disorders that predispose to the occurrence of acute arterial occlusion than it is in the course of normal hemostasis.

The processes of platelet adhesion and aggregation offer several possible points of intervention for antithrombotic therapy. Those most actively evaluated for the development of new drugs involve adhesion receptors. As just outlined, during the initial response of platelets to vascular injury, there may be considerable differences between normal hemostasis and pathologic thrombosis. Indeed, the nature of the thrombogenic surfaces is likely to be different, as the composition of a ruptured atherosclerotic plaque does not resemble normal tissue exposed after trauma. Moreover, the presence of stenosis and the occurrence of abnormal vasospasm generate hemodynamic conditions that may be uniquely different from those prevailing in the normal circulation. It appears, then, that pathways particularly susceptible to the influence of shear stress, like those depending on von Willebrand factor and platelet glycoprotein Ib, should be an obvious target in a strategy aimed at blocking thrombosis without obliterating normal hemostatic responses. Perhaps the local inhibition of thrombin, an agonist that may be generated in excess in vascular lesions, may achieve the same result. The selective blockade of the glycoprotein IIb-IIIa complex, the key receptor involved in aggregation, should also prove useful, particularly if ligand-specific inhibitors will become available. A differential inhibition of fibrinogen and von Willebrand factor binding to glycoprotein IIb-IIIa, for example, should allow the antiplatelet intervention to be modulated and favor the blockade of high shear-dependent pathways, most likely involving von Willebrand factor. Thus, on the basis of ongoing research on pathophysiologic mechanisms, progress should be forthcoming in identifying selective inhibitors of specific adhesive interactions. Whether and how this will provide new and better antithrombotic drugs remain a challenge for the future on which many investigators are working today.

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REFERENCE

1. Rodgers GM: Novel antithrombotic therapy. West J Med 1993; 159:670-674

Indications for Surgery in Necrotizing Pancreatitis

ANY DISCUSSION OF operative indications in severe acute pancreatitis must consider the need for an objective assessment of its severity in each patient. Such an assessment provides information about the prognosis, and this usually influences the clinical management—placement of the patient into an intensive care unit, the prophylactic use of antibiotics, and the like. In addition, some have suggested that if a specific level of severity is exceeded, this in itself could be an indication for operation.

Several prognostic scoring systems have been applied to acute pancreatitis in an effort to identify those patients who might benefit from more aggressive therapy. The Ranson system described in Frey's article in this issue of the journal has been used widely.[1,2] A number of modifications have been reported, but all of them, as well as the Ranson approach, are cumbersome to use and have been validated only for the first 48 hours of the disease. Thus, their applicability is limited for most patients with severe pancreatitis whose disease evolves over several weeks or more.

The Acute Physiology and Chronic Health Evaluation (APACHE II) score has been shown to correlate with the degree of pancreatic necrosis and eventual morbidity.[3,4] For example, in patients with less than 30% necrosis, the average APACHE II score is 8.4, which rises to 12.2 or more if more than 50% necrosis is present.[3] Nevertheless, the APACHE II calculations are also cumbersome and require a computer for effective application.

Computed tomography (CT) with a rapidly infused contrast medium provides the most accurate information about the adequacy of pancreatic perfusion and the presence of pancreatic necrosis, which correlates well with the prognosis.[5] We agree with Frey that it is the most valuable study in the management of this group of patients and that it provides information that is often critical in decisions about overall management, including whether to intervene surgically. A CT scan is indicated in patients who appear clinically to have severe pancreatitis or when there is no improvement with standard medical treatment after 48 to 72 hours. It should also be done in patients with a protracted clinical course to their disease or those in whom there is a change in condition that suggests a complication. The subject has been reviewed recently.[6]

Balthazar and co-workers have graded pancreatitis according to information derived from a CT scan about the degree of pancreatic enlargement, inflammation, and the presence of fluid collections.[7] They suggested that these data could be combined with information from the contrast-enhanced CT scan to create a CT severity index. In their experience, if the score was less than 2, the morbidity rate was 4% and no patients died. If the score was between 7 and 10, the morbidity rate was 92% and the death rate was 17%. This approach may deserve additional evaluation, but there is no evidence that it is better than existing methods (APACHE II, contrast-enhanced CT alone) for assessing severity.

Indications for Surgical Therapy

Many authors have used imprecise terms to describe their indications for surgical intervention in severe acute pancreatitis—such as sepsis, pain, anorexia, fever, mass effect, phlegmon, pancreatic abscess. The term "sepsis" is vague and undefined. There is general agreement that the term "phlegmon" should be eliminated. The term "pancreatic abscess" has been used wrongly to describe all types of pancreatic infection. This practice has made it

impossible to compare and contrast the experience from different centers and to arrive at a consensus about some of the indications.

We briefly describe our current indications for surgical intervention in patients with severe acute pancreatitis. Some are generally accepted; others are more controversial and the subject of continuing debate.

Differential Diagnosis

Today the diagnosis is unclear in only about 5% of cases of acute pancreatitis, and other intra-abdominal conditions—perforated duodenal ulcer, gangrenous cholecystitis, bowel obstruction—are seriously considered.[8,9] Because each of these requires surgical intervention, the pancreatitis is discovered at operation. Although diagnostic laparotomy does not exacerbate the pancreatitis, it may increase the incidence of subsequent pancreatic infection in patients with severe pancreatitis.[8] This is considered to be an acceptable risk, however, because a delay in the diagnosis and treatment of one of the other abdominal conditions mentioned could be catastrophic.

Biliary Pancreatitis

In patients with gallstones and mild acute pancreatitis, cholecystectomy should be done during the same hospital admission once the pancreatitis has resolved.[9] A recent study suggested that early (<24 hours) endoscopic stone extraction or sphincterotomy (or both) benefited patients with even mild biliary pancreatitis.[10] We remain skeptical that any intervention is indicated in these patients because almost all have spontaneous resolution of their symptoms. In those few patients with severe biliary pancreatitis and persistent signs and symptoms, or if cholangitis is present, endoscopic or surgical relief of the biliary obstruction is indicated within the first 48 hours. We prefer an endoscopic approach if skilled personnel are available.

Infected Pancreatic Necrosis

The presence of infected pancreatic necrosis is an undisputed indication for surgical intervention in patients with acute pancreatitis. Poorly enhanced pancreatic tissue as shown by contrast-enhanced CT scan correlates well with the presence of pancreatic necrosis.[6] Bacterial contamination of the necrotic pancreas occurs in as many as 70% of cases, and if gas bubbles are seen in the region of the pancreas on the scan, infection may be presumed to be present. Otherwise, local fluid or necrotic tissue should be aspirated percutaneously and Gram's stain and culture done. Because it has been documented that at least 50% of patients with infection may not show clinical sepsis, such as fever or leukocytosis, we generally aspirate in all patients who have undergone a CT scan in whom fluid is present. If infection is proved, an operation is indicated. Aspiration is safe, and the chances of missing an infection as a result of sampling error are low.[11] If unable to prove infection, we would repeat the CT scan and aspiration at weekly intervals. Deterioration in a patient's condition might require earlier aspiration or even an operation, however.

In this issue of the journal, Frey rightly stresses that patients with infected pancreatic necrosis require surgical debridement and drainage of the infection. Nonoperative methods such as the percutaneous placement of drains by radiologic techniques are doomed to failure because the thick particulate nature of the infected material rapidly plugs these drains.

Pancreatic Abscess

Pancreatic abscesses should be distinguished from infected pancreatic necrosis in that little or no necrotic material is present. They also typically appear later in the course of pancreatitis, often four weeks or more after the start of the attack. The diagnosis can be made with CT scan and percutaneous aspiration of the infected fluid. Because the pus usually contains little particulate material, our experience has been that percutaneous drainage is often effective and surgical drainage is usually not necessary. If, however, the septic clinical condition is not reversed rapidly after a percutaneous drain is placed, an operation should be done promptly.

Sterile Pancreatic Necrosis

Whether to operate on patients with sterile pancreatic necrosis is controversial. Beger and colleagues found that the extent of pancreatic necrosis influenced the mortality rate. When less than 30% of the gland was necrotic, 7% of their patients died. When all of the gland was necrotic, the mortality was 50%. Moreover, the likelihood of bacterial contamination was directly related to the degree of pancreatic necrosis.[12,13] When the extent of necrosis was 30%, 29% of the patients were infected. When the necrosis involved more than 50% of the gland, 71% of the patients were infected. Based on such data, these authors believe that operation is indicated in most patients with more than 50% gland necrosis as demonstrated on contrast-enhanced CT scan.

Other surgeons try to avoid an operation in patients with sterile pancreatic necrosis, regardless of its extent. They reason that an operation can be done if infection supervenes and that the available techniques for proving infection are safe and reliable. Bradley and associates have observed that many such patients recover without surgical intervention; others have had a similar experience.[14,15] Currently we use this approach for our patients, and there is no evidence that the outcome is any different with this more conservative method.

Persistent Disease, Deteriorating Clinical Course, and Organ System Failure

Some patients with sterile pancreatic necrosis will fail to improve with maximal nonoperative treatment. They may have persistent fever, abdominal pain, and an inability to eat. Computed tomographic scans may reveal an edematous and swollen pancreas, with or without fluid collections. Others deteriorate clinically despite their intensive care, often with failure of one or more organ systems. Both of these groups deserve serious consideration for operative intervention. The logic for operation in-

cludes the possibility that infection is present, but that it has been impossible to prove it with nonoperative techniques. It may also be that even without infection, the pancreas continues to release various poorly defined "toxic" substances, such as enzymes or vasoactive substances, whose drainage would benefit the patient. Finally, in rare cases a patient may have ductal obstruction that continues to exacerbate the inflammation.

In the presence of a mechanical cause for the pancreatitis, such as pancreatic duct stricture, an operation should be done promptly. In its absence, it is unclear how long to wait before an operation is undertaken. With stable but persistent disease and no organ system failure, we usually wait several weeks, with the hope that improvement will occur and an operation can be avoided. With a deteriorating course, and especially with one or more organ systems failing, we often operate within a few days. Nevertheless, because as many as 25% of patients recover from pulmonary, renal, or cardiovascular dysfunction without surgical therapy, it must be admitted that absolute criteria for an operation are lacking in these patients.[16]

Can the Decision to Operate Be Made More Objective?

It has been suggested that limits be set in terms of specific indicators of severity and that surgical therapy be undertaken when these are exceeded. For example, an operation might be done if the APACHE II score was greater than 12 or if the CT severity index (Balthazar) was more than 7. We are skeptical that this "cookbook" approach to clinical decision making is better than the judgment of an experienced surgeon.

As more organ systems fail, the mortality rate rises.[17-19] This is true for many diseases in addition to pancreatitis. In a group of patients with severe pancreatitis, the survivors had an average of 1.4 organ systems involved; those who died had 3.2. In Büchler and associates' patients, pulmonary insufficiency occurred in 24% of those with sterile necrosis and about half of those with infected necrosis. Renal insufficiency and shock were also seen in 20% to 30% of cases (Table 1).[16] Thus, there has been a tendency to intervene surgically when organ systems begin to fail and when they remain unresponsive to the usual medical measures. Of course, we do not know whether surgical intervention is responsible for the reversal in organ system deterioration that is sometimes seen. This question needs to be studied prospectively.

Surgical Principles

Extensive debridement of necrotic pancreatic and peripancreatic tissue is the cornerstone of surgical management. Infected tissues should be debrided, fluid evacuated, and the areas irrigated copiously. Viable pancreas should not be removed. We also place a feeding jejunostomy tube in most of these critically ill patients. Even if all of the patient's caloric needs cannot be supplied this way, it is important to maintain the integrity of the gut mucosa by providing luminal nutrients. There is evidence from patients with other critical illnesses that this decreases the incidence of bacterial translocation and may prevent the "sepsis syndrome."[17,18,20]

TABLE 1.—*Incidence of Organ Failure and Clinical Sepsis in 134 Patients With Acute Necrotizing Pancreatitis**

Complication	Necrotic Pancreatitis: Infected Patients (n = 55) No.	%	Necrotic Pancreatitis: Sterile Patients (n = 79) No.	%
Pulmonary insufficiency†	27	49	19	24
Renal insufficiency‡	18	33	15	19
Shock§	12	22	6	8
Sepsis‖	27	49	9	11

*Modified from Büchler et al.[16] Note that only half of the patients with infection were clinically septic and that 11% of patients with sterile necrosis had evidence of sepsis.
†Po_2 <60 torr.
‡Serum creatinine level >120 μmol per liter.
§Systolic blood pressure <80 mm of mercury for >15 minutes.
‖Temperature >38.5°C; leukocyte count <4 × 10^9 per liter (4,000 per μl) to >12 × 10^9 per liter (12,000 per μl); platelet count <1.5 × 10^9 per liter (<150,000 per μl); metabolic acidosis >−4 mmol per liter.

There has been discussion about the merits of "closed" versus "open" techniques of drainage. Büchler and coworkers have popularized the closed approach in which postoperative lesser sac lavage is accomplished through large drains placed at the time of the operation.[16] The abdominal incision is closed, and there is no planned reexploration. The open approach has been promulgated by Bradley and well described by Frey.[1,21] Because the results from both approaches appear to be equivalent, we usually use the closed technique, which requires fewer resources and is simpler. In patients with extensive necrosis where effective postoperative lavage may not be possible, we agree with Frey that the open technique may be better. Even with the closed technique, reoperation is required in as many as 30% of patients, usually for recurrent or persistent infection and occasionally for hemorrhage.[16]

Summary

The decision to operate on a patient with severe acute pancreatitis is often difficult and requires mature clinical judgment. Indications that are widely accepted include to establish the differential diagnosis, when the surgeon is concerned that the symptoms are due to a disease other than pancreatitis for which an operation is mandatory; in persistent and severe biliary pancreatitis, when an obstructing gallstone is lodged in the ampulla of Vater and cannot be managed endoscopically; in the presence of infected pancreatic necrosis; and to drain a pancreatic abscess, if percutaneous drainage does not produce the desired result. Other indications that are less well defined and somewhat controversial are the presence of sterile pancreatic necrosis involving 50% or more of the pancreas, when the pancreatitis persists despite maximal medical therapy, and when a patient's condition deteriorates. For these last three indications, guidelines have been presented that permit a logical approach to management, although uncertainty remains. Surgeons should strive to describe in detail and precisely the clinical state

of their patients at the time that an operation is done, as well as the findings and technical details of the operation. This should allow further refinement in the management of this vexing problem.

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REFERENCES

1. Frey CF: Management of necrotizing pancreatitis. West J Med 1993; 159:675-680

2. Ranson JHC, Rifkind KJM, Roses DF: Objective early identification of severe acute pancreatitis. Am J Gastroenterol 1974; 61:443-451

3. Larvin M, McMahon MJ: APACHE II score for assessment and monitoring of acute pancreatitis. Lancet 1989; 2:201-205

4. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: Severity of disease classification system. Crit Care Med 1985; 13:818-829

5. Bradley EL 3d, Murphy F, Ferguson C: Prediction of pancreatic necrosis by dynamic pancreatography. Ann Surg 1989; 210:495-504

6. Freeny PC: Incremental dynamic bolus computed tomography of acute pancreatitis—State of the art. Int J Pancreatol 1993; 13:147-158

7. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JHC: Acute pancreatitis: Value of CT in establishing prognosis. Radiology 1990; 174:331-337

8. Ranson JHC: The role of surgery in the management of acute pancreatitis. Ann Surg 1990; 211:382-393

9. Poston GJ, Williamson RCN: Surgical management of acute pancreatitis. Br J Surg 1990; 77:5-12

10. Fan ST, Lai ECS, Mok FPT, Lo CM, Zheng SS, Wong J: Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993; 328:228-232

11. Banks PA, Gerzof SG, Robbins AH, et al: Diagnosis of pancreatic infection by CT-guided aspiration: An update. Presented at the American Pancreatic Association meeting, Chicago, Ill, November 1988, abstract 590

12. Beger HG, Krautzberger W, Bittner R, Block S, Büchler M: Results of surgical treatment of necrotizing pancreatitis. World J Surg 1985; 9:972-979

13. Beger HG, Büchler M, Bittner R, Block S, Nevalainen T, Roscher R: Necrosectomy and postoperative local lavage in necrotizing pancreatitis. Br J Surg 1988; 75:207-212

14. Bradley EL 3d, Allen KA: Management of necrotizing pancreatitis: Results of prospective longitudinal trial. Am J Surg 1991; 161:19-25

15. Reber HA: Surgical intervention in necrotizing pancreatitis (Editorial). Gastroenterology 1986; 91:479-482

16. Büchler M, Uhl W, Isenmann R, Bittner R, Beger HG: Necrotizing pancreatitis: Necrosectomy and closed continuous lavage of the lesser sac—The Ulm experience, *In* Beger HG, Büchler M, Malfertheiner P (Eds): Standards in Pancreatic Surgery. Berlin, Springer, 1993, pp 191-202

17. McFadden DW: Organ failure and multiple organ system failure in pancreatitis. Pancreas 1991; 6:S37-44

18. Fry DE: Multiple organ system failure. Surg Clin North Am 1988; 68:107-122

19. Warshaw AL, Gongliang J: Improved survival in 45 patients with pancreatic abscess. Ann Surg 1985; 120:690-702

20. Carrico CJ, Meakins JL, Marshall JC: Multiple organ failure syndrome. Arch Surg 1986; 121:196-208

21. Bradley EL 3d: Open packing for infected pancreatic necrosis, *In* Beger HG, Büchler M, Malfertheiner P (Eds): Standards in Pancreatic Surgery. Berlin, Springer, 1993, pp 220-232