

# Update in Nonpulmonary Critical Care

## Recent Advances in Critical Care Gastroenterology

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As a result of pharmacologic and technologic advances, the intensive care unit treatment of many acute gastrointestinal diseases has changed significantly over the last decade. This Update focuses on new approaches to the management of acute variceal hemorrhage, acute colonic pseudo-obstruction, and severe necrotizing pancreatitis.

### MANAGEMENT OF ACUTE VARICEAL HEMORRHAGE

#### Introduction

Bleeding from esophageal and gastric varices remains one of the most devastating complications of end-stage liver disease, accounting for approximately 80% of upper gastrointestinal bleeding episodes. Bleeding risk is markedly increased in decompensated cirrhosis because 60% of patients have varices and a concomitant reduction in clotting factors is often present. Recent advances in pharmacologic management and endoscopic techniques have improved the capacity to control active bleeding and reduce the risk of rebleeding. Improvements in patient survival have been more difficult to demonstrate; variceal hemorrhage continues to carry a mortality of 30–50% (1).

#### Pharmacologic Therapy

Until recently, the combination of vasopressin and nitroglycerin, often initiated after admission to the ICU, was used to treat acute variceal hemorrhage. Although somewhat effective in initial control of bleeding, the lack of significant impact on rebleeding rates and survival, as well as the high rate of complications, prompted a search for more effective and safer agents. Somatostatin and its long-acting analogue octreotide decrease portal and intravariceal pressures by blocking the release of vasodilator substances such as glucagon. Older randomized, controlled trials suggested that somatostatin was superior to both placebo and to vasopressin in controlling active bleeding and preventing early rebleeding. A recent meta-analysis comparing somatostatin and vasopressin found that the former was 1.6 times more likely to achieve initial control of bleeding from acute esophageal varices while being free of adverse effects (0% somatostatin versus 10% vasopressin) (1).

An area of recent interest has been the use of pharmacologic therapy delivered *very early* after the onset of bleeding and prior to endoscopic therapy. A study of 205 cirrhotics found that somatostatin, started within 12 h of the initial clinical signs of bleeding (and continued for 120 h), was more effective in controlling active variceal hemorrhage (65% versus 45%,  $p = 0.004$ ) and was associated with improved survival

compared with placebo (2). Similarly, a randomized trial investigated the combination of an intravenous injection of terlipressin (an analogue of vasopressin) and nitroglycerin initiated *prior* to hospitalization in cirrhotics suspected of having variceal hemorrhage (3). Compared with placebo, patients receiving active treatment had better control of bleeding and a reduced bleeding-related 15- and 42-d mortality. Early effective pharmacologic therapy and resultant cessation or slowing of bleeding may result both in more rapid hemodynamic stabilization and in providing a clearer visual field for subsequent endoscopy (2).

#### Endoscopic Therapy

Emergency endoscopic treatment (sclerotherapy or band ligation) remains the definitive approach for patients with acute hemorrhage from esophageal varices. A meta-analysis of 7 randomized controlled trials found that, compared with sclerotherapy, band ligation decreased rebleeding risk (odds ratio, [OR]: 0.52, 95% CI: 0.37–0.74), overall mortality (OR: 0.67, 95% CI: 0.46–0.98), mortality related to bleeding (OR: 0.49, 95% CI: 0.24–0.996) and procedure related complications (4). A subsequent study showed cessation of active variceal hemorrhage in 97% of patients treated with banding compared with 76% treated with sclerotherapy ( $p = 0.009$ ) (5). Despite these data, many endoscopists feel that sclerotherapy is technically easier to perform in the setting of active variceal bleeding. One reason may be that sclerotherapy can be effective even if the injection is paravariceal, whereas bands must be placed directly on the varix.

#### Combination Therapy

Sclerotherapy appears to be superior to vasopressin in achieving control of active bleeding and in reducing early rebleeding (6). In contrast, a meta-analysis of 5 studies concluded that treatment with somatostatin or octreotide is as effective as sclerotherapy in the management of acute variceal hemorrhage (6). In a study comparing band ligation with and without octreotide, combined therapy decreased the risk of rebleeding (9% versus 38%,  $p < 0.001$ , relative risk: 0.22), decreased the need for balloon tamponade (2% versus 21%) and tended to reduce 30-d mortality (11% versus 23%, relative risk: 0.45) (7). A double-blinded study randomized 199 patients to either sclerotherapy alone or sclerotherapy in combination with octreotide (25  $\mu\text{g/h}$  for 5 d) (8). Although overall mortality was unchanged, the combined therapy group had a higher proportion of patients surviving without rebleeding (87% versus 71%,  $p = 0.009$ ) and had a decreased need for blood transfusion in the first 24 h (1.2 units versus 2 units,  $p = 0.006$ ). Lastly, somatostatin (250  $\mu\text{g/h}$  for 5 d) was compared with somatostatin plus sclerotherapy in a randomized trial of 100 patients (9). Although complications were higher with combined therapy, it resulted in better control of active bleeding (92% versus 76%), less rebleeding and less need for blood transfusion.

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sion. These randomized controlled trials indicate that combining pharmacologic and endoscopic therapy is superior to either approach alone for both control of active bleeding and prevention of early rebleeding.

#### Salvage Therapy with the Transjugular Intrahepatic Portosystemic Shunt (TIPS)

In the past, the 20% of patients in whom initial endoscopic therapy failed were treated with either repeat endoscopy, balloon tamponade, portal decompressive surgery, esophageal transection, or emergent liver transplantation. Recently, investigators described a technique for creating a portosystemic shunt (TIPS) by passing a needle catheter into the hepatic vein (via the transjugular approach), advancing it through the hepatic parenchyma into a branch of the portal vein and then deploying an expandable metallic stent. In a retrospective study of 38 patients with bleeding uncontrolled by sclerotherapy, TIPS was associated with a lower 30-d mortality (42% versus 79%,  $p < 0.05$ ) and lower rebleeding rate (16% versus 26%) when compared with esophageal transection with devascularization (10). In an observational study, TIPS was successful at achieving hemostasis in 29 of 30 patients who continued to bleed after sclerotherapy (11). Similarly, TIPS achieved control of bleeding in 53 of 56 (95%) of patients who required balloon tamponade after combined pharmacologic and endoscopic therapy failed (12). Major complications of TIPS included hemoperitoneum, cardiorespiratory arrest, cardiac failure, acute renal failure, and bacteremia. In addition, 14% experienced rebleeding within one week. Other authors have noted a relatively high rate of stent occlusion after emergent TIPS (4/11 patients, 36%) (13).

#### Gastric Varices

Bleeding from *isolated* gastric varices raises the possibility of underlying splenic vein thrombosis, an entity best treated with splenectomy. In contrast, the management of bleeding gastric varices in patients with portal hypertension is more challenging, because standard sclerosants are relatively ineffective in achieving control of active bleeding and the risk of rebleeding may be as high as 90%. Although investigators have recently looked at using novel sclerosing agents such as cyanoacrylate and thrombin (14), randomized controlled trials are not yet available. TIPS may be the best option because in one study hemostasis was achieved in 90% (18/20) of patients with uncontrolled bleeding from ruptured gastric varices (15).

#### Variceal Hemorrhage and Bacterial Infection

Patients with cirrhosis who are admitted with acute gastrointestinal bleeding have a high risk of developing bacterial infections. Twenty-two percent of these patients become infected within 48 h of admission with the rate rising to 35–66% within 7–14 d (16). The presence of bacterial infection correlates both with poor outcomes and with failure to control gastrointestinal hemorrhage, perhaps related to adverse alterations in hemostasis (17, 18). A recent meta-analysis examined 5 published trials (totaling 534 patients) of antibiotic prophylaxis for the prevention of infection in cirrhotic patients presenting with gastrointestinal bleeding (19). Oral antibiotics alone or combinations of intravenous and oral agents including fluoroquinolones (ciprofloxacin and ofloxacin), amoxicillin plus clavulanic acid, oral aminoglycosides, vancomycin, nystatin, and colistin were administered for 4 to 10 d. The analysis concluded that patients treated with antibiotics had significantly fewer episodes of bacterial infection, bacteremia, and spontaneous bacterial peritonitis, and experienced improved survival compared with untreated patients.

#### Summary Recommendations

Patients with cirrhosis and upper gastrointestinal bleeding should receive either somatostatin (250  $\mu\text{g}$  bolus followed by a continuous infusion of 250  $\mu\text{g}/\text{h}$ ) or octreotide (50  $\mu\text{g}$  bolus followed by a continuous infusion of 25–50  $\mu\text{g}/\text{h}$ ) for 5 d. This treatment should be started expeditiously, even before the patient reaches the intensive care unit. Once the patient is hemodynamically stable and therapy to reverse coagulopathy is initiated, endoscopy should be performed to identify the source of bleeding. Depending on the preference of the operator, emergent endoscopic treatment can consist of either injection sclerotherapy or band ligation, although the latter appears to be superior. If therapy fails to control active bleeding, or rebleeding occurs within 48 h, a TIPS should be considered.

All cirrhotic patients admitted to the intensive care unit for acute gastrointestinal bleeding should also receive short-term prophylactic antibiotics after obtaining appropriate cultures. A reasonable antibiotic choice is ciprofloxacin, delivered intravenously during active bleeding followed by oral administration for at least 3 d after the cessation of bleeding.

#### MANAGEMENT OF ACUTE COLONIC PSEUDO-OBSTRUCTION

Acute colonic pseudo-obstruction is an uncommon condition in critically ill patients. Although predisposing conditions include trauma, infection, and cardiac surgery, approximately 50% of cases are associated with narcotic administration or metabolic imbalances. Colonic pseudo-obstruction is characterized by massive dilatation of the cecum (diameter  $> 10$  cm) and right colon on abdominal X-ray. In the absence of distal bowel gas, a radiographic enema is required to rule out distal obstruction.

Traditionally, initial treatment included discontinuing drugs that slow colonic motility (e.g., narcotics, anticholinergics), correcting electrolyte abnormalities (e.g., hypokalemia) and withholding enteral feeding. Decompression is routinely attempted using a nasogastric or orogastric tube, a rectal tube or colonoscopy if distal distension is present, or by positional changes (e.g., placing the patient in a prone position). Despite these maneuvers, the rate of recurrence is high.

A recent trial randomized 21 patients with documented acute colonic pseudo-obstruction to receive either 2.0 mg of neostigmine (a cholinergic agent) or placebo delivered intravenously (20). Exclusion criteria included a heart rate less than 60 bpm or a systolic blood pressure less than 90 mm Hg. Patients failing to respond to the initial injection received open-label neostigmine 3 h later. Ten of eleven patients receiving neostigmine had prompt colonic decompression (median time to response: 4 min, range: 3–30 min) compared with 0/10 receiving placebo ( $p < 0.001$ ). Seven patients in the placebo group received open-label neostigmine and all had prompt decompression as did the one nonresponder in the initial treatment group. Two patients who had an initial response to neostigmine had recurrence of distension and one required surgery. Adverse effects of neostigmine included transient moderate-to-severe abdominal cramping, vomiting, and excessive salivation. Two patients had symptomatic bradycardia requiring atropine.

#### Summary Recommendation

Intravenous neostigmine should be considered for patients with well documented colonic pseudo-obstruction who have failed 24–48 h of conservative management. Atropine should be readily available for any patient receiving treatment.

## MANAGEMENT OF ACUTE NECROTIZING PANCREATITIS

### Introduction

Necrosis of pancreatic tissue occurs in 20–30% of the 185,000 cases of acute pancreatitis that occur in the United States each year (21). Mortality is unusual in patients without necrosis whereas those with necrosis have a mortality of approximately 10%, rising to 30% should the necrotic tissue become infected (21). The differentiation between interstitial (non-necrotic) and necrotic pancreatitis requires dynamic contrast enhanced computerized tomographic (CT) scanning (22). Necrotic areas lack the normal enhancement pattern because of disruption of the microcirculation. At present, the routine use of CT scanning to differentiate between interstitial and necrotizing pancreatitis is controversial (23). Although identifying necrotizing pancreatitis has prognostic implications, there are no randomized trials documenting improved outcome when a CT scan is performed early in the course of the disease. An abdominal CT scan is indicated in patients with severe acute pancreatitis if there is a suspicion of infected necrosis, as indicated by either deterioration or failure to improve with conservative management.

### Prevention of Pancreatic Infection

Experimental models suggest that secondary infection of the necrotic pancreas is chiefly due to bacterial translocation across the colonic mucosa. Investigators have examined the role of prophylactic antibiotics to prevent secondary infection of pancreatic tissue. A multicenter trial of 102 patients with severe acute pancreatitis randomized patients to either selective gut decontamination (oral and rectal norfloxacin, colistin and amphotericin; and intravenous cefotaxime 500 mg every 8 h) or standard treatment (24). Selective decontamination decreased the need for laparoscopy and reduced late (> 2 wk) mortality owing to a significant reduction of gram-negative pancreatic infection ( $p = 0.003$ ). Overall mortality fell from 35% in controls to 22% ( $p < 0.05$ ) in the selective decontamination group. Secondary analysis of surveillance oropharyngeal and rectal cultures from control patients found that gram-negative colonization (organisms other than *Escherichia coli*) significantly correlated with the later development of pancreatic infection (relative risks: 73.7 [ $p < 0.001$ ] and 13.6 [ $p < 0.001$ ], respectively). Gram-negative intestinal colonization was also associated with a 3.7-fold increase in mortality ( $p = 0.004$ ) (25).

Previous investigations indicated that systemic antibiotics alone were ineffective in preventing secondary infection, but these studies included patients without necrosis and used antimicrobial agents with poor penetration into pancreatic tissue. A recent trial found fewer infectious complications and lower mortality among patients with alcohol-induced necrotizing pancreatitis randomized to prophylactic intravenous cefuroxime (4.5 gm/d) versus no antibiotics (26). Agents such as imipenem and fluoroquinolones have an even more favorable pharmacologic profile, demonstrating both outstanding penetration into pancreatic tissues and excellent activity against the most prevalent organisms. A retrospective study found that 75 patients with necrotizing pancreatitis who received 4 wk of imipenem had a significant decrease in the incidence of pancreatic infection (27% versus 76%) and a trend toward improved mortality compared with historical controls (27). A controlled trial of 74 patients with necrotizing pancreatitis by CT scan found that patients randomized to imipenem (500 mg administered intravenously every 8 h) had a 2.5-fold reduction in pancreatic infectious complications and a trend toward reduced mortality (7 versus 12%) (28). A randomized comparison of pefloxacin (400 mg twice a day) with imipenem (500 mg 3 times a day), started within 120 h of onset

of symptoms and continued for 2 wk, found that imipenem decreased the likelihood of both pancreatic (10% versus 34%) and extrapancreatic infection (20% versus 44%), though mortality was similar (29).

### Interventions for Infected Pancreatic Necrosis

The onset of infected necrosis may be heralded by failure to improve, or by clinical deterioration despite standard care. Under these circumstances, CT-guided fine needle aspiration can be used to discern whether a necrotic pancreatic bed is infected or sterile. Recently, ultrasonographic fine needle aspiration, a procedure that can be performed at the bedside, was shown to have a sensitivity of 88% and a specificity of 90%, a level of accuracy only slightly below that seen with CT-guided aspiration (30).

Infected pancreatic necrosis is uniformly fatal without intervention in the form of tissue debridement (21). The most commonly used method is open surgical necrosectomy, a process which typically requires several operations. Delaying surgery may allow for better demarcation between necrotic and viable regions, and this strategy appears to improve mortality compared with early necrosectomy performed within 48–72 h of disease onset (31). Another approach is percutaneous drainage using multiple large bore percutaneous catheters placed via CT scan guidance, followed by aggressive irrigation of the pancreatic bed (32, 33). Endoscopic debridement involves the placement of several transgastric or transduodenal drainage catheters (34). Although enthusiasm for these less invasive debridement options remains high, in the absence of randomized controlled trials, an open surgical approach remains the gold standard.

### Nutritional Support of Patients with Necrotizing Pancreatitis

Classically, patients with severe acute pancreatitis were treated with total parenteral nutrition (TPN) because enteral feeding was thought to stimulate the pancreas and worsen pancreatic injury. In contrast, recent data suggest that TPN does not hasten pancreatic recovery and that enteral feeding is actually well tolerated. Potential benefits of enteral feeding include decreased gut permeability, prevention of bacterial translocation, and therefore a reduction in secondary pancreatic infection. Enteral feeding is also significantly less expensive than TPN and is associated with fewer cases of catheter-related sepsis.

Several prospective randomized studies have examined the role of enteral feeding, initiated within 48 h of the onset of severe acute pancreatitis, administered via a tube advanced into the jejunum under radiographic guidance (35–37). These studies, which included approximately 100 patients in total, suggest that enteral nutrition results in fewer total and septic complications, significantly improves acute phase responses and disease severity scores and can be delivered at one-third to one-fifth the cost of TPN.

### Summary Recommendations

An abdominal CT scan should be obtained in patients with severe acute pancreatitis who either deteriorate or fail to improve with conservative treatment. Given the data suggesting that prophylactic antibiotics can decrease the incidence of secondary infection, it is recommended that patients with necrotizing pancreatitis or those with disease severity warranting intensive care unit admission receive 2–4 wk of imipenem. Once infection is documented, open surgical necrosectomy is the procedure of choice.

Although reductions in pancreatic infection and mortality are yet to be demonstrated, enteral nutrition is less expensive than TPN and is associated with fewer complications. In the absence

of severe ileus, patients with acute necrotizing pancreatitis should have a nasojejunal feeding tube placed early in the disease course and receive enteral rather than parenteral feeding.

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