistant organisms.

References

1. Bell, R.C., Coalson, J.J., Smith, J.D. and Johanson., W.G. (1983) Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med*, **99** (3), 293−8.
2. Sutherland, K.R., Steinberg, K.P., Maunder, R.J. *et al.* (1995) Pulmonary infection during the acute respiratory distress syndrome. *Am J Respir Crit Care Med*, **152** (2), 550−6.
3. Chastre, J., Trouillet, J.L., Vuagnat, A. *et al.* (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*, **157** (4 Pt 1), 1165−72.
4. Delclaux, C., Roupie, E., Blot, F. *et al.* (1997) Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: Incidence and diagnosis. *Am J Respir Crit Care Med*, **156** (4 Pt 1), 1092−8.
5. Markowicz, P., Wolff, M., Djedaini, K. *et al.* (2000) Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS study group. *Am J Respir Crit Care Med*, **161** (6), 1942−8.
6. Seidenfeld, J.J., Pohl, D.F.,Bell, R.C. *et al.* (1986) Incidence, site, and outcome of infections in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis*, **134** (1), 12−6.
7. Andrews, C.P., Coalson, J.J., Smith, J.D. and Johanson., W.G. (1981) Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury. *Chest*, **80** (3), 254−8.
8. Wunderink, R.G. (2000) Radiologic diagnosis of ventilator-associated pneumonia. *Chest*, **117** (4 Suppl 2), 188S−90S.
9. Chastre, J. and Fagon., J.Y. (2002) Ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **165** (7), 867−903.
10. Kirtland, S.H., Corley, D.E., Winterbauer, R.H. *et al.* (1997) The diagnosis of ventilator-associated pneumonia: A comparison of histologic, microbiologic and clinical criteria. *Chest*, **112** (2), 445−57.
11. Winer-Muram, H.T., Steiner, R.M., Gurney, J.W. *et al.* (1998) Ventilator-associated pneumonia in patients with adult respiratory distress syndrome: CT evaluation. *Radiology*, **208** (1), 193−9.
12. Meduri, G.U., Reddy, R.C., Stanley, T. *et al.* (1998) Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. *Am J Respir Crit Care Med*, **158** (3), 870−5.
13. Chollet-Martin, S., Jourdain, B., Gibert, C. *et al.* (1996) Interactions between neutrophils and cytokines in blood and alveolar spaces during ARDS. *Am J Respir Crit Care Med*, **154** (3 Pt 1), 594−601.
14. Lesur, O., Kokis, A., Hermans, C. *et al.* (2000) Interleukin-2 involvement in early acute respiratory distress syndrome: Relationship with polymorphonuclear neutrophil apoptosis and patient survival. *Crit Care Med*, **28** (12), 3814−22.

15. Chollet-Martin, S., Gatecel, C., Kermarrec, N. *et al.* (1996) Alveolar neutrophil functions and cytokine levels in patients with the adult respiratory distress syndrome during nitric oxide inhalation. *Am J Respir Crit Care Med*, **153** (3), 985−0.
16. Chollet-Martin, S., Montravers, P.,Gibert, C. *et al.* (1992) Subpopulation of hyperresponsive polymorphonuclear neutrophils in patients with adult respiratory distress syndrome. Role of cytokine production. *Am Rev Respir Dis*, **146** (4), 990−6.
17. Chollet-Martin, S., Montravers, P., Gibert, C. *et al.* (1993) High levels of interleukin-8 in the blood and alveolar spaces of patients with pneumonia and adult respiratory distress syndrome. *Infect Immun*, **61** (11), 4553−9.
18. Grenier, A., Combaux, D. and Chastre, J. *et al.* (2001) Oncostatin M production by blood and alveolar neutrophils during acute lung injury. *Lab Invest*, **81** (2), 133−41.
19. Martin, T.R., Rubenfeld, G.D., Ruzinski, J.T. *et al.* (1997) Relationship between soluble CD14, lipopolysaccharide binding protein, and the alveolar inflammatory response in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*, **155** (3), 937−44.
20. Ricard, J.D., Dreyfuss, D. and Saumon., G. (2003) Ventilator-induced lung injury. *Eur Respir J Suppl*, **42**, 2s−9s.
21. Rello, J., Gallego, M., Mariscal, D. *et al.* (1997) The value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **156** (1), 196−200.
22. Trouillet, J.L., Chastre, J., Vuagnat, A. *et al.* (1998) Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med*, **157** (2), 531−9.
23. Fagon, J.Y., Chastre, J., Vuagnat, A. *et al.* (1996) Nosocomial pneumonia and mortality among patients in intensive care units. *Jama*, **275** (11), 866−9.
24. Kollef, M.H., Sherman, G., Ward, S. and Fraser., V.J. (1999) Inadequate antimicrobial treatment of infections: A risk factor for hospital mortality among critically ill patients. *Chest*, **115** (2), 462−74.
25. Niederman, M.S., Craven, D.E., Bonten, M.J. *et al.* (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, healthcare-associated pneumonia. *Am J Respir Crit Care Med*, **171** (4), 388−416.
26. Dennesen, P.J., van der Ven, A.J., Kessels, A.G. *et al.* (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **163** (6), 1371−5.
27. Combes, A., Figliolini, C., Trouillet, J.L. *et al.* (2003) Factors predicting ventilator-associated pneumonia recurrence. *Crit Care Med*, **31** (4), 1102−7.
28. Luna, C.M., Blanzaco, D., Niederman, M.S. *et al.* (2003) Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med*, **31** (3), 676−82.
29. Vidaur, L., Gualis, B., Rodriguez, A. *et al.* (2005) Clinical resolution in patients with suspicion of ventilator-associated pneumonia: A cohort study comparing patients with and without acute respiratory distress syndrome. *Crit Care Med*, **33** (6), 1248−53.
30. Luyt, C.E., Guerin, V., Combes, A. *et al.* (2005) Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **171** (1), 48−53.
31. Harbarth, S., Holeckova, K., Froidevaux, C. *et al.* (2001) Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med*, **164** (3), 396−402.

14

Assessment of Patients with Poor Resolution of Hospital-Acquired Pneumonia

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Introduction

The development of nosocomial pneumonia as a significant threat to the hospitalised patient has become increasingly prevalent over recent decades [1,2]. Continuing changes in the microbial etiology and characteristics of the pathogens responsible for nosocomial pneumonia have led to a shift in the approach to management. Historically, strategies in the management of nosocomial pulmonary infections were targeted towards developing new antibiotic agents. Lack of new classes of antibiotics has more recently forced the emphasis to shift towards limiting duration of antibiotic therapy in attempts to prevent the emergence of multidrug resistant MDR pathogens [3].

Since the natural history of nosocomial pneumonia is still poorly understood, selection and duration of antibiotic therapy remains largely at the discretion of the individual physician. Inappropriate and/or ineffective antibiotic therapy is prevalent and, when it occurs, increases the threat to select for MDR pathogens. Failure to respond to initial empiric antimicrobial therapy represents a great diagnostic and therapeutic challenge, since both infectious and noninfectious etiologies can be responsible.

The majority of morbidity and mortality associated with hospital-acquired pneumonia (HAP) results from ventilator-associated pneumonias (VAP). The approach to

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VAP has gone through many changes in the decades since mechanical ventilation became routinely available. The initial focus was on developing new antibiotics to treat the dramatically broader spectrum of microorganisms causing pneumonia, in particular the increasing prevalence of Gram-negative bacteria. However, with each new antibiotic added to the antimicrobial armamentarium, bacteria counteracted with the development and propagation of effective resistance mechanisms. Physicians then responded with increasingly broad spectrum and potent antibiotics. This pattern of escalation continued until physicians began to realize that broad-spectrum therapy was not only costly but its injudicious use was actually increasing the incidence of MDR pathogens.

Management strategies in VAP then shifted towards improving diagnostic testing, with the naïve assumption that if the clinician could clearly define which patient had pneumonia, correct narrow-spectrum treatment based on antibiotic sensitivities of the cultured pathogen would follow logically. This ushered in the era of quantitative culture debates. A large number of studies attempted to define the operating characteristics of a variety of quantitative culture techniques. Ultimately, randomised trials of management based on different diagnostic criteria were required. While, at best, the debate regarding which diagnostic strategy remains unresolved, a common pattern to emerge was that minimizing antibiotic exposure leads to lower mortality. This benefit appears to be due to the prevention of subsequent infections with MDR microorganisms by antibiotic selective pressure [3,4]. This concept is a major emphasis of the new American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) guidelines for HAP management [5], as well as other management strategies.

Meanwhile, the emphasis in VAP management was shifting to the role effective initial empiric antibiotic therapy. Inappropriate initial empiric therapy is consistently associated with an increased mortality [4–6] despite the culture method used to determine appropriateness of therapy. While clearly important in improving outcome, appropriate initial empiric therapy alone may still not be sufficient to lead to a decrease in mortality. Even when inappropriate antibiotic therapy was decreased from 50 to $< 6\,\%$, no corresponding survival benefit was found in a before/after study [7].

Definition of Failure to Respond

The concept of nonresolving nosocomial pneumonia was originally described by Amberson in 1943. Generally, an appropriate response to therapy in the setting of nosocomial pneumonia is defined clinically or microbiologically [8]. Clinical markers such as resolution of fever, radiographic improvement ($> 50\,\%$ clearance following more than two weeks of therapy), resolution of leukocytosis, improvement in oxygenation, absence of progression to mechanical ventilator support and absence of the need to change antibiotic therapy within 48–72 hours of initiation of therapy project a favourable response [8,9]. Clinical parameters alone, however, are not sufficient to determine resolution from HAP. These limitations were demonstrated in one study where the mean time for complete resolution by clinical parameters alone was nine days [10].

More objective assessments have been attempted in several studies. The clinical pulmonary infection score (CPIS), developed to consolidate objective data and assign a scoring system that could be used for diagnosis of pneumonia, has been adapted to follow response to therapy. Studies looking at the application of this system, as originally designed by Pugin *et al.* [11], as well as modified versions of the system, have demonstrated a benefit of a more objective assessment in the response of nosocomial pneumonia to therapy. Singh *et al.* [3] demonstrated that, by limiting the course of empiric therapy for suspected nosocomial pneumonia based on changes in CPIS, development of subsequent infection with MDR pathogens could be lessened by 20%.

Epidemiology of Failure to Respond

Frequency of Failure to Respond

Currently, more than 40–60% of HAPs have an unfavourable outcome, defined as death, recurrence of pneumonia or extrapulmonary infection [12]. Similar numbers of nosocomial pneumonias demonstrate a failure to resolve following initial empiric antimicrobial treatment [13]. A large portion of the mortality associated with nonresolving nosocomial pneumonia occurs in VAP [14]. As many as 62% of patients with VAP diagnosed by quantitative culture criteria meets a set of objective criteria for failure to respond [15].

Pharmaceutical industry sponsored trials tend to have lower failure rates, probably because of selection bias against the most ill patients. However, in large trials, the clinical failure rates of now-standard antibiotic therapy for patients with MDR microorganisms may be as high as 40–50% [16–21]. Many of these studies, especially of Gram-negative VAP, mandated monotherapy for the antibiotic to be approved for the indication by the Food and Drug Administration (FDA). Conceivably, failure rates may have been lower with the use of combination therapy, although this is not necessarily true [5, 16].

Microbiologic Etiology in Failure to Respond

The predominant microorganisms associated with the failure of therapy are *Pseudomonas aeruginosa, Acinetobacter* species [12, 16, 18] and methicillin-resistant *Staphylococcus aureus* (MRSA) [18, 22–24]. The clinical failure rates for *Pseudomonas* VAP are commonly 50%, while 40% failure of therapy for MRSA VAP is the norm. In particular, recurrent *Pseudomonas* VAP after initial treatment occurs in a large percentage of patients [25–29]. Enterobacteriaceae with extended spectrum β-lactamases can also be a cause of antibiotic failure. *Acinetobacter* spp. are a problem in some institutions as well [30]. VAP due to very unusual microorganisms, such as *Stenotrophomonas, Burkholderia* or *Aspergillus,* more likely occurs in the setting of patients with various end-stage disease processes and multiple prior courses of antibiotics. While failure of therapy is common in patients infected with these pathogens, treatment failure itself is unlikely to affect the already dismal prognosis.

Table 14.1 Causes of failure to respond to antibiotics in VAP

Host factors
- Overt immunocompromise i.e. acute leukaemia, AIDS
- Acquired 'immunoparalysis'
- Genetic susceptibility

Bacterial factors
- Occult resistance/tolerance
- Acquired resistance
- Toxin production

Antibiotic factors
- Inadequate local levels
  - Abscess
  - Empyema
- Ineffective agents

Other infections
- Concomitant infections, i.e. sinusitis, catheter-related infections
- Complications, i.e Clostridium difficile colitis

Noninfectious
- Drug-induced fever
- ARDS/DAD
- Bronchiolitis obliterans
- Acute eosinophilic pneumonia
- Pulmonary haemorrhage

Interestingly, the spectrum of microorganisms associated with failure of therapy overlaps almost exactly with the spectrum of agents associated with inappropriate initial antibiotics. Therefore, one explanation for the lack of association between lowering the inappropriate initial therapy rate to $<6\%$ and improved survival is that, even though the antibiotics were appropriate, they were ineffective. Failure of antibiotic therapy is usually not an issue for non−MDR pathogens. If failure to respond does occur in this setting, it is likely to be due to noninfectious reasons or nosocomial superinfections (Table 14.1).

Noninfectious Etiology in Failure to Respond

Although the most common cause for nonresolving pneumonia is persistent or nosocomial superinfection, investigation must be directed towards one of a host of noninfectious causes, especially when evidence for infection is absent. In one study, up to two-thirds of ventilated patients with nonresolving nosocomial pneumonia were found to have noninfectious causes [31]. Noninfectious causes for nonresolving pneumonia have been reported to occur in as much as 16% of cases [15]. Noninfectious complications in mechanically ventilated patients can often be mistaken for antibiotic failure. Probably the most common are atelectasis, pulmonary edema and acute lung injury. Antibiotic and drug induced fever also contribute to the differential of nonresolving pneumonia since fever is the most common surrogate marker. Other

inflammatory disorders that either precipitated admission to the intensive care unit (ICU) in the first place or are complications occurring simultaneously with VAP, are often difficult to distinguish from VAP failure. A few examples are listed in Table 14.1.

Noninfectious etiologies for nonresolving pneumonias are less common in the non-ventilated patient. Organizing pneumonia, vasculitic processes and malignancy being the most common among non-ventilated patients (Table 14.1). Other simultaneously occurring inflammatory states that result in the patient's admission to the ICU can also be confused for nonresolution of nosocomial pneumonia.

Causes of Failure to Respond

Patient (Host) Related Factors

Specific populations, for example patients with various immunosuppressed states, chronic lung disease and acute respiratory distress syndrome (ARDS), are not discussed in this chapter. These patients represent a unique population that, in many cases, warrants a specialized approach to diagnosis and evaluation in the setting of nonresolving nosocomial pneumonia.

Critically ill, ventilated patients, on the other hand, also suffer from a type of immunocompromise state. One form of 'immunoparalysis' is seen in some patients after major trauma and sepsis where they are tolerant to endotoxin, as demonstrated by *in vitro* testing [32, 33]. Certain patients are more prone to nosocomial infections, since only a small percentage of all ventilated patients have a disproportionate number of nosocomial infections. One study found an average of more than 2.5 potential causes of fever in patients suspected of having VAP [34]. This susceptibility may result from underlying disease, therapeutic interventions or genetic predisposition. This concept has led some to believe that patients die *with* VAP rather than *from* VAP and that no attributable mortality exists for VAP alone [31]. A difference in mortality based on diagnostic testing [3, 4] or appropriate antibiotics [35] suggests that this contention is not completely true.

As tempting as it is to blame the patient, characteristics of the pathogens and of antibiotic therapy, the latter under control of the physician, can cause failure of therapy.

Microbiological Related Factors

Various forms of occult resistance can compromise the effectiveness of antimicrobial therapy. One is repressed chromosomal resistance genes, such as the chromosomal β-lactamase present in some *P. aeruginosa* and *Enterobacter* sp. If a culture is obtained prior to any β-lactam therapy, minimum inhibitory concentration (MIC) testing may suggest that the microorganism is sensitive to β-lactam antibiotics. However, once the patient is given a β-lactam, the gene is derepressed, allowing the microorganism to proliferate despite antibiotic. This derepression of an already

present resistance gene may be the explanation for the apparent rapid induction of resistance in some studies [18]. This 'acquired' resistance appears to have a higher associated mortality than if the resistance is present in initial susceptibility testing [36].

A second form of occult resistance has been described as heteroresistance. A large inocula of bacteria is likely to harbour a few mutant colonies that carry antibiotic resistance genes. Sensitivity testing in most clinical laboratories only assays the predominant phenotype. However, once antibiotic therapy suppresses or kills the more sensitive colonies, the resistant isolates may emerge. This phenomenon has been described for *S. aureus,* in which as many as 74 % may show unstable heteroresistance [37]. The frequency of documented heteroresistance in patients with recurrent or persistent MRSA bacteraemia is significantly increased [38].

Another form of occult resistance is tolerance. Antibiotic tolerance is defined as the ability of bacteria to survive but not proliferate in the presence of antibiotics. The exact definition of tolerance is debatable but a minimum bactericidal concentration (MBC)/MIC ratio of at least eight has been used. Clinical laboratory testing only uses the MIC, which would not be able to detect tolerant strains. Antibiotic tolerance is best described in Gram-positive bacteria such as the pneumococcus and *S. aureus* [39]. Tolerance is thought to occur in as many as 40 % of clinical isolates of MRSA.

The role of these latter two forms of occult antibiotic resistance may come into question with the recent information regarding quorum sensing and biofilms. Essentially, quorum sensing is the mechanism by which the number of like-bacteria in the same locale affects gene transcription and protein production, usually with a shift toward more invasive characteristics. One aspect of quorum sensing is the enhanced ability to incorporate new genes, including virulence or resistance genes.

An under-appreciated aspect of the bacterial armamentarium in VAP is toxin production by bacteria. This inattentiveness has changed recently with the emergence of a Panton–Valentine Leukocidin (PVL) toxin-producing strain of MRSA in the community [40]. Support for the role of toxin production in antibiotic failure of VAP also comes from a recent study of MRSA. Patients with antibiotic failure were more likely to be infected with a strain of MRSA that carries a mutant of the accessory group regulator (agr) II gene [41]. Carriage of this mutant and renal insufficiency were the only predictors of clinical failure in a multivariate analysis. This gene may also be responsible for some vancomycin heteroresistance [42].

Type III secretion in *Pseudomonas* pneumonias has also been associated with worse clinical outcome [43]. Many of the enzymes and toxins [44] released cause a necrotizing pneumonia and abscess formation, limiting antibiotic penetration. Many of the toxins secreted by microorganisms such as *P. aeruginosa* and *Aspergillus* sp. are vasoinvasive as well. The resultant thrombosis may lead to antibiotic failure because intravenous antibiotics cannot get to the site of infection.

Treatment Related Factors

By far, the most important antibiotic issue leading to the failure to respond in VAP is inadequate dosing. Given the high failure rate for VAP, maximum doses of antibiotics should be given in all cases due to MDRs [5]. Antibiotics used for VAP

are notoriously under-dosed. Unfortunately, not even the doses used in the original clinical trials that demonstrated benefit are used in many cases. This is particularly important for antibiotics with poor lung penetration, such as vancomycin [45] and aminoglycosides.

Suboptimal pharmacokinetics may also interfere with outcome of VAP treatment. Cell wall active agents, such as vancomycin and β-lactam antibiotics, typically depend on time above MIC for optimal killing. Frequent dosing and even continuous infusion may be optimal for these agents [46]. In contrast, fluoroquinolone and aminoglycoside killing is dose-dependent, suggesting that higher doses, less frequently would have better outcome. Use of single daily dose regimens of aminoglycosides is associated with lower toxicity with equal to better efficacy [47].

Inability to penetrate into the pleural space or abscess cavities is another reason for antibiotic failure [15]. The former requires a drainage procedure, while the latter may require locally instilled antibiotics.

Prolongation of antibiotic therapy for patients who do not seem to be responding appears to be a futile response [25]. If antibiotic therapy longer than eight days is needed of for an episode of VAP, the microorganism is likely to have developed antibiotic resistance or the drug is simply ineffective.

Diagnosis of Failure to Respond

Several studies have been performed to identify prognostic factors for poor resolution of nosocomial pneumonia. Identification of a clinical or biologic marker for nonresolution would potentially allow for more rapid modification of therapy, potentially improving outcomes.

Clinical Response

Several studies have examined the routine clinical parameters used by most clinicians to assess response to therapy. The median time for usual clinical parameters, such as fever and leukocytosis in patients with ultimately successful VAP treatment, was three days [10]. This means that 50 % or more take longer than three days to resolve, making these individually very unreliable predictors [9]. Several studies have suggested that the improvement in oxygenation is the most reliable criteria for distinguishing patients who are responding to antibiotic treatment from those who are not [9, 12].

Unfortunately, oxygenation is unreliable in patients with ARDS [48], a group of patients in which detecting the failure of antibiotic therapy is particularly crucial. In ARDS, only fever distinguished successful from poor response and time to become afebrile was delayed compared with non-ARDS patients. At Day 7−8 of treatment, when antibiotics for VAP should be stopped [5, 25], 35 % of ARDS patients with VAP were still febrile.

Clinical response is therefore helpful if oxygenation and fever improve quickly, that is by 72 hours. Unfortunately, clinical response does not distinguish between

failure of antibiotics and slow resolution. In addition, clinical response is not often valuable in determining the reason for failure to respond.

Microbiologic Response

Disappearance of bacteria from sputum cultures has been used to assess response [49]. Combined with clinical response, this is the most common method of assessing response to therapy in pneumonia, both clinically and for most FDA-registration trials. However, tracheal aspirates in intubated patients are unreliable because of persistent colonization, possibly due to viable bacteria embedded in the glycocalyx on the endotrachael tube [50]. Persistent positive cultures from tracheal aspirates can therefore occur despite complete resolution of the pneumonia. It has long been known that only 23 % of colonized patients subsequently develop nosocomial pneumonia [51]. Even semi-quantitative cultures take a prolonged time to clear in successfully treated patients [10].

Microbiological response by more accurate methods has only been used rarely. Most (85 %) of quantitative cultures of protected specimen brushes (PSB) are sterile after 72 hours of antibiotic therapy [24]. However, those that are not sterile are more likely to have a poor outcome. Serial bronchoscopic cultures have the advantage that it is possible to exclude pneumonia as the cause of poor response and to separate nosocomial superinfection from persistence of the original infection [25]. Nonbronchoscopic bronchoalveolar lavage (BAL) and PSB have also been performed serially to detect antibiotic failure and also to correlate with outcome, often clarifying response earlier than clinical parameters [52].

Biochemical Response

Molecular markers may also be used as an alternative or to supplement clinical response. Several markers have been proposed, such as procalcitonin, interleukin (IL)-6 levels [15], C-reactive protein and soluble triggering receptor expressed on myeloid cells (sTREM) [53, 54]. One multivariate analysis demonstrated that the presence of an elevated serum IL-6 level on Day 1 was predictive of nonresponse to treatment [15]. Elevated procalcitonin levels not only reflect the presence of VAP but also function as a marker for disease severity. VAP survivors have a significantly lower serum concentration of procalcitonin during the clinical course of VAP than nonsurvivors. The procalcitonin level at Day 3 of therapy discriminates between clinical success and failure of VAP, with an area under the receiver operating curve (ROC) of 0.87 [12].

Unfortunately, none of the markers is specific for VAP and most will be elevated in sepsis [55], ARDS and other proinflammatory disorders common to VAP patients. Therefore, while a persistently high level may indicate that problems exist, the elevated marker may be caused by other infections or causes of inflammation as well. Procalcitonin has been associated with other bacterial infections but not with nonbacterial infections or other inflammatory states not related to infection. Further testing would be needed to define the cause of persistent mediator activation [15].

Management of Failure to Respond

Clinical failure is consistently associated with increased mortality from VAP, particularly in non-ARDS patients [9, 24, 48]. Heightened awareness of the frequency of antibiotic failure is the first step in management. Quantitative cultures (prior to any antibiotic change) are more reliable than nonquantitative tracheal aspirates in sorting out the possibility of persistence of the original pathogen versus colonization versus superinfection pneumonia. An aggressive workup of alternative sites of infection, including antibiotic induced colitis, line sepsis and sinusitis is warranted. Chest computerised tomography may be helpful in excluding empyema or lung abscess as the cause of failure. Prospective trials are clearly needed to determine if, when criteria for failure are met (clinical, microbiological, molecular or a combination), a diagnostic or treatment algorithm leads to improved outcome. Clearly, appropriate diagnostic testing is needed to avoid 'spiralling empiricism' [56].

Treatment strategies are even more difficult once antibiotic failure is diagnosed. For MRSA persistence, linezolid appears to be more effective than standard dose vancomycin [35] and can be used for salvage therapy [57]. For *Pseudomonas* VAP, switching to a different treatment [16] combination or addition of aerosolised antibiotics may be the only alternative [5, 58].

Conclusions

Failure to respond to antibiotic therapy is a common problem in nosocomial pneumonia and presents a continuing diagnostic and therapeutic challenge. The causes may be infectious as well as noninfectious in etiology. Ineffective antibiotics or a variety of factors influencing either host defence or microorganism pathogenicity are likely to contribute to the complexity of the management. The diagnosis of antibiotic failure and distinguishing failure from superinfection or noninfectious mimics is difficult because clinical criteria alone are inadequate. The appropriate diagnostic strategy and treatment algorithms have not been fully addressed and more research is clearly needed.

References

1. Richards, M.J. *et al*. (1999) Nosocomial infections in medical intensive care units in the United States. National nosocomial infections surveillance system. *Crit Care Med*, **27** (5), pp. 887–92.
2. Tablan, O.C. *et al*. (2004) Guidelines for preventing healthcare-associated pneumonia, 2003: Recommendations of CDC and the healthcare infection control practices advisory committee. *MMWR Recomm Rep*, **53** (RR-3), pp.1–36.
3. Singh, N. *et al*. (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med*, **162** (2 Pt 1), pp. 505–11.

4. Fagon, J.Y. *et al*. (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med*, **132** (8), pp. 621–30.
5. Guidelines for the management of adults with hospital-acquired, ventilator-associated, healthcare-associated pneumonia. *Am J Respir Crit Care Med*, 2005, **171** (4), pp. 388–416.
6. Rello, J. *et al*. (1997) The value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **156** (1), pp. 196–200.
7. Ibrahim, E.H. *et al*. (2001) Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med*, **29** (6), pp. 1109–15.
8. Luna, C.M. and Niederman, M.S. (2002) What is the natural history of resolution of nosocomial pneumonia. *Semin Respir Crit Care Med*, **23** (5), pp. 471–9.
9. Luna, C.M. *et al*. (2003) Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med*, **31** (3), pp. 676–82.
10. Dennesen, P.J. *et al*. (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **163** (6), pp. 1371–5.
11. Pugin, J. *et al*. (1991) Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis*, **143** (5 Pt 1), pp. 1121–9.
12. Luyt, C.E. *et al*. (2005) Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **171** (1), pp. 48–53.
13. Alvarez-Lerma, F. (1996) Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-acquired pneumonia study group. *Intensive Care Med*, **22** (5), pp. 387–94.
14. Arancibia, F. *et al*. (2000) Antimicrobial treatment failures in patients with community-acquired pneumonia: Causes and prognostic implications. *Am J Respir Crit Care Med*, **162** (1), pp. 154–60.
15. Ioanas, M. *et al*. (2004) Causes and predictors of nonresponse to treatment of intensive care unit-acquired pneumonia. *Crit Care Med*, **32** (4), pp. 938–45.
16. Brun-Buisson, C. *et al*. (1998) Treatment of ventilator-associated pneumonia with piperacillin–tazobactam/amikacin versus ceftazidime/amikacin: A multicenter, randomized controlled trial. VAP study group. *Clin Infect Dis*, **26** (2), pp. 346–54.
17. Fagon, J. *et al*. (2000) Treatment of Gram-positive nosocomial pneumonia. Prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial pneumonia group. *Am J Respir Crit Care Med*, **161** (3 Pt 1), pp. 753–62.
18. Fink, M.P. *et al*. (1994) Treatment of severe pneumonia in hospitalised patients: Results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem–cilastatin. The severe pneumonia study group. *Antimicrob Agents Chemother*, **38** (3), pp. 547–57.
19. Shorr, A.F. *et al*. (2005) Levofloxacin for treatment of ventilator-associated pneumonia: A subgroup analysis from a randomized trial. *Clin Infect Dis*, **40**Suppl 2, p. S123–9.
20. Wunderink, R.G. *et al*. (2003) Continuation of a randomized, double-blind, multicenter study of linezolid versus vancomycin in the treatment of patients with nosocomial pneumonia. *Clin Ther*, **25** (3), pp. 980–92.
21. Zanetti, G. *et al*. (2003) Cefepime versus imipenem–cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: A multicenter, evaluator-blind, prospective, randomized study. *Antimicrob Agents Chemother*, **47** (11), pp. 3442–7.
22. Fagon, J.Y. *et al*. (1993) Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. *Am J Med*, **94** (3), pp. 281–8.

23. Lowenkron, S.E. and Niederman, M.S. (1992) Definition and evaluation of the resolution of nosocomial pneumonia. Semin Respir Infect, **7** (4), pp. 271−81.
24. Montravers, P. *et al*. (1993) Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. *Am Rev Respir Dis*, **147** (1), pp. 38−44.
25. Chastre, J. *et al*. (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: A randomized trial. *Jama*, **290** (19), pp. 2588−98.
26. Crouch Brewer, S. *et al*. (1996) Ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. *Chest*, **109** (4), pp. 1019−29.
27. Rello, J. *et al*. (1998) Recurrent *Pseudomonas aeruginosa* pneumonia in ventilated patients: Relapse or reinfection. *Am J Respir Crit Care Med*, **157** (3 Pt 1), pp. 912−6.
28. Silver, D.R., Cohen, I.L. and, Weinberg, P.F. (1992) Recurrent *Pseudomonas aeruginosa* pneumonia in an intensive care unit. *Chest*, **101** (1), pp. 194−8.
29. Talon, D. *et al*. (1998) Risks and routes for ventilator-associated pneumonia with *Pseudomonas aeruginosa*. *Am J Respir Crit Care Med*, **157** (3 Pt 1), pp. 978−84.
30. Rello, J. *et al*. (1999) Variations in etiology of ventilator-associated pneumonia across four treatment sites: Implications for antimicrobial prescribing practices. *Am J Respir Crit Care Med*, **160** (2), pp. 608−13.
31. Timsit, J.F. *et al*. (1996) Mortality of nosocomial pneumonia in ventilated patients: Influence of diagnostic tools. *Am J Respir Crit Care Med*, **154** (1), pp. 116−23.
32. Peters, M. *et al*. (1999) Acquired immunoparalysis in paediatric intensive care: Prospective observational study. *Bmj*, **319** (7210), pp. 609−10.
33. Wolk, K. *et al*. (1999) Comparison of monocyte functions after LPS − or IL-10-induced reorientation: Importance in clinical immunoparalysis. *Pathobiology*, **67** (5−6), pp. 253−6.
34. Meduri, G.U. *et al*. (1994) Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest*, **106** (1), pp. 221−35.
35. Wunderink, R.G. *et al*. (2003) Linezolid vs vancomycin: Analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest*, **124** (5), pp. 1789−97.
36. Carmeli, Y. *et al*. (1999) Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: Comparison of risks associated with different antipseudomonal agents. *Antimicrob Agents Chemother*, **43** (6), pp. 1379−82.
37. Plipat, N. *et al*. (2005) Unstable vancomycin heteroresistance is common among clinical isolates of methiciliin-resistant *Staphylococcus aureus*. *J Clin Microbiol*, **43** (5), pp. 2494−6.
38. Khosrovaneh, A. *et al*. (2004) Frequency of reduced vancomycin susceptibility and heterogeneous subpopulation in persistent or recurrent methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*, **38** (9), pp. 1328−30.
Tuomanen, E. *et al*. (1988) Microbiological and clinical significance of a new property of defective lysis in clinical strains of pneumococci. *J Infect Dis*, **158** (1), pp. 36−43.
40. Fridkin, S.K. *et al*. (2005) Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med*, **352** (14), pp. 1436−44.
41. Moise-Broder, P.A. *et al*. (2004) Accessory gene regulator group II polymorphism in methicillin-resistant *Staphylococcus aureus* is predictive of failure of vancomycin therapy. *Clin Infect Dis*, **38** (12), pp. 1700−5.
Sakoulas, G. *et al*. (2003) *Staphylococcus aureus* accessory gene regulator (agr) group II: Is there a relationship to the development of intermediate-level glycopeptide resistance. *J Infect Dis*, **187** (6), pp. 929−38.
43. Hauser, A.R. *et al*. (2002) Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. *Crit Care Med*, **30** (3), pp. 521−8.

44. Schulert, G.S. *et al*. (2003) Secretion of the toxin exou is a marker for highly virulent *Pseudomonas aeruginosa* isolates obtained from patients with hospital-acquired pneumonia. *J Infect Dis*, **188** (11), pp. 1695–706.
45. Lamer, C. *et al*. (1993) Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. *Antimicrob Agents Chemother*, **37** (2), pp. 281–6.
46. Wysocki, M. *et al*. (1995) Comparison of continuous with discontinuous intravenous infusion of vancomycin in severe MRSA infections. *J Antimicrob Chemother*, **35** (2), pp. 352–4.
47. Nicolau, D.P. *et al*. (1995) Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*, **39** (3), pp. 650–5.
48. Vidaur, L. *et al*. (2005) Clinical resolution in patients with suspicion of ventilator-associated pneumonia: A cohort study comparing patients with and without acute respiratory distress syndrome. *Crit Care Med*, **33** (6), pp. 1248–53.
49. Schentag, J.J. (1990) Correlation of pharmacokinetic parameters to efficacy of antibiotics: Relationships between serum concentrations, MIC values, bacterial eradication in patients with Gram-negative pneumonia. *Scand J Infect Dis Suppl*, **74**, pp. 218–34.
50. Sottile, F.D. *et al*. (1986) Nosocomial pulmonary infection: Possible etiologic significance of bacterial adhesion to endotracheal tubes. *Crit Care Med*, **14** (4), pp. 265–70.
51. Johanson, W.G. Jr *et al*. (1972) Nosocomial respiratory infections with Gram-negative bacilli. The significance of colonization of the respiratory tract. *Ann Intern Med*, **77** (5), pp. 701–6.
52. Garrard, C.S. and A'Court, C.D. (1995) The diagnosis of pneumonia in the critically ill. Chest, **108** (2 Suppl), p. 17S–25S.
53. Gibot, S. *et al*. (2005) Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis. *Crit Care Med*, **33** (4), pp. 792–6.
54. Gibot, S. *et al*. (2004) Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. *N Engl J Med*, **350** (5), pp. 451–8.
55. Gibot, S. *et al*. (2005) Surface triggering receptor expressed on myeloid cells 1 expression patterns in septic shock. *Intensive Care Med*, **31** (4), pp. 594–7.
56. Kim, J.H. and Gallis, H.A. (1989) Observations on spiraling empiricism: Its causes, allure, and perils, with particular reference to antibiotic therapy. *Am J Med*, **87** (2), pp. 201–6.
57. Moise, P.A. *et al*. (2002) The efficacy and safety of linezolid as treatment for *Staphylococcus aureus* infections in compassionate use patients who are intolerant of, or who have failed to respond to, vancomycin. *J Antimicrob Chemother*, **50** (6), pp. 1017–26.
58. Brown, R.B. *et al*. (1990) Double-blind study of endotracheal tobramycin in the treatment of Gram-negative bacterial pneumonia. The endotracheal tobramycin study group. *Antimicrob Agents Chemother*, **34** (2), pp. 269–72.

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Approach to Patients with Recurrent Ventilator-Associated Pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) is the most frequent intensive care unit (ICU) acquired infection among patients under mechanical ventilation (MV), as noted elsewhere in this book [1]. Mortality attributed to VAP is approximately 30% depending on the pathogen isolated [2,3], especially when initial antibiotic therapy is inappropriate [4]. VAP also increases both length of stay in the ICU and duration of MV [5–7], raising significantly the costs in the ICU.

Despite an enormous amount of research and many official statements, the diagnosis and treatment of VAP remain problematic. As patients with endotracheal tubes are often colonized with bacteria that are not necessarily associated with pneumonia [8], the key issue is how to distinguish colonization from infection of the lung parenchyma. It should not be surprising then that differentiating between a primary episode of VAP and a second episode is even more controversial.

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VAP is usually diagnosed using a combination of clinical, radiographic and microbiological criteria with a high sensitivity but low specificity. As a result, antibiotics are probably often prescribed unnecessarily, leading to adverse side effects in patients and further favouring the selection and induction of multidrug resistant (MDR) pathogens. The addition of quantitative cultures of samples obtained with bronchoscopic techniques increases specificity and may decrease unnecessary antibiotic use [9]. Chest radiographs are considered of limited value for defining clinical improvement in patients with pneumonia [10], although rapidly deteriorating abnormalities are suggestive of recurrent episodes of VAP.

When then is an episode of VAP considered a new infection rather than failure of treatment of an existing one? In cases where there are clinical features of increasing pulmonary sepsis, a new pathogen is identified or the infiltrate occurs in a distinctly separate region of the lung it is relatively straightforward. When a new pathogen is identified this is usually referred to as a superinfection [11–14].

More difficult is distinguishing between recurrence when therapy is ceased (relapse) because of the failure to eradicate the pathogen(s) causing VAP by the end of antibiotic therapy, and recurrence of infection in the same area of lung as the initial episode when the same pathogen is involved (re-infection). Molecular typing of the different isolates from patients with multiple episodes of VAP can differentiate between relapse and reinfection but is not routinely available in many clinical settings. Demonstration of a change in antibiotic sensitivities is suggestive of re-infection rather than relapse but as this is known to occur during antibiotic therapy, especially for *Pseudomonas* spp., it cannot be considered definitive proof of a new infection.

The pathogenesis of recurrent VAP is in many respects the same as in primary VAP. It requires repetitive bacterial colonization of the tracheobronchial tree and aspiration of contaminated secretions into the lower airway. Endotracheal tubes facilitate both processes through mucosal injury, pooling of contaminated secretions above the endotracheal tube cuff and abolition of the cough reflex. Moreover, it is suspected that infection of the biofilm on the inner surface of the endotracheal tube could be a source for recurrent seeding of pathogenic bacteria into the lungs, causing recurrent VAP. It has been shown that some microorganisms can adhere to the surface of the endotracheal tube and exude an exopolysaccharide that acts as a slime-like adhesive. Bacteria encased in this matrix are highly resistant to the effects of antimicrobials and host defences [15–17]. In addition, several studies have shown that the exopolysaccharide can prevent penetration of antibiotics into the biofilm [17, 18]. It remains unclear whether this represents a source of infection or contamination. A recent study showed that endotracheal tubes removed from patients with VAP are covered with biofilm more frequently than those of uninfected controls [19]. Bacterial biofilm, however, may play an important role in recurrent pulmonary infections [20–22].

An appreciation of the role of biofilms in the development of VAP has resulted in the experimentation with novel approaches aimed at limiting biofilm formation, such as biomaterial surface modification and deposition of anti-adherent coatings to reduce the adherent potential of microorganisms to the endotracheal tube [15].

Unfortunately, it is not clear whether these technologies influence the adherence of airway secretions on the surface of endotracheal tubes [23].

Epidemiology of Recurrent VAP

Several studies have tried to determine the incidence and etiology of recurrent VAP with different conclusions. Recently, Combes *et al.* reported a VAP recurrence rate of 23 % overall, with a higher rate (27 %) among the survivors [11]. Other groups have documented recurrent VAP rates in 15−30 % of cases, with most cases developing at least two weeks after the onset of the first episode. Clearly, recurrent VAP is a common problem in patients requiring prolonged MV.

The microorganisms most frequently isolated in recurrent VAP episodes are nonfermenting Gram-negative bacilli (NF−GNB) like *Pseudomonas aeruginosa, Acinetobacter* and *Stenotrophomonas maltophilia,* and streptococci [11]. Clinical responses to therapy for VAP occur within the first six days of therapy; endotracheal colonization with Gram-negative bacteria persists despite susceptibility to therapy and acquired colonization usually occurs in the second week of therapy, frequently preceding a recurrent episode.

Pseudomonas aeruginosa is the main pathogen involved in recurrent VAP episodes. A major reason for the high prevalence of *P. aeruginosa* infections in patients with VAP worldwide is the difficulty in eradicating it from compromised airways. Niederman *et al.* [8] have reported that colonization with *P. aeruginosa* is often prolonged. Dennesen *et al.* [24] also demonstrated that *P. aeruginosa* was more difficult to eradicate than other pulmonary pathogens in patients with VAP, even though patients were on adequate therapy. Persistent or recurrent episodes of pneumonia are common [3, 14], especially in patients with acute respiratory distress syndrome (ARDS) [14]. A recurrent episode of VAP, caused by *P. aeruginosa,* may result from persistent colonization, acquired colonization from exogenous sources, or selection of endogenous colonization. Rello and coworkers recently described using molecular biotyping to determine that recurrent episodes of *P. aeruginosa* VAP are due to the persistence of strains rather than new infection [14]. In addition, this bacteria is the most frequently isolated pathogen in MV patients with respiratory superinfections [25].

Pseudomonas aeruginosa is also known to produce exopolysaccharide and generate the complex biofilm structure, which allows adhesion to abiotic surfaces and protection against antibiotic action [19, 20, 23]. This pathogen also has many virulence factors that appear to facilitate lung infection [26]. The most important are a family of secreted exotoxins (ExoS, ExoT, ExoU and ExoY) that are injected directly into the cytoplasm of host cells, using the type III secretion system [27]. The presence of type III exotoxins is associated with increased mortality [28, 29]. The strains expressing ExoU appeared to have the greatest virulence. Although increasing MDR continues to complicate therapy, the pathogenicity of *P. aeruginosa* appears to be related mainly to its toxin repertoire [28].

Risk Factors for Recurrent VAP

In mechanically ventilated patients, a number of factors compromise normal host defence mechanisms. Additionally, critical illness, comorbidities [30] and malnutrition [31] negatively impact the ability of the immune system to respond effectively. Once a patient is intubated and goes under MV, the airway loses sterility and becomes colonized within hours [32].

Factors associated with recurrence or superinfection may be host dependent (severe underlying condition), bacteria dependent (highly resistant nosocomial bacteria) or treatment dependent (poor tissue diffusion or inappropriateness of antibiotic treatment and/or its duration). Indeed, the optimal duration of antibiotic therapy for VAP has not been clearly determined. A recent study demonstrated that three days of antibiotics may be sufficient for patients suspected of having VAP [33]. Other work has shown that the application of clinical guidelines for the treatment of VAP increased the initial administration of adequate antimicrobial treatment, decreased the overall duration of antibiotic treatment and was associated with fewer recurrences [34]. Interestingly, Dennesen *et al.* reported that infection variables showed significant resolution within the first six days of appropriate antibiotic therapy [24]. Evolution variables during the first week of VAP treatment might be predictive of VAP recurrence.

Unlike those for primary VAP, specific factors associated with VAP recurrence have scarcely been described in the literature and the few reports published focused only on *P. aeruginosa* VAP recurrence [3, 14, 35]. Combes and colleagues found that the radiological score >7, the persistence of fever and the presence of ARDS and MV on Day 8 were associated with recurrent VAP [11]. These factors were linked to the severity of lung injury and persistence of fever, but not to first-episode pathogen(s), although a higher frequency of relapses was noted for a first episode involving NF−GNB [11]. A strategy for selecting the duration of antibiotic treatment based only on the microbiology of the initial episode may not be optimum. Evaluating the severity of lung injury after eight days of treatment may, therefore, contribute more to optimising treatment duration than knowing the type of bacteria responsible for the first episode.

Silver and coworkers [35] demonstrated that recurrence of *Pseudomonas* VAP was associated with chronic pulmonary disease and with higher Acute Physiology and Chronic Health Evaluation II scores at the end of the first episode. However, only the presence of ARDS was associated with VAP recurrence in a study developed by Rello *et al.* [14]. ARDS increases the occurrence of nosocomial pneumonia in ventilated patients and bacteria grown in this setting are frequently highly antibiotic resistant [11].

Several studies have shown that alveolar macrophages and polymorphonuclear cells retrieved from the lungs of patients with ARDS have impaired phagocytic function and a lower capacity to express maximum activity after *ex vivo* stimulation by bacterial products than do corresponding cells from normal subjects, which could explain why these patients are at high risk of presenting recurrent pulmonary infections [36, 37]. This phenomenon is most likely part of the immunoparalysis or compensatory anti-inflammatory response syndrome discussed below.

Development of clinical recurrences may be associated more with patient related risk factors, such as interference with host defence mechanisms, rather than with pathogen related factors. Further studies should explore the molecular mechanisms that account for persistent colonization, since it should be possible to intervene in the factors mediating clonal persistence to eliminate such recurrent infections.

Clinical Impact and Prognosis of Recurrent VAP

VAP is the most frequently ICU nosocomially acquired infection in patients on MV [5, 25, 38] and is associated with prolonged hospital stay and higher ICU mortality [2, 39]. Patients with recurrent VAP have a greater mortality than those with single episodes, even when caused by the same microorganism. Combes *et al.* reported that recurrence significantly prolonged durations of MV, ICU and hospital stays after the onset of the first VAP episode. ICU mortality was also higher for patients with VAP recurrence [11].

The inability to reduce the bacterial burden from the lower respiratory tract within the first few days of therapy for VAP is associated with increased mortality [40]. Some bacteria are particularly difficult to eradicate, principally *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). Therefore, it is likely that patients with these highly resistant organisms may have an increased attributable mortality [2, 41−43]. Whether the increased severity associated with *P. aeruginosa* or MRSA infection is related to host factors or to a putative increased virulence of these strains remains unsettled.

Considering VAP due to *P. aeruginosa,* several studies have tried to describe the pathogenicity of this bacterium. Higher mortality rates appear to be related mainly to its toxin mechanisms. Indeed, metallo-β-lactamases (MBLs) are emerging enzymes that hydrolyse virtually all β-lactams; data from Zavascki *et al.* have recently shown that MBL-*Pseudomonas aeruginosa* VAP is associated with higher mortality rates [44].

P. aeruginosa isolates able to secret type III proteins are of increased virulence, and pulmonary infections caused by these strains are associated with higher mortality and high recurrence rates [28, 45]. This finding has important clinical implications, as patients infected with type-III-secreting strains would possibly benefit from more aggressive and prolonged antibiotic therapy. The development of diagnostic assays to determine which *P. aeruginosa* isolates secrete type III proteins may be useful to identify the subgroup of patients likely to benefit from passive immune therapy directed against the type III system. In fact, vaccines targeted against components of the type III secretion system are likely to be effective in humans. Although such vaccines do not prevent *P. aeruginosa* VAP, they may significantly reduce the morbidity and mortality associated with severe disease.

A number of investigators have searched for prognostic markers that can rapidly and reliably distinguish patients who will have favourable or unfavourable outcomes from VAP. Several studies showed that clinical and biologic parameters evolved differently for patients with or without recurrent VAP, but the parameters chosen

proved not to be predictive of outcome [13]. Early identification of patients at high risk of VAP recurrence may enable a change in the treatment strategy to improve outcome.

Recently, Duflo and colleagues reported that serum procalcitonin could be used as a complementary diagnostic marker of VAP and that its serum levels were higher in nonsurvivors than survivors [46]. Luyt *et al.* found that patients with VAP who developed recurrent episodes had higher levels of procalcitonin throughout their ICU stay when compared with patients with favourable outcomes [13]. Serum procalcitonin levels may therefore be useful in stratifying patients with VAP and may provide an early indicator of outcome. However, further studies are still required to establish the role of procalcitonin as an adjunct to clinical assessment.

Prevention Measures

Recurrent VAP is associated with prolonged hospitalisation and higher mortality rates [11]. As a result, a primary goal of clinicians should be to prevent VAP, and especially prevent a recurrence after a primary episode. While the most obvious intervention is the earliest possible removal of mechanical ventilation, even the most aggressive weaning protocols cannot change the fact that this is not physiologically possible in a large number of patients. General principles for preventing the immunocompromised state associated with recurrent VAP include adequate source control of an initial infection, avoiding the immunosuppressive effects of repetitive blood transfusion [47] and attention to adequate nutrition in the critically ill.

Specific strategies aimed at preventing recurrent VAP usually focus on reducing the burden of bacterial colonization in the aerodigestive tract, decreasing the incidence of aspiration. To reverse the increasing rates of antimicrobial resistance, more effective strategies for using antibiotics have been advocated. For example, changing or rotating the antibiotic classes used for treating infections may reduce the rates of VAP caused by MDR pathogens [48].

Tracheal colonization with MDR pathogens frequently occurs during the second week of antibiotic therapy in patients with VAP. Therefore, it can be hypothesized that a shorter duration of therapy would reduce the selective pressure for colonization and the risks of recurrent infection with MDR pathogens [24]. Ibrahim and colleagues observed that shortening antibiotic treatment to seven days was associated with fewer recurrent episodes [34]. Therefore, eliminating or reducing the unnecessary use of antibiotics should be the primary goal in prevention [49].

Just as they hold some promise for reducing primary VAP, silver-coated endotracheal tubes may reduce recurrent VAP by reducing colonization and biofilm formation [50]. In a randomised multicentre feasibility study [51] a reduced burden of bacterial airway colonization was demonstrated; further studies are required to see whether these devices will provide clinically relevant protection in general use.

Determining whether subsequent episodes of VAP are reinfection or relapse may also alter the preventative strategy. As reported by Rello *et al.* [14], if there is considerable reinfection as a result of continuing transmission of an exogenous strain,

traditional infection control measures should be reinforced. In contrast, if there are relapses, the focus of control should be based on the early identification and eradication of airway colonization of persistent carriers.

Immunoparalysis

Given that tracheal colonization almost always occurs before VAP develops [52], yet only a third of colonized patients develop pneumonia, suggests that other patient factors, such as altered immunity, must be present. Moreover, most nosocomial infections occur in a subgroup of critically ill patients suffering multiple synchronous and sequential infections.

Immunoparalysis, also known as post-sepsis immunodepression, endotoxin tolerance or compensatory anti-inflammatory response syndrome (CARS), is a phenomenon that has been recognized for decades. Beginning with descriptions of impaired Mantoux tests after major burns [53], it became appreciated that a major factor in the development of nosocomial infections, including VAP, is the reduced immunity to infection that follows any major inflammatory response [54, 55]. Immunoparalysis is characterized mainly by impaired expression of the monocytic major histocompatibility complex class II, leading to impairment of cellular immunity [56–58]. Neutrophil defects including impaired bactericidal activity are also well described [59].

Studies on the pathogenesis of immunoparalysis have demonstrated that interleukin-10 (IL-10) is a major driver of immunoparalysis [57], but as blocking IL-10 does not stop experimental immunoparalysis [60] other mechanisms are clearly important. Other cytokines thought to be key drivers of immunoparalysis are interleukin-13 and transforming growth factor beta [61] but the complete pathogenesis is still far from fully understood.

The current ‘gold standard’ for the quantification of immunoparalysis is the response of whole blood or peripheral blood mononuclear cells (PBMCs) to lipopolysaccharide (LPS, also known as endotoxin) [62, 63]. Expression of human lymphocyte associated class II (HLA II) proteins has also been used as a surrogate marker for immunoparalysis, with some correlation between the absolute reduction in HLA II expression and the time to recovery of HLA II expression and the subsequent risk of nosocomial infection [64–66], although this may not be as accurate as LPS stimulation studies [67]. The pattern of HLA II expression also correlates well with the concept of a temporary immune dysfunction predisposing to nosocomial infections. In survivors, HLA II levels normalize within the first week. Conversely, subsequent infections seem to blunt the recovery of HLA–DR expression [68], setting up a vicious cycle of one infection leading to an increased risk of recurrent infections. Whether measuring the degree of immunoparalysis, by HLA II expression or some other means, moves from a research setting into routine clinical practice depends on whether effective strategies to reverse it can be developed.

Another factor likely to be contributing to whether patients have recurrent episodes of VAP or not is genetic predisposition.The strong inheritable risk of infection is

well documented and a number of specific genetic polymorphisms in important components of the host's response to infection have been associated with an increased risk of infection [69].While some of these polymorphisms are likely to interfere with the ability to recognize bacterial antigens (such as those in mannose binding lectin [70] or the immunoglobulin-G2 receptor [71]),others may even contribute to the duration or severity of immunoparalysis (such as those in IL-10 [72] or interferon gamma (IFN-γ)[73]).It is easy to envisage that the combination of impaired antigen presentation secondary to immunoparalysis combined with a genetic background of reduced innate immune response could lead to a very high risk of recurrent VAP.Future research will hopefully delineate the impact of genetic differences on immune response in patients with VAP, but at present the knowledge that any specific mutation is carried is yet to find a clinical use.

Potential Immunomodulatory Strategies

Given the undoubted contribution of immunoparalysis to recurrent infections in critically ill patients, some form of treatment to reverse immunological defects is obviously attractive. Immunomodulatory therapy could be aimed either at reducing the risk of acquiring infection or improving treatment once VAP is established. While there are no specific data in the setting of recurrent VAP, a number of obvious candidates, including granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF) and INF-γ have been studied in critically ill patients and the findings are highly relevant.

G-CSF is one of a family of glycoproteins that controls haematopoyesis [74]. G-CSF has a significant affect on polymorphonuclear cell (PMN) function, increasing the response to chemotoxins, enhancing phagocytosis, increasing the respiratory burst, delaying neutrophil apoptosis and increasing bactericidal and fungicidal activity [74, 75]. G-CSF also accelerates the development of PMNs, leading to an increased rate of release from the bone marrow [75], and enchances alveolar macrophage functions, which are also affected during immunoparalysis [76]. Weiss and colleagues suggested that administration of G-CSF might reduce the risk of nosocomial infection [77, 78], and certainly in rats G-CSF appears to help prevent secondary sepsis after an initial traumatic insult [79]. However, the link between neutrophil function and nosocomial infection in non-neutropenic patients remains very unclear.

Since PMNs have been implicated in the development of multiorgan dysfunction, including ARDS [80, 81]; the potential for harm from G-CSF therapy in some patients is also of concern. PMNs newly released from bone marrow appear to sequester preferentially in the lung microvasculature [82], raising further concern about an increased risk of ARDS. Adding to the concern is that G-CSF appears to increase the likelihood of lung injury in mechanically ventilated rats [83].

Animal pneumonia models demonstrate both potentials of G-CSF treatment. Karzai and colleagues [84] used an endobronchial instillation model to demonstrate that G-CSF had a beneficial effect in *S. aureus* infected rats while *E. coli* infected rats had increased pulmonary injury and mortality with G-CSF treatment. A significantly

greater drop in peripheral PMN counts in *E. coli* infected rats was consistent with neutrophil mediated lung injury secondary to adherence to endothelium and subsequent degranulation, to which the lung is particularly susceptible [85]. The dose of *E. coli* given was also five-fold greater than the dose of *S. aureus,* raising the possibility that the *E. coli* arm actually produced a model of acute lung injury rather than pneumonia.

Initial studies of G-CSF in non-neutropenic human patients with pneumonia were encouraging [86], but subsequent studies were disappointing. Studies of non-neutropenic patients with nosocomial pneumonia have produced mixed results, with the largest trial finding no survival advantage [87]; however, recent studies have suggested a slight beneficial effect giving G-CSF as a pre-treatment [88–91]. Fortunately no adverse effects have been reported giving G-CSF to non-neutropenic patients with nosocomial infection [77, 78, 88, 92–94].

Given that there is some limited encouragement in patients with pneumonia, further human studies may well eventuate if a population in whom G-CSF is likely to beneficial can be clearly defined. Patients with immunoparalysis-induced neutrophil dysfunction may be one such subgroup. However, given the concerns about potential detrimental effects of G-CSF, further studies are unlikely to be successful until faster, more accurate techniques are available for quantifying and monitoring immunoparalysis in patients.

GM-CSF is another haematopoyetic growth factor that has attracted interest as a therapeutic agent in patients with sepsis-related complications. Unlike G-CSF, as its name implies GM-CSF has much greater effect on cells of the monocyte–macrophage lineage [95]. A pilot study of GM-CSF in patients with sepsis-induced respiratory failure found modest improvements in gas exchange and faster ARDS resolution in the treatment group compared to a placebo group [96]. Rosenbloom and colleagues [97] conducted a randomised, placebo-controlled, unblinded trial of GM-CSF in 40 non-neutropenic patients with sepsis in whom 45 % were immunosuppressed due to solid-organ transplants; a significantly greater rate of clinical and microbiological cure or improvement was found. While there are some parallels, immunoparalysis produces a much more subtle defect in innate immune response than that induced by transplant immunosuppressive regimes; therefore it is not possible to generalize the findings between the groups. Again, further human studies in VAP or immunoparalysis are unlikely to evolve until the patient subgroups most likely to benefit are further defined.

Another interesting immunostimulatory agent that may normalize macrophage function in patients with immunoparalysis is INF-γ. A recent study demonstrated that the administration of inhaled INF-γ in patients with immunoparalysis resulted in the recovery of levels of HLA-II expression in alveolar macrophages and protected severely injured patients from VAP [98]. Moreover, INF-γ increased pro-inflammatory markers such as platelet-aggregating factor (PAF) and phospholipase A_2 and decreased anti-inflammatory cytokines such as IL-10. In spite of the apparent beneficial immune effects, INF-γ therapy did not improve overall mortality. However, neither was it associated with any adverse effects [98]. Other work tested INF-γ applied subcutaneously in septic patients with low monocytic HLA-DR expression.

Interestingly, INF-γ restored the deficiency and resulted in the clearance of sepsis in almost every patient [56]. The discrepancy between the results of some studies could be attributable to different study groups and to the IFN-γ administration mode. In fact, the systemic administration of INF-γ does not reach the lung epithelial surface.

Currently, IFN-γ is the most promising agent studied in the setting of patients with immunoparalysis. However, IFN-γ is expensive and the data currently available is far from conclusive. Further studies are still needed to define the patient groups most likely to benefit from IFN-γ, the dose and method of administration. Other potential agents include other cytokines designed to stimulate monocytic function, such as interleukin-12 and agents such as anti-IL-10 that are designed to counter the cytokines driving immunoparalysis.

Conclusion

Patients with recurrent VAP have a prolonged duration of MV, longer ICU stay and a greater mortality than those who have a single episode, even when the second episode is caused by the same microorganism. Recurrent VAP occurs in 15−30% of patients who have a primary episode of VAP and is much more frequently due to MDR bacteria than primary VAP.

Factors associated with recurrent VAP may be host dependent (severe underlying condition), bacteria dependent (highly resistant nosocomial bacteria) or treatment dependent (poor tissue diffusion or inappropriateness of antibiotic treatment).

If there is a considerable rate of reinfection, traditional infection control measures should be reinforced. Conversely, if there are relapses, the efforts should be based on early identification and eradication of persistent carriers.

Several studies have shown that immune defences are transiently depressed in ICU patients (immunoparalysis), which may be a major risk factor for recurrent infections. Patients with recurrent VAP have evidence of immunosuppression. The precise mechanisms for this compromise of immunity remain unclear. Both a temporary immunoparalysis and underlying genetic predisposition are likely to play a role.

Adequate treatment of the initial infection is required to reverse the temporary immunoparalysis, whereas specific immunomodulatory therapies can retrieve the markers of this transient phase and may help to prevent recurrent infections. A potential strategy could be the use of immunostimulation agents like G-CSF or INF-γ, which enhance host defences without any major adverse effects. Further studies are needed to improve the knowledge of this pathology.

References

1. Vincent, J.L., Bihari, D.J., Suter, P.M. *et al.* (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European prevalence of infection in intensive care (EPIC) study. EPIC international advisory committee. *JAMA*, **274** (8), 639−44.

2. Fagon, J.Y., Chastre, J., Hance, A.J. *et al.* (1993) Nosocomial pneumonia in ventilated patients: A cohort study evaluating attributable mortality and hospital stay. *Am J Med*, **94** (3), 281−8.
3. CrouchBrewer, S., Wunderink, R.G., Jones, C.B. *et al* (1996) Ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. *Chest*, **109** (4), 1019−29
4. Luna, C.M., Vujacich, P., Niederman, M.S. *et al.* (1997) Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest*, **111** (3), 676−85.
5. Chastre, J. and Fagon, J.Y. (2002) Ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **165** (7), 867−903.
6. Hugonnet, S., Eggimann, P., Borst, F. *et al.* (2004) Impact of ventilator-associated pneumonia on resource utilization and patient outcome. *Infect Control Hosp Epidemiol*, **25** (12), 1090−6.
7. Rello, J., Ollendorf, D.A., Oster, G. *et al.* (2002) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest*, **122** (6), 2115−21.
8. Niederman, M.S., Mantovani, R., Schoch, P. *et al.* (1989) Patterns and routes of tracheobronchial colonization in mechanically ventilated patients. The role of nutritional status in colonization of the lower airway by pseudomonas species. *Chest*, **95** (1), 155−61.
9. Grossman, R.F. and Fein, A. Grossman, R.F. and Fein, A. (2000) Evidence-based assessment of diagnostic tests for ventilator-associated pneumonia. Executive summary. *Chest*, **117** (4 Suppl 2), 177S−81S.
10. Fagon, J.Y., Chastre, J., Hance, A.J. *et al.* (1988) Detection of nosocomial lung infection in ventilated patients. Use of a protected specimen brush and quantitative culture techniques in 147 patients. *Am Rev Respir Dis*, **138** (1), 110−16.
11. Combes, A., Figliolini, C., Trouillet, J.L. *et al.* (2003) Factors predicting ventilator-associated pneumonia recurrence. *Crit Care Med*, **31** (4), 1102−7.
12. Combes, A., Luyt, C.E., Fagon, J.Y. *et al.* (2004) Impact of methicillin resistance on outcome of *Staphylococcus aureus* ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **170** (7), 786−92.
13. Luyt, C.E., Guerin, V., Combes, A. *et al.* (2005) Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **171** (1), 48−53.
14. Rello, J., Mariscal, D., March, F. *et al* (1998) Recurrent *Pseudomonas aeruginosa* pneumonia in ventilated patients: Relapse or reinfection. *Am J Respir Crit Care Med*, **157** (3 Pt 1), 912−16.
15. Adair, C.G., Gorman, S.P., Feron, B.M. *et al.* (1999) Implications of endotracheal tube biofilm for ventilator-associated pneumonia. *Intensive Care Med*, **25** (10), 1072−6.
16. Adair, C.G., Gorman, S.P. and O´Neill, F.B.*et al* (1993) Selective decontamination of the digestive tract (SDD) does not prevent the formation of microbial biofilms on endotracheal tubes. *J Antimicrob Chemother*, **31** (5), 689−97.
17. Brown, M.R., Allison, D.G. and Gilbert, P. (1988) Resistance of bacterial biofilms to antibiotics: A growth-rate related effect. *J Antimicrob Chemother*, **22** (6), 777−80
18. Hoyle, B.D., Jass, J. and Costerton, J.W. (1990) The biofilm glycocalyx as a resistance factor. *J Antimicrob Chemother*, **26** (1), 1−5.
19. Bauer, T.T., Torres, A., Ferrer, R. *et al.* (2002) Biofilm formation in endotracheal tubes. Association between pneumonia and the persistence of pathogens. *Monaldi Arch Chest Dis*, **57** (1), 84− 7.
20. Cai, S., Zhang, J. and Qian, G. (2001) [Correlation of endotracheal tube biofilm and recurrent ventilator-associated pneumonia with *Pseudomonas aeruginosa*]. *Zhonghua Jie He He Hu Xi Za Zhi*, **24** (6), 339−41.
21. Rumbak, M.J. (2002) The pathogenesis of ventilator-associated pneumonia. *Semin Respir Crit Care Med*, **23** (5), 427−34.

22. Safdar, N., Crnich, C.J. and Maki, D.G. (2005) The pathogenesis of ventilator-associated pneumonia: Its relevance to developing effective strategies for prevention. *Respir Care*, **50** (6), 725–39.
23. Kollef, M.H. (2004) Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med*, **32** (6), 1396–405.
24. Dennesen, P.J., Van derVen, A.J., Kessels, A.G. *et al.* (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **163** (6), 1371–5.
25. Rello, J., Quintana, E., Ausina, V. *et al* (1991) Incidence, etiology, and outcome of nosocomial pneumonia in mechanically ventilated patients. *Chest*, **100** (2), 439–44.
26. Sadikot, R.T., Blackwell, T.S., Christman, J.W. *et al.* (2005) Pathogen-host interactions in *Pseudomonas aeruginosa* pneumonia. *Am J Respir Crit Care Med*, **171** (11), 1209–23.
27. Galan, J.E. and Collmer, A. (1999) Type III secretion machines: Bacterial devices for protein delivery into host cells. *Science*, **284** (5418), 1322–8.
28. Hauser, A.R., Cobb, E., Bodi, M. *et al.* (2002) Type III protein secretion is associated with poor clinical outcomes in patients with ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. *Crit Care Med*, **30** (3), 521–8.
29. Roy-Burman, A., Savel, R.H., Racine, S. *et al.* (2001) Type III protein secretion is associated with death in lower respiratory and systemic *Pseudomonas aeruginosa* infections. *J Infect Dis*, **183** (12), 1767–74.
30. Johanson, W.G., Pierce, A.K. and Sanford, J.P. (1969) Changing pharyngeal bacterial flora of hospitalised patients. Emergence of Gram-negative bacilli. *N Engl J Med*, **281** (21), 1137–40.
31. Sigalet, D.L., Mackenzie, S.L. and Hameed, S.M. (2004) Enteral nutrition and mucosal immunity: Implications for feeding strategies in surgery and trauma. *Can J Surg*, **47** (2), 109–16.
32. Ewig, S., Torres, A. and El-Ebiary, M. (1999) Bacterial colonization patterns in mechanically ventilated patients with traumatic and medical head injury. Incidence, risk factors, and association with ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **159** (1), 188–98
33. Singh, N., Rogers, P., Atwood, C.W. *et al.* (2000) *Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription*. *Am J Respir Crit Care Med*, **162** (2 Pt 1), 505–11. t
34. Ibrahim, E.H., Ward, S., Sherman, G. *et al.* (2001) Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med*, **29** (6), 1109–15.
35. Silver, D.R., Cohen, I.L. and Weinberg, P.F. (1992) Recurrent *Pseudomonas aeruginosa* pneumonia in an intensive care unit. *Chest*, **101** (1), 194–8.
36. Chollet-Martin, S., Jourdain, B., Gibert, C. *et al* (1996) Interactions between neutrophils and cytokines in blood and alveolar spaces during ARDS. *Am J Respir Crit Care Med*, **154** (3 Pt 1), 594–601.
37. Martin, T.R., Pistorese, B.P., Hudson, L.D. *et al.* (1991) The function of lung and blood neutrophils in patients with the adult respiratory distress syndrome. Implications for the pathogenesis of lung infections. *Am Rev Respir Dis*, **144** (2), 254–62.
38. Fagon, J.Y., Chastre, J., Domart, Y. *et al.* (1989) Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. *Am Rev Respir Dis*, **139** (4), 877–84.
39. Fagon, J.Y., Chastre, J., Vuagnat, A. *et al.* (1996) Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA*, **275** (11), 866–9.

40. Baughman, R.P. and Kerr, M.A. Baughman, R.P. and Kerr, M.A. (2003) Ventilator-associated pneumonia patients who do not reduce bacteria from the lungs have a worse prognosis. *J Intensive Care Med*, **18** (5), 269−74.
41. Kollef, M.H., Silver, P., Murphy, D.M. *et al.* (1995) The effect of late onset ventilator-associated pneumonia in determining patient mortality. *Chest*, **108** (6), 1655−62.
42. Rello, J., Jubert, P., Valles, J. *et al.* (1996) Evaluation of outcome for intubated patients with pneumonia due to *Pseudomonas aeruginosa*. *Clin Infect Dis*, **23** (5), 973−8.
43. Rello, J., Torres, A., Ricart, M. *et al.* (1994⟩) Ventilator-associated pneumonia by *Staphylococcus aureus*. Comparison of methicillin-resistant and methicillin-sensitive episodes. *Am J Respir Crit Care Med*, **150** (6 Pt 1), 1545−9.
44. Zavascki, A.P., Barth, A.L., Fernandez, J.L. *et al.* (2006) Reappraisal of *Pseudomonas aeruginosa* hospital-acquired pneumonia mortality in the era of metallo-beta-lactamase-mediated multidrug resistance: A prospective observational study. *Crit Care*, **10** (4), R114.
45. Valles, J., Mariscal, D., Cortes, P. *et al.* (2004) Patterns of colonization by *Pseudomonas aeruginosa* in intubated patients: A 3-year prospective study of 1,607 isolates using pulsed-field gel electrophoresis with implications for prevention of ventilator-associated pneumonia. *Intensive Care Med*, **30** (9), 1768−75.
46. Duflo, F., Debon, R., Monneret, G. *et al.* (2002) Alveolar and serum procalcitonin: Diagnostic and prognostic value in ventilator-associated pneumonia. *Anesthesiology*, **96** (1), 74−9.
47. Hebert, P.C., Wells, G., Blajchman, M.A. *et al.* (1999) A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian critical care trials group. *N Engl J Med*, **340** (6), 409−17.
48. Kollef, M.H., Vlasnik, J., Sharpless, L. *et al.* (1997) Scheduled change of antibiotic classes: A strategy to decrease the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med*, **156** (4 Pt 1), 1040−8.
49. Goldmann, D.A., Weinstein, R.A., Wenzel, R.P. *et al.* (1996) Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *JAMA*, **275** (3), 234−40.
50. Hartmann, M., Guttmann, J., Muller, B. *et al.* (1999) Reduction of the bacterial load by the silver-coated endotracheal tube (SCET), a laboratory investigation. *Technol Health Care*, **7** (5), 359−70.
51. Rello, J., Kollef, M., Dìaz, E. *et al.* (2006) Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal, tube in a randomized multicenter feasibility study. *Crit Care Med*, **12** (5), 364−8.
52. George, D.L., Falk, P.S., Wunderink, R.G. *et al.* (1998) Epidemiology of ventilator-acquired pneumonia based on protected bronchoscopic sampling. *Am J Respir Crit Care Med*, **158** (6), 1839−47.
53. Wood, J.J., Rodrick, M.L. and O´Mahony, J.B. *et al.* (1984) Inadequate interleukin 2 production. A fundamental immunological deficiency in patients with major burns. *Ann Surg*, **200** (3), 311−20.
54. Bone, R.C. (1996) Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med*, **24** (7), 1125−8.
55. Munford, R.S. and Pugin, J. (2001) Normal responses to injury prevent systemic inflammation and can be immunosuppressive. *Am J Respir Crit Care Med*, **163** (2), 316−21.
56. Docke, W.D., Randow, F., Syrbe, U. *et al.* (1997) Monocyte deactivation in septic patients: Restoration by IFN-gamma treatment. *Nat Med*, **3** (6), 678−81.
57. Giannoudis, P.V., Smith, R.M., Perry, S.L. *et al.* (2000) Immediate IL-10 expression following major orthopaedic trauma: Relationship to anti-inflammatory response and subsequent development of sepsis. *Intensive Care Med*, **26** (8), 1076−81.

58. Woiciechowsky, C., Asadullah, K., Nestler, D. *et al.* (1998) Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. *Nat Med*, **4** (7), 808−13.
59. Stephan, F., Yang, K., Tankovic, J. *et al.* (2002) Impairment of polymorphonuclear neutrophil functions precedes nosocomial infections in critically ill patients. *Crit Care Med*, **30** (2), 315−22.
60. Junger, W.G., Hoyt, D.B., Liu, F.C. *et al.* (1996) Immunosuppression after endotoxin shock: The result of multiple anti-inflammatory factors. *J Trauma*, **40** (5), 702−9
61. Deng, J.C. and Standiford, T.J. (2005) The systemic response to lung infection. *Clin Chest Med*, **26** (1), 1−9.
62. Volk, H.D., Reinke, P. and Docke, W.D. (2000) Clinical aspects: from systemic inflammation to immunoparalysis. *Chem Immunol*, **74**, 162−77.
63. Wolk, K., Docke, W. and vonBaehr, V. *et al.* (1999) Comparison of monocyte functions after LPS- or IL-10-induced reorientation: Importance in clinical immunoparalysis. *Pathobiology*, **67** (5-6), 253−6.
64. Monneret, G., Elmenkouri, N., Bohe, J. *et al.* (2002) Analytical requirements for measuring monocytic human lymphocyte antigen DR by flow cytometry: Application to the monitoring of patients with septic shock. *Clin Chem*, **48** (9), 1589−92.
65. MullerKobold, A.C., Tulleken, J.E., Zijlstra, J.G. *et al.* (2000) Leukocyte activation in sepsis; correlations with disease state and mortality. *Intensive Care Med*, **26** (7), 883−92.
66. Peters, M., Petros, A., Dixon, G. *et al.* (1999) Acquired immunoparalysis in paediatric intensive care: Prospective observational study. *Bmj*, **319** (7210), 609−10.
67. Ploder, M., Pelinka, L., Schmuckenschlager, C. *et al.* (2006) Lipopolysaccharide-induced tumor necrosis factor alpha production and not monocyte human leukocyte antigen-DR expression is correlated with survival in septic trauma patients. *Shock*, **25** (2), 129−34.
68. Flohe, S., Lendemans, S., Schade, F.U. *et al.* (2004) Influence of surgical intervention in the immune response of severely injured patients. *Intensive Care Med*, **30** (1), 96−102.
69. Waterer, G.W. and Wunderink, R.G. (2005) Genetic susceptibility to pneumonia. *Clin Chest Med*, **26** (1), 29−38.
70. Dommett, R.M., Klein, N. and Turner, M.W. (2006) Mannose-binding lectin in innate immunity: past, present and future. *Tissue Antigens*, **68** (3), 193−209.
71. Yuan, F.F., Wong, M., Pererva, N. *et al.* (2003) FcgammaRIIA polymorphisms in *Streptococcus pneumoniae* infection. *Immunol Cell Biol*, **81** (3), 192−5
72. Temple, S.E., Lim, E., Cheong, K.Y. *et al.* (2003) Alleles carried at positions -819 and -592 of the IL10 promoter affect transcription following stimulation of peripheral blood cells with *Streptococcus pneumoniae*. *Immunogenetics*, **55** (9), 629−32.
73. Ovsyannikova, I.G., Ryan, J.E., Vierkant, R.A. *et al.* (2005) Immunologic significance of HLA class I genes in measles virus-specific IFN-gamma and IL-4 cytokine immune responses. *Immunogenetics*, **57** (11), 828−36.
74. Welte, K., Gabrilove, J., Bronchud, M.H. *et al.* (1996) Filgrastim (r-metHuG-CSF): the first 10 years. *Blood*, **88** (6), 1907−29.
75. Dale, D.C., Liles, W.C., Llewellyn, C. *et al.* (1998) Effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) on neutrophil kinetics and function in normal human volunteers. *Am J Hematol*, **57** (1), 7−15.
76. Shieh, J.H., Peterson, R.H. and Moore, M.A. (1991) Modulation of granulocyte colony-stimulating factor receptors on murine peritoneal exudate macrophages by tumor necrosis factor-alpha. *J Immunol*, **146** (8), 2648−53.
77. Weiss, M., Gross-Weege, W., Harms, B. *et al.* (1996) Filgrastim (RHG-CSF) related modulation of the inflammatory response in patients at risk of sepsis or with sepsis. *Cytokine*, **8** (3), 260−5.

78. Weiss, M., Gross-Weege, W., Schneider, M. *et al.* (1995) Enhancement of neutrophil function by *in vivo* filgrastim treatment for prophylaxis of sepsis in surgical intensive care patients. *J Crit Care*, **10** (1), 21−6.
79. Bauhofer, A., Lorenz, W., Kohlert, F. *et al.* (2006) Granulocyte colony-stimulating factor prophylaxis improves survival and inflammation in a two-hit model of haemorrhage and sepsis. *Crit Care Med*, **34** (3), 778−84.
80. Fujishima, S. and Aikawa, N. (1995) Neutrophil-mediated tissue injury and its modulation. *Intensive Care Med*, **21** (3), 277−85.
81. Weiss, S.J. (1989) *Tissue destruction by neutrophils*. *N Engl J Med*, **320** (6), 365−76.
82. Fillion, I., Ouellet, N., Simard, M. *et al.* (2001) Role of chemokines and formyl peptides in pneumococcal pneumonia-induced monocyte/macrophage recruitment. *J Immunol*, **166** (12), 7353−61.
83. Karzai, W., Cui, X., Heinicke, N. *et al.* (2005) Neutrophil stimulation with granulocyte colony-stimulating factor worsens ventilator-induced lung injury and mortality in rats. *Anesthesiology*, **103** (5), 996−1005.
84. Karzai, W., vonSpecht, B.U., Parent, C. *et al.* (1999) G-CSF during Escherichia coli versus Staphylococcus aureus pneumonia in rats has fundamentally different and opposite effects. *Am J Respir Crit Care Med*, **159** (5 Pt 1), 1377−82
85. Bersten, A. and Sibbald, W.J. (1989) Acute lung injury in septic shock. *Crit Care Clin*, **5**(1), 49−79.
86. deBoisblanc, B.P., Mason, C.M., Andresen, J. *et al.* (1997) Phase 1 safety trial of filgrastim (r-methug-CSF) in non-neutropenic patients with severe community-acquired pneumonia. *Respir Med*, **91** (7), 387−94.
87. Hartmann, P., Lammertink, J., Mansmann, G. *et al.* (2005)A randomised, placebo-controlled study of the use of filgrastim in non neutropenic patients with nosocomial pneumonia. *Eur J Med Res*, **10** (1), 29−35.
88. Heard, S.O., Fink, M.P., Gamelli, R.L. *et al.* (1998) Effect of prophylactic administration of recombinant human granulocyte colony-stimulating factor (filgrastim) on the frequency of nosocomial infections in patients with acute traumatic brain injury or cerebral haemorrhage. The filgrastim study group. *Crit Care Med*, **26** (4), 748−54.
89. Pettila, V., Takkunen, O., Varpula, T. *et al.* (2000) Safety of granulocyte colony-stimulating factor (filgrastim) in intubated patients in the intensive care unit: Interim analysis of a prospective, placebo-controlled, double-blind study. *Crit Care Med*, **28** (11), 3620−5.
90. Schafer, H., Hubel, K., Bohlen, H. *et al.* (2000) Perioperative treatment with filgrastim stimulates granulocyte function and reduces infectious complications after esophagectomy. *Ann Hematol*, **79** (3), 143−51.
91. Winston, D.J., Foster, P.F., Somberg, K.A. *et al.* (1999) Randomized, placebo-controlled, double-blind, multicenter trial of efficacy and safety of granulocyte colony-stimulating factor in liver transplant recipients. *Transplantation*, **68** (9), 1298−304.
92. Gross-Weege, W., Weiss, M., Schneider, M. *et al.* (1997) Safety of a low-dosage filgrastim (rhG-CSF) treatment in non-neutropenic surgical intensive care patients with an inflammatory process. *Intensive Care Med*, **23** (1), 16−22.
93. Nelson, S., Belknap, S.M., Carlson, R.W. *et al.* (1998) A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalised patients with community-acquired pneumonia. cap study group. *J Infect Dis*, **178** (4), 1075−80.
94. Nelson, S., Heyder, A.M., Stone, J. *et al.* (2000) A randomized controlled trial of filgrastim for the treatment of hospitalised patients with multilobar pneumonia. *J Infect Dis*, **182** (3), 970−3.
95. Hamilton, J.A. and Anderson, G.P. (2004) GM-CSF Biology. *Growth Factors*, **22** (4), 225−31.

96. Presneill, J.J., Harris, T., Stewart, A.G. *et al.* (2002) A randomized phase ii trial of granulocyte-macrophage colony-stimulating factor therapy in severe sepsis with respiratory dysfunction. *Am J Respir Crit Care Med*, **166** (2), 138−43.
97. Rosenbloom, A.J., Linden, P.K., Dorrance, A. *et al.* (2005) Effect of granulocyte-monocyte colony-stimulating factor therapy on leukocyte function and clearance of serious infection in non-neutropenic patients. *Chest*, **127** (6), 2139−50.
98. Nakos, G., Malamou-Mitsi, V.D., Lachana, A. *et al.* (2002) Immunoparalysis in patients with severe trauma and the effect of inhaled interferon-gamma. *Crit Care Med*, **30** (7), 1488−94.

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Costs for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

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Introduction

Hospital-acquired pneumonia (HAP) remains a major cause of morbidity and mortality. Although the second most common nosocomial infection, patients who develop HAP face crude mortality rates nearing 30–50 % [1]. In critically ill subjects in the intensive care unit (ICU), ventilator-associated pneumonia (VAP) is the most frequently diagnosed nosocomial infection and significantly prolongs the duration of mechanical ventilation (MV) [1]. Presently, controversy exists regarding whether HAP or VAP are associated with attributable mortality [1]. In other words, those who develop either HAP or VAP may die with these infections rather than because of them. Assessing attributable mortality is difficult since it requires appropriate selection of a comparative population and adjustments for many parameters. Despite uncertainty regarding the impact of HAP and VAP on mortality, there is general consensus that these substantially affect costs. Multiple studies using a variety of

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approaches confirm that HAP and VAP not only prolong hospital stay but that they also add significantly to overall costs.

Overview of Cost

Before proceeding to a review of prior analyses describing the costs and outcomes associated with HAP and VAP it is important to highlight issues with cost in medicine. Any question of cost necessarily presupposes the issue of: 'cost to whom?' Costs can be evaluated from the perspective of the hospital, a third-party payer or society. In each instance the components that comprise the costs of interest will vary. For example, a hospital might only be concerned with costs arising from hospitalisation and the costs for acquiring antimicrobials. A third-party payer would be further concerned about how costs for hospital-acquired complications drive outpatient costs, such as the need for long-term care, outpatient physicians visits and hospital readmission rates. Finally, from society's perspective, costs related to lost productivity also need to be included. Hence, a careful reader of health cost literature focuses not only on costs but the perspective used to ascertain those costs. Formal guidelines for conducting cost-effectiveness analyses suggest that costs should generally be viewed from society's perspective. [2, 3] It is the most comprehensive means of assessing the impact of any intervention or event on outcomes. However, analysing costs from society's perspective is often difficult since it requires the evaluation of issues related to healthcare costs over a subject's lifetime. As a result, the majority of cost reports dealing with HAP and VAP generally describe a hospital or third-party payer perspective. This may not be expressly stated, but it is often evident from the types of costs included in the study.

Use of the term 'cost' also presumes that the numerical values described represents an economic value. This is distinct from charges. Costs should reflect the value an efficient market places on goods or services. Medicine, however, rarely functions as a perfect market. Moreover, charges in healthcare are often artificial and arbitrary. Unfortunately, some investigators use the terms cost and charge interchangeably. This is technically incorrect and accepted methods for converting charges to cost exist. In the United States, for example, the Centers for Medicaid and Medicare Services, publish cost-to-charge ratios. This allows charges to be converted to cost via multiplication and serves to facilitate comparisons across hospitals. In non-US nations, cost accounting mechanisms vary. In Europe, costs for ICU care are often derived by converting a measure of workload intensity (Therapeutic Interventions Severity System, TISS) to cost such that each TISS point is associated with a set cost [4, 3]. Although all of these mechanisms have limitations few other alternatives exist. The issues with cost and charge, though, illustrate the difficulty with cross-national comparisons.

Finally, any discussion of cost must address types of economic analysis. The four varieties of economic analysis in healthcare are: cost-minimization, cost-benefit, cost-effectiveness and cost-utility. Cost-minimization assumes that the outcome of interest (e.g. cases of HAP prevented) is fixed and that differing approaches to accomplishing

this goal are equally effective. The concern in this case is simply which alternative costs less. In the ICU, though, few interventions achieve similar results. When both costs and outcomes differ, the various options must be given a value in some common rubric (such as dollars). After converting potential results of interventions into dollars it is possible to proceed with cost-benefit analysis.

Cost-benefit analysis is employed infrequently in healthcare, as many outcomes are difficult to convert into dollar values (e.g. the dollar value of a life).

Cost-effectiveness acknowledges the limitations of cost-benefit and thus leaves the outcome (or denominator) in clinical terms. Now costs per some common measure of efficacy are contrasted. Often-used examples in healthcare describe costs per year of life saved or per ICU days avoided.

Cost-utility analysis takes cost-effectiveness further by adjusting the main outcome for the quality related to that event. The standard denominator for such projects is the quality-adjusted life-year (QALY). The QALY concept acknowledges that a year of life spent in a long-term ventilator facility is not viewed by the patient as being of the same quality as a year of life spent being fully functional. Although arbitrary, most consider 'cost-effective' interventions that yield a price per QALY saved of between US$50 000 and $100 000 [4, 3].

Cost of Disease State Studies in HAP and VAP

Studies describing costs related to HAP and VAP suffer from a number of limitations. Often they are based on retrospective analyses and employ uncertain criteria for the diagnosis of HAP and VAP. They also vary as to the types of costs included in the final accounting. Nonetheless, recent studies all underscore that HAP and VAP increase hospital costs substantially via their effect on the need for subsequent MV and duration of hospitalisation.

Administrative Databases

Rello and colleagues examined costs related to HAP through a review of a large administrative database in the US [5]. They included subjects with both HAP and VAP and observed that neither affected mortality. Compared to non-infected controls, however, HAP led to nearly $40 000 in extra hospital charges ($104 983 vs $63 689, $p < 0.001$). Among 842 cases, the duration of both MV and ICU stay were doubled compared to the control population. One strength of this analysis is that it represented a multicentre experience and hence reflected a range of patient types. However, it is unclear if diagnoses based on administrative discharge diagnosis coding are adequate for identifying subjects actually suffering from HAP and VAP. If one conservatively corrects the charges to cost via a cost-to-charge ratio of 0.3, these findings suggest that HAP and VAP cost more than $10 000 per event.

Building on this effort through exploration of administrative databases, Kollef *et al*. examined outcomes for patients with various forms of pneumonia that required hospitalisation or which arose while the patient was hospitalised [6]. Unique to

this project was an effort to identify 'healthcare-associated pneumonia' (HCAP). HCAP represents pneumonia in a person who is not an inpatient in an acute care hospital when the infection is diagnosed but who has substantial interaction with the healthcare system. Examples of such individuals include those undergoing chronic outpatient dialysis or wound care, persons in long-term care facilities and others who have recently been hospitalised. The sample size was large (n = 4543) and comprised information from over 50 hospitals in the United States. Total charges for subjects with VAP were astronomical, nearing $150 000. Note, however, that this amount represents charges for the entire hospital stay and not those simply due to the nosocomial infection. For HAP total charges were $65 000. This study is one of the few that have separated VAP specifically from HAP and again illustrates the profound differential in charges that arises when caring for patients requiring MV vs persons not in the ICU. Charges for HCAP were significantly lower than those for either HAP or VAP ($27 647). Despite the large sample size and the fact that the data provide a distinct perspective since many of the study hospitals were non-academic community hospitals, this report can only provide a crude estimate of the costs for HAP and VAP as it did not expressly focus on the attributable-burden of these infections.

Consistent with the observations of Rello *et al*. and Kollef *et al*., work with an administrative database of purely surgical patients documented that, even in a more select group of patients, VAP and HAP make an important contribution to overall costs. Reviewing HAP in a population of over 600 000 subjects who underwent intra-abdominal surgery, Thompson *et al*. observed that HAP was independently associated with a more than four-fold increase in the risk of discharge to a skilled nursing facility [7]. The attributable-hospital length of stay arising due to HAP was 11 days. This translated into a 75 % increase in total hospital charges. This difference of $28 000 was independent of multiple co-variates that might extend the need for hospitalisation. In summary, exploring administrative data provides crucial insights into the epidemiology and costs of HAP and VAP. Limited because of the use of discharge codes to identify subjects, these endeavours are robust because of the very large sample sizes studied. In turn, this affords sufficient statistical power to control for multiple factors that affect cost.

Single Institution Studies

Perhaps one of the more rigorous analyses of the cost of VAP used a different approach, but reached similar conclusions to those seen with administrative data sets. Warren and co-workers, as part of a prospective analysis at a non-teaching hospital, identified subjects with VAP and compared them to uninfected controls undergoing MV in the ICU [8]. Charges were derived from hospital billing records and were appropriately converted to costs. The 127 persons with VAP were different from the control population (n = 819) in many ways. Controlling for multiple parameters, including age, severity of illness and care process, though, indicated that the cost of VAP was nearly $12 000 per case (95 % CI: $5265−$26 214). VAP was associated

with a higher unadjusted ICU length of stay (LOS) (26 vs 4 days; $p < 0.001$) and hospital LOS (38 vs 13 days; $p < 0.001$).

It is unclear if the costs for HAP and VAP are similar across differing patient types. Clearly trauma patients suffering from HAP may be infected with a different spectrum of pathogens than the immunosuppressed subject in a medical ICU [1]. Hence, to bracket the uncertainty surrounding the costs of VAP and HAP it is necessary to examine outcomes in other settings. In that vein, Cocanour *et al*. focused exclusively on the costs of VAP in critically ill trauma patients [9]. During a 21-month period, there were 91 subjects with VAP and 571 subjects requiring more than 24 hours of MV that were never diagnosed with VAP. From this population 70 cases were compared to 70 controls. Factors matched in the selection of controls included age and severity of illness. These authors calculated that the attributable-cost of VAP was over $50 000 per event. It seems, however, more likely that they were reporting charges rather than cost. Even adjusting for this, though, places the costs for a case of VAP in a trauma patient at nearly $15 000. One additional limitation of this study is that cases were identified based on clinical criteria alone; the authors did not require microbiological confirmation of infection. Again, as others have reported, the main drivers of cost in this setting were the impact of VAP on ICU length of stay and the need for continued MV. Pharmacy costs, representing the likely direct costs for the medications need to treat VAP and HAP, were a small overall contribution to the total cost.

Non-US Perspectives

From an alternative, European perspective several groups of researchers have attempted to estimate the costs of HAP and VAP. Hugonnet and colleagues reviewed outcomes and cost related to VAP in a Swiss ICU [10]. Using a case-control methodology, they matched for duration of MV, ICU admitting diagnosis, total number of discharge diagnoses and age. Unique to this study was the fact that more than 70 % of cases had microbiological confirmation of the diagnosis of pneumonia. On average, subjects with VAP required an additional five days of MV and one week of ICU care. Median costs, which were calculated through a means validated for use in Swiss hospitals, were $24 727 in those with VAP vs $17 438 in persons lacking VAP ($p < 0.001$). Despite difficulties with adjustments for exchange rate, this estimate is much like those reported in US studies.

Dietrich *et al*. also examined cost issues associated with VAP from a European vantage point [11]. In a small prospective case−control analysis 29 persons with VAP were compared to 37 controls. Extra costs were nearly DM 15 000. When attempting to control for a society's perspective and utilizing the criteria of the German statutory health agencies, the cost difference due to VAP fell to approximately DM 8000.

Research from South America appears consistent with findings from both Europe and the United States. In a case−control study of over 300 persons with nosocomial pneumonia, researchers from Argentina concluded that HAP and VAP resulted in the patient needing an added nine days of care in an ICU [12]. Interestingly, because of differences in cost accounting between the United States, Europe and South America,

the attributable-cost of HAP and VAP was less in Argentina than elsewhere [12]. In this instance, the authors estimated that a case of HAP only cost an additional $2255. This discordance underscores difficulties with cross-national comparisons of cost. Not only are costs calculated differently based on the organization of healthcare systems (totally funded via the federal government vs a mix of public and private funding sources) but conversion to US dollars from other currencies also complicates matters. Therefore, when evaluating costs across international boarders it may be more appropriate to emphasize length of stay and extension in the duration of MV rather than just cost. With this methodology, it can be seen that no matter what the country, HAP and VAP appear to add approximately a week to the ICU stay.

Microcosting

Assessing differences in total aggregate costs for hospitalisation is only one method of estimating the costs related to HAP and VAP. Alternatively, microcosting could be employed, in which the component pieces that go into care of the patient with HAP and VAP are determined and then a cost estimate is assigned to each of these pieces. Summing the individual costs leads to a total estimate of the cost per case. Microcosting represents one means of overcoming the hurdles related to international comparisons noted above. For microcosting, however, it is necessary to delineate the various aspects of care for VAP. Certainly these would include added pharmacy and radiology costs in addition to various diagnostic costs. The effect of VAP on LOS would also need to be considered. One conservative estimate using this strategy suggested that the cost for VAP was approximately $5400 [13]. Safdar and co-workers recently performed a more precise microcosting analysis [14]. After a substantial systematic review and meta-analysis reviewing studies describing the effect of VAP on ICU LOS and MV duration, they determined that this disease increased ICU stay by six days (95 % CI: 5.32−6.87 days). They were cautious in that they only included trials that had clear criteria for the diagnosis of VAP. Based on the added time in the ICU on MV because of VAP, along with the costs for additional laboratory and radiology examinations, and the costs for antibiotics, Safdar *et al*., concluded that the costs for VAP equalled $10 019 [14].

In short, many reports utilizing different techniques and examining the issue in differing nations indicate that the costs for VAP are substantial. All of these reports though suffer from common limitations. First, they generally address only ventilated patients. Defining pneumonia in the ventilated patient may be more straightforward than in the nonventilated subject. However, since dealing nearly exclusively with those on MV when they develop pneumonia it seems unlikely these results are applicable to those not ventilated when diagnosed with HAP. In other words, since the ward patient is less severely ill than the ICU patient when HAP is diagnosed, it is to be suspected on this fact alone that costs would differ.

Second, all efforts to adjust for parameters have limitations and are necessarily imprecise. Clearly, those with VAP are systematically different from those without VAP complicating their course of MV. Using a case−control methodology suggests that there may be important parameters for which cases and controls are not adequately

matched. Alternatively, a modelling effort with either linear regression or propensity scoring is exposed to concerns that other important co-variates not included in the model are major drivers of cost. More specifically, matching for severity of illness at time of ICU admission is crucial, as severity of illness drives resource consumption. But patients who develop a nosocomial process have been in the ICU for some period before the new infection, and during that time may have become either more or less severely ill. No present analyses attempt to correct for this phenomenon or even acknowledge it as a major parameter.

A further limitation of all cost analyses investigating HAP and VAP is that they mainly describe short-term costs. Collection of cost information seems to end once the patient leaves the hospital. It seems reasonable to assume that HAP and VAP have effects on the patient that extend beyond the hospital. For example, some patients with VAP may require tracheotomy and care in a long-term ventilator facility. Others will develop complications from their infections that necessitate home antibiotic therapy. Beyond these direct costs, HAP and VAP certainly have associated indirect costs. In all likelihood those with HAP cannot return to work upon discharge while family members may have to limit their employment so that care can be provided. Unfortunately, the question of post-discharge outcomes in HAP and VAP remains unexplored. Hence any effort to assess these costs other than to state that they must exist represents pure speculation. Looking at survivors of severe sepsis and septic shock, though, suggests that these post-hospital costs can be as high as those that arise during the acute hospital stay. Cost analyses to date have also exclusively examined the issue from the hospital's perspective. More simple to calculate because of access to computerised billing systems, hospital costs also undoubtedly underestimate the true impact of HAP and VAP.

Cost-Effectiveness Analyses

Multiple cost-effectiveness analyses (CEAs) have been conducted in areas related to HAP and VAP. Broadly these fall into two categories: assessments of preventive strategies and evaluations of various antimicrobial treatment regimens. Few of these reports are true 'CEAs' in that they rely on QALYs or a similar measure to capture outcomes. Rather, most would more aptly be described as cost-minimization studies that look at alternative strategies for either preventing or treating HAP.

Prevention

Because of the great expense associated with VAP, any intervention that successfully prevents this infection is likely to be cost-effective. Furthermore, the prevention option needs not be very effective in order to yield net savings so long as the intervention itself is not overly costly.

As an example of these principles, one early cost-minimization study of VAP prevention addressed the role of continuous subglottic suctioning (CSS) in preventing. VAP [15] Several trials have demonstrated the efficacy of CSS in preventing VAP

but the CSS tube itself is more expensive to purchase than a traditional endotracheal tube [16–18]. Relying on decision modelling, Shorr *et al*. revealed that CSS tube use resulted in a savings of $5000 per case of VAP avoided [15]. Employing conservative estimates for the efficacy of CSS and the costs of VAP, it was concluded that regular reliance on CSS tubes could result in major savings. A questionable assumption underlying this model, though, was the assertion that both early and late onset VAP are equally costly. The CSS tube has only been shown to prevent VAP due to generally low risk pathogens such as *Haemophilus influenzae*. Prevention of VAP due to this pathogen is not likely to be as significant as prevention of VAP dues to methicillin-resistant *Staphylococcus aureus* (MRSA). Multiple sensitivity analyses partially addressed this concern. Even if the cost of a case of VAP was less than $2500, the CSS approach appeared linked to overall net savings.

In a less formal cost-minimization project, Mullins *et al*. evaluated the financial implications of kinetic therapy with a lateral rotation bed [19]. Some preliminary data suggest that lateral rotation may bolster efforts at VAP prevention [20]. Lateral rotation is presently not a formally recommend option for VAP prevention [21]. Modelling their institution's experience with VAP in trauma patients, Mullins and colleagues proposed that this would result in a cost savings of $6695 per patient. Unfortunately, their analysis suffers from a number of serious limitations [19]. First, rather than bias their model inputs against rotation therapy in order to be conservative and to be consistent with guidelines for the conduct of CEAs, an overly optimistic estimate of rotation therapy's efficacy was used. Second, the analysis relied on a somewhat inflated cost for VAP that more resembled the charges described above rather than actual costs. Third, sensitivity analyses to evaluate the robustness of the conclusion across the likely uncertainty for the model inputs were not conducted. Although it is possible that kinetic therapy with a lateral rotation bed can bring cost-savings, further research is needed to confirm this hypothesis.

In contrast to lateral rotation, less frequent changing of the in-line suction devices used with MV is an evidenced-based recommendation for avoiding VAP. In this case, it represents what is often called a dominant strategy in health economics. In other words, less consumption of resources (fewer new suction devices) is associated with a clinical benefit (less VAP). Alternatively, such 'dominant' strategies can be viewed as opportunities to improve outcomes and save money simultaneously. The issue then becomes what is the magnitude of the effect. Stoller *et al*. recently attempted to examine this in their ICU [22]. In a non-randomised before–after study both the incidence of VAP and the costs for in-line suction devices over two periods were recorded. In the first period, suction devices were changed daily while in the second they were changed every seven days or as needed. In over 2000 patient-days of MV, actual rates of VAP changed little. Direct costs for acquiring suction catheters diminished by 75%. On an annualised basis, Stoller *et al*. showed this would save their hospital $18 000. Note that despite this being a 'dominant' approach, the actual net saving is small and could easily be overwhelmed by the direct costs related to 3–4 additional cases of VAP. This fact illustrates the need to look at cost issues in terms of both relative factors (e.g. proportional differences) and absolute factors (e.g. net total financial difference).

Two studies have tried to evaluate the financial ramification of an integrated approach to preventing VAP [23, 24]. In the first trial, Zack *et al*. implemented a multifaceted prevention paradigm [23]. Both educational efforts directed towards nurses and clinicians were coupled with a hospital policy for VAP prevention. Participants took a test to measure their increase in knowledge and investigators emphasized prevention during daily ICU rounds. The incidence of VAP fell from 12.6 cases per 1000 MV days to 5.7 cases per 1000 MV days. Extrapolating from a range of potential costs for VAP, and after subtracting the costs associated with the program's creation and conduct, Zack *et al*. calculated the post-intervention savings to range from $400 000 to $4 million annually. The second initiative was carried out in a smaller non-academic hospital [24]. Central to this effort was the use of a ventilator bundle that emphasized best practices for VAP prevention. Following this, VAP rates declined by more than 50%. These authors did not approximate savings indirectly as Zack *et al*. did. Instead, costs per patient stay in the ICU were reported. From this it was seen that the average cost fell by 21%. Both these endeavors validate the hypothesis that systematic prevention leads to tangible savings for hospitals willing to take ownership of this issue.

Treatment

Reflecting the difficulties is assessing outcomes in VAP and the paucity of data regarding post-ICU survival following HAP and VAP, there are few formal analyses of various treatment paradigms for HAP and VAP. Some have addressed the role of continuous infusion of antimicrobials (e.g. ceftazadime, vancomycin) as a way of minimizing pharmacy and nursing costs while optimising pharmacokinetics [25, 26]. The net difference between approaches studied in these trials is small, based on both per patient and total institutional costs. More recent activity has concentrated on novel antimicrobials for MRSA.

MRSA HAP and VAP appear particularly more expensive relative to infection with methicillin-sensitive *S. aureus* (MSSA). [27, 28] Debate persists about whether MRSA VAP confers an increased risk of death [29]. Notwithstanding this dispute, multiple researchers have highlighted that MRSA VAP increases both duration of MV and cost in VAP. Shorr *et al*. underscored this concern in a review of a large administrative database and documented that MRSA VAP cost nearly $8000 more in direct hospital costs relative to MSSA [27]. In a subsequent appraisal of outcomes with MRSA and MSSA VAP, patients with MRSA spent more than an extra week in the ICU [28]. This difference arose despite all patients receiving initially appropriate antibiotic therapy.

For MRSA VAP therapy, three cost-effectiveness studies have compared linezolid to vancomycin. Each used different methodologies; they were conducted in separate countries. From a Brazilian healthcare outlook, Machado and co-workers used decision analysis to determine the relative cost-effectiveness of linezolid [30]. Based on the results of clinical trials with linezolid and the costs of care in Brazil, it was concluded that costs per additional survivor were 40% lower with linezolid. Limiting

the conclusions, however, is the fact that no sensitivity analyses were performed and only short-term survival was dealt with.

Grau *et al*. were more thorough and evaluated the cost-effectiveness of linezolid vs vancomycin for the Spanish healthcare system [31]. Instead of extrapolating from studies in sepsis about the quality of life of survivors of VAP, information from time−trade off analyses conducted among patients was relied upon. Employment of linezolid generated significantly more QALYs than vancomycin primarily because of its impact on survival. Additional costs with linezolid were also higher given the price for directly acquiring the drug in Spain. Comparatively, though, the added cost per QALY with linezolid was less than 2000. This observation persisted across a range of sensitivity analyses and was well below European regulatory agencies' definitions of 'cost-effective'.

The final cost-effectiveness investigation for linezolid was based on United States healthcare costs [32]. Decision analysis formed the foundation for this report and it too looked to the published clinical trials for model input. As with the Spanish study, QALYs served as the primary end point and the model was biased heavily against linezolid. Despite this, linezolid meet criteria for cost-effectiveness. Specifically, the cost per additional QALY equalled $30 000. Even in a worst-case scenario where the price of linezolid was increased, its efficacy diminished and the healthcare costs of survivors elevated, linezolid remained cost-effective. Hopefully, future work will build on these attempts to gauge the cost-effectiveness of specific alternative therapies so that clinicians and policy leaders can make more informed decisions.

Conclusions

Over the last decade tremendous advances have been made in the understanding of the pathogenesis and prevention of HAP and VAP. Progress has also been made in developing new agents for treating HAP and VAP. Mirroring this increased research effort has been an evolution in our knowledge regarding the costs and outcomes related to HAP and VAP, and the means for assessing these. Clearly these two infections adversely affect costs and are perhaps the most expensive hospital-acquired complications which clinicians see routinely but which also are preventable. Further research is necessary to understand how to translate the findings from cost and cost-effectiveness analyses into formats that facilitate change in the hospital such that these infections can be better contained.

References

1. American Thoracic Society, and Infectious Diseases Society of America. (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*, Feb 15, **171** (4), 388−416.
2. Siegel, J.E., Weinstein, M.C., Russell, L.B. *et al*. (1996) Recommendations for reporting cost-effectiveness analyses. Panel on cost-effectiveness in health and medicine. *JAMA*, Oct 23−30, **276** (16), 1339−41.

3. Rubenfeld, G.D., Angus, D.C., Pinsky, M.R. *et al*. (1999 Jul) Outcomes research in critical care: Results of the American Thoracic Society critical care assembly workshop on outcomes research. The members of the outcomes research workshop. *Am J Respir Crit Care Med*, **160** (1), 358−67.
4. Shorr, A.F. (2002 Aug) An update on cost-effectiveness analysis in critical care. *Curr Opin Crit Care*, **8** (4), 337−43.
5. Rello, J., Ollendorf, D.A., Oster, G. *et al*. (2002 Jun) Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest*, **122** (6), 2115−21.
6. Kollef, M.H., Shorr, A., Tabak, Y.P. *et al*. (2005 Dec) Epidemiology and outcomes of healthcare-associated pneumonia: results from a large US database of culture-positive pneumonia.*Chest*, **128** (6), 3854−62.
7. Thompson, D.A., Makary, M.A., Dorman, T. *et al*. (2006 Apr) Clinical and economic outcomes of hospital acquired pneumonia in intra-abdominal surgery patients. *Ann Surg*, **243** (4), 547−2.
8. Warren, D.K., Shukla, S.J., Olsen, M.A. *et al*. (2003 May) Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. *Crit Care Med*, **31** (5), 1312−7.
9. Cocanour, C.S., Ostrosky-Zeichner, L., Peninger, M. *et al*. (2005) Cost of a ventilator-associated pneumonia in a shock trauma intensive care unit. *Surg Infect (Larchmt)*, Spring, **6** (1), 65−72.
10. Hugonnet, S., Eggimann, P., Borst, F. *et al*. (2004 Dec) Impact of ventilator-associated pneumonia on resource utilization and patient outcome. *Infect Control Hosp Epidemiol*, **25** (12), 1090−6.
11. Dietrich, E.S., Demmler, M., Schulgen, G. *et al*. (2002 Apr) Nosocomial pneumonia: A cost-of-illness analysis. *Infection*, **30** (2), 61−7.
12. Rosenthal, V.D., Guzman, S., Migone, O. *et al*. (2005 Apr) The attributable cost and length of hospital stay because of nosocomial pneumonia in intensive care units in three hospitals in Argentina: A prospective, matched analysis. *Am J Infect Control*, **33** (3), 157−61.
13. Shorr, A.F. and O'MalleyP.G. (2001 Jan) Continuous subglottic suctioning for the prevention of ventilator-associated pneumonia: Potential economic implications. *Chest*, **119** (1), 228−35.
14. Safdar, N., Dezfulian, C., Collard, H.R. *et al*. (2005 Oct) Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. *Crit Care Med*, **33** (10), 2184−93.
15. Mahul, P., Auboyer, C., Jospe, R. *et al*. (1992) Prevention of nosocomial pneumonia in intubated patients: Respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intensive Care Med*, **18** (1), 20−5.
16. Kollef, M.H., Skubas, N.J. and Sundt, T.M. (1999 Nov) A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients. *Chest*, **116** (5), 1339−46.
17. Smulders, K., van derHoeven, H., Weers-Pothoff, I. *et al*. (2002 Mar) A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. *Chest*, **121** (3), 858−62.
18. Mullins, C.D., Philbeck, T.E.Jr, Schroeder, W.J. *et al*. (2002 Aug) Cost effectiveness of kinetic therapy in preventing nosocomial lower respiratory tract infections in patients suffering from trauma. *Manag Care Interface*, **15** (8), 35−40.
19. Ahrens, T., Kollef, M., Stewart, J. *et al*. (2004 Sep) Effect of kinetic therapy on pulmonary complications. *Am J Crit Care*, **13** (5), 376−83.
20. Dodek, P., Keenan, S., Cook, D. *et al*. (2004) Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med*, Aug 17, **141** (4), 305−13.

21. Stoller, J.K., Orens, D.K., Fatica, C. *et al*. (2003 May) Weekly versus daily changes of in-line suction catheters: Impact on rates of ventilator-associated pneumonia and associated costs. *Respir Care*, **48** (5), 494–9.
22. Zack, J.E., Garrison, T., Trovillion, E. *et al*. (2002 Nov) Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. *Crit Care Med*, **30** (11), 2407–12.
23. Jain, M., Miller, L., Belt, D. *et al*. (2006 Aug) Decline in ICU adverse events, nosocomial infections and cost through a quality improvement initiative focusing on teamwork and culture change. *Qual Saf Health Care*, **15** (4), 235–9.
24. Nicolau, D.P., McNabb, J., Lacy, M.K. *et al*. (2001 Jun) Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. *Int J Antimicrob Agents*, **17** (6), 497–504.
25. Wysocki, M., Delatour, F., Faurisson, F. *et al*. (2001 Sep) Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: Prospective multicentre randomized study. *Antimicrob Agents Chemother*, **45** (9), 2460–7.
26. Shorr, A.F., Tabak, Y.P., Gupta, V. *et al*. (2006a) Morbidity and cost burden of methicillin-resistant Staphylococcus aureus in early onset ventilator-associated pneumonia. *Crit Care*, **10** (3), R97.
27. Shorr, A.F., Combes, A., Kollef, M.H. *et al*. (2006b Mar) Methicillin-resistant Staphylococcus aureus prolongs intensive care unit stay in ventilator-associated pneumonia, despite initially appropriate antibiotic therapy. *Crit Care Med*, **34** (3), 700–6.
28. Combes, A., Luyt, C.E., Fagon, J.Y. *et al*. (2004) PNEUMA Trial group. Impact of methicillin resistance on outcome of Staphylococcus aureus ventilator-associated pneumonia. *Am J Respir Crit Care Med*, Oct 1, **170** (7), 786–92.
29. Machado, A.R., ArnsCda, C., Follador, W. *et al*. (2005 Jun) Cost-effectiveness of linezolid versus vancomycin in mechanical ventilation-associated nosocomial pneumonia caused by methicillin-resistant Staphylococcus aureus. *Braz J Infect Dis*, **9** (3), 191–200.
30. Grau, S., Alvarez-Lerma, F., del Castillo, A. *et al*. (2005 Apr) Cost-effectiveness analysis of the treatment of ventilator-associated pneumonia with linezolid or vancomycin in Spain *J Chemother*, **17** (2), 203–11.
31. Shorr, A.F., Susla, G.M. and Kollef, M.H. (2004 Jan) Linezolid for treatment of ventilator-associated pneumonia: A cost-effective alternative to vancomycin. *Crit Care Med*, **32** (1), 137–43.

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Note: Figures and Tables are indicated by *italic page numbers*; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; HCAP = healthcare-associated pneumonia; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus* infections; VAP = ventilator-associated pneumonia

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