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Preface



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Guest Editors

Recent advances in scientific knowledge, biomedical technology, and multidisciplinary translational efforts have impacted the evaluation and treatment of many disorders, especially those of the pancreas. Disorders of the pancreas have, in the past, been very frustrating because the diagnosis was often made late in the course of the disease, and no significantly beneficial interventions were available. This situation is rapidly changing, because new insights from multiple perspectives are integrated and focused on each step of complex processes. This issue of *Gastroenterology Clinics of North America* highlights a number of areas of rapid progress in inflammatory and neoplastic disorders of the pancreas. Each article represents the integrated knowledge and perspective of expert faculty from molecular medicine, genetics, epidemiology, gastroenterology, therapeutic endoscopy, molecular and surgical pathology, minimally invasive surgery, surgical oncology, oncology, and abdominal imaging. This issue is also unique because each article includes physicians and scientists who work together on tough cases on a daily basis at the University of Pittsburgh, University of Pittsburgh Medical Center, and clinics of the UPMC Liver-Pancreas Institute. Indeed, these multidisciplinary approaches are needed to understand newly appreciated clinical problems of autoimmune pancreatitis, alcoholic pancreatitis, management of severe acute pancreatitis, evaluation and treatment options for IPMNs, cystic lesions, "incidentalomas," and nonfunctional neuroendocrine tumors. Improved interventions are also highlighted from both endoscopic and surgical perspectives. Together, these articles represent the most up-to-date

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analysis of state-of-the art approaches to complex issues in the evaluation and treatment of pancreatic disorders.

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Alcohol-Associated Pancreatitis

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Excessive alcohol use is a major cause of morbidity and mortality in the United States [1]. The economic cost of alcohol abuse in the United States increased 25% between 1992 and 1998 and was over $180 billion in 1998 [2]. Heavy alcohol use is the most common cause of chronic pancreatitis and the second commonest cause of acute pancreatitis in developed countries.

It is well known that alcohol alone is not sufficient to cause pancreatitis. This has been shown in animal studies, where in addition to alcohol, another stimulus is required to initiate pancreatic injury. Similarly, only a very small proportion of humans abusing alcohol ever develop pancreatitis. In addition to alcohol, other factors are important in the development of pancreatitis. This article focuses mainly on the epidemiology and the role of genetic susceptibility in alcoholic pancreatitis. The possible role of yet unknown cofactors (host, environmental, or their interactions) in susceptibility to pancreatitis in individuals with excessive alcohol use is highlighted.

EPIDEMIOLOGY OF ALCOHOL USE AND SMOKING IN THE UNITED STATES AND SELECTED EUROPEAN COUNTRIES

Alcohol and smoking are the two environmental factors shown to have an association with alcoholic pancreatitis. It is important to understand the patterns and trends for alcohol use and smoking in the general population. Although these aggregate data provide information at a population but not at an individual level, they are very helpful to understand the distribution of risk factors and trends in the general population.

Several federal surveys are conducted in the United States to determine the distribution of risk factors and measures of health in the general population.

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One such survey is the National Health Interview Survey, administered by the Centers for Disease Control and Prevention's National Center for Health Statistics since 1957. The National Health Interview Survey is conducted yearly in a sample of civilian United States noninstitutionalized population by household interviews. Data from the 2004 survey on the distribution of alcohol and smoking in the United States adult population 18 years of age and older are provided in Tables 1 and 2 [3,4]. Several important observations can be made from these data. The proportion of current drinkers and smokers was the highest among white men and women compared with African Americans and Hispanics or Latinos. A large proportion of current drinkers were moderate drinkers (4–14 drinks/week in men and 4–7 drinks/week in women), and heavier drinkers (>14 drinks/week in men and >7 drinks/week in women) comprised less than 10% of all current drinkers. These data parallel the distribution of risk

Table 1
Alcohol consumption and smoking by adults 18 years of age and older by selected characteristics according to the National Health Interview Survey 2004

	All		Whites		Black or African-American		Hispanic or Latino	
Characteristic	Male	Female	Male	Female	Male	Female	Male	Female
Drinking status								
Lifetime abstainer	17.9	30.7	14.6	23	28.8	46	22.3	51.4
Former infrequent drinker	6.9	9	6.7	9	8	10.3	6.4	8.9
Former regular drinker	8	5.3	8.4	5.9	7.9	4.5	8.2	4.1
Current infrequent drinker	10	16.3	9.9	16.9	9.7	15.1	10.6	14.9
Current regular drinker	56.5	38.3	59.9	44.8	43.9	23.8	51.8	20.4
Smoking status								
Nonsmoker	51.6	63.4	48.9	58.1	58.4	71.9	60.1	79.4
Former smoker	25.4	17.9	27	20.7	18.6	11.4	22.3	10.1
Current smoker	—	—	—	—	—	—	—	—
Some day smokers	4.4	3.5	3.9	3.6	4.4	4.1	5.9	2.9
Everyday smoker	18.6	15.2	20.2	17.7	18.6	12.6	11.8	7.6

Values are proportions.

Lifetime abstainer, <12 drinks in his or her lifetime; former drinker, ≥12 drinks in his or her lifetime and none in the past year; former infrequent drinker, former drinker who had <12 drinks in any one year and no drinks in the last year; former regular drinker, former drinker who had ≥12 drinks in any one year and no drinks in the last year; current drinker, ≥12 drinks in his or her lifetime and ≥1 drink in the past year; current infrequent drinker, current drinkers who had <12 drinks in the past year; current regular drinkers, current drinker who had ≥12 drinks in the past year.

Nonsmoker, never smoked >100 cigarettes in his or her lifetime; smoker, smoked >100 cigarettes in his or her lifetime but currently does not smoke at all; current smoker, ever smoked >100 cigarettes in his or her lifetime and currently smokes; some day smoker, current smoker who smokes on some days; everyday smoker, current smoker who smokes every day.

Data from Lethbridge-Cejku M, Rose D, Vickerie J. Summary health statistics for US adults: National Health Interview Survey, 2004. National Center for Health Statistics. Vital Health Stat 2006;10(228).

Table 2
Pattern of alcohol consumption (among current drinkers) by adults ages 18 years and older (age-adjusted) by selected characteristics based on the National Health Interview Survey, 2004

	Total (all races)	
Current drinkers[a]	Males	Females
Level of drinking		
Light	60.8	79.7
Moderate	31.5	13.6
Heavier	7.7	6.7
Number of days in the past year with ≥5 drinks		
No days	57.8	79.1
At least 1 day	42.2	20.9
1–11 days	21.5	14.5
≥12 days	20.7	6.4

Light drinking, drinking ≤3 drinks/week; moderate drinking, 4–14 drinks/week in men, 4–7 drinks/week in women; heavier drinking, >4 drinks/week in men, >7 drinks/week women.

[a]The data represent patterns of drinking among those classified as ''current drinkers.'' Definition of ''current drinkers'' provided in footnote of Table 1.

Data from National Center of Health Statistics. Health, United States, 2006. With chartbook on trends in the health of Americans. Hyattsville (MD): National Center of Health Statistics; 2006.

factors in patients with chronic pancreatitis. Traditionally, the group considered to be at high-risk for developing alcoholic pancreatitis is heavier drinkers. It is increasingly being recognized, however, that many patients with chronic pancreatitis, especially those seen at tertiary centers, may not fall into this category and have mild to moderate alcohol use or smoking. This could partly be caused by a referral bias but it does highlight the lack of understanding about the role of mild-moderate alcohol use in pancreatitis.

There is a large variation in alcohol consumption between countries. In developed countries (Table 3), where social use of alcohol is more common, per capita alcohol consumption is much higher than many Asian and African countries [5]. In the United States, per capita alcohol consumption peaked in the 1970s. Since then, it has progressively decreased and seems to have reached a plateau over the last decade (Table 4) [6]. Similarly, smoking rates in the general United States population have decreased almost by half from 1965 to 2004 [3]. The per capita alcohol consumption and smoking rate in the United States is modest compared with many European countries (see Table 3; Table 5) [5,7].

EPIDEMIOLOGY OF ALCOHOLIC PANCREATITIS

Several population-based studies, mainly from Europe and the United States, have described the epidemiology of first-attacks of acute pancreatitis [8–22]. The studies differ widely in design and most are retrospective [10–17,19–22]. Only a few studies have reported on etiology-specific incidence trends [16,20]. Other studies evaluating trends have correlated the incidence of acute

Table 3
Per capita alcohol consumption in selected Western countries in the Year 2000 or 2001

Country	Per capita consumption (liters of ethanol per year)
Canada	8.26
Denmark	11.93
Finland	10.43
France	13.54
Germany	12.89
Iceland	5.74
Italy	9.14
Netherlands	9.74
Norway	5.81
Switzerland	11.53
United Kingdom	10.39
United States	8.51

Data from World Health Organization. Alcohol: global status report on alcohol 2004. Available at: http://www.who.int/entity/substance_abuse/publications/global_status_report_2004_overview.pdf.

pancreatitis with diseases associated with common risk factors like gallstones and alcohol [11,12,21,23].

Over the last four decades, the overall incidence of acute pancreatitis has progressively increased. The main reason for this increase in the last two decades is attributed to an increase in the incidence of gallstone pancreatitis.

Table 4
Trends in the per capita alcohol consumption for selected years in United States from 1940 to 2003

Year	Per capita consumption (gallons of ethanol per year)[a]
1940	1.56
1945	2.25
1950	2.04
1955	2.00
1960	2.07
1965	2.27
1970	2.52
1975	2.69
1980	2.76
1985	2.62
1990	2.45
1995	2.15
2000	2.18
2003	2.22

[a]Based on population age ≥15 before 1970 and on population age ≥14 after 1970.

Data from Lakins NE, Williams GD, Yi H, et al. Surveillance Report #73. Apparent per capita alcohol consumption: national, state, and regional trends, 1977–2003. National Institute on Alcohol Abuse and Alcoholism. Available at: http://pubs.niaaa.nih.gov/publications/surveillance73/CONS03.pdf.

Table 5
Prevalence of smoking in adult population in selected European countries

Country	Year	Total	Male	Female	Definition/Criteria
Denmark	2002	28	31.2	27	Daily smokers; age 15+ years
Finland	2002	23	27	20	Daily or regular smokers; age 15–64 years
France	2000	27	33	21	Daily smokers; age 18+ years
Germany	2000	36.4	40.3	32.2	No definition available; age 20–54
Iceland	2000	24.1	25.3	22.9	Daily smokers; age 18–69 years
Italy	1999	25	32.4	17.4	Daily smokers; age 14–65 years
Netherlands	2001	30	33	27	Daily or occasional smokers; age 15+ years
Norway	2001–2002	29.6	29.5	29.7	Daily smokers; age 16–74 years
Switzerland	1997	33	39	28	Regular or occasional smokers; age 15–74 years
United Kingdom	2001	27	28	26	Current smokers; age 16+ years

Data from World Health Organization. European country profiles on tobacco control 2003. Available at: http://www.euro.who.int/document/E80607.pdf. Data from individual countries in this report were taken from national and international sources, which are identified in the report.

This observation was found in individual studies evaluating etiology-specific trends [16,20], studies correlating the incidence rates with risk factors [11], and speculated in a recent systematic review of population-based studies [24]. A recent United States–based population study from California found that the incidence of gallstone pancreatitis increased 32% from 1994 to 2001 [16].

In contrast to gallstone pancreatitis, the trend for acute alcoholic pancreatitis differs among studies. Reports from the United Kingdom and Finland indicate an increase in alcoholic pancreatitis correlating with an increase in the per capita alcohol consumption [23,25,26], whereas others report a decrease resulting from a reduction in alcohol consumption [11,20]. In Sweden, the incidence of alcoholic pancreatitis increased in the 1970s because of an increase in alcohol consumption [21,22]. Over the last two decades, the incidence of alcoholic pancreatitis and other common alcohol-associated disorders, like cirrhosis and delirium tremens, has been decreasing [20]. In the United States, the per capita alcohol consumption peaked in the 1970s. Since then it has been decreasing and has almost reached a plateau in the last decade [6]. A recent United States

study from California found that the increase in the incidence of acute alcoholic pancreatitis from 1994 to 2001 was much smaller at 12% (from 7.5–8.4 cases per 100,000) [16].

Only a few population-based studies have reported on the epidemiology of chronic pancreatitis [8,19,21,23,25–30] or provided etiology-specific incidence rates [19,23,26,30]. The annual overall incidence of chronic pancreatitis varies widely in these studies (1.9–14.1 per 100,000) [8,19,23,26–28,30]. The reasons for these wide variations are differences in study designs, years of study, and prevalence of risk factors. Individual studies from the United States (1940–1969), Denmark (1970–1979), and the United Kingdom (1960–1984 and 1989–1990 to 1999–2000) have reported an increase in the incidence of alcoholic chronic pancreatitis [23,26,27,30] caused by an increase in alcohol consumption. Except for the United Kingdom, the other studies are older and recent trends for chronic pancreatitis in these countries are not known. The prevalence of chronic pancreatitis has been reported from Copenhagen (27.4 per 100,000 in 1979) [8] and Japan (28.9 per 100,000 in 1994) [29].

Several conclusions can be drawn from these data. The incidence of alcoholic pancreatitis varies widely between countries. The reasons for this could be differences in the distribution of risk factors, criteria used for diagnosis and case-ascertainment, or differences in susceptibility. The incidence of alcoholic pancreatitis has increased in some but not all countries. Data on the prevalence of chronic pancreatitis are limited (available only from two countries). The incidence of chronic pancreatitis seems to be higher in newer studies. A part of this increase could be a result of widely available newer imaging techniques (endoscopic retrograde cholangiopancreatography, CT scan, MRI), making the detection of anatomic abnormalities easier.

RISK OF ALCOHOLIC PANCREATITIS WITH INCREASING ALCOHOL USE

Population-based studies report a dose-dependent relationship between alcohol use and development of liver disease [31–33]. A threshold of 30 g/d (2–3 drinks/d) has been observed for chronic liver disease [33]. The relative risk of chronic liver disease increases in a linear fashion above 7 to 13 drinks per week in women, and 14 to 27 drinks per week in men [31]. In very heavy alcoholics (>120 g/d), the risk of alcoholic liver disease and cirrhosis is 7.8% and 5.7%, respectively [33].

There are no population-based studies assessing the risk of pancreatitis in relation to the amount of alcohol use. Virtually all studies have used a case-control design. The odds ratio obtained in case-control studies can be used as a surrogate for relative risk; however, it may not help in understanding the threshold for developing a disease accurately. Sarles and colleagues [34] initially reported a possible dose-response relationship between the amount of alcohol use and development of pancreatitis in a log-linear model. Subsequently, numerous studies have shown that the amount of alcohol consumption in

patients with alcoholic pancreatitis is significantly higher than controls and is well over 100 g/d (>8 drinks/d) for a prolonged period of time (>5–10 years) [35–38].

Based on their observations in a defined German population, Lankisch and colleagues [39] predicted that the risk of developing alcoholic pancreatitis in heavy drinkers (defined as alcohol intake of ≥60 g/d) over a 20- to 30-year period is likely to be 2% to 3%. In a male veteran population attending an outpatient detoxification program, it was found that the prevalence of definite alcoholic pancreatitis after chart review in this high-risk population was at least 3% [40]. Among those with definite alcoholic pancreatitis, documented chronic pancreatitis was present only in one third of cases indicating a low prevalence of alcoholic chronic pancreatitis in heavy alcoholics [40]. The risk of pancreatitis with heavy alcohol consumption is much lower than alcoholic liver disease or cirrhosis. A recent meta-analysis looking at the dose-response relationship between alcohol and the risk of several alcohol-related conditions also indicated that the risk for pancreatitis is weaker than cirrhosis and many other disorders [41].

Because the threshold below which the risk of pancreatitis is constant is unknown, the role of mild-moderate amounts of alcohol use in the development or progression of pancreatitis remains unclear. The concept of individual susceptibility to smaller amounts of alcohol use in pancreatitis was explored by Lankisch and colleagues [42]. They reported that smaller amounts of alcohol use (<50 g/d) in subjects with idiopathic pancreatitis resulted in an earlier onset of disease compared with those with no alcohol intake [42].

The conclusions that can be drawn from these data are that the risk of pancreatitis in heavy drinkers is low. Because only a very small proportion of alcoholics develop pancreatitis, in addition to alcohol, there must be a role of other yet unknown cofactors (environmental, genetic, or their interactions).

COFACTORS IN ALCOHOLIC PANCREATITIS

Smoking

Apart from alcohol, the other major environmental risk factor associated with alcoholic pancreatitis is smoking. This association was initially reported by Yen and colleagues [43], and has been confirmed in several subsequent studies [35,37,44–46]. Because more than 90% of patients with alcoholic pancreatitis are also chronic smokers [35,37], most epidemiologic studies have used a case-control design to determine the independent role of smoking in alcoholic pancreatitis after controlling for the amount of alcohol consumption [35,37,46]. Controls in most of these studies were drawn from either the general population [35,37,44,45] or were hospitalized patients [43,46], and subjects with diseases associated with alcohol use or smoking were usually excluded. Not all studies, however, evaluating the role of smoking in alcoholic pancreatitis found an association [36,47]. Haber and colleagues [36] reported that the proportion of smokers among alcoholic subjects with pancreatitis was similar to those

without pancreatitis (86.5 versus 87.2%, $P = $ NS). They argued that the associations detected in prior studies may have resulted from their choice of controls or assessment of tobacco consumption [36,48].

A limitation of these studies is their case-control design and the high prevalence of smoking in patients with heavy alcohol use. The ideal way to evaluate the association between smoking and alcoholic pancreatitis is to compare the risk (cohort study, prospective or retrospective) or prevalence (case-control) of pancreatitis in alcoholics with and without smoking. Such a study is difficult to do for two reasons: alcohol and smoking habits are usually coexistent, and because only a small proportion of heavy alcoholics ever develop pancreatitis, a very large sample size is needed. One recent retrospective cohort study reported on the risk of developing alcoholic pancreatitis in greater than 120,000 subjects who enrolled for health care with Kaiser Permanente from 1978 to 1985 and supplied information on smoking at enrollment. The relative risk of developing alcoholic pancreatitis (follow-up until 1998) in smokers (versus nonsmokers) was 4.9 (95% confidence interval [CI], 2.2–11.2, $P < .001$) [49]. The independent role of smoking in pancreatitis is also indicated by the observations that smoking leads to disease progression in alcoholic pancreatitis and it accelerates the development of calcifications in alcoholic pancreatitis [50,51] and idiopathic pancreatitis [52].

The role of smoking is believed to be more important in alcoholic pancreatitis than other alcohol-associated diseases, such as alcoholic cirrhosis [35,53]. Lowenfels and colleagues [53] reported that the odds of being a smoker among men with alcoholic pancreatitis were 12.5 (95% CI, 1.9–82, $P = .008$) compared with alcoholic cirrhosis. They also found a dose-dependent relationship with the amount of smoking for pancreatitis but not cirrhosis. Bourliere and colleagues [35] noted smoking to be more prevalent in alcoholic chronic pancreatitis than alcoholic cirrhosis (94% versus 83%, $P < .05$). After stratifying subjects based on the amount of tobacco and alcohol use, they found that heavy smokers were also heavy drinkers for both pancreatitis and cirrhosis. Only in patients with chronic pancreatitis, however, was the reverse true (ie, heavy drinkers were also heavy smokers) [35].

Race

Racial differences in the susceptibility to pancreatitis have been recognized. Lowenfels and colleagues [54] compared the racial status among patients hospitalized for chronic pancreatitis or alcoholic cirrhosis in two United States hospitals (one Veterans Administration and the other a community hospital) and one hospital in Portugal. They found a significantly higher proportion of blacks among chronic pancreatitis than alcoholic cirrhosis patients (50% versus 23%). After adjusting for gender and hospital location, compared with cirrhosis, the odds of chronic pancreatitis patients to be blacks were 2.5 (95% CI, 1.9–3.2, $P < .001$) [54]. The racial differences were observed for both genders in the United States hospitals [54]. In a cohort study, Morton and colleagues [49] reported a relative risk of developing alcoholic pancreatitis in blacks to be 2.6

(95% CI, 1.8–3.9) compared with whites. Similarly, in a recent population-based study from California, the incidence of first-attacks of alcoholic-pancreatitis per 100,000 population in year 2000 was the highest in African Americans (21.6 ± 1.2) compared with whites (16.7 ± 0.5), Hispanics (8.1 ± 0.4), or Asians (2.1 ± 0.2) [16].

The reasons for a higher risk of alcoholic pancreatitis in African Americans are unclear. It has been speculated that this could be related to differences in alcohol consumption between the two races or a higher susceptibility in African Americans to the effects of alcohol [16,54]. The aggregate data on self-reported alcohol consumption and smoking in the National Health Interview Survey (see Table 1, 2004 data) indicate that the proportion of current drinkers and smokers is lower for African Americans than whites [4]. The age-adjusted prevalence of current smokers among African Americans 25 years of age and older was higher (7%–11% points) from 1965 to 1990. Since then, this difference has been decreasing and has been between 2% and 5% over the last few years [3]. Although conclusions at an individual level using aggregate data cannot be made with certainty (ecologic fallacy), such data provide important direction for research in understanding the differences seen in patient or individual level studies. In context to alcoholic pancreatitis, studies examining differences in exposure to alcohol and smoking in alcoholic pancreatitis patients based on race will help to understand whether such differences explain a higher racial susceptibility to alcoholic pancreatitis or whether other factors (environmental or genetic) are responsible for such differences.

Diet and Drinking Pattern

The data on the role of dietary factors and alcoholic pancreatitis are conflicting. Although some studies report an association of alcoholic chronic pancreatitis with a high-fat, high-protein diet [47,55,56], others have found no association [57,58]. An important reason for these differences is that retrospective assessment of dietary intake is difficult and even more challenging than alcohol and smoking. Similar to diet, the role of binge drinking in alcoholic pancreatitis is conflicting [57,59,60]. Animal studies have shown that withdrawal from prolonged alcohol intake could lead to hyperstimulation of the pancreas from loss of inhibitory regulation in the brain and an exaggerated response at the acinar level. This could be an initiating event for an attack of acute pancreatitis [61]. Nordback and colleagues [62] found that in a large proportion of patients who present with acute alcoholic pancreatitis, symptoms started in the withdrawal period after cessation of long-term drinking. They speculated that an attack of alcoholic pancreatitis could be a manifestation of alcohol withdrawal. Clearly, more studies are needed to understand the role of drinking patterns and diet.

GENETICS AND ALCOHOLIC PANCREATITIS

Alcohol Metabolizing Enzymes

Because products of alcohol metabolism can be toxic and in the context of inflammation promote fibrosis [63], an interest has been to study the role of

genetic polymorphisms in alcohol metabolism pathway enzymes in alcoholic pancreatitis [64–70]. The primary alcohol metabolizing enzymes are alcohol dehydrogenase and aldehyde dehydrogenase [71]. In heavy alcoholics, there is induction of microsomal cytochrome P-450 system and the nonoxidative pathway to metabolize the excess alcohol in the pancreas [72]. This leads to generation of reactive oxygen species and lipid peroxidation products that have proinflammatory and profibrogenic effects [63,72,73]. It has been hypothesized that polymorphisms in alcohol metabolizing enzymes lead to an increased generation of reactive oxygen species and lipid peroxidation products or decreased detoxification resulting in organ damage [74].

Polymorphisms in alcohol dehydrogenase-2 and aldehyde dehydrogenase-2 have been attributed to the risk of alcoholic cirrhosis, pancreatitis, and alcoholism in Asians [75–78]. Similar studies among whites, however, report conflicting results [64–70]. The amount of alcohol used to define alcoholism has varied widely between studies, which could lead to heterogeneity in the patient population and make comparisons between studies difficult. Most studies have concentrated on evaluating the role of single polymorphisms in groups of subjects with and without disease. Currently, there is no clear evidence to support the role of the known polymorphisms in alcoholic pancreatitis in whites.

ROLE OF *CFTR*, *PRSS-1*, AND *SPINK-1* MUTATIONS

Mutations in three genes, the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) [79,80], the cationic trypsinogen gene (*PRSS1*) [81,82], and the serine protease inhibitor Kazal type 1 (*SPINK1*) [83,84], have all been shown to increase susceptibility to acute or chronic pancreatitis. Each of these genes has also been studied in patients diagnosed with alcoholic chronic pancreatitis [80,83,85–88]. Although the prevalence of polymorphisms and mutations in these genes is usually increased in alcoholic chronic pancreatitis compared with control populations, none of these genes has been found to be the major cofactor in alcoholic chronic pancreatitis.

Two severe mutations in the *CFTR* gene leads to cystic fibrosis, an autosomal-recessive disorder characterized by dysfunction of epithelial cells in the respiratory system; sweat glands; vas deferens; digestive tract (including meconium ileus); and chronic pancreatitis [89]. Recurrent acute pancreatitis is a feature of atypical cystic fibrosis, a *CFTR* mutation-associated disorder with mild or isolated cystic fibrosis–associated features. Patients with atypical cystic fibrosis have functionally less severe *CFTR* mutations with typical genotypes reflecting a combination of severe plus mild-variable, or two mild-variable mutant *CFTR* alleles [90]. In addition, some patients without any other evidence of cystic fibrosis and chronic pancreatitis have an increased incidence of *CFTR* mutations, including patients diagnosed with alcoholic pancreatitis [91,92]. Although it seems that some *CFTR* mutations do increase the risk of pancreatitis, it is currently unknown exactly which mutations and variants, in which combination, contribute to the development of chronic alcoholic pancreatitis, especially in subjects with only moderate alcohol intake.

Gain-of-function mutations in the *PRSS1* gene, including R122H [81] and N21I [82], cause hereditary pancreatitis, a high-penetrance, autosomal-dominant disorder characterized by recurrent acute pancreatitis beginning in childhood, chronic pancreatitis developing as a young adult, and pancreatic cancer developing later in life [93]. In the authors' experience, a few patients with hereditary pancreatitis have been diagnosed with alcoholic pancreatitis even though they never drank alcohol in their lives, based on the fact that they had chronic pancreatitis. In addition, members of hereditary pancreatitis families state that they are very sensitive to any alcohol, with several drinks triggering mild attacks of acute pancreatitis. The early age of onset of hereditary pancreatitis versus alcoholic pancreatitis, however, and the use of genetic testing indicate that hereditary pancreatitis and alcoholic pancreatitis are two separate disorders.

Mutations in the *SPINK1* gene, and especially the N34S allele [84,94], are common in most populations throughout the world (1%–2%) [95]. *SPINK1* polymorphisms are associated with multiple types of pancreatitis [96], including idiopathic chronic pancreatitis in children [94], familial chronic pancreatitis [84], tropical pancreatitis [97–99], and alcoholic chronic pancreatitis [83,88]. The weakest association between the *SPINK1* N34S allele and the various chronic pancreatitis etiologies is in patients with alcoholic chronic pancreatitis. Most recent studies that included alcoholic chronic pancreatitis in *SPINK1* gene analysis failed to identify a statistically significant association. The three studies that did report an association, reported odds ratios ranging from 4.12 to 11.08 [83,86,88], which is much less than the odds ratios found between *SPINK1* polymorphisms pancreatitis classified by other etiologies. This suggests that subjects who have *SPINK1* polymorphisms and drink alcohol are at moderate increased risk of chronic pancreatitis [88]. Most patients with alcoholic acute and chronic pancreatitis do not have *SPINK1* mutations, however, and the primary cofactor is yet to be discovered.

MODEL FOR ALCOHOLIC PANCREATITIS

A model can be thought of as a simplified copy or representation of something that is known or understood. The link between alcohol and pancreatitis is complex, requiring some unknown factors in addition to exposure to alcohol. Consequently, it has been difficult to develop good models of alcoholic pancreatitis.

In 1999, the Sentinel Acute Pancreatitis Event (SAPE) hypothesis model was proposed [100] to link genetic and environmental risk factors, the proinflammatory and anti-inflammatory immune responses, the stellate cells, and pancreas-targeting events into a systems-based, time-depended hypothetical model. The key element of the model was the stochastic, sentinel acute pancreatitis event, which was both necessary and sufficient to activate the immune system, including the pancreatic stellate cells [101,102]. The SAPE hypothesis model allowed all of the risk factors, including the timing of exposure, to be organized with respect to a specific point in time. It also provided clarity on which factors were susceptibility factors (eg, genetic and environmental factors that cause

acute pancreatitis), and which factors were modifier factors (eg, genetic and environmental factors that accelerated fibrosis). Finally, it allowed for specific experiments to be developed that tested specific hypotheses at steps within the model.

In evaluating the SAPE model it becomes clear why alcohol is so closely linked to chronic pancreatitis [103]. Alcohol is both a susceptibility factor for acute and recurrent acute pancreatitis; an immune modulator that suppresses the proinflammatory innate immune system in favor of the anti-inflammatory response; and a factor that drives the activated stellate cells (both directly and indirectly), which cause fibrosis (Fig. 1). Tobacco smoking, the model suggests, also drives fibrosis because it is a strong anti-inflammatory cytokine promoter (eg, interleukin-10) by the carbon monoxide, heme oxygenase system [104,105].

A SAPE model for alcoholic chronic pancreatitis was recently tested in rats [106]. Rats were fed either a standard alcohol-supplemented diet or control diet. It was found that there was no pancreatic damage, even though the pancreas of the alcohol-fed animals was under metabolic stress [106]. There was little difference between alcohol-fed rats and control-diet rats after one episode of acute pancreatitis, except that suppression of the proinflammatory response to acute

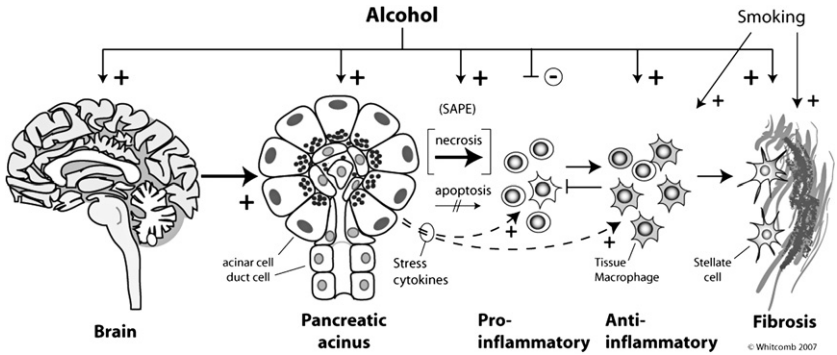

Fig. 1. Sites of alcohol-related risk for pancreatitis. Chronic alcohol alters the neurohormonal control of the pancreas within the brain causing pancreatic hyperstimulation, increasing risk of acute pancreatitis. Alcohol also causes acinar cell stress, which lowers the threshold for trypsinogen activation and pancreatitis, causes release of stress signals (stress cytokines), but also blocks cell death by apoptosis. Alcohol suppresses the acute inflammatory response and the pancreas remains histologically normal. If acute pancreatitis is triggered (eg, SAPE), then the immune system is activated including proinflammatory and later anti-inflammatory cells, chemokines, and cytokines (ie, all elements to the right of the acinus are recruited to the pancreas or activated). Acinar cell death by necrosis (rather than apoptosis) strongly stimulates the inflammatory response. The anti-inflammatory response is associated with inhibition of the acute inflammatory response and with healing (including scaring), which is mediated by the pancreatic stellate cells. If the stellate cells are over activated (eg, driven by the effects of alcohol and smoking on tissue macrophages and stellate cells), then excessive fibrosis occurs, the hallmark of chronic pancreatitis. (*Courtesy of* D. Whitcomb, MD, PhD, Pittsburgh, PA.)

injury was suppressed in alcohol-fed rats. After three episodes of acute pancreatitis the pancreases of the control-diet rats made full histologic recovery, but the pancreases in the alcohol-fed rats had evidence of chronic pancreatitis with marked increase in key proinflammatory and anti-inflammatory cytokines (interleukin-10 and transforming growth factor-β), in expression of collagen 1α and procollagen α2 mRNA, and in all markers of fibrosis. The development of alcoholic pancreatitis in this rat model required both the SAPE and recurrent activation of the immune system.

CLINICAL PRESENTATION AND NATURAL HISTORY

The clinical presentation and natural history of alcoholic pancreatitis is elegantly described in studies from several countries [107–110]. The disease is more common in men with the male/female ratio ranging from 2.5 to over 5 [109,111]. Acute alcoholic pancreatitis typically presents between the age of 35 to 44 years in men and 25 to 34 years in women, whereas chronic alcoholic pancreatitis presents a decade later [19]. Most patients have abdominal pain or recurrent attacks of acute pancreatitis as their initial symptom. Approximately 85% to 90% patients have abdominal pain at sometime during their course [107,109]. Amman and Muellhaupt [107] have described two pain patterns in patients with alcoholic chronic pancreatitis (type A: intermittent, short duration, usually controlled medically; and type B: persistent, longer duration, associated with the need for surgery). Surgery is needed in 40% to 45% of patients at some point in time, mainly for persistent pain or complications [107,109]. The time to achieve pain relief (spontaneously or following surgery) is variable and may occur several years after disease onset [107,109]. The proportion of subjects developing exocrine or endocrine insufficiency and calcifications increases with the duration of the disease and is seen in 80%, 50%, and 70% of cases, respectively, after 10 years of disease onset [107]. The natural history in alcoholic chronic pancreatitis differs from idiopathic chronic pancreatitis [109,112]. Stopping alcohol use after disease onset may reduce pain and slow the progression of the disease [113,114].

IS ACUTE PANCREATITIS CAUSED BY ALCOHOL MORE SEVERE THAN OTHER ETIOLOGIES?

The data on differences in etiology-specific severity and mortality in acute pancreatitis are mixed. This could partly be caused by small sample size for deaths after stratification for disease etiology in many studies. Although some studies have found a higher mortality in pancreatitis from etiologies other than alcohol [115,116], others have not [9,117,118]. A recent population-based study from California found that the odds of dying from acute alcoholic pancreatitis were higher compared with gallstone and idiopathic pancreatitis (odds ratio 1.9 and 1.2, respectively; $P < .05$) after controlling for demographic factors like age, race or ethnicity, and gender [16].

Recently, Papachristou and colleagues [119] reported that patients with acute pancreatitis who had chronic alcohol use (>2 drinks/d) are at an increased risk

of developing pancreatic necrosis. The finding in this two-arm study (a prospective and retrospective phase) of an association between chronic alcohol ingestion and higher rates of pancreatic necrosis, regardless of the etiology of acute pancreatitis, is novel and unexpected [119]. The pancreas of alcoholics may be at higher risk of ischemic injury or segmental necrosis because it is already under metabolic stress and has decreased reserve and tolerance for injury. Another intriguing possibility is that chronic alcohol exposure shifts the mechanism of cell death from apoptosis to necrosis [120,121].

QUALITY OF LIFE IN ALCOHOLIC PANCREATITIS

No standardized or widely accepted disease-specific instruments currently exist for assessing quality of life (QOL) in patients with chronic pancreatitis. Most investigators have used general QOL instruments (SF-36, SF-12) for such studies [122–125]. Using these instruments has helped investigators to compare the QOL in chronic pancreatitis with population controls and patients with other common diseases [122–125]. Questions specific to pancreatitis (pain, diarrhea, diabetes, disease duration, surgery, alcohol consumption, and so forth) have been used to assess their impact on QOL.

The QOL in chronic pancreatitis is significantly impaired compared with age- and gender-matched population controls and many other common diseases [122–126]. The factors affecting physical QOL include abdominal pain, body mass index, diarrhea, unemployment, early retirement, increasing age, diabetes, and surgery, whereas the mental QOL is affected by pain and chronic diarrhea [123,125]. In addition to symptoms specific for pancreatitis, other factors affecting QOL were found to be fear of future health problems, difficulty sleeping, and fatigue [126].

Data on differences in QOL among different forms of chronic pancreatitis are limited. This is mainly because of the small number of patients in many studies and a large proportion of them having alcoholic chronic pancreatitis. Wehler and colleagues [123] found no differences in QOL on the basis of disease etiology. They did report, however, that compared with other forms of chronic pancreatitis, the QOL in alcoholic pancreatitis was impaired in the vitality domain and ongoing alcohol use or alcoholic etiology was associated with unemployed or retiree status [123].

SUMMARY

Only a small proportion of heavy-drinking individuals ever develop pancreatitis, indicating a role of cofactors in individual susceptibility to alcohol. The two cofactors identified to play a role in alcoholic pancreatitis are smoking and race. The known genetic variations in *PRSS-1*, *CFTR*, and *SPINK1* genes and polymorphisms in alcohol metabolizing pathway do not seem to play an important role in alcoholic pancreatitis. Newer developments in the understanding of complex disorders will allow clinicians to understand better the role of

cofactors and interactions between known and yet unknown environmental and genetic factors in causing alcoholic pancreatitis.

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Autoimmune Pancreatitis

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Autoimmune pancreatitis (AIP) is a benign fibroinflammatory form of chronic pancreatitis that has unique clinical, radiographic, and histopathologic features and tends to respond to corticosteroid therapy. This form of chronic pancreatitis was first described by Sarles and colleagues [1] in 1961 as a primary inflammatory and sclerotic process of the pancreas. It was associated with hypergammaglobulinemia that was thought to be autoimmune in nature. In 1995, based on the Japanese experience with this form of pancreatitis, Yoshida and colleagues [2] proposed the term "autoimmune pancreatitis." Numerous other terms have been used to described AIP (and similar processes), including chronic sclerosing pancreatitis [3], nonalcoholic duct-destructive pancreatitis [4], idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration or idiopathic duct-centric chronic pancreatitis [5], lymphoplasmacytic sclerosing pancreatitis [6], and idiopathic tumefactive chronic pancreatitis [7]. The more general term "autoimmune pancreatitis" has persisted and seems to be the current name of choice, even though the underlying pathogenesis has not been fully elucidated and a specific autoimmune target has not been identified.

Over the past 10 years, more information has been gained about AIP. During this time, AIP has been found to be associated with increased IgG4 levels within the serum and increased IgG4-positive plasma cells within the inflamed pancreatic tissue. More recently, elevated numbers of IgG4-positive cells have also been identified in other organs of patients with AIP, and other forms of

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IgG4-related fibroinflammatory diseases have been reported, including sclerosing sialadenitis, retroperitoneal fibrosis, and sclerosing cholangitis. Based on these more recent observations, AIP is now believed to be one manifestation of a systemic IgG4-related sclerosing disease [8].

Even though the pathogenesis of AIP and its associated inflammatory sclerotic diseases are still being characterized, the knowledge of the existence of this form of chronic pancreatitis is imperative. AIP can often mimic pancreatic ductal adenocarcinoma and a diagnosis of AIP could prevent unnecessary surgery. This article covers the clinical presentation, imaging findings, and histopathologic features that are unique to AIP. The pathogenesis, diagnostic criteria, and therapeutic options for AIP are also covered.

CLINICAL FEATURES OF AUTOIMMUNE PANCREATITIS

The clinical presentation of AIP may include pancreatic or extrapancreatic manifestations:

- Pancreatic manifestations
  - Obstructive jaundice
  - Diabetes
  - Steatorrhea
  - Upper abdominal discomfort or pain
  - Weight loss
  - Acute pancreatitis (rare)
- Extrapancreatic manifestations
  - Biliary strictures
  - Sclerosing cholangitis
  - Sialoadenitis
  - Retroperitoneal fibrosis
  - Hilar or abdominal lymphadenopathy
  - Chronic thyroiditis
  - Interstitial nephritis
  - Inflammatory bowel disease

Because the knowledge about AIP has been evolving over the last few years, its full clinical spectrum is still unclear. Most reports in the literature consist of case series and reports; the proportion of patients with several of the clinical features is highly variable. AIP tends to occur more commonly in men and usually presents in the sixth and seventh decade of life [9–11]. The most common presentation, seen in over two thirds of patients with an acute presentation, is obstructive jaundice associated with a biliary stricture and a focal mass or diffuse enlargement of the pancreas [9,10,12]. The major differential diagnosis in this situation is pancreatic or biliary cancer, often leading to surgical resection [7,13]. Other pancreatic manifestations include the presence of a pancreatic mass, diffuse or focal enlargement of the pancreas in the absence of obstructive jaundice, and new onset or worsening of existing diabetes or steatorrhea [9,10,14–17]. In contrast to other forms of chronic pancreatitis, abdominal pain and attacks of acute pancreatitis are uncommon manifestations of AIP.

Most patients with AIP have no or mild abdominal pain or discomfort that is controlled by nonnarcotic analgesics [7,10]. Pancreatic enzyme elevations may be seen in some patients [14,16].

AIP has been associated with involvement of several other organs. These extrapancreatic manifestations of AIP can be seen in up to 49% of patients [10] and include biliary strictures, sclerosing cholangitis [2,18–20], sialadenitis [2,21,22], retroperitoneal fibrosis [21,23], hilar or abdominal lymphadenopathy [17,21,23], chronic thyroiditis [5,13,23], interstitial nephritis [24,25], and inflammatory bowel disease [5,13,23]. The extrapancreatic manifestations may occur concurrently with pancreatic disease, may be present before the recognition of pancreatic disease, or can occur weeks to months after their initial presentation [10,23].

IMAGING STUDIES IN AUTOIMMUNE PANCREATITIS

Although several distinguishing imaging features of AIP have been proposed in the literature, the lack of familiarity of this entity by radiologists and referring clinical services often results in an errant diagnosis of pancreatic carcinoma. Box 1 summarizes the imaging features of AIP. The characteristic appearance of AIP observed by various imaging modalities is that of a diffusely enlarged pancreas; calcifications, stones, and pseudocysts are typically not seen.

On CT, in addition to appearing diffusely enlarged (Fig. 1A), the pancreas has delayed and prolonged contrast enhancement and can have a capsule-like low-density rim surrounding the pancreas [26–29]. In a large study by Sahani and colleagues [30], uniform pancreatic enlargement and isoenhancement were common features in most patients with diffuse AIP; peripancreatic infiltration, when present, was minimal. Absence of normal pancreatic clefts and a subtle rim of hypoattenuation were thought to be caused by inflammatory exudates (Fig. 2A). More focal AIP, typically within the head and uncinate process, was difficult to distinguish from pancreatic carcinoma.

Similar morphologic changes in the pancreas have also been described at MRI (Fig. 1B). Decreased T1 and increased T2 signal intensity, uniform enhancement, global pancreatic enlargement, and a hypointense peripancreatic capsule have been reported in several small MRI case series [27–29]. Unfortunately, as with CT, a stand-alone MRI diagnosis of more focal AIP is difficult, if not impossible.

On endoscopic retrograde cholangiopancreatography (ERCP), the pancreatic duct has an irregular contour and can be either segmentally or diffusely narrowed [31]. If the proximal duct is strictured, there is often dilation of the distal pancreatic duct or proximal common bile duct. Unlike ERCP, MRCP may not be able to detect the irregular narrowing of the main pancreatic duct, but the MRCP findings of skipped, nonvisualized main pancreatic duct lesions, in conjunction with other imaging studies, are useful in supporting a diagnosis of AIP [32].

Diffuse pancreatic enlargement can also be visualized by endoscopic ultrasound (EUS) imaging (Fig. 2B). Currently, however, EUS alone cannot reliably

Box 1: Features of autoimmune pancreatitis by various imaging modalities

General findings

Diffusely or focally enlarged pancreas

With structuring of the main pancreatic duct, can see dilatation of the upstream pancreatic or common bile ducts

Typically absent: calcifications, pancreatic duct stones, and pseudocysts

CT

Diffuse pancreatic enlargement, uniform enhancement, minimal pancreatic infiltration

The focally enlarged pancreas can mimic pancreatic cancer

Capsule-like low-density rim surrounding the pancreas

MRI

Global pancreatic enlargement decreased T1 signal, increased T2 signal, peripancreatic decreased signal intensity

ERCP

Segmental or diffuse irregular narrowing of the main pancreatic duct

MRCP

Skipped, nonvisualized main pancreatic duct lesions ± upstream dilatation

Segmental or diffuse irregular narrowing of the main pancreatic duct may not be seen

EUS

During routine evaluation of a pancreatic mass, EUS can provide targeted fine-needle aspirates or core biopsies to aid in the distinction between carcinoma and AIP

distinguish between a neoplastic and an inflammatory mass. The EUS-targeted core biopsy combined with staining for IgG4 or the EUS-guided fine-needle aspiration combined with staining for IgG4 or molecular analysis may prove to be useful in the diagnosis of AIP (see later).

SEROLOGIC MARKERS IN AUTOIMMUNE PANCREATITIS

AIP is associated with many specific and some nonspecific serologic markers. One antibody that has shown promise as a serologic marker for the diagnosis of AIP is IgG4. In normal adults, IgG4 typically comprises about 4% of the total circulating IgG [33]. Elevated IgG4 levels have been reported in

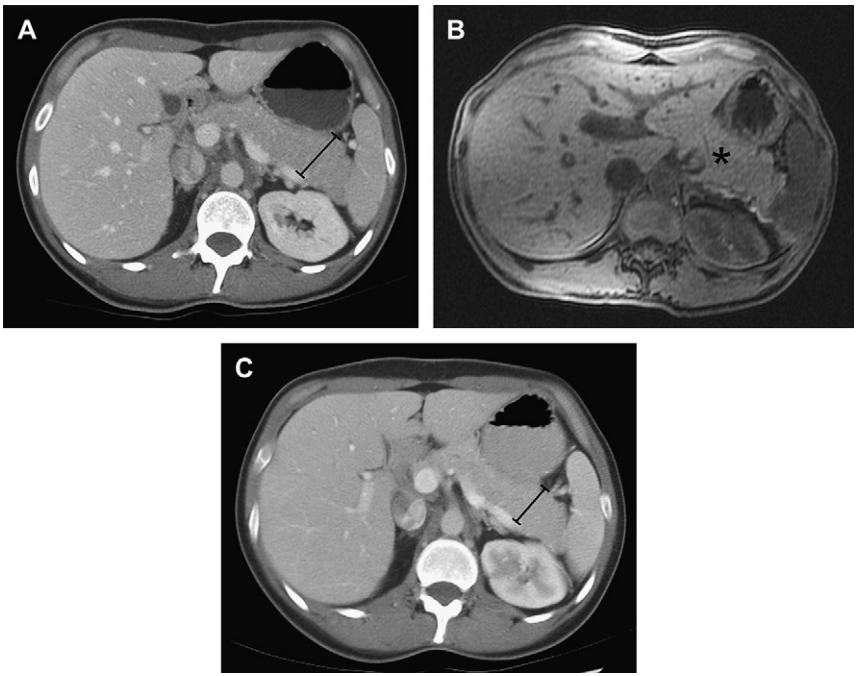

Fig. 1. Images from a 42-year-old woman with mild abdominal pain and history of undifferentiated connective tissue disease. (*A*) Contrast-enhanced CT shows global pancreatic enlargement. The pancreas enhances uniformly. (*B*) Fat saturation T1-weighted image shows diffuse pancreatic enlargement (*asterisk*). (*C*) Contrast-enhanced CT performed after steroid treatment shows a decrease in size of the pancreas (compare measure bar with Fig. 1A).

dermatologic illnesses, such as pemphigus vulgaris, pemphigus foliaceus [34], atopic dermatitis [35], and some parasitic infections [36–38]. IgG4 elevation has also been reported in chronic sclerosing sialadenitis (Kuttner's syndrome) [39,40] and Mikulicz's disease [41], conditions that are thought to be extrapancreatic manifestations of IgG4-related sclerosing disease [42].

In a study by Hamano and colleagues [43], an elevated serum IgG4 level defined as greater than 135 mg/dL was found to be 97% specific and 95% sensitive for differentiating AIP from pancreatic ductal adenocarcinoma in cases with equivocal radiologic findings. Subsequent studies have reported elevated IgG4 levels in 62% to 94% of patients who met other clinical, histologic, and radiologic features of AIP [42,44–47]. Chari and colleagues [10] reported elevated IgG4 levels in 71% of patients with AIP. Interestingly, those patients without elevated serum IgG4 levels did have IgG4-positive cells within their pancreatic tissues [10]. Autoantibodies (other than IgG4) have also been shown to emerge over time in AIP [48]. Measuring serial IgG4 levels might be helpful in cases with high suspicion of AIP and a normal IgG4 level at presentation. Once patients with AIP are treated with corticosteroids, IgG4 levels have

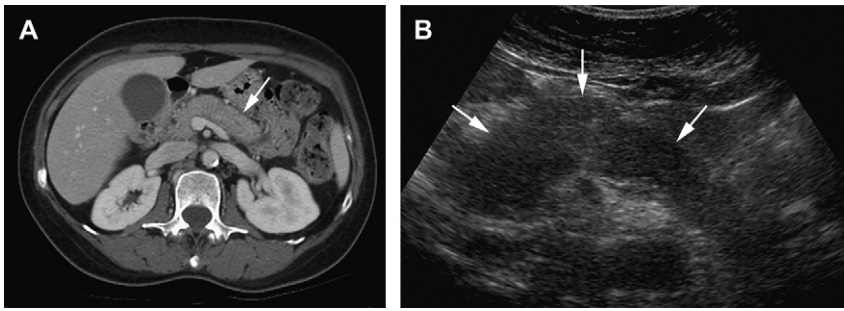

Fig. 2. Images from a 43-year-old woman with history of abdominal pain. (*A*) Contrast-enhanced CT shows an absence of normal pancreatic lobulation and subtle peripancreatic low attenuation (*arrow*). (*B*) Transabdominal ultrasound shows global pancreatic enlargement (*arrows*).

been shown to decline in parallel with the resolution of pancreatic inflammation; persistent elevation or fluctuating levels might indicate incomplete resolution or recurrence of AIP [49,50].

Recently, some reports have questioned the specificity of IgG4 as a diagnostic marker for AIP. One study performed on a cohort of patients with primary sclerosing cholangitis found elevated IgG4 levels in 9% (12 of 127, with elevated IgG4 defined as >140 mg/dL) [18]. Elevated IgG4 levels in pancreatic ductal adenocarcinoma have also been reported. In two case reports, two patients had evidence of both AIP (based on imaging studies and elevated serum IgG4 levels) and pancreatic ductal adenocarcinoma [51,52]. In another case report, a patient who had histopathologic confirmation of pancreatic ductal adenocarcinoma also had an elevated IgG4 level of 433 mg/dL; it was postulated that the elevated IgG4 level in this patient was the result of an IgG4-related systemic disease that had no clinical manifestations other than lymphadenopathy [53]. Based on these reports, interpretation of elevated IgG4 levels should be done carefully in conjunction with the clinical history, laboratory, pathologic, and radiographic findings.

Other serologic abnormalities and autoantibodies have been detected in patients with AIP, but these markers are not as specific for AIP as is IgG4. Hypergammaglobulinemia (>2 g/dL) and elevated serum IgG levels (>1800 mg/dL) have been detected in 53% to 76% [54–57] and 53% to 71% [54] of AIP patients, respectively. Autoantibodies that have been detected in patients with AIP include antinuclear antibodies, rheumatoid factor, antilactoferrin antibodies, anti–carbonic anhydrase-II antibodies, and anti–smooth muscle antibodies [14,44,58]. Asada and colleagues [59] recently proposed that anti–pancreatic secretory trypsin inhibitor antibody of IgG1 subclass might be a highly specific diagnostic marker for differentiating AIP from other pancreatic diseases; they found that this antibody was detected in 43.5% patients with AIP (n = 26) and none of healthy controls (n = 12) or negative controls (n = 53).

HISTOPATHOLOGY OF AUTOIMMUNE PANCREATITIS

Understanding the histopathology of AIP provides insights into its clinical and radiologic manifestations (Box 2 summarizes the pathologic features of AIP). On gross examination, the fibroinflammatory process within the pancreas can mimic pancreatic ductal adenocarcinoma because it is commonly localized in the head of the pancreas. Occasionally, the fibrosis is centered in the body or tail of the pancreas and diffuse involvement of the gland can be seen. The involved area is firm and gray to white; the normal lobular architecture is lost and the fibrosis can sometimes be seen infiltrating the peripancreatic soft tissue (Fig. 3). When AIP involves the head of the pancreas, involvement of the main pancreatic duct results in proximal stenosis or obstruction and distal dilatation; the common bile duct is also usually involved (in greater than 90% of the cases) and appears thickened and stenotic with proximal dilatation [60]. Unlike other forms of chronic pancreatitis, such as alcoholic pancreatitis and hereditary pancreatitis, calcifications, duct dilatation within the fibrotic areas, fat necrosis, and pseudocysts are typically not seen in AIP; however, long-standing or recurrent AIP can be associated with stone formation [12].

Histologically, the hallmark feature of AIP is an intense lymphoplasmacytic inflammatory cell infiltrate accompanied by fibrosis around large- and medium-sized interlobular ducts, and hence the alternate name for this disease, "lymphoplasmacytic sclerosing pancreatitis" (LPSP) (Fig. 4) [5,60]. Scattered macrophages and eosinophils are typically present, lymphoid follicles with

Box 2: Pathologic features of autoimmune pancreatitis

Characteristic findings

Firm, tumor-like mass within the head of the pancreas

Lymphoplasmacytic inflammation with associated fibrosis (periductal or lobular)

Obliterative venulitis

Increased numbers of IgG4-positive plasma cells (>10/high-powered field)

Less commonly seen

Diffuse fibrosis

Neutrophilic infiltrate within the lobules and ducts with occasional microabscess formation

Lobular fibrosis without significant inflammation

Not typically seen

Ductal dilatation

Calcifications or stones

Fat necrosis

Pseudocyst formation

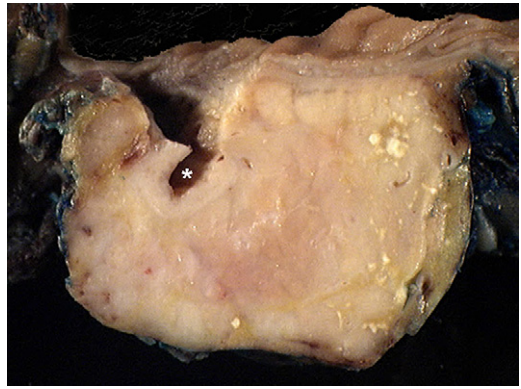

Fig. 3. Gross appearance of AIP. A cross section through the pancreas is shown. Dense, white fibrotic tissue has replaced the normal pancreatic parenchyma. There is enhancement of the process around the common bile duct (*). There are foci of fat necrosis present in this example (*yellow flecks*). The brown, velvety mucosa of the duodenum can be seen near the top right of the picture.

germinal centers can be seen, but neutrophilic infiltration is rare [5,60]. Lymphocytes can occasionally be seen infiltrating the ductal epithelium, but this is not a consistent finding. The fibroinflammatory process can involve the adjacent parenchyma and result in complete destruction and obliteration of the acini. This fibrotic process can demonstrate a storiform pattern [6] and characteristically contains the same lymphoplasmacytic infiltrate that is present around the ducts, which is in contrast to the broad bands of fibrosis without significant inflammation that can be seen in other forms of chronic pancreatitis. In severe cases, the fibroinflammatory process has no boundaries and can extend into the peripancreatic fat and can mimic superior mesenteric vein invasion by imaging studies. Such marked cases of fibrosis and inflammation can result in expansion of the involved area, resulting in a mass that can be described as an "inflammatory pseudotumor" or "tumefactive" AIP; mass lesions of up to 10 cm have been reported [7,61–64].

Another characteristic histologic feature of AIP is venulitis. Inflammatory cells not only surround small- and medium-sized veins, they also infiltrate the walls and the endothelium, which results in an obliterative venulitis (Fig. 4D). The finding of obliterative venulitis, in conjunction with periductal lymphoplasmacytic inflammation, is considered diagnostic of AIP [10].

One study, which used the term "idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration" for AIP, presents evidence that there are two histologic variants of AIP: LPSP, with the characteristic findings as described previously, and "idiopathic duct-centric chronic pancreatitis (IDCP) [5]. There is some overlap between the two entities, but IDCP differs histologically from LPSP in the following ways: (1) the inflammatory process in focused on the lobules with the presence of neutrophils, lymphocytes, plasma cells, and

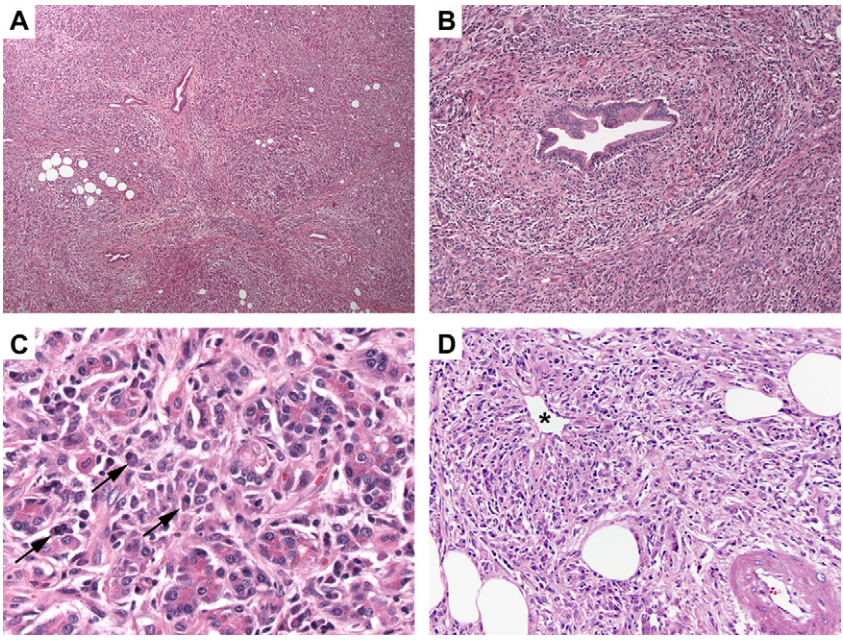

Fig. 4. Histopathologic features of AIP. (*A*) Low magnification showing a fibroinflammatory process diffusely involving and destroying the pancreatic parenchyma (hematoxylin-eosin, original magnification ×40). (*B*) Periductal inflammation and fibrosis extends into the adjacent parenchyma; the ductal epithelium is relatively spared (hematoxylin-eosin, original magnification ×100). (*C*) On higher magnification, destruction of the normal acini by plasma cells (*arrows*), lymphocytes, and fibroblasts can be seen; the acinar cells contain pink cytoplasmic granules (hematoxylin-eosin, original magnification ×400). (*D*) Obliterative venulitis is a characteristic finding in AIP. Here, the vein lumen (*) is nearly obliterated by the inflammatory process; an uninvolved artery is present in the lower right corner (hematoxylin-eosin, original magnification ×200).

edema; (2) there is less inflammation within the fibrotic areas; (3) neutrophils are prominent in the ducts and are associated with epithelial destruction; (4) in some cases, neutrophils are not prominent and the periductal chronic inflammation and fibrosis resides just beneath the ductal epithelium; and (5) venulitis is uncommon and tends to be patchy, if present. These features of IDCP are similar to those previously described as nonalcoholic duct-destructive pancreatitis [4]. Because there are no clear clinical differences between LPSP and IDCP, these two patterns of chronic pancreatitis suggest that, at least histologically, AIP is a heterogeneous disease.

Because elevated IgG4 serum levels are typically identified in patients with AIP, the presence of IgG4 plasma cells, detected by immunohistochemistry, is another characteristic histopathologic finding of AIP and can be used as a diagnostic tool in AIP and related sclerosing diseases. A dense infiltration of IgG4-positive plasma cells in the pancreas is characteristic of AIP (Fig. 5). In

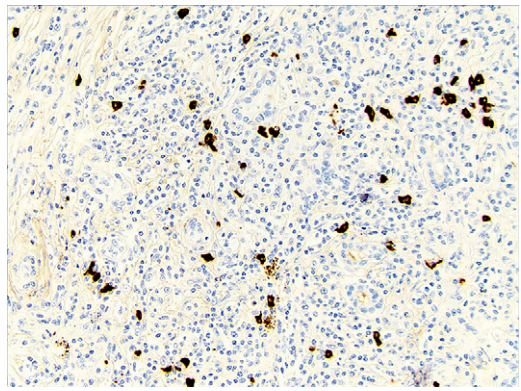

Fig. 5. Numerous IgG4-positive plasma cells are present in this case of AIP (IgG4 immunostain, original magnification ×400).

the Japanese literature, "dense" is defined as greater than 30 IgG4-positive cells per high-power field (hpf) [8]. A recent publication by the Mayo Clinic divides the IgG4-positive infiltrate into mild (<10/hpf), moderate (11–30/hpf), and marked (>30/hpf) [65]. They found that patients with AIP often had moderate or marked infiltration by IgG4-positive plasma cells in their pancreatic tissue [65]. This was particularly true in classic LPSP, in which 16 (94%) of 17 cases showed elevated numbers of IgG4-positive cells, compared with 5 (42%) of 12 cases of IDCP, highlighting yet another difference between these two histologic variants of AIP [65]. Both sets of researchers rarely found IgG4 staining in patients with chronic alcoholic pancreatitis and pancreatic ductal adenocarcinoma [8,65]. Based on these studies of IgG4 staining in AIP, another diagnostic feature of AIP is the presence of a lymphoplasmacytic infiltrate with greater than 10 IgG4-positive cells/hpf in the pancreas [66].

PATHOPHYSIOLOGY OF AUTOIMMUNE PANCREATITIS

Both humoral and cellular immune mechanisms seem to be active in AIP. Because the characteristic histopathologic finding is a lymphoplasmacytic infiltrate involving the pancreatic duct or lobules, the ductal (or ductular) epithelium may be the primary immunologic target. The lymphocytic infiltrate has been characterized immunophenotypically and is composed of a predominance of $CD3^+$ T cells (both $CD4^+$ and $CD8^+$) over $CD20^+$ B cells, and the intraepithelial lymphocytes are T cells [4,14]. The ductal epithelium has also been shown to express major histocompatibility complex class I and class II antigens, at least focally [4,14]. Similar to other autoimmune diseases, there seems to be an association of the HLA haplotype DRB1*0405-DQB1*0401 with AIP in the Japanese population [54].

Patients with AIP can have various autoantibodies, such as antinuclear antibody and antibodies to rheumatoid factor, lactoferrin, carbonic anhydrase-II,

and smooth muscle [14,44,67]. Carbonic anhydrase-II and lactoferrin have been proposed as the potential targets of the immune response in AIP because these antibodies are elevated in patients with AIP and the antigens are present within the ductal cells of the pancreas [44,68,69]. Most patients with AIP also have hypergammaglobulinemia with elevated serum IgG levels [55–57,70] and, more specifically, elevated serum IgG4 levels [42–47]. The elevation in serum IgG4 levels corresponds to the increased numbers of IgG4-postive cells in the diseased pancreas, and increased numbers of IgG4-positive cells in other organs. Although neither the trigger nor the impact of increased IgG4-producing cells is currently unknown, IgG4 seems to play a major role in the pathogenesis of AIP.

The recent concept of IgG4-related sclerosing disease proposed by Kamisawa and Okamoto [8] suggests that AIP (or at least most cases of AIP) may be one component of a systemic disease process. The extrapancreatic sites (and their diseases) that can be involved in patients with AIP include the salivary gland (sclerosing sialadenitis); bile duct (sclerosing cholangitis, distinctly different from primary sclerosing cholangitis); gallbladder (sclerosing cholecystitis); retroperitoneum (retroperitoneal fibrosis, not the isolated or idiopathic form); thyroid (Riedel's thyroiditis); and orbit (orbital pseudotumor). The lesions at all these sites show similar histopathologic findings to those seen in AIP, including a fibroinflammatory process with numerous lymphocytes and plasma cells, occasional phlebitis, and infiltration by IgG4-positive cells [8,40,71]. Interestingly, abundant IgG4-positive plasma cells are not characteristic of such conditions as primary sclerosing cholangitis, Sjögren's syndrome, sialolithiasis, or chronic alcoholic pancreatitis. When multiple sites are involved, the term that had been used in the past was "multifocal fibrosclerosis," but it seems that this entity may represent a systemic IgG4-related sclerosing disease, of which AIP is included.

DIAGNOSTIC CRITERIA FOR AUTOIMMUNE PANCREATITIS

Because AIP can mimic pancreatic cancer both clinically and radiographically, and because it is responsive to steroid therapy, the goal is to make a diagnosis preoperatively to avoid unnecessary surgery. The overall impact of a missed diagnosis of AIP is not trivial. In one large series, 11 (2.5%) of 442 Whipple resections were for AIP; all were thought to be malignant preoperatively [72].

Diagnostic criteria for AIP have been published, and similar to the evolving understanding of the pathogenesis and spectrum of AIP, these diagnostic criteria for AIP have also evolved over time. The Japanese published diagnostic criteria in 2002 based on their experience, which incorporated imaging data (diffuse narrowing of the pancreatic duct with an irregular wall extending for more than one third length of the main pancreatic duct and diffuse gland enlargement) and laboratory data (autoantibodies or elevated gammaglobulins or IgG) or histopathology (marked lymphoplasmacytic inflammation and fibrosis) [31]. As more data were gathered on AIP across the world, the diagnostic criteria shifted [10,73–75]. Several centers reported segmental narrowing of the

main pancreatic duct, in addition to cases with diffuse narrowing. With the discovery that AIP is an IgG4-related disease, IgG4 levels were incorporated into the diagnostic criteria. Knowing that AIP is responsive to steroid therapy, unlike other forms of pancreatitis and pancreatic cancer, some centers incorporated the response to steroid therapy as a diagnostic criterion. The Japanese have recently proposed a revision of their diagnostic criteria, emphasizing that malignancy must be excluded; they also site the importance of extrapancreatic lesions and associated disorders (Box 3) [9]. Chari and colleagues [10] from the Mayo Clinic recently published the criteria that they use to diagnose AIP (Table 1). These criteria have been shown to enhance diagnostic sensitivity without sacrificing specificity [66]. Based on one of their diagnostic groups (Group A), histology alone can be diagnostic.

Can a tissue biopsy be the gold standard for the diagnosis of AIP? Theoretically, the answer is yes, because there are histopathologic features of AIP that are distinct from other forms of chronic pancreatitis [5,7,13,76]. AIP is a heterogeneous disease, however, and the diagnostic features could be missed on a single core biopsy. Interestingly, in the study by Chari and colleagues [10], 7 (44%) of 16 core biopsies showed the characteristic features of AIP, including periductal lymphoplasmacytic inflammation with fibrosis and obliterative phlebitis, and in 15 of 16 biopsies, abundant IgG4-positive plasma cells were seen. In a separate report by the same institution, the diagnosis of AIP could not be

Box 3: Revised Japanese criteria

Clinical diagnostic criteria

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal ultrasonography, CT, and MRI
2. High serum γ-globulin, IgG, or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas

Diagnosis of autoimmune pancreatitis is established when criterion 1, together with criterion 2 or 3, are fulfilled. It is necessary to exclude malignant diseases, however, such as pancreatic or biliary cancers.

Relationship to extrapancreatic lesions and other associated disorders

AIP may be associated with sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis. Most AIP patients with sclerosing sialadenitis show negativity for both anti-SSA and anti-SSB antibodies, which may suggest that AIP differs from Sjögren's syndrome. Sclerosing cholangitis-like lesions accompanying AIP and primary sclerosing cholangitis respond differently to steroid therapy and have different prognoses, suggesting that they are not the same disorder. Further studies are necessary to clarify the role of autoimmune mechanisms in AIP.

Table 1
Proposed criteria for the diagnosis of AIP

Group A: Diagnostic pancreatic histology	Presence of one or both of the following criteria 1. Resection specimen or core biopsy showing the full spectrum of changes of LPSP, such as periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis (the presence of a lymphoplasmacytic infiltrate without other features of LPSP is insufficient). 2. ≥10 IgG4-positive cells/HPF on IgG4 immunostain of pancreatic tissue.
Group B: Typical imaging and serology	Presence of all the following criteria 1. CT or MRI showing diffusely enlarged pancreas with delayed and ''rim'' enhancement 2. Pancreatogram showing diffusely irregular pancreatic duct 3. Elevated serum IgG4 levels
Group C: Response to steroids	Presence of all the following criteria 1. Unexplained pancreatic disease after negative work-up for known etiologies including cancer 2. Elevated serum IgG4 levels or other organ involvement confirmed by presence of abundant IgG4-positive cells 3. Resolution or marked improvement in pancreatic or extrapancreatic manifestations with steroid therapy

Patients meeting the criteria for one or more of the groups have AIP.

Abbreviations: HPF, high power field; LPSP, lymphoplasmacytic sclerosing pancreatitis.

Modified from Chari ST, Smyrk TC, Levy MJ, et al. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. Clin Gastroenterol Hepatol 2006;4:1010–6; with permission. © 2006 The American Gastroenterological Association Institute.

made in patients undergoing EUS with fine-needle aspiration (nine patients) because of the lack of tissue architecture, but in 14 patients who had EUS with trucut biopsy, histology or IgG4 immunohistochemistry was diagnostic in eight, strongly suggestive in four, and showed nonspecific pancreatitis in two [66]. They reported that the results of the trucut biopsies altered the management of all 14 patients, who then received steroid therapy and were spared surgical intervention. In earlier studies in which IgG4 staining in tissue sections was not used, the diagnostic yield of a both core biopsies and fine-needle aspirations was low, but the findings were supportive of AIP, given appropriate correlation with other findings [13,77,78].

EUS–fine-needle aspiration cytology is currently more widely used than core biopsies in the work-up of a pancreatic mass or lesion. EUS–fine-needle

aspiration, however, has a low sensitivity for pancreatic masses or lesions in the setting of chronic pancreatitis [79,80]. Can the yield of EUS–fine-needle aspiration be improved, especially in the setting of chronic pancreatitis? In addition to technical improvements, such as increasing the number of needle passes, repeating the EUS–fine-needle aspiration, using on-site cytology interpretation, and having an experienced pancreatic cytopathologist involved in the diagnosis [81], the addition of molecular tests to the cytologic samples may also be helpful. Khalid and colleagues [82] demonstrated that DNA analysis (k-*ras* mutational analysis along with loss of heterozygosity analysis using a broad panel of tumor suppressor gene–linked microsatellite markers) of EUS–fine-needle aspiration specimens can improve the yield of suspected pancreatic ductal adenocarcinoma and differentiate adenocarcinoma from benign disease, including AIP. With the diagnostic aid of IgG4 immunohistochemistry, pancreatic tissue biopsies, and even possibly fine-needle aspirations with construction cell blocks and addition of molecular analysis, may become the gold standard in the diagnosis of AIP. For now, however, the diagnosis of AIP should be based on a combination of imaging, histologic-cytologic, and serologic criteria.

TREATMENT OF AUTOIMMUNE PANCREATITIS

The treatment of choice for AIP is steroid therapy, which has been shown to improve the symptoms, reverse the inflammatory process, and resolve of the radiographic and laboratory abnormalities (see Fig. 1C) [16]. Recommended doses vary in the literature. One recommended regimen is a 30- to 40-mg dose of prednisone per day for 4 weeks, tapered to 5 to 10 mg/day over 4 to 6 weeks with the maintenance dose of 5 to 10 mg/day to be continued until clinical, laboratory, or radiographic abnormalities fully resolve [56]. Another regimen suggests 50 to 75 mg of prednisone per day as a starting dose, with a slow taper of 2.5 to 5 mg/wk [75]. In a recent review of AIP, Finkelberg and coworkers [83] provided a diagnostic and treatment algorithm for AIP. Once a diagnosis of AIP was made, they considered using an initial dose of 40 mg of prednisone daily for 1 week, followed by a taper of the daily dose by 5 mg per week [83]. Patients should respond to steroid therapy within 2 to 4 weeks of the initiation of therapy; if imaging and laboratory studies fail to show improvement, the diagnosis of AIP should be re-evaluated [57]. Interestingly, some patients have shown spontaneous resolution without therapy, so treatment with corticosteroids is not mandatory in AIP [75]. There is limited reported experience with other medications, such as ursodeoxycholic acid and azathioprine [84,85]. If obstructive jaundice or cholangitis complicates the course of AIP, ERCP is the first-line endoscopic procedure. If at any point during the work-up or treatment of AIP malignancy is suspected and cannot reliably be excluded, surgery is warranted.

SUMMARY

AIP is a benign, IgG4-related, fibroinflammatory form of chronic pancreatitis that can mimic pancreatic ductal adenocarcinoma both clinically and

radiographically. Clinically, AIP most commonly presents as obstructive jaundice associated with a biliary stricture and tends to respond to steroid therapy. Radiographically, AIP can appear as a focal lesion or mass, or can diffusely involve the pancreas (on CT or MRI) with associated focal or diffuse narrowing of the pancreatic duct (on ERCP). Histopathologically, the hallmark features of AIP are a periductal lymphoplasmacytic infiltrate; obliterative phlebitis; and abundant (>10 cells/hpf) IgG4-positive plasma cells. These features are used as diagnostic criteria in AIP. Because AIP is often a component of a systemic IgG4-related sclerosing disease, sclerosis, lymphoplasmacytic inflammation, and increased IgG4-positive cells can be seen at other sites.

Making a diagnosis of AIP can be challenging but is important to prevent unnecessary surgery. Diagnostic criteria have been proposed that incorporate histologic, radiographic, serologic, and clinical information, including the presence of other associated diseases and response to steroid therapy. Because the distinction between AIP and pancreatic cancer is difficult to make in many cases, every attempt needs to be made to exclude the possibility of malignancy, even if it results in a pancreatic resection for benign disease in some patients.

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Incidence, Risk Factors, and Prevention of Post-ERCP Pancreatitis

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Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), with the reported incidence ranging from 1.8% to 7.2% in most prospective series [1–7]. The reported incidence can vary widely (up to 40%), however, depending on the criteria used to diagnose pancreatitis, the type and duration of patient follow-up, and case mix.

The generally accepted criteria for the diagnosis of post-ERCP pancreatitis were proposed in 1991 during a consensus workshop. These criteria include the new onset of pancreatic-type abdominal pain associated with at least a threefold increase in serum amylase or lipase occurring within 24 hours after an ERCP, and the pain symptoms need to be severe enough to require admission to the hospital or to extend the length of stay of patients who are already hospitalized [8].

The determination of the severity of post-ERCP pancreatitis can also vary depending on the criteria used to categorize the pancreatitis. The consensus workshop in 1991 graded the severity of pancreatitis based on the length of hospital stay required after developing this complication. Mild pancreatitis was characterized as that requiring an unplanned admission or prolongation of a hospitalization by 2 to 3 days. Moderate post-ERCP pancreatitis required a hospitalization of 4 to 10 days, and severe post-ERCP pancreatitis required a hospitalization of greater than 10 days or a hospitalization requiring intensive care or intervention for local complications of pancreatitis.

Other clinicians define the severity of post-ERCP pancreatitis differently, based on the presence of organ failure or the presence of local complications. Severe pancreatitis, which occurs after 0.3% to 0.6% of ERCPs, has been defined as the presence of 3 or more markers out of a total of 11 markers on the Ranson score or a score of greater than 8 on Acute Physiologic and Chronic Health Evaluation II system. The Atlanta Criteria, proposed in 1992, created a definition of the severity of acute pancreatitis based on the

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presence of local and systemic complications, organ failure, and the need for surgical intervention (Box 1) [9].

Mild post-ERCP pancreatitis is a clinical entity that is acceptable to most well-informed patients and physicians because it has a minimal impact on the patient's quality of life. In addition, mild pancreatitis is associated with an acceptable overall increase in health care expenditures. Severe post-ERCP pancreatitis, which is unacceptable to all, can be life threatening and can having a devastating impact on patients' quality of life and health care expenditures.

Because of the potential risks and consequences of post-ERCP pancreatitis, considerable efforts have been made to define patient- and procedure-related factors that may be associated with an increased risk of this complication, along with determining interventions that can reduce post-ERCP pancreatitis.

One of the most important steps to prevent post-ERCP pancreatitis is to avoid the procedure altogether whenever possible, especially in patients who

Box 1: Definition of severe pancreatitis, Atlanta Symposium 1992

Systemic complications

1. Infection documented by cultures
2. Refractory hypotension
3. Acute renal failure (serum creatinine >2 mg/dL in the absence of chronic kidney disease or increase in creatinine >1 mg/dL from baseline in those patients with chronic kidney disease
3. The new onset of pulmonary insufficiency (O_2 saturation <90% in the absence of underlying chronic pulmonary disease)
4. Symptomatic pleural effusion
5. New-onset pulmonary edema or focal infiltrate
6. Adult respiratory distress syndrome
7. New-onset cardiac dysfunction
8. Acidemia (pH <7.25)
9. Gastrointestinal bleeding (>500 mL/24 hours)
10. New-onset disseminated intravascular coagulation defined by platelets <100,000/mm^3, fibrinogen <1 g/L, or fibrin split products >80 μg/mL

The presence of local complications

1. Pancreatic pseudocysts
2. Pancreatic ascites
3. Pancreatic fistula
4. Pancreatic necrosis

Adapted from Bradley EL III. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11–13, 1992. Arch Surg 1993;128:586–90.

are thought to be at high-risk for this complication. With the development and increased availability of alternative imaging techniques, such as multidetector helical CT scanners, magnetic resonance cholangiopancreatography, endoscopic ultrasound, and laparoscopic intraoperative cholangiography, accurate diagnostic imaging of biliary and pancreatic ductal systems can be obtained in a manner that can avoid the risk of causing pancreatitis. The National Institutes of Health published a consensus statement in 2002 that recommends that diagnostic ERCPs should be avoided whenever possible [10].

MECHANISMS OF POST–ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY PANCREATITIS

There have been numerous theories about the mechanisms of post-ERCP pancreatitis. The most widely accepted theory is that mechanical trauma to the papilla or pancreatic sphincter, caused during instrumentation, creates transient obstruction of outflow of pancreatic juice. This theory has gained more acceptance after the findings from multiple prospective randomized controlled trials (RCT) showed that the placement of a prophylactic pancreatic duct (PD) stent in patients at high risk for post-ERCP pancreatitis greatly reduced the risk of this complication and nearly eliminated the incidence of severe post-ERCP pancreatitis.

Another theory suggests that the increased hydrostatic pressures in the PD caused by injection of contrast or saline could cause injury to the PD or parenchyma. This theory has gained some support after studies showed that the use of continuous perfusion manometry catheters in evaluation of patients with suspected sphincter of Oddi dysfunction resulted in much higher rates of postprocedural pancreatitis when compared with aspirating manometry catheters (32% versus 4%, respectively) [11]. In addition, some studies have also shown that acinarization of the pancreas during a pancreaticogram, suggesting increased contrast injection and increased PD hydrostatic pressures, is an independent risk factor for post-ERCP pancreatitis [2,12].

Pancreatic infection by injection of intestinal bacteria into the pancreas has also been proposed as a potential mechanism of post-ERCP pancreatitis. This hypothesis is supported by a RCT showing the use of prophylactic antibiotics before ERCP significantly reduced the rate of postprocedure pancreatitis when compared with placebo [12].

Regardless of the mechanism behind the induction of post-ERCP pancreatitis, the cascade of events after the initiation of injury remains the same as pancreatitis caused by other etiologies. The initial injury is thought to cause premature activation of proteolytic enzymes causing autodigestion of the pancreas and impaired acinar secretion, which in turn prevents the protective flushing activity of the PD. These insults lead to the activation of the inflammatory cascade causing both local inflammation and systemic effects.

A patient's response to this pancreatic injury, which is related both to the severity of the insult to the pancreas and the magnitude of inflammatory response to that injury, determines whether the patient develops mild pancreatitis with a quick recovery versus severe pancreatitis with organ failure and severe local injury.

HIGH-RISK PATIENTS

Numerous prospective trials have evaluated patient- and procedure-related risk factors for post-ERCP pancreatitis. One of the most important results of this extensive body of work has been the determination that a patient's preprocedural characteristics confer as much of that patient's risk to develop post-ERCP pancreatitis as does the physicians' endoscopic techniques and maneuvers (Boxes 2 and 3).

Female patients undergoing ERCP have been found to be at 2.51 times higher risk of developing postprocedure pancreatitis compared with men undergoing ERCP when evaluated by multivariate analysis ($P < .0001$) [1]. When evaluated by a meta-analysis of 15 prospective clinical studies the relative risk for women was 2.23 (95% confidence interval [CI], 1.75–2.84; $P < .0001$) [13]. Patients under the age of 60 years were also found to be at higher risk of post-ERCP pancreatitis (odds ratio [OR] 2.11; $P < .001$) [5].

Suspected sphincter of Oddi dysfunction (SOD) has been found to increase greatly a patient's risk for developing post-ERCP pancreatitis. In a prospective study of 2347 patients undergoing ERCP, 52 (19%) of 272 of patients

Box 2: Patient-related risk factors for post-ERCP pancreatitis seen in multivariate studies

Factors that definitely increase the risk for post-ERCP pancreatitis

High-risk indications
- Suspected sphincter of Oddi dysfunction

High-risk patients
- Female gender
- Young patients
- Prior history of post-ERCP pancreatitis
- History of recurrent acute pancreatitis
- Absence of chronic pancreatitis

Factors that may increase the risk for post-ERCP pancreatitis

The lack of choledocholithiasis

Normal serum bilirubin

Factors that have not proved to increase the risk for post-ERCP pancreatitis

Allergy to contrast media

Small common bile duct diameter

Periampullary diverticula

Pancreatic divisum

Prior failed ERCP

Indication for procedure: diagnostic versus therapeutic

Partial gastrectomy from Billroth II

Box 3: Procedure-related risk factors for post-ERCP pancreatitis seen in multivariate analysis and prospective randomized trials

Factors that definitely increase the risk for post-ERCP pancreatitis

Difficult or failed cannulation

Pancreatic duct injection

Pancreatic sphincterotomy

Failed attempts at placing pancreatic duct stent

Precut sphincterotomy

Pancreatic or biliary sphincterotomy for sphincter of Oddi dysfunction

Factors that may increase the risk for post-ERCP pancreatitis

Pancreatic acinarization with contrast

Pancreatic brush cytology

Low endoscopist volume

Involvement of trainee during ERCP

Ampulectomy

Balloon dilation of intact biliary sphincter

Factors that have not proved to increase the risk for post-ERCP pancreatitis

Intramural contrast injection

Pain during ERCP

Sphincter of Oddi manometry when using aspiration catheter

Biliary sphincterotomy

Therapeutic ERCP

Techniques that have proved to reduce the risk of post-ERCP pancreatitis

Placement of a pancreatic duct stent in high-risk patient

Techniques that may reduce the risk of post-ERCP pancreatitis

The use of a soft guidewire to access bile duct before contrast injection

The use of a pure-cut current during endoscopic sphincterotomy

undergoing an ERCP for suspected SOD developed pancreatitis compared with 75 (3.6%) of 2075 of patients undergoing ERCP for other indications (adjusted OR 5.01; $P < .001$). In addition, the rate of severe pancreatitis in patients with suspected SOD (2.7% versus 0.05%) was markedly elevated [2]. When evaluated by a subsequent meta-analysis, the relative risk of post-ERCP pancreatitis in suspected SOD patients was 4.09 [13].

A prior history of post-ERCP pancreatitis also confers a considerable increased risk for recurrence of this complication. In two large prospective studies, a prior history of post-ERCP pancreatitis was determined to be an independent

risk factor for postprocedural pancreatitis with the incidence ranging from 11% to 28.4%. [1,2,6,7]. In addition, if a patient has a history of recurrent acute pancreatitis, the incidence of pancreatitis ranges from 16% to 23% [4,6].

Unfortunately, these risk factors for post-ERCP pancreatitis are also thought synergistically to increase a patient's risk for postprocedure pancreatitis regardless of the type of endoscopic therapy performed. In one prospective study of 1963 consecutive patients undergoing ERCP, researchers found the incidence of postprocedural pancreatitis to be 2.75% in female patients. In a female patient with normal bilirubin, suspected SOD, and a difficult ampulary cannulation, however, the risk for post-ERCP pancreatitis increased 16.8-fold, with an incidence of pancreatitis of 46.3%. Additionally, multiple studies have demonstrated that most patients who develop severe post-ERCP pancreatitis are patients with multiple risk factors. An excellent illustration of this point was demonstrated in the previously mentioned large prospective study. Only 6 (0.3%) of the 1963 patients undergoing ERCP developed severe pancreatitis. All of the patients developing severe postpancreatitis, however, had multiple risk factors; all six patients were women age 60 or below, had recurrent abdominal pain with normal serum bilirubin, and had difficult cannulations. Four of the six patients also had suspected SOD as an indication for the procedure [1].

Some patient factors seem to be somewhat protective for the development of post-ERCP pancreatitis. In one study the incidence of post-ERCP pancreatitis was 4.3% in patients with a history of chronic pancreatitis, and 7.2% in patients without this diagnosis ($P = 0.04$) [1].

HIGH-RISK ENDOSCOPIC TECHNIQUES

In addition to multiple patient-related factors known to increase the risk of post-ERCP pancreatitis, there are numerous procedure-related risk factors for this complication that have been demonstrated by large prospective studies with multivariate analysis.

One of the most well-recognized procedural-related risks for post-ERCP pancreatitis is the injection of contrast into the PD. This risk increased incrementally with the number of PD injections. In a large multicenter prospective trial, 16.8% of patients with two or more PD injections develop pancreatitis. In multivariate analysis this produced an OR of 1.5 ($P = .03$) [7]. In a meta-analysis examining 4802 patients from six trials, 3.27% of patients with PD injection developed pancreatitis, compared with 1.6% without PD injection ($P < .021$) [13]. Other research also suggests that there is a progressively higher incidence of post-ERCP pancreatitis with an increased extent of opacification of the PD during an ERCP. In a retrospective study of 14,487 patients undergoing ERCP, the incidence of pancreatitis was 1% in patients who had no attempt at PD injection, 3.5% in patients with contrast injection of the PD up to the pancreatic head, 4.6% with opacification up to the body of the pancreas, and 8.5% with complete opacification of the PD [14].

Difficulty in cannulation, which can produce papillary trauma, has also proved to be an independent risk factor for procedural complications [1–3,6].

This risk increases incrementally with the number of failed cannulations. In a prospective study of 1223 patients from a single referral center, pancreatitis occurred in only 3.3% of patients who required less than five attempts at cannulation; 9% when 6 to 20 cannulation attempts were required; and 14.9% when the cannulation was considered difficult, requiring more than 20 attempts [6].

Precut sphincterotomy has also been shown in multiple prospective trials to increase the risk of post-ERCP pancreatitis [2,5,13]. Pancreatitis occurred in 17 (15.3%) of 111 of patients requiring precut sphincterotomy compared with a rate of 4.5% (100 of 2236) in all other patients undergoing ERCP. Additionally, when a precut sphincterotomy was performed for suspected SOD, the rate of post-ERCP pancreatitis was 35.3% compared with 11.3% when done for other indications. The risk for severe pancreatitis was also extremely high in the suspected SOD group, with 25% of patients having a severe course compared with only 2% of patients undergoing precut sphincterotomy for other indications. The reasoning for this high rate of both mild and severe pancreatitis associated with precut sphincterotomy has been attributed to two main factors. The precut technique may have a higher risk of injuring the pancreatic sphincter, causing edema and duct obstruction. Secondly, the maneuver is often performed after a prolonged effort at cannulation has occurred. The increased risk associated with the precut technique, however, has been demonstrated to be an independent risk factor when adjusting for other confounding variables.

In other studies, the frequency of post-ERCP pancreatitis after precut sphincterotomy did not differ from the patients undergoing traditional endoscopic sphincterotomy. This was illustrated in a retrospective study of 2105 undergoing ERCP, where 33% of patients underwent precut sphincterotomy. In this study, the rate of post-ERCP pancreatitis in those patients undergoing precut sphincterotomy was very low, around 1.5% [15].

Balloon dilation of an intact biliary sphincter is used in some centers, mostly in Europe and Asia, to allow biliary stone extraction without a sphincterotomy. In a large multicenter study in the United States, balloon dilation of an intact biliary sphincter was shown to be an independent risk factor for post-ERCP pancreatitis. In this study, 5 (16.1%) of 31 patients undergoing balloon dilation of a biliary sphincter developed pancreatitis compared with 126 (6.5%) of 1932 patients not undergoing the technique (adjusted OR of 4.51; $P = .0027$) [1]. A recent prospective study of 1000 patients undergoing balloon dilation of an intact biliary sphincter for bile duct stones removal, however, did not show an increase in the rate of postprocedural pancreatitis. In this study, 963 of 1000 patients, with a mean age of 69.1 years, underwent ERCP with successful removal of bile duct stones using only endoscopic papillary balloon dilation. In this study, only 4.8% of all 1000 patients developed post-ERCP pancreatitis, and only one patient developed severe pancreatitis [16].

Pancreatic sphincterotomy has also proved to be an independent risk factor for post-ERCP pancreatitis. In one study, 29.8% of patients undergoing pancreatic sphincterotomy developed pancreatitis compared with 5.3% of patients who did not [1].

HIGH-RISK ENDOSCOPISTS

Most studies have demonstrated that the overall complication rate of ERCP is lower when performed by high-volume endoscopists [1,2]. An increased risk of post-ERCP pancreatitis with a lower-volume endoscopist, however, has been more difficult to establish.

In a large multicenter study from the Unities States, the overall success rate for bile duct access was significantly higher with the high-volume endoscopists (>2 ERCP a week, 96.5% versus 91.5%; $P = .0001$), but failed to show a significant reduction in postprocedural pancreatitis in multivariate analysis [1]. Another large study showed that higher-volume endoscopists (>1 sphinterotomy/week) had a significantly lower number of attempts needed for successful cannulation and fewer PD injections when compared with lower-volume endoscopists (<1 sphincterotomy/w). The overall rate of post-ERCP pancreatitis, however, was nearly the same (5.5% with high-volume endoscopists versus 5.3% with lower-volume endoscopists) [2]. These results may reflect a different case-mix seen by high- and low-volume endoscopists. High-volume endoscopists are often at tertiary referral centers that see a higher proportion of high-risk patients, such as those with suspected SOD or a prior history of pancreatitis. In addition, few of the physicians who were in the high-volume category performed enough ERCPs generally thought required to reduce the rate of pancreatitis (>250 ERCPs/y).

Possibly support for the theory that high-volume centers and endoscopists may reduce the risk of post-ERCP pancreatitis was seen in a multicenter study from Italy, where the case-mix is more homogeneous between high- and low-volume centers. In this study, the rate of post-ERCP pancreatitis was significantly lower, but only when evaluated by univariate analysis, in centers performing more than 200 ERCPs a year when compared with lower-volume centers (relative risk 2.797; CI, 1.352–5.789). Interestingly, in a recent large multicenter prospective trial, the risk of post-ERCP pancreatitis was significantly higher by multivariate analysis when trainees (fellows) were involved in the ERCP (OR 1.5; $P = .03$) [7].

ENDOSCOPIC TECHNIQUES THAT REDUCE POST–ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY PANCREATITIS

One of the most important advancements to occur in the past 15 years in the field of pancreatobiliary endoscopy is recognition of the benefits of placement of a prophylactic transpapillary PD stent in patients at high risk for post-ERCP pancreatitis. One of the theories regarding the mechanism of developing post-ERCP pancreatitis involves the thought that trauma to the papilla or pancreatic sphincter during instrumentation can cause obstruction of the flow of pancreatic juices. This obstruction is thought to induce injury to the pancreas and initiate the inflammatory cascade. The use of PD stents is thought to mitigate the PD obstruction and reduce the risk of injury to the pancreas.

In one prospective study of patients thought to be at high risk of developing post-ERCP pancreatitis, 74 patients were randomized for the placement

a prophylactic PD stent or no PD stent. Of the 38 patients who underwent PD stent placement, only two patients (5%) developed post-ERCP pancreatitis compared with 10 (28%) of 36 patients of the patients in the control arm. In addition, all the patients who developed severe pancreatitis (3 of 74) were in the control arm of the study and did not receive PD stent placement [17]. In a meta-analysis of five trials involving a total of 481 patients, 12 (5.8%) of 206 patients who had prophylactic pancreatic stent placed developed mild to moderate pancreatitis compared with 36 (13.1%) of 275 patients without PD stent placement (OR of 0.35). In addition, all patients who developed severe post-ERCP pancreatitis, 7 of the total 481 patients, were in the control arm without prophylactic stent placement [18].

One important caveat to these otherwise remarkable findings is the potential for severe complications with failed PD stent placement. A retrospective study examined 225 patients undergoing high-risk therapeutic ERCPs with attempts for prophylactic stent placement. Pancreatic stent placement was successful in 222 (98.6%) out of 225 attempts. A total of 32 (14.4%) of 222 patients with successful PD stent placement developed pancreatitis compared with two of three patients who had failed PD stent placement. In addition, one of three patients with failed PD stent placement developed severe pancreatitis, whereas none of the patients with successful PD stent placement developed severe pancreatitis [19].

Another potential complication of PD stent placement is risk for iatrogenic injury to the PD. Studies suggest that these PD stents, even when left in place for a relatively short duration, can cause stricturing of the PD and changes to the pancreatic parenchyma. The clinical impact, however, of these changes occurring after short-term PD stent placement is uncertain. It is recommended, however, that smaller-diameter PD stents, such as a 3F to 4F catheter stent, rather than 5F to 7F catheter stent, be used for prophylactic pancreatic stenting. In addition, if the stent has not migrated out of the PD spontaneously within 2 weeks, the stent should be removed endoscopically.

In addition to the use of prophylactic PD stents in high-risk patients, it has been suggested that the use of pure-cut electrosurgical current may reduce the risk of post-ERCP pancreatitis when compared with using a blended current. Some have suggested that the thermal injury that occurs in the pancreatic sphincter and papilla may contribute to obstruction of PD flow. By using a pure-cut current, the thermal injury to the surrounding tissue may be decreased. The risk of bleeding complications may increase, however, with pure-cut current. A RCT of 111 patients (86 patients treated with pure-cut current and 84 with blended current) did show a statistically significant decrease in post-ERCP pancreatitis; 3% (3 of 86) in the pure-cut group developed pancreatitis compared with 12% (10 of 84) in the blended current group. In addition, none of the patients in the pure-cut group developed moderate to severe pancreatitis, whereas 30% of those in the blended group were graded as such [20]. A different prospective RCT of 246 patients undergoing ERCP, however, failed to show a statistically significant different incidence of postprocedure

pancreatitis (7.8% pure-cut versus 6.1% blend; $P = .62$) [21]. Additionally, the use of an automated electrosurgical current delivery system, such as an ERBE generator set to the "endocut" mode, failed to show a difference in the incidence of post-ERCP pancreatitis when compared with patients randomized to a electrosurgical generator set to a blended current; 4.5% of the patients randomized to the ERBE "endocut" arm developed pancreatitis versus 5.4% randomized to standard blended current ($P > .50$) [22].

Another technique that may reduce the risk of post-ERCP pancreatitis is the guidewire technique, in which a soft-tipped guidewire is used to cannulate the bile duct before contrast injection. This is thought to reduce the amount of trauma to the papilla, because the papilla is cannulated over a guidewire. In addition, this technique prevents the injection of contrast medium into the PD and prevents submucosal injections in the papilla. A study of 400 consecutive patients from Italy supported this hypothesis. In this study, one endoscopist performed all ERCPs. Patients were randomized into one group of 200 patients where all patients had bile duct access using a soft-tipped Teflon tracer 0.035-in guidewire through a 6F catheter double-channeled sphincterotome before any contrast injection. In the other group of 200 patients, the bile duct was cannulated with the sphincterotome using standard techniques. This study showed that none of the patients in the guidewire technique arm developed pancreatitis, whereas eight cases (six mild, one moderate, one severe) in the standard technique developed pancreatitis [23].

PHARMACOLOGIC PROPHYLAXIS

Numerous attempts have been made to find a pharmacologic agent that can be used to reduce the incidence and severity of post-ERCP pancreatitis (Box 4). An ideal agent is highly effective in reducing post-ERCP pancreatitis, is safe for the patient, well tolerated, relatively affordable, and does not have a prolonged administration time. Unfortunately, nearly all of the agents investigated have fallen short of these goals, but several agents have shown some promise.

One of the most promising agents studied thus far is the protease inhibitor gabexate, which is not available in the United States. This agent inhibits trypsinogen, which in theory could prevent the intraluminal activation of proteolytic enzymes. An initial prospective trial, performed in Italy, randomized 418 patients to the treatment arm consisting of infusion of 1 g of gabexate 30 to 90 minutes before the ERCP and for 12 hours thereafter. This study showed a significantly lower rate of pancreatitis in the treatment arm (2.4%) when compared with the control group (7.6%) ($P = .03$) [24]. Unfortunately, subsequent studies have provided conflicting results. A prospective RCT and meta-analysis published in 2002 produced an OR of 0.58 for the reduction of post-ERCP pancreatitis. The 95% CI, (0.34–0.99) was close to 1, suggesting the agent is barely effective for reducing pancreatitis. In addition, the number of patients need to prevent one case of pancreatitis was 35, making the drug's cost effectiveness questionable. This meta-analysis also showed that a short-term infusion of gabexate (<4 hours) was ineffective in reducing the incidence

Box 4: Drug prophylaxis for post-ERCP pancreatitis

Drugs that have proved to reduce the incidence of post-ERCP pancreatitis

Gabexate when infused for 12 hours before procedure

Drugs that may be effective in reducing the incidence of post-ERCP pancreatitis

Antibiotics
Nitroglycerine
Octreotide
Somatostatin when infused in 12- to 24-hour infusion before procedure
Ulinastatin
Allopurinol
Diclofenac

Drugs found ineffective in reducing the incidence of post-ERCP pancreatitis

Corticosteroids
Calcium channel blockers
Heparin derivatives
Lidocaine applied topically to amplua
Interleukin-10 [25,26]
Platelet activating factor [27]
Nonionic contrast agents [28]
Intravenous *N*-acetylcysteine

of pancreatitis [3]. Conflicting these results, a RCT done in China using 300 mg of gabexate infused 30 minutes before the procedure and continuing up to 4 hours after the procedure showed an incidence of pancreatitis of 3.1% (3 of 98) in the gabexate group and 10.5%(10 of 95) in the control group [29].

Another protease inhibitor, ulinastatin, was compared with gabexate in another prospective RCT performed in Japan. In this study, 139 patients were randomized into (1) a gabexate group (46 patients), receiving 300 mg of gabexate in a continuous infusion starting 1 hour before ERCP and continuing 12 hours after the completion of the procedure; (2) a high-dose ulinastatin group, receiving 150,000 units three times (1 hour before, during the ERCP, and 11 hours after the procedure); and (3) a low-dose ulinastatin group, receiving 50,000 units at the same time points as the high-dose group. The rate of pancreatitis was 4.3% in the gabexate group, 6.5% in the high-dose ulinastatin group, and 8.5% in the low-dose ulinastatin group. The major limitation of this study is the lack of a placebo-controlled group, making the applicability of these results to other patient populations somewhat limited [30].

Two other agents, somatostatin and octreotide, have been studied extensively with conflicting results. Both of these agents inhibit acinar cell secretion.

A total of 10 RCTs have been published evaluating the efficacy of somatostatin, which is unavailable in the United States. The most recent study, published in 2004, was a double-blinded RCT of 372 patients randomized into three treatment arms: (1) a placebo group consisting of 122 patients; (2) one treatment group consisting of 118 patients, which received a bolus injection of somatostatin totaling 4 μg/kg at the time of cannulation; and (3) a second treatment arm consisting of 116 patients, in which the patient received an infusion of 3 mg of somatostatin infused 30 minutes before the procedure and continuing for 12 hours after the procedure. This studied showed a statistically significant reduction in post-ERCP pancreatitis in both of the treatment groups (1.7%) compared with 9.8% in the placebo group ($P < .05$) [30]. Interestingly, a meta-analysis of the nine preceding studies involving both long- and short-term infusions of somatostatin found the drug to be ineffective (OR 0.68; 95% CI, 0.44–1.04; $P = .075$) [31].

Studies evaluating octreotide, which is available in the United States, in preventing post-ERCP pancreatitis have also produced conflicting results. The most recent study, which was performed in China, randomized 961 patients into a placebo group, consisting of 482 patients, and the treatment group, consisting of 470 patients, who received an intravenous infusion of 0.3 mg of octreotide starting 1 hour before the ERCP and continued for 6 hours after the procedure. The treatment arm then received 0.1 mg of subcutaneous injection of octreotide 6 hours after the procedure and 12 hours after the procedure. This study showed a statistically significant decrease in the incidence of post-ERCP pancreatitis in the octreotide group (10 [2.42%] of 414) when compared with the control group, with a 17.6% rate of pancreatitis ($P = .046$) [32]. In another randomized, double-blind, placebo-controlled trial, patients in the treatment arm received 500 μg of octreotide subcutaneously three times daily, starting 24 hours before the ERCP. The incidence of post-ERCP pancreatitis was significantly lower in the octreotide group (2 [2%] of 100) compared with the placebo group (9 [8.9%] of 101 ($P = .3$) [33]. Unfortunately, prior studies were not so supportive. In a meta-analysis of 10 clinical trials, octreotide was not found significantly to reduce post-ERCP pancreatitis, with 7.6% of the pooled patients receiving octreotide developing pancreatitis compared with 5.5% of patients in the placebo arm (OR 1.43; 95% CI, 0.82–2.49) [34].

Another agent showing some potential is diclofenac, a cheap, widely available agent with a short, easy method of administration. Diclofenac, an oral or suppository nonsteroidal anti-inflammatory drug, inhibits phospholipase A_2, which is thought to play a critical role in the early inflammatory cascade. In the only published study to date, 220 patients undergoing ERCP were randomized to 100 mg of diclofenac or a placebo immediately after completion of the ERCP. Seven (6.4%) out of 110 patients receiving diclofenac compared with 17 (15.5%) of 110 patients receiving the placebo ($P < .05$) developed pancreatitis. Unfortunately, the incidence of pancreatitis in SOD patients was not different in the placebo and treatment groups (11.5%) [35]. These results are

somewhat encouraging, but several factors raise concern including the relatively high rate of pancreatitis in the control group, and the *P* value bordering on statistical significance.

A single study showed that prophylactic antibiotics showed a reduction in the incidence of post-ERCP pancreatitis [12]. In this prospective study, 321 patients were randomized to receive 2 g of cephtazidime, a third-generation cephalosporin, 30 minutes before ERCP versus placebo. The control group was found to have a significantly higher incidence of pancreatitis (15 [9.4%] of 160) than the antibiotic group (4 [2.6%] of 155) [36]. Further studies showed that when antibiotics were mixed with the contrast media used for ERCPs, however, the rates of post-ERCP pancreatitis were not decreased.

Several pharmacologic agents have been investigated with hopes of inducing relaxation of the sphincter of Oddi, improving drainage of the PD. These agents include topical lidocaine applied to the papilla [37], oral calcium channel blockers [38,39], and transdermal glyceryl trinitrate, all of which have not proved to be effective [40].

Both intravenous *N*-acetylcysteine and allopurinol have been proposed as potential agents to reduce the risk of post-ERCP pancreatitis with the goal of inhibiting the generation of oxygen-derived free radicals. *N*-acetylcysteine was not found to be effective in a RCT with a rate of 12.1% in the *N*-acetylcysteine group developing post-ERCP pancreatitis compared with an incidence of 9.6% in the placebo group [41].

Studies evaluating the effect of allopurinol have provided mixed results. One study evaluating oral allopurinol at a dose of 600 mg, 4 hours before, and 300 mg, 1 hour before, ERCP did not show a reduction in the frequency or severity of post-ERCP pancreatitis. [42]. These results agreed with that of another study evaluating the efficacy of allopurinol when used along oral prednisone [43]. Another similar study using slightly higher doses of allopurinol (600 mg of oral allopurinol 15 hours and 3 hours before ERCP), however, showed a marked decrease in the incidence of post-ERCP pancreatitis with 4 (3.2%) of 125 patients in the treatment arm developing pancreatitis and 21 (17.8%) of 118 control patients developing pancreatitis when compared with multinomial regression analysis [44]. Because of the variable results of the studies, further large prospective randomized trials must be completed before the use of allopurinol can be recommended.

Other agents thought to have anti-inflammatory effects, such as low-molecular-weight heparin [45] and corticosteroids [12,44,46], have not been shown to be effective in reducing post-ERCP pancreatitis.

FACTORS INFLUENCING THE MAGNITUDE OF INFLAMMATORY RESPONSE

A considerable amount of progress has been made in determining patient, procedure, and operator characteristics that increase a patient's risk for developing post-ERCP pancreatitis. Clinicians still have yet to elucidate, however, why two similar patients undergoing comparable endoscopic procedures can have

two vastly different clinical courses when subjected to similar stresses or injuries to the pancreas that may occur during an ERCP. It has yet to be determined why one patient may quickly recover from an episode of pancreatitis without any sequelae, whereas another similar patient develops multisystem organ failure, severe local complications, and a multitude of long-term complications or possibly even death.

Only part of this variable response can be attributable to differences in the severity of the injury to the pancreas. Other aspects, such as genetic susceptibility, may alter the magnitude of inflammatory response to a given stress. Alternatively, these genetic susceptibilities may alter the threshold for which one develops inflammation of the pancreas after a physiologic stress (Fig. 1).

Clinicians have begun to understand genetic variables that may confer an increased risk for the development of acute pancreatitis with a severe inflammatory response. Recent research has shown that a common polymorphism in the promoter region for an early inflammatory response gene called the monocyte chemotactic protein-1 can confer an increased risk of a person developing severe acute pancreatitis (Fig. 2). Research has shown that patients who develop severe acute pancreatitis had a significantly higher frequency of a G/G or G/A genotype at the -2518 G allele for the monocyte chemotactic protein-1 gene than did control subjects (OR 7.9; 95% CI, 1.7–37; $P < .003$) or patients who developed mild acute pancreatitis (OR 7; 95% CI, 1.5–34; $P < .007$). Additionally, patients with the AA genotype had a low risk of developing severe acute pancreatitis (OR 0.13; 95% CI, 0.01–0.61; $P < .003$) [47].

Based on these findings, the researchers at the University of Pittsburgh have launched a prospective study called the Post-ERCP Pancreatitis Severity

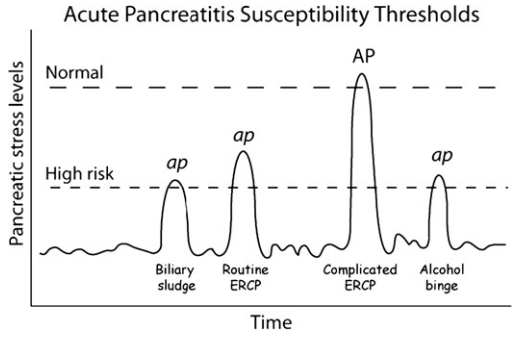

Fig. 1. Demonstrated is a hypothetical relationship between risk factors for pancreatitis and physiologic stressors that can induce an episode of pancreatitis. Genetic susceptibly may alter one's threshold for developing acute pancreatitis. This altered threshold may allow relatively small insults to the pancreas (biliary sludge, routine ERCP, alcohol binge), which typically do not trigger the inflammatory cascade in a patient at average risk, to induce an episode of acute pancreatitis (*ap*) for those individuals with increased genetic susceptibility. Other larger injuries, such as a complicated ERCP, induce an episode of acute pancreatitis (AP) in patients both at high risk and normal risk. (*Courtesy of* D. Whitcomb, MD, PhD, Pittsburgh, PA.)

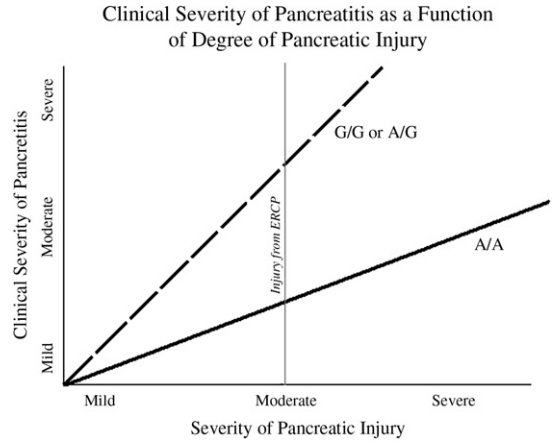

Fig. 2. Clinical severity as a function of pancreatic injury. Hypothetical effect of the polymorphisms in the MCP-1 G allele on shifting of the severity of pancreatitis for a pancreatic injury. Note that a moderate degree of injury to the pancreas, such as hypothetical ERCP, causes only mild pancreatitis in patients with the A/A genotype. Patients with the G/G or G/A polymorphism at the –2518 allele, however, develop moderate or severe acute pancreatitis with the same injury.

Indication Study to help determine if these polymorphisms in monocyte chemotactic protein-1 and other early response genes confer an increased risk of developing post-ERCP pancreatitis.

FUTURE DIRECTIONS

In the future, this extensive list of patient- and procedural-related risk factors for post-ERCP pancreatitis can be used to risk stratify patients better for this complication before the procedure. This risk stratification should be used as part of the consent process to inform each patient better what are his or her potential risks for postprocedure pancreatitis. In addition, this information should be used to help physicians decide if preventative measures, such as drug prophylaxis or PD stenting, should be performed in patients deemed at higher risk.

In addition, as clinicians gain a better understanding of genetic factors, such as polymorphisms in inflammatory response genes, that may increase ones risk of developing post-ERCP pancreatitis, this can be used to provide further preprocedural risk stratification.

Some groups have also recommend that patients be provided a detailed account of how many ERCPs a physician has performed along with their casemix and their rate of post-ERCP complications. This helps patients make better informed choices about who performs their ERCP.

Despite increasing knowledge of the risk factors for post-ERCP pancreatitis, severe acute pancreatitis after this procedure continues to occur in thousands of

patients a year in the United States, with hundreds of deaths occurring annually. With ongoing efforts, however, this potentially devastating complication can be further reduced by three main methods: (1) the ongoing use of alternative, less invasive, imaging techniques to investigate the pancreatobiliary system, avoiding unnecessary ERCPs; (2) by continuing efforts to risk stratify patients; and (3) by further improving knowledge of interventions that can be done, either pharmacologically or endoscopically, to reduce the risk of post-ERCP pancreatitis.

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Risk and Markers of Severe Acute Pancreatitis

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Acute pancreatitis (AP) is a common acute inflammatory process of the pancreas that affects approximately 100,000 individuals in the United States annually [1]. The clinical course of AP varies significantly between individuals. In most patients, the condition is mild and self-limiting, but approximately 20% of patients suffer severe attacks associated with prolonged hospitalization, significant morbidity, and mortality ranging between 30% and 50% [2]. The process is initiated by activation of pancreatic zymogens, resulting in pancreatic autodigestion and an inflammatory response mediated by the innate immune system. The inflammatory reaction is initiated at the site of injury and, if marked, can lead to systemic inflammation. The immune response is independent of the event or process that initiates activation of the digestive enzymes and pancreatic injury in AP, but accounts for much of the subsequent damage.

Cytokines play a critical role in the pathogenesis of pancreatitis by driving the subsequent inflammatory response. Knowledge of the inflammatory cascade is important in recognizing when the peak response occurs for various cytokines and inflammatory mediators. A number of studies provide information of the profile of inflammatory markers that peak on the day AP occurs, at 24 hours, 48 hours, and later. These studies also examine the potential of inflammatory markers to discriminate patients into high-risk and low-risk groups based on their physiologic measurements and clinical outcome. Early prognosis of severity in AP subjects remains unsatisfactory, however, and an extensive

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search for objective tools that predict severity and outcome at the time of hospital admission remains a major challenge.

MULTISYSTEM ORGAN FAILURE AND PANCREATIC NECROSIS

Eighty percent of patients with AP develop abdominal pain and elevated pancreatic enzyme levels in the blood and urine for a few days. Twenty percent of patients progress to a more severe course with a prolonged hospitalization or death. About 50% of deaths in subjects with severe AP occur within the first week. An exaggerated inflammatory response and the resultant multisystem organ failure are the primary causes of death when early mortality occurs [3]. The first sign of multisystem organ failure in AP subjects is commonly impaired lung function caused by adult respiratory distress syndrome. Systemic inflammation also affects the cardiovascular system, kidneys, and liver.

Severe AP can be defined in several ways. The Atlanta classification system [4] defines severe AP based on organ dysfunction, including systolic blood pressure less than 90 mm Hg, Pa_{O_2} less than 60, serum creatinine greater than 2 mg/dL after rehydration, and gastrointestinal bleeding greater than 500 mL/24 hours. Furthermore, severe AP is defined using the Ranson's criteria with a score greater than or equal to 3 [5] and the Acute Physiology and Chronic Health Evaluation (APACHE)-II criteria with a score greater than or equal to 8 [6]. Evidence of pancreatic parenchymal pathology (primarily necrosis) on contrast-enhanced CT imaging is also included in the Atlanta classification of severe AP.

Pancreatic necrosis (PNEC) is an important complication of AP. PNEC reflects pancreatic parenchymal infarction. It occurs in the context of significant inflammation and volume depletion (often reflected by hemoconcentration and an elevated hematocrit at presentation). PNEC does not, by itself, present a major morbidity risk in the short term. The necrotic tissue, however, serves as a potential nidus for infection. Infection occurs in 40% to 70% of patients with PNEC and represents the primary cause of late death in patients with AP [1].

RECENT INSIGHTS IN THE PATHOPHYSIOLOGY OF SEVERE ACUTE PANCREATITIS

The severity of AP is a function of the intensity of the inflammatory response, particularly in the early course of the disease [1]. In the past it was assumed that there was a close correlation between the degree of pancreatic injury and the inflammatory response. This assumption was based in autopsy studies, because there had been no other adequate measurement for the pancreatic injury. In clinical practice, however, patients with seemingly mild pancreatic injury (ie, observed during endoscopic retrograde cholangiopancreatography without pancreatic duct injection) may develop severe AP, whereas other subjects with extensive pancreatic injury might have a relatively mild disease course [7]. The correspondence between the degree of pancreatic injury and the severity of the ensuing immune response remains poorly understood. To address these observations, research has been focused on common and uncommon

variations in DNA and on assessing environmental and metabolic factors between patients with mild and severe AP, to determine whether any of the previously mentioned variants is associated with a severe disease course.

Chronic Alcohol Consumption and Pancreatic Necrosis

A recent two-arm study, with a prospective and retrospective phase, showed that chronic alcohol consumption constitutes a major risk factor for PNEC [8]. The finding of an association between excessive alcohol ingestion (>2 drinks per day) and higher rates of PNEC is novel. The association found in the newest report was an unexpected finding because it had been previously reported that alcohol as a cause of AP was not associated with an increased risk of PNEC [9,10]. Potential mechanisms linking alcohol consumption to segmental PNEC have not been explored. The pancreas of alcoholics may be at higher risk of ischemic injury or segmental necrosis because it is already under metabolic stress and has decreased reserve and tolerance for injury [11,12]. Another intriguing possibility is that chronic alcohol exposure shifts the mechanism of cell death from apoptosis to necrosis [13]. Interestingly, a higher rate of PNEC in alcoholics did not translate into a higher mortality rate. Because mortality in AP seems to be directly related to the intensity of the inflammatory response [1], this observation could suggest impaired innate immunity in alcoholics.

Obesity

Obesity has been shown to be an independent risk factor for severe outcome in patients with AP [9,14–18]. Recently, Martinez and colleagues [19] conducted a meta-analysis suggesting that obesity (body mass index >30 kg/m^2) increases overall severity (odds ratio [OR] 2.6; 95% confidence interval [CI], 1.5–4.6) through local and systemic complications. The role of central obesity was implicated with severity in a study that found that waist-to-hip ratio and waist circumference were significantly associated with severity (OR 9.23; 95% CI, 1.67–51.07; and OR 13.41; 95% CI, 2.43–73.97, respectively) [18]. The role of obesity in AP is of particular interest because adipose tissue and adipokines have been shown to be important in diseases, such as inflammatory bowel disease and type II diabetes mellitus, in which there is altered immune function. A recent prospective study proposed that obesity might increase the severity of AP by amplifying the immune response to injury [20] through a fat-dependent overexpression of adipokines.

GENETICS OF SEVERE ACUTE PANCREATITIS

Monocyte Chemotactic Protein-1

Any genetic factor that alters the expression of regulatory cytokines-chemokines could potentially alter the inflammatory response to pancreatic injury. This theory has recently been shown with a prototypic inflammatory regulator, monocyte chemotactic protein-1 (MCP-1). MCP-1 is a chemokine released by mononuclear cells to attract further monocytes, lymphocytes, mast cells, and eosinophils. A single nucleotide polymorphism in the distal regulatory region of the MCP-1 gene (G to A) at position -2518 results in a significantly greater

serum levels of MCP-1 following an inflammatory stimulus when compared with the wild-type sequence [21].

In preliminary studies, the MCP-1 -2518 A/G polymorphism predicted that the physiologic response to pancreatitis would be severe and associated with death [22]. The G allele was present in 87% of severe pancreatitis, 45% of mild pancreatitis, and 43% of controls. The presence of the G allele significantly increased the risk of severe AP from any cause about sevenfold (approximately 40%), whereas subjects with an AA genotype had a low risk of severe AP (approximately 5%).

A theoretical explanation of how the MCP-1 -2518 G allele could markedly increase the proportion of patients with AP who develop a severe clinical course is based on the interaction of genetics and pancreatic injury. The assumption is that the magnitude of the injury to the pancreas (mild, moderate, severe) is independent of the MCP-1 allele. A moderate injury results in a mild clinical response (Ranson's score of 1 and APACHE-II of 4) in patients with the normal MCP-1 A/A genotype; the same moderate injury results in a severe clinical course (Ranson's $\geq$3 and APACHE-II $\geq$8) in subjects who possess the high-risk MCP-1 G allele. Subjects with the MCP-1 -2518 A/A genotype only develop severe AP following a severe pancreatic injury or when another confounding variable is present. These types of insights may allow physicians to predict a severe episode of AP before the injury occurs, not 24 to 48 hours afterward as with the currently used clinical scores.

Glutathione-S- Transferase-Theta-1

The pancreatic response to oxidative stress is hypothesized to play a major role in determining the outcome of cellular injury and susceptibility to AP and the severity of the subsequent acute inflammatory response. One physiologic mechanism of protection from oxidative stress is the up-regulation of antioxidant enzyme activity. The glutathione-S- transferases (GSTs) are an important family of antioxidant enzymes, of which four classes have been described: (1) alpha (A); (2) mu (M); (3) pi (P); and (4) theta (T). Genetic polymorphisms affecting the production of GST class enzymes include homozygous deletion of the whole GSTM-1 and GSTT-1 genes [23]. Normal or functional genotypes of the GSTT-1 enzyme are designated as GSTT-1*A, and nonfunctional genotypes as GSTT-1 null.

A recent European study on genetic polymorphisms of antioxidant enzymes in AP showed that the functional GSTT-1*A genotype is more prevalent in severe pancreatitis (96%) compared with mild pancreatitis (78%) and control groups (76%) [24]. GSTT-1 null polymorphism seems to be protective against severe AP. Normal expression of the GSTT-1 enzyme, however, seems to result in an increased inflammatory response to pancreatic injury. It seems contradictory that the functional form of the GSTT-1 gene is associated with severe AP because it is believed to protect against oxidative stress; the authors hypothesized that the effect seen may be the result of the production of toxic metabolites or depletion of glutathione by the enzyme. A subsequent study, however, did not observe this association in a North American population

[25]. The relative frequency of functional GSTT-1 genotypes in the second study was nearly identical in subjects with severe AP, mild AP, and healthy controls. The contrasting results between the two studies cannot be easily explained on the basis of study design, phenotypic features ascertained, or classification systems. The prevalence of the GSTT-1 null phenotype was significantly higher in the European control group, however, suggesting that the populations themselves may be different.

Cytokine Polymorphisms as Disease Severity Modifiers

The acute inflammatory response is a highly regulated process with proinflammatory and anti-inflammatory factors interacting in sequential and coordinated ways. A number of cytokines that regulate the local inflammatory response in AP have been described, including tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-10 [26].

TNF-α, the earliest cytokine to be released, is a key early mediator of the immune response to endotoxin [27]. Systemic release of TNF-α has been associated with septic shock and fatal outcome. A polymorphism has been reported at the position -308 of the TNF-α gene. TNF2 (-308G) results in increased TNF-α production and is the rare allele, so the TNF2/2 genotype is rarely found. A recent study suggested that the TNF1/2 genotype is associated with severe AP ($P = .046$) [28]. In studies from China, however, the TNF1/2 genotype seems to be associated with death from septic shock rather than the inflammatory response to AP alone [29,30]. The effect of the TNF-308G allele in other diseases seems to be small (OR approximately 1.5), so large studies are needed to determine the risk in AP.

IL-1 and IL-1-receptor antagonist (IL-1RA) polymorphisms, members of the IL-1 gene cluster, have also been implicated in modifying the severity of AP. Penta-allelic and biallelic polymorphisms exist in the IL-1RN and IL-1β genes, respectively. In a single study, the allele 1 of the IL-1RN polymorphism was significantly increased in all AP cases when compared with controls (72% versus 63%; $P = .029$); in severe cases compared with controls (82% versus 63%; $P = .004$); and in severe cases compared with mild cases (82% versus 67.5%; $P = .046$). The frequency of IL-1RN allele 2 was significantly decreased in severe cases compared with controls (18% versus 33%; $P = .026$) and in severe cases compared with mild cases (18% versus 32.5%; $P = .046$) [31]. The genetic balance between IL-1 and IL-1RA expression seems to influence severity of AP in this English population. In Chinese subjects, the IL-1β +3594T polymorphism was investigated and there was no association with pancreatitis severity [32].

IL-8 is a proinflammatory chemokine produced by macrophages and other cell types, such as epithelial cells. IL-8 attracts neutrophils to the site of inflammation. Polymorphisms in the IL-8 gene seem to be associated with a more severe course of AP [33].

IL-10 is an anti-inflammatory cytokine and plays an important role in downregulating cell-mediated inflammatory responses. Three single base pair substitutions in the IL-10 gene promoter at positions -1082 G/A, -819 T/C, and -592

A/C from the transcriptional start site have been identified. A recent study demonstrated that IL-10 polymorphisms do not determine susceptibility or severity in AP [32]. The IL-10 -1082 G allele seems to play an important role, however, in the susceptibility of patients with severe AP to septic shock [32].

CD14 is a membrane-anchored protein that acts as pattern-recognition receptor for several microbial products, including lipopolysaccharide, and interacts with the toll-like receptor 4. CD14 is expressed on the surface of neutrophils, monocytes, macrophages, and fibroblasts, all of which can produce cytokines, such as IL-1 and TNF-α, in response to lipopolysaccharide stimulation [34]. Recently, a polymorphism in the promoter region of CD14 gene has been identified at position -260. Two studies have suggested that the CD14 -260 C/T polymorphism is not associated with severity in AP [32,35], but might be linked with the pathogenesis of AP in alcoholics [36]. The CD14 -159 promoter polymorphism was not found to be associated with the severity of AP [28,32]. Toll-like receptor 4 gene polymorphisms do not seem to alter the susceptibility or severity of AP [33].

Heat shock proteins (HSP) are molecular chaperones that are induced during stress and play a critical role in protecting cells from oxidative stress, inflammation, and apoptotic death. HSP70 is one of the major heat shock proteins expressed in the acinar cell [37]. HSP70 seems to be protective against severity in rodent AP models [38,39]. The HSP70-2 G allele at position +1267 was compared between groups of patients with mild or severe AP and a significant association was identified (19% versus 53%; $P < .001$) [28]. Of special note, the A/A genotype was markedly more frequent among the patients with mild AP [28], perhaps demonstrating the importance of HSP70 in protecting cells from ongoing injury during AP.

PREDICTORS OF SEVERE OUTCOME

Much effort has been placed into identifying objective predictive markers to grade the severity of AP at the time of hospital admission. This is based on the notion that early prediction can help guide the clinician in directing patients at high risk to intensive care with prompt institution of aggressive interventions, which could potentially improve outcome. Although disease-specific therapy for AP remains limited at this time, various therapeutic modalities, such as cytokine inhibitors and novel anti-inflammatory regimes, are being evaluated in ongoing clinical trials. These treatments must be instituted at a very early stage in the course of AP, because the chances for success diminish rapidly over time.

The ideal predictor is rapid, reproducible, inexpensive, and minimally invasive [40]. It should also have a high negative likelihood ratio, which indicates that the odds of severe disease are low when a test is negative. This allows a high proportion of patients with mild disease to be managed in low-cost hospital beds. Furthermore, a predictor that is able to assist in monitoring the progress of the disease is desirable. To date, numerous predictive markers have been studied in assessing severity in AP, including clinical assessment, clinicophysiologic scoring systems, imaging techniques, and biochemical markers.

Clinical Assessment

The ability of clinicians to differentiate mild from severe AP has been evaluated in various clinical trials [41–44]. Clinical assessment is reasonably good in identifying mild cases as early as at the time of admission (specificities between 83% and 98%). The poor sensitivities displayed (34%–64% on admission), however, suggest that a significant proportion of patients with severe disease would be misidentified and undertreated.

Multifactorial Scoring Systems

The first attempt to describe the clinical features that reflected the inflammatory response and predicted morbidity and mortality was developed by Ranson and coworkers in 1974 [5]. This system is still used today in clinical trials and remains useful in pointing the physicians' attention to the organ systems that are likely to fail in patients with systemic inflammation. Five of these signs can be measured on admission and the remaining six items are measured at 48 hours into the hospital course. There have been a number of modifications on Ranson's original criteria including the scoring system from Glasgow [45].

The most widely used system in the assessment of AP is APACHE-II. APACHE-II was developed in 1985 for evaluation of severely ill patients regardless of the primary disease [6]. The acute physiology score uses the most abnormal value of 12 representative physiologic measures with weighting based on the degree of deviation from normal. Additional points are added based on patient's age and severity of baseline chronic disease. The major advantages of the APACHE-II system are the ability to calculate a score on admission and to be updated daily during the hospital course, allowing for monitoring of disease progression and response to therapy. There is significant inconvenience associated with the APACHE-II system, however, because of its complexity. In well-designed prospective studies, Ranson's, Glasgow Coma Score, and APACHE-II scoring systems have shown reasonable accuracy as predictors of severity and outcome in AP [43,44,46,47].

Recently, a modification of the APACHE-II scoring system with the addition of obesity was proposed [48]. The APACHE-O scale, which adds one point for body mass index between 25 and 30 and two points for body mass index greater than 30, has shown encouraging preliminary results [48]. A subsequent study did not confirm, however, that the admission APACHE-O score improves the predictive accuracy of APACHE-II for severe outcome in AP [20].

Routine Laboratory Data as Predictors of Pancreatic Necrosis and Mortality

Previous studies have demonstrated that hemoconcentration on admission (hematocrit $\geq$47%) or failure of admission hematocrit to decrease within 24 hours represent strong risk factors for the development of PNEC [49]. These findings were confirmed in two follow-up studies [50,51], but not in a large trial that used lower hematocrit cutoff levels (43% for male and 39.6% for female patients) [52]. Although hemoconcentration seems to be a strong risk factor for PNEC, only a fraction of patients with AP and elevated admission serum

hematocrit develop PNEC [53]. Hemoconcentration alone remains a poor positive predictor of PNEC.

Pathologic chest radiographs (presence of pleural effusion or infiltrate) within 24 hours of admission have been suggested to correlate with an increased mortality risk, PNEC, and the development of infected necrosis [54]. Furthermore, when both the chest radiograph and the serum creatinine levels (>2 mg/dL) are abnormal, the risk seems to rise substantially. Another large study suggested that routine admission laboratory parameters (elevated serum creatinine >2 mg/dL and blood glucose >250 mg/dL) are significantly correlated with mortality in AP [55].

Pancreatic Imaging

Contrast-enhanced CT scan has been shown to be sensitive and accurate in the detection of PNEC [56]. With the use of incremental bolus technique, contrast-enhanced CT has an overall accuracy of 87% with a sensitivity of 100% for detection of extended PNEC and a sensitivity of 50% if only minor necrotic areas are present [57].

The presence of peripancreatic inflammation, the identification of peripancreatic fluid collections, and the extent of PNEC have been shown to predict disease severity and outcome. Balthazar and colleagues [58] developed a grading system for AP severity based on the findings in contrast-enhanced CT, such as extent of pancreatic edema, presence of peripancreatic fluid collections, and PNEC, which was named the CT severity index. Patients with a severity index of 0 to 1 exhibited no morbidity or mortality, whereas 4% morbidity rate and no mortality were seen with CT severity index of 2. In contrast, patients with a CT severity index of 7 to 10 yielded a 92% morbidity and 17% mortality rate. In recent larger studies, AP patients with a CT severity index greater than 5 were eight times more likely to die, 17 times more likely to have a prolonged hospital course, and 10 times more likely to require necrosectomy [59,60].

Markers of the Inflammatory Response

C-reactive protein (CRP) is an acute-phase reactant produced by the hepatocytes. CRP synthesis is induced by the release of IL-1 and IL-6. CRP peaks 72 hours from the onset of pain, which is after IL-1 and IL-6 peak. Detailed evaluation has determined CRP to be a useful predictor of severe AP at 48 hours from the onset of symptoms, but not in the early phase of AP [47,61–65]. CRP testing at 48 hours has shown a sensitivity ranging from 65% to 100% and a positive predictive value of 37% to 77%, which is similar to APACHE-II (Table 1) [66]. CRP is the best studied and most widely used single predictor of severity in AP because of its low cost and easy availability. Multiple cutoff levels have been studied, and a level of 150 mg/L is currently the standard for distinguishing mild from severe disease [67]. Its ability to discriminate mild from severe disease, however, is unsatisfactory.

Polymorphonuclear (PMN) elastase is a potent hydrolytic enzyme released by activated PMN granulocytes that degrades the extracellular matrix [66].

Table 1
Makers of severity in AP

Markers/Cutoff/Ref	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
CRP 24 h/150 mg/dL [47]	0	90	0	75	69
CRP 48 h/150 mg/dL [47]	65	73	37	90	72
PMN-E 24 h/300 μg/L [68]	93	99	97	98	98
PMN-E 24 h/400 μg/L [65]	85	76	82	81	81
PCT 24 h/110 μg/L [70]	92	91	78	96	91
MDA 24 h/2.75 mmol/L [75]	93	52	54	93	60
TRX-1 adm/100 ng/mL [76]	83	94	88	92	91
IL-1 24 h/1 pg/mL [79]	72	87	76	85	82
IL-1/IL-1RA 48–72 h [80]	75	71	55	86	72
IL-6 24 h/400 pg/mL [79]	89	87	80	93	88
IL-6 24 h/2.7 pg/mL [82]	100	86	80	100	91
IL-8 24 h/100 pg/mL [79]	50	87	69	75	74
IL-8 24 h/30 pg/mL [82]	100	81	75	100	88
sTNFR 24 h/8.8 ng/mL [81]	95	100	100	94	96
sCD40 L 48 h/1000 pg/L [90]	77	62	63	74	70
UrCAPAP 0 h/100 nm/L [90]	92	89	69	98	90
UrT-2 24 h/2000 mc/L [63]	62	85	62	85	79
T-2 24 h/1000 mc/L [95]	91	71	76	88	81
T-2AAT 24 h/760 mc/L [76]	80	67	76	67	NA
UrTAP 24 h/35 nm/L [47]	68	74	44	89	73
TAP 24 h/2.8 nmol/L [78]	70	78	61	84	76
PMN-E 24 h + CRP 48 h [109]	100	95	94	100	97
CRP + UrTAP 24 h [47]	40	91	57	83	79
CRP + UrT-2 24 h [63]	51	90	68	83	79
IL-10 + Ca adm [111]	88	93	81	96	92

Only data on the most promising predictors of severity in AP from representative studies with documented sensitivity, specificity, positive predictive value, negative predictive value, and accuracy are presented. Accuracy is defined as the rate of correct predictions made by the model over a data set. Accuracy is defined for a two-by-two confusion matrix: $(a + d)/(a + b + c + d)$.

Abbreviations: CRP, C-reactive protein; IL, interleukin; MDA, malondialdehyde; PCT, procalcitonin; PMN-E, polymorphonuclear elastase; sCD40L, serum CD40 L; sTNFR, soluble tumor necrosis factor receptor; TAP, trypsinogen activation peptide; TRX, thioredoxin 1; UrCAPAP, urine carboxypeptidase B activation peptide; UrT-2, urine anionic trypsinogen.

PMN-elastase levels have been shown to be a very sensitive prognostic marker in various inflammatory conditions [68,69]. Studies have demonstrated that PMN-elastase reaches significantly higher serum levels in severe AP than in mild disease at 12 hours from the onset of symptoms [68]. At 24 hours, the accuracy of PMN-elastase levels greater than 300 μg/L ranges from 81% to 98% [65,69], where accuracy is defined as the proportion of subjects for whom the test corresponds to the diagnosis (positive or negative). A rapid automated immunoassay has recently become commercially available; it can facilitate the clinical use of this accurate early predictor of AP severity.

Procalcitonin (PCT), a propeptide of calcitonin, is another marker that has been applied in many infectious and inflammatory processes [66]. PCT has shown promising results as an early marker of severity in AP with an accuracy

of 86% in a small study [62]. A rapid serum dipstick assay has been recently developed, which has the potential of wide future use in the clinical practice. A study using this assay and a cutoff of 110 μg/L revealed a sensitivity of 92% and specificity of 91% in predicting severe AP when PMN-elastase is measured on the first morning of admission [70]. A recent prospective study found that the most accurate prediction of disease severity was provided by the APACHE-II score on the day of admission (receiving operator characteristic area under the curve [ROC-AUC]: APACHE-II, 0.78 and PCT, 0.61) and by CRP after 48 hours (ROC-AUC: CRP, 0.94 and PCT, 0.71) and concluded that PCT is of limited additional value for early assessment of severity and etiology in AP [71]. A subsequent meta-analysis, however, showed an overall sensitivity of 74% and specificity of 83% [72].

The production, deposition, and degradation of the extracellular matrix are associated with hypercytokinemia and occur actively as a result of interactions with the complicated cytokine network. In a recent study, the serum levels of matrix metalloproteinase (MMP)-1, tissue inhibitor of metalloproteinases (TIMP)-1, the MMP-1–TIMP-1 complex, TNF-α, and transfer growth factor-β1 were determined by ELISA in patients with AP [73]. The TIMP-1/MMP-1 ratio and the transfer growth factor-β1 levels were found to be significantly lower and the levels of MMP-1, the MMP-1–TIMP-1 complex, and TNF-α were significantly higher in patients with severe disease. A significant correlation was observed between MMP-1 levels and TNF-α levels. A significant negative correlation was noted, however, between MMP-1 levels and transfer growth factor-β1 levels. The results suggest that the activity of the extracellular matrix catabolic enzyme MMP-1 is related to the severity of AP.

MMP-9 degrades basement membrane components in inflammation. In a recent study, serum MMP-9 level, CRP, TNF-α, and APACHE-II score were measured at 1 hour and 48 hours after admission [74]. APACHE-II scores, serum MMP-9, TNF-α, and CRP levels were significantly increased in patients with severe AP compared with those with mild AP and control subjects at 1 hour after admission ($P < .01$). Furthermore, significant positive correlation was found between serum MMP-9 level and TNF-α, CRP level, and APACHE-II score in patients at 1 hour after admission (MMP-9–TNF-α, $r = 0.956$; MMP-9/CRP, $r = 0.935$; MMP-9/APACHE-II score, $r = 0.957$; $P < .01$). These results suggest that MMP-9 is involved in severe AP and serum MMP-9 level could become a valuable assessment marker for the severity in AP.

Release of oxygen free radicals is increased in AP. Malondialdehyde, a marker of lipid peroxidation, and superoxide dismutase, an oxygen free radical scavenger, were assessed as predictors of severity in AP [75]. Plasma levels of malondialdehyde and erythrocyte content of superoxide dismutase were measured at 0, 12, 24, 48, 72, 96, and 120 hours after admission. Plasma malondialdehyde greater than 2.75 μmol/L at 12 hours after admission had high overall accuracy for predicting severe AP. Superoxide dismutase levels were found to be decreased in AP, but no substantial significant difference was demonstrated between severe and mild AP patients.

Thioredoxin 1 (TRX-1), a redox-regulating protein with antioxidant activity, is induced by oxidative stress and serum TRX-1 levels are recognized as an oxidative-stress marker. Serum TRX-1 levels were recently determined on admission in 18 patients with severe AP and 36 patients with mild AP [76]. A cutoff value of 100 ng/mL for TRX-1 revealed a sensitivity, specificity, and accuracy of 83%, 94%, and 91%, respectively. A significant correlation was observed between serum TRX-1 levels and Ranson score ($r = 0.674$); CRP ($r = 0.718$); IL-6 ($r = 0.712$); leukocyte count ($r = 0.642$); and serum amylase ($r = 0.436$).

Heat shock factor-1 (HSF-1) transcribes stress proteins that protect against cellular damage. Systemic activation of HSF-1 was found to be greatest in patients with mild AP compared with severe AP ($P = .036$). Furthermore, HSF-1 was inversely correlated with APACHE-II score ($r = -0.47$, $P = .026$). These data suggest that HSF-1 activation may protect against severe AP [77].

Cytokines and Surface Receptors

A number of cytokines have been implicated in regulating the local inflammatory response in AP. Serum values for certain cytokines (eg, TNF), however, have shown low accuracy as predictors of disease severity [61,78]. This could be explained by their short half-life in serum, the presence of circulating inhibitors, or because they may achieve high concentrations locally within the pancreatic fluid rather than systemically.

TNF-α has been found to be less useful as a predictor of severity in AP [79,80]. Soluble TNF receptor (sTNFR) seems to attenuate the effects of TNF by binding to TNF in the serum [80] and can be viewed as an anti-inflammatory molecule. sTNFR levels have been found to predict severity in AP with an accuracy of 96% and also to have high sensitivity for mortality [81].

IL-1 has similar accuracy to IL-6 in predicting severe AP on admission (82% versus 88%, respectively) [79]. IL-1 RA seems to have the best accuracy among numerous markers, including IL-6 and CRP, within the first 48 hours [68]. In a prospective study of ICU patients, IL-1 levels at 48 to 72 hours from symptom onset have been found to be predictive of PNEC with an accuracy of 88%; the IL-1/IL-1 RA ratio could identify septic complications with an accuracy of 72% [80].

IL-6 is released by macrophages in response to tissue injury and constitutes the principal mediator in the synthesis of acute-phase proteins, such as fibrinogen and CRP. IL-6 represents the most accurate early predictor of severity in AP presently available, with 89% to 100% sensitivity and 90% accuracy within the initial 24 hours [69,82–85]. It has been shown to be superior to CRP [56] and APACHE-II [55] on Day 1. The accuracy of the test decreases after the first hospital day, however, and has low predictive value for mortality.

IL-8 has a profile similar to IL-6 and has potential as an early marker, with 74% to 88% accuracy within the first 24 hours [82,85,86]. Further studies are needed to assess reported disparities in the sensitivity of the test.

IL-18 is a cytokine produced from Kupffer cells and activated macrophages. IL-18 acts on Th1 cells and, in combination with IL-12, strongly induces production of interferon-γ. Serum IL-18 concentrations were determined by

ELISA in 43 patients with AP at the time of admission. Serum IL-18 levels were significantly elevated in patients with AP when compared with controls. Furthermore, the CD4-CD8 rate of lymphocytes, IL-6 levels, and IL-8 levels were positively correlated with serum IL-18 levels suggesting that IL-18 levels are also correlated with disease severity [87].

MCP-1 serum concentrations have shown a dramatic increase in patients with AP who develop local complications or remote organ failure. A close correlation has also been found between the incidence of remote organ failure and the degree of MCP-1 level elevation [22,88]. Macrophage migration inhibitory factor (MIF) is a unique protein, participating in inflammation, immune response, and cell growth. Serum MIF levels have been found to be higher in severe AP patients than mild AP patients and healthy controls [89].

CD40, a member of the TNF receptor family, is expressed on the membrane of a variety of cells, including B lymphocytes, monocytes, and biliary and acinar cells. CD40 binds to its ligand CD40 L, a membrane glycoprotein, to mediate major immunoregulatory signals involved in inflammation. In a recent study, serum CD40 L concentrations were measured 48 hours after admission in patients with AP and were found to be significantly higher in severe disease [90]. Using a cutoff of 1000 pg/L, the sensitivity and specificity of serum CD40 L were 78% and 62%, respectively, compared with 72% and 81% for CRP.

Severe AP is frequently associated with immune suppression, which increases the risk of infections, organ failure, and death. A proposed parameter for "immunoparalysis," a down-regulation of HLA-DR expression on monocytes, has been detected in patients with severe but not mild AP. In a recent study, when analyzing the serial change of HLA-DR expression, it is clear that HLA-DR expression was gradually up-regulated in the survival group and was persistently down-regulated in the late mortality group ($P < .001$) [91]. The optimal cutoff value of the percentage of monocytes expressing HLA-DR on Day 10 for predicting late mortality was 52.3% with 94% sensitivity and 86% specificity.

Pancreatic Zymogens and Enzymes

During the last decade, a wide spectrum of pancreas-specific markers has been evaluated as predictors of severity in AP. This research is based on the logical concept that during a severe inflammatory pancreatic process, a larger amount of pancreatic content may spill into the systemic circulation in comparison with a mild process.

Amylase and lipase constitute established and accurate tools in the diagnosis of AP. They could be clinically useful because these enzymes are synthesized in their active form and concentrations in blood or urine can be easily calculated by measuring enzyme activity. Several studies concluded that the levels of serum amylase and lipase do not correlate with the severity of disease [92], although these findings are not universal [93].

Pancreatic associated protein is normally undetectable in the pancreas. Initial trials measuring pancreatic associated protein levels in the blood showed

encouraging preliminary evidence as a predictive marker [94]. Subsequent studies using a commercially available assay have demonstrated poor correlation, however, between serum pancreatic associated protein levels and severity in AP [95].

Procarboxypeptidase-B is a major zymogen produced in the pancreas. As with pancreatic associated protein, initial reports were promising [96]; however, confirmatory studies have shown poor correlation with disease severity in AP [97,98]. Carboxypeptidase B activation peptide (CAPAP) constitutes the largest activation peptide resulting from the cleavage of procarboxypeptidase-B. This peptide is very stable in serum and urine. Reports have showed a potential use of urine CAPAP in predicting severity in AP [99,100]. A recent study has demonstrated that serum CAPAP levels within 48 hours can predict PNEC with accuracy of 92% [98].

Trypsinogen constitutes the proenzyme of trypsin and has different isoforms. Cationic trypsinogen (PRSS1) predominates in the circulation at baseline, whereas anionic trypsinogen (PRSS2) seems preferentially to be elevated in AP, especially in alcoholics. The development of a rapid urine dipstick method able to measure anionic trypsinogen (T-2) makes the use of this marker particularly attractive [63]. T-2 is not specific for AP, however, and has been found elevated in other intra-abdominal processes [101]. Overall, the present data suggest greater use for T-2 as a diagnostic tool for AP rather than a predictor of severity [102,103].

Trypsinogen is cleaved by enterokinases into trypsin and trypsinogen activation peptide (TAP). Trypsin is then responsible for the activation of all other proenzymes into derivatives with catalytic properties. α_1-Antitrypsin, however, serves as a systemic gatekeeper by forming a complex with trypsin in serum, rendering it inactive. It has been hypothesized that severe AP occurs when the degree of trypsin spilled into the systemic circulation exceeds the neutralizing capacity of α_1-antitrypsin. Several trials have studied the trypsin–α_1-antitrypsin complex as predictor of severity in AP and demonstrated high accuracy during the initial 24 hours [104,105].

TAP has been thoroughly studied. An ELISA was developed to facilitate the clinical application of TAP levels. The results of the ELISA in predicting severity in AP using serum and urine have been encouraging [47,106]. Elevated levels of TAP have been demonstrated early after the symptom onset and peak within 24 to 48 hours.

Phospholipase A_2 (PLA-2) is an enzyme produced in the pancreas that contributes to lipid peroxidation. PLA-2 occurs as two subtypes. Although pancreatic PLA-2 does not seem to be involved in the pathogenesis of AP, a strong correlation has been demonstrated between PLA-2 type II and severity in AP, occurrence of pulmonary and renal complications, and infected PNEC [107,108].

Combination of Serum Markers

Because all of the prognostic biochemical markers reviewed have shortcomings, several studies have evaluated the accuracy of combining markers. The

combination of PMN-elastase value on Day 1 and CRP levels on Day 2 has been found to be 97% accurate in predicting severity [109,110]. The combination of CRP levels grater than 150 mg/dL and a urinary TAP value greater than 35 nmol/L has been found to be 79% and 83% accurate in predicting severity in AP at 24 and 48 hours, respectively [47]. Additionally, the combination of a CRP value greater than 150 mg/L and a T-2 value greater than 2000 μg/L has demonstrated an accuracy of 79% at 24 hours [63].

A model containing eight variables (age, CRP, respiratory rate, Pa_{O_2} on room air, arterial pH, serum creatinine, white cell count, and Glasgow Coma Score) was found to be able to discriminate between a severe and mild attack (ROC-AUC, 0.82) with a sensitivity and specificity of 87% and 71%, respectively (higher than admission APACHE-II scores [ROC-AUC, 0.74]).

In a recent study, 19 prognostic markers were analyzed in patients with AP [111]. Plasma IL-10, serum glucose, and serum calcium were identified as independent predictors of organ failure. The combination of IL-10 (>50 pg/mL) or calcium (<1.65 mmol/L) was a significantly better predictor than any single marker or APACHE II score, with a sensitivity of 88% and specificity of 93%.

PROTEOMIC PROFILING

A pilot study assessed the use of proteomic profiling in discriminating severe from mild AP early in the course of the disease [112]. Proteomic analysis using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry with the Ciphergen ProteinChip (Ciphergen Biosystems, Fremont, California) was performed. The initial analysis of admission serum from 28 AP patients (7 severe and 21 mild) provided distinctive patterns. Of 200 peak clusters identified among the profiles, 27 were found to have a statistically significant difference in mean peak intensity between the mild and severe cases ($P < .001$). Because of the small number of samples in each group, an elaborate cross-validated evaluation of classification was not possible. These initial data suggest that serum proteomic profiles contain features that discriminate between mild and severe AP. The more important questions surround the identity of the key protein peaks. One of the peak clusters identified (at 11.7 kd) is of interest because in a previous study in nasopharyngeal cancer patients using the same technique, a similar m/z peak was identified as serum amyloid A [113]. This possible identification of serum amyloid A in the severe AP samples is of interest.

SUMMARY

To date, CRP remains the single best biochemical marker for predicting the severity in AP. Because the combination of clinicophysiologic scores and CRP provides good information at 48 hours, current research has been focused on the predictive ability of various markers during the initial 24 hours of disease. After detailed review of the literature, the authors conclude that there is yet no single marker that could serve as an optimal predictor of disease severity in AP. There are, however, data to support the use of certain markers to improve clinicians' predictive ability. These include admission APACHE-II

Box 1: Tools for predicting severity in AP available for clinical use

On admission

APACHE-II score >7

IL-6 ELISA, cutoff level >400 pg/mL

At 24 hours

PMN-elastase ELISA, cutoff level >300 μg/L

Urinary T-2 ELISA, cutoff level >35 nmol/L

Urinary trypsinogen activation peptide dipstick, cutoff level >2000 μg/L

At 48 hours

Ranson/Glasgow Coma Score >2

C-reactive protein automated, cutoff level >150 mg/L

score and IL-6, and urine TAP, urine T-2, and serum PMN-elastase at 24 hours (Box 1). These markers only help clinicians if they can be performed locally and if the results are available in a timely manner. Future research focusing on promising markers, such as PCT, MMP-9, malondialdehyde, TRX-1, HSF-1, sTNFR, IL-1RA, IL-8, IL-18, MCP-1, MIF, CAPAP, PLA-2, and other novel markers, and combinations of markers is required.

FUTURE DIRECTIONS

The conventional research approach in predicting severity used in the last 15 years has limitations and it seems that it has reached its maximal potential. Novel conceptions and approaches, such as identification of genetic polymorphisms that predispose to severe clinical course and complications in AP, are needed for a quantum step forward.

The genetics of AP will likely become very important in the future. The early findings that a variety of cytokines and regulators of the inflammatory process significantly alter the severity of AP support the importance of genetic and environmental factors as disease severity modifiers. What is needed is a modeling framework that integrates all this information and provides practical algorithms for rapid identification of patients at risk of severe AP. New and patient-specific prophylactic and therapeutic strategies, possibly also model-based, must be developed and used so that this new knowledge can be applied in a way that minimizes morbidity and mortality from severe AP [114].

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Nutrition Support in Severe Acute Pancreatitis

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Knowledge of the pathophysiologic response is crucial to understand why feeding a patient who has acute pancreatitis is so difficult. The recognition that acute pancreatitis is initiated by the intracellular activation of proteolytic enzymes, such as trypsin, and that food stimulates the further production of trypsinogen, led to the avoidance of oral or enteral feeding. However, although long-term fasting "rested" the pancreas, it led to high rates of body nitrogen and protein loss, which was shown to increase mortality. The advent of total parenteral nutrition (TPN) enabled "pancreatic rest" to be maintained while preventing nitrogen loss, but increased inflammatory and infectious complications by its adverse effects on gut function and innate immunity, and also by increasing hyperglycemia and septicemicias. Despite the known pancreatic stimulatory effects of proximal enteral feeding, metanalysis of all the randomized controlled trials performed to date has shown that enteral feeding is superior to TPN, particularly with regard to reducing inflammatory and infectious complications. These results are best explained by the positive effects of enteral feeding on gut function and immunity, and by the avoidance of TPN complications. The results of two recent studies indicate that nasogastric (NG) feeding is feasible, but there is concern that the mortality rates were unacceptably high and that NG feeding will be ineffective in patients who have compression of the upper gastrointestinal tract by pancreatic inflammatory masses. Although technically more difficult, the endoscopic positioning of feeding tubes beyond the compression and sites of pancreatic stimulation (eg, midjejunal) has the potential to increase the delivery of nutrients and suppress acute pancreatitis. There is an urgent need for sufficiently powered randomized controlled trial studies to identify what is the optimal feeding method and whether it can prevent multiple organ failure and improve patient outcome and survival.

Nutritional support can improve the outcome from severe acute pancreatitis in two ways: first by providing the building blocks for tissue repair and recovery, and second, by modulating the inflammatory response and preventing

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organ failure, both of which are responsible for most of the morbidity and mortality associated with the disease. This review discusses the evidence on which these statements are based.

NUTRITIONAL SUPPORT FOR TISSUE REPAIR AND RECOVERY

Earlier studies concluded that acute pancreatitis was one of the most hypermetabolic and catabolic of disease conditions [1]. Furthermore, studies showed that the higher the rate of catabolic nitrogen loss, the higher the mortality [2]. In the authors' recent studies, based on enteral and intravenous infusions of isotope labeled amino acids, they have shown that the splanchnic bed takes the brunt of the catabolic response, which is expected from the known pathophysiology of the condition [3]. However, only patients who have severe and necrotizing disease had accelerated amino acid oxidative losses, indicating that patients who have the milder forms of the disease may be managed conservatively without nutritional intervention during the first week of illness [4]. In contrast, patients who have initially severe disease, or those who have high predictive severity scores, should be immediately started on nutritional support, because protein stores would be consumed within the week if nutrient stores were not supplemented.

NUTRITIONAL MODULATION OF THE INFLAMMATORY RESPONSE

The excess mortality of severe acute pancreatitis is associated with the consequences of pancreatic injury rather than the pancreatic damage itself. In contrast to patients who have mild disease, those who have severe pancreatitis develop a systemic inflammatory response characterized by a flood of proinflammatory cytokines, which impairs respiratory, renal, and intestinal function resulting in multiple organ failure (Fig. 1) [5,6]. This process has been extensively studied in animal models. The initiating factor in the inflammatory cascade is accepted to be an increase in intracellular calcium flux with premature activation of trypsinogen within the pancreas, leading to intracellular proteolysis or "autophagia" [7,8].

Fig. 1 helps illustrate some of what is known to happen in the evolution of multiple organ failure, and emphasizes the key role of the intestine in its genesis and how feeding may influence its development. Intracellular injury results in generation of a cascade of proinflammatory cytokines such as IL-1b, TNF alpha, IL-17, IL-18 by way of activation of periacinar myofibrocytic NF kappa B, and MAP kinase [9–11]. This in turn stimulates the release of IL- 6 and the cytoattraction of neutrophils, which in turn leads to further cytokine generation. The intense inflammatory response with endothelin-A activation results in the arterial constriction with resultant apoptosis and necrosis, affecting not only the pancreas, but also the intestine [12,13]. Splanchnic and whole body protein catabolism is accelerated [14]. If the inflammation were contained within the pancreatic bed, the disease process would be far less serious. Unfortunately, the cytokines are released into the circulation, and a secondary

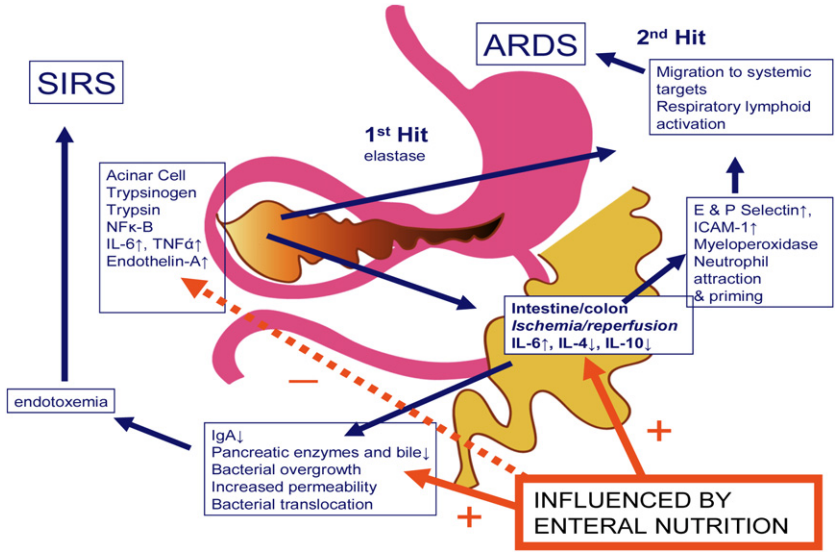

Fig. 1. Generation of the SIRS and acute respiratory distress syndrome by acute pancreatitis and where enteral feeding may influence it.

response commences approximately 48 hours later, which leads to the generation of PG-2, thromboxane, LTB-4, and oxygen-derived free radicals within the bronchial and intestinal mucosa leading to cytotoxic injury [15]. The situation is compounded further by the release of proteolytic enzymes, such as trypsin, elastase, phospholipase, and caspase l into the circulation, which leads to amplification of cell injury within the lung ("2nd hit") and gastrointestinal tract leading to acute respiratory distress syndrome (ARDS), intestinal ischemia, bacterial translocation, and the well-recognized systemic inflammatory response syndrome (SIRS) [16–20]. It is these complications that account for the high mortality rates, which can approach 30% to 50%, in severe necrotizing pancreatitis.

Despite the accumulating knowledge of the mechanisms involved, there have been no major breakthroughs in treatment. Most of the improvement in mortality can be attributed to better supportive management in the ICU. One of the key "supportive" measures is nutritional support. Well known is the potential for oral feeding to exacerbate the disease, as we know oral feeding stimulates the synthesis of trypsinogen and therefore adds "fuel to the fire" (see Fig. 1). Less known is the potential for enteral feeding to suppress the systemic inflammatory response. There is abundant experimental evidence that much of the severe systemic inflammatory response is generated or amplified within the gut lumen and mucosa. Two key pathways are indicated on Fig. 1, namely the prevention of intestinal ischemia, and the prevention of luminal stasis and bacterial overgrowth. Intestinal ischemia is a common event in patients

who have severe acute pancreatitis and can be so severe as to produce gangrene and perforation [21]. Experimental studies suggest that the ischemia is secondary to vasoconstrictors released from the injured pancreas such as endothelin [13]. Intestinal ischemia in turn leads to mucosal leakage and the risk of bacterial organism and endotoxin translocation. For example, Rahman and colleagues [22] demonstrated in patients who have severe acute pancreatitis that the urinary excretion of intestinal fatty acid binding protein, an accepted measure of intestinal ischemia, correlated positively with severity of disease, mucosal permeability (urinary polyethylene glycol 400:3500), C-reactive protein, and with endotoxin levels. Enteral nutrition plays a key role in preventing this cycle of events because it is the most potent stimulator of blood flow, through stimulation of the release of trophic gut peptides and incretins, such as GLP-1 and 2 [23,24], and of its content of arginine, the natural precursor for nitric oxide [24]. Experimental studies in the rat acute pancreatitis model have shown that nitric oxide antagonizes endothelin-A and that endothelin-A receptor blockade abolished the acute pancreatitis–associated capillary constriction and attenuated the inflammation-associated leukocytic response and pancreatic injury [25].

NUTRITION AND ITS EFFECT ON GASTROINTESTINAL IMMUNITY

There have been previous clinical and laboratory studies that have provided the evidence that the enteral processing of nutrients induce effects that affect the metabolic response to septic insults and improve host defenses. Gut barrier function related to mucosal immunity and intestinal priming of neutrophils seems interrelated and influenced by the route and type of nutrition. Several studies have shown a significantly lower incidence of pneumonia and a reduction in the intra-abdominal abscesses and sepsis rate in patients who have moderate to severe injury when fed by direct small bowel feeding formula diet [26]. Studies of diets enriched in omega-3 fatty acids, arginine, and nucleotides and/or glutamine have shown a significant reduction in the septic complications and developments of multiorgan dysfunction syndrome in patients who have moderate to severe intra-abdominal injuries [27]. Peyer's patches found in the small intestine are the principal site responsible for sensitization and maintenance of mucosal immunity [28]. Multiple extrinsic mechanisms such as the mucous coat, gylcocalyx, microbial flora, peristalsis, proteolytic secretions and other mucosal factors (lactoferrin, peroxidases), and secretory IgA assist in maintaining the state of immunity. T and B cells interact in a specific way under the influence of cytokines to induce mucosal immunity. Native B cells mature and/or proliferate within the mesenteric lymph nodes and are transformed to plasma cells, and T cells produce either Th-2 type IgA–stimulating (IL-4, IL-5, IL-6, IL-10, and IL-13) or Th-1 type IgA-inhibiting (IFN gamma, TNF- beta, IL-2) cytokines [29]. Clinical and experimental evidence support the importance of enteral stimulation on the gut associated lymphoid tissue (GALT) and its

nutritional manipulation [30]. The type and route of nutrition by affecting the cytokine levels and expression, circulating IgA levels, and expression of mucosal immunity reinforce the common mucosal hypothesis. Studies in animal models have shown that with 3 days of parenteral feeding, the percentage of CD4 and CD8 cells within the Peyer's patches remained stable in contrast to a significant reduction in the lamina propria, with a change in CD4:CD8 ratio from 2:1 to 1:1, suggestive of significant shifts in cell and cytokine profiles [31]. Furthermore, animal studies have shown that after 5 days of parenteral feeding, levels of IFN-gamma, IL-5, and IL-6 remained stable, but levels of IL-4 and IL-10 mRNA and IgA dropped by approximately 50% in lamina propria GALT cells [32]. Also there is evidence of a loss in respiratory mucosal immunity when the gastrointestinal tract is not stimulated with enteral feeding [33]. Mucosal addressin cellular adhesion molecule-1 (MAdCAM-1) in Peyer's patches is the gateway molecule for cellular migration into the mucosal immune system. Lack of enteral feeding during parenteral nutrition rapidly decreases Peyer's patches MAdCAM-1, leading to drops in mucosal T and B cells and intestinal and respiratory IgA. Studies looking at the level of MAdCAM-1 using dual monoclonal antibody techniques found similar changes to those identified in the mucosa [34]. The critical importance of luminal nutrients in inducing these changes has been shown by comparative enteral and parenteral feeding studies, whereby the same quantity of nutrients given parenterally may even have the opposite effect of promoting Th-1 responses [31–33]. One exception may be the ability of intravenous glutamine supplementation to elevate IgA levels and reduce bacterial translocation in experimental animals [35], but these findings have not been reproduced in humans. The finding that the administration of bombesin to animals with TPN-induced GALT atrophy stimulated recovery of GALT cell population and returned intestinal and respiratory IgA levels to normal without enteral feeding [36] suggests that the beneficial effects of enteral feeding is mediated by neuropeptide (gastrin-releasing peptide, neurotensin, cholecystokinin, and gastrin) release. The two-hit hypothesis, which results after a second insult such as tissue injury, causes the primed cells (first hit) to react with in an increased response and causes an increased endothelial injury within the target organs such as the lungs [37].

In summary, in patients who are at risk of developing septic complications, enteral feeding has a strong potential to limit the rate of development of multiple organ dysfunction. Route and type of nutrition has effects in modulating the immune response by protecting from intraluminal bacteria and toxic products. Changes in cytokine levels and expression influence the vascular endothelial response to septic conditions. Extensive experimental evidence suggests that this is related to maintenance of the mucosal-associated lymphoid tissue, which provides immunologic protection for both the gastrointestinal and respiratory tracts against microbial flora and infectious pathogens and supports a communication between GI and mucosal surfaces throughout the body (Fig. 2) [38].

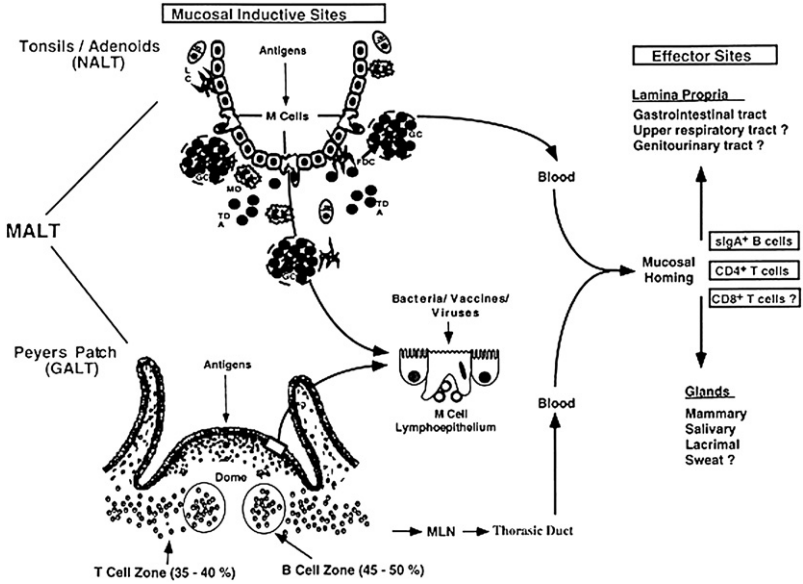

Fig. 2. M cells and the induction of mucosal immunity. M cells are present in mucosal inductive sites in both the intestinal and upper respiratory tract, specifically in Peyers patches and the nasal-associated lymphoid tissue, the tonsils and adenoids. M cells are thought to play an important role in antigen processing and possibly the induction of antigen-specific mucosal immunity in mucosal effector sites. Sites followed by question marks are presumed sites since limited data are available on these sites. (*From* Alverdy JC. Effects of glutamine-supplemented diets on immunology of the gut. JPEN J Parenter Enteral Nutr 1990;14(4 Suppl):109S–113S; with permission from the American Parenteral and Enteral Nutrition [A.S.P.E.N.].)

IS NO FEEDING AN OPTION?

The cornerstone of management of acute pancreatitis has traditionally been pancreatic rest, because the presence of food in the proximal gut is the most potent stimulus for trypsin synthesis and secretion [39], and continued trypsin synthesis can be expected to perpetuate the inflammatory response. If pancreatic rest is useful, then fasting is the surest way of imposing it. However, no study has compared feeding to fasting in the long-term management of severe acute pancreatitis, although it is standard practice to initially fast patients for 48 hours on admission to hospital [40]. On the other hand, starvation has two potential dangers: the effects of nutrient depletion on wound healing, and impairment of mucosal and intestinal function. Studies have shown that the cytokine response provokes protein catabolism. If protein catabolism is unopposed by feeding, severe nitrogen loss occurs, and it has been demonstrated that mortality is related to the degree of nitrogen loss [2]. Clearly, the demand for amino acids is high to repair splanchnic tissues. While protein stores have been estimated to last approximately 14 days in healthy subjects [41], catabolic patients will become depleted considerably sooner, and it is of concern that survival was found to be lower in nonfed patients who have acute pancreatitis recovering

from pancreatic surgery [42]. A further concern is that starvation results in disuse atrophy of the mucosa, stasis, bacterial overgrowth and increased permeability, and increased risk of infection from enteric organisms, thus exacerbating the patholologic changes illustrated in Fig. 1.

THE PROBLEM WITH TOTAL PARENTERAL NUTRITION AND BOWEL REST

The development of TPN was heralded as a potential major breakthrough because, for the first time, feeding could be maintained while maintaining pancreatic rest. The authors have shown in human studies that TPN is efficacious in meeting nutritional requirements without stimulating the pancreas [38,43]. Unfortunately its use was also associated with an alarming increase in metabolic (namely, hyperglycemia) and septic complications. Indeed, one study showed that TPN use worsened outcome in patients who had mild acute pancreatitis when compared with no feeding at all [43]. The explanation is complex. First, TPN and bowel rest probably exacerbate the intestinal and distant organ dysfunction that characterizes acute pancreatitis. Kudsk's studies in rats showed that TPN and bowel rest result in atrophy of the mucosa and the gut immune system, with suppression of Th-2 responses and activation of adhesion molecules, which leads to neutrophil priming and migration to distant targets, such as the lung, producing a first-hit phenomenon [31–33]. This is remarkably similar to what is found in the acute pancreatitis associated gut injury shown on Fig. 1. Other studies have shown that IL-6 is the mediator of gut barrier dysfunction [44], and acute pancreatitis and TPN induce intestinal IL-6 production [45,46]. The use of TPN (ie, failure to feed patients enterally) further reduces motility and blood flow, increases the risk of small bowel bacterial overgrowth with antegrade colonization with colonic organisms, and increases mucosal permeability, thus exacerbating the pathophysiologic response to acute pancreatitis [47,48]. This may be of critical importance, because the organisms most commonly responsible for pancreatic infections are of colonic origin [49], and endotoxemia commonly accompanies severe disease [50]. Second, the presence of a central vein catheter in TPN-fed patients provides an open conduit for nosocomial infections. Third, intravenous feeding invariably results in hyperglycemia in patients who have severe acute pancreatitis, because (1) the glycemic effect of glucose administered parenterally is greater than if it is given enterally [29], (2) acute pancreatitis impairs pancreatic endocrine function resulting in a relative insulin deficiency [51], and (3) the acute inflammatory response and secretion of counter-regulatory hormones increases endogenous glucose production and creates insulin resistance [52]. Recent studies have demonstrated that hyperglycemia worsens outcome in any form of critical illness [53]. In hyperglycemia, leukocyte function is impaired and intestinal motility is reduced leading to increased infection risk from enteric pathogens [54]. Consequently, it is likely that the potential benefits of TPN on resting the pancreas are overshadowed by its detrimental effects on intestinal function and mucosal integrity, and by its septic and metabolic complications.

WHY ENTERAL FEEDING IS SUPERIOR TO TOTAL PARENTERAL NUTRITION AND BOWEL REST

The complications associated with TPN have led the authors and others to explore the use of specialized forms of enteral feeding. In the five major randomized comparative studies published thus far [39,55–58], and their metanalysis [59], enteral feeding has been shown consistently to be superior to TPN with regard to cost, complications, and outcome. Marik and Zaluga [59] have recently published a metanalysis, which searched the National Library of Medicine's Medline database, Embase, and the Cochrane Database of Systematic Reviews looking for randomized controlled clinical trials comparing enteral to parenteral feeding in acute pancreatitis conducted between 1966 and 2004. Although the search identified 117 studies, only 6 fulfilled the criteria for inclusion, with a total population of 263 patients who had acute pancreatitis. This included 4 of the studies previously reviewed in more detail, namely Abou-Assi, Kalfarentzos, McClave, and Windsor. The authors noted that 4 of the 6 had low Jahad scores less than 3, indicating poor quality, and that there was considerable heterogeneity in patient selection and study design, limiting the power of their conclusions. Fig. 3 illustrates the chief conclusion that enteral feeding was associated with a lower incidence of infections (relative risk [RR] 0.45, $P < .0004$). This almost chiefly reflects the avoidance of TPN sepsis, although the suppression of enteral bacterial overgrowth may also have been a factor. In addition, they found that enteral feeding was associated with reduced hospital stay (mean reduction 2.9 days, $P < .001$), and reduced need for surgical interventions (RR 0.48, $P = .05$).

How can these observations be reconciled with the pathophysiology of acute pancreatitis previously outlined, whereby enteral feeding may exacerbate the initiating factors in the inflammatory cascade? It is not because any of the specialized forms of feeding used in these studies avoided pancreatic stimulation.

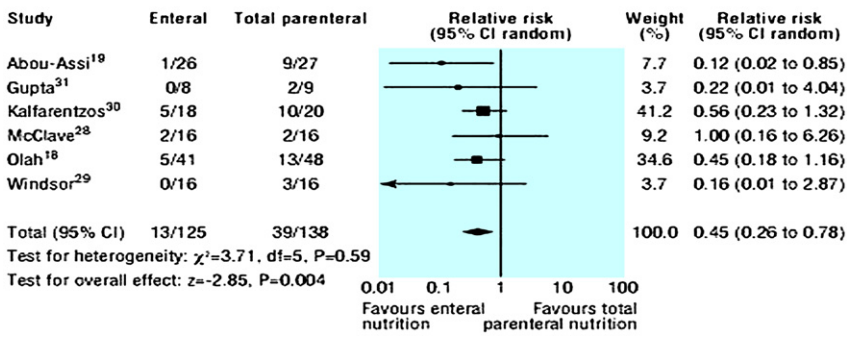

Fig. 3. Random effects model of relative risk (95% confidence interval) of infections associated with enteral feeding compared with parenteral nutrition. (*From* Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. Br Med J 2004;328(7453):1407; with permission.)

The authors' studies in healthy volunteers show that all these modes of enteral feeding stimulate the pancreas [38,51,60]. Another suggestion, based on experimental studies, was that the pancreas becomes unresponsive in acute pancreatitis. Again, the authors' investigations have shown that although the secretory response to feeding in acute pancreatitis is reduced, trypsin synthesis continues [3] and can be stimulated [60]. The predominant difference seems to be the ability of enteral feeding to reduce systemic inflammation, as previously discussed, and infective complications. In a more recent prospective nonrandomized study of 87 patients who had necrotizing pancreatitis, Modena and colleagues [61] found that jejunal feeding without antibiotics reduced pancreatic infections from 74% with TPN and antibiotics to only 20%, multiple organ failure (MOF) from 85% to 51%, and death from 35% to 5% ($P < .001$). Another consistent finding has been the ability of enteral feeding to reduce hyperglycemia, and, as Van den Berge and colleagues [53] have shown, hyperglycemia is associated with adverse outcome in all forms of critical illness. Clinical evidence for the importance of tight glucose control with insulin infusions has emerged from a recent report from Sweden whereby 48 patients were randomized to early enteral nutrition versus TPN [62]. Although hyperglycemia was more common in TPN-fed patients, insulin infusions were started when levels increased over 16 mmol/l (ie, 280 mg/dL). Unlike any other study reported to date, total complications were more common in the enteral feeding group, although most consisted on atelectasis and pleural effusions within the first 3 days—the significance of which remains questionable.

In general, these findings lead to the conclusion that the superiority of enteral feeding over TPN was accounted for not by any beneficial effect of enteral feeding on the pancreas, but by the greater efficiency of enteral feeding in preserving intestinal function and splanchnic metabolism, and by the avoidance of TPN-associated complications.

IS PANCREATIC REST IMPORTANT?

In clinical practice, it is possible to feed and maintain pancreatic rest by using either TPN, or by feeding enterally 40 to 60 cm past the ligament of Treitz [63,64]. The fact that proximal enteral feeding has proven superior to TPN dose not mean that pancreatic rest is unimportant, because, as previously discussed, the explanation probably involves the avoidance of the septic and metabolic side effects of TPN and the greater ability of enteral feeding to support intestinal and splanchnic function. To date, no study has compared stimulatory to nonstimulatory enteral (or feeding $>$ 40 cm down the jejunum) feeding. The recent publication of two randomized controlled trials demonstrating that NG feeding was as effective as "nasojejunal" feeding in the management of patients who have severe acute pancreatitis seemed, at first glance, to suggest that pancreatic rest is unimportant. Unfortunately, the trials compared like with like as both forms of feeding were stimulatory to the pancreas. As discussed in the authors' review [65], Eatock and colleagues' [58] study compared NG feeding to a mixture of nasoduodenal and nasojejunal feeding, and Kumar and colleagues'

[66] study compared NG against *nasoduodenal*–despite the fact that they titled the article "NG versus Nasojejunal"! Consequently, neither study fed far enough down the jejunum to avoid pancreatic stimulation. Furthermore, it could be argued that both were bad rather than good because the mortality in both arms was unacceptably high at 25% to 30%.

NASOGASTRIC VERSUS NASOJEJUNAL FEEDING

Despite the reservations most of us initially had, nasogastric feeding is technically feasible in acute pancreatitis as illustrated by recent publication of the Eatock and colleagues [58] and Kumar and colleagues [66] studies. The question remains, however, whether it is an effective form of nutritional support. We know that gastric emptying is impaired in critically ill patients, and better powered and controlled studies have been performed in nonpancreatic ICU ventilated patients which have clearly shown that (1) the efficiency of true jejunal feeding was higher than NG feeding in supplying approximately 20% more calories and protein and (2) that the incidence of pneumonias was higher with NG feeding [67]. It is possible that these differences will be amplified in patients who have severe complicated acute pancreatitis because of the added problem of gastroduodenal compression due to the adjacent pancreatic inflammatory mass. In keeping with this concern, the authors note that the Kumar study had to supplement patients in the first week with intravenous feeding, and, even then, there was deterioration in nutritional status. Nonetheless, both studies reported that outcome was similar in NG-fed patients to postpyloric-fed patients, leading to their conclusion that NG feeding should be the preferred method, because it is easier to place, quicker to start, and less expensive. This has made it an attractive alternative to the more complex jejunal tube placement, which is dependent on radiologic or endoscopic placement skills, which may be limited or unavailable in some hospitals. The problem is that small scale clinical trials such as these can lead to erroneous conclusions, and sufficiently powered clinical trials have to be performed before standards of practice are changed.

CAN ENTERAL FEEDING BE GIVEN WITHOUT STIMULATING THE PANCREAS?

A recent publication of the authors' findings [63] has supported the results of an earlier study from Holland [64], that it is possible to use enteral feeding without stimulating the pancreas, if the infusion is delivered 40 to 60 cm down the jejunum. This makes physiologic sense, because there has to be a null point in between the duodenum, where feeding stimulates through cholinergic reflexes and cholecystokinin release, and the ileum where feeding inhibits by way of the ileal brake mechanism [68]. The authors have shown that this distance is easy to achieve in clinical practice with transnasal endoscopic placement of tube systems that are commercially available [69,70]. There is extensive literature that the presence of nutrients (in particular long chain fatty acids [71,72], carbohydrate [72], and amino acids [73]) in the ileum suppresses pancreatic secretion in humans, principally through release of GLP-I and

peptide-YY (PYY) from ileal L-cells and neurotensin from N-cells [74]. Activation of the ileal brake in this way may have the additional benefits by suppressing acute pancreatitis and inhibiting gastric acid secretion [74] and the need for NG decompression. Fascinating recent studies in animal models of lethal necrotizing pancreatitis have shown that PYY infusions given either prophylactically or therapeutically reduce the histologic evidence of pancreatitis and the IL-6 systemic cytokine secretion, preventing death [75,76].

DOES AVOIDANCE OF PANCREATIC STIMULATION IMPROVE OUTCOME?

No study has prospectively investigated this question. However, we know that trypsinogen activation within the pancreas is the initiating factor, or "trigger," in the disease, leading to the SIRS in patients who have the severe form of the disease. A recent prospective study from Scotland, designed specifically to evaluate the therapeutic use of Lexipafant, a platelet-activating antagonist, examined the relationship between SIRS and mortality in the subgroup that had severe disease (n = 121) and found that the incidence of SIRS on admission, at 24 hours and 48 hours, as well as the persistence of SIRS, was correlated with survival as shown in Table 2 in Fig. 4 [77]. The authors also examined the relationship between MOF and death risk, and showed that transient MOF (ie, MOF that resolved with the first week) was associated with no mortality, but "permanent" or progressive MOF was associated with a mortality rate of 55%. More recently, a full evaluation of all the patients who had severe disease enrolled in the UK Lexipafant study (n = 290) was reported confirming the predictive value of permanent MOF on mortality [78]. In addition, they examined the relationship between MOF and local complications, such as pancreatic necrosis and infection. They found that there was a significant association, such that 52% of patients who had permanent MOF developed local

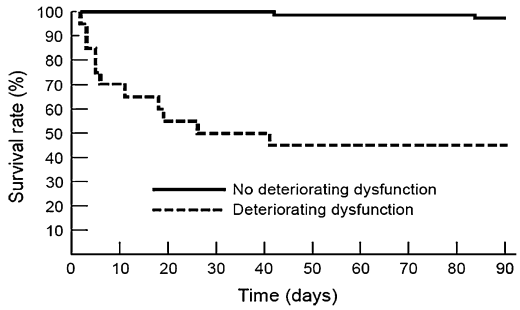

Fig. 4. The dynamic nature of early MOF determines outcome in acute pancreatitis. (*From* Buter A, Imrie CW, Carter CR, et al. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. Br J Surg 2002;89:300; with permission.)

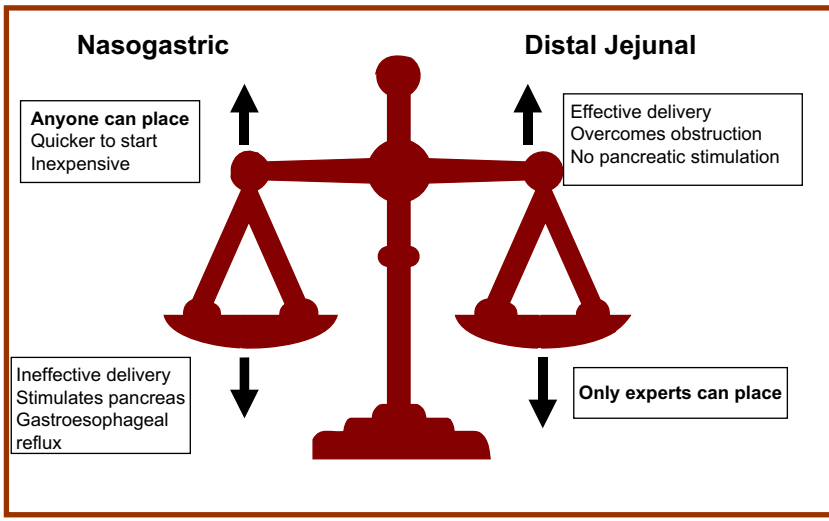

Fig. 5. Nasogastric versus distal jejunal feeding.

complications, as opposed to none who had no organ failure and 26% who had transient MOF ($P < .001$). These studies suggest that there is a "window of opportunity" in the first week of hospitalization to reduce mortality if we can apply measures to suppress the development of SIRS, and thus MOF. Enteral feeding has the potential to do this by maintaining gut function and suppressing the inflammatory response. It remains to be seen whether distal feeding adds benefit by avoiding exacerbation of pancreatic inflammation and by stimulating the PYY release.

Box 1: The pros and cons of various nutritional approaches

1. The proinflammatory cytokine "storm" activates proteolysis, resulting in protein catabolism, increasing the demand for protein for tissue repair, either from body stores or the diet.
2. Starvation produces pancreatic rest and prevents further trypsinogen activation within the inflammatory mass, but deprives the intestine of luminal nutrition, thus exacerbating the mucosal damage initiated by the acute pancreatitis cytokine response. Furthermore, it results in severe negative nitrogen balance and protein deficiency due to unopposed protein catabolism, thus impairing tissue repair.
3. TPN also rests the pancreas but aggravates the intestinal injury in the same way described for starvation. It does, however, stem the loss of body protein.
4. Enteral Feeding, as currently practiced, aggravates the pancreatic injury by stimulating trypsinogen production, but counteracts the intestinal injury by providing luminal nutrition and suppressing the systemic inflammatory response while, at the same time, supporting splanchnic metabolism and recovery.

SUMMARY

Knowledge of the pathophysiologic response is crucial to understand why feeding a patient who has acute pancreatitis is so incredibly difficult. The pros and cons (Fig. 5) of the various nutritional approaches advocated, namely, fasting, TPN, and enteral feeding, are summarized in Box 1.

Strong circumstantial evidence has been presented that shows that enteral feeding has the potential to reduce the inflammatory response and the subsequent development of the complications that lead to mortality from the disease. Although the authors' center favors distal jejunal feeding, there are pros and cons to both distal jejunal and NG feeding, as summarized. As suggested in Heyland's metanalysis [79], the ultimate balance can only be determined by the conduct of a sufficiently powered multicenter clinical randomized comparative trial incorporating patients at risk of developing the complications associated with high mortality rates, and whose illness is likely to be protracted, making nutritional support essential for survival.

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GASTROENTEROLOGY CLINICS
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Necrotizing Pancreatitis

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Necrotizing pancreatitis continues to challenge clinicians, and few other medical subjects currently elicit as much debate. Parenchymal necrosis, as a complication of acute pancreatitis, occurs in 10% to 25% of patients requiring hospital admission, and continues to be associated with a mortality rate of approximately 25% [1]. Host characteristics or underlying differences in pathophysiology that lead to pancreatic necrosis remain poorly understood.

Severe pancreatitis follows a two-phase clinical course. The early first phase manifests the features of the systemic inflammatory response syndrome, and the second late phase is characterized by infectious complications. This article presents a multidisciplinary literature-based approach to the treatment of patients with necrotizing pancreatitis.

INITIAL DISEASE SEVERITY ASSESSMENT AND MANAGEMENT

The diagnosis of acute pancreatitis remains straightforward and easily confirmed, and most of these patients (approximately 80%) experience a relatively benign clinical course. The real challenge in initial management is early identification of the patient destined for systemic manifestations. The underlying cause of pancreatitis is not predictive of subsequent complications, and there is a lack of predictors of necrosis. Beginning with Ranson and Pasternack's [2] publication describing 11 objective criteria capable of predicting mortality that included five items easily measured on presentation, many authors have proposed increasingly complex risk stratification tools capable of predicting pancreatitis-related morbidity and mortality. These algorithms have not found their way into routine clinical practice, however, and most experienced clinicians continue to rely on Ranson's criteria committed to memory to guide initial clinical management.

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These key initial decision-making points include determining the level of nursing care and monitoring necessary, anticipating the required volume of resuscitative fluids, and exploring potential complications in a cost-effective manner. The authors' general practice and recommendation is to manage patients with three or more positive Ranson's criteria or an APACHE II Score greater than 7 in an ICU. Initial care of these patients is centered on adequate saline resuscitation, often guided by invasive hemodynamic monitoring and support of organ dysfunction.

MANAGEMENT OF THE PATIENT WITH SEVERE PANCREATITIS: EARLY PHASE INTERVENTIONS

Diagnosis of Pancreatic Necrosis: Role of Imaging

Pancreatic necrosis has been defined by the International Symposium on Acute Pancreatitis in 1992 as the presence of one or more diffuse or focal areas of nonviable pancreatic parenchyma. Pancreatic glandular necrosis is always associated with inflammation and often necrosis of peripancreatic fat in the mesentery and retroperitoneum (Fig. 1).

Although pancreatic necrosis may be identified at surgery or autopsy, cross-sectional imaging, especially CT, allows confident noninvasive assessment. The hallmark of pancreatic necrosis is lack of pancreatic parenchymal enhancement in a bolus contrast-enhanced CT scan. Contrast-enhanced CT is considered the reference standard for the noninvasive diagnosis of necrosis, with an accuracy of greater than 90%. Magnetic resonance imaging can assess necrosis if intravenous contrast is contraindicated [3]. CT allows assessment of the extent of glandular necrosis and the presence and extent of peripancreatic fluid collections. Multisystem impairment may be suggested by CT evidence of pulmonary edema, pleural effusions, anasarca, and diminished renal enhancement. Infected pancreatic necrosis is indicated by the presence of multiloculated gas within the gland and surrounding tissues (Fig. 2A–C). All of these CT criteria have been incorporated into various CT staging schemes, such as those presented by Balthazar and colleagues [4], and these have strong predictive value in correlating with patient morbidity and mortality. In practice, the authors may not commit the Balthazar or Ranson criteria to memory or assign a "score," but they do incorporate these objective criteria into their assessment of the patient with acute severe pancreatitis.

Although parenchymal nonenhancement accompanied by multilocular gas is essentially diagnostic of infected pancreatic necrosis, absence of gas does not exclude infection. When clinical signs and symptoms suggest pancreatic infection or necrosis, repeat CT evaluation is warranted. CT- (or ultrasound) guided fine-needle aspiration of the pancreatic bed is often required for early confirmation of infected necrosis (see Fig. 1D).

Image-guided placement of drainage catheters may help to decompress infected pancreatic fluid collections, but surgical debridement is usually required to remove the semi-solid necrotic debris (Fig. 2D, E). On occasion, the authors have used a percutaneously placed catheter as a guide to follow into the pancreatic bed when surgery is subsequently performed.

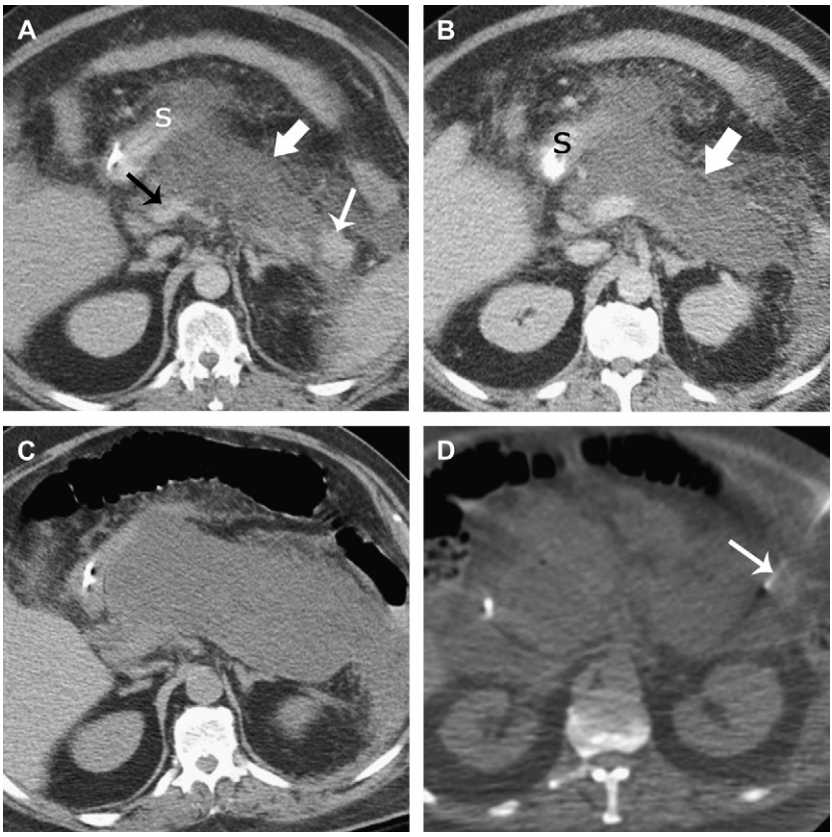
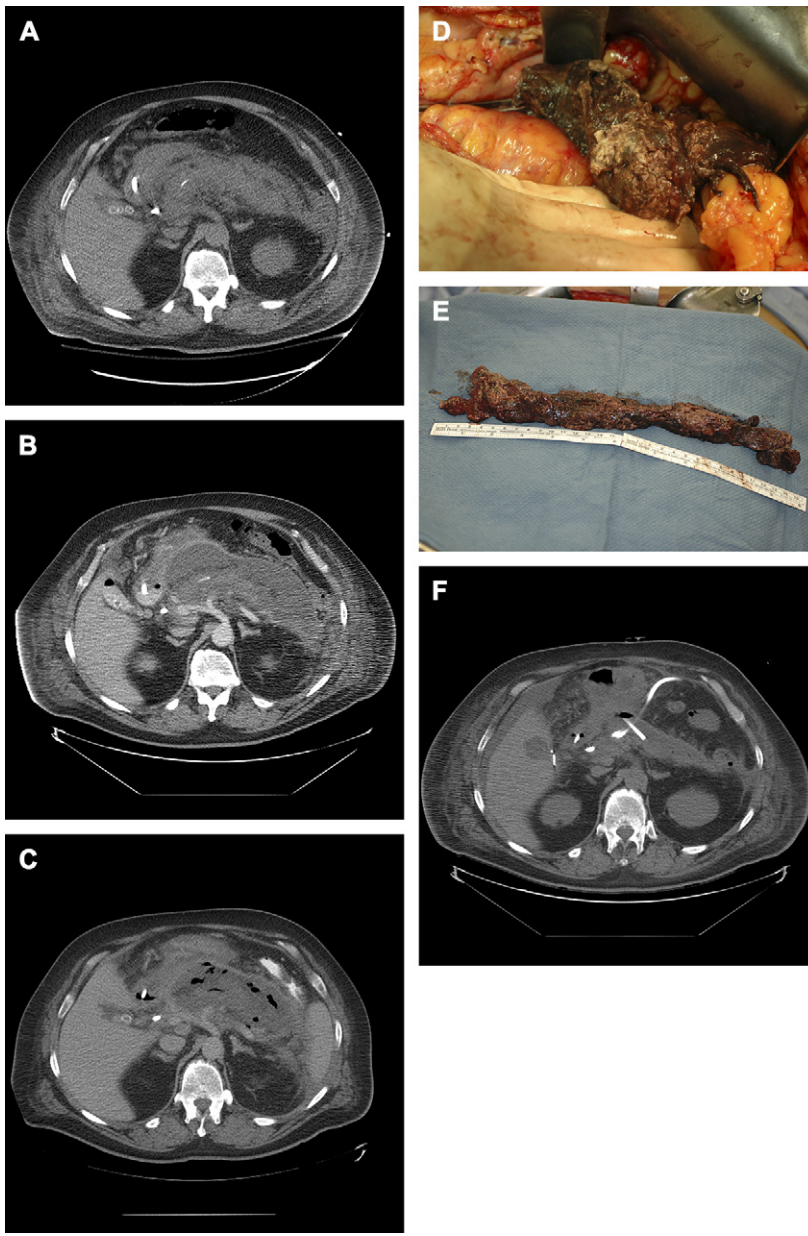


Fig. 1. A 67-year-old man with gallstone-induced pancreatitis. (*A*) Contrast-enhanced CT section on the day of admission (December 2nd) shows lack of enhancement of the pancreatic parenchyma (*thick white arrow*). A small ''island'' of normally enhancing pancreas is present in the tail segment (*thin white arrow*). Black arrow, splenic-portal confluence; S, stomach. (*B*) Repeat contrast-enhanced CT scan 7 days later (December 9th) shows extension of the inflammation and necrosis into the mesentery and retroperitoneal fat planes. The entire gland (*arrow*) is now necrotic. S, stomach. (*C*) Repeat nonenhanced CT scan 18 days after admission (December 20th) shows a more homogeneous collection of fluid and debris within the pancreatic bed. (*D*) A thin needle (*arrow*) was placed under CT guidance for aspiration of a sample of fluid from the pancreas on December 22nd. The fluid was culture-positive for bacteria.

The use of Prophylactic Antibiotics

Infection occurs in 20% to 40% of patients with necrotizing pancreatitis [5,6], and a number of small randomized prospective studies have suggested possible benefit to prophylactic antibiotic administration in patients with evidence of pancreatic necrosis. The extent of necrosis is predictive of the risk of subsequent infection (Table 1) [7]. Imipenem-cilastin was the first antibiotic agent shown to be effective in reducing infectious complications in this patient

population [8]. More recent data have shown that imipenem-cilastin is superior to perfloxacin [9], and that the alternative regimen of a fluoroquinolone combined with metronidazole often used in patients with a penicillin allergy is inadequate [6]. In the authors' institution a 2-week course of imipenem-cilastin



is recommended for patients with necrotizing pancreatitis. Recent data suggest there may be benefit to the initiation of therapy on admission, rather than after necrosis as a complication has been identified [10].

Candida infection complicates severe pancreatitis in 8% to 15% of patients [1], and concern has been raised that the use of prophylactic antibiotics predisposes patients to fungal infections, yet this fear has not been substantiated by clinical investigation [11]. As such, the coadministration of antifungal preparations is controversial.

Nutrition

Recently, there has been great clinical interest in the aggressive use of enteral nutrition delivered distal to the ligament of Treitz in patients with severe pancreatitis. This topic is addressed in detail elsewhere in this issue. Briefly, the value of enteral nutrition to gut-barrier function is well established, and most infectious complications encountered in patients with severe pancreatitis are caused by enteric organisms. It is not surprising that recent reports suggest that enteral nutrition for patients with severe pancreatitis is safe and associated with reduced rates of infectious complications [12]. Mortality rates, however, have not yet been shown to decrease [12]. Presently and in contrast to past opinion, most experts believe total parenteral nutrition should be avoided in lieu of postpyloric enteral nutrition with an elemental formula. Although additional investigation is warranted, it is also important to note that this

Fig. 2. A 62-year-old man with gallstone-induced pancreatitis. (*A*) The patient developed acute respiratory and renal insufficiency, and was maintained on enteral nutrition and intravenous imipenem and fluconazole. This CT scan performed 10 days after onset of symptoms (December 24th) and without intravenous contrast because of his renal failure shows generalized edema of the peripancreatic fat planes in a pattern essentially diagnostic of acute pancreatitis. The absence of intravenous contrast material precludes evaluation for pancreatic necrosis. The pancreas seems to be fairly homogeneous, however, and no large pancreatic or peripancreatic fluid collections or foci of extra luminal gas are identified. (*B*) On a follow-up contrast-enhanced CT obtained on January 4th after resolution of the patient's acute renal failure, minimal enhancing pancreatic parenchyma can be identified. An evolving lesser sac inflammatory process is evident. (*C*) The patient recovered from multiorgan system dysfunction and was discharged home 27 days after onset of symptoms. At home he was maintained on clear liquids supplemented by nasojejunal feedings. He returned 23 days later (50 days after onset of his symptoms) with complaints of intermittent fevers. His white blood count was normal but his CT scan shows a large collection replacing most the pancreatic body tail and head. Although not significantly changed in size or extent it now contains numerous internal gas bubbles throughout all portions, signifying infection of this area. (*D*) Exploration of the lesser sac revealed a small amount of fluid and extensive necrotic tissue. The necrotic tissue was well demarcated from surrounding viable tissues, and could be easily separated from these viable tissues using gentle blunt dissection. The necrotic tissue was delivered upward from the lesser sac, beginning with the left-sided tissues. (*E*) With gentle manipulation, the necrotic tissue could be delivered out as a single intact specimen comprising virtually the entire pancreas tissue. (*F*) A follow-up CT scan obtained 9 days after the pancreatic debridement procedure shows virtually complete removal of the necrotic tissues. Two drains can be seen lying in the lesser sac.

Table 1
Relationship of extent of necrosis to risk of infection

% Extent of Necrosis	% Sterile	% Infection	*P* Value
<30 of the pancreas	56	10	<.00001
30–50 of the pancreas	28	10	NS
>50 of the pancreas	16	80	<.00001

Adapted from Buchler MW, Gloor B, Muller CA, et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg 2000;232:623; with permission.

observation has led some to question the value of prophylactic antibiotics in patients who are successfully nourished by enteral means.

Adrenal Insufficiency and other Medical Management Considerations

A new development in the care of critically ill patients is an appreciation of the frequency with which relative adrenal insufficiency affects these patients. Muller and colleagues recently reported that in patients with severe pancreatitis, cortisol levels decrease during the development of necrosis [13,14]. This, along with observed decreases in corticosteroid-binding globulin levels, suggests that relative adrenal insufficiency is present in patients with severe pancreatitis. Given that adrenal insufficiency is known to promote acinar cell apoptosis, the authors have further hypothesized that deficient cortisol levels may contribute to the pathophysiology of pancreatic necrosis. Presently, adrenal support in patients with severe acute pancreatitis by administration of exogenous corticoids seems reasonable, but additional investigation is necessary to determine if this intervention lowers morbidity or mortality.

A number of other interventions aimed at damping the systemic inflammatory response that characterizes the early phase of severe pancreatitis or interventions aimed at inhibiting pancreatic secretion have been clinically assessed. To date, randomized placebo-controlled studies of gabexate (Xigris), aprotinin, lexipafant, and octreotide have failed to prove medical benefit [12].

Indications for Early Operative Intervention

Early endoscopic retrograde cholangiography improves outcome in the subset of patients with biliary pancreatitis and a persistently impacted common bile duct stone [15,16]. Most current guidelines recommend endoscopic sphincterotomy when biliary obstruction or cholangitis are present. In these patients, the severity of illness results not only from the systemic inflammatory response elicited by the acute pancreatitis, but also from the concomitant cholangitis.

Perhaps the most exciting advance in the care of the early phase of severe pancreatitis comes from the recent elucidation of the systemic effects of abdominal hypertension leading to an abdominal compartment syndrome ([ACS] defined by intra-abdominal pressure >25 mm Hg). ACS results in reduced venous return and diaphragmatic excursion and leads to hemodynamic compromise, acute renal failure, and increased ventilator requirements. It has been recently reported that the in-hospital mortality rate for patients with

severe pancreatitis and ACS is 50% compared with 15% in patients without ACS [17]. Although the prevalence of ACS in severe acute pancreatitis remains unknown, it has been estimated to be present in about 40% of patients and to meet criteria for surgical decompression in up to 10% [18].

ACS is treated by decompressive laparotomy and often results in a rapid, remarkable improvement in the patient's hemodynamic status and respiratory and renal functions. Given the limited nature of the procedure and the challenges and risks encountered in attempting to transfer these critically ill patients to the operating suite, the authors have often elected to perform the laparotomy in the ICU setting. They have not encountered a need for significant support from operating room–based personnel because they typically do not explore the lesser space in this situation. A number of options are subsequently available for managing the open abdomen; the authors' group favors the use of a vacuum-assisted closing dressing.

The concept of ACS contributing to the systemic effects of severe pancreatitis segues into the controversial subject of timing of operative debridement. Is the often-observed improvement in a patient's condition after early debridement actually related to decompression of an ACS? Early debridement has been practiced at a number of high-volume tertiary medical centers, but this practice is falling out of vogue as evidence mounts that delayed surgical intervention is associated with better outcomes [19,20]. The impact of early decompressive laparotomy for ACS without concurrent pancreatic debridement on the morbidity and mortality of severe acute pancreatitis has yet to be evaluated.

MANAGEMENT OF THE PATIENT WITH SEVERE PANCREATITIS: LATE-PHASE INTERVENTIONS

The late phase of severe pancreatitis is encountered approximately 3 weeks following initial presentation but in essence occurs over a broad time frame and is characterized by infectious or hemorrhagic complications. Without surgical management the mortality in the setting of infection approaches 100%, whereas with surgical management the mortality is approximately 25%. Infected pancreatic necrosis remains a clear indication for surgical intervention. Other indications include the drainage-debridement of persistent symptomatic fluid collections, and prolonged failure-to-progress with ongoing organ dysfunction in the absence of documented infection.

Intraluminal and intra-abdominal hemorrhage are rare complications of severe pancreatitis, but remain independent predictors of mortality [21]. Operative approaches to these complications can easily result in failure caused by ongoing inflammation in the retroperitoneum impacting the dissection, and by decreased integrity of tissues resulting in their failure to hold sutures. Most high-volume centers initially manage bleeding complications angiographically. Angiography is 96% sensitive in identifying the source of hemorrhage, and embolization is feasible and successfully controls hemorrhage in approximately 60% of patients [22]. Surgical exploration for management of hemorrhage is reserved for angiographic failure.

Surgical Approaches, Timing, and Complications

The standard of care for operative management is not well established, and a number of differing approaches continue to be used. Delayed intervention (2 weeks) is associated with reduced morbidity [20]. One possible reason for this observation is that the liquefaction and demarcation of necrotic tissues facilitates a single exploration, debridement, and external drainage. Occasionally, the local inflammatory process is adequately mature to allow debridement and creation of a communication to the gastrointestinal tract in a manner similar to creation of a pancreatic cystogastrostomy. This approach allows for any residual necrotic debris to drain internally once it has become liquefied and avoids the need for external drainage that may result in a persistent pancreaticocutaneous fistula. Although this technique is most often applicable in the setting of a late infection (usually >6 weeks after initial presentation), in the setting of proved infection leading to even mild sepsis surgical intervention should not be delayed to attempt this mode of treatment.

With later surgical intervention leading to better demarcation of the extent of necrosis and maturation of the local inflammatory response, serial exploratory laparotomy with open packing has been supplanted when possible by a single exploration using smaller incisions with primary closure of the abdomen. A recent CT scan can be invaluable in guiding safe dissection and localizing small loculated pockets of fluid away from the immediate peripancreatic region. All necrotic material is debrided (Fig. 2D). Drains are left in the pancreatic bed to manage leakage of pancreatic juice, and many advocate continuous irrigation of these drains to reduce the risk of clogging and to facilitate removal of residual debris. The authors' group is divided on the use of combination sump drains. These large drains clearly are more effective in the drainage of viscous particulate effluent, but may increase the risk of erosion into surrounding structures leading to fistula formation or hemorrhage. They routinely place a combination decompressive gastrostomy–feeding jejunostomy Silastic catheter.

Early and late morbidity (Table 2) caused by wound complications and enteric fistula from exposed loops of bowel have plagued pancreatic surgeons [21,22], and fostered enthusiasm for minimally invasive approaches to infected necrotizing pancreatitis. Reported series of laparoscopic-assisted necrosectomy have shown the technique to be feasible in most patients, and associated with low morbidity and mortality [23]. Comparison with more traditional open procedures, however, has not been made.

Finally, Papachristou and colleagues have recently reported their series of patients with walled-off pancreatic necrosis treated by per oral endoscopic drainage-debridement [24]. They have reported successful treatment with this natural-orifice technique in 43 of 53 patients attempted. Adjuvant percutaneous drainage was required in 40% of the patients, and operative intervention was necessary in 20% of the patients. Morbidity was otherwise acceptable. The surgical management of infected pancreatic necrosis is currently in evolution. Active investigation should be able to determine the impact of these minimally invasive approaches on mortality, morbidity, ICU and hospital stay, and costs related to pancreatic necrosis.

Table 2
Early and late complications of surgical management of pancreatic necrosis

	Number (%)	Mortality (N)	Univariate significance (*P* Value)
Early complications			
One or more complication	82 (92)	25 (28)	NA
Organ failure	44 (50)	19	.004
Vein thrombosis	11 (13)	0	NA
Cardiovascular	14 (16)	5	NS
Pneumonia	4 (5)	2	NS
Colonic necrosis	2 (2)	2	.08
Fistulae	4 (5)	1	NS
Hemorrhage	10 (11)	7	<.01
Fungal infection	28 (32)	13	<.01
Late complications			
One or more complication	39 (62)	—	
Biliary stricture	4 (6)	—	
Pseudocyst	5 (8)	—	
Pancreatic fistula	8 (13)	—	
Gastrointestinal fistula	1 (2)	—	
Delayed fluid collection	3 (5)	—	
Incisional hernia	1 (2)	—	
Exocrine insufficiency	16 (25)	—	
Diabetes mellitus	19 (33)	—	

Adapted from Connor S, Alexakis N, Raraty MG, et al. Early and late complications after pancreatic necrosectomy. Surgery 2005;137:502, 503.

SUMMARY

Severe acute pancreatitis is a diverse disease process, and there is a relative lack of prospective randomized data to guide management. The clinical course of these patients can be demarcated into two phases: an early, aseptic inflammatory phase characterized by capillary leak and organ dysfunction, and a late phase where local or disseminated infectious complications ensue. Current best practice suggests that the early phase be managed nonoperatively, with the exception of surgical release of ACS; early necrosectomy in the absence of infection is not warranted. The use of prophylactic antibiotics is supported by current data, and this clinical practice has not been proved to result in an increased prevalence of fungal infections. The use of enteral rather than parenteral nutrition may reduce the risk of developing infected pancreatic necrosis and thereby render obsolete the current practice of administering prophylactic antibiotics. CT and fine-needle aspiration are sensitive methods to identify infection as a complication of necrosis, and this remains a definitive indication for necrosectomy. Comparisons of open repeated debridement and packing with minimally invasive or single surgical procedures with lavage favor the latter. Late complications of surgical intervention are common, however, and despite this management strategy, the mortality associated with severe acute pancreatitis remains approximately 25%.

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Genetic Counseling for Nonsyndromic Pancreatitis

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It has been 10 years since hereditary pancreatitis (HP) was linked to the long arm of chromosome 7 (7q35) [1–3] and mutations in the cationic trypsinogen gene [4–7]. Since that initial finding, genetic causes of nonsyndromic pancreatitis have transitioned from being thought of as a mendelian single-gene disorder to a complex genetic disorder with a mendelian subset. This has profound implications for genetic counseling. Appropriate pretest and posttest counseling is essential to help individuals and families appreciate this complexity, decide whether to pursue genetic testing for pancreatitis, and understand what their personal results mean. Without proper counseling, it is easy for individuals to draw incorrect conclusions regarding test results and the associated implications (authors'quo; personal observations). This article focuses on the approach to genetic counseling for pancreatitis and implications of recent advances.

Genetic testing differs from other types of laboratory testing in several ways. Genetic test results have implications not only for the individual tested, but also other family members. Genetic test results may have a powerful impact on an individual's life and reproductive choices. Genetic test results do not change, nor does their relevance fade with time. The differences between genetic and other types of laboratory tests require a different approach for genetic testing to ensure an informed decision that respects patient autonomy.

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Differing constraints affect how counseling sessions for pancreatitis are conducted, but each session should include the features discussed next. At the beginning of a session, the knowledge base and goals of the patient and family should be ascertained. It is important to then discuss how their goals will be addressed and met during the session. If this is not clearly explained at the beginning of a session, patients may not pay attention to other important information being covered because they are wondering if their questions will be answered. A detailed discussion of the benefits, risks, and limitations of genetic testing should follow so individuals can make an informed decision whether to have testing performed. Any concerns about risks or benefits should be acknowledged and addressed. It is important that individuals consider with whom they will share test results and what reactions they might anticipate from family members, because one individual's test results may significantly impact their relatives.

During a genetic counseling session for pancreatitis, a detailed three- to four-generation family history should be obtained. This information can narrow the genes to be tested, provide opportunities to learn about the communication patterns and dynamics of family relationships, and prove useful later on when discussing ways of coping and how to inform relatives about their risk.

It is particularly important to obtain information on relatives diagnosed with pancreatitis (acute or chronic if known), who have experienced unexplained abdominal pain, or been diagnosed with diabetes, pancreatic cancer, or adenocarcinoma of unknown primary. Relevant information includes age of onset, age at diagnosis, current age or age at death, and any known triggers. Causes of death for deceased relatives should be noted. Inquiry should also cover symptoms of pancreatic insufficiency (eg, diabetes and diarrhea-steatorrhea). It is helpful to ask whether anyone in the family takes pancreatic enzymes, because they may mask exocrine failure. Other pertinent questions include whether relatives have had cystic fibrosis (CF), cystic fibrosis transmembrane conductance regulator (*CFTR*) screening or testing, chronic sinusitis, a chronic cough, or male infertility. Positive responses to these questions suggest a greater likelihood of finding *CFTR* gene mutations. Because hyperlipidemia places a person at risk of developing pancreatitis, any history of high levels of triglycerides in patients or relatives should be queried. Relatives dying of early onset heart disease can be a strong indicator of inherited hyperlipidemia. Noting which relatives smoke or drink alcohol is useful and can add weight to a relative's affected or unaffected status. It is also important to inquire whether individuals in the family have been diagnosed with other cancers and whether the patient or others have had any genetic testing. This is the only time that most individuals give such a detailed family history, presenting an opportunity to identify families with strong histories of cancer for referral to a genetic counselor specializing in cancer genetics. Moreover, predisposition for pancreatic cancer is weighted differently in a family already known to have a cancer predisposition.

After taking a detailed family history, a discussion of the testing options is appropriate. The discussion should include why mutations in certain genes

are likely or unlikely given family history. The testing strategy to be pursued should be explained, including whether a stepwise approach or pancreatitis panel will be used. This decision may vary given constraints specific to an individual clinic.

Before ending the appointment, future steps should be discussed, including how long it takes to receive test results, how those results will be communicated to the patient, and which clinicians (if any) will also receive results. The availability of posttest counseling to address the implications of the test results should also be mentioned. The counselor provides the patient and other family members with his or her contact information should there be questions that arise in the interim.

GENES ASSOCIATED WITH AN INCREASED RISK OF PANCREATITIS

Three genes are believed to play a substantial role in the development of pancreatitis. The cationic trypsinogen gene (*PRSS1*; 7q35) was the first gene found to be associated with mendelian inheritance of an increased risk of developing pancreatitis [3]. Within 4 years of the identification of *PRSS1*, variant in the *CFTR* and *SPINK1* genes were recognized as complex risk factors associated with the occurrence of pancreatitis. Additional genes that may contribute to the development of pancreatitis are currently under investigation.

Cationic Trypsinogen

Cationic trypsinogen is an enzyme that activates other digestive enzymes. Mutations in the cationic trypsinogen gene are associated with HP, a rare disorder characterized by recurrent attacks of pancreatitis. HP is inherited in an autosomal-dominant manner with approximately 80% penetrance by age 20 years [8]. HP accounts for approximately 1% of pancreatitis cases [9]. The clinical course is exceedingly variable, with some individuals experiencing acute attacks beginning in early childhood, whereas others suffer late-onset acute attacks. Disease severity differs greatly; some individuals rapidly progress to chronic pancreatitis with endocrine and exocrine failure, whereas others never develop chronic pancreatitis. A wide range of clinical variation can be seen in the same family. About 20% of individuals who carry a mutation in the *PRSS1* gene never experience symptoms of pancreatitis [10]. Currently, at least 19 variants (17 amino acid changes) in *PRSS1* have been described [9]. The most common mutations (R122H, N29I, and A16V) account for 60% to 75% of families with HP [11]. Targeted mutation analysis for these variants is available on a clinical basis. In addition, complete sequencing of the *PRSS1* coding regions is available (Ambry Genetics, Aliso Viego, California). Mutations located at codons other than 29 or 122 do not seem to cause high-penetrance autosomal-dominant patterns of pancreatitis [12]. Despite detailed testing, 20% of families with HP do not have an identifiable *PRSS1* mutation, suggesting that one or more additional genes associated with HP remain to be identified [11,13]. A study of concordant and discordant monozygotic twin pairs with mutations in *PRSS1* suggested that

modifier genes and shared environmental factors are not the only factors explaining reduced penetrance of HP. Random events, such as epigenetic changes or mitochondrial DNA changes, may play a role [14].

Individuals with HP have a greatly increased risk (53 times the general population) of developing pancreatic cancer [15,16]. Age- and sex-matched individuals with HP, who have not developed pancreatic cancer, have fewer cases of diabetes and pancreatic calcification than individuals with HP who develop pancreatic cancer, implying the risk of cancer is related to the severity and duration of pancreatitis [15]. This hypothesis is supported by a study that looked at pancreatic cancer risk in HP as a function of years from symptom onset. Cumulative risk of pancreatic cancer was 8.5% at 40 years after symptom onset, 25.3% at 60 years, and 44% at 70 years [13].

Cystic Fibrosis Transmembrane Conductance Regulator

CFTR encodes an anion channel protein, which also regulates other transporters, including those associated with chloride-coupled bicarbonate transport [17]. Mutations in *CFTR* known to cause classic CF were first associated with idiopathic chronic pancreatitis (ICP) in 1998 [18,19]. Over 1500 described mutations throughout the 27 exon CFTR gene [20] can be divided into "severe mutations" (CF^{sev}) and "mild-variable" ($CF^{m\text{-}v}$). CF^{sev} mutations eliminates almost all (>95%) CFTR-mediated anion conductance, whereas $CF^{m\text{-}v}$ mutations retain higher levels (approximately 10%–30%) of channel function. Individuals with two severe mutations reliably develop severe lung disease associated with classic CF, whereas individuals with at least one mild-variable mutation typically develop atypical CF [21,22]. Recently, combined data from two studies estimated the relative risk of developing ICP in *CFTR* compound heterozygotes (regardless of mutation severity) is increased approximately 40-fold (95% confidence interval [CI], 22–63), whereas the risk of ICP in a compound heterozygote with one CF^{sev} mutation is increased approximately 80-fold (95% CI, 45–152) [21]. Until recently, there has been ongoing debate regarding whether increased risk of pancreatitis is conferred by one *CFTR* mutation or whether two *CFTR* mutations are required. Much of this debate can be attributed to differing mutation detection rates among *CFTR* testing methods used in studies. Recent data from two separate studies demonstrate that CF carriers, regardless of mutation class, have a threefold to fourfold increased risk of developing chronic pancreatitis versus the general population [22,23]. In one study where *SPINK1* sequencing was performed, the risk of ICP in CFTR carriers was not dependent on having a mutation in S*PINK1* [22].

It is important that clinicians remember that commercially available targeted mutation analysis panels for *CFTR* screening were designed to detect mutations generally associated with classic CF with lung disease. Recent studies have shown that only a limited percentage of CFTR mutations found in participants with ICP would have been detected using these panels since the mutation panels were not designed to detect less severe or less communications [22,24]. This has important implications for clinical genetic

testing in pancreatitis because negative *CFTR* mutation panel results could be falsely reassuring to the physician and patient. Due to the lower detection rates using targeted mutation panels, *CFTR* gene sequencing should be used when testing individuals with pancreatitis for *CFTR* mutations.

Serine Protease Inhibitor of the Kazal Type

The *SPINK1* gene (5q32) encodes a pancreatic secretory trypsin inhibitor (PSTI) called *s*erine *p*rotease *in*hibitor of the *K*azal type (SPINK). The human form of the protein is usually designated PSTI and the gene *SPINK1*, although SPINK1 is also used for the protein product. SPINK1-PSTI is an acute-phase protein that is markedly up-regulated in acute inflammation. SPINK1-PSTI is capable of inhibiting trypsin activity by binding to active trypsin with a one-to-one ratio. Mutation in the *SPINK1* gene have been associated with chronic pancreatitis, but not acute pancreatitis [25,26]. Approximately 2% of individuals in the general population exhibit high-risk nucleotide variants in the *SPINK1* gene; however, in the absence of other factors less than 1% of those individuals with mutations develop chronic pancreatitis [26,27]. This observation, along with the fact that the clinical severity of pancreatitis seems unaffected by whether an individual is heterozygous, homozygous, or compound heterozygous for variants in *SPINK1*, suggests that *SPINK1* variants alone are not sufficient to cause pancreatitis and instead act as a risk modifier in recurrent acute pancreatitis, facilitating the development of chronic pancreatitis [27]. In general, individuals who carry one *SPINK1* mutation (N34S or -2C > A) have an approximately 12-fold (95% CI, 5.1–29.3) increased risk of developing ICP over the general population. Individuals who are compound *CFTR* heterozygotes and also carry a *SPINK1* variant have approximately 500 times (95% CI, 163–1545) the general population risk of developing ICP [21]. Genetic testing for *SPINK1* variants does not provide a large amount of useful information at this time, unless other mutations or variants (in other genes or *SPINK1* itself) are also present.

OTHER MODIFIER GENES

At this point in time, other genes are under investigation to determine their role in the development of pancreatitis. The North American Pancreatitis Study 2 is a national multicenter study focused on the impact of genetic contributions to the development of pancreatitis through the enrollment of 1000 consecutive patients affected with either recurrent acute pancreatitis or chronic pancreatitis. Findings from this large study are expected to contribute significantly to the understanding of genetic susceptibility to pancreatitis.

One gene of interest is cathepsin B (*CTSB*), a lysosomal cysteine proteinase, which activates trypsinogen in vitro and has been hypothesized to play a role in the development of pancreatitis. Investigation into the role of cathepsin B in human pancreatic disease, however, has just begun. Mahurkar and colleagues [28] found a significant association between *CTSB* and tropical calcific

pancreatitis. The effect of various polymorphisms in this gene seems to be markedly different from one another, and these results have not yet been confirmed. Whether *CTSB* truly plays a role in the development pancreatitis requires further investigation.

INDICATIONS FOR GENETIC TESTING FOR PANCREATITIS SUSCEPTIBILITY

Genetic testing for pancreatitis should be considered when a patient affected with pancreatitis fulfils one or more of the following criteria [29]:

- A family history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis without a known cause
- Relatives known to carry mutations associated with pancreatitis
- A series of recurrent acute attacks of pancreatitis for which there is no other explanation
- An unexplained documented episode of pancreatitis as a child
- Idiopathic chronic pancreatitis (especially when onset of pancreatitis precedes age 25)
- Patients eligible for approved research protocols

Moreover, asymptomatic family members at risk of inheriting a *PRSS1* mutation may wish to be tested after a mutation has been identified in the family. Individuals considering presymptomatic testing of *PRSS1* need fully to understand implications of testing including what information can and cannot be gained (eg, whether symptoms will ever develop). Testing asymptomatic individuals for *CFTR* or *SPINK1* mutations is not recommended because a large fraction of those who carry mutations in these genes never develop pancreatitis. *CFTR* carrier testing should be offered to unaffected relatives if a *CFTR* mutation that is capable of causing classic CF has been found in a family. It cannot be overemphasized that the implications of making a diagnosis of CF should never be made on genetic testing alone; it also requires functional testing at an approved center because of the devastating implications of short life expectancy and tremendous cost to the patient and family.

Genetic testing of children who present with symptoms of pancreatitis is not uncommon. Testing asymptomatic children for genes associated with pancreatitis is generally not recommended because there is no apparent medical benefit in identifying carriers at a young age [30] and benefits of testing rarely outweigh risks [31]. Testing asymptomatic children removes their right to make an autonomous decision to have testing or not when they are adults. Genetic testing may also cause harm through altered self-image, distorted parental views, increased anxiety or guilt, altered expectations, or disclosure of nonpaternity or adoption. Genetic discrimination in insurance coverage and employment opportunities must also be considered. If, after thorough pretest counseling, a child's parents determine the benefits of testing outweigh risks, those wishes should be taken into account because parents are in the best position to judge the interests of their child and in most cases act in those interests [29].

MANAGEMENT ISSUES

The management of patients with a genetic susceptibility to pancreatitis is different from other individuals with pancreatitis in a few key ways. Currently, different ways of treating pancreatitis and attempting to prevent recurrent attacks may differ based on the etiology of the pancreatitis. Patients who are CFTR compound heterozygotes may benefit from promoting bicarbonate secretion and reducing intra-acinar trypsinogen activation [21], although these approaches must be further tested and standardized. Recently, a phase I trial looking at the use of a calcium channel blocker in patients with HP was performed [32]. If calcium channel blockers are able to ameliorate the symptoms of HP, genetic testing for HP will have important medical implications.

Genetic information related to susceptibility for pancreatitis may also prompt a search for other diagnoses and symptoms. The discovery that an individual with pancreatitis is a *CFTR* compound heterozygote should induce a thorough search for other CFTR-related manifestations, such as congenital bilateral absence of the vas deferens. Counseling regarding reproductive options and risks may be appropriate to offer.

Screening for pancreatic cancer should be offered to individuals with HP who are 40 years old or older, ideally as part of a multicenter protocol assessing the efficacy of screening protocols [33]. Silent carriers of *PRSS1* mutations do not have an increased risk of developing pancreatic cancer as long as they are truly unaffected. Care should be taken to ensure that subclinical attacks of pancreatitis have not occurred and been attributed to other causes of abdominal pain. Indeed, some individuals who have been diagnosed with chronic pancreatitis were never diagnosed with acute pancreatitis, demonstrating that the absence of acute attacks of pancreatitis should not be the sole method used to determine whether an asymptomatic *PRSS1* carrier has an increased risk of developing pancreatic cancer.

SUMMARY

Genetic testing for nonsyndromic pancreatitis may significantly alter an individual's choices and the medical management of their disease. Pretest and posttest counseling are essential for patients and families fully to benefit from genetic testing for a susceptibility to develop pancreatitis. Indeed, subtle or overt harm can result when genetic testing occurs in the absence of the informed consent process. The clinician, often working directly with a qualified counselor, must ensure that patients and families appreciate the benefits and limitations of genetic tests, that results are interpreted accurately, and that patients understand the implications of genetic information for both their medical care and personal decisions.

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Pain in Chronic Pancreatitis and Pancreatic Cancer

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Chronic pancreatitis (CP) is defined as a continuous inflammatory disease of the pancreas characterized by irreversible morphologic changes that typically cause pain and/or permanent loss of function [1]. Histologic changes from the normal pancreatic architecture include irregular fibrosis, acinar cell loss, islet cell loss, and inflammatory cell infiltrates [2–4]. Functional changes in CP include loss of exocrine function, leading to maldigestion, diarrhea, and weight loss, often followed by eventual islet-cell dysfunction, leading to diabetes mellitus [1,4,5]. Although the lost function can be replaced with pancreatic enzyme supplements and management of diabetes mellitus, the most challenging and debilitating symptom associated with CP is pain.

CP is a complex process that begins with episodes of acute pancreatitis (ie, the Sentinel Acute Pancreatitis Event, or SAPE hypothesis), and progresses to end-stage fibrosis at different rates in different people, likely due to different mechanisms [6]. Pain is a symptom of stress or injury, and the various factors that contribute to CP likely cause different pain types and patterns that may

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overlap. However, abdominal pain, involving the upper abdomen and epigastric area, is usually described. In many patients, pain is characterized as deep, penetrating, radiating to the back, and is often worse after meals [7]. Prevalence of pain in this condition does seem to vary with etiology, although this point, too, is debated. In alcohol-induced CP, painless courses are a rarity, with pain being the predominant feature in approximately 90% of patients in the often-quoted Zurich series [7–9]. However, in "senile" or delayed-onset idiopathic CP, the percentage of patients who do not have painful course was much higher, approaching 50% [10]. These findings were not seen in another cohort [11]. In the series followed by Amman and colleagues [12], two different pain patterns were noted in long-term follow-up. The first, termed *type A*, was characterized by recurrent bouts of short-term, relapsing pain episodes. *Type B* pain is characterized as prolonged and persistent. It is thought to be associated with large-duct CP, presumably associated with increased intraductal pressure, or secondary complications of CP (eg, pseudocysts or biliary obstruction). Pain was noted to decrease over time, with spontaneous relief occurring after an average of 5.5 years, and over 80% experiencing pain relief within 10 years from symptom onset in conservatively treated patients. There was no significant difference in duration of pain between surgically and nonsurgically-treated groups. Pain relief corresponded to the occurrence of exocrine dysfunction and led to the "burn-out" hypothesis of pain in CP [9,12]. Arguments against this theory cite potential for selection bias in this cohort, because none of the patients in the nonsurgical group were admitted to the hospital with type B pain, and patients in the surgical group had twice as many hospitalizations for pain on average. Further evidence against spontaneous pain relief being the rule in CP was provided by Lankisch and colleagues [13], who followed 335 patients who had painful CP for over 10 years. In his series, most never experienced pain relief, whether treated surgically or conservatively. Regardless of either result, pain associated with CP is a debilitating condition that can last many years. Although spontaneous relief occurs, the duration of symptoms is unpredictable, and the effects of chronic pain can have lasting repercussions, including depression, opiate addiction, unemployment, and social alienation. This may be exacerbated by the stigma of alcoholism associated with the disease, which is often not the underlying etiology.

Despite the advances being made in our understanding of the pathophysiology underlying CP, such as genetic predisposition and neurologic alterations, there is still no therapy directed toward the inflammatory process that leads to progression of this disease. As such, symptom control is the primary directive of treatment, with pain being the dominant symptom. This review focuses on pain in this setting. Since this topic was last reviewed in 1998 in the American Gastroenterological Association Technical Review [14], and again in 2002 [7], some significant advances have been published regarding etiology and treatment of pain in patients with CP. These include new insights in alterations of pancreatic innervation, genetic factors associated with pain, and new treatments. In addition, outcome assessment has traditionally been extremely

variable in therapeutic trials for pain in CP, leading to much controversy in interventional efficacy. These concepts are discussed as well as some new insights into etiology and treatment of pain in the setting of pancreatic cancer. Rather than provide a comprehensive review of these topics, the authors focus on updates in the literature since prior reviews. Controversies regarding the diagnosis, classification, and etiologies of CP, as well as therapy for diabetes, steatorrhea, and extrapancreatic complications such as pseudocysts, duodenal stenosis, and gastric varices lie outside of the scope of this review.

PAIN MECHANISMS IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

So what is the cause of pain in CP? Many theories have been proposed over the years, but in all likelihood, the correct answer is that it is multifactorial and variable between patients. The earliest ideas centered on inflammation and morphologic factors. These theories suggest the earliest changes occur in the pancreatic ductal system, starting with the intercalated and canalicular ductules. Ductular calcification occurs due to precipitates of lactoferrin, which form glycoprotein plugs and subsequently complex with calcium carbonate [15,16]. This is thought to lead to gradual involvement of the main duct, with postinflammatory stricture and stone formation leading to duct dilatation [16,17].

PANCREATIC DUCT HYPERTENSION

The formation of duct dilatation and hypertension due to downstream obstruction of the pancreatic duct is one of the most widely accepted theories for the cause of pain in CP and the primary reasoning behind surgical and endoscopic drainage procedures [16]. However, this theory has been challenged by multiple series of patients. Some show similar incidence of ductal dilatation with and without pain, and others experience severe pain with both presence and absence of stricture and dilatation [11,16,18–20].

Although presence of duct obstruction may be an important contributing factor to pain, as evidenced by high rates of short-term pain relief after endoscopic and surgical drainage procedures, failures suggest that it is not the only etiology. Pancreatic duct pressure measurements have been performed intraoperatively since the 1950s, using direct needle puncture of the pancreatic duct [21]. Since the 1970s, endoscopic retrograde cholangiopancreatography (ERCP) has been used to determine normal pancreatic ductal pressures, which lie between 8 and 20.4 mmHg (translating to 10.8–27.2 cm water) [22–25]. Proof of the ductal hypertension theory initially rested upon a case report of a man who had a drainage catheter in a fistula tract who reproducibly developed pain when saline infusion led to ductal pressures greater than 25 cm H_2O [26]. A series of 19 patients who underwent decompressive surgical procedures found the pancreatic ductal pressure averaged 33 cm H_2O, but had no controls [27]. Subsequent experiments attempted to correlate ductal pressure measurements with pain in patients who have CP. However, they have been marred by inappropriate comparison of intraoperative measurements in CP patients to endoscopic

manometry in controls. Only one report, by Sato and colleagues [28], compared intraoperative measurements in patients undergoing surgical drainage procedures to patients undergoing surgery for gastric cancer, and found significantly increased pressures in the patients who had CP. In trials comparing endoscopic manometry of the pancreatic duct between patients who have CP and those who do not [24,29–32], only one, by Okazaki and colleagues [33], has shown a significant difference in pressure. Of these, the only trial to separate patients who had CP by the presence or absence of pain demonstrated no difference in pressure levels [29].

PANCREATIC TISSUE PRESSURE

More recently, a technique pioneered by Ebbohøj and colleagues [34], using a needle probe directly inserted into the pancreatic parenchyma, was used to measure pancreatic tissue pressure intraoperatively in patients who underwent surgical drainage procedures. They found significantly higher pressures in patients who had painful CP compared with pain-free controls, and were able to correlate postoperative improvement with more than 10 mmHg drop in pancreatic tissue pressure during the operation. During follow-up, pancreatic tissue pressure was reassessed using a percutaneous technique, which was subsequently developed. Recurrence of pain at 1 year was associated with a significant increase in pressure compared with postoperative levels [35]. These findings are interesting, but were not reproduced by another investigator [36].

Elevated pancreatic tissue pressure may be associated not only with hypertension in the main pancreatic duct, but also side branches, reflecting what has been described as a compartment syndrome induced by fibrosis of the peripancreatic capsule as well as the perilobular parenchyma. This theory is supported by feline models of CP, which found basal interstitial pressures were higher, and blood flow was lower than controls. Furthermore, under secretin stimulation, interstitial pressures increased and blood flow further diminished, as opposed to controls, in which pressures were unchanged and blood flow increased with secretory stimulation [37]. In a similar experimental model, Patel and colleagues [38] evaluated interstitial blood flow and pH under basal and stimulated conditions, and followed the changes over a 6-week period. They found a similar decrease in pancreatic blood flow associated with tissue acidosis after stimulation with cholecystokinin and secretin. A corollary human experiment was reported in the same article, in which interstitial pancreatic pH was measured in patients who had CP undergoing surgical treatment. Comparison to pH in surgical controls demonstrated significantly more acidotic tissue in those who had CP (7.25 versus 7.02, $P < .05$). The tissue acidosis was thought to be secondary to ischemia, correlating to the aforementioned compartment-like syndrome. Although no pain data were collected in this experiment, it was speculated that the acidosis may stimulate pancreatic nociceptors, resulting in pain. Indeed, transient receptor potential vanilloid-1, also known as the capsaicin receptor, is activated by H^+ ions and has been shown to be responsible for pain and neurogenic inflammation in a rat model of acute pancreatitis [39–41]. Based upon these findings,

one might speculate that decreased stimulation of the pancreas would decrease the secretagogue-induced tissue ischemia and lead to improvement in pain. Indeed, this was the theory behind using pancreatic enzyme supplementation, octreotide, and proton-pump inhibitors to reduce stimulation of exocrine function by various mechanisms. In addition, it would make sense that surgical drainage procedures may decrease the elevated tissue pressure that would lead to a compartment-like syndrome, similar to a fasciotomy.

NEURAL ALTERATIONS

In the mid 1980s, the first of several articles, which are summarized in Table 1, was published demonstrating interesting alterations of the neuroanatomy of the pancreas in the setting of CP. Keith and colleagues [42] reported pathologic tissue findings of 50 patients who had CP in whom clinical data were collected on pain severity. They found perineural inflammatory infiltrates with a disproportionate percentage of eosinophils, which correlated with pain severity. In the first controlled experiment of this type, in which tissue resected from patients who had CP was compared with organ donor tissue, similar perineural inflammatory infiltrates were found with increased neural diameter (eg, Fig. 1).

Table 1
Neural factors associated with chronic pancreatitis

Changes compared with controls	Increased pain intensity	Increased pain frequency
Increased perineural infiltrate with eosinophilia [42]	Y	—
Increased diameter, compromised neural sheath [43]	—	—
Interleukin 8 [44]	—	—
Calcitonin gene–related peptide [45]	—	—
Substance P [45]	—	—
Neurokinin-1 receptor [47]	Y	Y
Growth-associated protein-43 [48]	Y	N
Nerve growth factor [49]	N	N
Tyrosine receptor kinase A [49]	Y	N
Brain-derived neurotrophic factor [50]	Y	Y
Artemin [53]	Y	Y
GDNF family receptor alpha 3 [53]	N	N

Summary of factors that have been studied and found to be present or have increased expression in tissue samples of patients who have chronic pancreatitis. In studies that evaluated clinical parameters, such as pain intensity and frequency, any association that was found is recorded as Y (yes) or N (no).

Abbreviation: GDNF, glial cell-line derived neurotrophic factor.

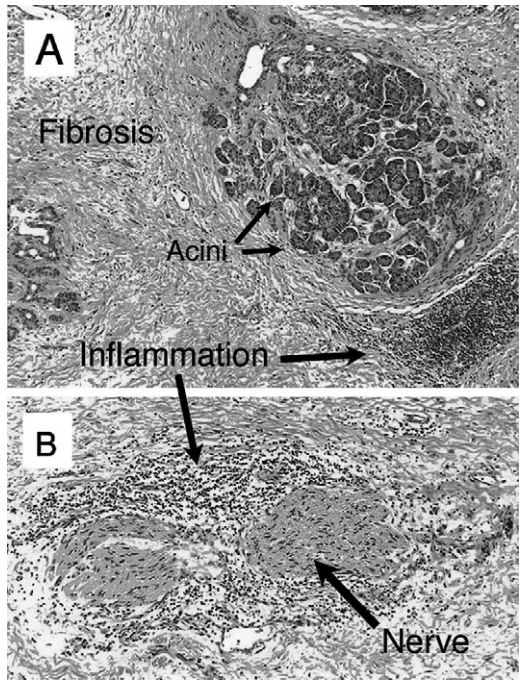

Fig. 1. Histologic appearance of chronic pancreatitis. (*A*) The acini have been largely replaced by inflammation and fibrosis. (*B*) Large nerve trunks are seen in chronic pancreatitis, but not in normal pancreatic tissue. Note the close association between chronic inflammation and the perineurium.

Alteration in the perineural sheath was also observed, indicating damaged barrier function and increased susceptibility to proinflammatory cytokines and growth factors [43]. Experiments to detect cellular expression of various chemokines in pancreata of patients who had CP found significantly increased expression of several compared to controls. These include IL-8, a chemotactic factor for neutrophils whose release is mediated by substance P (SP) [44]. Immunohistochemical staining of pancreatic nerves found significantly increased staining for calcitonin gene-related peptide (CGRP) and SP, two widely recognized mediators of nociception, in the setting of CP [45]. Following that, pancreatic tissue was tested for preprotachykinin A, the gene that encodes substance P. Northern blot analysis demonstrated no difference in preprotachykinin A expression, but markedly increased expression of IL-8. Expanding from the previous study, these findings suggest the increased SP found in the pancreatic tissue of patients who have CP is not encoded by neurons whose cell bodies lie within the pancreas. Rather, they likely lie within the dorsal root ganglia and send SP to the pancreas by way of axonal projections [46]. Along the same line, mRNA expression of neurokinin-1 receptor, the receptor for substance P, was significantly increased in CP, localized to the pancreatic

nerves and perineural inflammatory cells, and correlated with intensity and frequency of pain [47]. Growth-associated protein 43, a protein associated with neuronal plasticity and axonal branching, was increased in pancreatic neurons of CP samples and significantly correlated with pain scores [48]. The overexpression of CGRP and SP in CP samples led to investigation of nerve growth factor (NGF), the trophic factor for peptidergic neurons (ie, those that express CGRP and SP), and its high-affinity receptor, tyrosine receptor kinase A. Samples of pancreatic tissue in CP demonstrated increased mRNA expression for NGF in metaplastic ductal cells and degenerating acinar cells. Evaluation of enlarged nerves within the tissue demonstrated NGF within the nerves and tyrosine receptor kinase A limited to the perineurium. Clinical correlates demonstrated no relationship between NGF and pain, but significant correlation between tyrosine receptor kinase A and pain intensity [49]. Lastly, brain-derived neurotrophic factor, thought to be a peripheral and central modulator of inflammatory pain, was evaluated. Increased expression was noted and limited to perineurium. Brain-derived neurotrophic factor expression also significantly correlated with pain scores [50]. One may argue that most of the patients in the aforementioned experiments were patients from Northern Europe who had alcohol-induced CP , and thus may be too homogeneous to apply to a broader patient population. However, Friess and colleagues [51] collaborated with investigators in India, who supplied tissue of patients who had tropical pancreatitis. Comparison of pancreatic tissue samples from patients who had alcohol-induced, tropical, and idiopathic CP with organ-donor controls found similar nerve changes regardless of etiology.

Most recently, the same group investigated artemin, a member of the glial cell-line derived neurotrophic factor family, which includes glial cell-line derived neurotrophic factor, neurturin, artemin, and persephin. All of these ligands bind two receptors, one common (tyrosine kinase RET) and one specific. For artemin, the specific receptor is called GFRα3 (glial cell-line derived neurotrophic factor family receptor alpha 3) [52]. Utilizing similar techniques to the aforementioned studies, Ceyhan and colleagues [53] found increased levels of artemin and GFRα3 in CP tissue of various etiologies. Moreover, novel artemin immunoreactivity was observed in intrapancreatic nerves, as well as Schwann cells and intrapancreatic ganglia (artemin is normally expressed only in smooth muscle cells of arteries). Similar but less impressive changes were noted for GFRα3, which is expressed in autonomic and sensory nerve fibers that innervate the pancreas. Artemin mRNA expression positively correlated with histologic neuropathic changes, as well as parenchymal fibrosis and pain scores.

In their discussion of these results, Ceyhan and colleagues [53] proposed that the increased expression of artemin and GFRα3 were part of a failed compensatory mechanism mounted by the pancreas to block the development of visceral hypersensitivity. This proposal was based on the report by Gardell and colleagues [54], which suggested that artemin has neuroprotective effects, at least in one model of neuropathic pain in rats. In these studies, neuropathic pain produced by spinal nerve ligation was reversed following peripheral

injections of artemin. However, similar studies in another laboratory found artemin had no effect on neuropathic pain [55]. In addition, two recent publications from the authors' center implicate artemin as an effector of inflammatory hyperalgesia [56,57]. In the first study, genetically altered mice that overexpress artemin in skin exhibited increased behavioral sensitivity to noxious heat and cold stimuli. Intracellular recordings from cutaneous sensory neurons found increased firing frequency in response to noxious heat and decreased firing thresholds [56]. In a companion study, injection of artemin into the footpad was found to produce profound hyperalgesia that lasted up to 24 hours, and when injected in combination with NGF, lasted up to 6 days [57]. Furthermore, recent studies demonstrate artemin to induce neurite outgrowth of sensory neurons in vitro, similar to NGF [58]. This type of data has previously been used to support the concept that tissues levels of NGF regulate pathologic sprouting of sensory neurons. Thus, it seems just as likely that the increase in artemin and GFRα3 seen in patients who have CP contributes to the development of visceral hyperalgesia.

Recent discoveries in basic science continue to support and elaborate on some of the pathology seen in human tissue specimens previously described. In a recent publication using a rat model of CP, Takamido and colleagues [59] found a significant decrease in the percentage of pancreatic spinal afferent neurons in dorsal root ganglia compared with controls. However, there was an increase in the number of axonal projections and nerve terminals within the pancreatic parenchyma. They also found that CGRP-positive nerve fibers (nociceptive visceral afferents) expressed increased growth-associated protein and tyrosine receptor kinase A, suggesting growth-associated protein and NGF contribute to the axonal outgrowth and branching. The authors propose chronic inflammation in the pancreatic tissue results in axonal degeneration of dorsal root ganglia neurons innervating the pancreas, inducing axonal branching of the remaining neurons. This was hypothesized to contribute to an increase in size and decrease in the firing threshold of existing nerve bundles.

In the case of pancreatic cancer, most patients do not experience pain until the late stages of disease, leading to late-stage disease at time of diagnosis and poor survival rates. In a mouse model of pancreatic cancer, multiple pathologic changes were observed weeks before demonstration of pain behavior. These findings included macrophage infiltration, which colocalized with expression of NGF, as well as increased capillary branching and increased density of CGRP+ nerve fibers. By the time the mice had advanced cancer, the central portions of the tumors necrosed, leaving increased nerves and blood vessels only around the outer capsule of the tumors. This destruction of the distal ends of the nerve fibers corresponded to initiation of pain behavior, and was theorized to be the underlying cause [60]. Subsequently, a quantitative analysis of the pancreatic innervation of the mouse was performed by the same authors, finding sensory innervation to be significantly greater in the pancreatic head compared with the body and tail. Clinical studies show tumors arising in the pancreatic tail to be more advanced at

diagnosis [61]. The authors postulate this may not only be due to less biliary and gastrointestinal complications, but also delayed onset of pain [62].

GENETIC FACTORS

Understanding the pathogenesis of pain in CP and the environmental factors that trigger this cascade are key components in studying pancreatic pain. However, it is also likely that an individual's genetics play a role in their overall pain experience. Many of the considerable differences between people in pain perception, tolerance, and response to treatment may be genetic [63]. The vast majority of studies investigating the influence of genetic variability on pain have concentrated on nonvisceral pain syndromes. Genetic polymorphisms involved in catecholamine metabolism, opiate receptors, dopamine regulation, and the function of sodium channels and NMDA receptors have been associated with disparate pain sensations regarding headache syndromes [64,65], postoperative pain [66], and the response to narcotics [67,68]. Recently, GTP cyclohydrolase, the rate-limiting enzyme for tetrahydrobiopterin synthesis, a key modulator of peripheral neuropathic and inflammatory pain, was shown to contain a functional polymorphism that was significantly associated with less pain following diskectomy for low-back pain [69].

Unfortunately, prior examinations of candidate gene polymorphisms in visceral pain syndromes have been less convincing or not reproducible [70,71]. In particular, clear evidence demonstrating the importance of genetic polymorphisms in chronic pancreatic pain is lacking. Whether this represents a dearth of thoughtful inquiry or lack of importance has not been proven. For example, correlation between neurotrophic factor up-regulation and pain intensity in CP [48,50,53] may simply be a by-product of chronic inflammation and injury. However, it may also suggest genetically predisposed individuals mount a more profound neuropathic response to chronic inflammation due to increased expression of various neurotrophic factors. Findings such as this serve as future targets for exploration. Why CP patients who have similar amounts of injury have divergent patterns of pain and suffering remains an elusive question. Genetic polymorphisms may contribute part of the solution to this dilemma.

TREATMENT OF PAIN ASSOCIATED WITH CHRONIC PANCREATITIS

Medical Therapy

Treatment with analgesic medications is the mainstay of pain management in CP. However, therapeutic trials investigating optimum agents and regimens are lacking. Given the population with CP, with high rates of alcoholism, narcotic addiction is clearly a challenge when assessing effectiveness of any treatment regimen. In Andren-Sandberg's [7] review, a three-stage approach is described, using acetaminophen first, followed by dextropropoxyphene and morphine as a last resort, but with patient comfort taking precedence over concerns of addiction. Tramadol was prospectively evaluated in comparison to morphine in this population, and was rated as an excellent analgesic by

a significantly higher percentage of patients, and had lower incidence of gastrointestinal side effects [72]. However, mean dosage was 840 mg per day, so one must remember that this medication must be titrated to optimum analgesia similarly to more typical narcotics.

Pancreatic enzyme supplementation has been studied in patients who have CP with six randomized prospective trials with the primary outcome of pain. The mechanism of pain relief is thought to be digestion of cholecystokinin-releasing peptide in the duodenum, decreasing the feedback loop of pancreatic exocrine activation. The results of these trials are described in the American Gastroenterology Association (AGA) technical review to more detail, but briefly, six studies were reviewed. The analysis was that two trials reported benefit using nonenteric coated enzyme formulations [73,74], and four studies found no benefit but used enteric-coated preparations [75–78], suggesting adequate duodenal levels of enzyme were not being reached using coated enzyme preparations. On the other hand, these same studies could have been interpreted that pancreatic enzymes in patients who have retained pancreatic function and "small ducts" benefit from enzymes, whereas four studies of end-stage disease with no residual function (eg, large duct disease and steatorrhea) showed not benefit. Taken together, these studies have since been criticized for methodologic differences in outcome assessment, heterogeneous populations, insufficient numbers, and use of medication preparation with delayed release in the jejunum. Thus, a therapeutic trial of adequate doses of pancreatic enzyme supplementation, such as six tablets containing 16,000 units of lipase with each meal, is generally advocated for 1 to 2 months, at which time pain can be reassessed and the medication discontinued if ineffective. If nonenteric-coated enzymes are used, the provider should add a proton-pump inhibitor or histamine-receptor 2 antagonist to prevent hydrolysis of the enzyme due to gastric acid. In addition, although no therapeutic trials attest to this, it is hypothesized that inhibition of gastric acid will lead to a higher duodenal pH and reduce secretin-induced pancreatic stimulation and pain.

Octreotide, being the most potent inhibitor of pancreatic secretion, has to date no statistically significant data to support its use in a randomized controlled trial. Previous trial results are discussed in the AGA technical review [14]. No more have been subsequently published.

Antioxidant therapy has been often evaluated in the setting of CP in the international literature. This stems from the observation that levels of antioxidants, such as carotenoids, vitamins C and E, methionine, and selenium, are often deficient and reactive oxygen species are altered in patients who have CP [79–86]. Several small trials have evaluated the use of antioxidants in CP, two of which were described in the AGA technical review [87,88]. The first, by Uden and colleagues in 1990, used an antioxidant cocktail and demonstrated a decrease in number of attacks and improvement in visual analog scores (VAS) assessing pain while on treatment compared with baseline and placebo periods. However, the trial was criticized for enrolling a heterogenous population consisting of recurrent-acute as well as CP. The second trial, by

Banks and colleagues [87], evaluated the use of allopurinol in 13 patients who had CP, postulating that reduction of reactive oxygen species through the inhibition of xanthine oxidase may improve pain in CP. Using a randomized, double-blind, crossover design, allopurinol did not reduce pain or improve activities of daily living in the 13 patients. In an Indian study of patients who had CP from tropical pancreatitis, 20 patients were treated with curcumin, an antioxidant component of turmeric, or placebo, in a randomized placebo-controlled design. Although serum markers of oxidative stress were reduced, there was no effect on pain [89]. The most recent trial to look at the use of antioxidants used a combined antioxidant preparation, called Antox, in a double-blind, placebo-controlled crossover trial lasting 20 weeks. They enrolled 36 patients who had CP and chronic abdominal pain, and evaluated the effect on quality of life (QOL) using the short form 36 (SF-36) questionnaire. Follow-up was only completed in 53% of patients, with a significant improvement in physical and social functioning, health perception, and a reduction in pain on the SF-36. Limitations of the study included lack of a "washout" period between crossover, and potential for responder bias given the poor follow-up rate [90]. Although these are not entirely convincing data in favor of antioxidant use, this trial was clearly a step in the right direction in methodology compared with previous trials. It presents the strongest data thus far in favor of using antioxidants, and introduces a product that may improve compliance by reducing the number of tablets required for supplementation. There is currently a phase III trial enrolling patients who have idiopathic and hereditary CP with a goal of 240 patients to further investigate the use of this supplement.

Endoscopic Therapy

Endoscopic therapy aimed at treating pain in CP thought to be due to pancreatic ductal obstruction from strictures or stones has been widely studied. Since the AGA technical review, several important articles have been published, including the largest series to date, consisting of over 1000 patients with a mean follow-up of 59 months [91]. Additionally, this subject was recently reviewed including all trials published up to this time [92]. In their review, although appropriately critical of the methodology used in the vast amount of data available, the authors report a collective rate of pain relief in approximately two thirds of patients. In the largest series [91], approximately 25% of patients eventually required surgery. There was an overall complication rate under 20%, and most complications were not severe. Ideal candidates were reported to be patients who had ductal stricture associated with upstream dilatation of the pancreatic duct. However, given variation of protocols across reports, there was no consensus regarding optimum protocol on stent exchange, with some investigators changing stents at regular intervals, and others replacing stents only when pain recurrs. One series reported on outcomes of 56 patients out of an initial 110 patients who had painful calcific CP with dilated duct who had undergone extracorporeal shock wave lithotripsy (ESWL) combined with endoscopic therapy with a mean follow-up of 14.4 years. With

intent-to-treat analysis, they found long-term clinical success (defined as $\leq$5 hospitalizations for pain during the total follow-up period and no surgery) was obtained in 66% of patients [93]. The authors are still awaiting studies with prospective design, randomization to some type of placebo arm, with standardized assessment of pain before and after the procedure. Despite this, because of the low complication rate and relative ease, most expert therapeutic endoscopists advocate an initial trial of endoscopic therapy in the patient who has CP who has chronic pain and dilated duct.

Regarding endoscopic treatment of pain in pancreatic cancer, there is some evidence to support this as well. Tham and colleagues [94] published an experience consisting of 10 patients who had pancreatic cancer and ERCP demonstrating main pancreatic duct stricture and pain. Seven of the 10 patients had pain characterized as "obstructive type," meaning it correlated with meals. The other 3 had constant pain. Stenting of the stricture relieved the pain in the 7 patients who had obstructive type pain, but none of the patients who had constant pain. Five of the 7 responders were able to discontinue narcotics completely. A more methodologically sound study was recently published with 20 patients, with unresectable pancreatic adenocarcinoma, main duct obstruction, and postprandial epigastric pain, who underwent ERCP with pancreatic duct stent placement. These patients were prospectively assessed with VAS and a QOL index, and reassessed postoperatively for up to 16 weeks. The procedure was technically successful in 19/20 patients. Five patients underwent one stent exchange, and 2 patients underwent two. Pain scores decreased significantly at 4 weeks, and remained down at 8 and 12 weeks. However, at 16 weeks, scores crept back up to still significantly lower levels than baseline. QOL also improved initially, but had dropped by 16 weeks postoperatively [95].

EXTRACORPOREAL SHOCK-WAVE LITHOTRIPSY

Since the 1998 technical review, two important articles were recently published on this topic. The first, by Guda and colleagues [96], in 2005, was a meta-analysis of ESWL in the management of chronic calcific pancreatitis. In this endeavor, 16 studies were analyzed (all case series) including 491 subjects who underwent ESWL $\pm$ ERCP for stone removal, with the outcomes being pain relief and duct clearance. Homogeneity of effect size was analyzed using a Q-statistic (resulting in elimination of the 17th study). The mean effect size for pain relief was 0.6215, which is interpreted as a large effect of ESWL. This suggests ESWL itself, or through facilitation of successful duct clearance by ERCP, is clinically useful for improvement of pain. However, one must remember there was not a single randomized controlled study in this analysis. More recently, to follow-up a pilot study suggesting ESWL alone is effective in treating patients who have painful calcific CP [97], the first randomized controlled trial was published evaluating the effect of ESWL alone compared with ESWL plus endoscopic therapy in 55 patients who had painful calcific CP and dilatation of the main pancreatic duct [98]. Patients were not blinded to intervention with sham endoscopy, but outcome assessment of pain recurrence was

performed by a blinded gastroenterologist, and radiologic improvement by a blinded radiologist. Mean follow-up was 51.3 months, with 7 patients lost to follow-up (but included in the analysis by intention-to-treat principle). At 2 years and persisting in those followed for 3 to 7 years post treatment, less than half of the patients in each group had relapse of pain. A few patients in the ESWL alone group required subsequent ERP for pain relapse at a mean 15.5 months post trial intervention. Celiac plexus block or surgery had to be performed in 5 patients in the trial. In a subgroup of patients who had experienced onset of CP 2 years or less before intervention, comparison was made with natural history data from the Zurich cohort, and found patients to experience pain relief a mean of 3.1 years earlier. Cost analysis revealed costs were three times greater in the group randomized to ESWL plus endoscopic therapy. While being underpowered to detect a significant difference between treatment arms and not blinding the patients to intervention, this trial not only elevates the methodology lacking in most trials involving CP, but demonstrates ESWL to be an effective solitary option as a first intervention in patients who have painful calcific CP and main pancreatic duct dilatation.

SURGICAL TREATMENT

Surgical therapy for pain associated with CP should be considered in patients who require routine use of narcotics for pain control, are unable to maintain satisfactory body weight, or are unable to maintain employment or normal daily routines because of chronic or recurrent symptoms. When abnormalities such as gastric outlet obstruction or a pancreatic pseudocyst are present, correction either alone or in combination with a ductal drainage or resection procedure may provide substantial symptomatic relief.

In the absence of such abnormalities, surgical efforts to relieve pain associated with CP are primarily guided by the phenotype of an individual's disease. In patients who have an obstructed dilated pancreatic duct, drainage and decompression of the duct may be effective, whereas in patients who have a dominant inflammatory mass, resection of the mass may be beneficial. If neither of these changes is present, surgical treatment options are limited. However, recently some success has been reported with total pancreatectomy and autotransplantation of recovered pancreatic islets.

Drainage of an obstructed pancreatic duct to achieve pain relief was first attempted by means of retrograde drainage through a pancreatostomy [99,100] or after resection of the tail of the pancreas [21]. Neither method achieved routine success because the presence of multiple strictures along the pancreatic duct frequently led to incomplete drainage and decompression of the distal pancreatic duct. Recognizing this limitation, Puestow and Gillesby [101] combined resection of the tail of the pancreas with longitudinal opening of the pancreatic duct and anastomosis to the small intestine. To improve drainage and preserve endocrine function, Partington and Rochelle [102] further modified this procedure by extending the opening of the pancreatic duct and preserving the tail of the pancreas. This technique continues to be used, and is associated with low

morbidity and low mortality rates as well as long-term pain relief typically reported in approximately 60% to 70% [103] of patients, although one group reported 98% of patients were pain-free with mean follow-up of 6.5 years [104]. Best results are achieved when an inflammatory mass does not affect the pancreatic head and when the pancreatic duct measures at least 7 mm in diameter, although some success is achieved with smaller ducts. In patients who fail to improve or develop recurrent symptoms, revision of the longitudinal pancreaticojejunostomy may be beneficial if drainage of the pancreatic duct is confirmed to be incomplete.

Patients who do not have a dilated main pancreatic duct are generally thought to have pain associated with inflammation and possibly nerve involvement as described previously. Drainage procedures are usually not effective among these patients, but if a dominant inflammatory mass is present, resection of the mass may be beneficial. As the pancreatic head is most frequently abnormal and has been characterized as the pacemaker of the disease process, resection of the pancreatic head has drawn particular interest and led to development and application of several operative procedures. The recent data that demonstrate neuropathic changes with nerve growth and large axonal trunks coursing through the pancreatic head lends new understanding to the previously observed importance of targeting the pancreatic head in these procedures. The standard Whipple procedure (pancreaticoduodenectomy), comprising resection of the pancreatic head, distal bile duct, antrum, and duodenum, and used for the treatment of periampullary malignancies, has also been used for resection of inflammatory pancreatic head masses. However, it may be associated with chronic gastrointestinal symptoms as well as diabetes mellitus in 20% [105,106], and has largely been supplanted by the pylorus preserving Whipple procedure described by Traverso and Longmire [107], which leads to pain relief in 85% to 95% after 5 years, and decreases the potential for postoperative dumping syndrome, peptic ulceration, and bile-reflux gastritis [108].

Other more limited and organ-preserving resections of the head of the pancreas have been developed for the treatment of CP. These include the duodenum-preserving pancreatic head resection (DPPHR), described by Beger [109], in which the neck of the pancreas is divided and the head of the pancreas and uncinate process are extensively excised without removal of the duodenum or intrapancreatic bile duct, and the Frey procedure, in which a more limited resection of the pancreatic head is performed in combination with a lateral (longitudinal) pancreaticojejunostomy and without division of the pancreas [109,110]. The Frey procedure may be technically easier than a Beger procedure, because dissection of the scarred inflamed pancreas away from the superior mesenteric and portal veins is not required, and reconstruction after excision of the pancreas is less complex. Both procedures are associated with low morbidity and mortality, and demonstrate a high percentage of sustained pain relief and return to productivity despite differences in the amount of pancreas excised.

Several small series have compared outcomes after Whipple, DPPHR, and Frey procedures. In a prospective randomized controlled trial, Buchler and colleagues [111] compared the DPPHR (n = 20) with the pylorus-preserving Whipple procedure (n = 20). There were no deaths in either group, and morbidity was similar. After 6 months, patients who underwent the duodenum-preserving resection had less pain, greater weight gain, better glucose control, and higher insulin secretion capacity. In a prospective-controlled but nonrandomized study, Witzigmann and colleagues [112] compared DPPHR with the standard Whipple procedure and observed lower postoperative pain intensity in the DPPHR group, although the frequency of acute episodes of pain and use of analgesic medications postoperatively did not differ in the two groups.

Izbicki and colleagues [113] compared the Frey procedure (n = 31) to the pylorus-preserving Whipple procedure (n = 30) in a prospective randomized trial. One patient died of cardiovascular failure in the Frey group. Morbidity was greater in the Whipple group. With median follow-up of 24 months, pain scores were equally decreased in the two groups, but improvement in global quality of life was greater in the Frey group. In a separate prospective randomized trial, the same group compared long-term outcomes in patients undergoing either DPPHR (n = 38) or Frey (n = 36) procedures. With median follow-up of 104 months, there were no differences in late mortality, QOL, pain, or endocrine or exocrine function [114].

Overall these results support resection of the pancreatic head when an inflammatory mass is present, and suggest that resection by means of a DPPHR or Frey procedure may provide better long-term QOL than a pylorus-preserving Whipple procedure. The final choice of operative procedure, however, should be guided by the experience of the individual surgeon.

If the pancreatic duct is not dilated, a dominant area of inflammation is not present, or pain recurs after an initial resection procedure, total or completion pancreatectomy may be considered. Although this is associated with the complete loss of beta cell function and brittle diabetes, techniques of autotransplantation of islet cells harvested from the resected pancreas have improved since first being described by Sutherland and colleagues [115]. A recently published series including 45 patients followed for a mean of 18 months demonstrated 40% were insulin-independent and 58% were narcotic-free [116]. Prior ductal drainage or resection procedures adversely affect the total islet yield and diminish the rate of postoperative insulin independence. If results with autotransplantation continue to improve, then in the future total pancreatectomy with islet autotransplantation may be considered in patients who have small duct diffuse inflammatory disease first, rather than duct drainage or partial resection procedures, to optimize islet yield.

NEUROLYSIS AND NERVE BLOCK

Working from the pancreas proximally toward the central nervous system, visceral afferents traverse the celiac ganglia, which lie adjacent to the aorta below the diaphragm at the level of the celiac trunk. They then follow the same

course as the sympathetic nerves, which relay motor signals to the gland. These afferents often cross the midline and travel along the splanchnic nerves adjacent to the spinal column before synapsing in the dorsal root ganglia and sending axons to the dorsal horn of the spinal cord [117]. The evolution of surgical and less-invasive techniques to disrupt the pancreatic afferent nerves to treat pain from both benign and malignant pancreatic conditions is nicely detailed in Bradley's review from 2003 [117]. In this update, the authors mainly focus on more recent techniques, including celiac plexus block (CPB) for CP; neurolysis for pancreatic cancer (NCPB); and thoracoscopic splancnicectomy, which is performed for both conditions.

The first study to evaluate celiac plexus neurolysis in randomized, prospective, blinded, placebo-controlled fashion with a standardized pre- and postoperative pain assessment was performed by Lillemoe and colleagues [118] in patients who had unresectable pancreatic cancer. They randomized 137 patients who had unresectable cancer determined intraoperatively to neurolysis or saline injection and compared preoperative and postoperative VAS, as well as survival. VAS scores were significantly lower in the neurolysis group beyond 6 months postoperatively. The unexpected finding was that patients who had preoperative pain who received neurolysis had a significantly increased survival, attributed to decreased stress levels from pain and its effect on nutrition and activity level. This effect on survival was not reproduced in a nicely designed randomized, controlled, blinded trial comparing fluoroscopically guided NCPB and systemic analgesic therapy versus sham injection with systemic analgesic therapy [119]. Pain scores similarly improved, but there was no positive effect on either QOL or survival. The topic of celiac plexus block and neurolysis was recently reviewed by Noble and Gress [120] with an overview of various techniques and data in each. NCPB, usually accomplished with concentrated ethanol solutions, is typically reserved for palliative care for unresectable malignancy. CPB, accomplished by similarly injecting a long-acting steroid and local anesthetic, is performed for benign conditions such as CP. Currently, endoscopic ultrasound is the procedure of choice for delivery of either NCPB or CPB. Endoscopic ultrasound–guided NCPB was first described by Wiersema and colleagues [121], demonstrating it to be a safe and effective treatment for patients who have pain due to pancreatic cancer or intra-abdominal metastases with a median follow-up of 10 weeks. Gress and colleagues [122,123] were the first to report endoscopic ultrasound–guided CPB in patients who have CP, demonstating its effect to have more durability and cost efficiency than a comparison group who underwent CT-guided technique.

A technique receiving a lot of attention in the literature involves surgical splanchnicectomy by way of videoscopic thoracoscopy (VSPL). This technique, when used to treat intractable pain due to pancreatic cancer, enjoys a high rate of sustained pain relief, with surgical series reporting rates between 60% and 100% using various techniques, including unilateral left [124,125], a mixture of unilateral and bilateral [126–128], or bilateral approaches [129–131]. However, in the CP population, the response rate is not initially as

high and tends to attenuate over time (see Table 2). This may be due to high rates of opiate addiction, as well as increased survival times during which ongoing inflammation may lead to alternative routes of neuropathic pain (eg, vagal, somatic, or central). Differential epidural analgesia (DEA) testing, first introduced by Bradley and colleagues [132], was used to stratify this population into groups more or less likely to respond to VSPL. This technique, using placebo and graded epidural injections of anesthetic, can differentiate placebo responders from patients who have primarily visceral (eg, pancreatic) or somatic (eg, retroperitoneal or pleural) sources of pain. Conwell and colleagues [133] evaluated 23 patients who had CP using DEA and found 78% to have nonvisceral pain. Both of these studies found markedly attenuated interventional benefit in the nonvisceral pain subgroups. Given these results, DEA may be a promising technique to incorporate clinically as well as in future trials to decrease placebo response as well as to eliminate patients unlikely to benefit from invasive interventions aimed at treating pancreatic pain.

''ALTERNATIVE'' TREATMENTS

An important aspect of the treatment approach to patients who have CP suffering from chronic pain is multidisciplinary. Given that one of the primary etiologies for CP is alcoholism, and one of the primary treatments is chronic use of opioids, psychiatric or psychologic treatment may be beneficial as adjunctive treatment. While there is minimal literature describing cognitive behavioral therapy in the treatment of CP, its use is well published in other chronic pain states such as migraine headaches, chronic back pain, irritable bowel syndrome, and so forth. One case report describes the significant improvement in narcotic use patterns and a decrease in narcotic requirements in a patient who has CP, using behavioral therapy [134].

In addition to psychotherapy, the pain clinic is another entity often used in treatment of chronic pain states. Besides expert use of narcotic and alternative analgesics, alternative therapies include transcutaneous electronic nerve stimulation, acupuncture, intrathecal pumps for infusion of opioids and anesthetic agents, and spinal cord stimulation. To date, there is only one publication on the use of transcutaneous electronic nerve stimulation and acupuncture for CP. In that study, patients were randomly assigned transcutaneous electronic nerve stimulation or acupuncture versus sham transcutaneous electronic nerve stimulation placement or acupuncture, and found no benefit to either therapy [135]. Use of an intrathecal pump delivering morphine and bupivacaine was reported in one patient, with good results [136]. However, to date, this is the only case report documenting the use of this technique in the treatment of CP. Spinal cord stimulation involves the implantation of epidural electrodes that deliver electrical impulses affecting the dorsal column with resultant inhibition of nociceptive signals through the lateral spinothalamic tract [137]. Placement is determined by the viscerotome associated with the visceral organ thought to be causing pain [138,139]. This technology seems to be promising based upon a case series of five patients who had CP and chronic pain, all of whom

Table 2
Neurolytic or nerve block procedures for chronic pancreatitis

Study	Approach	# of patients	Population characteristics	Follow-up (months)	Outcome measure	Results
Videothoracoscopic splanchnicectomy (VSPL)						
Stone et al, 1990 [159]	Unilateral (left) with conversion to bilateral in 5 bilateral truncal vagotomy	15	N/A	16	Subjective assessment	Pain relief in 66% to long-term, 5 patients with conversion to bilateral with 80% long-term relief
Andren-Sandberg et al, 1996 [129]	Bilateral	14	N/A	13	VAS	93% with significant improvement at 1 mo, persisting for duration of follow-up
Bradley et al, 1996 [132]	Unilateral (5) and bilateral (11)	16	% alcoholic N/A; 13/16 with visceral pain on DEA testing; 3/16 with somatic pain on DEA testing	23.3	VAS	Visceral pain—77% with ≥50% short-term improvement, maintained in 80% at end of follow-up No response in patients with somatic pain

Ihse et al, 1999 [131]	Bilateral	21	57% alcoholic	43	VAS	100% with short-term improvement 9.5% with long-term failure 100% followed to 48 mo with improvement
Maher et al, 2001 [160]	Unilateral (left for left-sided and midline pain, right for right-sided pain) 7/15 reoperated on opposite side	15	N/A	68	VAS	100% improvement in short-term, attenuated in all patients
Makarewicz et al, 2003 [147]	Unilateral (left)	32	100% alcoholic	12	FACT-PA, VAS	2/5 scales improved at 12 mo Mean VAS improved at 12 mo
Buscher et al, 2002 [161]	Bilateral	44	54.5% alcoholic	36	VAS	46% with improvement at 24 months and 48 mo
Howard et al, 2002 [158]	Bilateral	55	16% alcoholic; all visceral pain on DEA testing	32	EORTC QLQ-30, VAS	81% with mod-marked improvement in VAS short term; 31% with sustained improvement

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Table 2
(*continued*)

Study	Approach	# of patients	Population characteristics	Follow-up (months)	Outcome measure	Results
Celiac Plexus Block						
Gress et al, 1999 [123]	Endoscopic ultrasound or CT-guided	10 endoscopic, ultrasound 8 CT	N/A	15 wk	VAS	Endoscopic ultrasound—significant improvement in 50% immediately, 40% at 8 wk, and 30% at 24 wk CT—25% immediate improvement, 12% at 12 wk
Gress et al, 2001 [122]	Endoscopic ultrasound	90	38% alcoholic; 32% congenital ductal anomaly; 24% idiopathic	8 wk	VAS	55% response at 8 wk 26% at 12 wk, 10% at 24 wk, 4% at 35–48 wk

Abbreviations: DEA, differential epidural analgesia; EORTC QLQ-30, European Organization for Research and Treatment of Cancer quality of life questionnaire; FACT-PA, functional assessment of chronic illness therapy pancreatic disease; VAS, visual analog scale.

experienced a reduction of at least 50% in VAS and 50% to 80% reduction in narcotic usage after implantation of a spinal cord stimulation device [140]. However, this case series is the extent of the literature for this method in CP, and until further experience is published, it must be considered experimental.

OUTCOME ASSESSMENT

In the field of pancreatology, a subject of much debate and study, involves appropriate measurement of outcomes in patients who have CP. Lack of standardization in outcome assessment is the norm rather than the exception, as can be seen in the studies reviewed in this article. Prominent figures in pancreatology have pled for more uniformity in reporting of results, advocating one measurement tool or another [141]. Several QOL scales have been used with some success, including the SF-36 [90,142–144], the SF-12 [145], the Functional Assessment of Chronic Illness Therapy Pancreatic Disease subscale [146,147], and the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) [148–152], which was originally designed for patients who have cancer. Recently, Fitzsimmons and colleagues [153] published an article describing the adaptation and development of a new, disease-specific module to accompany the QLQ-C30, called the QLQ-PAN26, originally designed for pancreatic cancer, in the assessment of patients who have CP. The tool was developed and has been assessed using an international patient population, and was systematically assessed for reliability and validity. Using this technique, the disease-specific module was amended to include two additional questions regarding alcohol abuse, and the name changed to QLQ-PAN28 (CP), and is ready for use in larger clinical trials to supplement its validity data. In addition, the core questionnaire has been used and validated in patients who have CP in several trials [148–152]. The SF-12 was recently compared with the SF-36, and found to have minimal loss of information, making this easily and quickly completed form an attractive option as well [145].

Regarding the measurement of pain, several tools exist, all of which have been extensively tested and validated in various clinical conditions, mostly in acute analgesic trials and in the population affected by chronic noncancer pain [154]. The available scales can be divided into two broad categories: unidimensional scales, most often used to measure pain intensity, and multidimensional scales. Of the unidimensional scales, two main types of scales for the measurement of clinical pain include the VAS and numeric rating scales. The standard VAS is a 10-cm line with "anchor" words at both ends of severity that usually refer to no pain and the worst pain imaginable. The numeric rating scales is usually a 0 to 10 scale, with zero representing no pain and 10 representing the worst pain imaginable. Comparison of VAS with a four-point numeric rating scales found the VAS to be accurate and more sensitive than numeric rating scales in registering chronic pain [155]. Moreover, the VAS has been used in most of the CP studies, which actually have a standardized pain outcome. Therefore, to compare future therapies to what has already been studied, this measurement may be more desirable.

Pain reports in the chronic setting tend to be less associated with true intensity changes, leading to uncertainty in the validity of pain relief ratings [156]. Due to this limitation of unidimensional scales, several multidimensional scales have been designed to capture the multidimensional nature of chronic pain. Among them, the McGill Pain Questionnaire has been used most in the assessment of chronic noncancer pain [154]. The McGill Pain Questionnaire has a recognized validity in assessing several dimensions of the pain experience, can be used to differentiate groups of patients who have various conditions causing chronic pain, and has established sensitivity to treatment effects [157]. Several different language translations are available for international studies. Drawbacks to the McGill Pain Questionnaire include its complexity, part of which is improved with the shorter form. However, the short form is not available in as many languages. In addition, its experience in the study of CP is limited, with only one study reporting its use in the study of allopurinol for pain in CP, in which no effect was found [87]. The authors' group, which is currently enrolling patients in the North American Pancreatitis Study-2, is using this tool.

SUMMARY

This review of pathophysiologic factors influencing pain in CP and pancreatic cancer, as well as treatment modalities and issues with outcome assessment, highlights several recent advances in the field. These include new insights in neurologic derangements associated with the disease, and possibly even propogating the disease, genetic factors, as well as encouraging results with some therapies, such as antioxidants [90], endoscopic therapy [91,93], ESWL [98], surgical procedures including total pancreatectomy with islet cell autotransplantation, denervation and nerve block procedures, and experimental treatments such as spinal cord stimulation. What is encouraging is an overall trend toward improved methodology in the literature. However, much of what is published still relies on case series, poor randomization techniques, questionable controls, and lack of uniformity in outcome assessment. Therefore, physicians treating this patient population still rely on guesswork and intuition.

As a general guideline, it is convenient to divide the population suffering from CP with chronic pain into those with duct dilatation and those without. Drainage procedures, whether endoscopic or surgical, tend to be unsuccessful in patients who do not have obvious ductal abnormalities. Thus, the small duct CP population is left with medical therapy using enzymes, analgesics, and antioxidants, nerve blocks such as CPB, surgical denervation procedures (eg, pancreatic head resections, total pancreatectomy, sympathectomy), and spinal cord stimulation. On the other hand, endoscopic and surgical drainage procedures, as well as ESWL do seem to have some utility in the population with ductal abnormalities and/or calcifications. One concern to keep in mind is that patients who have longer courses of disease and previous pancreatic surgery tend to have less success with nerve block or denervation procedures [122,158]. Whether this is due to parietal (somatic) or centralized pain, psychogenic

components or opioid dependence is not known at this time. However, it does suggest that more aggressive treatment earlier in the course of disease may lead to improved outcomes by arresting the process before a significant neuropathic component or chronic illness behavior develops. Another promising approach to patient selection is the use of DEA, which may decrease the number of fruitless aggressive interventions. A general rule of thumb in all patients suffering from this disease is the use of a multidisciplinary approach involving gastroenterologists, surgeons, pain clinics, and mental health professionals to try to prevent steady decline in function and opioid addiction.

From a research standpoint, the pancreatology community must come together to standardize trial designs and outcome assessments. There are promising tools that still require further validation, but QOL must be assessed in this population rather than unidimensional pain scores alone (eg, VAS), which only provide information on pain intensity at one point in time in a disease of chronic nature. In addition, QOL must be measured prospectively as well as after interventions with enough lag time to assess true changes in functionality (eg, going back to work, stabilization of interpersonal relationships, mental and physical health) which take more than a few weeks to change. Given the small numbers of patients overall, multicentered trials are necessary to recruit adequate numbers to appropriately power studies. The current direction is encouraging that this will happen, so hopefully we will be able to rely less on art than evidence in the future.

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GASTROENTEROLOGY CLINICS
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Cystic Neoplasms of the Pancreas

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With the increased use of sophisticated imaging, particularly computed tomography (CT), cystic masses in the pancreas are being recognized with greater frequency. Several recent review articles serve as an introduction to the clinical and imaging features of these masses [1–4]. Although imaging alone may not provide a specific diagnosis in many cases, a combination of imaging characteristics, clinical presentation, and judicious use of additional procedures, such as cyst aspiration, allows appropriate management.

This article presents the approach to the most commonly encountered pancreatic cystic masses that the authors employ at the University of Pittsburgh Medical Center. Variations on this approach are to be expected, based on several factors, including the availability of sophisticated imaging equipment and personnel.

ETIOLOGY OF CYSTIC PANCREATIC MASSES

Pancreatic cystic masses may be the result of congenital, inflammatory, or neoplastic processes, as listed in Box 1 and Table 1 [5]. Some of these, such as anaplastic carcinoma, cystic teratoma, and hydatid disease, will be considered too rare to warrant further discussion in this article. Intraductal papillary mucinous neoplasm is considered important enough to discuss in a separate article of this issue.

Congenital

"True" cysts of the pancreas are those that are neither neoplastic nor the result of prior inflammation. These are rare and cannot be distinguished from other cystic masses except for the presence of an epithelial lining [6]. Congenital cysts are usually single and small (1–2 cm), although larger symptomatic cysts have been reported in children.

Multiple pancreatic cysts may be encountered in several syndromes and multisystem disorders, including autosomal dominant polycystic disease, cystic

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Box 1: Cystic pancreatic masses

Congenital
True (epithelium-lined) cyst
Syndromes causing multiple cysts
- Autosomal dominant polycystic disease
- von Hippel-Lindau
- Cystic fibrosis

Inflammatory
Pseudocyst
Pancreatic abscess
Hydatid cyst

Neoplastic
Benign
- Serous (microcystic) cystadenoma
- Cystic teratoma
- Lymphoepithelial cyst

Malignant or potentially malignant
- Mucinous cystic neoplasm
- Solid and papillary epithelial neoplasm

Other (tumors that may have a cystic component)
Intraductal papillary mucinous neoplasm (IPMN)
Islet cell tumor
Anaplastic carcinoma
Metastases to pancreas (eg, ovarian cystadenocarcinoma)

fibrosis, and von Hippel-Lindau disease. The pancreatic cysts are of no clinical concern in these settings, and differential diagnosis is generally not a problem. In polycystic disease, family history and the presence of cysts in other organs are diagnostic. In cystic fibrosis, the pancreas contains not only cysts but also fatty replacement of the pancreatic parenchyma. In patients who have von Hippel-Lindau disease, solid neoplasms develop in the brain, spinal cord, kidneys, and adrenals. These patients are also prone to developing pancreatic cysts and serous (microcystic) cystadenoma.

Inflammatory

A pseudocyst is the result of acute or chronic pancreatitis, or pancreatic trauma (especially in children). A pseudocyst is usually regarded as the most common etiology of a symptomatic pancreatic cystic mass. This "cyst" lacks an epithelial

Table 1
General characteristics of pancreatic cystic lesions

	Morphology	Cytology	CEA	Fluid characteristics
Serous	Microcystic	Small, cuboidal cells without mucin	Low or absent	Thin, clear
Mucinous	Macrocystic, usually septated	Mucinous epithelial cells	Moderately increased	Clear, mucoid, viscous
Malignant	Mural nodularity, septation	Malignant mucinous epithelial cells	Markedly increased	Clear, mucoid, viscous
Pseudocyst	Thin walled, usually nonseptated	Inflammatory cells	Low	Thin, dark

Abbreviation: CEA, carcinoembryonic antigen.

lining, is walled off by fibrous and granulation tissue, and contains fluid that comprises pancreatic juice and variable amounts of necrotic debris and hemorrhage. Pseudocysts should be distinguished from fluid collections in pre-existing spaces, such as the lesser sac, that develop and resolve rapidly following an attack of acute pancreatitis.

Imaging characteristics of a mature pseudocyst include near water-attenuation fluid contents and a thin wall (rarely with curvilinear calcification). Less-mature cysts have complex fluid and inflammatory infiltration of adjacent structures such as the gastric wall and mesenteric fat (Fig. 1A). Septations are uncommon, and enhancing mural nodules are absent. Pseudocysts usually show a fairly rapid (days to weeks) evolution in size, unlike cystic neoplasms. CT and MR generally show ancillary findings that help to establish the diagnosis of pseudocysts, such as signs of acute or chronic pancreatitis (inflammatory infiltrates, ductal dilation, calcifications, and so forth) (Fig. 1B, C).

Cyst contents are generally thin fluid (unless grossly infected) that may look like a cola beverage. Analysis shows an elevated amylase level (often >10,000 IU) that is diagnostic. However, mature noncommunicating pseudocysts may lose amylase activity with time.

Pseudocysts generally take 4 to 6 weeks to develop a fibrous wall. Even mature pseudocysts may resolve spontaneously, often by erosion into the stomach or bowel, and do not require intervention except for complications such as infection, hemorrhage, or persistent obstruction of bowel or bile ducts. Intervention is also required for persistent symptomatic cysts causing abdominal pain and/or early satiety.

For symptomatic pseudocysts, management options include percutaneous drainage, endoscopic drainage (transpapillary or transmural), or surgical drainage (cyst enterostomy). An experienced multidisciplinary team, taking into account patient wishes, ductal anatomy, and surgical risk, best makes management decisions.

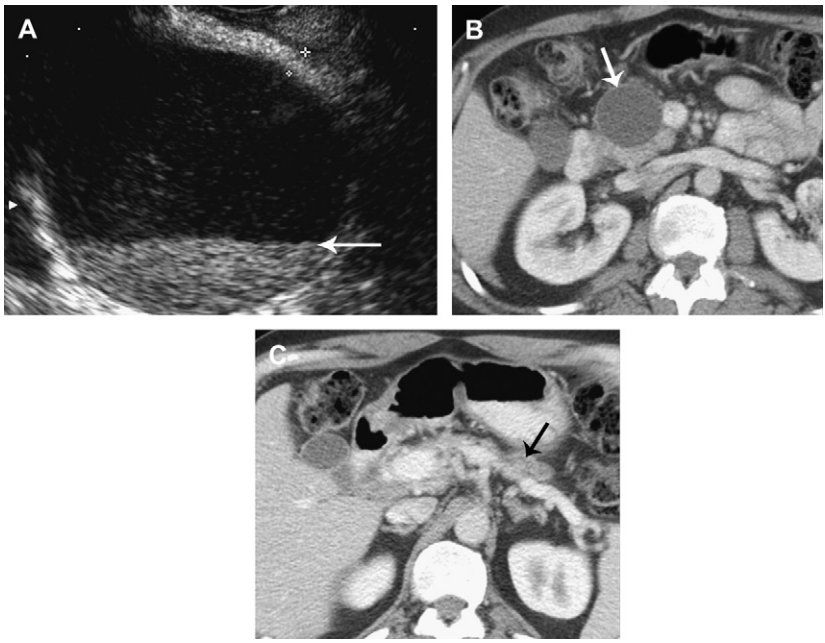

Fig. 1. Fifty-six-year-old man who has a pancreatic pseudocyst. (*A*) Endoscopic ultrasound image shows a spherical mass with a thin but measurable wall (*between cursors*) and a fluid-debris level (*arrow*) in its dependent portion. (*B*) A CT scan performed 2 months later shows decrease in size of the pseudocyst (*arrow*), a thin wall, and near-water-attenuation contents. (C) The body-tail segment of the pancreas (*arrow*) is atrophic and the pancreatic duct is dilated, indicating chronic pancreatitis.

A pancreatic abscess is generally the result of severe acute pancreatitis and is usually not a diagnostic problem. Infected pancreatic necrosis is a dreaded complication of necrotizing pancreatitis and would not be confused with a cystic neoplasm, based on the clinical presentation.

Benign Neoplasms

Cystic teratoma

Cystic teratoma occurs rarely in the pancreas. Imaging evidence of liquid fat plus calcification and soft tissue may allow preoperative diagnosis.

Lymphoepithelial cyst

Lymphoepithelial cyst is another rare pancreatic tumor with imaging characteristics (septated cystic mass in the body/tail segment) that often cannot be distinguished from cystic neoplasm (see later discussion) [7].

Serous (microcystic) cystadenoma

Serous (microcystic) cystadenoma is an uncommon tumor that typically occurs in elderly women, with a female/male ratio of 1.5–4.5:1. The median age at

diagnosis is approximately 70, and 80% of reported cases have been in patients over the age of 60 [8–10].

Serous microcystic adenomas occur with increased frequency in patients who have von Hippel-Lindau disease. Even in patients who do not have other features of von Hippel-Lindau disease, similar genetic mutations are found in most patients who have serous cystadenomas.

The typical imaging appearance of a serous cystadenoma is that of a sponge or honeycomb, with innumerable tiny cystic spaces separated by thin septa (Fig. 2A). The septa may coalesce into a central scar that may calcify. The small size of the cysts and the numerous septa may cause the mass to appear solid on imaging. Thin-section, contrast-enhanced CT or MR allows confident diagnosis in 20% to 30% of cases [10]. The septa and peripheral capsule of this well-circumscribed tumor show brisk contrast enhancement. MR shows these features as well as CT. In addition, the fluid content of the mass may be more evident on MR as low signal (dark) on T1-weighted images, and high signal (bright) on T2-weighted images.

A macrocystic variant of serous cystadenoma has been reported by several groups of investigators [11–13]. Rather than having innumerable tiny cysts, these are characterized by a single cystic mass with or without one or more thin septa. This variant may be difficult to distinguish from a mucinous cystic tumor. The serous mass is favored by having a thin nonenhancing wall, a lobulated surface, and presence within the pancreatic head. Cyst aspiration is required for further evaluation.

Endoscopic ultrasonography (EUS) is now frequently employed for further evaluation of cystic lesions discovered by cross-sectional imaging. EUS evaluation (typically at 5 MHz) provides high-resolution imaging that highlights the sponge-like or honeycomb appearance of the microcystic serous cystadenoma (Figs. 2B and 3A, B). The macrocystic variant may mimic a mucinous

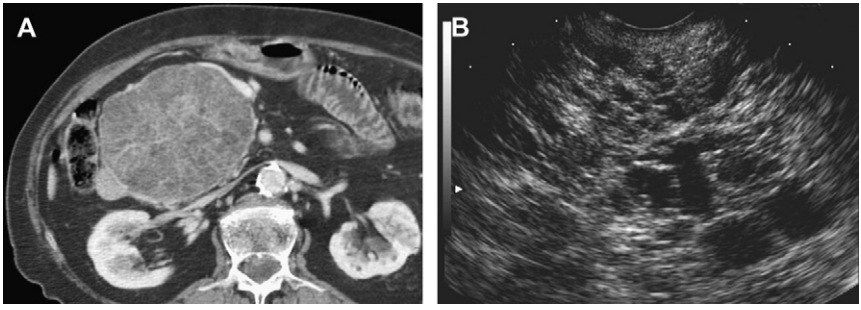

Fig. 2. Eight-two-year-old woman who has a serous microcystic adenoma. (*A*) A contrast-enhanced CT scan shows a large spherical mass within the pancreatic head, having an appearance of a sponge, with innumerable tiny cystic spaces separated by thin, enhancing septa. (*B*) EUS confirms the innumerable tiny cystic spaces and septa. The patient had minimal symptoms related to the mass, and no surgery was performed.

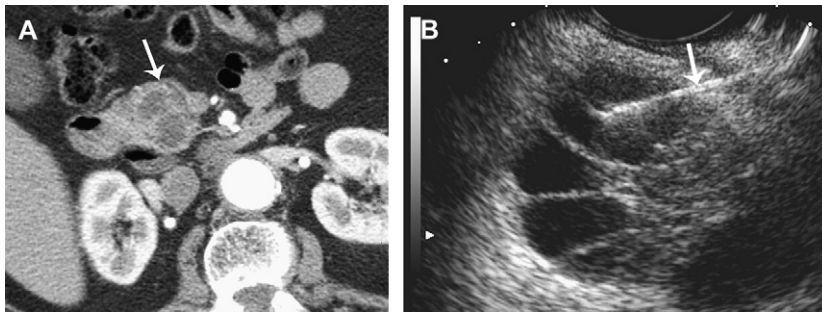

Fig. 3. Seventy-three-year-old man who has serous microcystic adenoma discovered on CT evaluation of an abdominal aortic aneurysm. (*A*) Contrast-enhanced CT shows a multicystic mass (*arrow*) in the pancreatic head. (*B*) EUS shows multiple small cystic spaces separated by thin septa. A fine needle aspiration needle (*arrow*) was inserted and yielded thin fluid with glycogen-rich cuboidal cells.

cystic neoplasm. Serous adenomas may also have few cystic spaces (''oligocystic''), and these may mimic side branch intraductal papillary mucinous neoplasm. EUS-guided cyst aspiration can prove helpful in this situation. The fluid content of macro- and microcystic serous tumors is thin and nonviscous. Glycogen-rich cuboidal epithelial cells, when seen in the cyst aspirate, are diagnostic [14]. The carcinoembryonic antigen (CEA) level, which is the most accurate tumor marker to diagnose a mucinous cystic neoplasm [15], is low or undetectable. The authors currently only aspirate the macrocystic or oligocystic variants to differentiate them from mucinous lesions. They consider the sponge-like or honeycomb appearance of the microcystic variant pathognomonic at EUS and, therefore, no longer perform fine needle aspiration (FNA) in this situation.

Serous cystadenomas are invariably benign and usually cause minimal symptoms unless they attain sufficient size to compress upper abdominal contents. Notably absent are any signs of invasion of blood vessels or ducts.

Confident diagnosis of a serous cystadenoma may be challenging but is important, because these are benign tumors that occur in elderly patients and often are best managed without surgery unless the patient has substantial symptoms, such as pain, early satiety, or jaundice.

Malignant or Premalignant Neoplasms

Mucinous cystic neoplasm (mucinous cystadenoma and cystoadenocarcinoma)

Mucinous cystic neoplasms are being diagnosed with considerable frequency that, in the authors' experience, exceeds the ''1% of all pancreatic malignancies'' figure that has been cited in prior studies and reviews. In the authors' practice, mucinous cystic neoplasms are encountered more frequently than pseudocysts, further supporting other centers' experiences that these are now the most common pancreatic cysts [4].

Mucinous cystic neoplasms tend to occur in a younger age group with a marked female predominance of approximately 80% [1,2,4,9]. Peak incidence is in the 6th decade, but it is not rare to diagnose these in women as young as 35 years old. Unlike serous tumors, approximately 70% to 95% of mucinous cystic tumors occur in the pancreatic body and tail segments.

Mucinous tumors are hypovascular, well-circumscribed masses with a wall of measurable thickness that is lined by tall, mucin-producing columnar cells and "ovarian-type stroma," which is now considered a required feature for confident diagnosis of mucinous cystic neoplasms [16–18]. The mass is generally unilocular or divided into fewer than six cystic spaces by septa (Fig. 4A, B). The septa and peripheral wall may calcify, said to occur in 10% to 25% of cases [16,18]. The mass may displace but usually does not obstruct the pancreatic duct.

Mucinous cystic neoplasms should be considered malignant or premalignant. The World Health Organization has classified the pathologic spectrum of mucinous cystic neoplasms using three dysplastic grades: (1) adenoma (mucinous cystadenoma), (2) borderline (mucinous cystic tumor–borderline), and (3) carcinoma in situ (mucinous cystadenocarcinoma–noninvasive). An invasive mucinous cystadenocarcinoma category exists, representing truly invasive cystadenocarcinomas [5]. Any imaging evidence of mural nodularity, enhancement or calcification, or ductal obstruction should be interpreted as suggestive of malignancy.

The mucinous content of these tumors is suggested by higher than water attenuation on CT and variable signal intensity (different than "simple" fluid) on MR, reflecting the proteinaceous nature of the fluid. This is confirmed with needle aspiration of the cyst contents, generally as part of the evaluation with EUS (Fig. 5A, B). EUS also allows high-resolution imaging of the cyst wall and may depict clues, such as mural nodularity, more readily than CT

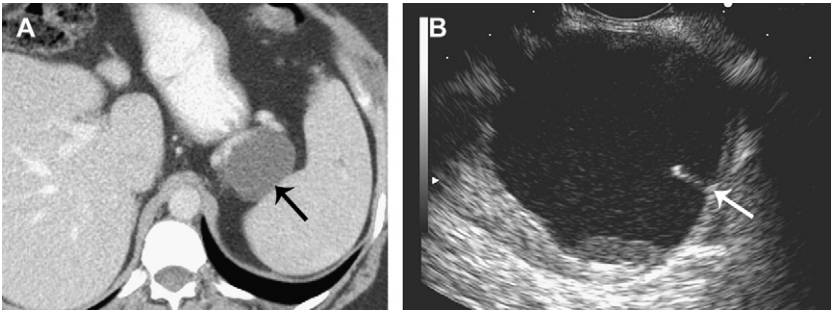

Fig. 4. Forty-seven-year-old woman who has a mucinous cystic neoplasm (cystadenoma)—surgically proven. (*A*) Contrast-enhanced CT shows a spherical mass (*arrow*) arising from the tail of the pancreas. A thin septum is visible near the dependent wall of the cyst. (*B*) EUS demonstrates the cystic mass. The septum (*arrow*) and debris or mural nodularity along the dependent wall are more evident than on CT.

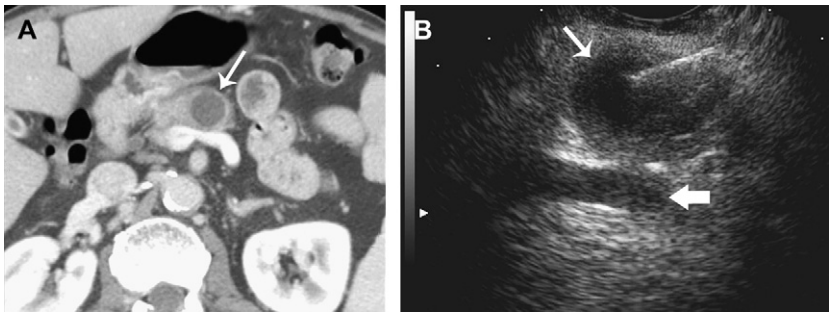

Fig. 5. Sixty-one-year-old man who has a mucinous cystic neoplasm (cystoadenocarcinoma)—surgically proven. (*A*) Contrast-enhanced CT shows a cystic mass (*arrow*) in the neck of the pancreas, immediately adjacent to the splenic vein. The mass has a detectable wall but no obvious mural nodularity. (*B*) EUS shows a thick-walled cystic mass (*arrow*) just ventral to the splenic vein (*block arrow*). The FNA needle is seen and aspiration yielded thick mucinous fluid with an elevated CEA level.

or MR. True mass components or mural nodules involving the cystic tumor can be accurately targeted by way of EUS-FNA for malignant cytologic confirmation. In the absence of a solid component, EUS-guided cyst aspiration is performed for diagnostic purposes. Cyst fluid is slightly viscous to thick and mucoid. The authors have rarely encountered mucinous cystadenomas with a thin serous aspirate. As cyst aspirate cytology suffers from poor sensitivity due to the paucicellular nature of the sample [2,4], cyst fluid tumor markers play an important diagnostic role. Cyst fluid CEA level is the most accurate tumor marker for diagnosis of a mucinous cystic neoplasm, with a diagnostic accuracy of 79% when levels are greater than 192 ng/mL [2].

Cyst fluid CEA level, unfortunately, cannot predict the presence or absence of malignancy. As the cellular content of cyst fluid aspirates is frequently suboptimal, it was hypothesized that cyst epithelial cells shed their DNA into the fluid during cell turnover. As pancreatic carcinogenesis is characterized by the accumulation of genetic defects, these mutations should be detectable through cyst fluid DNA analysis. Additionally, an evolving or frankly malignant cyst should have a higher DNA content due to a higher cell turnover rate, and more mutations should be present. To test this hypothesis, molecular analysis of EUS-guided cyst fluid aspirates was performed by way of polymerase chain reaction amplification of individual microsatellite markers associated with pancreatic carcinogenesis, along with direct sequencing of the k-ras-2 gene [15]. The DNA amount within the fluid (reported as optical density), number of mutations, and temporal sequence of mutations were shown to accurately predict the presence of malignancy. A first-hit k-ras mutation followed by an allelic loss was highly predictive of malignancy. Although based on this small preliminary experience, molecular analysis may serve as an adjunct test in the evaluation of cystic pancreatic lesions and is currently being evaluated in a multicenter study.

Although mucinous cystic tumors are to be considered premalignant, the natural history of these tumors and true malignant risk are largely unknown. Therefore, surgical resection is not necessarily required in all patients. Management decisions should be based on many factors including the characteristics of the tumor itself, the general age and condition of the patient, and the availability of surgical expertise. Factors that would favor a more conservative approach would include advanced patient age or comorbidity; a pancreatic cyst that was small, thin-walled, and noninvasive; a low cyst-fluid CEA level; and a molecular analysis that revealed a low amount of poor-quality DNA with an absence of mutations. A more aggressive approach is often warranted in younger patients who have fewer comorbid factors, a larger or symptomatic cyst, and the availability of a surgeon experienced and expert at partial pancreatic resection. Frankly malignant cysts, when diagnosed, should be surgically resected if the patient is an acceptable operative candidate.

Solid and papillary epithelial neoplasm

This is a rare tumor of low malignant potential that has been reported under various names including solid and pseudopapillary neoplasm, and solid and cystic tumor. Solid and papillary epithelial neoplasm has a predilection for young women, with over 90% of cases being reported in women under the age of 35, usually in non-Caucasians (Asian or African-American) [19]. The tumor is slow growing and may cause little or no discomfort until large.

Because of its indolent nature, solid and papillary epithelial neoplasm is often diagnosed when it has attained considerable size (on average, >10 cm). It is a hypovascular well-circumscribed mass, most often located in the pancreatic body/tail segments (Fig. 6A–C). Depending on the extent of necrosis and hemorrhage within the tumor, a solid and papillary epithelial neoplasm may appear almost completely cystic or solid, though a poorly enhancing mass with central and scattered necrosis is the most characteristic finding.

EUS-FNA can generally provide an accurate preoperative diagnosis, which can then direct the surgical approach (open or laparoscopic resection) [20].

Lymph node and liver metastases occur rarely and late in the disease. Complete surgical excision is generally possible and curative.

Cystic islet cell tumor

Pancreatic neuroendocrine (islet cell) tumors are usually hypervascular solid masses and may be benign or malignant. Those that produce excessive amounts of active polypeptide hormones, such as insulin or glucagon, are generally diagnosed while the tumors are small (1–3 cm). Tumors that are "nonfunctional" are more likely to be diagnosed after they have attained large size; although in the authors' experience, smaller incidental nonfunctioning tumors are being detected, given increased use of abdominal imaging modalities [21–23].

Rarely, an islet cell tumor may be largely cystic (Fig. 7A, B). By imaging, these cannot be distinguished from other pancreatic cystic masses, especially if the mass is less than 2 cm in diameter. The diagnosis may be suggested

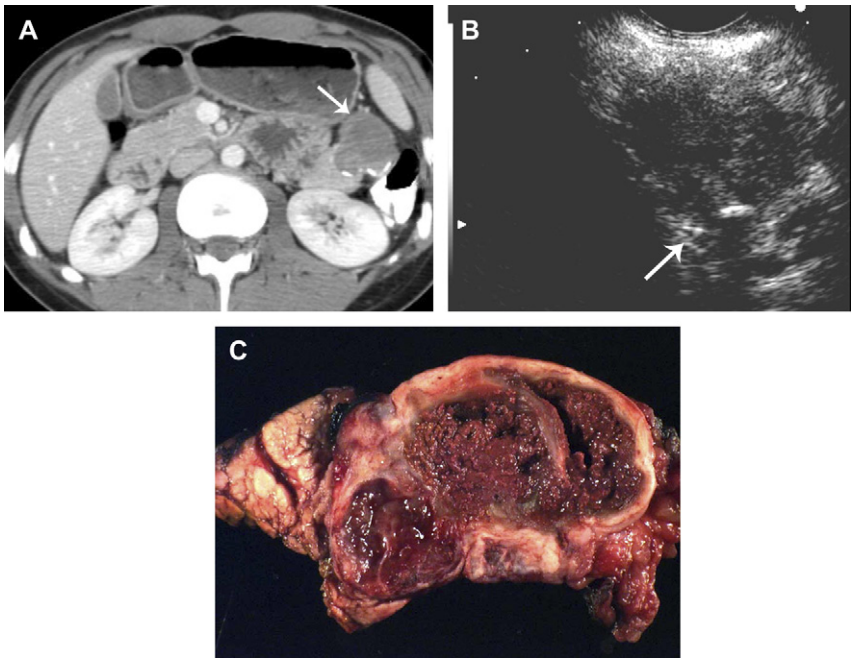

Fig. 6. Twenty-two-year-old woman who has a solid and papillary epithelial neoplasm. (*A*) Contrast-enhanced CT shows a mass (*arrow*) arising from the pancreatic tail. Peripheral calcification and enhancing nodules are seen along with cystic or necrotic areas. (*B*) EUS shows a complex cystic mass with peripheral calcifications (*arrow*). (*C*) Photograph of resected mass shows an encapsulated tumor with foci of cystic necrosis and solid tumor.

by evidence of hypervascular liver metastases or clinical signs or symptoms such as palpitations, tremor, and headache (hypoglycemia due to an "insulinoma").

EUS imaging typically reveals a thick-walled unilocular cyst, and EUS-FNA can provide a definitive diagnosis on the basis of cytologic immunostaining patterns. Surgical resection is the treatment of choice.

SUMMARY

Pancreatic cystic lesions represent an increasingly common diagnostic and therapeutic challenge. Many cystic masses are pancreatic pseudocysts, and this diagnosis is usually made readily by clinical history and imaging findings of a unilocular pancreatic or peripancreatic mass with associated findings of acute or chronic pancreatitis. CT and MR allow accurate depiction of the morphology of cystic pancreatic masses, and when in doubt, EUS-FNA can provide diagnostic information based on fluid viscosity, CEA and/or amylase level, and molecular analysis. In patients who have large, symptomatic, or complex cystic neoplasms and are suitable candidates for major surgery, preoperative

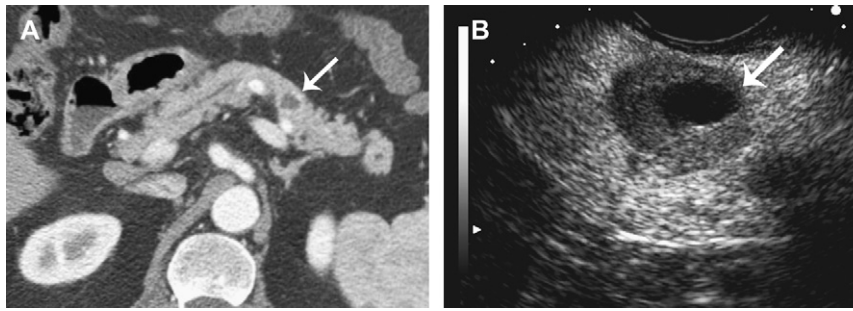

Fig. 7. Sixty-six-year-old man who has a cystic islet cell tumor. (*A*) Contrast-enhanced CT shows a small mass (*arrow*) in the pancreatic body that is mostly cystic, with a briskly enhancing wall. (*B*) EUS confirms the small mass (*arrow*) with a central cystic space and a thicker wall than was evident on CT.

evaluation by other imaging tests or cyst aspiration may be unnecessary. For lesions that are small, asymptomatic, or occur in patients who have high surgical risk, further evaluation with endoscopic ultrasonography is often useful.

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GASTROENTEROLOGY CLINICS
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Intraductal Papillary Mucinous Neoplasia

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Intraductal papillary mucinous neoplasia (IPMN) is a neoplastic disorder of varying degree and extent that affects the pancreatic ductal epithelium. Synonymous with mucinous duct ectasia, mucin-producing tumor of the pancreas, and duct ectatic mucinous cyst adenoma in the past, this disorder was formally defined in 1996 by the World Health Organization as an "intraductal mucin-producing neoplasm with tall columnar mucin-containing epithelium with or without papillary projections, involving the main pancreatic duct and/or major side branches, and lacking ovarian stroma characteristic of mucinous cystic neoplasms" [1]. A disorder with presentations varying from an asymptomatic incidental finding to obstructive jaundice, there are little natural history data to predict the risk of neoplastic progression. Previously believed to be a rare disorder affecting the Far East, and only first described in 1982 [2], IPMN has been recognized at a growing rate, likely because of improved recognition rather than increasing incidence. This may be because of incidental detection of asymptomatic lesions resulting from widespread use of cross-sectional abdominal imaging. Now, with better classification systems, retrospective reviews have reclassified cases predating 1982 in the United States [3]. This article discusses the pathogenesis and pathology of IPMN, clinical diagnosis aided by imaging modalities, management, and surveillance.

PATHOLOGIC FEATURES

IPMNs are characterized by cystic dilatation of the main pancreatic duct or its branches as the result of an intraductal proliferation of mucin-producing cells

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that form papillae, at least focally. The most important observation on gross examination is the communication of the cyst with the pancreatic ductal system; this finding helps to distinguish IPMNs from mucinous cystic neoplasms (MCNs), which do not typically communicate with the ductal system. Although most IPMNs arise within the head of the gland, they can be seen in any location and can occasionally involve the entire ductal system [4]. Because IPMNs can involve the main pancreatic duct (main duct–type) or its branches (branch duct–type), the macroscopic appearance depends on the segment and extent of the duct involved. IPMNs can appear as a solitary cyst localized to one segment of the pancreatic duct; as a diffusely dilated pancreatic duct (either caused by neoplastic involvement of the entire duct, or as the result of upstream dilatation); or as multiple cysts within the pancreas (Fig. 1). Main duct IPMNs tend to be larger and intraductal papillary structures or excrescences are often seen on gross examination; communication with the main pancreatic duct is easily documented. Branch duct IPMNs, however, tend to be smaller, may not have a readily identifiable proliferative epithelial lining, and the communication with the main pancreatic duct can be difficult to ascertain. When an IPMN is incised, mucinous material is usually evident within the cyst cavity. Careful inspection of the cyst wall may reveal firm, white areas that are suspicious for invasive adenocarcinoma.

Microscopically, the dilated ducts are lined by mucinous epithelium with areas of papillae formation. The papillary architecture can be composed of villous-appearing structures, or can be quite complex with abundant branching and epithelial proliferation (Fig. 2). Various histologic subtypes have been described and include intestinal; pancreaticobiliary; oncocytic; and gastric (or branch duct) types [4–8]. Intestinal-type IPMNs can resemble intestinal villous adenomas with villous architecture and columnar epithelial cells containing

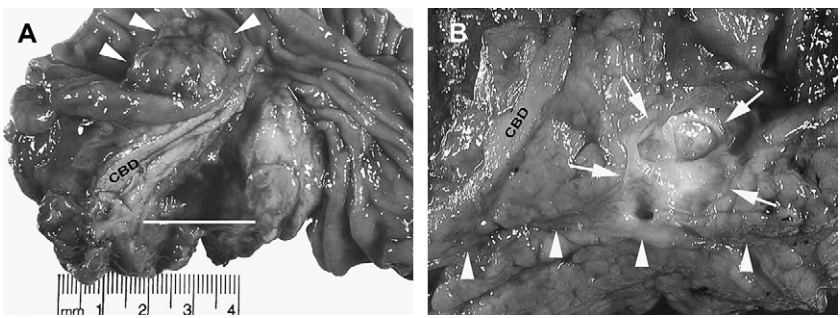

Fig. 1. Gross appearance of IPMN. (*A*) In this example, the pancreatic duct is markedly dilated (*white bar*) and the lining of the duct is irregular and thickened (*). This IPMN is associated with a mucinous adenocarcinoma, which has invaded through the duodenal wall and protrudes into the lumen of the duodenum (*arrowheads*). CBD, common bile duct. (*B*) This is an example of a branch duct–type IPMN. The common bile duct (CBD) and main pancreatic duct (*arrowheads*) are unremarkable. A cyst with a smooth lining is noted to be in communication with a branch of the main pancreatic duct (*arrows*).

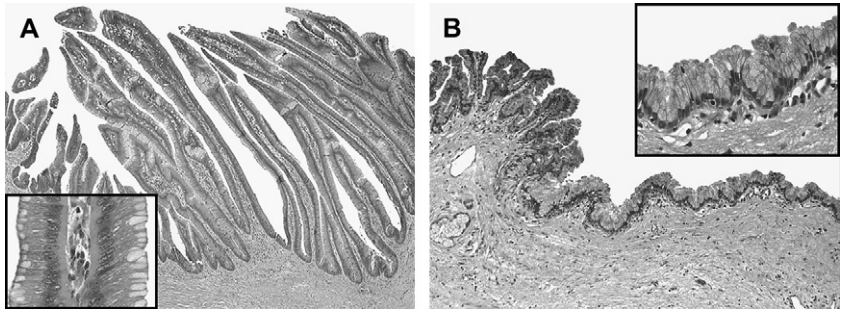

Fig. 2. Microscopic appearance of IPMN. (*A*) Long villous papillary structures protrude into the lumen of the cyst that involves the main pancreatic duct. At higher magnification (inset), the papillae are lined by columnar, mucin-producing epithelial cells with overlapping, elongated nuclei containing stippled chromatin (intestinal-type IPMN). (H&E ×40, inset ×400). (*B*) This branch duct–type IPMN is lined by columnar, mucin-producing epithelial cells; most of the lining is flat or undulating, but there are focal areas of short papillae formation. At higher magnification (inset), the epithelial cells resemble gastric foveolar cells with apical mucin and small, basally oriented nuclei (gastric-type IPMN). (H&E ×100, inset ×400).

elongated, pseudostratified nuclei with coarse chromatin, but they can also be lined by cells that resemble gastric foveolar epithelium. Pancreaticobiliary-type IPMNs tend to exhibit complex, arborizing papillary structures; the epithelium is cuboidal, the cytoplasm is more acidophilic and less obviously mucinous, and the nuclei are rounded and contain prominent nucleoli. Gastric-type IPMNs exhibit shorter and thicker finger-like papillae and are lined by gastric foveolar-type epithelium, with basally oriented nuclei and mucin-filled cytoplasm. These histologic subtypes also express different apomucins, as detected by immunohistochemistry. Intestinal-type IPMNs tend to express MUC2 and MUC5AC, the pancreaticobiliary-type typically express MUC1 and MUC5AC, and the gastric-type tends to only express MUC5AC [6,8,9]. Interestingly, IPMNs with prominent MUC1 expression tend to be high grade, associated with invasive carcinoma, and have a significantly worse survival [6,10].

IPMNs can be classified based on the degree of cytoarchitectural atypia as IPMN adenoma (benign with low-grade atypia or dysplasia); IPMN borderline (moderate atypia); or intraductal papillary mucinous carcinoma (severe atypia without evidence of invasion) [11]. Histopathologically, the differential diagnosis of IPMN includes MCN and pancreatic intraepithelial neoplasia. One important finding that distinguishes IPMN from MCN is the communication of the pancreatic ductal system with the cyst (MCNs are not typically connected to the ductal system), but documenting this communication can be difficult, especially with branch duct–type cysts. Histologically, the main distinguishing feature is the presence of an "ovarian-type stroma," which is required for the diagnosis of MCN [12,13]. The distinction between IPMN and pancreatic intraepithelial neoplasia can also be challenging, especially when the cysts are

small and papillary structures are not a prominent feature, as can be encountered particularly in branch duct–type IPMNs. In 2004, a group of international experts on precursor lesions of pancreatic cancer proposed a consensus classification for IPMN and pancreatic intraepithelial neoplasia (Box 1) [14]. Although these definitions improved interobserver agreement [15], there are cysts that fall into a gray area and are difficult to classify. For example, cysts that are between 0.5 and 1 cm in size, or cysts that lack characteristic papillary or villous morphology, may be either large pancreatic intraepithelial neoplasia or flat IPMNs. Epithelial cysts of this type have been described in the literature as "mucinous nonneoplastic cysts"; retention cysts (with mucinous lining); and "mucinous ductal ectasia" [16–20]. For cysts such as these that are difficult to classify as nonneoplastic or preneoplastic (pancreatic intraepithelial neoplasia or IPMN), it has been suggested to use a descriptive term, such as "proliferative intraductal lesion of undetermined type," until additional markers are identified to classify these lesions correctly [15].

CLINICAL PRESENTATION

The presentation spectrum of IPMN varies immensely, from that of silent and incidental disease to symptomatic obstructing lesions. Indeed, the detection of incidental IPMN has increased because of widespread use of abdominal imaging modalities [21,22]. The incidental IPMNs, in the authors' experience, are small branch duct lesions mimicking small cysts; however, asymptomatic main duct disease can also present as incidental main duct dilatation. Advanced IPMN is more likely to present symptomatically with upper abdominal or back pain [23,24], whereas jaundice may also occur if there is involvement of the ampulla or tumor or cyst compression of the common bile duct. Not infrequently, patients come to clinical attention with acute or relapsing pancreatitis caused by secreted mucin obstructing the main pancreatic duct. Chronic duct obstruction caused by main duct IPMN may result in pancreatic insufficiency, with steatorrhea, weight loss, and diabetes at the time of presentation [21,22].

Box 1: Definitions of pancreatic intraepithelial neoplasia and IPMNs

Pancreatic intraepithelial neoplasia is a microscopic papillary or flat, noninvasive, epithelial neoplasm arising in the pancreatic ducts. Pancreatic intraepithelial neoplasia is characterized by columnar-to-cuboidal cells with varying amounts of mucin and degrees of cytologic and architectural atypia. Pancreatic intraepithelial neoplasia usually involves ducts <5 mm in diameter.

IPMN is a grossly visible, noninvasive, mucin-producing, predominantly papillary, or rarely flat, epithelial neoplasm arising from the main pancreatic duct or branch ducts, with varying degrees of duct dilatation. IPMNs usually produce a lesion >1 cm in diameter and include a variety of cell types with a spectrum of cytologic and architectural atypia.

The differential diagnosis of IPMN is usually generated from abnormal findings on cross-sectional imaging, and may also include chronic pancreatitis, pancreatic pseudocyst, MCN, and ampullary stenosis with a resultant dilated pancreatic duct.

IMAGING AND ASSESSMENT

There are several imaging studies that are helpful in evaluating patients with IPMN, including endoscopic retrograde cholangiopancreatography (ERCP), CT, magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS). Most patients generally come to attention based on CT findings suspicious for IPMN. CT scans are performed to evaluate patient complaints of abdominal or back pain, but findings are often serendipitous.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

ERCP historically had been the diagnostic test of choice to assess IPMN. Main duct disease with a bulging ampullary orifice extruding mucus is heralded as the classic finding (Fig. 3). Filling defects representing mucin or mural nodules are also considered hallmark findings. In the setting of significant main duct disease, washing catheters can be introduced into the pancreatic duct for mucin aspiration to send for cytology and molecular analysis. Additionally, there is limited experience using ultra-thin "baby scopes" that can be introduced into a dilated main pancreatic duct to assist in diagnosis and surgical planning [25].

The diagnosis of IPMN is fairly straightforward for main duct IPMN; it can be more challenging for branch duct variants because these can mimic true mucinous or serous cystic neoplasms. Demonstration of communication between the pancreatic duct and cystic spaces helps to confirm the diagnosis of branch duct IPMN, and ERCP can be helpful in this situation; however, a lack of communication at ERCP does not exclude branch duct disease because viscous

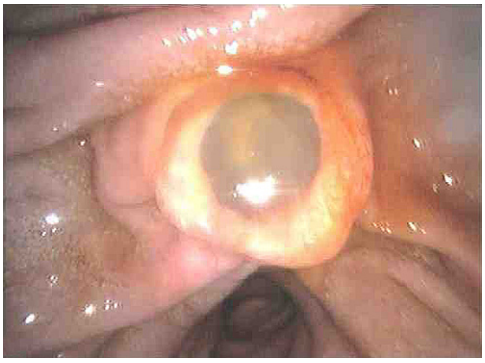

Fig. 3. Endoscopic image of a dilated ampullary orifice extruding mucus (fish mouth deformity).

mucin may obstruct the flow of contrast. With the advent of MRCP, EUS, and helical CT, these imaging modalities are replacing ERCP in the evaluation and assessment of IPMN.

CT AND MAGNETIC RESONANCE CHOLANGIOPANCREATOGRAPHY

Both CT and magnetic resonance provide accurate depiction of the characteristic morphologic abnormalities in IPMN [26–30]. Both modalities can display cross-sectional images in multiple planes, or even in curved planes of reformation, which may aid in recognition of the presence of cystic dilatation of the pancreatic duct, the presence of mural nodules, and communication with cystic masses. MRCP is especially useful in depicting ductal abnormalities (Fig. 4).

CT and magnetic resonance can aid in the differential diagnosis and staging of IPMN. The presence of a communication between a pancreatic cystic lesion and the main pancreatic duct is one of the most reliable findings for IPMN [26,27], being absent in most cases of MCN and serous cystadenomas. Side branch IPMN may resemble serous cystadenoma (Fig. 5); the presence of mural nodules favors IPMN [26–28]. Main duct IPMN and chronic pancreatitis may both result in a dilated duct and glandular atrophy; calcifications favor pancreatitis, whereas mural nodularity and protrusion of the major papilla into the duodenum favor IPMN (Fig. 6).

The following morphologic features have been identified on CT and magnetic resonance as favoring invasive malignancy in patients with IPMN: involvement of the main pancreatic duct; marked dilatation of the pancreatic

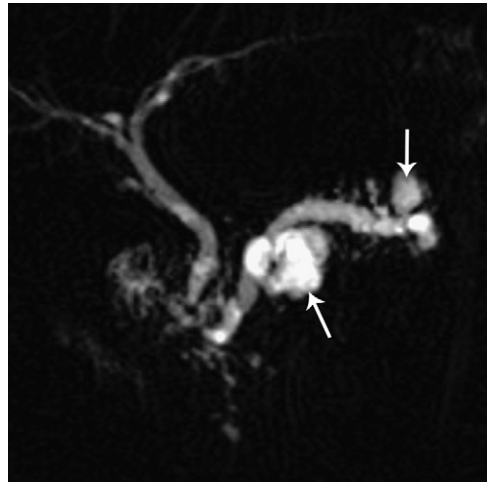

Fig. 4. Main and side branch IPMN. Coronal plane magnetic resonance cholangiopancreatography shows cystic masses (*arrows*) that communicate with a dilated main pancreatic duct. The bile ducts are normal.

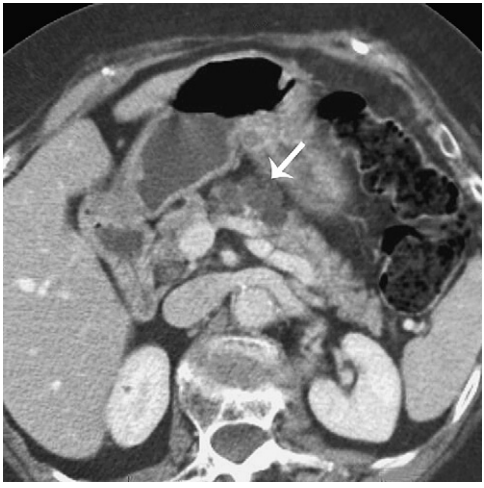

Fig. 5. Side branch IPMN. Axial CT sections show multiple cysts in the head and neck portions of the pancreas (*arrow*) that communicate with the pancreatic duct, which is of normal caliber in the body-tail segment.

duct (>10 mm); diffuse or multifocal dilatation of the pancreatic duct; mural nodules or a solid mass along the pancreatic duct; calcified material within the pancreatic duct; obstruction of the common bile duct; and lymph node or distant metastases.

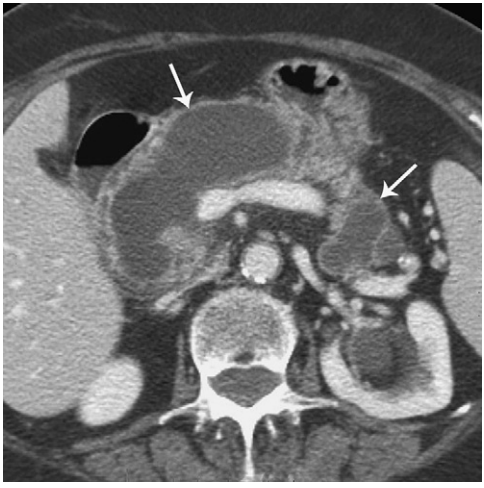

Fig. 6. Main duct IPMN with carcinoma in situ. Axial CT sections show massive dilatation of the pancreatic duct (*arrows*).

ENDOSCOPIC ULTRASOUND

EUS has been a major advance in imaging pancreatic lesions given its coupling of high-frequency ultrasonography and proximity to the area of interest. High-resolution imaging is possible, which has improved the ability to evaluate pancreatic solid and cystic lesions; hence, EUS is increasingly used for this purpose. When evaluating cystic pancreatic lesions or duct dilation, IPMN should be considered in the absence of parenchymal changes typical of chronic pancreatitis [31]. Accurate measurements of duct diameter and cystic branch ducts can be obtained with EUS, and most importantly, mural nodules can be readily identified (Figs. 7 and 8). The findings of a main duct diameter greater than or equal to 10 mm, branch duct greater than 40 mm in size with irregular septations, or the presence of large mural nodules greater than 10 mm are highly suggestive of malignancy, which can be accurately assessed with EUS [21].

EUS-guided fine-needle aspiration (EUS-FNA) allows for accurate targeting of lesions for aspiration biopsy. Aspirates can be obtained from cystic branch ducts or the main duct itself, where the aspiration of viscous mucin supports the diagnosis of IPMN. Cytologic analysis of pancreatic juice and mucin can establish the diagnosis, but in the authors' experience, suffers from poor sensitivity. Mural nodule aspirates, however, increase the accuracy of the diagnosis of malignant IPMN [32]. It is the authors' practice to perform EUS-FNA on all mural nodules; adherent mucin can sometimes mimic true malignant nodularity.

MANAGEMENT

There are two approaches to the management of IPMN: surgical and conservative. The management decision is generally based on the operative candidacy of the patient. Poor surgical candidates are followed conservatively and receive palliative therapy in the setting of true malignancy. Resection should be considered in appropriate surgical candidates, respecting the fact that the

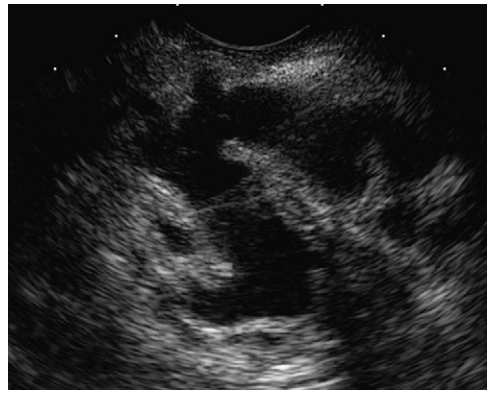

Fig. 7. Linear EUS image of mixed-type IPMN affecting the pancreatic head.

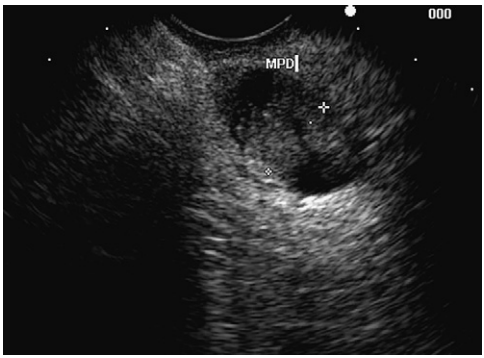

Fig. 8. Mural nodule. Linear EUS image of a 13-mm (*calipers*) main pancreatic duct (MPD) with an intraductal mural nodule.

natural history and malignant risk of small (<2 cm) branch duct disease is unknown.

Definitive criteria for resection in appropriate patients include symptomatic lesions, main duct IPMN greater than 10 mm in diameter, branch duct IPMN greater than 30 mm, and presence of mural nodules. These findings are associated with coexisting malignancy. Incidental asymptomatic lesions without the aforementioned findings have a low risk of prevalent cancer and probable low risk of progressing to invasive cancer in short-term follow-up (12–36 months) [13].

Three large surgical series have been recently published, which have greatly enhanced the understanding of this disease [33–35]. The findings of these collective studies from the Memorial Sloan Kettering Cancer Center and the Adelaide and Meath Hospital in Dublin, Ireland, the Massachusetts General Hospital and the University of Verona, Italy, and Johns Hopkins University Hospital, incorporating 339 patients, are consolidated and presented in Table 1. The Salvia and colleagues [34] study was limited to only patients with main duct disease.

Demographics of the population reveal an average age in the seventh decade of life, with an almost equal male/female ratio. Most (73%–81%) patients were symptomatic: abdominal pain (49%–65%); weight loss (29%–44%); jaundice (17%–18%); acute pancreatitis (13%–23%); diabetes (12%–14%); and steatorrhea (7%–10%). Jaundice, weight loss, and new-onset diabetes were independent predictors for the presence of carcinoma across these surgical series [33–35].

Approximately two thirds of patients underwent pancreaticoduodenectomy in all three series. Distal pancreatectomy was performed in 12% to 23%, total pancreatectomy in 10% to 19%, and central enucleations in 1% to 2% of patients. Early histology, defined as IPMN adenoma, was found in 10% to 12% of patients. Borderline dysplasia, carcinoma in situ, and invasive carcinoma were seen in 15% to 29%, 18% to 34%, and 38% to 48% of patients,

Table 1
Surgical studies of patients with intraductal papillary mucinous neoplasia

Study Characteristics	D'Anjelica et al [33] (N = 63)	Salvia et al [34] (N = 140)	Sohn et al [35] (N = 136)
Demographics			
Mean age (years)	70	65	67
Male/female ratio	31:32	71:69	78:58
Smokers (%)	45	56	NR
Symptoms on presentation			
Any symptoms (%)	81	73	NR
Abdominal pain (%)	49	65	52
Weight loss (%)	43	44	29
Jaundice (%)	18	17	17
Acute pancreatitis (%)	NR	23	13
Diabetes (%)	14	12	NR
Steatorrhea (%)	10	7	NR
Distribution of pancreatic duct location of IPMN			
Main duct (%)	69	100	28
Branch duct (%)	31	NR	46
Combined (%)	NR	NR	26
Type of surgery			
Pancreaticoduodenectomy (%)	66	63	71
Distal pancreatectomy (%)	23	17	12
Total pancreatectomy (%)	10	19	15
Central pancreatectomy (%)	1	1	2
Results of surgical pathology			
Adenoma (%)	10	12	10
Borderline (%)	15	29	18
Carcinoma in situ (%)	27	18	34
Invasive carcinoma (%)	48	41	38
5-year postoperative survival			
Patients with benign disease (%)	90[a]	100[a]	77[b]
Patients with malignant disease (%)	58[a]	60[a]	43[b]

Abbreviations: IPMN, intraductal papillary mucinous neoplasia; NR, not reported.
[a]Disease-specific survival.
[b]Overall survival.
Data from McGrath K, Slivka A. Diagnosis and management of intraductal papillary mucinous neoplasia. Nat Clin Pract Gastroenterol Hepatol 2005;2:320.

respectively. Five-year postoperative survival ranged from 77% to 100% for those patients with benign disease (IPMN adenoma and borderline dysplasia). Those with frank malignancy had 5-year survival rates of 43% to 60%, which is significantly better than the dismal survival of solid ductal adenocarcinoma of the pancreas. These surgical series also attempted to determine the time course of progression to malignancy by comparing ages of patients with benign and

malignant disease. There was a 5- to 6-year difference in age between patients with benign and malignant disease, suggesting that progression from IPMN adenoma to invasive cancer may occur over 5 to 10 years. Lead-time bias, however, was not accounted for; the true malignant risk and rate of progression remains unknown.

Based on surgical data, a consensus guideline statement recommends resection of all main duct– and mixed–type IPMNs in good surgical candidates with a reasonable life expectancy, given the reasonable 5-year survival data for invasive carcinomas [13]. Recommendations regarding branch duct disease are somewhat more controversial. The frequency of malignancy in branch duct IPMN has ranged from 6% to 46% (mean, 25%) [13,36–42]. One must respect referral bias in this instance, however, where larger, more ominous branch duct lesions are being resected. It seems that asymptomatic, incidentally detected branch duct IPMN has a low prevalence of invasive cancer [37,39,42]. In the Sugiyama and colleagues [42] study, 53% of branch duct IPMNs undergoing resection were asymptomatic lesions, with none harboring invasive cancer. The strongest predictors of malignancy in branch duct disease are size greater than 30 mm and the presence of mural nodules [39,42]. Good operative candidates with either of these findings, or a symptomatic lesion, should undergo surgical resection. Controversy revolves around the asymptomatic branch duct IPMN less than 30 mm in size without mural nodularity. The natural history of smaller incidental lesions is unknown. At the University of Pittsburgh, decisions are tailored based on the individual clinical scenario and surgical risk (Fig. 9). High-risk stigmata are defined as main duct diameter greater than 10 mm, branch duct size greater than 30 mm, or presence of a mural nodule. Small lesions are defined as less than 2 cm in size. The authors use EUS-FNA in most cases to assess better the morphologic features and obtain a cytologic sample. Because cytology has a low sensitivity for detecting mucinous lesions by EUS-FNA, the authors also perform a detailed molecular analysis of aspirated fluid from these lesions. Although still an early experience, they have found that a high quantity of good-quality DNA with associated K-*ras* mutation or allelic loss is predictive of malignancy in mucinous pancreatic cystic lesions [43]. The authors consider this molecular analysis an adjunct to other parameters, such as carcinoembryonic antigen level and cytology.

SURVEILLANCE

Because IPMN is generally a multifocal disease, postoperative surveillance is necessary unless a total pancreatectomy is performed. There is a 10% recurrence rate in patients with noninvasive IPMN who undergo partial pancreatic resection with negative margins [44]. Unfortunately, there are no published data to define the type and frequency of surveillance. The recent consensus guideline suggests yearly CT or magnetic resonance for patients with benign resected disease, with 6-month intervals recommended for those with malignant disease [13]. The authors recommend that any perceived changes seen on surveillance to suggest recurrence be investigated with EUS ± FNA.

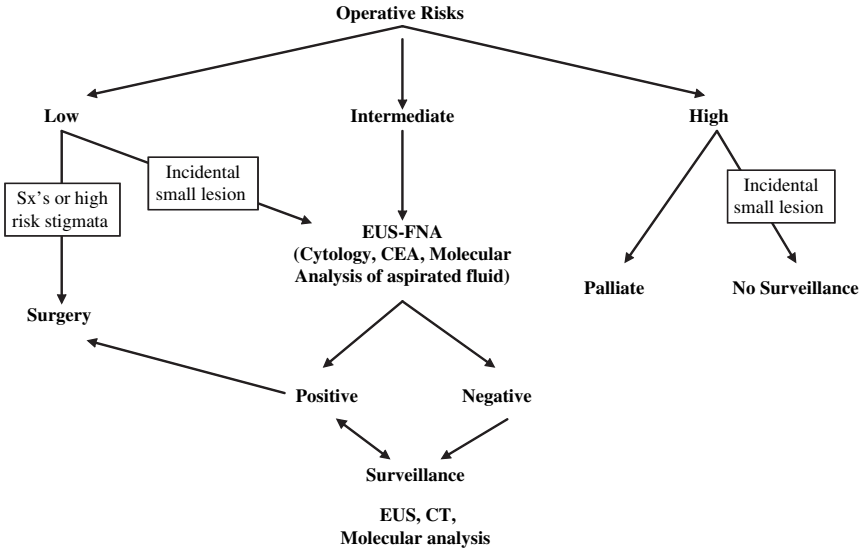

Fig. 9. Algorithm for management of IPMN at University of Pittsburgh Medical Center. CEA, carcinoembryonic antigen; EUS, endoscopic ultrasound; FNA, fine-needle aspiration.

SUMMARY

IPMN is being increasingly recognized. Harbingers of malignancy include symptoms of jaundice, weight loss, or new-onset diabetes. Radiographic findings associated with malignancy include a main duct diameter greater than 10 mm, a branch duct greater than 30 mm, or the presence of a mural nodule. Resection should be considered in appropriate operative candidates with any of the aforementioned findings. EUS-FNA can be very helpful in further evaluation of lesions to aid in clinical decision making. In the absence of findings that correlate with malignancy, natural history is unknown. Management of these patients is controversial, and should be individualized based on surgical risk. A conservative approach in this setting can be recommended, with enrollment in a surveillance program with surgical intervention should high-risk stigmata evolve. A tremendous amount will be learned about this disease in the next decade given heightened awareness, improved diagnosis, and creation of surgical and surveillance databases.

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Multimodality Therapy for Pancreatic Cancer

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The 5-year survival of patients with pancreatic cancer has remained 3% to 6% for decades [1–3] with some estimates as low as 0.4% [4,5]. Patients typically present with advanced disease and have a median survival time of 3 to 6 months [2]. Although improved survival has been observed following complete surgical resection with microscopically negative margins (R0 resection), fewer than 10% of patients have resectable tumors at the time of diagnosis [6,7]. An analysis of more than 100,000 patients entered into the National Cancer Database demonstrated that fewer than 9% of patients with pancreatic cancer underwent surgery [3], whereas 58% of patients received no treatment whatsoever.

For the select group of patients with localized pancreatic cancer, recent advances in surgical technique combined with specialized care at high-volume centers have increased the 5-year survival rate to approximately 10% to 24% [3,4]. Although surgery remains the cornerstone of therapy for pancreatic cancer, most patients undergoing resection eventually develop metastases and succumb to their disease [8]. This observation suggests that recurrence represents either incomplete surgical resection of the primary tumor or the presence of occult metastases at the time of surgery. As a result, multimodality treatments including chemotherapy and radiation have been used with variable results before (neoadjuvant) and after (adjuvant) surgical resection to improve survival [9]. Neoadjuvant radiotherapy was first reported for patients with resected pancreatic adenocarcinoma in 1980 but demonstrated only a modest reduction in local recurrence rates without improving 5-year survival [10–12].

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Neoadjuvant chemoradiotherapy (CRT) with novel agents has recently gained in popularity and may improve survival for patients with resectable tumors [13–16]. The relative value of each component in the multimodality treatment for pancreatic adenocarcinoma remains unknown. Surgery has been shown to prolong survival [3] and provide palliation for symptoms of pancreatic cancer [6,17]. The role of radiation therapy (RT) is more controversial [9,18–21], but data regarding newer methods of RT (eg, intensity-modulated RT and stereotactic radiosurgery [Cyberknife; Accuray, Sunnyvale, California]) and dosing regimens for RT are promising [22–24]. In view of data that gemcitabine prolongs the survival of patients with resected [25] and metastatic pancreatic cancer [26], chemotherapy regimens including gemcitabine will likely remain an important component of future multimodality regimens.

SURGICAL RESECTION OF PANCREATIC CANCER

Although surgery offers the longest survival advantage of any single modality for patients with pancreatic cancer, 5-year survival rates remain in the 10% to 25% range after resection [27]. To clarify the role of surgical resection and neoadjuvant therapy for pancreatic cancer, one must consider several outcome variables including the status of the surgical resection margin, presence of lymph node involvement, and the extent of resection.

The goal of surgical therapy is microscopically complete removal of tumor. A positive surgical margin is the most important prognostic factor indicating short survival following resection [28–31]. Microscopically complete resection (R0) confers the longest survival benefit [32]. Patients with grossly complete resection but microscopically positive margins on histologic examination (R1) and those with grossly positive resection margins (R2) fare progressively worse [6,31,32]. Evaluation of the resection margins in pancreatic surgery has undergone considerable refinement. Previously, only the margin of the transected pancreas was evaluated. The status of the circumferential soft tissue margin adjacent to the tumor was not reported in earlier series, even though this is the margin most commonly involved by tumor. Incomplete evaluation of the surgical margin makes comparisons between older and more recent studies of surgical resection inherently unreliable. Six pathologic margins should be evaluated by the pathologist and reported individually depending on the type of resection performed (proximal versus distal pancreatectomy): (1) the pancreatic transection margin, (2) the bile duct margin, (3) the retroperitoneal soft tissue margin, (4) the proximal bowel margins, (5) the distal bowel margins, and (5) the portal vein margin.

There is no commonly accepted definition of surgically resectable pancreatic cancer. Typically, a resectable patient is a medically fit individual without pancreatic cancer extending beyond the immediate peripancreatic nodal basin or involving the superior mesenteric artery, celiac axis, aorta, and inferior vena cava. Modern surgical techniques allow for resection and reconstruction of any peripancreatic vessel adjacent to locally infiltrating tumors including the superior mesenteric vein–portal vein complex. Elective resection of superior

mesenteric vein–portal vein adds significant complexity to the procedure but has been shown to be safe and oncologically effective [33,34]. Resection and reconstruction of the superior mesenteric vein–portal vein complex during a Whipple procedure provides patients with the same survival benefits as surgery for tumors that do not involve these venous structures [34]. European and Japanese data are more pessimistic regarding the survival benefit of superior mesenteric vein–portal vein resection and reconstruction [35,36]. Patients with tumors arising near the superior mesenteric vein–portal vein seem to respond better than those with large tumors that traverse the pancreatic neck to involve the vein [33].

Approximately one third of patients present with locally advanced tumors but no evidence of metastasis. This large subset of patients may be termed "marginally resectable" or unresectable at the time of initial evaluation. The likelihood of a positive surgical margin is highest in this group. Resection and reconstruction of the superior mesenteric artery, hepatic artery, or celiac artery is not considered standard care. Data from a 1973 study on regional pancreatectomy (en bloc resection of pancreas, portal vein, and superior mesenteric artery) suggested unacceptably high mortality (23%) after surgery without a clear oncologic benefit [37,38]. A follow-up report published 25 years later demonstrated greatly improved mortality (5.3%) [39] but no substantial improvement in 5-year survival when comparing regional pancreatectomy with standard pancreatectomy.

In the past, total pancreatectomy was thought to be superior to the standard Whipple procedure because total pancreatectomy eliminated the possibility of a positive transection margin and the risk of pancreatic leak. A retrospective review of over 600 pancreatic resections from Johns Hopkins included 37 total pancreatectomies performed for tumors of the pancreatic head, neck, and uncinate process [32]. Median survival after total pancreatectomy was significantly worse than following Whipple resection (11 versus 18 months, $P = .05$). In combination with the long-term medical sequelae of brittle diabetes, the lack of a demonstrable survival benefit following total pancreatectomy limits this operation to the rare patient with a diffuse or multifocal pancreatic cancer who provides the possibility of a negative surgical margin after resection.

Finally, node-positive patients have a statistically higher rate of recurrence and shorter survival by comparison with node-negative patients [6,40]. An analysis of SEER data demonstrated that survival after curative pancreatic resection is proportional to the number of resected lymph nodes on a stage-for-stage basis [41]. This fact suggested that extended lymphadenectomy might improve cure rates after surgery, and an early prospective European trial suggested a modest survival benefit for node-positive patients undergoing extended lymphadenectomy [40]. A subsequent prospective trial of 294 patients at Johns Hopkins, however, demonstrated no obvious survival benefit after extended dissection including distal gastrectomy and extended retroperitoneal lymphadenectomy despite the expense of increased operative times and blood loss [42]. Extended lymphadenectomy is no longer routinely performed in the United States.

RECURRENCE AFTER R0 SURGICAL RESECTION

Surgical patients with the most favorable outcome are those with margin-negative, node-negative resections for small tumors. Five-year survival reached 41% in this small subset of 64 patients among 1000 consecutive pancreatic resections at Johns Hopkins and is not typical for the pancreatic cancer population as a whole [21].

In the absence of adjuvant or neoadjuvant therapy, recurrence after R0 resection was observed in 81% of patients with periampullary cancer [27]. Local recurrence was documented in 33% of patients, whereas distant metastases were seen in 66%. Most metastases were intra-abdominal. The time to recurrence was equally disappointing: within 6 months of R0 resection, 10% of patients developed local recurrence and 41% developed distant metastases.

Hepatic metastases were reported in 57% to 92% of all resected patients, whereas local and hepatic recurrence accounted for 97% of all recurrences [6,43]. Isolated lung metastases were exceptionally rare (approximately 3%) [6]. About one half of recurrent hepatic metastatic disease was apparent within 6 months of potentially "curative" surgery (Table 1). It is likely that most surgical patients have microscopic metastases that escape detection by preoperative CT, endoscopic ultrasound, and intraoperative exploration of the abdomen. This hypothesis is supported by a recent study of 11 patients who underwent an R0 Whipple procedure but displayed elevated preoperative serum levels of CA19-9 and developed isolated liver metastases during follow-up [44]. By extrapolating from the CA19-9 levels, the authors concluded that 8 out of 11 patients must have had liver metastases at the time of resection that had gone unrecognized.

Table 1
Recurrence of pancreatic ductal adenocarcinoma after surgery alone

	Sperti et al [6]	Nakagohri et al [36]	De Castro et al [27]
% Overall relapse	—	77	81
% Local recurrence	33	73	33
% Hepatic metastases as a component of failure	61 (24[L])	55	83
% Extra-abdominal metastases	7	23	5
≤6 Months to recurrence	—	—	—
% Local	44	—	10
% Metastatic	48[L]	—	41
Median time to recurrence	—	—	—
Local	9.5 mo	—	—
Hepatic	9 mo	—	—
Local and hepatic	6 mo	—	—
Disease-free survival	8 mo	—	21 mo
Resection margin status	R0 and R1	R0 and R1	R0 resection

Certain data not reported.
Abbreviation: L, liver exclusively.

INDICATIONS FOR NEOADJUVANT THERAPY

The potential benefits of neoadjuvant therapy for patients with pancreatic cancer include the following:

- Improved response of low-volume metastatic disease to systemic therapy provided earlier in the course of the disease
- Potential downstaging of initially unresectable, locally advanced tumors [45–47].
- Avoidance of surgical resection among patients with rapidly progressive disease unresponsive to therapy. Neoadjuvant therapy allows time for occult metastases to become identifiable in patients who do not respond to treatment [48,49]. A secondary benefit is reducing the number of patients experiencing complications from nontherapeutic operations [50].

Neoadjuvant therapy is a cancer-directed treatment given before planned surgical resection. Neoadjuvant CRT maximizes the number of patients receiving systemic therapy. Postoperatively, as many as 20% to 30% of surgical patients do not receive adjuvant treatment either because of health problems related to surgery or because of decreased patient acceptance of additional treatment [51]. Some of the objectives of neoadjuvant therapy include reducing the size of the tumor, improving the rate of surgical resection, and increasing the likelihood of tumor-free resection margins. Neoadjuvant multimodality therapy is accepted for treating rectal cancer [52,53] and has been shown to have efficacy in the treatment of colon [54], esophageal [55–59], breast [60–62], and soft tissue tumors [63–66].

There is only one retrospective study comparing preoperative with postoperative CRT in a small cohort of patients with pancreatic cancer [47]. No prospective studies have been performed. As a result, the potential pitfalls of neoadjuvant therapy have not been properly evaluated but may include the following:

- Increased risk of disease progression for patients receiving an ineffective regimen. Disease progression has been observed in 29% of patients with locally advanced pancreatic cancer who may have had occult metastases at the time treatment was initiated [33].
- CRT-induced morbidity or mortality, particularly nausea and vomiting requiring hospitalization [67–69] and biliary sepsis in patients with obstructive jaundice [70–72]. Although biliary infection can be ameliorated by stenting, stent failure is not uncommon [73,74].
- Late complications of CRT, such as visceral arterial stenosis and intestinal infarction [73,74].
- Increased perioperative bleeding [47,75] caused by radiation-induced fibrosis and resulting technical difficulties during resection.

Three scenarios describe the use of neoadjuvant treatment for pancreatic cancer. The first scenario applies to patients who are considered resectable at the time of diagnosis. The rationale behind preoperative treatment for these patients is to improve the rate of margin-negative resection (R0 resection) and

disease-free survival by attacking well-vascularized cancer cells with systemic agents before surgery. The second scenario applies to patients with locally advanced pancreatic cancer who are not considered candidates for surgical resection at the time of diagnosis based on the surgeon's assessment of a low likelihood of an R0 resection. These patients are re-evaluated after neoadjuvant treatment and offered surgical exploration if sufficient radiographic response is observed [46]. A small subset of these patients eventually undergoes surgical resection with curative intent. At the University of Michigan, only 9 (13%) of 67 patients treated with gemcitabine and radiation underwent surgical resection following neoadjuvant treatment [76]. The third cohort of patients receiving neoadjuvant therapy constitutes the group of patients for whom CRT becomes their definitive treatment. This scenario applies to most patients with locally advanced pancreatic cancer who are found to have unresectable or metastatic disease (typically liver and vascular involvement) after treatment. Median survival for this group of patients (58 [87%] of 67 patients) was 11.9 months, as opposed to 17.6 months in the small group of patients undergoing surgery [76]. Most studies report time to progression, quality of life, various response and benefit indices, and survival separately for these unresected patients [76,77].

CURRENT STATUS OF ADJUVANT THERAPY

The clinical trial used as the basis for combining 5-fluorouracil (5-FU) chemotherapy with radiation in the treatment of pancreatic cancer is a 1969 report by Moertel and coworkers [78]. In 1985, The Gastrointestinal Study Group conducted a two-arm randomized trial comparing 5-FU and external beam RT with no treatment in patients with resected pancreatic cancer. Median survival in the adjuvant therapy group (20 months) was significantly better than that in the surgery-only arm (11 months) causing the trial to be stopped prematurely. Subsequent 5-year survival rates for the adjuvant-treated and untreated patients were 18% and 8%, respectively. Recently, two major randomized trials of adjuvant therapy were conducted in Europe. The European Organization for Research and Treatment of Cancer (EORTC) [79] compared adjuvant CRT with observation alone, whereas the European Study Group for Pancreatic Cancer (ESPAC) compared adjuvant chemotherapy with adjuvant CRT in a complex study design among multiple centers [51,80]. The EORTC randomized 218 postresection patients between 1987 and 1995 into two groups (110 to adjuvant treatment and 108 to observation). This study demonstrated a trend toward improved survival in the postresection 5-FU–RT arm compared with the observation arm but did not reach statistical significance. The ESPAC-1 trial, and subsequent ESPAC-plus data, incorporated a complicated two-by-two factorial design that randomly assigned resected pancreatic adenocarcinoma patients to CRT alone (20 Gy over a 2-week period plus 5-FU); to chemotherapy alone (5-FU); to both CRT and chemotherapy; and to observation alone. A meta-analysis of these adjuvant therapy data [81] demonstrated no significant difference in median survival between CRT and observation

alone (15.8 versus 15.2 months, respectively), whereas the median survival of the chemotherapy arm was significantly better (19 versus 13.5 months) than observation alone. Additional data from the RTOG 9704 phase III trial comparing pre–5-FU and post–5-FU with gemcitabine showed improved median and 3-year survival when gemcitabine was added to 5-FU–based adjuvant chemoradiation in resected patients [82], an effect that may be caused by the gemcitabine component of the regimen.

Risks and Benefits of Neoadjuvant Therapy

Table 2 provides a comparison of recent trials [83–88], chemoradiation regimens, response and resectability rates, and pathologic outcomes. A complete histopathologic response to neoadjuvant CRT is relatively uncommon but has been observed with both 5-FU [74,89] and gemcitabine-based [16] CRT regimens. The most consistent finding among studies of neoadjuvant CRT is an improvement in the proportion of microscopically margin-negative and node-negative pancreatic specimens. Although a survival benefit is occasionally observed with the addition of neoadjuvant CRT to resection, the heterogeneity of study designs and methodologies precludes making any reliable conclusions.

From a clinical standpoint, true downstaging of tumor stage is rarely observed after any therapy [90]. A study from 1998, however, used a chemotherapy-only regimen (5-FU, leucovorin, mitomycin-C, dipyridamole) in initially unresectable patients with a 10% rate of subsequent R0 resection [91]. In 2000, Wanebo and colleagues [92] downstaged two of four locally advanced pancreatic cancers following neoadjuvant CRT. In that same year, Snady and colleagues [93] downstaged and resected 29% of their cohort using a neoadjuvant CRT regimen of 5-FU and cisplatin. A more recent trial using the same neoadjuvant CRT protocol [46] resulted in downstaging and R0 resection for 21% of patients initially presenting with unresectable tumors.

Synchronous treatment with chemotherapy and RT has a potent tumoricidal effect but is also toxic to healthy tissues. Older studies emphasized the role of RT and delivered 45 to 60 Gy to a wide field including the tumor and its nodal basin and occasionally included prophylactic liver irradiation. Substantial RT-related morbidity was observed in many of these trials, including nausea, vomiting, dehydration, fatigue, and weight loss sometimes requiring hospitalization. Alternative strategies limited either the chemotherapy or the RT dose and its duration to reduce toxicity. A recent North American multi-institutional phase II trial reduced the total RT dose to 36 Gy over daily 2.4-Gy fractions [16]. Patients received concurrent full-dose gemcitabine (1000 mg/m^2 intravenously) as a radiation-sensitizer. The results were impressive in regards to toxicity (all patients completed the prescribed regimen without a need for toxicity-related hospitalization) and surgical resectability (85%, with R0 resection in all but one case).

Differentiating between potentially resectable and locally advanced pancreatic cancer can be challenging. There is no preoperative method that can accurately determine neoplastic involvement of the peripancreatic vasculature. In

Table 2
Chemoradiotherapy in neoadjuvant settings

Author/ references	N	RT Dose	Chemo	% Major Toxicity	Death on CRT (%)	% Progression on CRT	% CR	% PR	% Resected	% Proportion of R0 Resection	% Proportion of LN neg
total/fraction						local					
Hoffman et al [70]	53	50.4/1.8	5FU + mitC	43.5	2/62 (3.2)[a]	16 (local) + 3.7 (distant)	0	8	45	67	81
Pendurthi et al [47]	70	50.4/1.8	5FU + mitC	15.7	2/70 (2.8)	4.6[b]	0	—	97	56	28
Safran et al [83]	44	50.4/1.8	Paclitaxel	23	0	24[b]	2.3	26	9.5	NR	NR
Epelbaum et al [84]	20/10	50.4/1.8	GEM	35	0	50[b]	5	15	10	10	NR
Li et al [85]	16	50.4–61.2/ 1.8	5FU versus GEM	19	0	75[b]	0	12.5	NA	NA	NA
	18			34	0	27.8[b]	27	22			
Magnin et al [86]	32	30/1.5 or 45/1.8	5FU + cis	9.3	1/32 (3.1)	31.2[b]	6.2	—	60	82	64
Viret et al [87]	13	40/2	Docetaxel	28	0	69[b]	0	7.6	NA	NA	NA

Moutardier et al [74]	39	50/2	5FU + cis	2.5	1/39 (2.5)	38[b]		5.1	—	59	91	50
Rich et al [88]	109	50.4/1.8	Paclitaxel	44	1%	NR		6	26	3	NR	NR
Ohigashi et al [101]	19	24/2.0	5FU	0	0	21		0	60	79	80	60
Mishra et al [71]	20	50.4/1.8	Iri + GEM	85	0	24[b]		0	12	NR	NR	NR
Mornex et al [72]	41	50/2	5FU + cis	65.8	0	25[b]		2.4	10	63	80	87
Talamonti et al [16]	20	36/2.4	GEM	5	0	5[b]		5		85	94	65

Number represents true number of patients receiving neoadjuvant therapy, not total number of patients per study. Major toxicity = grade III–IV toxicity.

Abbreviations: CR, complete response; CRT, chemoradiotherapy; LN, lymph nodes; NA, data not analyzed or not included as end points of the study; NR, data not reported; PR, partial response; RT, radiotherapy.

[a]Trial reported toxicity in 62 patients, but only 53 were included in final analysis according to eligibility criteria.

[b]Site of progression of disease not specified.

many cases, patients with CT evidence of vascular involvement do not have true histologic invasion. Pancreatitis, pancreatic cancer, and radiation-induced changes are all associated with fibrosis along the adventitial plane of the portal vein, which can masquerade as tumor invasion. Only 40% to 50% of those with radiographic evidence for venous involvement actually have microscopic confirmation of vascular invasion in resected specimens [36,94].

Neoadjuvant Therapy for Potentially Resectable Disease (Stages I and II)

In 2001, the MD Anderson Cancer Center reported descriptive data on 132 patients with resectable pancreatic cancer who received neoadjuvant CRT [95]. Several different chemotherapy agents were used, including 5-FU, gemcitabine, and paclitaxel. RT was administered concurrently, either by standard fractionation to 50.4 Gy or rapid fractionation involving high-dose RT of shorter duration. All patients received additional chemotherapy on completing RT. At 14-month median follow-up, 32% of patients were alive without disease, whereas 49% had died of pancreatic cancer. Median survival was an impressive 25 months for patients with microscopically negative margins and 20 months if the margins were positive. No survival differences were noted among the various types of preoperative CRT. A subgroup of 35 patients treated with paclitaxel CRT was analyzed in greater detail [96]. These patients received rapid fractionation radiation of 30 Gy over 2 weeks with concurrent paclitaxel, followed by a 4- to 6-week recovery period. At radiologic restaging, 10 patients (29%) had evidence of disease progression. The remaining 25 patients were surgically explored, and 20 (80%) were resected. A 3-year survival of 28% was observed in the resected group.

A subsequent multi-institutional phase II trial combining preoperative full-dose gemcitabine with radiotherapy was conducted in 20 patients (10 men and 10 women) with potentially resectable pancreatic carcinoma by the group at Northwestern University [16]. Patients were treated preoperatively with three cycles of full-dose gemcitabine (1000 mg/m^2 intravenously); with radiation during the second cycle (36 Gy in daily 2.4-Gy fractions); and surgery 4 to 6 weeks after the last gemcitabine infusion. Nineteen patients completed uninterrupted therapy, whereas one experienced grade 3 gastrointestinal toxicity. All 20 patients were taken to surgery, and 17 underwent resection (16 Whipple and 1 distal pancreatectomy). Pathologic analysis demonstrated negative margins in 16 (94%) of 17 patients and negative lymph nodes in 11 (65%) of 17 specimens. Preliminary survival data were promising. At median follow-up of 18 months, 7 (41%) of the 17 patients with resected disease were alive without recurrence; 3 (18%) were alive with distant metastases; and 7 (41%) had died. The authors concluded that neoadjuvant CRT using gemcitabine was effective for pancreatic cancer based on the high rate of negative margins and lymph nodes.

Neoadjuvant Therapy for Locally Advanced Disease (Stage III–T4 Tumors)

Long-term survival after surgical resection of locally advanced pancreatic adenocarcinoma varies between 7% and 34% depending on the definition of the

term "locally advanced" [6,97–99]. The American Joint Committee on Cancer has officially defined locally advanced cancer as stage III disease, meaning locally unresectable T4 tumors without extranodal metastases. In pancreatic cancer, patients with locally advanced disease typically demonstrate tumor invasion into the superior mesenteric artery or celiac axis (Fig. 1) that precludes complete surgical resection with negative margins unless regional pancreatectomy with arterial resection and reconstruction is performed. Although resections of this magnitude are not the mainstream of surgical therapy, a recent experience at the University of Southern California reported three distal pancreatectomies combined with en bloc resection of the celiac axis and demonstrated a short perioperative stay (average 8.3 ± 1.1 days) with a 14-month disease-free survival at the time of the publication [100].

Several studies have explored the role of neoadjuvant CRT combined with surgery for patients with locally advanced disease. In 1990, a prospective trial of neoadjuvant CRT was performed to determine the feasibility of surgical resection and to evaluate survival in patients with locally advanced pancreatic or periampullary cancer [13]. Fifteen patients with pancreatic cancer (14 head, 1 body) and one patient with duodenal cancer received combination treatment with infusional 5-FU, bolus injection of mitomycin-C, and RT (four patients were treated off protocol). Subjects were restaged 3 weeks after completing RT to evaluate resectability, and 13 patients underwent exploration. Three had evidence of extrapancreatic disease, and 10 were surgically resected. One patient had no residual tumor in the specimen. The others had residual tumor with evidence of necrosis and hyalinization, but all surgical margins were free of tumor. There were two perioperative deaths from sepsis, and one death from myocardial infarction at 9 months. One patient died of recurrent disease at 19 months. The remaining patients were alive and free of disease at 40, 32, 11, 11, 10, and 4 months after their initial cancer diagnosis. In 1998, Fox Chase Cancer Center coordinated an Eastern Cooperative Oncology

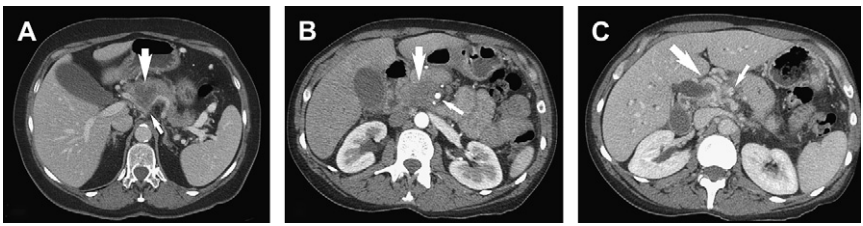

Fig. 1. Examples of locally advanced pancreatic cancer identified on axial CT. (*A*) Pancreatic body carcinoma (*large arrow*) encasing the celiac bifurcation (*small arrow*) and the origins of the hepatic and splenic arteries. (*B*) Carcinoma of the pancreatic head (*large arrow*) encasing the superior mesenteric artery (*small arrow*) and its tributaries. (*C*) Cavernous transformation of the portal vein (*large arrow*), portal vein occlusion. Subtle infiltrative changes can be seen at the pancreatic neck (*small arrow*) and correspond to the region of biopsy-proved adenocarcinoma on endoscopic ultrasound. The portal vein is occluded inferior to this image.

Group Study trial investigating neoadjuvant infusional 5-FU and mitomycin-C combined with 50.4-Gy external beam RT in patients with locally advanced adenocarcinoma of the pancreas [70]. Fifty-three patients were enrolled into the study; 41 underwent surgery, and 24 were resected (19 Whipple, 4 total pancreatectomy, and 1 distal pancreatectomy). Many of the toxicities from CRT were hematologic, although a comparable number of treated patients suffered biliary tract complications caused by cholangitis. The median survival for the entire group was 9.7 months, and 15.7 months for resected patients. The 2-year survival rate of resected patients was 27%, with most experiencing metastases to the liver. The authors attributed the poor survival outcomes to the advanced stage of disease at presentation.

Given the observation that hepatic metastases are the most frequent cause of failure after preoperative CRT, Ohigashi and colleagues [101] recently tested a combination of preoperative and postoperative CRT with postoperative liver perfusion chemotherapy for patients with locally advanced pancreatic cancer. Nineteen patients with T3 pancreatic head tumors received 5-FU and RT delivered at 24 Gy over 12 fractions. Following neoadjuvant CRT, 15 patients were found to be resectable, whereas four had evidence of metastases. A Whipple procedure was performed on 15 patients, and catheters were placed into the gastroduodenal artery and the superior mesenteric vein. During the first 28 postoperative days, 5-FU was infused continuously by the hepatic artery and portal vein (3.5 g/28 days $\times$ 2). Finally, RT of 36 Gy in 18 fractions with 5-FU (3 g/6 days) was applied to the pancreatic bed. Postsurgical mortality was 0%, and the 3-year overall survival rate was 53%. In addition, the 3-year disease-free survival rate was 66% among patients who had more than a 50% pathologic response rate versus 0% in patients who were poor responders ($P = .04$).

Large Scale Trials of Neoadjuvant Therapy

A few large-scale studies have investigated the efficacy of neoadjuvant CRT for patients with potentially resectable and locally advanced pancreatic cancer. A 2001 study reported the effects of neoadjuvant 5-FU chemotherapy combined with RT in 111 patients with radiographically localized, pathologically confirmed, pancreatic adenocarcinoma evaluated at Duke University Medical Center between February 1995 and October 2000 [67]. These tumors were defined as potentially resectable (N = 53) in the absence of arterial involvement and venous occlusion, or locally advanced (N = 58) if arterial involvement or venous occlusion was identified by CT. Five patients were not restaged either because of death (N = 3) or intolerance of therapy (N = 2). Twenty-one patients (19%) manifested distant metastatic disease on restaging CT. Twenty-eight patients with initially resectable tumors (53%) and 11 patients (19%) whose initial tumors were locally advanced were resected after completing CRT. Histologic examination of resected specimens demonstrated significant fibrosis and two complete pathologic responses. The surgical margins were negative in 72%, and lymph nodes were negative in 70% of resected patients. At 16-month

follow-up, median survival has not yet been reached in resected patients. The postresection survival rate in this study was comparable with or better than that observed following resection with adjuvant treatment. Additionally, there was evidence that neoadjuvant CRT reduced the morbidity of surgical resection among patients with occult metastatic disease and downstaged a few patients with locally advanced pancreatic cancer.

In 2004, Moutardier and colleagues [74] studied 87 patients with ductal adenocarcinoma localized to the pancreatic head. Seventeen patients had surgery alone (group I), whereas 39 patients with potentially resectable (group II) and 31 patients with locally advanced pancreatic carcinoma (group III) received neoadjuvant 5-FU–cisplatin CRT. The groups were statistically comparable in terms of age, gender, and pretherapeutic stage. Median survival and 2-year overall survival in group I (surgery only) were 13.7 months and 31%, respectively. Twenty-three patients (59%) in group II underwent a Whipple procedure (group IIa) and 16 patients (41%) did not undergo resection (group IIb). Median survival and overall 2-year survival were as follows: group IIa, 26.6 months and 51%; group IIb, 6.1 months and 0%, respectively. In group IIa, pathologic examination revealed eight major responses (35%) including two complete pathologic responses, and none of the patients developed locoregional recurrence. None of the patients in group III (locally advanced) was found to be resectable at exploration. Median survival was 8 months, with one 2-year survivor (3%). This study demonstrated a formidable response rate and good local control, but there was no control over patient selection. Moreover, patients who could not be resected after neoadjuvant CRT were analyzed separately.

A third study compared survival parameters for patients with locally advanced pancreatic cancer receiving neoadjuvant CRT with a group of pancreatic cancer patients with resectable tumors who did not receive presurgical treatment [93]. The locally advanced patient group (N = 68) received 54 Gy RT in 2-Gy fractions with concurrent 5-FU, streptozotocin, and cisplatin. Following the course of neoadjuvant CRT, a total of 20 patients (29%) underwent resection. The treated group was compared with a more favorable cohort of 91 pancreatic cancer patients, who were initially resectable by radiologic criteria and went on to have surgical resection as their primary treatment. Sixty-three of these 91 patients received adjuvant chemotherapy with or without radiotherapy. Despite having a more advanced stage at diagnosis, the survival of the locally advanced patients receiving neoadjuvant CRT was significantly better than for the resectable group (median survival 24 versus 14 months, $P = .006$). Neoadjuvant CRT seemed to reverse the anticipated outcome of this trial.

Although there are no prospective trials comparing neoadjuvant and adjuvant treatments, one retrospective analysis compared these two treatment strategies in a consecutive series of patients at Fox Chase Cancer Center [47]. A total of 70 patients with pancreatic adenocarcinoma were enrolled in a neoadjuvant CRT protocol of 5-FU, mitomycin-C, and RT dose of 50.4 Gy given in

1.8-Gy fractions. Twenty-five of the treated patients with pancreatic head cancer underwent pancreaticoduodenectomy with curative intent. Following the closure of neoadjuvant CRT protocol, 23 patients who underwent pancreatic resection without pretreatment were given adjuvant CRT with a similar RT dose and a variable 5-FU–based chemotherapy regimen without mitomycin-C. Although there was no significant survival difference observed and local failure rates were equal in the two groups, a significantly smaller proportion of lymph node involvement was observed in the neoadjuvant CRT group (28% versus 87%) and a nonsignificant increase in the R0 resection rate (28% versus 56%). Overall, fewer lymph nodes were recovered from neoadjuvant CRT patients (average of 11 versus 22 nodes per patient). Toxicity was similar for both the neoadjuvant and adjuvant CRT patients; 22% of patients scheduled for postoperative treatment never received treatment for a variety of reasons.

NOVEL THERAPIES: IMMUNOTHERAPY, TARGETED THERAPY, AND VACCINES

Recent advances in molecular medicine have led to the development of targeted therapeutics for pancreatic cancer. Many of these novel agents have only been tested in small trials of patients with advanced pancreatic cancer. Examples of these agents include modulators of biologic growth factors, such as vascular endothelial growth factor (bevacizumab); epidermal growth factor (cetuximab); and HER-2-neu (trastuzumab) [102,103]. Additional examples of targeted reagents include apoptosis regulators and effectors (cyclooxygenase-2 inhibitors) [103]; tyrosine kinase inhibitors (erlotinib, gefitinib) [104]; matrix metalloproteinases (BAY 12-9566) [105]; farnesyl transferase inhibitors (tipifarnib) [103]; and tumor vaccines. Most agents are in the preclinical or pilot stages of development.

Two biologic agents have demonstrated promising efficacy as additions to standard chemotherapy for pancreatic cancer. Erlotinib (Tarceva) is an orally active, reversible inhibitor of the epidermal growth factor receptor tyrosine kinase that is overexpressed in pancreatic adenocarcinoma [106,107]. A recent phase III trial of the National Cancer Institute of Canada Clinical Trials Group [104] demonstrated that erlotinib combined with gemcitabine was superior to gemcitabine alone among 569 patients with advanced or metastatic pancreatic cancer. Overall 1-year survival was 24% for the patients who also received erlotinib versus 17% in those who received only gemcitabine ($P = .025$). The survival benefit was a modest 0.4 months in the erlotinib group. Interferon-α is a second biologic agent with activity against pancreatic cancer in the laboratory setting [108]. In combination with infusional 5-FU and cisplatin, interferon-α has demonstrated impressive 5-year actuarial survival of 55% as adjuvant therapy for 43 patients with resected pancreatic adenocarcinoma at Virginia Mason [109]. Although a national trial of the Virginia Mason protocol was stopped by the National Cancer Institute because of toxicity, the combination remains under study at the MD Anderson Cancer Center and at Virginia Mason.

Finally, a recent trial of neoadjuvant interleukin-2 immunotherapy in pancreatic cancer patients was recently reported by a group in Italy. Interleukin-2 is necessary for the development of immunologic memory by T cells, facilitates the production of immunoglobulins by B cells, and induces the differentiation and proliferation of natural killer cells. A recombinant form of interleukin-2 (Proleukin) is currently used to treat malignant melanoma and renal cell carcinoma [110,111]. Nineteen patients with pancreatic cancer scheduled for the Whipple procedure were divided into two groups matched for age, gender, and stage [112]. The first group of nine patients was treated with preoperative interleukin-2 (9 million IU of interleukin-2 subcutaneously for 3 consecutive days), whereas the second group of 10 patients underwent Whipple resection without neoadjuvant treatment. Although histologic findings were not different in the two groups, the interleukin-2 group had a 2-year survival of 33% compared with 10% in the untreated group. One significant advantage of neoadjuvant interleukin-2 is that the duration of treatment is only 3 days.

SUMMARY

Neoadjuvant CRT can be administered safely to patients with pancreatic cancer. Complete pathologic responses are rare, however, and the benefits of this approach compared with standard adjuvant therapy are uncertain. Only 13 out of 251 patients treated with neoadjuvant CRT demonstrated a complete pathologic response in resected specimens [67,69,89,92,93].

Interpreting the results of neoadjuvant therapy trials in single institution series can be challenging at best. The potential for selection bias is a constant problem. Single institution series tend to be statistically underpowered and dependent on heterogeneous protocols for chemotherapy and radiation. Intraoperative external beam RT may also be given to selected patients. Toxicities and patient drop-out rates differ from study to study, as do the number of patients deemed resectable following CRT. The type of resection (Whipple, total, or distal pancreatectomy) differs between studies, and the extent of resection may affect survival and other outcomes. Nevertheless, there is evidence that tumors of the ampulla and bile duct have a better prognosis than those within the pancreas [100], and that the resectability rate of body and tail lesions (left-sided) is lower than that of head, neck, and uncinate tumors (right-sided) [32,113].

If a study of neoadjuvant CRT reports good postsurgical outcomes, it is likely that the authors will attribute the enhanced outcomes to efficacious therapy, whereas poor outcomes are typically attributed to the advanced stage of disease on presentation. The only way to evaluate the efficacy of neoadjuvant CRT is a prospective trial involving a uniform patient population comparing the results of neoadjuvant and adjuvant therapy and a cohort receiving surgery alone. Such a study can be designed in an ethically sound manner but requires the collaboration of numerous institutions and careful coordination to achieve statistically conclusive results. The future of pancreatic cancer research rests on

the availability and rapid transfer of new therapies from the laboratory to clinical research.

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Early Detection and Staging of Adenocarcinoma of the Pancreas

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The premise that early detection and treatment will lead to improved overall survival is a concept that has held true for breast, colon, lung, and prostate cancers [1]. However, there are only retrospective data to support the concept that early detection and treatment will lead to improved survival in patients who have pancreatic cancer. Sohn and colleagues [2], in one of the largest retrospective analyses of prognostic factors in pancreatic cancer, showed that in 616 patients undergoing potentially curative resection margin status, lymph node involvement and tumor size less than 3 cm were strongly correlated with improved survival. Survival in patients who had small tumors, negative resection margins, and no lymph node involvement was markedly better than survival in other patients in this series (31% versus 15% 5-year survival). Similarly, in a smaller study, Ariyama and colleagues [3] showed 100% 5-year survival in patients undergoing resection of pancreatic tumors less than 1 cm in size. Together these data provide some hope that early detection through screening may improve the outcome for adenocarcinoma of the pancreas.

Only a small proportion of patients diagnosed with pancreatic cancer will benefit from surgical exploration and potentially curative resection. Therefore the accurate staging of patients who have pancreatic cancer is critical to identify those who have locally advanced or metastatic disease, and thereby avoid the morbidity of an unnecessary surgical procedure. Accurate staging can also increase the likelihood that patients will be resectable at the time of laparotomy. In most retrospective analyses of factors influencing long-term outcome for adenocarcinoma of the pancreas, completeness of surgical resection has had the greatest impact [2]. This further underscores the importance of accurate

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staging, because patients who have arterial or retroperitoneal margins that are positive postoperatively will not survive any longer than unresected patients.

Another important aspect of staging is the ability to compare equivalent groups in clinical trials. Accurate staging of pancreatic cancer identifies patients who are most likely to benefit from surgical intervention and referral to a tertiary care center with extensive experience in managing patients who have pancreatic cancer. Patients who are identified as having locally unresectable or metastatic tumors may be offered less-invasive palliative procedures. Accurate staging allows patients who have locally advanced tumors to be offered neoadjuvant protocols in an attempt to downstage the tumors and render them resectable. Although there is some evidence that supports this approach, some studies have argued that the benefit may be modest at best [4–7].

This article provides a review of current methods and results for the early detection and staging of pancreatic cancer, and discusses some potential areas for future development.

GENERAL REQUIREMENTS FOR A SCREENING TEST FOR ADENOCARCINOMA OF THE PANCREAS

The general requirements for an effective screening test for pancreatic cancer have been examined by Lowenfels [8]. In an analysis of screening for pancreatic cancer starting at the age of 50, and assuming only 40% to 50% survival after surgery, he found that the additional years of life expectancy gained is critically dependent on the risk of pancreatic cancer in the population and the sensitivity and specificity of the screening test. From this analysis it can be concluded that a screening test with a sensitivity and specificity greater than 90% will benefit high-risk groups. Screening tests that can identify tumors at an even earlier stage (perhaps even in the premalignant stage whereby survival after treatment would be expected to be greater than the 40% to 50% assumption in this model) would be expected to yield more significant improvements in life expectancy. Current clinically available screening regimens approach 80% to 90% specificity and sensitivity, and therefore their usefulness is limited to individuals who have high-risk factors for pancreatic cancer. More widespread screening awaits development of more sensitive and specific markers of this disease.

Current Use of Screening Tests for Pancreatic Adenocarcinoma in High-Risk Individuals

Early experience with screening populations at high risk for pancreatic cancer using invasive techniques like endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) has been encouraging [9,10]. The University of Washington reported the results of EUS-based screening of several high-risk kindreds [11]. In this program, screening was initiated at 50 years of age or 10 years younger than the earliest age of onset of pancreatic cancer in a family member, and surveillance used EUS and ERCP (evaluation of spiral CT and serum CA19-9 and CEA levels did not show these tests to be useful). In their algorithm, high-risk kindreds were offered EUS screening, and a study

was considered positive if there were findings of parenchymal heterogeneity, echogenic foci, or hypoechoic nodules, similar to findings in chronic pancreatitis. Patients who had abnormal EUS results were then offered an ERCP. The presence of irregular or ectatic ducts or sacculations were considered indicative of underlying pancreatic pathology. Patients demonstrating abnormal EUS and ERCP were then offered a laparoscopic "tailectomy" for histologic evaluation. If this evaluation demonstrated PanIN III, a total pancreatectomy or continued close surveillance was advised. The management of PanIN II lesions was less clear, with some individuals being offered surgery but most being offered continued surveillance.

In several reports describing these kindreds, approximately 50% of these high-risk patients have been found to have an abnormal EUS, and half of these patients have also been found to have an abnormal ERCP [12,13]. Among 75 patients screened in this manner, thus far 15 patients have undergone surgery (12 total and 3 distal pancreatectomies) with pathologic findings of PanIN III in 10 patients and PanIN II in 5 patients, but no invasive cancers have been identified [11]. There have been no deaths. The 12 patients undergoing total pancreatectomy were rendered diabetic. Postoperative complications have small bowel ulcers [2] and a bile duct stricture [1]. A cost analysis of this screening program suggested that screening was cost-effective versus no screening as long as the prevalence of the cancer in the screened population was assumed to be 16% or greater (16,885 per year of life saved) [14].

Similarly, Canto and colleagues [9,10] at the Johns Hopkins Hospital have reported their experience with EUS-based screening. Study candidates have included individuals who had Peutz-Jeghers syndrome and members of familial pancreatic cancer kindreds. A total of 116 high-risk individuals were screened by EUS and CT [15]. If the EUS was abnormal (ie, a focal lesion such as a mass, nodule or cyst, or at least three of nine EUS features of chronic pancreatitis), fine needle aspiration was performed and a multidetector CT was performed. Patients who had an abnormal EUS were also offered an ERCP. The presence of saccules and grade of chronic pancreatitis were assessed, and chronic pancreatitis-like changes of the ducts were classified as absent, mild, moderate, or severe. Patients who were suspected of having a pancreatic neoplasm because of a mass, cystic lesion, or nodule detected on imaging studies or because of high-grade dysplasia in their fine needle aspirates were referred for surgical evaluation. High-risk patients who had an abnormal EUS who did not undergo surgery were offered follow-up EUS/FNA and CT within 3 to 6 months to assess the stability of the abnormal finding; all others were offered repeat EUS within 1 year of the baseline study. Findings in the high-risk group were compared with findings in patients undergoing EUS or ERCP for nonpancreatic indications.

Of these patients, eventually 29 were identified as having "neoplastic-type lesions" on the basis of EUS, ERCP, and/or CT. Of these 29 patients, 15 have gone on to surgery, although how these patients were selected for surgery is unclear [15]. Final pathologic evaluation revealed 6 invasive cancers or high-grade

lesions (PanIN III or intraductal papillary mucinous neoplasm [IPMN] with carcinoma in situ), 11 low-grade lesions (PanIN II or IPMN), and 6 nonneoplastic lesions. Although CT was found to be inferior in this study for the detection of pancreatic lesions, it did identify 6 synchronous extrapancreatic neoplasms.

Together the experience of these two centers provides provocative evidence that intensive EUS-based screening can detect pancreatic cancer and its early precursor lesions. However, several caveats are worth noting. First, both centers reported resection of a significant number of patients (30% University of Washington, 40% Johns Hopkins Hospital) of patients who had PanIN II lesions or benign IPMN only. The malignant potential of these lesions is not well established in either the high-risk or the general population. A better understanding of the natural history of these lesions will be necessary before widespread agreement about resection can be reached.

Second, it is unclear that subtotal pancreatectomy decreases the risk of development of subsequent benign or invasive lesions. It remains to be seen if resecting the radiographically abnormal portion of a gland that has a genetic field defect decreases the lifetime risk of cancer. In addition, subtotal pancreatectomy may potentially make future surveillance of the residual pancreas more difficult. It is also not clear that the morbidity of a total pancreatectomy, as performed routinely in the University of Washington series, is justified in the setting of PanIN I/II or benign IPMN.

Third, both studies found a high rate of abnormalities on screening EUS that led to more costly and morbid interventions (ERCP or surgical biopsy). This is not surprising given that both of these studies examined individuals from extremely high-risk populations. However, these individuals represent a small fraction of the 35,000 to 40,000 new pancreatic cancers identified each year. In their present form, neither of these reported approaches to screening would be appropriate for anyone other than such individuals at extremely high risk. Widespread screening of even moderate- to low-risk individuals awaits development of less-invasive screening tests (eg, blood-based assays) with high sensitivity and specificity. Clearly there is great need for improvement in diagnostic classification of these radiographically identified lesions to prevent unnecessary surgical interventions. Further risk stratification by novel serum or pancreatic fluid assessment may enrich the population to be screened or select individuals who have radiographically identifiable lesions for more intensive invasive testing.

AVAILABLE SERUM MARKERS FOR EARLY DETECTION OF PANCREATIC CANCER

Given the accessibility of the serum to rapid and repeated assessment, much work on the early detection of pancreatic cancer has focused on the development of serum biomarkers. Various serum tumor markers that correlate with the presence of pancreatic cancer have been described in the literature (Table 1). Probably the most widely used is CA 19-9. Most studies, using various cut-off points, have found a high degree of correlation between elevated CA19-9 levels and the presence of pancreatic cancer. Sensitivity and specificity

Table 1
Serum tumor markers in pancreatic cancer

Putative serum marker	Sensitivity	Specificity	Reference
CA 19-9	70–90	90	[10]
CEA	16–92	49–93	[68]
CA 50	65–90	58–73	[68]
CA-72-4	—	—	[69]
CA-242	57–83	79–90	[70]
CA125	45–60	76–86	[71]
CA-195	89	73	[72]
Tissue polypeptide specific antigen	50–98	22–97	[11,68]
TIMP-1	60–99	60–99	[12]
Span-1	50–87	50–90	[73]
Mesothelin	NT	NT	[14]
Insulin-llike growth factor/binding protiens	NT	NT	[74]
MMP 2,3,7,9	NT	NT	[75–77]
Prostate specific stem cell antigen	NT	NT	[78]

Abbreviation: TIMP-1, tissue inhibitor metalloproteinase 1.

for CA19-9 have been reported to be 70% to 90%, and 90%, respectively [16]. Unfortunately, there is much overlap between pancreatic cancer and various benign inflammatory conditions of the pancreas, limiting the clinical applicability of CA19-9 as a specific early detection/screening marker.

Tissue polypeptide specific antigen, a breakdown product of the extracellular matrix, is another recently described serum tumor marker that has been reported to provide improved discrimination between pancreatitis and pancreatic cancer over CA19-9. Using a cut-off level of 200 U/mL, Slesak and colleagues [17] recently reported tissue polypeptide specific antigen to have a sensitivity of 97% and a specificity of 98% versus normal controls. However, tissue polypeptide specific antigen was also found to be elevated in 17% to 20% of patients who have chronic pancreatitis. Similarly, tissue inhibitor metalloproteinase 1, a stromal factor with multiple functions, when evaluated in conjunction with CA 19-9 only showed a sensitivity of 60% [18]. Most recently macrophage inhibitory factor cytokine 1 has been identified as a sensitive and specific serum marker for pancreatic cancer. Koopman and colleagues [19] reported that serum measurement of macrophage inhibitory factor cytokine 1 was more sensitive and specific than serum measurement of CA19-9, tissue inhibitor metalloproteinase, or osteopontin. Numerous other serum markers including CEA, CA-125, and mesothelin have also been examined for their ability to accurately diagnose pancreatic cancer and have been found to be of insufficient sensitivity and specificity to warrant clinical use at the present time [20,21].

Extensive evaluation of individual serum markers has failed to produce a single sensitive and specific marker for this disease. The authors hypothesize that this is because no single tumor-derived marker can accurately detect, describe, and quantify the tumor-bearing state in all or even a large proportion of

patients who have pancreatic cancer. There is an increasing body of evidence that supports the hypothesis that the development of an invasive cancer requires not just the accumulation of genetic events in the tumor cell alone, but also specific and measurable permissive changes in the host at the proteomic and cellomic level. In particular, pancreatic cancer is associated with an intense desmoplastic response in the host pancreas. Iacobuzio-Donahue and colleagues [22] have recently screened at the genetic level for these changes by performing serial analysis of gene expression (SAGE analysis). Using libraries of fresh pancreatic tumors and pancreatic tumor cell lines, they were able to identify 12 to 14 genes that were up-regulated only in the peritumor host epithelium. More recent work by this group has described tumor-induced production of SPARC (secreted protein acidic and rich in cytokine), a matricellular glycoprotein with roles in cell adhesion and proliferation as well as tumorigenesis and metastasis, by peritumoral fibroblasts [23]. Studies such as these suggest that there will be a broad range of specific, detectable, and measurable tumor- and host-derived biomarkers that can be assayed at the proteomic level. The authors hypothesize that multiplexed panels that can sensitively and specifically measure these biomarkers, derived from nascent tumor and the host response, will have much greater value and superior performance characteristics than that of individual tumor-derived proteins. Several groups have now reported the performance of combinations of markers [19,20,24]. These combinatorial assessments (multiplex) of relevant markers improve both sensitivity and specificity of the detection of pancreatic cancer. In the authors' hands, they have found that a panel of serum inflammatory markers and tumor antigens demonstrated superior sensitivity and specificity over CA19-9 alone in distinguishing normal individuals and individuals who have chronic pancreatitis from patients who have pancreatic cancer [25]. Statistical analysis demonstrated that although correlation of each of the identified markers with pancreatic cancer was modest when evaluated alone, a combined biomarker panel showed strong association with malignant disease. Combinations of several serum markers as measured by LabMAP technology provided a sensitivity of 86% at a specificity of 92% for comparison of pancreatic cancer with healthy controls. As a diagnostic panel, these markers perform better than CA 19-9 alone in distinguishing pancreatic cancer from normal controls and chronic pancreatitis. Moreover, this panel has demonstrated higher performance than any published single pancreatic cancer–associated marker [14,15] or marker combination (ie, the combination of CA 19-9 with CEA and CA 72-4) [14,15]. Although the diagnostic power of this multicytokine panel is still below the required threshold for screening populations at medium and average risk of pancreatic cancer, inclusion of additional markers having high association with pancreatic cancer may further increase the diagnostic power of the assay. These initial results demonstrate a strong potential to accurately discriminate cancer status with only a moderate number of samples. The authors are now actively examining the ability of these cytokines as a panel to serve as biomarkers of prognosis and response to therapy in patients who have pancreatic cancer.

The ultimate extension of combining serum markers is serum proteomic profiling. In this approach, extremely sensitive proteomic detection systems are used to develop a "fingerprint" of the serum proteome without specific knowledge of these individual markers. The authors and others have reported early experience suggesting that unique, specific serum proteomic profiling can accurately distinguish normal individuals from those who have chronic pancreatitis and pancreatic cancer [26–29] using the SELDI-TOF proteomic platform. A recent report demonstrated that SELDI-TOF serum profiling in a murine model that closely recapitulates the development of human pancreatic cancer had a sensitivity of 90% and specificity of 97.7% in predicting the presence of PanIN. This study suggests that it will be possible to detect early premalignant pancreatic lesions in the serum proteome alone. However, despite early promising results, enthusiasm for these proteomic-fingerprinting approaches has been lacking. Concerns over the ability to standardize these extremely sensitive techniques as well as cumbersome requirements for serum collection have slowed development. It is hoped that newer more powerful proteomic profiling techniques that allow for rapid identification of the individual species within the fingerprint will address these concerns.

Several groups have evaluated commonly mutated oncogenes in pancreatic cancer as putative specific and sensitive biomarkers for the detection of pancreatic cancer. The most frequently mutated oncogene in pancreatic cancer is *K-ras*, demonstrated in greater than 95% of pancreatic cancers. Several groups have detected *K-ras* mutations in the serum [30], pancreatic fluid, or stool of patients who have pancreatic cancer using polymerase chain reaction methods [31–33]. Similarly, several reports have suggested that *p53* mutations may also be detected in the serum of patients who have pancreatic cancer [34,35]. Despite the promise of higher specificity for these techniques, they are not currently clinically useful because several benign and premalignant lesions of the pancreatic epithelium have also been demonstrated to contain *K-ras* mutations [36]. In addition, these genomic techniques are technically cumbersome, difficult to quantitate, and therefore impractical for widespread clinical testing at this time.

STAGING OF PANCREATIC CANCER

CT Scanning

Computed tomography (CT) is perhaps the most widely used and most important single test used in preoperative staging of pancreatic cancer and in assessment of tumor resectability [4,37]. Conventional CT scanning with intravenous contrast administration can provide important information regarding tumor size and location, local tumor extension and infiltration, regional vessel involvement, and the presence of extrapancreatic lymph nodes and distant metastases. The criteria used for assessing tumor unresectabilty include the presence of extrapancreatic disease, encasement of the superior mesenteric artery, and occlusion of the superior mesenteric vein–portal vein confluence (Fig. 1). Many other criteria used to assess tumor resectability are largely institutionally

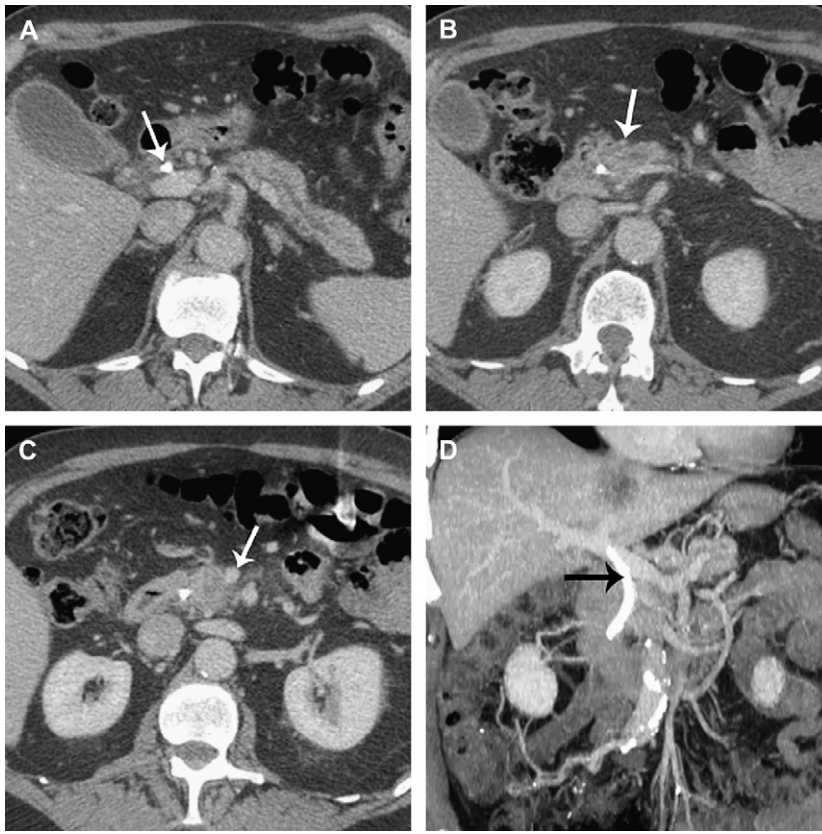

Fig. 1. ''Unresectable'' pancreatic head carcinoma. (*A*) Axial CT section shows a dilated pancreatic duct and infiltration of the planes surrounding the celiac artery. A plastic biliary stent (*arrow*) is noted. (*B*) The hypodense tumor (*arrow*) obliterates the splenic-portal confluence. (*C*) The tumor touches the superior mesenteric artery and surrounds approximately half the circumference of the superior mesenteric vein. (*D*) Coronal reformation of the CT scan shows the biliary stent (*arrow*) and the patent superior mesenteric vein and portal vein, but the splenic vein is not seen.

dependant and mainly consider various forms of regional vascular involvement to be evidence of unresectability.

The widespread availability of multidetector row CT scanning has ushered in a new era of pancreatic imaging [38]. New CT scanners with multiple rows of detectors and continued advances in engineering mean that large volumes of tissue can be imaged while acquiring both arterial and venous phases in shorter periods of time [39,40]. This technique of dual phase, contrast-enhanced multidetector CT scanning is now standard of care at most high-volume pancreatic cancer centers. In a recent review, multidetector pancreatic protocol CT scanning was shown to be superior to most other imaging modalities in accurately predicting resectability and staging of pancreatic adenocarcinoma [41,42].

Another recent innovation in CT scanning is the development of three-dimensional reconstruction (Fig. 2). Recent studies support the superiority of three-dimensional computed tomography (3D-CT) scanning in assessing the local tumor burden and degree of local vascular invasion in staging periampullary neoplasms [43–45]. 3D-CT scanning may enhance the assessment of vascular invasion by allowing the periampullary structures to be viewed in planes not seen by conventional imaging modalities. In a recent study of preoperative 3D-CT, the extent of tumor burden in patients who have periampullary tumors was accurately predicted in 93% of patients studied and accurately

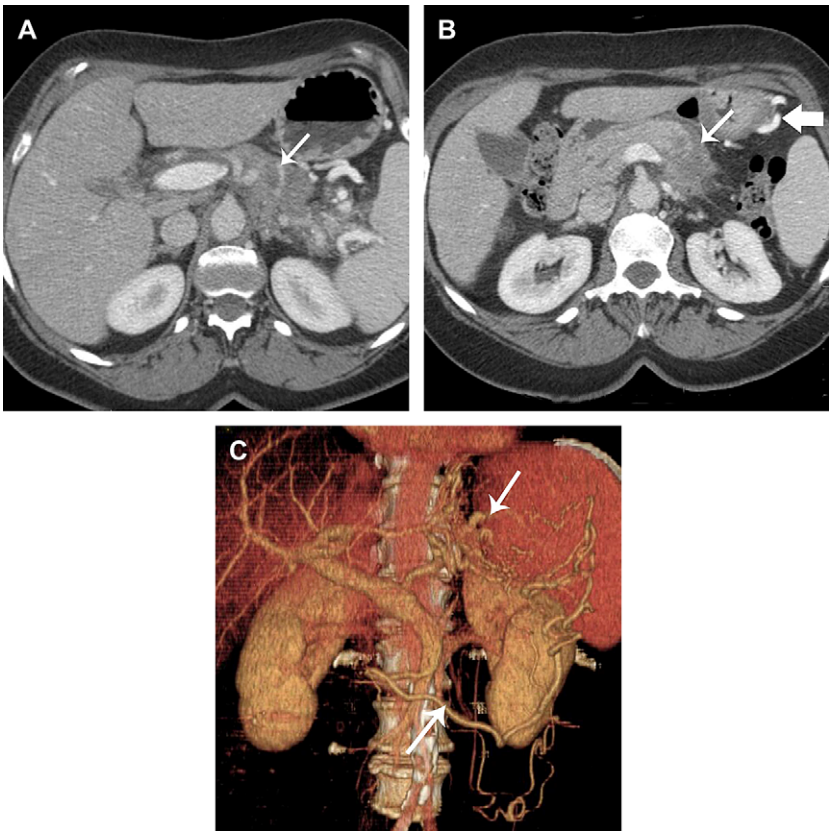

Fig. 2. Sixty-year-old man who has unresectable pancreatic body carcinoma. (*A*) Axial CT scan shows a hypodense mass in the pancreatic body (*arrow*) that encases the celiac artery and its branches. (*B*) Note the interface between the hypodense tumor (*thin arrow*) and the normally enhancing pancreatic neck, just ventral to a patent portion of the distal splenic vein. Also note the venous collaterals (*thick arrow*) surrounding the stomach. (*C*) Three-dimensional reformation of CT data shows a patent superior mesenteric and portal vein but no splenic vein opacification. Multiple collateral veins (*arrows*), including short gastric and gastroepiploic, are noted.

predicted resectability and margin-negative resection in 98% and 86% of patients, respectively [44].

Endoscopic Ultrasound

EUS has emerged in the past several years as an extremely powerful pancreatic imaging and staging modality. Clearly one of the greatest strengths of EUS as a staging tool is its ability to image small pancreatic tumors (Fig. 3). In a study of 100 patients who had pancreatic masses less than 2 cm in size, EUS correctly identified 100 pancreatic masses. EUS was much better than other commonly used imaging modalities such as ERCP and CT, which demonstrated the same mass 57% and 29% of the time, respectively [46]. Superior results for EUS in detecting small pancreatic tumors [47,48] and the diagnostic accuracy of EUS

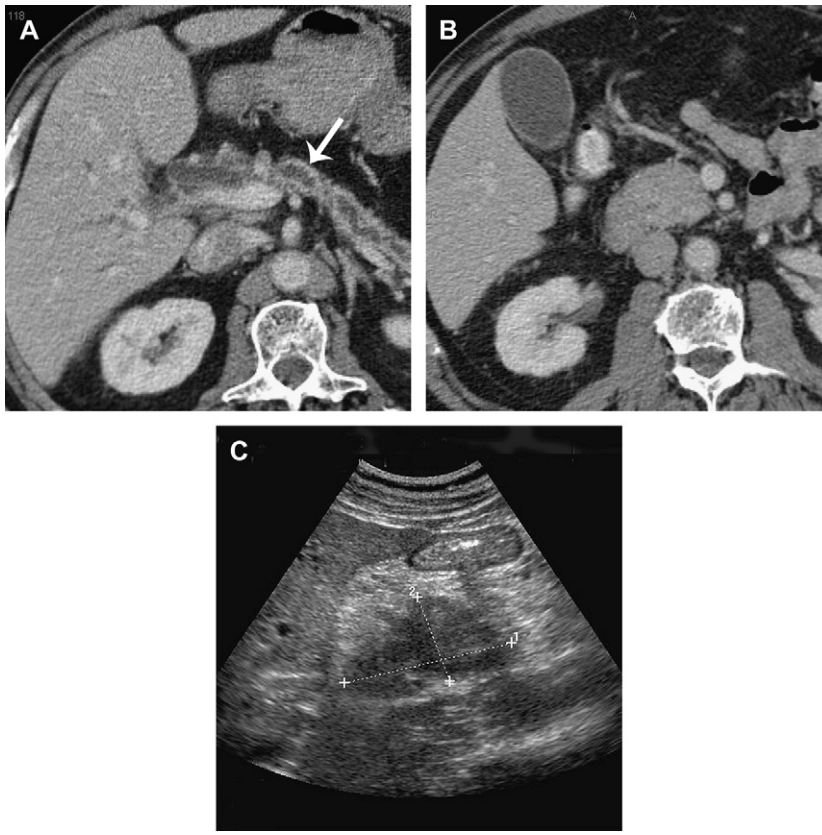

Fig. 3. ''Resectable'' pancreatic head carcinoma. (*A*) Axial CT shows pancreatic ductal dilation (*arrow*) within the atrophic body and tail of pancreas. (*B*) Axial CT shows a rounded mass in the pancreatic head, with clear fat planes round the superior mesenteric artery and most of the mesenteric vein. (*C*) Endoscopic ultrasonography shows a hypoechoic mass (*cursors*) within the pancreatic head and showed no lymphadenopathy or vascular invasion.

in assessing the tumor and regional lymph nodes in patients who have potentially resectable pancreatic cancer has been reported by several authors. Rosch and colleagues [49] evaluated the diagnostic accuracy of EUS in assessing portal vein invasion compared with conventional CT imaging. EUS was 95% accurate at predicting portal vein invasion, which was significantly better than conventional CT imaging.

There are, however, some inherent limitations of EUS in local staging of pancreas cancer. The imaging obtained by means of EUS, unlike CT, is apt to be operator dependent. The ability of EUS to accurately detect locoregional invasion or encasement of vessels other than the portal vein may be limited [47]. Consequently there is considerable regional difference in the optimal staging modality of resectable pancreatic cancers. Multidetector row CT scanning may be more accurate than EUS at giving a comprehensive picture of the upper abdominal arterial tree and the proximity of a cancer to the celiac axis and superior mesenteric artery. A recent study compared the accuracy of CT and EUS in predicting unresectability of locally advanced tumors. Both helical CT and EUS were found to predict unresectability with an accuracy of 90% [48].

These findings underscore the importance of tailoring the preoperative workup of patients who have pancreatic cancer so as to improve the preoperative staging of patients and offer them the optimal treatment approach. Pancreas-dedicated CT scanning may provide the most information about the tumor including proximity to regional arteries and veins, locoregional lymph nodes disease, and distant metastases, whereas EUS may be used to support CT scan findings, to provide information that may change the approach in patients with equivocal CT scan results, or to provide a preoperative biopsy.

The increased availability of protocol-based therapies in the management of patients who have pancreatic cancer has increased the interest in firmly establishing a preoperative diagnosis in patients who have presumed pancreatic cancer. EUS combined with fine-needle aspiration (EUS-FNA) can reliably and accurately diagnose cancer in patients who have presumed periampullary malignancies [50], and can overcome many of the limitations of transabdominal ultrasound and CT for staging patients who have pancreatic cancer. The specificity of EUS in detecting periampullary malignancies increases when combined with FNA [51]. EUS can safely and accurately establish a cytologic diagnosis of cancer in patients who have both early-stage and advanced pancreatic cancer. This enables patients and physicians to consider all treatment options including neoadjuvant chemotherapy–based protocols in the management of patients who have these cancers. Many believe that EUS-guided FNA is superior to CT-guided FNA [52].

Positron Emission Tomography

Though the mainstay of diagnosis and staging of pancreatic cancer comes from anatomic imaging modalities, there are some limitations to these techniques that may be better served by functional imaging modalities like FDG positron emission tomography (PET) scanning. FDG-PET scanning may be superior to

conventional imaging techniques in detecting lesions smaller than 2 cm in size [53,54]. In an early study, PET was found to have much greater sensitivity compared with conventional CT scanning for the detection of small pancreatic cancers. The small study group size and older generation CT techniques used in this study require confirmation in larger trials using contemporary imaging techniques and will likely narrow these widely disparate findings [54]. CT and EUS are better at assessing the relationship of the tumor to other organs and regional vascular structures. It seems that PET scans may be most helpful in assessing smaller lesions, some cystic lesions, and for the presence of distant metastases [55,56]. Another potential application of PET is the assessment of response to neoadjuvant treatment protocols. Despite a response to such treatment, CT or EUS imaging may fail to show signs of improvement; several pilot studies have suggested that decrease in FDG avidity correlates to histologic response and better survival in patents who have adenocarcinoma of the pancreas [57,58].

Combining anatomic and biologic (PET/CT fusion) data may be particularly useful in imaging malignant or potentially malignant pancreatic masses. Recently, Lemke and colleagues [59] have demonstrated that retrospective fusion of CT and FDG-PET resulted in improved sensitivity of both imaging modalities (CT: 76%; PET: 84.4%; fused: 89.1%) [55]. In addition, fusion images also resulted in slight but statistically insignificant improvement in the sensitivity for detecting lymph node metastasis compared with each imaging modality taken separately. More recently, Heinrich and colleagues [60] have investigated the cost-effectiveness of using integrated PET/CT in managing patients who have potentially resectable pancreatic tumors. Although the accuracy of FDG-PET for detecting pancreas cancer was similar to that of previous studies, fusion scans detected occult metastatic disease in 5 of 59 patients studied (8%). Though these patients required further confirmatory procedures (ie, EUS- or CT-guided biopsies), they were spared surgical explorations. The combination of PET-CT scanning may therefore result in significant cost savings in managing patients who have pancreas cancer by avoiding unnecessary procedures and hospitalizations.

The strength of FDG-PET/CT scanning may be in its ability to detect pathology and characterize lesion morphology at the time. In some patients this may provide information that helps to differentiate benign from potentially malignant pancreatic lesions. In this setting, fusion FDG/PET may provide information that alters management (ie, close observation versus exploration) and leads to superior diagnosis and staging. The exact role of PET and of fusion PET/CT scanning in the diagnosis and staging of pancreatic cancer has yet to be fully elucidated.

Endoscopic Retrograde Cholangiopancreatography

ERCP remains a valuable tool in the evaluation of patients who have suspected periampullary neoplasms. ERCP is a highly sensitive imaging tool in evaluating patients who have suspected hepatobiliary disease [61,62]. ERCP allows for

sampling of pancreatic fluid and acquisition of brush cytology, which may allow for detection of molecular alterations identifying patients at high risk of adenocarcinoma of the pancreas [62]. ERCP is mainly performed in patients with evidence of biliary obstruction with the option of performing a therapeutic intervention in the same setting. Abrupt stricture of the common bile duct and pancreatic duct, commonly known as the "double duct sign," strongly supports the diagnosis of pancreatic cancer. In this setting, ERCP can be combined with multidetector row CT scanning and/or EUS to provide a likely diagnosis and provide important information concerning regional involvement, vascular integrity, and distant metastatic disease.

Laparoscopy

Existing radiographic staging modalities are inaccurate at detecting low-volume small peritoneal implants and small liver metastases [63]. Diagnostic laparoscopy has been accepted as an integral component of the staging of pancreatic cancers. In a recent study by Jimenez and colleagues [64,65], 31% of 125 patients who had clinical stage II and III disease preoperatively were discovered at laparoscopy to have unsuspected metastatic disease. The apparent benefit to these patients was the avoidance of an unnecessary laparotomy and its associated morbidity and delay in definitive therapy. Several studies suggest that the incidence of CT-occult metastases ranges between 5% and 15%. This has led some centers to perform diagnostic laparoscopy in all patients who have potentially resectable pancreatic cancer, whereas some centers perform diagnostic laparoscopy only in patients believed to be at higher risk for having CT-occult metastases (eg, presence of ascites, large primary tumor, markedly elevated CA19-9 level). Other groups have concluded that this frequency is too small to warrant routine diagnostic laparoscopy.

Diagnostic laparoscopy has also been used to stage more fully patients being considered for neoadjuvant chemotherapy and radiation treatment protocols [66,67]. Recently, Traverso and colleagues [67] have advocated the use of laparoscopy in the further staging of patients who have locally advanced unresectable tumors by conventional CT scanning, as the presence of metastatic disease in these patients would likely preclude treatment with radiation. Up to 50% of patients who have unresectable left-sided pancreatic cancer and 25% of patients who have unresectable head cancers may be found to harbor occult metastatic disease.

SUMMARY

Early diagnosis is likely to improve the outcome and survival in patients who have pancreatic cancer. The sensitivity and specificity of current screening methods, however, limit their applicability to individuals at high risk for developing pancreatic cancer. Further development of serum markers may lead to improved diagnostic accuracy and allow screening to be implemented more broadly. Proteomic profiling and evaluation of panels of markers hold particular promise for the future.

The accurate staging of pancreatic cancer is an important step in the appropriate management of patients who have these aggressive tumors. Multidetector row CT scanning and EUS play dominant roles in the contemporary staging of pancreatic malignancies. Advances in these techniques have resulted in progressively more accurate assessment of tumor resectability and regional lymph node involvement. Selective use of PET imaging and diagnostic laparoscopy may further stratify patients into better treatment modalities and spare some patients of unnecessary laparotomy.

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Pancreatic Endocrine Tumors

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Pancreatic endocrine tumors (PET) are believed to arise from immature stem cells of the neuroendocrine system [1,2]. They are discovered most commonly in the fourth and fifth decades of life with a slight female predominance [3]. These tumors may be associated with a clinical syndrome related to hormone release, eg, insulin, gastrin, glucagon, pancreatic polypeptide, vasoactive intestinal peptide (VIP), and somatostatin. PET are classified as functional or nonfunctional depending on the presence or absence of symptoms related to hormone release. Previously, the majority of identified PET were functional (70% of cases); however, the widespread use of improved cross-sectional imaging has led to the identification of small incidental PET with increasing frequency [4]. The most common PET are insulinomas followed by gastrinomas. Most insulinomas are found in the pancreas (approximately 90%), and up to 80% of gastrinomas are located in the gastrinoma triangle [3,5]. Insulinomas are less likely (<10% of cases) to display a malignant phenotype characterized by nodal and distant metastasis than other PET (50% to 90% of cases) [6–8].

The clinical presentation of functional PET depends on the hormone secreted in excess, and elevated serum hormone levels are diagnostic. MEN1 (multiple endocrine neoplasia type 1) is the syndromic occurrence of pituitary tumors (90% of cases) and parathyroid tumors (90% of cases), along with PET (80% of cases) [9]. PET associated with this syndrome include nonfunctioning PET (80% to 100%), gastrinomas (54%), and insulinomas (21%). Therefore, the diagnostic evaluation of patients with PET should include calcium, parathyroid, and prolactin levels to evaluate for other tumors occurring in a syndromic fashion. Patients demonstrating a clinical suspicion for functioning PET who also have elevated serum hormone levels should undergo tumor localization.

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This article focuses on recent developments in the areas of PET diagnosis and localization, prognostication, and treatment.

PET DIAGNOSIS AND LOCALIZATION

The accuracy of diagnostic imaging depends primarily on PET size. Nonfunctioning PET are usually discovered in an incidental fashion and tend to be larger (4 to 10 cm) then functioning PETs. They may have a heterogeneous appearance and contain cystic areas reflecting degeneration and necrosis [10–12]. Noninvasive techniques for localizing tumors include transabdominal ultrasound (TAUS), CT scan, MRI, and somatostatin receptor scintography (SRS). Sensitivity of TAUS is highly operator dependent and, at best, detects 50% of tumors [13–15]. New multidetector helical CT provides higher resolution than older helical CT machines. Several small studies have shown improved sensitivity (>80%) in localizing PET, particularly insulinomas [16–19]. For gastrinomas, however, the sensitivity of CT is low, around 40% [20]. Likewise, MRI has greater than 80% sensitivity for detection of insulinomas, but far less for gastrinomas [21–23].

Since more than 80% of gastrinomas, carcinoids, nonfunctioning PET, and glucagonomas possess somatostatin receptors, labeled octreotide can be injected for tumor localization by nuclear SPECT imaging. SRS is able to localize 88% of carcinoids, 77% of gastrinomas, 83% of nonfunctioning PET, and 100% of glucagonomas [24–27]. This technique can also be used for the detection of distant metastases, including to lymph nodes, bone, and liver [28]. SRS displays only 63% sensitivity for detecting insulinomas, as roughly half of these tumors express somatostatin receptors [29,30]. Other limitations of SRS include less specific tumor localization within the pancreas and inability to determine whether uptake is in an intrapancreatic PET versus an adjacent lymph node.

Arterial stimulation with secretagogues followed by selective venous sampling (ASVS) is now rarely employed to localize PET. ASVS combined with angiography achieves a localization rate of greater than 80% for insulinomas, but only 41% for gastrinomas [31–33].

Endoscopic ultrasound (EUS) has become the preferred modality for diagnosing and localizing PET. EUS-guided fine-needle aspiration (FNA) allows for accurate sampling of lesions smaller than 1 cm [34,35]. Anderson and colleagues [36] undertook a prospective study of 82 patients referred for EUS with clinical, biochemical, and radiological evidence of neuroendocrine tumor. Overall, EUS correctly localized the PET in 93% of cases; 100% of gastrinomas and 88% of insulinomas. The mean tumor diameter was 1.51 cm with 71% of the tumors less than 2 cm in size. Most tumors were hypoechoic, homogeneous with distinct margins, and located in the pancreatic head. In a small series, malignant nonfunctioning tumors appeared hypoechoic with an irregular central echogenic area as compared with benign nonfunctioning tumors, which were more homogeneous. These results should be interpreted with caution given the small number of patients [37]. EUS has proven more cost effective in the evaluation of suspected PET compared with other localization techniques [38].

Intraoperative ultrasound (IOUS) and intraoperative endoscopic transillumination are also used to localize PET more accurately than noninvasive methods of localization. IOUS is successful in detecting 85% of PET localized to the pancreas or liver [39,40]. However, for PET in extra-pancreatic sites, the sensitivity of IOUS falls to less than 50% [41]. In contrast, intraoperative endoscopic transillumination may be highly effective (80%) for detecting extra-pancreatic PET such as duodenal gastrinomas [42].

PET PROGNOSTICATION

The clinical distinction between benign and malignant PET remains uncertain, and there is no commonly accepted staging or grading system for PET that accurately predicts their long-term biological behavior. With the increasing detection of incidental PET, accurate outcomes data are essential for clinical decision making. Autopsy series show that a significant proportion of PET are indolent lesions. Identifying these lesions in marginal operative candidates is particularly important. Moreover, identifying patients with localized PET but high risk for systemic metastasis is equally important. The histopathological evaluation following surgical resection can provide some of this information. One classification system (the Capella classification) uses tumor size, differentiation, vascular invasion, functional lineage, and Ki-67 status to classify tumors into benign, borderline, low-grade malignant, and high-grade malignant categories [43–45]. In the recent World Health Organization (WHO) classification [46], well-differentiated tumors are divided into tumors with benign behavior and those with uncertain behavior. The benign PET are confined to the pancreas, lack angioinvasion and perineural invasion, have a diameter less than 2 cm, manifest fewer than 2 mitotic figures per 10 high-power fields, and display less than 2% Ki-67–positive cells. PET with uncertain behavior are confined to the pancreas and have any of the following features: angioinvasion, perineural invasion, diameter greater than or equal to 2 cm, 2 to 10 mitoses per 10 high-power fields, and a frequency of Ki-67–positive cells higher than 2%. Well-differentiated endocrine carcinomas are locally invasive or metastatic. Poorly differentiated endocrine carcinomas exhibit greater than 10 mitotic figures per 10 high-power fields [46].

A variety of studies have shown the utility of these indicators in various combinations. For example, in a series of 61 PET, vascular or neural invasion, Ki-67 proliferative index higher than 2%, mitotic rate of 2 or more, size 4 cm or larger, capsular penetration, nuclear atypia, lack of progesterone receptors, and presence of calcitonin correlated with malignancy. The first two characteristics were most sensitive and specific. In combination with metastasis, the presence of vascular or perineural invasion and Ki-67 of 2% or more correlated with survival [47,48]. Deshpande and colleagues [49] evaluated 101 resected PET and found that necrosis, vascular invasion, perineural invasion, and cytokeratin-19–positive cells correlated with malignant PET. Hochwald and colleagues [50] evaluated 136 PET and found that mitotic rate and necrosis correlated strongly with survival.

A number of studies have attempted to use molecular markers as surrogate end points for PET prognostication. It is clear that the development and progression of PET is associated with genetic abnormalities. Recent literature suggests that chromosomal losses occur more often than gains or amplifications in PET [51–54], and the degree of mutational damage appears to correlate with tumor size and extent. These data suggest that genetic alterations accumulate during malignant transformation [52]. For example, losses of chromosome 1 and 11q as well as gains of 9q occur early in the development of PET, as these abnormalities appear more frequently in small tumors (<2 cm) [52]. On the other hand, losses of chromosomal arms 3p, 6pq, and 10pq and gains of 5q, 12q, 18q, and 20q occur with the onset of malignant behavior [52,55,56].

These data suggest that molecular analysis of PET can provide useful information with clinical and prognostic applications. All of these studies investigated the molecular profiles of PET by analyzing resected tissue samples. However, the ability to detect these molecular abnormalities in scant, preoperatively obtained cytologic samples has not been well studied. We recently performed [57] microdissection-based LOH (loss of heterozygosity) analysis on EUS-FNA cytology samples from PET using 17 polymorphic microsatellite markers on chromosomes 1p, 3p, 5q, 9p, 10q, 11q, 17p, 17q, 21q, and 22q. Fractional allelic loss (FAL) was calculated for each tumor and defined as the number of chromosomal arms on which allelic loss is observed divided by the number of chromosomal arms for which allelic markers were informative. A total of 25 patients with PET underwent EUS-FNA over a 32-month period. Mean follow-up time was 23.2 months. Thirteen PET were classified histologically as benign PET limited to the pancreas, and 12 were classified as malignant (invasive or metastatic). Mean FAL in the benign and malignant PET was 0.03 and 0.37 ($P < .0001$), respectively. Additionally, the mean FAL was significantly greater in those with disease progression as compared with patients with stable disease (0.45 versus 0.09 respectively, $P < .0001$). This study shows that a broad-panel microsatellite loss analysis of EUS-FNA samples from PET can be reliably performed. The LOH profile (FAL) differentiates benign and malignant PET and provides important prognostic information [57].

Another evolving field of interest is the role of microRNAs as a marker of PET differentiation and clinical behavior. MicroRNAs are small, noncoding RNAs that regulate gene expression by degrading or inhibiting the translation of specific mRNAs. MicroRNAs may contribute to PET development and progression and may have prognostic value [58].

TREATMENT

Surgical resection and debulking are the mainstays of treatment for patients with PET. The aggressive surgical approach is based on good data from 2 previous studies demonstrating 74% 5-year survival and symptomatic improvement in 90% of patients after complete surgical excision or debulking of metastatic PET [59,60]. For small, benign-appearing PET, enucleation is favored over surgical

resection. Laparoscopic pancreatic resection has recently been shown to be feasible and at least as safe and effective as open resection [61–63]. For patients with PET who cannot undergo surgery, octreotide infusion may alleviate symptoms and retard tumor growth. Response rates of PET to systemic chemotherapy regimens including streptozotocin and doxorubicin are generally poor (<20%) despite initial enthusiasm for their use [64]. Studies evaluating the efficacy of interferon-alfa, dacarbazine (DTIC), or hepatic arterial chemoembolization for metastatic neuroendocrine tumors are ongoing.

Accurate preoperative diagnosis and localization are key if surgical resection is contemplated for advanced disease. A recent retrospective analysis of patients with hepatic metastases (total 48; 36 carcinoid and 12 islet cell tumors) compared conservative therapy (total 17; octreotide = 7, observation = 6, systemic chemotherapy = 4) to hepatic artery embolization (total 18) and surgical treatment (total 13; resection = 6, ablation = 4, combined resection and ablation = 3). Median follow-up was 20 months. Improved 3-year survival was noted in the surgically treated patients compared with medical therapy or embolization (83% versus 31%, $P = .01$) [65].

The treatment of PET and duodenal endocrine tumors in the setting of MEN1 (10% to 20% of cases) present a set of unique challenges. Insulinomas should be enucleated or resected in patients with MEN1. Recommendations for gastrinoma are not as clear, especially for tumors less than 2 to 3 cm in size. These tumors are often small, multiple, and widespread in MEN1 and thus difficult to remove without leaving the patient with surgically induced diabetes. Additionally, recurrence is frequent after excision. The clinical course of gastrinoma is often indolent in these patients but eventually results in the development of hepatic metastases, which are the most common cause of death. In a prospective study of 81 patients with MEN1 and Zollinger-Ellison syndrome (ZES), 17 patients with limited disease (single PET 2.5-6 cm) and 31 patients with locally advanced disease (two or more lesions, 2.5 cm or larger, or one lesion larger than 6 cm) underwent surgery, and outcomes were compared. Patients with single PET lesions less than 2.5 cm and diffuse liver metastasis did not undergo surgery. In the group with limited disease, 35% had multiple PET, and 65% had lymph node metastases. In the locally advanced group, 88% had multiple PET, 71% had lymph node metastases, and 12% had hepatic metastases. Follow-up was performed for a mean of 6.9 years. No patient was disease-free at 5 years. Hepatic metastases developed in 6% of patients in both groups, and the 15-year survival rates were similar, albeit significantly better than the non-operative group with diffuse liver disease. The authors concluded that nearly 40% of patients with MEN1 and ZES have advanced disease and benefit from surgical resection [66]. Patients with ZES but not MEN1 or metastatic disease have a high cure rate with resection and should be offered surgery [67].

Evolving areas of therapy include endoscopic ablation with alcohol under EUS guidance [68]. Currently this approach should only be considered as part of a research protocol.

SUMMARY

Incidental, nonfunctional PET are coming to attention with increasing frequency. The majority of these are insulinomas. EUS with FNA has evolved to play a significant role in the localization and tissue diagnosis of PET. Establishing PET behavior as aggressive or indolent remains challenging especially preoperatively. Newer techniques including DNA and micro-RNA analysis may play a role in this arena. Small benign PET may be enucleated or removed laparascopically. Surgery is also the mainstay of treating advanced disease including those with metastases in appropriate candidates and ZES. The management of MEN1 continues to be a challenge, including treating symptoms, targeted resections and close observation. The diagnosis, management, and prognostication of PET are under evolution and a number of changes in these fronts are anticipated.

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Minimally Invasive Treatment of Pancreatic Disease

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Advances in laparoscopic surgical skills and techniques combined with advances in laparoscopic technology have encouraged the application of laparoscopy to the evaluation and treatment of solid organs including the pancreas. Although open surgical procedures remain the standard for both benign and malignant diseases of the pancreas, in recent years a wide variety of surgical procedures performed on the pancreas have been completed laparoscopically. Single and multi-institutional case series have demonstrated these various types of laparoscopic pancreatic surgery can be performed with low complication rates, although randomized prospective trials that evaluate the safety, benefits, and cost of laparoscopic pancreatic surgery in comparison with open pancreatic surgery have yet to be conducted. Whereas trials have shown the benefits of laparoscopic colon and bariatric surgery, conduct of similar trials has been delayed by the relative infrequency of pancreatic surgery. Nevertheless, general experience with minimally invasive abdominal surgery suggests that benefits of laparoscopic pancreatic surgery may include decreased incisional complications, less postoperative pain, faster return of digestive function, faster return to normal activities, development of fewer intra-abdominal adhesions, and diminished procedure-related inflammatory responses and alterations in host immune function.

This article reviews the application of minimally invasive surgery to the management of pancreatic disease. Basic familiarity with laparoscopy and laparoscopic instrumentation is sufficient to perform laparoscopic staging of pancreatic cancer. The ability to dissect tissues laparoscopically is necessary to perform enucleation, distal (left) resection, or debridement procedures. When reconstruction is also required, as in performing a pancreaticoduodenectomy (Whipple procedure), longitudinal pancreaticojejunostomy (Puestow-type procedure), or internal drainage of a pancreatic pseudocyst (cystgastrostomy or Roux-en-Y cystjejunostomy), further laparoscopic expertise is required.

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ACUTE PANCREATITIS

Early management of acute pancreatitis is medically based and focused on fluid resuscitation, nutritional support, and prophylaxis against pancreatic and peripancreatic infection. In the absence of pancreatic or peripancreatic necrosis, early surgical intervention is rarely necessary in patients with acute pancreatitis. In the setting of necrosis, however, approximately 25% of patients require surgical debridement and drainage when areas of necrosis become infected. Operative intervention may also be necessary in patients with sterile necrosis who fail to improve despite aggressive medical treatment. The indications for and timing of surgery in the treatment of acute pancreatitis are discussed in greater detail elsewhere in this issue.

Debridement and drainage of areas of pancreatic and peripancreatic necrosis is typically performed through a generous upper abdominal incision. If areas of necrosis cannot be readily separated from healthy tissues, repeated debridement procedures may be necessary. Management in this manner may be lifesaving, but complications, such as bleeding, intestinal fistulae, or complex abdominal wounds, frequently arise and have prompted interest in minimally invasive techniques of performing pancreatic necrosectomy.

Several techniques have been described, although prospective randomized trials have not been completed that compare these techniques with each other or with open debridement procedures. Alverdy and coworkers [1] reported two patients treated by means of intracavitary debridement of pancreatic and peripancreatic necrosis. This method is illustrated in Fig. 1. The tissues that surround the area of necrosis are characteristically thickened as a result of the ongoing inflammatory changes and thereby create a cavity or space into which one or more guidewires can be placed under either CT or ultrasound direction. Over these guidewires, ports can then be placed into the cavity and a working space can be created by insufflating with carbon dioxide at low pressures. Necrotic tissues can then be removed using grasping instruments and suction-irrigating devices. Once the debridement procedure has been completed, the ports can be replaced by large drains; if further debridement is deemed necessary, these drains can be exchanged once again for ports.

Alternatively, using ports placed into the peritoneal cavity, the lesser sac and pancreatic bed can be accessed in a manner similar to that used in open debridement procedures. The lesser sac can be approached from its anterior aspect, but this dissection may be difficult because the plane of dissection between the stomach and the transverse mesentery may be obliterated. Instead, the lesser sac can be entered through the transverse mesocolon by an infracolic approach [2,3]. If the area of necrosis is adjacent to the posterior wall of the stomach and sufficient time has elapsed to allow formation of a fibrous capsule surrounding it, transgastric laparoscopic debridement can be performed in the same manner as creation of a laparoscopic pancreatic cystogastrostomy [4,5] for internal drainage of a retrogastric pseudocyst (see later). This method allows for internal drainage of any residual areas of necrosis, avoids the need for placement of external drains, and eliminates the risk of a subsequent pancreaticocutaneous fistula.

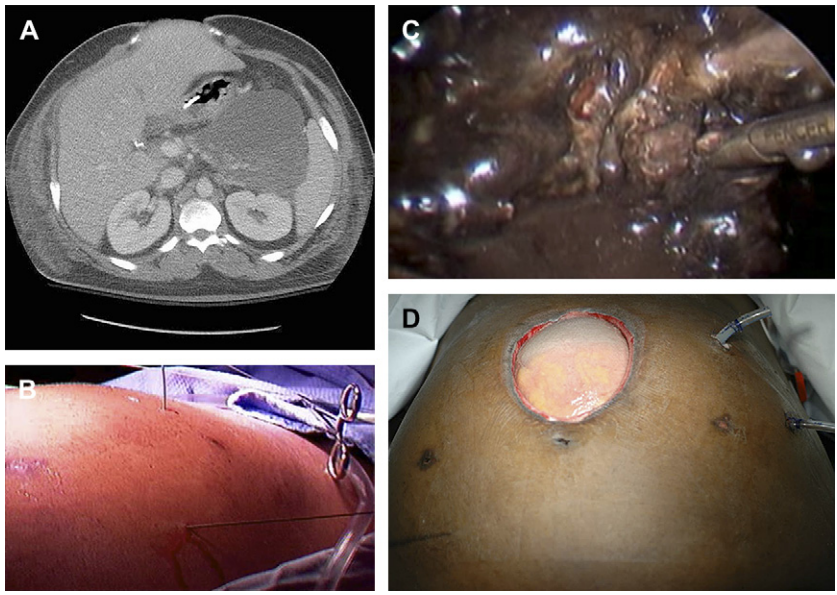

Fig. 1. (*A*) Pancreatic necrosis in a patient who required an emergency bedside celiotomy for decompression of an acute abdominal compartment syndrome. His abdomen was then closed using absorbable mesh. A few weeks later he developed persistent fevers and fine-needle aspiration of this large area of fluid and necrotic debris confirmed the presence of infection. As seen in this image, his liver is adherent to the margins of his abdominal wall defect, impeding open debridement and drainage of the infected necrosis. (*B*) Under ultrasound guidance, two guidewires have been placed into the areas of necrosis. Introducer assemblies consisting of a dilator and peel-away sheath are then advanced over the guidewires, and through the sheath a 5-mm port is then inserted. In this figure, the dilator has been advanced over the guidewire in the epigastrium. (*C*) With two ports placed, necrotic tissue in the lesser sac cavity is debrided using a grasping instrument. (*D*) On completion of the necrosectomy, the ports are replaced with large drains. In this patient, intermediate-sized chest tubes were used, because these provided effective drainage and permitted easy reinsertion of ports if further debridement was necessary.

When the areas of pancreatic and peripancreatic necrosis extend toward the flank or down the paracolic space, debridement can be performed through a limited flank or retroperitoneal incision rather than through a more extensive celiotomy. Debridement in this manner can be guided using a laparoscope inserted into the same incision alongside the surgeon's fingers or instruments used for the debridement [6]. Although this technique has been most often applied to the left side of the abdomen, it may be particularly helpful when debridement is necessary in proximity to the duodenum or major vessels near the head and neck of the pancreas.

CHRONIC PANCREATITIS

Patients with chronic pancreatitis may develop biliary or gastric outlet obstruction. As described later, relief of both can be achieved laparoscopically. In

contrast to patients with malignant biliary obstruction, however, relief of biliary obstruction in patients with chronic pancreatitis should not be accomplished by means of a cholecystojejunostomy, because this is not likely to be durable. Laparoscopic creation of either a choledochoduodenostomy or a hepaticojejunostomy has been reported but requires greater surgical expertise [7–9].

Surgical interventions in chronic pancreatitis are most commonly performed for relief of pain. If a pseudocyst is present, drainage of the pseudocyst may provide symptomatic relief and should be considered. Several techniques for laparoscopic internal drainage of pancreatic pseudocysts have been described with recurrence and complication rates similar to those reported for open internal drainage procedures. A posterior cystgastrostomy can be created either by fashioning an anterior gastrostomy through which instruments are then passed [10], or by insertion of ports directly into the stomach [11]; with the latter method, further visualization can be achieved by passage of a flexible endoscope per os into the stomach. With either technique, a posterior cystgastrostomy is then made. If the posterior wall of the stomach and anterior capsule of the pseudocyst are well approximated and adherent to one other, creation of an opening that connects the stomach to the pseudocyst using electrocautery or ultrasonic dissecting instruments may suffice. Otherwise, the stomach and pseudocyst capsule can be mechanically approximated to one another using endoscopic staplers. If the thickness of the gastric wall or pseudocyst capsule prevent application of a stapler, the stomach and pseudocyst can be held together using laparoscopically placed sutures.

Park and coworkers [12,13] have described an additional method for creating a pancreatic cystgastrostomy in which the lesser sac is entered and the interface between the posterior wall of the stomach and the pseudocyst is identified. Immediately adjacent to this interface corresponding openings are made in the posterior wall of the stomach and the pseudocyst, and through these openings an endoscopic stapling device is inserted and then fired, thereby creating an anastomosis between the posterior wall of the stomach and the pseudocyst. These authors suggest that the absence of an anterior gastrostomy is an advantage of this method.

Finally, a cystjejunostomy can be created laparoscopically using either a Roux limb or a jejunal loop [14–16]. The large numbers of laparoscopic Roux-en-Y gastric bypasses now being performed annually have provided effective preparation for laparoscopic Roux-en-Y pancreatic cystjejunostomy procedures.

If the pancreatic duct is dilated, longitudinal drainage of the pancreatic duct into a Roux limb (Partington-Rochelle modification of the Puestow procedure) may be beneficial. Recently, two groups have shown that this procedure can be safely and effectively completed laparoscopically. Tantia and colleagues [17] reported a series of 17 patients in whom laparoscopic longitudinal Roux-en-Y pancreaticojejunostomies were attempted. In one patient the procedure was converted to open because of bleeding from a tributary of the splenic vein. The procedure was converted to open in three patients because of inability

to isolate the main pancreatic duct; in this series laparoscopic ultrasonography was not available. In all patients the pancreatic duct was at least 9 mm in diameter, and the anastomosis of the jejunum to the pancreatic duct was performed as a two-layer hand-sewn anastomosis. There were no deaths among these patients. Two (11.8%) complications occurred and consisted of a wound infection and an internal hernia through the mesocolic rent that required surgical correction on the twenty-third postoperative day. On follow-up, 14 (82.3%) patients had obtained pain relief, and weight gain or stabilization was found in 16 (94%) patients.

Palanivelu and colleagues [18] recently reported a series of 12 patients undergoing laparoscopic longitudinal pancreaticojejunostomies. The average duct diameter was 14.7 mm, and in all patients the procedure was completed laparoscopically. There were no deaths and no major complications among these 12 patients. Mean operating time was 172 minutes, and mean postoperative length of stay was 5 days. With median follow-up of 4.4 years, 10 patients had complete pain relief and two had partial pain relief; all patients had significant weight gain.

Resection of focal areas of disease may also be beneficial in chronic pancreatitis. In particular, the head of the pancreas frequently is severely diseased and enlarged, and resection of this portion of the pancreas leads to symptomatic improvement in up to 90% of patients [19]. Resection of the pancreatic head can be accomplished by means of a Whipple-type procedure (pancreaticoduodenectomy). Such procedures have been completed laparoscopically. Reported series, however, have predominantly included patients with periampullary neoplasms rather than chronic pancreatitis, and the extensive fibrosis found with chronic pancreatitis is likely substantially to increase the difficulty of performing such procedures laparoscopically. Duodenum-sparing resection of the head of the pancreas (Beger procedure) and resection of the pancreatic head combined with a longitudinal pancreaticojejunostomy (Frey procedure) both require sharp excision of parenchyma from the head of the pancreas, and to date neither has been reported as a laparoscopic procedure. Because the excision in a Frey procedure is limited, however, this procedure seems feasible to complete laparoscopically in view of the experiences reported by Tantia and coworkers [17] and Palanivelu and coworkers [18].

PANCREATIC NEOPLASMS

Laparoscopic Staging and Palliation of Pancreatic Cancer

Despite preoperative evaluation using CT and other imaging modalities, metastatic disease that precludes a curative resection may be found in patients undergoing open surgical exploration. A number of groups have studied the usefulness of laparoscopy for the minimally invasive detection of such CT-occult disease. Jimenez and colleagues [20] from the Massachusetts General Hospital, for example, found occult metastases in 17% of patients with pancreatic head cancers. Conlon and colleagues [21] performed more detailed laparoscopic

evaluations that included evaluation of the peritoneal cavity, liver, lesser sac, porta hepatic, duodenum, and transverse mesocolon and selective biopsy of celiac, portal, and perigastric lymph nodes in 115 patients with radiologically resectable peripancreatic cancers, and identified liver metastases in 20 and extrapancreatic-peritoneal involvement in 16 patients. Among 67 patients considered to have resectable disease on completion of the laparoscopic evaluation, five were found on open exploration to have small deep liver metastases.

The authors evaluated the usefulness of routine diagnostic staging laparoscopy in a series of 82 patients with confirmed periampullary malignancies without evidence on triphasic helical CT of either locally advanced or metastatic disease. In 77 patients laparoscopy was performed; in the remaining five, laparoscopy was unsuccessful because of extensive adhesions or was not attempted because of the need to palliate gastric outlet obstruction. Laparoscopic evaluation consisted of visual inspection of the surface of the liver and accessible peritoneal and visceral surfaces, and was at times facilitated by placement of an additional 5-mm port. No attempt was made routinely to divide adhesions or to enter the lesser sac. Suspicious findings were biopsied laparoscopically and sent for frozen section microscopic evaluation (Fig. 2). Port placement and laparoscopic evaluation required 15 to 20 minutes to complete; when suspicious findings were identified, an additional 15 to 20 minutes was required to obtain a biopsy and perform frozen section evaluation of the biopsy.

In 67 (87%) patients there were no findings of metastatic disease on laparoscopy, and exploration of the abdomen was then performed. In nine (11.7%) patients metastases not identified preoperatively were found on laparoscopy. In these patients the operative procedure was concluded and resection was not attempted. In one (1.3%) patient frozen section evaluation was inconclusive and the operative procedure was terminated. On subsequent final pathologic evaluation there were no findings of malignancy, and resection by means of a pancreaticoduodenectomy (Whipple procedure) was performed as a subsequent separate procedure after confirmation that no CT-occult metastases were present.

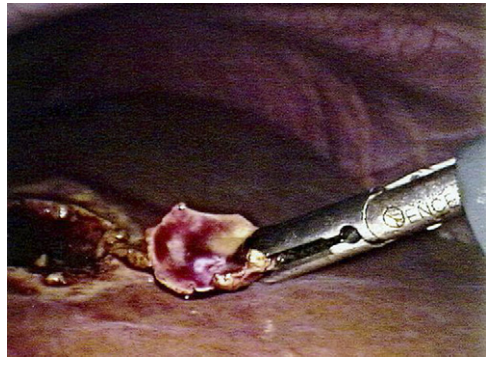

Fig. 2. Laparoscopic wedge biopsy of a CT-occult liver metastasis identified with laparoscopy.

Among the 67 patients who underwent formal exploration of the abdomen, complete resection of the tumor was performed in 63 patients. In three patients surface metastases were found that were on liver or peritoneal surfaces that could not be readily visualized laparoscopically; in one patient a very small metastasis not seen on preoperative CT imaging was palpated just beneath the surface of the liver. In this series, initial laparoscopy avoided abdominal exploration in 11.7% of the patients. If the initial laparoscopy had detected the surface implants found on exploration in the three additional patients, an abdominal exploration would have been avoided in 16% of the patients. This incidence is similar to the incidence (4%–15%) of occult peritoneal or liver metastases found in several recent series of patients with CT-resectable disease undergoing open abdominal exploration [22–25].

Because the identification of occult metastases using laparoscopy may avoid a nontherapeutic laparotomy, allow early discharge from the hospital, and permit prompt commencement of systemic therapy, the authors have adopted staging laparoscopy as a standard part of the surgical management of pancreatic cancer. Many other centers also perform routine laparoscopy for all patients considered to be possible candidates for curative resection. In contrast, other groups have maintained that the incidence of CT-occult metastases is too low to justify the nontherapeutic prolongation of operating time that approximately 85% to 90% of patient experience if routine laparoscopy is performed [23]. In other centers, selective use of laparoscopy in patients believed to be at higher risk for the presence of occult metastases has been favored. Factors that may signify higher risk of metastases include larger tumor size; presence of ascites; suspicious but indeterminate CT findings; and signs suggestive of advanced disease, such as significant malnutrition, back pain, or markedly elevated tumor markers [26].

Laparoscopic ultrasonography may be used in combination with diagnostic laparoscopy to assess for locally advanced disease and to evaluate for possible metastases within the parenchyma of the liver (Fig. 3) that are not detected by CT. The usefulness of laparoscopic ultrasonography is limited, however, by the increasing use of endoscopic ultrasound for preoperative staging. Endoscopic ultrasound can provide detailed evaluation of the primary tumor and its relationship to adjoining structures, such as the superior mesenteric vessels and the portal vein. Peripancreatic and celiac lymph nodes and the left lateral segment of the liver can be evaluated and biopsied under endoscopic ultrasound guidance.

Laparoscopic identification of metastases avoids a nontherapeutic laparotomy provided that neither a palliative nor a prophylactic open bypass procedure needs to be performed. Some investigators have argued that routine laparoscopy is unnecessary because open surgical palliation of gastric outlet or biliary obstruction is usually required. For example, Barreiro and colleagues [27] reviewed a series of 119 patients with pancreatic head or periampullary cancers found on CT to be potentially resectable. Laparoscopy was not performed; instead, all patients underwent open abdominal exploration. In 20 of

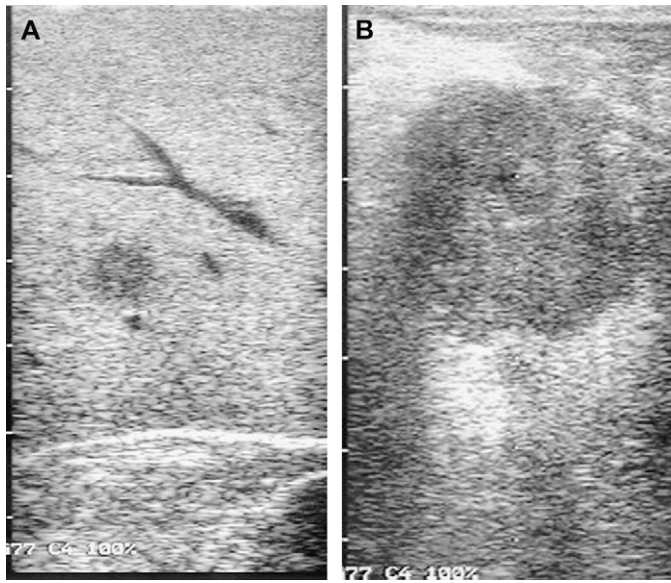

Fig. 3. (*A*) Laparoscopic ultrasound of the liver identifying small liver metastasis. (*B*) Laparoscopic ultrasound evaluation of pancreatic cancer.

23 patients found to have metastatic disease, surgical palliation was performed, leading the authors to conclude that laparoscopy would have avoided abdominal exploration in only three (2.5%) patients. The indications for surgical palliation in this series were not, however, specified. In contrast, Espat and colleagues [28] reported that in a series of 155 patients who were followed expectantly after being found on laparoscopic staging to have metastatic (115) or locally advanced (40) disease, only three (2%) subsequently required an open procedure to treat biliary or gastric outlet obstruction. These data suggest that when laparoscopic staging detects metastatic or locally advanced disease, prophylactic surgical bypass procedures are unwarranted.

Laparoscopic staging in patients with biliary or gastric outlet obstruction is of little value if open surgical bypass is routinely performed to relieve such obstruction. Alternatively, when staging laparoscopy confirms the presence of unresectable disease, proceeding with a laparoscopic biliary or gastric bypass procedure can be considered in patients who require relief of biliary or gastric outlet obstruction. Because life expectancy with metastatic pancreatic cancer is in the range of 4 to 6 months and biliary obstruction can be effectively relieved by endoscopic or percutaneous means, surgical biliary bypass, whether open or laparoscopic, may be best reserved for patients with locally advanced rather than metastatic disease [29], when these nonsurgical methods have been unsuccessful, or if concurrent gastric outlet obstruction prevents repeated access to the ampulla of Vater. When the cystic duct remains patent, laparoscopic biliary

bypass can be readily accomplished by stapling the gallbladder to the jejunum to create a cholecystoenterostomy. A hand-sewn choledochojejunostomy can also be created but requires more advanced laparoscopic suturing skills. The safety and effectiveness of a laparoscopic stapled gastrojejunostomy has been shown in several series of patients with malignant gastric outlet obstruction, and in the vast experience with laparoscopic gastric bypass surgery. It should be considered together with endoluminal stenting as an alternative to an open surgical bypass procedure [30–35].

Finally, even among patients deemed not to be candidates for surgical resection by virtue of locally advanced disease found on routine imaging studies, laparoscopy may provide more accurate staging and determine whether systemic therapy should be administered alone or in combination with locoregional therapy [36,37].

Laparoscopic Treatment of Pancreatic Neoplasms

Pancreatic endocrine tumors can at times be enucleated from the substance of the pancreas. When a pancreatic endocrine tumor is large or involves the main pancreatic duct, partial resection of the pancreas may be more suitable. Other pancreatic neoplasms, such as ductal carcinomas, cystic neoplasms, and intraductal papillary mucinous neoplasms, should be resected by means of a pancreaticoduodenectomy (Whipple-type procedure), central pancreatectomy, distal (left) pancreatectomy, or total pancreatectomy as dictated by the location and extent of the neoplasm. Each of these procedures has been successfully performed laparoscopically.

Several small series [38–40] have described successful laparoscopic enucleation of pancreatic endocrine tumors (Fig. 4). As with open enucleation of such tumors, this procedure is better suited for tumors that are located near the surface of the pancreas, and disruption of the main pancreatic duct during the dissection that results in a pancreatic fistula remains a risk of such procedures. When the tumor is not readily visible, use of intraoperative ultrasonography may help to localize

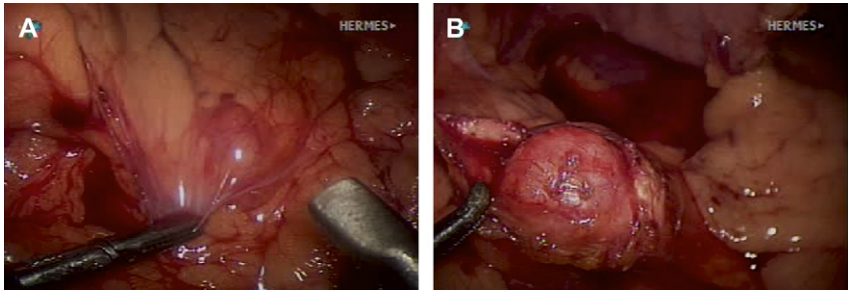

Fig. 4. Enucleation of a pancreatic endocrine tumor. (*A*) The lesser sac has been opened, and with the stomach elevated the tumor is visible protruding to the surface of the pancreas. (*B*) Enucleation of pancreatic endocrine tumor. The mass has been gently separated from adjoining normal pancreatic parenchyma.

the tumor. The visual magnification afforded by the use of laparoscopy may aid in identification of the pancreatic duct and potentially decrease the risk of disruption of the pancreatic duct.

With a central pancreatectomy, a section of the pancreas usually situated near the neck of the pancreas is removed, leaving two divided edges of the pancreas. The edge toward the head of the pancreas is closed as with a distal pancreatectomy, whereas the edge toward the tail of the pancreas is anastomosed to either the small intestine or the stomach, as with a pancreaticoduodenectomy. This procedure is performed as a means of preserving pancreatic parenchyma when treating benign or low-grade malignant neoplasms, but is not frequently performed because of the need for reconstruction and the potential for leakage from both cut edges of the pancreas [41,42]. Orsenigo and colleagues [43] have reported a laparoscopic central pancreatectomy performed for treatment of a well-differentiated neuroendocrine tumor arising within the neck and proximal body of the pancreas. In this procedure, the body and tail of the pancreas were drained into a Roux limb by means of a sewn two-layer end-to-side pancreaticojejunostomy.

Greater experience with laparoscopic resection of the pancreatic head (pancreaticoduodenectomy or Whipple-type procedures) or body and tail of the pancreas (distal or left pancreatectomy) has been accrued, and moderate-sized single or multi-institutional series of each have been reported. Laparoscopic pancreaticoduodenectomy was first described in 1994 by Gagner and Pomp [44] and several groups [45,46] have since reported small series and individual cases. Recently, Palaninvelu and colleagues [47] have reported a remarkable series of 35 patients undergoing laparoscopic pancreaticoduodenectomy. In this series, mean operating time (400 minutes), average blood loss (395 minutes), and average hospital stay (10.2 days) were all comparable with results reported in various series of open pancreaticoduodenectomy. Only two pancreatic fistulas occurred, and overall morbidity was reported to be 10% to 20%. No postoperative pulmonary complications, such as atelectasis or pneumonia, occurred. These reports demonstrate the feasibility of performing laparoscopic pancreaticoduodenectomy or total pancreatectomies, but the benefits, usefulness, appropriateness for treatment of malignant disease, and ability to disseminate these procedures beyond highly specialized centers and individuals remains uncertain.

Laparoscopic resection of the body and tail of the pancreas does not require reconstruction and has attracted growing interest among pancreatic and minimally invasive surgeons (Fig. 5). A recent European multicenter study [48] reported 97 laparoscopic distal pancreatectomies (with or without splenectomy), of which 86 (89%) were completed laparoscopically. The pancreas was transected using an endoscopic linear stapler (90%), harmonic shears (9%), or monopolar cautery (1%). Median operative time was 200 minutes (65–400 minutes) and median length of stay was 7 days. Pancreatic fistulae or fluid collections occurred in 31 patients (36%). Seven patients required surgical reexploration, and 10 required percutaneous drainage procedures. There were no operative deaths in this series. The authors concluded that left-sided

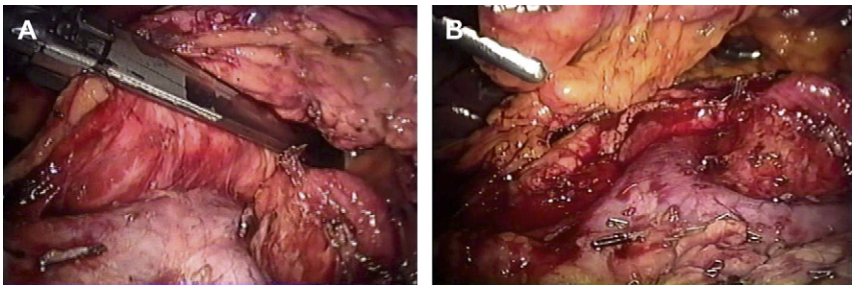

Fig. 5. (*A*) Laparoscopic distal pancreatectomy. At the neck of the pancreas, the inferior border of the pancreas has been dissected free and elevated upward. With the posterior aspect of the pancreas exposed, the splenoportal confluence has been identified and the splenic vein has been separated from the pancreas. The splenic artery has been dissected free along the superior border of the pancreas. The superior border of the pancreas has been freed at the neck, and a linear cutting staple has been applied across the neck of the pancreas. (*B*) Laparoscopic distal pancreatectomy. The pancreas has been divided using the liner stapler, and the staple line at the divided neck of the pancreas is visible. The body of the pancreas has been reflected toward the left and the portal vein coursing toward the liver can readily be seen.

laparoscopic pancreatectomies are feasible and safe in selected patients, but that management of the pancreatic stump remains the challenge of this procedure.

At the University of Pittsburgh, the authors have amassed what is to their knowledge the largest single institution experience with laparoscopic distal pancreatectomies. Between January 1, 2000, and November 30, 2005, laparoscopic distal pancreatectomies were attempted in 53 patients and successfully completed in 45; none were performed as a hand-assisted procedure. Most of these procedures included a splenectomy; in seven patients additional procedures were performed (cholecystectomy, four; Nissen fundoplication, two; left colectomy, one). The pancreas was transected using a linear stapler in all patients, and a drain was routinely left in the resection bed. In most patients the pancreas was transected and then mobilized in a medial-to-lateral fashion, although in some instances a lateral-to-medial mobilization, similar to that for laparoscopic splenectomy, was used.

A total of 85% of the procedures were performed by residents or fellows under the supervision of eight different attending surgeons (case totals ranging from 1–21). Procedures were converted to open resections because of intraoperative bleeding (one); failure to progress (three); need for exploration of the pancreatic duct (one); proximity to the superior mesenteric vein (one); tumor size (one, 19 cm); and need to obtain an additional margin (one). Median length of stay, and blood loss among these patients were all decreased when compared with contemporaneous patients undergoing open distal pancreatectomies for benign or low-grade neoplasms. Satisfactory resection margins were achieved in all laparoscopic resections except for one; in this patient, intraoperative frozen section evaluation of the margin was normal, but final permanent sections were abnormal.

Postoperative complications occurred in 15 (33%) patients. Pancreatic fistulae or fluid collections were the most common complication (10 [22%]). Surgical re-exploration was not required in any patients, however, and only one patient required placement of a percutaneous drain.

The authors' single institution experience with laparoscopic distal pancreatectomies has confirmed the feasibility and safety of this procedure. It has also confirmed that satisfactory margins of resection can be routinely achieved, and shown that the procedure can be taught to surgical trainees. Like the European multicenter study, in the authors' experience the pancreatic stump has been a frequent cause of morbidity. The incidence of complications related to the pancreatic stump, however, is similar to that currently being reported by other investigators after open distal pancreatectomy [49]. In comparison with the authors' own contemporaneous albeit nonrandomized series of patients undergoing open distal pancreatectomies, the incidence of pancreatic stump complications was similar, but postoperative length of stay and blood loss were decreased in patients undergoing laparoscopic distal pancreatectomies. Overall, these results suggest that laparoscopic distal pancreatectomy is superior to open distal pancreatectomy for treatment of benign and low-grade neoplasms arising in the body or tail of the pancreas, and in their institution it has become the preferred procedure for such abnormalities. Although these results also provide a basis for extending this procedure to treatment of pancreatic cancers arising in the body or tail of the pancreas, randomized trials are needed to confirm the safety and benefit of laparoscopic resection of the pancreas and applicability to treatment of pancreatic cancer.

SUMMARY

Case series and case reports have confirmed the feasibility of performing a wide range of procedures for the treatment of pancreatic diseases. As experience with laparoscopic distal pancreatectomy demonstrates, laparoscopic treatment of pancreatic disease may have benefits in comparison with open treatment. Such procedures as laparoscopic staging and laparoscopic distal pancreatectomy can be readily taught to surgical trainees and have great practical value because they can be readily disseminated beyond specialized centers. In contrast, the role of complex procedures, such as laparoscopic pancreaticoduodenectomy, remains to be defined and for the present such procedures are likely to performed at specialized centers. As laparoscopic skills and technology continue to improve, however, even such complex procedures are apt to become more widely performed, emphasizing the importance of future trials that confirm the safety and benefit of these laparoscopic procedures.

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Endoscopic Palliation of Pancreatic Cancer

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Pancreatic ductal adenocarcinoma is the second most common gastrointestinal malignancy and the fourth leading cause of cancer-related deaths in the United States [1]. Despite advancements in surgical techniques and chemoradiation therapy, the median survival remains less than 6 months with a 5-year survival rate between 3% and 5% [2]. The 5-year survival rate is the lowest among all known cancer types. The American Cancer Society estimates that 33,730 people will be diagnosed with pancreatic cancer in 2006 with over 32,000 cancer-related deaths [3]. Most patients present with locally advanced disease precluding curative surgical resection secondary to either local vascular invasion or metastatic disease. For the minority of patients eligible for curative surgical resection, the 5-year survival rate remains dismal at 15% to 20%. Palliative treatments constitute the cornerstone of care in most patients presenting with pancreatic cancer. Palliative options include chemotherapy, surgery, radiologic interventions, and endoscopic treatments. The goal of these palliative therapies is to alleviate symptoms, decrease hospitalizations, improve quality of life, and potentially improve morbidity and mortality.

Endoscopic therapy has become an important modality for addressing the three major symptoms attributable to locally advanced disease: (1) obstructive jaundice, (2) gastric outlet obstruction (GOO), and (3) intractable abdominal pain caused by either neoplastic infiltration of adjacent nerve terminals or obstruction of the pancreatic duct. Endoscopic biliary, enteral, and pancreatic stenting techniques, and endoscopic ultrasound (EUS)-guided celiac plexus neurolysis (CPN) have remarkable efficacy in treating these symptoms with low morbidity and mortality. Furthermore, the emergence of novel endoscopic therapies over the past few years has further contributed to the armamentarium for managing advanced pancreatic cancer. Endoscopic approaches are considered first-line treatment for palliation in cases of inoperable or unresectable pancreatic tumors.

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PALLIATION FOR MALIGNANT BILIARY OBSTRUCTION

Indications

Approximately 70% to 80% of patients with pancreatic adenocarcinoma present with obstruction of the common bile duct resulting in jaundice, pruritus, ascending cholangitis, hepatic dysfunction, and coagulopathy secondary to vitamin K malabsorption [4]. Biliary decompression is a primary goal for therapy. Biliary drainage can be achieved by one of three approaches: (1) surgical biliary-enteric bypass; (2) radiologically placed biliary stents by a percutaneous, transhepatic approach; or (3) endoscopic placement of plastic or metal stents. Before palliative biliary decompression, it is important to confirm that the jaundice is resulting from biliary obstruction and not secondary to extensive intrahepatic metastasis. Several hepatic imaging studies, preferably triphasic CT or magnetic resonance imaging, can assess the degree of intrahepatic metastasis, which also yields important information regarding local unresectability and distant metastases [5].

Quality of life improvement is a major goal for palliation. It is important to assess if alleviating the jaundice is likely to provide true quality of life improvement for the patient. Prolonged biliary obstruction may result in pruritus, recurrent cholangitis, and hepatic dysfunction. Moreover, relief of jaundice could provide a much needed psychologic boost to both the patient and family members. Until recently, however, there have been limited objective data to support this concept. A recent study prospectively assessed the impact of endoscopic biliary decompression on different physical, psychologic, and social components of quality of life in patients with unresectable pancreatic cancer without liver metastases [6]. In patients with baseline bilirubin less than 14 mg/dL, biliary stenting resulted in improvement of the general and specific well-being. Despite successful biliary decompression in patients with a baseline bilirubin greater than 13, these subjects reported a decline in both social function and mental health as assessed by a SF-36 Health Survey questionnaire. Although there are limitations to this study, these results may ultimately lead to better patient selection for palliative biliary decompression. Additional prospective studies are necessary to validate these findings before implementing in clinical practice.

Endoscopic Management of Biliary Strictures

The first step in performing an effective biliary drainage procedure is obtaining a complete cholangiogram to identify the location and extent of the stricture. A noninvasive magnetic resonance cholangiopancreatography (MRCP) allows localization and characterization of the stricture before scheduling a therapeutic endoscopic retrograde cholangiopancreatography (ERCP). MRCP becomes particularly useful when evaluating strictures involving the hepatic confluence or intrahepatic ducts. Characterizing the stricture with MRCP before ERCP may avoid unnecessary contrast injection into inaccessible areas for biliary drainage and potentially limit risks for infection. Although not necessary for all cases of suspected biliary strictures, the authors' practice is to obtain an MRCP before ERCP for every case of a suspected hilar stricture.

ERCP is performed under moderate sedation. Although conscious sedation with a benzodiazepine (versed, valium) and opiate (fentanyl, Demerol) has been the traditional form of sedation, monitored anesthesia care with propofol or even general endotracheal anesthesia may be more appropriate for difficult cases requiring additional therapeutic techniques. Deep selective cannulation of the common bile duct is achieved with a biliary catheter, followed by manipulation of a guidewire across the stricture into the obstructed bile ducts to maintain access and facilitate exchange. Hydrophilic guidewires can expedite passage through tight and tortuous strictures when compared with Teflon-coated guidewires. Furthermore, curved guidewires may also assist in negotiating difficult strictures.

When indicated, tissue sampling (transpapillary wire-guided brush cytology, endoluminal forceps biopsy, or transductal fine-needle aspiration) may be obtained from the stricture before stenting [7,8]. These techniques are usually performed under fluoroscopic guidance or occasionally under direct vision by oral choledochoscopy [9]. The specificity and positive predictive value for these techniques approaches 100% [10], indicating that a positive specimen is virtually diagnostic of malignancy. The sensitivity of tissue sampling is relatively low, however, ranging from 15% to 70%; therefore, a negative result does not exclude malignancy. Combining a second or third tissue sampling technique has been shown to increase sensitivity [11]. Recently, Sanders and colleagues [12] reported, in abstract form, their experience with an expanded tissue sampling protocol incorporating a novel forceps biopsy technique (SMASH) at ERCP. SMASH biopsies were obtained with either 5F or 6F catheter biopsy forceps, and the tissue specimen was squashed between cytology slides to undergo rapid Papanicolaou's staining for intraprocedural cytologic analysis. The expanded tissue sampling protocol also included cytology brushings, transductal fine-needle aspiration, and biopsies for hematoxylin-eosin staining. The overall sensitivity for diagnosing malignant biliary strictures was 80%, with 90% sensitivity for pancreatic cancer and 100% sensitivity for cholangiocarcinoma. Although these results produced the highest sensitivity reported to date, additional studies at other centers are necessary further to validate these findings. Alternatively, EUS with fine-needle aspiration, which has a sensitivity greater than 80% for detecting pancreatic cancer, is being routinely performed before ERCP at many expert centers [13], including the authors' (Fig. 1). Moreover, EUS evaluation before ERCP provides useful information regarding staging and surgical resectability and potentially obviates the need for additional invasive procedures (ie, ERCP for biliary decompression) if surgical resection is planned.

Before stent placement, dilation of the stricture with a catheter or dilating balloon may be performed, although this is rarely necessary [14]. Several techniques have been described for stent deployment. The most widely used procedure involves advancing a stiff polyethylene inner catheter with radiopaque markers (guide catheter) over a guidewire. The plastic biliary stent is then advanced over the complex guidewire–inner catheter using an outer

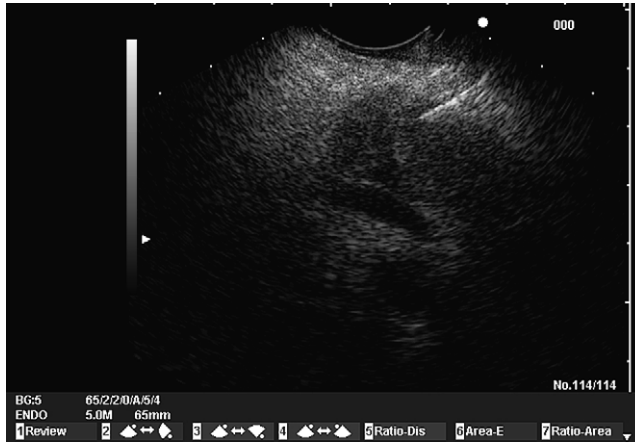

Fig. 1. EUS-FNA of mass in need of pancreas.

pusher device as a three-layer system. The inner catheter and guidewire are then withdrawn leaving the stent in position. A single-assembly stent delivery system is available from several manufacturers. In a small randomized trial, stent insertion seemed to be easier and faster with these systems compared with the standard three-layer system [15]. Although studies have shown that biliary sphincterotomy is not generally necessary for stent placement [16], it may be performed to facilitate future exchange or placement of additional stents. It remains controversial whether or not biliary sphincterotomy increases the complications of the procedure. A retrospective study suggested that the incidence of acute complications of biliary stent placement was higher in patients undergoing sphincterotomy and concluded that sphincterotomy is not necessary for placement of 10F catheter polyethylene stents [17]. In contrast, a smaller case series reported that biliary sphincterotomy seemed to reduce the risk of post-ERCP pancreatitis in patients with proximal malignant biliary strictures requiring plastic stents greater than or equal to 9 cm long [18]. The authors of this study hypothesized that the proximal biliary stricture may serve as a fulcrum leading to medial deflection of the stent and compression of the pancreatic orifice. Nevertheless, the decision to perform a biliary sphincterotomy before stent placement is often left to the discretion of the therapeutic endoscopist.

Although rarely seen in pancreatic cancer, complex hilar strictures represent a unique challenge for the biliary endoscopist. Ideally, stent placement should relieve both jaundice and cholestasis and can be achieved by draining only one major segment of the liver [19]. Conflicting reports have been published regarding the efficacy of unilateral versus bilateral biliary drainage in complex hilar strictures. In a retrospective series, patients with malignant hilar obstruction and bilateral contrast opacification at ERCP with only one system subsequently

drained faired poorly when compared with subjects with bilateral opacification and bilateral stent drainage and those with only unilateral opacification and unilateral drainage [20]. In a randomized controlled trial of unilateral versus bilateral stenting for malignant biliary obstruction, however, De Palma and colleagues [21] reported less morbidity in patients randomized to unilateral drainage. As a result of these findings, many expert centers have adopted the strategy of Hintze and colleagues [22] in obtaining an MRCP before ERCP in all patients suspected of having biliary obstruction at the hilum.

Most endoscopic failures for biliary decompression occur secondary to prior gastrointestinal surgery or tumor infiltration precluding access to the major duodenal papilla, unsuccessful cannulation of the common bile duct, or inability to traverse a complex stricture with a guidewire. In tertiary centers with adequate experience, endoscopic stent placement has a technical success of greater than or equal to 90%. Complications include acute pancreatitis, bleeding, cholangitis, and perforation. Acute cholangitis is seen with unsuccessful or incomplete drainage. When serum bilirubin remains persistently elevated despite biliary decompression, the stent patency or position should be assessed by repeat ERCP.

Types of Biliary Stents

Plastic stents

Plastic stents were first introduced in 1979 by Soehendra and Reynders-Frederix [23], and have been widely used given their relative ease of placement and low cost. Typically, the stent configuration is either straight or slightly curved with flanges located at either end to minimize the risk of proximal or distal migration, which may occur in up to 9% of patients [17]. The stent should be placed with the proximal flange located above the stricture and the distal flange just outside the papilla within the duodenal lumen.

The main disadvantage of plastic stents is their patency rate (approximately 3 to 5 months), which may lead to recurrent jaundice and ascending cholangitis. Although bile is ordinarily sterile, stent placement across the papilla disrupts the barrier function, leading to rapid colonization of the biliary system with intestinal flora [24]. Stent occlusion involves a complex process beginning with the formation of sludge and a biofilm on the inner surface of the stent. This biofilm consists of cellular debris and microcolonies of bacteria in a matrix of extracellular anionic fibrillar material [25]. Once formed, this biofilm is impossible to eliminate from an indwelling stent. Consequently, stent function becomes impaired within weeks or months necessitating stent exchange in up to 30% to 60% of surviving patients [26].

Several approaches to prolong stent patency have been studied. Despite promising results in vitro, oral administration of mucolytic agents (ie, aspirin) or choleretic agents (ie, ursodeoxycholic acid) in combination with different antibiotics has not proved effective in preventing biliary stent occlusion [27–29]. Stent design has focused on developing stents from ultrasmooth materials to prevent bacterial adherence or impregnating with bactericidal agents to prevent

biofilm formation [30]. Unfortunately, these designs have not proved successful. Preliminary uncontrolled studies suggested a prolonged patency of "Tannenbaum" Teflon stents without side holes compared with traditional polyethylene stents with side holes [31]. Teflon has a significantly lower coefficient of friction compared with other plastics, which may impede bacterial adherence [32]. Furthermore, the microturbulence produced by side holes can lead to bacterial encrustation, formation of sludge, and stent clogging [33]. Subsequent randomized trials, however, revealed no difference in stent patency between Teflon and polyethylene stents with or without sideholes [34–36]. Recently, a pilot study reported the success of a novel biliary stent without a central lumen in obtaining adequate biliary drainage [37]. The unique, "winged" stent design facilitates the flow of bile around the stent, eliminating the possibility of luminal obstruction from biofilm or sludge formation, potentially translating into prolonged biliary drainage. Although the hypothesis is intriguing, prospective comparative trials are needed to further define the role of this novel stent design.

The most direct approach to prolonged stent patency is increasing the diameter of the inserted plastic stent. In theory, a larger-diameter stent provides greater flow through its lumen, leading to the notion that larger stents have longer patency rates.

There is clinical evidence that 10F stents have significantly longer patency compared with 7F and 8F stents [38,39]. The 11.5F stents have not shown prolonged patency, however, compared with 10F stents [40]. The 10F stents are usually the preferred choice.

Determining the optimal interval for stent exchange remains debatable. Stent occlusion may occur anywhere from days to months after placement, with an average of 3 to 5 months for 10F stents. Some experts recommend exchanging every 3 months, whereas others wait for the earliest clinical or laboratory signs of stent occlusion. Although the former practice may result in unnecessary stent exchanges, the latter option carries the risk of developing severe cholangitis and biliary sepsis. It is probably wise to personalize the endoscopic stent replacement strategy. Planned stent exchange is usually preferable in patients who are unable to maintain close follow-up, whereas compliant patients with easy access to the system may follow an on-demand stent exchange strategy [41].

Metal stents

To overcome the shorter duration of plastic stent patency and need for reintervention, self-expandable metal stents (SEMS) were introduced into clinical practice in the late 1980s. Currently, several different types of biliary SEMS are available, varying in shape, design, and metal alloy. Examples include the Wallstent (Boston Scientific, Natick, Massachusetts); the Zilver Stent (Wilson-Cook Medical, Winston-Salem, North Carolina) (Fig. 2); and the Luminex (Bard, Billerica, Massachusetts) [40]. All these types of stents are delivered in a collapsed configuration over a 7F or 8F catheter delivery system.

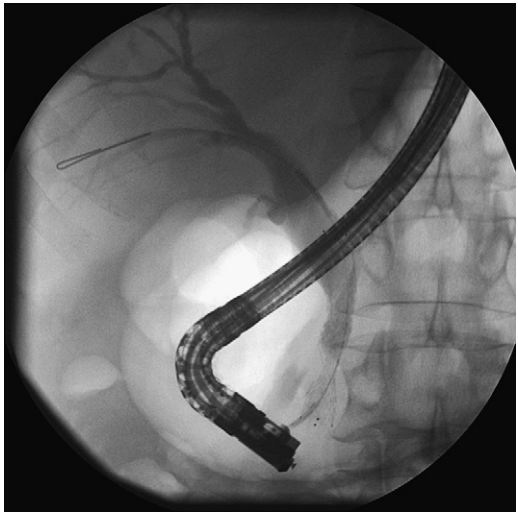

Fig. 2. Zilver SEMS deployment for management of malignant biliary stricture.

The Wallstent, a tubular mesh composed of stainless steel alloy, has been studied extensively and has the most published experience. The device is passed over a 0.035-in guidewire and positioned across the malignant stricture under fluoroscopic guidance with the aid of radiopaque markers on the delivery system. Coordination between the endoscopist and assistant is required for controlled slow release and accurate deployment of the stent. On full expansion, the Wallstent can reach a diameter of 30F catheter. Because of its inherent expansile properties, it can foreshorten up to 30% to a designated length of 40, 60, or 80 mm. Once fully expanded, the Wallstent embeds into the bile duct wall resulting in superficial necrosis of the underlying biliary epithelium. This inflammatory response progressively incorporates the stent, limiting the possibility of stent migration [42]. Moreover, once these stents are fully implanted, they are permanently embedded into the bile duct and cannot be removed. Although there have been isolated reports of removing uncovered biliary Wallstents, removal of these stents can be extremely difficult [43]. If the clinical management is undetermined, a plastic stent is generally recommended with the possibility of metal stent placement, if indicated, at the time of first stent exchange.

Several studies comparing the performance of different stents have been performed. Metal stents may vary in both material and cell design. A retrospective comparison of Wallstent and Ultraflex Diamond (Boston Scientific, Natick, Massachusetts) stents (an open mesh metal stent popular in Europe) in patients with distal malignant biliary obstruction demonstrated no differences in efficacy of biliary drainage or in long-term stent patency [44]. A subsequent retrospective study, however, showed higher patency rates for the Wallstent

compared with the Diamond stent [45]. A recent randomized clinical trial compared the Wallstent with spiral Z-stents for the treatment of malignant biliary obstruction and found no differences in ease of placement, occlusion rates, and overall patency [46]. Another recent, three-armed, multicenter randomized study, presented in abstract form, compared the 10-mm Wallstent with the 6-mm and 10-mm Zilver stents for management of malignant strictures below the hepatic bifurcation [47]. The study concluded that the 6-mm Zilver stent demonstrated lower patency rates with early stent occlusion and increased rates of cholangitis; however, there were no differences observed between the 10-mm Wallstent and 10-mm Zilver stent with regards to stent patency, ease of placement, or complications. The 6-mm Zilver stents should not be used for treatment of distal malignant biliary strictures.

Despite their larger diameter and lower incidence of sludge and bacteria deposition, metal stent occlusion still occurs in approximately 22% to 33% of patients [48,49]. Several factors may contribute to stent occlusion including: (1) tumor ingrowth through the interstices of the metal mesh, (2) tumor overgrowth at either end of the stent, (3) hyperplasia of the biliary epithelium, and (4) sludge formation. Recanalization of occluded metal stents can be achieved endoscopically with insertion of additional metal or plastic stents through the occluded stent [50]. Diathermic debulking of the obstructing tissue has been performed; however, it carries a high risk of bleeding, ductal injury with perforation, and stent fragmentation [51,52]. Moreover, the effect is only temporary and is generally not recommended. To reduce tumor ingrowth or biliary epithelial hyperplasia, covered metal stents were developed in the 1990s. In a recent uncontrolled study, the polyurethane-covered Wallstent demonstrated a low occlusion rate of 14% at a mean of 6 months [53]. A recent retrospective study comparing covered with uncovered Wallstents for the management of distal malignant biliary obstruction, however, reported no significant difference between stent patency rates [54]. Covered metal stents are more prone to dislocation and migration and can also become occluded by adherence of bacteria to the membrane coating. There is also concern that covered stents may occlude the cystic duct orifice leading to acute cholecystitis in up to 3.5% of patients [55]. Further studies involving the use of covered SEMS are warranted to determine the long-term outcomes and efficacy when compared with traditional uncovered SEMS.

Endoscopic versus Surgical versus Percutaneous Palliation for Malignant Biliary Obstruction

Several randomized trials have compared surgical with endoscopic palliation of malignant obstructive jaundice [26,56,57]. The procedure success rate and efficacy in relieving jaundice were comparable between both techniques at 90%. The procedure-related morbidity and mortality and length of initial hospital stay were significantly lower, however, in the endoscopic group. This initial benefit favoring endoscopic therapy was balanced by the higher rate of late complications mainly because of stent dysfunction and subsequent need for

frequent hospitalizations. Although the 30-day mortality rate was lower for the endoscopic approach, there was no difference in terms of overall survival between the two groups.

A recent meta-analysis recommended the endoscopic approach for patients with a predicted survival of less than 6 months, accounting for most pancreas cancer patients, and palliative surgery in patients with longer life expectancy [58]. These results should likely be readdressed, however, given recent stent advances. The current availability of SEMS favors the endoscopic approach because of a reduced rate of stent occlusion compared with the plastic stents and the development of enteral stents for treatment of GOO nonoperatively. Recent advances in laparoscopic biliary bypass with reduced immediate complication rate and lower length of initial hospitalization, however, might favor the surgical approach.

Several studies have compared percutaneous transhepatic with endoscopic stent placement in malignant biliary obstruction. The endoscopic approach proved to be safer and more effective compared with the transhepatic technique when using plastic stents [59]. There are no studies, however, comparing endoscopic versus percutaneous metal stent placement. In most institutions where both techniques are available, the endoscopic approach is considered the preferred choice, with a percutaneous transhepatic route reserved for cases of endoscopic failure.

The preoperative use of biliary stents to reduce serum bilirubin levels and improve nutritional status in patients with resectable pancreatic cancer is controversial. Multiple trials have reported inconsistent effects on operative morbidity and mortality [60–63]. A recent meta-analysis of the available data concluded that there is no positive or negative effect of preoperative stent placement on the outcome of surgery in pancreatic cancer patients [64]. Nevertheless, in everyday clinical practice, many patients continue to undergo preoperative biliary stenting.

Endoscopic placement of biliary stents should be recommended in nonoperative subjects because of locally advanced or metastatic disease or substantial comorbid illnesses. For those patients in the intermediate category in terms of tumor burden, general health status, and expected survival, the decision is more complex. The patient and physician should decide between a surgical approach, which is more invasive, expensive, and has a higher risk of immediate complications, but may be more effective in the long-term, versus an endoscopic approach, which is a quicker and safer method, but may require reintervention.

Metal versus Plastic Stents

Plastic stents are inexpensive and effective but unfortunately have a limited patency interval (3–5 months). SEMS are expensive and remain patent longer, but can also occlude secondary to tumor ingrowth, overgrowth, or sludge formation. Four randomized controlled trials have been reported directly comparing SEMS with plastic stents [48,49,65,66]. Overall, metal stents have shown

significantly longer patency rates. Plastic stents are associated with a higher rate of stent occlusion and cholangitis with more prolonged hospitalizations compared with metal stents. Although more expensive, metal stents have been shown to be more cost-effective in patients surviving beyond 3 to 4 months because the overall number of ERCPs required for stent exchange was reduced by 28% [48]. There was no significant difference in overall patient survival in this study.

Identifying patients at risk for early metal stent occlusion may help to guide stent selection and avoid unnecessary SEMS placement and the associated costs. A recent study reported that metal stent patency is not affected by tumor type, stricture morphology, stent length, patient age, or initial bilirubin level. The ease of passage across a stricture with a large-caliber catheter before stent placement and adequate expansion of the stent following deployment, however, predicted prolonged stent patency [67]. The patency rates between metal and plastic stents have been shown to run parallel during the first 3 months [68]. Thereafter, the curves diverge in favor of metal stents. Insertion of a metal stent becomes cost-effective only in patients with a life expectancy exceeding 3 months. The presence or absence of liver metastases can also be used as an indicator of stent selection. Patients with liver metastases have a short life expectancy and should preferably receive plastic stents, whereas metal expandable stents are more cost-effective in patients without tumor spread to the liver [69].

PALLIATION FOR GASTRIC OUTLET OBSTRUCTION

Enteral Self-expandable Metal Stents

GOO is usually a late complication of advanced pancreatic malignancy. Approximately 10% to 15% of patients with pancreatic cancer develop GOO at some point before death. Until recently, gastroenteric bypass surgery (most commonly gastrojejunostomy) was the only option for restoring luminal continuity from malignant obstruction of the stomach or duodenum. Although surgical palliative bypass is still considered the standard approach and can now be performed laparoscopically [70], enteral SEMS placement has emerged as a viable alternative to surgery, especially in poor operative candidates. Enteral stents are designed to treat malignant luminal obstruction and can be deployed within the stomach, small bowel, and colon.

Enteral SEMS can be placed either by a gastroenterologist under endoscopic and fluoroscopic guidance or an interventional radiologist with only the aid of fluoroscopy. Endoscopic placement has the advantage of better access to the duodenum with the ability to pass most stents directly through the working channel of the endoscope. Interventional radiologists may have more experience with guidewire manipulation, however, and SEMS deployment. Enteral stents are composed of a variety of metal alloys and are available in several shapes and sizes depending on the individual manufacturer. Covering membranes are now being developed to prevent tumor ingrowth through the mesh wall and subsequent reobstruction [71].

In the United States, only the Enteral Wallstent (Boston Scientific, Natick, Massachusetts) has been approved by the Food and Drug Administration for placement in the duodenum for palliative treatment of GOO. The stent is housed in a 10F catheter sheath with a diameter ranging between 16 and 22 mm and available in lengths of 6 and 9 cm. Outside the United States, a variety of covered SEMS are available for gastroduodenal placement [72–74]. Furthermore, commercially available esophageal stents in the United States have also been used for treatment of GOO [75]. The major advantage of the Enteral Wallstent, however, is that it can be placed through the channel of the endoscope (through the scope insertion).

Technique of Enteral Stenting

Before enteral stent placement, it may be helpful further to define the location and length of the stricture with an upper gastrointestinal radiographic contrast study. This may not be possible, however, in the setting of complete obstruction when the contrast may subsequently interfere with endoscopic and fluoroscopic visualization. Usually, a standard upper endoscope reaches the strictured area; however, more distal obstructions may require the use of a colonoscope. Some endoscopists prefer a standard duodenoscope with a 3.8-mm channel to allow wire and stent manipulation with the elevator. The patient is placed in the left lateral decubitus or prone position under intravenous sedation. The supine position should be avoided because of risks for aspiration in patients with complete GOO. Some endoscopists may even prefer elective endotracheal intubation with general anesthesia further to protect the airway. A room equipped with fluoroscopy and a skilled nursing assistant is also mandatory.

Once the stricture has been reached with the endoscope, attempts to traverse the stricture with gentle force and manipulation of the scope may be used; however, excessive force to the endoscope or aggressive dilatation with dilating balloons is not necessary and increases the risk of perforation. If the endoscope passes through the stricture easily, a stiff guidewire with a floppy tip is then advanced through the endoscope channel beyond the point of obstruction. If the obstruction precludes passage of the endoscope, a hydrophilic guidewire preloaded through a standard biliary catheter is advanced through the stricture and then exchanged for a stiffer guidewire before stent deployment. Water-soluble radiographic contrast injection may be performed distal to the obstruction to confirm both luminal access and distal patency.

The selected stent should be at least 3 to 4 cm longer than the stricture to allow an adequate margin of stent on both sides of the obstructing tumor. The stent is passed over the guidewire, through the working channel, and is deployed from the distal end under direct endoscopic and fluoroscopic guidance, while maintaining proximal position in the desired location. After deployment, the ends of the stent should be inspected fluoroscopically. If either end is not fully expanded, then the stent may not cover the entire length of the

stricture. At this point, a second overlapping stent may be required to adequately to treat the stricture [71].

In patients with pancreatic cancer complicated by GOO, coexistent biliary obstruction may be present and usually occurs before the GOO. Moreover, biliary complications can occur after placement of enteral SEMS for GOO. Some studies have reported up to 40% of patients undergoing duodenal stent placement subsequently requiring biliary intervention with either ERCP or percutaneous transhepatic cholangiography [76]. Placement of a metal biliary stent should always be attempted in subjects with known or impending biliary obstruction before placement of a duodenal stent (Fig. 3). When biliary obstruction occurs after a duodenal stent placement across the papilla, percutaneous transhepatic cholangiography is usually used for biliary decompression, although cases of ERCP through preplaced enteral stents have been reported.

Failure to place an enteral stent endoscopically usually results from inability to traverse the stricture with a guidewire or inaccessibility secondary to postsurgical anatomy. If no clinical improvement is observed following stent placement, this may be explained by distal sites of intestinal obstruction, peritoneal carcinomatosis with bowel encasement, or functional GOO from neuronal tumor infiltration of the celiac axis. Immediate complications may include aspiration, perforation, bleeding, and stent malposition. Late complications include stent migration, bleeding, perforation, and fistula formation. Symptomatic stent occlusion from tumor ingrowth or overgrowth requires endoscopic intervention with placement of additional stents within the obstructed stent. In addition, use of argon plasma coagulation to treat tumor ingrowth and

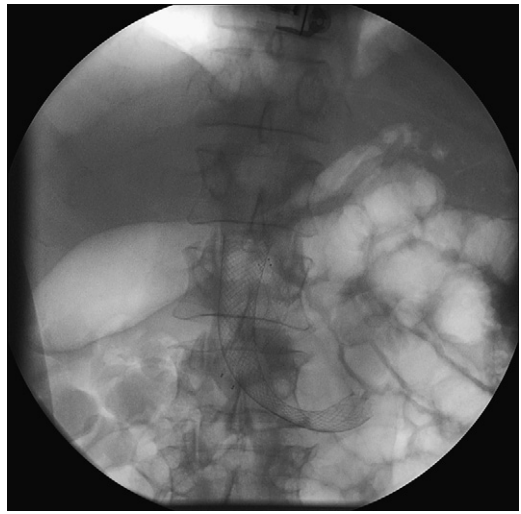

Fig. 3. Combined placement of biliary and enteral SEMS for endoscopic management of GOO and impending biliary obstruction.

epithelial hyperplasia and "unzipping" of the distal end of the stent to relieve obstruction has also been reported [77].

Outcomes

Most of the published series of endoscopic SEMS placement as palliation for malignant GOO are retrospective with a variety of different stent types used [78–84].

Overall, the technical success rate was between 90% and 100%, with the clinical success rate, defined as ability to tolerate oral nutrition, approximately 80% to 90%. The largest study involved 36 subjects and showed a significant improvement in dietary score following SEMS placement [82].

Two retrospective studies have compared SEMS placement with surgical bypass. Duodenal stent placement resulted in lower overall costs and an earlier discharge from the hospital [80]. Furthermore, more than half of the subjects in the gastrojejunostomy group developed delayed gastric emptying after surgery, whereas patients in the duodenal stent group were able to tolerate a soft diet the day following the procedure [84]. The overall survival seemed to be similar in both groups (approximately 90 days). A recently published, small, prospective randomized comparative trial of surgical gastrojejunostomy and endoscopic SEMS placement also reported a significantly shorter time to oral intake and shorter hospital stay in the stent group [85]. Enteral SEMS placement is less expensive, provides shorter recovery time, and should probably be considered the procedure of choice in most patients with malignant GOO.

In end-stage patients with GOO and limited life expectancy, another alternative for gastric decompression is endoscopic placement of a venting gastrostomy tube for alleviation of refractory nausea and vomiting.

PALLIATION OF INTRACTABLE ABDOMINAL PAIN

Celiac Plexus Neurolysis

Most pancreatic cancer patients have pain [86], and pain control becomes of primary importance when managing patients with end-stage disease. Although opiates alleviate some of the discomfort, dosing may be limited by side effects, such as constipation, drowsiness, and respiratory depression. Moreover, narcotics offer variable responses in controlling abdominal pain. Abdominal pain from pancreatic cancer is generally transmitted though the celiac plexus. CPN was first described in 1914 and has undergone several modifications through the years [87]. A neurolytic agent, typically alcohol or phenol, is injected into the celiac plexus in hopes of disrupting visceral afferent pain transmission. Traditionally, this has been performed by direct injection of the celiac plexus at the time of attempted resection, or percutaneously through a posterior approach under fluoroscopic guidance by trained anesthesiologists. Randomized studies have reported improved pain scores following CPN with both techniques, although opioid use is generally still necessary [88–90].

Concerns for potential neurologic complications, such as paresis and paresthesias, with the fluoroscopically guided posterior approach has led to the

development of anterior approaches under sonographic or CT guidance with similar efficacy [91–93]. Punctures of a hollow-viscus or solid organ remain a concern, however, with the anterior approach. Fortunately, major complications with both anterior and posterior approaches are rare.

The first experience with EUS-guided CPN was reported by Wiersema and colleagues in 1995 [94]. The anatomic location of the celiac trunk to the gastric lumen makes this an ideal approach. Linear endosonographic imaging from the posterior lesser curve of the stomach allows easy identification of the celiac trunk. Under real-time EUS guidance, a saline-primed needle (22- or 19-gauge) is advanced anterior to the origin of the celiac trunk in the antecrural space. Following aspiration of the needle to ensure no blood return, varying amounts of 0.25% bupivacaine (6–20 mL) and 98% dehydrated alcohol (10–20 mL) are injected into the region of the celiac plexus [95,96]. Alcohol injection results in an echogenic cloud that diffuses into the antecrural space surrounding the celiac plexus, providing neurolysis. Patients are generally monitored for 2 hours before discharge, because complications of EUS-guided CPN are rare but include increased pain (9%), postural hypotension (20%), and diarrhea (17%), all of which are generally transient [97].

The largest experience with EUS-guided CPN reported significant improvement in pain scores following neurolysis. Forty-five (78%) of 58 patients experienced a decrease in pain score, with overall scores significantly lower 2 weeks after CPN. Pain relief from concomitant adjuvant therapy increased over time, and opioid use was not altered. Multivariate analysis showed sustained pain relief for 24 weeks independent of adjuvant therapy and opioid use [97]. Although optimistic, this small uncontrolled trial also reported that the benefit of CPN decreased at 8 to 12 weeks in patients not receiving adjuvant therapy.

Unfortunately, there are no comparative trials between EUS-guided and a posterior approach for CPN in patients with pancreatic malignancy. Although a comparison of the two approaches in patients with chronic pancreatitis (celiac plexus block) revealed that most patients (67%) preferred the EUS approach [98], larger randomized controlled studies are necessary to determine the efficacy of EUS-guided CPN. Although superior localization of the neurolytic injection by EUS guidance may offer better efficacy, this hypothesis remains to be proved.

Pancreatic Stenting

Pain related to pancreatic duct obstruction occurs in approximately 15% of patients with advanced pancreatic cancer. The pain is usually postprandial and associated with pancreatic enzyme elevation. At times, the severity of the pain may be difficult to control with narcotics alone. Neoplastic compression of the pancreatic duct results in ductal obstruction with upstream dilatation and subsequent ductal hypertension, considered the cause of pain in these patients. Placement of a pancreatic stent across the stricture reduces the ductal hypertension, thereby alleviating the pain. Before considering palliative pancreatic

stent placement, an abdominal CT or MRCP should be performed to confirm pancreatic duct dilation.

Two recent studies have assessed the effect of pancreatic stenting in subjects with pancreatic cancer and dilation of the main pancreatic duct beyond the ductal stricture [99,100]. Approximately 50% to 60% of the subjects became symptom-free, and another 20% to 25% significantly reduced the amount of analgesic consumption. There were no procedure-related complications reported. Endoscopic pancreatic stenting should be considered an effective alternative for palliation of pancreatic cancer in selected patients with obstructive pain not responding to analgesics. The need for and timing of stent exchanges in this population are unknown and warrant further study.

EMERGING ENDOSCOPIC PALLIATIVE THERAPIES

Several new and exciting techniques for endoscopic palliation have emerged over the past few years. These include endoscopic placement of drug-eluting biliary SEMS, EUS-guided placement of fiducials for Cyberknife radiotherpay, endoscopic creation of gastrojejunstomies, and EUS-guided placement of gene vectors into pancreatic tumors for control of local disease. Although these advancements represent promising future directions for palliative therapy, additional studies are necessary to determine the clinical efficacy and safety of these techniques. Additional techniques are continuing to emerge, further expanding the role for endoscopic palliation in advanced pancreatic cancer.

Drug-eluting Stents

Traditional biliary SEMS inserted for biliary decompression have no antitumor effect and serve only to maintain biliary patency. A stent covered with a topical chemotherapeutic agent may potentially retard tumor growth, however, while avoiding harmful systemic side effects. A metallic stent covered with a paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, New Jersey) incorporated membrane has been developed and studied in an animal model [101]. Lee and colleagues [101] recently reported the effect of paclitaxel-DES on normal porcine bile ducts. One month after insertion into a normal porcine bile duct, histologic examination revealed no evidence for transmural necrosis or perforation, supporting the safety of this product with respect to the biliary epithelium. Although the study established the safety of paclitaxel-DES in normal porcine bile ducts, clinical trials are necessary to further investigate the safety and efficacy for treatment of malignant biliary strictures.

Endoscopic Ultrasound–guided Placement of Fiducials for Cyberknife Radiotherapy

Cyberknife stereotactic radiotherapy was approved by the Food and Drug Administration in 2001 for the treatment of tumors anywhere within the body. This specialized system delivers multiple beams of precisely directed radiation using real-time image guidance. Radiographic markers (fiducials) are implanted at the tumor site as reference points to target the radiation beams. Traditionally, fiducials have been placed either surgically or percutaneously under

ultrasound or CT guidance. Recently, Pishvaian and colleagues [102] reported the first series of patients undergoing EUS-guided fiducial placement for Cyberknife radiotherapy in patients with mediastinal and abdominal malignancies, including pancreatic cancers. Of the 13 patients in the series, seven had unresectable pancreatic cancer. Fiducial placement was successful in 86% of patients with failure in a single case secondary to GOO. Although one complication of infection occurred within the series, no complications occurred in the patients with unresectable pancreatic cancer. EUS-guided fiducial placement seems to be safe and feasible; however, additional studies are needed to determine the efficacy of this technique with Cyberknife radiotherapy. Infectious complications may be limited by using sterile precautions and prophylactic antibiotic therapy.

Endoscopic Creation of a Gastrojejunostomy

An alternative to surgical gastrointestinal bypass or placement of enteral SEMS for management of GOO is endoscopic creation of a gastroenteric (EGAM) anastomosis using magnets. Chopita and colleagues [103] recently reported the safety, efficacy, and long-term patency rates of anastomoses created using this novel technique. A total of 15 patients with malignant GOO underwent EGAM anastomosis using magnets. Surgery was considered inappropriate in these subjects secondary to advanced disease and poor status according to the American Joint Committee on Cancer classification. Magnetic gastroenteric compression was obtained using coated rare-earth magnets placed in the stomach and distal duodenum for a period of 7 to 10 days. An extractor magnet was used to remove the magnet endoscopically followed by placement of a "yo-yo" stent through the magnetically created fistula. The procedure was successful in 88% of patients with a mean survival of 5.2 months. Of the two failures, one resulted from inability to traverse the duodenal stricture for balloon dilatation and placement of the duodenal magnet. In the second patient, a perforation occurred at the anastomosis likely secondary to manipulation of an immature fistula, which subsequently required immediate surgical intervention and gastrointestinal bypass. All successful cases were able to resume normal intake of solid food 48 hours after completion of the procedure with all patients continuing to ingest solids until their time of death. Four minor complications (31%) occurred during the follow-up period: two instances of distal migration of the stent (found in stools); one proximal migration; and one obstruction with solid food. The latter two complications were resolved endoscopically. Although additional clinical trials are needed, this minimally invasive technique represents a viable alternative to enteral SEMS and surgical gastrointestinal bypass, which may be associated with higher morbidity and mortality.

Endoscopic Ultrasound–guided Placement of Gene Vectors (TNFerade)

An exciting area of development is the endoscopic delivery of gene vectors into locally advanced pancreatic tumors for locoregional control and potential downstaging for curative surgical resection. Chang and colleagues [104]

recently presented, in abstract form, results from a multicenter clinical trial involving the transfer of a gene vector (TNFerade) into locally advanced pancreatic cancer by EUS or percutaneous guidance. TNFerade is a replication-deficient adenoviral vector containing the human tumor necrosis factor-α gene regulated by a chemoradiation inducible promoter, Egr-1. Patients were treated for 5 weeks with weekly injections of TNFerade, continuous infusion of 5-fluorouracil, and radiation therapy. Of the 37 patients, stabilization of tumor was observed in 83% at 1 month and 74% at 3 months. Tumor area reduction of greater than 25% and 50% occurred in 31% and 11% of cases at 1 and 3 months, respectively. Survival without overall progression was 63% at 1 month and 47% at 3 months. The therapy was generally well tolerated and considered safe and effective. This technique represents an exciting development in transitional medicine with the potential for delivering genetic vectors by EUS or percutaneous guidance to other gastrointestinal malignancies [105]. Although the initial results are promising, randomized trials are necessary to determine the safety, efficacy, and long-term outcomes of these treatments.

SUMMARY

Endoscopic approaches have revolutionized the palliation of advanced pancreatic cancer. They have become an indispensable tool for the management of unresectable pancreatic tumors. The ideal management consists of a multidisciplinary approach involving surgeons, endoscopists, radiologists, and oncologists. Further technical improvements are necessary to address the limitation of premature stent occlusion and its associated morbidities. Concurrent advances in the fields of interventional radiology and laparoscopic surgical oncology should also be readdressed and directly compared with endoscopic approaches in randomized controlled trials. Exciting novel endoscopic techniques are being developed and evaluated; however, these approaches require further validation with randomized clinical trials to determine the safety and efficacy when compared with more traditional approaches.

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