

Controversies in acute pancreatitis

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Pancreatitis has been one of the most challenging conditions for practicing physicians. Estimates of the incidence of acute pancreatitis (AP) range from about 5 to 25 cases per 100,000 populations. Roughly 60 patients are admitted in the surgical ward of Tribhuvan University Teaching Hospital (TUTH). In large series from referral hospitals, the mortality associated with acute pancreatitis has ranged from 5% to 10%; however, this range is probably high because of referral of complicated cases, as recent estimates using more comprehensive hospital databases have documented an overall mortality of about 2%. Mortality varies with etiology, the development of complications or necrosis, and the number and severity of co-morbid medical conditions. The treatment of acute pancreatitis has four goals:

1. Provide supportive care
2. Minimize or reduce the local necrosis and the systemic inflammatory process (maximum organ preservation)
3. Recognize and treat complications; and
4. Prevent subsequent attacks

A review in the May 15, issue of *American Family Physician* highlights the best practices for diagnosing and treating acute pancreatitis.

- Total enteral nutrition is as good as or more effective than total parenteral nutrition for nutritional management of severe pancreatitis (evidence level A).
- Urgent endoscopic retrograde cholangiopancreatography (ERCP) is indicated in patients with or at risk for biliary sepsis or obstruction, cholangitis, or worsening or persistent jaundice (evidence level A).
- Endoscopic retrograde cholangiopancreatography is useful to evaluate for less common causes of

pancreatitis (including sphincter of Oddi dysfunction, pancreas divisum, and pancreatic duct strictures; evidence level C).

- Contrast-enhanced computed tomography (CT) is useful to diagnose acute pancreatitis (evidence level C).
- Whether antibiotics improve survival in patients with necrotic pancreatitis remains controversial (evidence level, B).

There is no debate about treating mild acute pancreatitis as the outcome is very good. However one must not neglect mild AP as hypotension at the initial phase may convert the milder form of disease to a severe one. Correction of hypovolemia is the single most important step in the management of AP. Most of these cases are treated nil per orally, intra venous fluid, analgesic and nasogastric tube suction, if necessary. Clinically milder form of disease can have severe necrosis and may be detected incidentally during contrast enhance CT scan. When it comes to treating Severe Acute Pancreatitis (SAP) there are three areas of controversies.

1. Feeding
2. Prophylactic antibiotics
3. ERCP and sphincterotomy

Feeding

Nutrition can be most neglected part in the management of AP. Ensuring adequate nutrition is important in patients with severe or complicated pancreatitis, but the optimal means of doing so remains controversial.¹ For many years traditional teaching said that oral or enteral feeding might be harmful in AP as feeding is thought to stimulate exocrine pancreatic secretion and accelerate the autodigestive process.

Nutritional support is useful for patients with SAP and for those with milder pancreatitis who nonetheless are unable to eat for more than ¹ 5-7 days. The preferred route of providing exogenous nutrients has changed. For years, total parenteral nutrition (TPN) has been the standard practice. Two small trials involving a total of 70 patients showed no significant reduction in adverse outcomes with enteral feeding through nasoenteric tubes, as compared with total parenteral nutrition² Accumulating evidence suggests that enteral nutrition (EN) is comparable or superior to TPN. Prospective, randomized trials have demonstrated that enteral feeding infused distal to the ligament of Treitz is associated with fewer complications. Today early enteral nutrition is considered an important mode of acute treatment and it is supported by several trials.

Most studies show that compared to parenteral nutrition, enteral feeding is cheaper, safe, fewer septic complications and improved clinical outcome. Nutritional support is the important part of the treatment in AP and enteral nutrition is the choice whenever possible.

This can be supplemented by parenteral nutrition if the intake is inadequate. Patients with acute pancreatitis do better when they have enteral nutrition. In severe acute pancreatitis, the protein catabolism may increase by 80% and energy expenditure by 20%, indicating that nutritional requirements are elevated and interventional nutrition support is mandatory. Because oral feeding may stimulate the synthesis of proteolytic enzymes and perpetuating autolysis, the cornerstone of nutritional support had been the total parenteral nutrition (TPN). Unfortunately, the use of TPN has been associated with major metabolic and infectious complications and nutritional alternatives have been looked for. Physiologic studies have shown that infusion of nutrients into the distal jejunum bypassed the stimulatory effect of feeding on pancreatic secretion and many studies compared TPN with jejunal feeding. Jejunal feeding is associated with fewer infections and metabolic complications, and moreover, less expensive than TPN. These observations have resulted in the general acceptance of jejunal nutrition as the best nutritional support in SAP². Reviewing 112 articles, Marik and Zaloga identified six trials in which 263 patients with acute pancreatitis were randomized to enteral or parenteral nutrition. They found that those who had had enteral nutrition, delivered through a nasojejunal tube, had significantly fewer infections or surgical interventions and were in hospital for a significantly shorter time than those who had had parenteral nutrition^{3,4}. Enteral feeding is usually well tolerated in patients with ileus.¹ 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 organ failure, both of which are responsible for most of the morbidity and mortality associated with the disease⁵ Enteral nutrition is less expensive than parenteral feeding, helps to maintain mucosal function, and limits absorption of endotoxins and cytokines from the gut as EN maintains the integrity of the mucosal barrier it is supposed to prevent transmigration of the gut bacterias^{4,5}. However, this has been challenged. This enteral nutrition can be delivered through feeding jejunostomy (FJ), through nasojejunal tube (NJ) or through nasogastric tube (NG). Earlier study supported FJ feeding, but this has been challenged by larger recent randomized study^{2,6}. The main practical challenge in using enteral jejunal feeding is placing and maintaining position of the nasojejunal tube. Results of a randomized study of nasogastric versus nasojejunal feeding in severe acute pancreatitis suggested that nasogastric feeding may also be safe, since little difference in pain, analgesic requirements, serum CRP concentrations, or clinical outcome was reported between the two methods⁶. As nasogastric feeding is simpler, cheaper, and easier to use than nasojejunal feeding, this study provides the basis for a very practical advance in the management of patients with acute pancreatitis.

However, total parenteral nutrition may be necessary for patients who cannot obtain sufficient calories through enteral nutrition or in whom enteral access cannot be maintained.⁵

Antibiotics

Use of antibiotics in SAP remains debatable. There is concern that their routine use is leading to a rise in drug-resistant or unusual organisms in pancreatic sepsis, and possibly even increased mortality when antibiotics are used inappropriately.⁷ Results of studies in the 1970s showed no benefit from routine antibiotic prophylaxis.⁷⁻⁹ Ampicillin has poor penetration (John Hopkin study, 1975, French 1976) However, the studies were probably underpowered, because patients with mild acute pancreatitis, who have a low morbidity and mortality, were included. In severe disease, secondary infection of necrotic pancreatic parenchyma is the leading cause of late mortality Three randomised studies comparing antibiotics with no antibiotics in acute necrotising pancreatitis. Buchler and colleagues reported that of ten different antibiotics tested, only imipenem, ofloxacin, and ciprofloxacin showed adequate tissue penetration and bactericidal properties to be useful in infected pancreatic necrosis¹⁰. Bassi and co-workers later randomly allocated 60 patients with necrotising acute pancreatitis either intravenous pefloxacin 400 mg twice daily

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or intravenous imipenem 500 mg three times daily, starting within 120 h of diagnosis and continuing for 2 weeks¹¹. Pancreatic—but not extrapancreatic—sepsis was reduced in the imipenem group, but mortality did not differ greatly between the two groups. The importance of early initiation of antibiotics is unclear. Yet in another study, early imipenem-cilastatin therapy seemed to substantially reduce the need for surgery and the overall number of major organ complications. Mortality was also lowered, but did not differ significantly¹². An alternative strategy for prevention of translocation of bacteria from the gut into the pancreatic bed is selective decontamination: Conclusive data are absent, but some preliminary results have been reported from animals and work in human beings.^{13,14} At present, the standard of care dictates that patients with acute pancreatitis complicated by necrosis should receive a prophylactic, broad-spectrum antibiotic, typically imipenem. Dambrauskas Z and coworker identified 10 randomized clinical trials concerning prophylactic parenteral antibiotics in patients with acute necrotizing pancreatitis. They performed a meta-analysis using the random-effects model to assess the impact of prophylactic antibiotics on development of infected pancreatic necrosis and sepsis, need for surgery, and overall mortality. They came to conclusion that patients with necrotizing acute pancreatitis should receive effective antibiotic prophylaxis (i.e., carbapenems intravenously) to decrease the risk of infected necrosis and sepsis and need of surgery¹⁵. Similarly Røkke O and coworker in randomized study in Norway using imipenem found that early prophylactic treatment with imipenem reduced the rate of septic complications in patients with severe pancreatitis¹⁶. The study may be underpowered as there were less than 40 patients in each arm.

Patchen E. Dellinger analyzed a multicenter, prospective, double-blind, placebo-controlled randomized study set in 32 centers within North America and Europe. One hundred patients with clinically severe, confirmed necrotizing pancreatitis: 50 received meropenem and 50 received placebo. Primary end point was time between onset of pancreatitis and the development of pancreatic or peripancreatic infection; all-cause mortality; requirement for surgical intervention; development of nonpancreatic infections within 42 days following randomization. There was no statistically significant difference between the treatment groups for pancreatic or peripancreatic infection, mortality, or requirement for surgical intervention, and did not support early prophylactic antimicrobial use in patients with severe acute necrotizing pancreatitis.¹⁷

Quite a number of studies are now emerging about the use

of broad spectrum antibiotic in SAP and its doubtful outcome. Unlike previous claim, we still need to do a large scale prospective study to confirm the role of antibiotics in SAP. However one should use antibiotics in the following situations till further guidelines emerge.

- Newly developed sepsis or sepsis inflammatory response syndrome.
- Failure of two or more organ systems proved infection.
- An increase in serum C reactive protein in combination with other evidence supporting the possibility of infection.

Endoscopic management.

The role of early endoscopic intervention, in the treatment of acute gallstone pancreatitis, remains controversial. Previous randomized trials have not focused on the subgroup of patients with clinical evidence of biliopancreatic obstruction.

Earliest study by Neoptolemos et al.¹⁸ found that the removal of gallstones on an emergency basis with the use of ERCP and endoscopic sphincterotomy in patients with severe acute gallstone-induced pancreatitis led to a lower morbidity rate than conventional medical treatment alone (24 percent vs. 61 percent). These data, however, were based on only 12 patients, who had stones removed from the common bile duct. This benefit included a reduction in complications (organ failure and others) and a trend (not statistically significant) toward lower mortality. These benefits were restricted to a subgroup of patients who were predicted to have a severe attack.

This level drops to between 3% and 33% if the evaluation is undertaken later in the clinical course.¹⁹ Further controlled trial found that the use of ERCP and endoscopic sphincterotomy within 24 hours of admission reduced the incidence of biliary sepsis¹⁹. Both these studies showed trends toward a reduction in mortality in treated patients. A third randomized trial attempted to reconcile these results by excluding patients with cholangitis or those at high risk for cholangitis (i.e., patients with jaundice). This study demonstrated no reduction in morbidity or mortality in patients with gallstone pancreatitis but without jaundice.²⁰ ERCP with sphincterotomy has its own risks (hemorrhage, perforation, and worsening of pancreatitis) and should be performed only by expert clinicians.

Three randomized trials involving a total of 511 patients with gallstone pancreatitis compared conservative management with ERCP and endoscopic sphincterotomy within 24 to 72 hours after admission. The studies showed

a significantly lower risk of pancreatitis-associated complications in the ERCP group (odds ratio, 0.27; 95 percent confidence interval, 0.14 to 0.53).²¹ This became a guide line until recently. This has now been challenged except in biliary sepsis.

A single-center randomized clinical trial was performed between May 2000 and September 2005. Of 238 patients, admitted within 48 hours after the onset of acute gallstone pancreatitis, 103 with a distal bile duct measuring ≥ 8 mm combined with a total serum bilirubin ≥ 1.20 mg/dL, were randomized to receive either endoscopic retrograde papillotomy for bile duct stones (EEI, n = 51) or early conservative management (ECM, n = 52). The study failed to provide evidence that early endoscopic intervention reduces systemic and local inflammation in patients with acute gallstone pancreatitis and biliopancreatic obstruction.²² It is now recommended urgent endoscopic retrograde cholangiopancreatography (ERCP) is indicated in patients with or at risk for biliary sepsis or obstruction, cholangitis, or worsening or persistent jaundice (evidence level A). We need a larger study to prove the efficacy of the endoscopic intervention in uncomplicated pancreatitis.

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