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Invited Lectures

Necrotizing Pancreatitis: Significance, Detection, and Treatment

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Clinicopathologic correlation of the clinical course of acute pancreatitis with tissue changes occurring within the pancreas has revealed that pancreatic necrosis is the principal determinant of clinical severity and overall survival from acute pancreatitis. Furthermore, we now know that secondary pancreatic infections (infected pseudocyst, pancreatic abcess, infected pancreatic necrosis) are decidedly rare in the absence of pancreatic necrosis. Since secondary pancreatic infections associated with pancreatic necrosis currently account for more than 80% of deaths from acute pancreatitis, the diagnosis and management of necrotizing pancreatitis has assumed increasing importance.

Serum tests capable of detecting significant amounts of pancreatic necrosis have not as yet proved reliable. Currently, dynamic contrast-enhanced CT scanning remains the gold standard for detecting pancreatic necrosis, with an overall accuracy rate exceeding 90%. Extensive sterile pancreatic necrosis can often be successfully managed by non-operative means, even when associated with organ faliure. Infected pancreatic necrosis, on the other hand, is uniformly lethal without operative debridement and drainage. Clinical differentiation between sterile pancreatic necrosis and infected pancreatic necrosis is often difficult, however. This distinction has been materially assisted by transcutaneous fine needle aspiration bacteriology. Infected pancreatic necrosis differs from all other types of surgical infections, in that recurrence of infection following initial debridement and drainage is the rule, rather than the exception. This pernicious feature may be a consequence of the loss of pancreatic ductal integrity due to parenchymal necrosis, with continued leakage of activated enzymes into the retroperitoneum. Surgical mortality rates for infected pancreatic necrosis of 15% or less have been reported from many centers using open packing and planned re-exploration. Although truly remarkable progress has been made in managing patients with severe acute pancreatitis in the past 15 years, much is left to be done.

Acute pancreatitis is a disease of protean clinical manifestations, ranging from mild abdominal pain and minor social inconvenience, to apocalyptic prostration and death. The pancreatic inflammatory process may remain localized in the superior retroperitoneum, undergo regional extension, or even result in systemic illness associated with remote organ dysfunction.

As a general rule, for every four patients with acute pancreatitis, three will recover uneventfully using supportive measures alone; the fourth, however, will suffer a complication, and stand a one-in-three chance of dying. With such diversity of presentation, variation in severity, and uncertainty of outcome, individualization is the key to successful management of patients with acute pancreatitis.

Significance of Pancreatic Necrosis

As a result of a policy of programmed pancreatic resection for severe acute pancreatitis in a number of European centers[1)~6)], it has become increasingly clear that the development of pancreatic parenchymal necrosis is a critical determinant of the clinical course of these patients. Clinicopathologic correlation has firmly established that the clinical severity of an episode of acute pancreatitis is principally determined by both the presence and extent of pancreatic necrosis[4)~6)]. Furthermore, it has recently become apparent that pancreatic infections (infected pseudocysts, pancreatic abscess, infected pancreatic necrosis) are decidedly rare in the absence of parenchymal necrosis[7)~9)]. This observation is of paramount clinical significance, since 80% of deaths currently resulting from acute pancreatitis occur as a result of infection developing in necrotic pancreatic tissues[10)11)]. Bacterial invasion of necrotizing pancreatitis is an ominous event, resulting in a marked escalation in

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mortality risk; rising from 5—10% with sterile pancreatic necrosis[12], to 30% and more when the necrotic tissues become infected[12)~15]. These observations serve to emphasize the pivotal role than pancreatic necrosis occupies in patients with acute pancreatitis, Accordingly, detecting pancreatic necrosis has emerged as a necessary component of optimum clinical management.

Detection of Pancreatic Necrosis

In prospective studies from western countries, the overall incidence of acute pancreatitis has been found to range from 27—55 cases per 100,000 persons per year[16)17)]. Only a fraction of patients with acute pancreatitis actually develop pancreatic necrosis, however. In a prospective study form our institution, macroscopic pancreatic necrosis was demonstrated in 20% of a group of 194 patients admitted with acute pancreatitis[18)]. In retrospective analyses of radiologic and surgical data, others have estimated the prevalence of necrosis in acute pancreatitis to range from 17—20%[19)20)]. Assuming for a moment that the forgoing prevalence figures also apply to Japan with a total population of 130 million, approximately 71,500 patients could be predicted to be seen in Japanese centers each year with acute pancreatitis, of which 14,3000 would evidence some degree of pancreatic necrosis.

Long before the importance of pancreatic necrosis as a determinant of clinical outcome from acute pancreatitis became evident, several groups had proposed that a constellation of clinical and laboratory parameters could be used to predict the hospital course of patients with acute pancreatitis[21)~24)]. Since these "prognostic systems" only reflect the systemic effects of histologic events which are actually taking place within the pancreas, the accuracy of such indirect monitoring systems has been suspect. In fact, these "prognostic" systems have proved to be in error in predicting severity in almost one patient in three with acute pancreatitis[25)]. Moreover, these multiple parameter systems have been found to correlate poorly with the presence or absence of pancreatic necrosis[26)~28)]. As a result of these observations, the clinical value of such systems has waned, particularly in the clinical management of individual patients.

A more specific approach to the non-invasive detection of pancreatic necrosis has centered around the search for a serum marker which actually measures circulating breakdown products of necrotizing pancreatitis. Currently, 21 candidate serum necrosis markers have been proposed[24)~46)] (**Table 1**). However, each of these putative necrosis markers suffers from one or more of the following limitations: lack of sensitivity and specificity, retrospective validation, or inadequate human evaluation. As a case in point, C-reactive protein, claimed by Buchler et al in a large retrospective study to have an overall accuracy of 95% in detecting pancreatic necrosis when serum levels exceeded 10 mg/dl[35)], was found in our prospective study to have an overall accuracy of only 52% in detecting complicated acute pancreatitis[47)]. In order for a putative serum marker to be clinically useful, it must not only detect pancreatic necrosis with a high degree of accuracy, it should optimize the distinction between clinically significant necrosis and trivial amounts of necrosis. Although the concept of a simple and reliable serum test for pancreatic necrosis is appealing, considerable clinical work remains to be done.

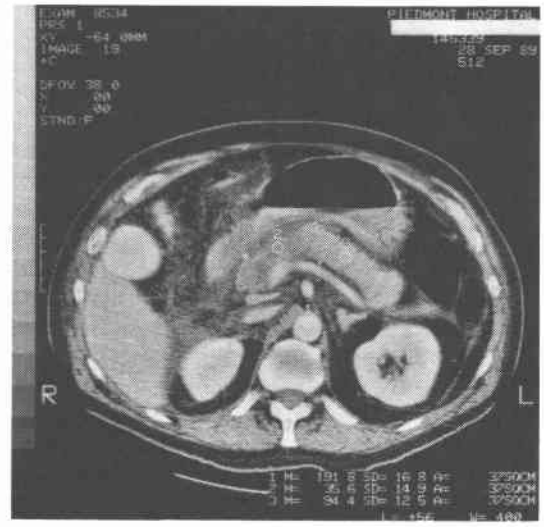
A novel approach to the detection of pancreatic necrosis was proposed by MacMahon et al who advocated diagnostic peritoneal lavage, comparing the lavage effluent to a colorimetric scale; the darker the fluid, the more likely that necrotizing pancreatitis was present[48)]. Widespread adoption of this approach has been limited by the cumbersome nature of the lavage process.

Routine imaging techniques, such as sonography[49)50)], computed tomography[51)], and magnetic resonance scanning[52)], have not proved useful in detecting pancreatic necrosis. A specialized imaging technique, bolus intravenous contrastenhanced computed tomography (dynamic pancreatography)[53)], has now become the "gold-standard" for the non-invasive detection of pancreatic necrosis. Using this technique, pancreatic necrosis is demonstrated by a failure of the affected portions of the pancreas to enhance following an intravenous bolus of contrast material (**Fig. 1**). Extensive experimental and human studies have demonstrated that the failure of pancreatic enhancement is due to microcirculatory thrombosis[54)55)]. In addition to an overall accuracy rate exceeding 90% for detecting the presence of pancreatic necrosis[56)~59)], dynamic pancreatography is also capable of estimating the extent of both intra-pancreatic and extra-pancreatic necrosis[59)]. This facility is of critical importance in planning an operative approach, should surgical intervention become necessary.

Table 1 Proposed serum markers for pancreatic necrosis

Ribonuclease (29)
Methemalbumin (30)
Fibrinogen (31)
Pa O_2 (<60 mm Hg) (32)
Hypocalcemia (33)
Deoxyribonuclease (34)
Alpha-1-antitrypsin (35)
Alpha-2-macroglobulin (35)
Complement C_3 and C_4 (35)
C-Reactive protein (35)
Pancreas specific protein (36)
Phospholipase A_2 (37)
Trypsinogen activation peptide (38)
Free fatty acids (39)
Fibronectin (40)
Absolute lymphocyte count (41)
Interleukin-6 (42)
PMN-Elastase (43)
Carbolic ester hydrolase (44)
Carbolic ester lipase (45)
Myoglobin (46)

Fig. 1 Dynamic contrast-enhanced pancreatogram in a patient with ERCP induced necrotizing pancreatitis. Note decreased contrast density in pancreatic head #2 (35.6 HU) versus the tail #3 (94.4 HU).



Natural History of Pancreatic Necrosis

Does pancreatic necrosis "evolve" with time? Is the demonstration of pancreatic necrosis a sufficient indication for surgery? What happens if the necrotic tissue is not removed?

In order to answer these and related clinical questions, we must first know something of the natural history of pancreatic necrosis. Now that a reliable non-invasive means for the detection of necrotizing pancreatitis exists, such questions may be specifically addressed.

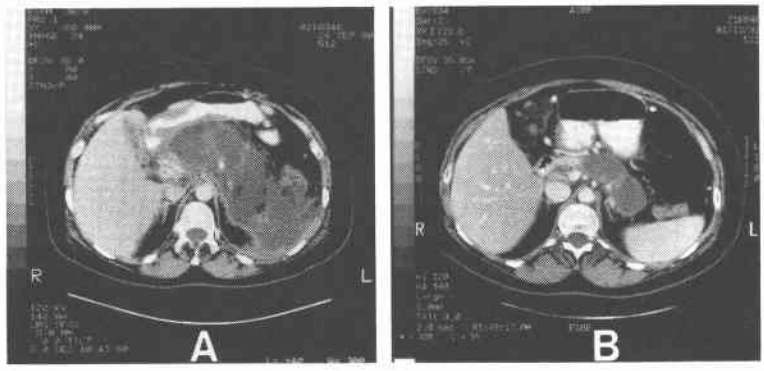
As we have noted, pancreatic necrosis was demonstrated by dynamic pancreatography in 38 (20%) of 194 consecutive patients admitted to our institution for acute pancreatitis[18]. The necrosis was evident on the admission CT scan in each of the 38 patients. In no instance was the CT scan performed later than 5 days after admission, nor more than 10 days after the onset of symptoms. These observations can be interpreted to mean that necrotizing pancreatitis occurs in approximately one-fifth of hospital admissions for acute pancreatitis, occurs early after the onset of acute pancretitis, and dose not "evolve with time", as suggested by some authors[60]. In retrospective studies, both Stanten et al, and Uhl and his co-workers, have made similar observations regarding the early onset of pancreatic necrosis in the course of acute pancreatitis. Such observations have important clinical implications, particularly in the management of biliary pancreatitis.

Infection developing in previously sterile pancreatic necrosis was documented by tissue culture in 27 of our 38 patients with necrotizing pancreatitis (71%)[18]. Based upon previous retrospective studies, the risk of secondary infection of sterile pancreatic necrosis had been estimated to range from 40—60%[9][12][13]. Accordingly, it seems reasonable to propose that secondary infection will develop in the majority of these cases, while pancreatic necrosis will remain sterile in more than one-third to one-half of afflicted patients.

Since infected pancreatic necrosis is uniformly fatal without surgical debridement and drainage[63][64], few would question the wisdom of considering the development of infection in previously sterile pancreatic necrosis to be an absolute indication for lsurgery. However, in contrast to infected necrosis, it is not as clear what the role of surgery should be, if any, in the management of sterile pancreatic necrosis.

Despite excessive mortality rates, even exceeding 60% in one series[4], a number of surgeons have advocated surgical debridement of sterile pancreatic necrosis whenever it is recognized[1]-[6][60]. The rationale which is frequently offered is that debridement "prevents" the development of remote organ dysfunction due to the

Fig. 2. Dynamic CT scan demonstrating necrotizing pancreatitis involving almost 85% of the gland (A). Despite coexisting pulmonary failure, the patient survived without operative intervention. Note marked contraction of the necrotic area 15 months later (B). Transcutaneous biopsy revealed extensive fibrosis in the area of previous pancreatic necrosis.



systemic absorption of the toxic breakdown products of pancreatic necrosis. However, since several groups have reported complete recovery of patients with sterile pancreatic necrosis in the absence of surgical intervention[18)65)66)], it is clear that not all patients with sterile pancreatic necrosis require prophylactic debridement.

Are there any patients with sterile pancreatic necrosis who might possibly benefit from surgical debridement, and if so how should we select them? Alternatively, how often can patients with sterile pancreatic necrosis be managed without surgery?

In an effort to improve patient selection, Beger et al have recently advised surgical debridement whenever sterile pancreatic necrosis is associated with organ failure[67)]. They also suggested that a failure of "overall improvement" in the condition of the patient after 72 hours of maximal supportive treatment represented another surgical indication. That associated organ failure can not be an absolute indicator for surgery is demonstrated by our recent observations that eleven consecutive patients with documented sterile pancreatic necrosis survived with enthusiastic supportive treatment alone, including six with associated renal or pulmonary failure[18)]. The average hospital course was 27 days, and included a mean of 15 days of intensive care. Since this report was published, an additional 6 patients with sterile pancreatic necrosis, involving 50—85% of the gland, have also been successfully managed by non-operative means, including two with pulmonary failure and one with renal failure. The putative role of surgery in sterile pancreatic necrosis has also been questioned by others. With regard to both overall mortality and prevention of organ failure, neither Smadja et al, nor Teerenhovi and his associates, were able to demonstrate any significant advantage to surgical debridement of sterile pancreatic necrosis[68)69)].

On the basis of existing data therefore, surgical debridement of sterile pancreatic necrosis can no longer be considered to be absolute necessity in the management of these patients, even if sterile necrosis is associated with organ failure. It is even possible that unnecessary surgical debridement may actually increase morbidity and mortality by introducing bacteria into previously sterile necrosis. At best, any putative role for surgical intervention in patients with sterile pancreatic necrosis remains undefined.

What is the long-term fate of sterile necrotizing pancreatitis managed without surgical debridement? In the past, many have assumed that following clinical recovery, complete morphologic and functional recovery of the gland took place[70)]. More recently, however, it has been demonstrated that both exocrine and endocrine abnormalities can be demonstrated in almost 50% of cases of necrotizing pancreatitis, even for as long as two years following clinical recovery[71)~74)]. Transcutaneous biopsies taken months following recovery in four of our patients have shown infiltrating fibrosis in the areas of previous pancreatic necrosis (**Fig. 2**). It is not difficult to hypothesize that the more extensive the original necrotizing process, the more fibrosis that will result, with corresponding decreases in ultimate exocrine and endocrine function.

Treatment of Infected Pancreatic Necrosis

Based upon the remarkable success of transcutaneous drainage in the treatment of other abdominal

abscesses, it was natural that these approaches would be tried in patients with infected pancreatic necrosis. Transcutaneous alternatives to surgical drainage have not proved useful in these patients, however. A number of workers have shown that CT guided transcutaneous drainage of infected pancreatic necrosis results in an undesirable rate of recurrent collections, an ultimate necessity for operative drainage, and unacceptable mortality[75)78)]. Failure of transcutaneous drainage in these patients has been attributed to the inability of the necrotic tissue fragments to negotiate the comparatively small calibre drainage catheters[79)].

Although most authorities are in agreement that surgical debridement is an absolute necessity for infected pancreatic necrosis, the precise form of subsequent surgical drainage has become controversial. The conventional surgical approach proposed by Altemeier and Alexander in 1963[80)], debridement followed by multiple penrose or sump drains, has been associated with historical mortality rates ranging from 30—60%[7)]. Although a few surgeons continue to cling to this approach[81)], alternative forms of drainage, which conform more closely to the underlying pathophysiology of infected pancreatic necrosis, have emerged as preferable surgical options.

In 1976, we became dissatisfied with the results of conventional surgical drainage for infected pancreatic necrosis, and embarked upon a technique which has come to be known as open packing[82)]. Originally, the procedure consisted of debridement, followed by placing laparotomy packs within a protective ring of non-adherent gauze, partial closure of the abdomen, and re-exploration and re-debridement every 2 days[83)]. The abdominal wound was permitted to heal entirely by secondary intention. More recently, whenever serial debridements have resulted in the formation of retroperitoneal granulation tissue, we have closed the abdominal wound over lavage catheters placed in the lesser sac. Using this evolved approach, the surgical mortality in patients with infected necrosis has been reduced from 16%[84)] to 10% in the last 22 cases. (unpublished data).

The technique of open drainage has received widespread clinical acceptance[61)85)~93)] (**Table 2**). In the combined series of 233 cases, the overall mortality for patients with infected pancreatic necrosis using this technique was 16.7%. The geographic scope of these reports establishes the essential validity of this approach, and the absence of appreciable variation in results between surgeons of diverse training demonstrates that the technique of open drainage is not operatordependent. Although a number of technical variations on this basic theme have been proposed, such as the use of Marlex and zippers[94)], daily re-explorations[95)], flank[96)], and posterior approaches[97)], the basic concept of scheduled re-explorations and re-debridement has remained the constant.

In contrast, surgeons choosing the conventional approach to draiange of infected necrosis have observed that unscheduled re-exploration for recurrent sepsis is necessary in one third to one-half of cases[98)~100)]. Unfortunately, however, the decisions to re-operate and the timing of re-operation are not always easy to make, as confirmed by

Table 2 World wide experience with open drainage for infected pancreatic necrosis

	Year	#Patients	MR
1.Bradley et al Atlanta (85)	1981 & ff*	68	14%
2.Knol et al Ann Arbor (86)	1983	3	0%
3.Levy et al Paris (87)	1984	26	23%
4.Waclawiczek Salzburg (88)	1986*	35	17%
5.Wertheimer & Norris Worcester (89)	1986	12	17%
6.Pemberton et al Rochester (90)	1986	17	18%
7.Garcia Sabrido et al Madrid (91)	1988	9	22%
8.Stanten & Frey Sacremento (61)	1990*	46	15%
9.Hottentrott & Kanish Frankfurt (92)	1991	13	15%
10.Hraguchi et al Tokyo (93)	1991	4	25%
Totals		233	16.7%

*updated by personal contact

the inordinate number of post-operative deaths which continue to be due to recurrent sepsis. In an extensive review of more than 1100 reported cases of pancreatic infections published from 1965-1985, more than three-quarters of post-operative deaths following debridement and conventional drainage were found to be due to persistent or recurrent infection! Although it may be theoretically possible to achieve mortality rates comparable to those obtained by open packing with conventional drainage is a sufficiently low threshold for re-exploration were entertained, the actual results strongly suggest that few surgeons have acquired the necessary expertise required to make these crucial decisions. At least part of the overall success of the open technique may be attributed to eliminating the difficult clinical decisions regarding re-operation.

Recent advances in our knowledge of the morbid anatomy of infected pancreatic necrosis may also assist in understanding the comparative success of open drainage. Several investigators have observed that the fluid which bathes the retroperitoneum following debridement and drainage of infected necrosis is rich in activated pancreatic enzymes, phospholipase, and kinins[65)85)]. Moreover, this toxic broth can be detected for up to three weeks following initial surgical debridement. Furthermore, it would appear that loss of pancreatic ductal integrity is a common occurrence in patients with extensive pancreatic necrosis, and may be the source of this toxic broth. Recently, we have noted that 7 of 8 patients with extensive infected pancreatic necrosis demonstrated discontinuity of the main pancreatic duct when studied by endoscopic pancreatography prior to initial debridement (**Fig. 3**). The defect in the ductal system occurred presumably as a result of the parenchymal necrotic process. Others have also demonstrated pancreatic duct disruption in unoperated patients with infected pancreatic necrosis[101)102)]. While the frequency of ductal necrosis in these patients is unknown, the large number of patients who develop pancreatic fistulas, following even minimal operative debridement, suggests that these ductal lesions may be more common than previously supposed. External pancreatic fistulas have been noted in 41% of our 68 patients undergoing blunt debridement for infected necrosis.

Given the observed ductal defect, exactly how the release of pancreatic juice into the retroperitoneum might contribute to the pathophysiology of these infections is a matter of conjecture. It is possible that zymogen

Fig. 3 ERCP demostrating loss of integrity of main pancreatic duct (arrow), with distal pooling of contrast. (A). Dynamic pancreatogram demonstrating necrotizing pancreatitis in body of pancreas corresponding to site of ductal rupture. (B).

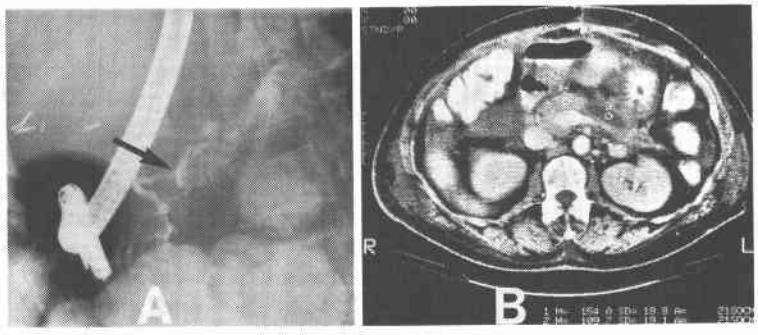


Table 3 Weight of necrotic tissue removed at initial operation and subsequent reexplorations*

	Patients (n)	Average weight (g)	Weight range (g)
Initial exploration	16	186±20	54—261
First re-exploration	16	67±31	33—101
Second re-exploration	16	29±23	7—64
Third re-exploration	14	15±12	0—38
Fourth re-exploration	13**	9±7	0—19

*Data taken from 16 recent patients

**Three patients had undergone secondary closure by fourth re-exploration

activation could occur as a result of bacterial peptidase, or even circulating proteolytic enzymes, such as plasmin. This theory could also account for the consistent observation that the necrotic process persists in these patients after initial debridement, as evidenced by the reformation of necrotic tissue despite adequate removal[65][85] (**Table 3**). In addition to eliminating the difficult clinical decisions regarding re-exploration, open drainage may owe its superior results to the periodic removal of these cytotoxic retroperitoneal re-accumulations.

An alternate surgical approach to drainage of infected pancreatic necrosis has been the institution of high volume lesser sac lavage. Mortality rates from this technique of drainage have been claimed by Beger and his co-workers to be equal to those achieved by open drainage and serial re-exploration[65]. Recurrent sepsis remains a problem with this technique, however, as re-exploration was necessary in 27% of this series.

Others have not had as favorable a mortality experience with lesser sac lavage for infected necrosis. Using this approach to drainage, Larvin et al[103], and Nicholson and his colleagues[104], reported mortality rates of 21% and 27%, respectively. Importantly, each of the deaths were found at autopsy to have been due to recurrent infection. Pederzoli and his co-workers were also unable to match the results of open drainage using lesser sac lavage, reporting an mortality rate of 28%[105]. Finally, in a small prospective study of 24 patients with infected necrosis undergoing surgical debridement and subsequently randomized to conventional drainage or continuous lesser sac lavage, Teerenhovi et al found no mortality advantage for lesser sac lavage over conventional drainage[106]. They observed that the principal feature influencing the 25% mortality rate was related to the extent of pancreatic necrosis, and not to either of these particular methods of drainage. Whether or not lesser sac lavage can produce mortality results equal to open drainage and serial re-exploration remains to be seen. Currently available data suggests that this will not be the case.

Surgeons choosing the technique of lesser sac lavage must also be aware of a major technical limitation. Because the continuous lavage technique requires that the lesser sac be intact and isolated from the remainder of the abdominal cavity in order to contain the lavage fluid, extensions of infected necrosis into the retrocolic spaces (a common occurrence) are not easily treated. If the splenic and hepatic flexures of the colon are taken down to debride the retrocolic spaces, the borders of the lesser sac will be compromised, and the lesser sac will communicate with the general peritoneal cavity. Accordingly, if lesser sac lavage is uniformly chosen over open drainage, a higher failure rate must be anticipated whenever retrocolic extensions of necrosis are present.

Conversely, not all patients with secondary pancreatic infections require open drainage and serial re-exploration. Patients with infected pseudocysts can be satisfactorily treated by CT guided transcutaneous drainage[107]. Pancreatic abscesses (well-walled off collections of purulence with minimal amounts of pancreatic necrosis) can be satisfactorily managed by conventional surgical drainage[81].

As a result of these combined observations, it seems reasonable to propose that lesser sac lavage is a viable option whenever infected necrosis is present, but limited in amount and restricted to the lesser sac. For more extensive infected necrosis, we contend that open drainage will result in fewer fatalities. Randomized studies are required to address these issues.

Finally, the timing of surgical intervention is crucial for success. While early surgical intervention (<7 days) has been recommended in necrotizing pancreatitis[1][2][6], delayed exploration (>10 days) has been shown to result in lower mortality and morbidity[13][60][108] regardless of the method of drainage employed.

In summary, great strides have been made in the surgical management of necrotizing pancreatitis within the past decade, but much is left to do. The future for patients who will be afflicted with acute pancreatitis appears considerably brighter.

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