Gastrointestinal Diseases in the Intensive Care Unit

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Cover Illustration by Christine Schaar

NOTE FROM THE PUBLISHER: This peer-reviewed publication has been developed without involvement of or review by the American Board of Internal Medicine.
I. INTRODUCTION

Patients with gastrointestinal diseases represent one of the largest groups of patients admitted to intensive care units (ICUs). The pathologic manifestations with which these diseases present are diverse and dynamic. Rapid changes in clinical status require in-depth clinical evaluation, attention to detail, and close monitoring. Included in this manual are 3 of the more common gastrointestinal diseases encountered in the ICU: pancreatitis, fulminant hepatic failure, and gastrointestinal bleeding. Early recognition and appropriate therapy can significantly improve the prognosis of patients with these conditions.

II. PANCREATITIS

CASE 1 PRESENTATION

Patient 1 is a 52-year-old woman who presents to the emergency department with severe, diffuse pain across the middle aspect of her upper abdomen and radiating through to her back. She reports some nausea and a single episode of vomiting.

Approximately 4 weeks ago, she presented to her primary care physician with intermittent sharp pains in the right upper quadrant of her abdomen. Her physical examination at that time was entirely normal. Laboratory data did not demonstrate hepatic dysfunction or elevation of her leukocyte count or amylase level. The patient was sent home and told to restrict her fat intake. Over the next 3 weeks she had intermittent pain. At times the pain lasted for several hours, but it always remitted on its own. On the night of admission the pain changed in character, becoming fairly diffuse and radiating.

Physical examination of patient 1 in the emergency department reveals a temperature of 101°F and a heart rate of 130 bpm. Examination of her chest shows mildly decreased breath sounds in the left lower lung zone. Her abdomen is diffusely tender with significant rigidity but no rebound.

- What laboratory tests should now be obtained in the evaluation of patient 1?
- What radiographs and/or other noninvasive diagnostic studies would be helpful in determining the etiology of patient 1’s abdominal pain?

INTRODUCTION

Pancreatitis is a relatively common disease, with an annual incidence of 10 to 50 cases per 100,000 persons. The most common causes of acute, primary pancreatitis in the United States are gallstones and alcohol abuse (Table 1). Pancreatitis is usually a mild to moderately severe self-limiting disease requiring analgesia, fluid resuscitation, and amelioration of the precipitating cause. In the vast majority of patients, the prognosis is good. Morbidity and mortality are dramatically higher in patients with severe pancreatitis.

ETIOLOGY AND PATHOPHYSIOLOGY

Patients with pancreatitis who are admitted to the ICU either have severe pancreatitis or have developed pancreatitis secondary to a preexisting severe illness or major surgery. Several conditions predispose patients to pancreatitis, including coronary artery bypass grafting, abdominal aortic aneurysm repair, transplant surgery (cardiac, renal, or hepatic), and shock. Common elements of presentation include hypoperfusion, external activation of inflammatory cytokines, immunosuppressive drugs, or some combination of these 3 factors. The final pathway leading to pancreatitis regardless of etiology is an intense inflammatory response caused by the
release of activated pancreatic enzymes. Sometimes the inflammatory response extends to other organ systems, leading to many of the early complications of acute pancreatitis. These complications include fluid collections in the abdomen, retroperitoneum, and chest; ileus and renal dysfunction. Severe complications include acute respiratory distress syndrome (ARDS) and multiple system organ failure.

CLINICAL PRESENTATION

Classically, pancreatitis presents with upper abdominal pain, nausea and vomiting, fever, and tachycardia. Laboratory studies demonstrate elevated pancreatic enzymes and a leukocytosis. In an already critically ill patient, symptoms may not be obtainable (ie, if the patient is sedated and/ or intubated) and clinical signs and laboratory indices may already be altered by a preexisting disease. Even in otherwise healthy patients, signs and symptoms may be vague or misleading. A high index of suspicion is required to make the diagnosis in a timely manner.

EVALUATION

Once the diagnosis of pancreatitis has been made, classification of severity and recognition of complications will help guide further therapy. Ranson’s criteria are a set of 11 factors (demographic, hemodynamic, biochemical, and hematologic) measured at admission and within the first 48 hours of illness (Table 2). The presence of 3 or more criteria indicates severe pancreatitis and a significantly increased risk of morbidity or mortality. Other signs of severe pancreatitis include failure of any other organ system or identification of pancreatic necrosis on a contrast-enhanced dynamic computed tomographic (CT) scan of the abdomen.

Laboratory Evaluation

Initial evaluation of a patient with pancreatitis includes a comprehensive metabolic profile to assess electrolyte and renal status, and to provide prognostic criteria (including liver enzymes and serum calcium levels). A complete hematologic profile is also obtained, including a coagulation profile in a patient who has alcoholism or another preexisting illness. Serum levels of the pancreatic enzymes amylase and lipase should be determined.

Arterial blood gas measurements should be obtained in intensive care patients to provide information regarding severity of illness and help determine oxygen and ventilatory management.

Imaging Evaluation

A chest radiograph and abdominal series (if an

<table>
<thead>
<tr>
<th>Table 1. Etiologies of Pancreatitis</th>
</tr>
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<tbody>
<tr>
<td><strong>Obstructive conditions</strong></td>
</tr>
<tr>
<td>Choledocholithiasis</td>
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<tr>
<td>Ampullary or pancreatic tumors</td>
</tr>
<tr>
<td>Duodenal obstruction</td>
</tr>
<tr>
<td>Pancreas divisum</td>
</tr>
<tr>
<td>ERCP-induced</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td><strong>Toxins</strong></td>
</tr>
<tr>
<td>Alcohols</td>
</tr>
<tr>
<td>Scorpion venom</td>
</tr>
<tr>
<td>Organophosphate insecticides</td>
</tr>
<tr>
<td><strong>Drugs</strong> (not a complete list):</td>
</tr>
<tr>
<td>Azathioprine, 6-mercaptopurine, valproic acid, estrogens, tetracycline, metronidazole, nitrofurantoin, pentamidine, furosemide, sulfonamides, methyldopa, cytarabine, cimetidine, sulindac</td>
</tr>
<tr>
<td><strong>Metabolic conditions</strong></td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td><strong>Infectious conditions</strong></td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Coxsackie virus infection</td>
</tr>
<tr>
<td>Mycoplasma infection</td>
</tr>
<tr>
<td>Hepatitis A and B virus infections</td>
</tr>
<tr>
<td>Epstein-Barr virus infection</td>
</tr>
<tr>
<td>Parasitic infections (ascariasis, clonorchiasis)</td>
</tr>
<tr>
<td>Campylobacter jejuni infection</td>
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<tr>
<td><strong>Vascular conditions</strong></td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Hypoperfusion/shock</td>
</tr>
<tr>
<td>Emboli</td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Penetrating duodenal ulcer</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
</tbody>
</table>

ERCP = endoscopic retrograde cholangiopancreatography.

abdominal CT is not initially performed) are necessary to evaluate for fluid collections and concomitant pulmonary disease processes, and to exclude other emergent intra-abdominal pathologic processes (eg, small bowel obstruction, perforation). Ultrasonography of the gallbladder may be used to evaluate for gallstones and ductal dilatation, and may help assess severity if the pancreas can be visualized. In high risk or severely ill patients, dynamic CT of the abdomen with contrast medium is necessary to clearly define the extent of pancreatic injury, and may demonstrate pancreatic necrosis. The presence of necrosis significantly alters the treatment of pancreatitis.

FURTHER MANAGEMENT OF PATIENT 1

Patient 1 is diagnosed with acute severe pancreatitis and is transferred to the ICU. She is hypotensive and is developing severe hypoxia. She is intubated and a pulmonary artery catheter is placed. A CT of the abdomen suggests the presence of necrotic pancreatic tissue.

- What therapeutic options are available for patients with severe necrotizing pancreatitis?
- What diagnostic tests should be undertaken in patient 1 at this time?
- Are antibiotics useful in patients with necrotizing pancreatitis?

TREATMENT OF PANCREATITIS

Supportive Therapy

The initial treatment of pancreatitis consists of supportive therapy, the intensity of which is tailored to the level of illness of the patient. Patients in the ICU often require ventilatory support and close hemodynamic monitoring, and possibly the use of pressor agents. Pulmonary artery pressure monitoring may be necessary in patients with underlying cardiovascular disease and in patients who do not respond to appropriate fluid resuscitation.

Nutrition should be provided within 48 hours of admission. Ideally, enteral feeding is provided via a nasoenteral tube placed distal to the ligament of Treitz. If ileus or the inability to place a tube precludes enteral feeding, then total parenteral nutrition is used, maintaining vigilance for signs of complications (eg, infection; electrolyte, triglyceride, hepatic enzyme abnormalities).

Treatment of Necrotizing Pancreatitis

A common complication of severe pancreatitis is the development of necrotic tissue, occurring in approximately 20% to 30% of cases. Necrotizing pancreatitis markedly increases mortality. Its presence also warrants additional therapeutic measures beyond supportive care.

Evidence of necrotizing pancreatitis includes lack of improvement of the patient after several days of appropriate therapy, or the deterioration of the patient after an initial phase of improvement. The presence of necrotic tissue may not manifest itself for several days to weeks following the onset of pancreatitis, and is not necessarily accompanied by a rise in serum amylase levels.

Initial evaluation of suspected necrosis requires contrast-enhanced dynamic CT of the pancreas. Necrotic areas appear as hypolucencies. Often, serial CT scans are necessary to determine the progression of pancreatitis. Once necrotic tissue has been identified, CT-guided percutaneous needle aspiration of the affected areas can be performed to determine whether the necrotic area is sterile.

The use of antibiotics, either systemically or enterally, has been shown to improve outcomes in necrotizing pancreatitis. Baron and Morgan recommend the use of imipenem with cilastatin as soon as the diagnosis of necrotizing pancreatitis is made, to be continued for 2 to 4 weeks.1 If percutaneous aspiration demonstrates sepsis, further aggressive measures should be undertaken.

Operative Management

Invasive treatment of pancreatitis is limited to cases of hemorrhagic pancreatitis, infected (septic) necrotizing pancreatitis, or obstruction of the ampulla of Vater with evidence of cholangitis.

Endoscopic retrograde cholangiopancreatography with sphincterotomy can be used for the relief of...
obstruction but should be limited to cases in which evidence for persistent obstruction is strong.\textsuperscript{1,2}

The presence of septic necrotic pancreatic tissue is demonstrated by a positive culture of the percutaneous aspirate and deterioration of the patient's status in spite of appropriate, aggressive medical management. Débridement is necessary; mortality is 100% without drainage. Surgery may be indicated in patients with sterile necrosis who remain acutely ill several weeks out from the onset, although benefit has not been definitively proven.\textsuperscript{2}

Several methods of débridement or drainage of necrotic tissue have been used. Conventional drainage, which consists of necrosectomy with standard surgical drains and reoperation as needed, has largely been abandoned because of poor outcomes. In the open technique of drainage, the wound is left open and is repacked frequently. In the semiopen technique, the abdominal wall is closed and repeated laparotomies are performed on a scheduled basis. The closed technique is similar to the conventional, but large drains are placed and continuous high-volume lavage of the lesser sac is performed.\textsuperscript{1}

Percutaneous drainage, and even débridement, via radiographically guided large-bore catheters has been performed. Even endoscopic drainage of necrotic material in select patients has been performed successfully.\textsuperscript{1}

Surgical Management of Patient 1

The day after being transferred to the ICU, patient 1 undergoes a pancreatic resection involving the middle portion and tail of the pancreas. The abdomen is left open for appropriate drainage. After a rocky course over the next 48 hours, the patient is eventually extubated and transferred out of the ICU.

III. FULMINANT HEPATIC FAILURE

CASE 2 PRESENTATION

Patient 2 is a 43-year-old man who recently returned from a trip to France, where he studied French cuisine. One week after his return to the United States, he noticed that he bruised easily and bled excessively after shaving. Several days later he noticed yellow discoloration of his sclerae and some difficulty with maintaining thought processes. At this point patient 2 presented to the emergency department.

On physical examination patient 2 appears to be in no acute distress, and looks his stated age. His sclerae are markedly icteric and there are large bruises below both knees. Examination of the chest and abdomen reveals only mild right upper quadrant tenderness. His mental status is mildly impaired but there are no other abnormalities noted on neurologic examination. The patient is admitted to the medical ward, but over the ensuing 8 hours his mental status deteriorates significantly and he is transferred to the ICU.

- What are the possible causes of patient 2's clinical condition?
- What laboratory values should be monitored in patients who are suffering from acute liver failure?

INTRODUCTION

Acute liver injury is not uncommon and may result from drugs, infectious organisms, or metabolic or hemodynamic derangements. Acute hepatic failure, or fulminant hepatic failure (FHF), is a rare event in the United States. It is usually defined as acute liver injury in a previously healthy person (ie, with no chronic active liver disease) with subsequent onset of encephalopathy. Persons with inactive or asymptomatic hepatitis B viral infection, Wilson’s disease, or chronic autoimmune hepatitis may suddenly develop liver failure as well, and these patients are also considered to have FHF.\textsuperscript{3,4}

Generally, encephalopathy occurs within 8 weeks of symptom onset. However, further subclassification is frequently used to help predict course.\textsuperscript{3} In hyperacute FHF, encephalopathy occurs within 7 days of symptom onset. In acute FHF, encephalopathy occurs 8 to 28 days after symptom onset, and in subacute FHF, encephalopathy occurs 29 days to 12 weeks after symptom onset. Hyperacute FHF carries the best prognosis, although it is more frequently associated with cerebral edema. Acute and subacute FHF have worse prognoses; acute FHF has a greater than 85% mortality rate. Patient 2's presentation is consistent with hyperacute FHF.

ETIOLOGY

The list of inciting agents for FHF is diverse (Table 3), and often no clear pathogen is identified. The most common cause of FHF worldwide is viral hepatitis, although the list of agents is long, and regional variations exist. In the United Kingdom, the usual cause is acetaminophen overdose. Of the viral hepatitides, hepatitis B virus, especially in conjunction with hepatitis D virus, is the most common agent. Hepatitis A viral infection rarely becomes fulminant, and hepatitis C virus is not considered to be an agent of FHF.\textsuperscript{3,4} Hepatitis E viral infection causes FHF primarily in women in the third trimester of pregnancy and is found primarily...
nonhepatotropic viral agents may also cause acute hepatitis and FHF, although this is a rare occurrence.

Drugs and other chemical substances may cause hepatic failure owing to direct injury (eg, acetaminophen, amanita mushroom toxin) or hypersensitivity reactions (eg, halothane, isoniazid).

**Pathophysiology and Clinical Correlates**

The primary manifestations of FHF are related to impairment of the synthesis and clearance functions of the liver.

**Table 3. Causes of Fulminant Hepatic Failure**

<table>
<thead>
<tr>
<th>Viral</th>
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<tbody>
<tr>
<td>Hepatitis viruses A, B, D, E</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>Adenovirus</td>
</tr>
<tr>
<td>Coxsackie virus</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>Acetaminophen toxicity</td>
</tr>
<tr>
<td>Ovordose</td>
</tr>
<tr>
<td>Acetaminophen toxicity associated with alcohol use</td>
</tr>
<tr>
<td>Other drug toxicities (not a complete list):</td>
</tr>
<tr>
<td>Isoniazid, halothane, valproic acid, phenytoin, diclofenac, sulfonamides, propylthiouracil, disulfiram, amiodarone, cyclophosphamide, other antimicrobials, methylene-dioxymethamphetamine (MDMA, Ecstasy)</td>
</tr>
<tr>
<td>Other toxins</td>
</tr>
<tr>
<td>Amanita phalloides (death cap mushroom), organic solvents, some herbal medicines, Bacillus cereus, Cyanobacteria toxins</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Pregnancy (acute fatty liver, HELLP syndrome)</td>
</tr>
<tr>
<td>Q fever</td>
</tr>
<tr>
<td>Reye's syndrome</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td>Right ventricular failure</td>
</tr>
<tr>
<td>Heat stroke</td>
</tr>
<tr>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>


Hepatic Synthesis Dysfunction

Loss of synthetic function leads to coagulopathy and decreased immune function. Levels of all clotting factors are diminished, although only factor V levels have been shown to have prognostic significance. Patients are predisposed to gastrointestinal bleeding, disseminated intravascular coagulation, and bleeding with invasive procedures.

The liver also synthesizes complement, and decreased levels lead to diminished opsonization of antigens and impairment of neutrophil function. Infective complications, especially by gram-positive cocci, are common. Most frequently the urinary or respiratory tracts are affected. Fungal superinfections often occur later in the course of the illness. The patient may not manifest infection in the usual manner (ie, with fever and an elevated leukocyte count). Patients typically present with more subtle findings, such as worsening encephalopathy or deterioration in hemodynamic status.

Glucogenogenesis and glycogenosis, processes that replace depleted glycogen stores, are also impaired. Patients with FHF develop hypoglycemia if glucose supplementation is not provided, and large amounts of intravenous dextrose may be required.

Hepatic Clearance Dysfunction

The liver removes ammonia and other toxins from the circulation, and hepatic Kupffer cells located in the reticuloendothelial space remove infectious organisms. The increase in toxins resulting from hepatic failure leads to encephalopathy, and Kupffer cell dysfunction increases the risk of infectious complications in the patient with FHF.

Encephalopathy is the hallmark of FHF, and the loss of the liver’s ability to clear ammonia from the circulation (along with other possible toxins, including aromatic amino acids) is the underlying cause of the encephalopathy. The clinical picture of encephalopathy associated with FHF is different from that associated with cirrhosis. The progression of encephalopathy in FHF is fairly rapid. Patients with FHF are more likely to experience agitation, euphoria, and disinhibition. The duration of agitation, delusion, and hyperkinesia is fairly short. Additionally, the encephalopathy of FHF does not respond to the usual measures used for cirrhotic patients.

In the early stages, encephalopathic changes may be subtle and detectable only with a focused neuropsychometric evaluation. Progression of hepatic encephalopathy is accompanied by more conspicuous findings, progressing to a depressed level of consciousness and finally coma (Table 4). Cerebral edema frequently
complicates the encephalopathy of FHF, occurring in up to 80% of patients. Edema occurs primarily in patients with stage III or IV encephalopathy and is a frequent cause of death. The exact etiology of the edema is not clear. Most likely, there is a combination of cytotoxic edema (glial cell/astrocyte injury) and vasogenic edema (endothelial changes).

Neuronal death is rare. Although its occurrence correlates with the encephalopathy of FHF, a physiologic mechanism has not been demonstrated.

Renal Dysfunction

Renal dysfunction occurs in up to 40% of FHF patients and its causes are multifactorial. Some agents (e.g., acetaminophen) have direct renal toxicity. Dehydration secondary to poor oral intake causes prerenal azotemia; shock due to sepsis or peripheral vasodilation may cause acute tubular necrosis. The kidney itself may remain structurally normal, but decreased intravascular volume, peripheral vasodilation, and decreased perfusion can cause oliguria, aldosterone synthesis, sodium retention, and edema. At an extreme, the hepatorenal syndrome develops; this is associated with a very poor prognosis. Because urea synthesis decreases in FHF, creatinine rather than blood urea nitrogen should be used as the biochemical marker for renal function.

Cardiorespiratory Dysfunction

Cardiorespiratory changes include the presence of a sepsislike hemodynamic state, with a high cardiac output, low peripheral vascular resistance, and poor tissue oxygen extraction. Cardiac arrhythmias are common. ARDS is not uncommon in FHF patients and carries a grim prognosis. Prophylactic antibiotic treatment has not been shown to be clearly effective, but in light of the high rate of infection, it is used by some clinicians. Evaluation for specific interventions includes hepatitis viral panels, acetaminophen levels, levels of other drugs (as appropriate), ceruloplasmin level, and possibly

<p>| Table 4. Clinical Stages of Hepatic Encephalopathy |</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Euphoria or depression, mild intellectual impairment, disordered sleep patterns, mild confusion, slight asterixis or tremor</td>
</tr>
<tr>
<td>II</td>
<td>Drowsiness, slurred speech, inappropriate behavior, incontinence, asterixis, hypactive reflexes</td>
</tr>
<tr>
<td>III</td>
<td>Somnolence, marked confusion, incoherence, paranoia or anger, asterixis (if cooperative), hyperactive reflexes</td>
</tr>
<tr>
<td>IV</td>
<td>Coma, asterixis lacking, dilated pupils</td>
</tr>
</tbody>
</table>


Early Recognition of Hepatic Injury

First, one must suspect the presence of hepatic injury. Early symptoms may be vague and nonfocal, such as fatigue, malaise, and poor appetite. A focused history to elicit any potentially treatable etiologies (e.g., acetaminophen toxicity, amanita toxicity, herpetic viral infection, viral hepatitis) should be obtained. The presence or lack of encephalopathy must also be determined. The presence of encephalopathy may be easily missed at stage I. Clinical findings include slowed speech, difficulty with serial numbers, difficulty concentrating, and personality changes.

Supportive Therapy and Specific Interventions

Next, appropriate testing and supportive measures are instituted. Intravenous hydration is initiated, and oxygen therapy or ventilatory support/airway protection is provided as needed. Basic coagulation, hematologic, hepatic, and renal studies are performed. Blood glucose should be monitored frequently and supplemented as needed.

Patients with FHF are often hypermetabolic and hypoglycemic, requiring large amounts of glucose. Adequate nutrition, including protein, is necessary to maximize hepatic regeneration. Protein supplementation should not be restricted; requirements may exceed 1 to 1.5 g/kg body weight per day to maintain a positive balance.

Prophylactic antibiotic treatment has not been shown to be clearly effective, but in light of the high rate of infection, it is used by some clinicians. Evaluation for specific interventions includes hepatitis viral panels, acetaminophen levels, levels of other drugs (as appropriate), ceruloplasmin level, and possibly

FURTHER MANAGEMENT OF PATIENT 2

Patient 2 is intubated to protect his airway. After questioning his spouse, it is determined that he probably ate toxic mushrooms. CT scan of his head demonstrates cerebral edema. His blood glucose level is 60 mg/dL and intravenous glucose is administered. Mechanical ventilation is adjusted to achieve a Pco2 of 30 mm Hg in an effort to reduce the cerebral edema.

• What are the principles of treatment of FHF?
• What therapeutic options are available if patient 2 continues to deteriorate?
• At what point should liver transplant be considered for patient 2?

TREATMENT

Treatment of FHF involves 3 interdependent areas.
factor V activity. Testing for amanita toxins may also be appropriate.

Direct hepatic ameliorative therapy is available for some causes of FHF. Any suspicion of acetaminophen toxicity, even if current blood levels are low, should lead to N-acetylcysteine (Mucomyst) therapy because this carries the potential for decreasing hepatic injury with minimal adverse effects.3,5 Herpetic viral infections (Herpes simplex virus, Coxsackie virus) may respond to acyclovir.4 Amanita toxicity may be ameliorated by the use of high-dose penicillin, silymarin, charcoal, and forced diuresis3,4 but these must be used early to be most effective.

**Treatment of Encephalopathy**

Encephalopathy is the most dangerous complication of FHF, and the most difficult to treat. It may progress rapidly, yet erratically. Treatment measures that are effective for cirrhotic hepatic encephalopathy are largely ineffective in FHF. Lactulose has minimal benefit and may cause ileus.3,5

The development of stage II4 or III3 encephalopathy should lead to strong consideration for transfer to a liver transplant center. The presence of worsening encephalopathy is a grave prognostic indicator, and the only proven therapy for the encephalopathy of FHF is orthotopic liver transplant.3–5 The encephalopathy clears rapidly after successful transplantation.

Supportive care for encephalopathy includes close monitoring for airway compromise and early endotracheal intubation if protection is needed. Stage III and IV encephalopathy is frequently accompanied by cerebral edema and increased intracranial pressure (ICP). Because the clinical indicators of increasing ICP are unreliable, many authors strongly suggest the use of ICP monitoring, either epidural or subdural.3,5 The goal of ICP monitoring is to maintain a cerebral perfusion pressure higher than 50 mm Hg.3,5

Hyperventilation will help to reduce vasogenic cerebral edema for short periods of time, but prolonged use leads to tachypnea, and may even decrease cerebral blood flow. Avoiding stimuli, including frequent suctioning, will help keep ICP down. Mannitol infusion as needed (0.5–1 g/kg body weight) is the mainstay of therapy for ICP increases and may be given regularly or as needed. Renal replacement therapy is required in patients with oliguria when using mannitol.3,5,7 Steroids are not useful in cerebral edema.

**Orthotopic Liver Transplant**

The final component of therapy uses the information obtained from the patient’s history, testing, and the response to supportive measures, to evaluate for the appropriateness of liver transplant. The ideal candidate is one who has a good chance for survival with a transplant, and a very poor prognosis without one. The prevailing criteria to determine whether a patient has a poor prognosis were introduced in 1989 by O’Grady and colleagues, using their experience at King’s College Hospital in London (Table 5).3,5,10 Unfortunately, there is no validated measure to predict a good prognosis and survival.3

Contraindications for orthotopic liver transplant include ARDS, uncontrollable ICP (cerebral perfusion pressure <40 mm Hg with therapy), sepsis, and necrotizing pancreatitis. These conditions are associated with poor survivability even with transplant.

“Bridging” therapies, designed to prolong survival to allow for eventual transplant, include charcoal hemoperfusion,7 auxiliary liver transplant,3 and therapeutic plasma exchange.8 The usefulness of these therapies is still being evaluated.

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**IV. GASTROINTESTINAL BLEEDING**

**CASE 3 PRESENTATION**

Patient 3 is a 54-year-old male binge drinker who is admitted to the emergency department with massive hematemesis. The patient has had 2 prior episodes of gastrointestinal bleeding, but the exact etiology of the bleeds is not known at this time. On admission to the emergency department the patient has a pulse of 130 bpm with orthostatic changes in both pulse and blood pressure. Laboratory data demonstrate a hemoglobin concentration of 8.0 g/dL, a normal leukocyte count, an elevated bilirubin level, normal electrolyte levels, and a blood urea nitrogen level of 6 mg/dL.

- What are the possible etiologies of patient 3’s bleeding?
- What are the indications for admitting a patient with gastrointestinal bleeding to the ICU?

**INTRODUCTION**

Gastrointestinal bleeding is a common cause of hospitalization and ICU admissions in the United States. Mortality overall ranges from 8% to 14%, with increasing risk with age and other comorbidities. Most commonly, the hemorrhage is from an upper gastrointestinal source (above the ligament of Treitz); lower gastrointestinal bleeding is most common in elderly persons and tends to be less severe. Initial evaluation and therapy of gastrointestinal bleeding is similar, regardless of the source.
Intensive care admission is dependent on the extent of the hemodynamic changes, the risk of further bleeding, and the potential consequences of further bleeding. Definitive therapy often can be accomplished medically or endoscopically, although surgery may be required in up to 10% of cases. Regardless of whether the bleeding is from an upper or lower source, it usually stops spontaneously.

**PATHOPHYSIOLOGY**

**Upper Gastrointestinal Bleeding**

Upper gastrointestinal bleeding can be differentiated into variceal and nonvariceal hemorrhage. Variceal hemorrhage occurs in patients with portal hypertension or obstruction. Usually a complication of cirrhosis, portal hypertension may also develop as a result of extraportal compression or portal or splenic vein thrombosis.

Nonvariceal bleeding is commonly associated with peptic ulcer disease, either gastric or duodenal. Ulcers usually are due to nonsteroidal anti-inflammatory drug (NSAID) use, *Helicobacter pylori* infection, alcohol use, smoking, or physiologic stress (ie, stress-related mucosal damage). Other causes of nonvariceal bleeding include erosive gastritis, Mallory-Weiss tears, angiodysplasia, Boerhaave's syndrome, and arteriovenous malformation. Rarely, one may see hemobilia, an aortoenteric or pancreatic fistula, or a Dieulafoy's lesion (ie, mucosal thinning with an abnormally large superficial vessel).

**Lower Gastrointestinal Bleeding**

Lower gastrointestinal bleeding is defined as bleeding from a source below the ligament of Treitz. It is less common than upper gastrointestinal bleeding, although it may be as severe. The most common source of bleeding is diverticular disease, which may bleed or ulcerate secondary to the use of NSAIDs. Other common etiologies of lower gastrointestinal bleeding are angiodysplastic lesions, neoplasm, and inflammatory infectious colitis. Less frequently, colonic ischemia secondary to atherosclerotic vascular disease or vasculitis may present with bleeding. HIV infection can lead to unique causes of colonic bleeding, including idiopathic ulcers and cytomegalovirus colitis. Thrombocytopenia can cause severe hemorrhoidal hemorrhage.

**EVALUATION**

**Clinical Presentation**

Presentation of the patient with gastrointestinal hemorrhage varies widely, ranging from several days of asymptomatic melena to bright red blood from both orifices and severe hemodynamic compromise.

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**Table 5. King's College Hospital Criteria for Nonsurvival for Patients with Fulminant Hepatic Failure**

<table>
<thead>
<tr>
<th>Patients with acetaminophen toxicity</th>
<th>Arterial blood pH &lt; 7.3 (regardless of stage of encephalopathy) or Prothrombin time &gt; 100 sec (INR &gt; 6.5) and serum creatinine level &gt; 3.4 mg/dL (in patients with stage III or IV encephalopathy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without acetaminophen toxicity</td>
<td>Prothrombin time &gt; 100 sec (INR &gt; 6.5) (regardless of stage of encephalopathy) or Any 3 of the following variables (regardless of the stage of encephalopathy): Age &lt; 10 years or &gt; 40 years Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reaction Duration of jaundice before onset of encephalopathy &gt; 7 days Prothrombin time &gt; 50 sec (INR &gt; 3.5) Serum bilirubin level &gt; 17.5 mg/dL</td>
</tr>
</tbody>
</table>

INR = international normalized ratio.


Demographic factors and past history may help to identify the source of bleeding. Indications of upper gastrointestinal sources include epigastric pain, NSAID use, hematemesis, a history of peptic ulcer disease, a history of pancreatitis or aortic surgery, or a history of liver disease or heavy alcohol use. Patients with lower gastrointestinal sources of bleeding may be older, have a history of diverticulitis/ diverticulosis, and have a more indolent disease course. Unfortunately, the type or color of rectal output—bright red blood or melena—is a poor indicator of the site of bleeding. However, bright red blood per rectum implies a poorer prognosis than does melena.

**Physical Examination**

The physical examination should include a digital rectal examination to evaluate for tumors or other anorectal and perineal pathology, as well as to evaluate for the presence of blood. The examination of the abdomen may give some indication of the etiology of the bleeding, and an abdominal series should be obtained if there is any pain or guarding on examination. The presence of orthostatic changes, frank
hypothesis, or tachycardia, especially in the presence of red hematemesis, indicates the presence of a severe hemorrhage. Nasogastric intubation to evaluate for the presence of blood in a patient without intractable vomiting has no therapeutic value and limited diagnostic and prognostic value, and is not mandatory.12

Indications for Admission to ICU

Management of the patient with gastrointestinal bleeding is guided by the severity of the bleeding and any underlying pathology. Indications for admission to the ICU include the need for emergent endoscopy, endotracheal intubation (to protect the airway of patients with emesis or with cardiovascular collapse), the presence of both hematemesis and hematochezia, inability to stabilize rapidly with crystalloid, and a high risk for recurrent or persistent bleeding.

FURTHER EVALUATION OF PATIENT 3

Patient 3 is admitted to the ICU and a gastrointestinal consultation is immediately requested and obtained. The patient undergoes upper endoscopy, and several actively bleeding varices are identified. Additional laboratory testing reveals a platelet count of 25,000/mm³ and an international normalized ratio (INR) of 2.2.

- What therapeutic interventions are appropriate to correct the bleeding and the hematologic abnormalities?

TREATMENT

Initial Management

Aggressive fluid resuscitation through a minimum of 2 large-bore intravenous catheters to restore hemodynamic stability is paramount. Care must be taken to avoid over-resuscitation with fluids to minimize the risk of increasing splanchnic pressure. Coagulopathy should be evaluated for and corrected, with a goal of restoring the INR to a maximum of 1.2 and the platelet count to a minimum of 50,000/mm³.13 Packed erythrocytes should be administered, with a goal of restoring the hemoglobin concentration to 8 to 10 g/dL. Nasogastric, and possibly endotracheal, intubation is necessary in patients with persistent or massive hematemesis or altered mental status. Histamine blockers are not indicated in the initial therapy of a gastrointestinal bleed.13

A central venous line should be placed and the central venous pressure monitored, with a goal of maintaining central venous pressure lower than 10 cm H₂O. The initiation of octreotide or somatostatin has become a standard of care for gastrointestinal bleeding, although definite benefit has not been clearly shown in the acute phase. However, the subsequent sclerosis of varices is thought to be easier, and the risk of rebleeding lessened.14

Patients with suspected variceal bleeding require urgent or emergent endoscopy to definitively delineate the source of hemorrhage. If the source is varices of the esophagus or lesser curvature of the stomach, definitive therapy with either sclerotherapy or banding can be initiated immediately. Bleeding varices elsewhere in the stomach require portal venous decompression, either with portosystemic shunt or transjugular intrahepatic portosystemic shunt (TIPS).15

Endoscopic Evaluation and Therapy

Once the patient has stabilized hemodynamically, assessment of the need for endoscopy and endoscopic therapy can proceed. Endoscopy serves 2 purposes: to identify the source of bleeding and provide risk assessment for further bleeding, and to provide definitive therapy if possible, obviating the need for surgical intervention. The benefit of upper endoscopy both emergently and electively in upper gastrointestinal bleeding has been clearly demonstrated.12,13,16 The role of endoscopy in lower gastrointestinal bleeding, especially emergently, is less clear.12,17

Regardless of the character of rectal bleeding, evaluation of the upper gastrointestinal tract via esophagogastroduodenoscopy (EGD) should be performed. Indications for early or emergent EGD include evidence of active bleeding (eg, inability to stabilize a patient hemodynamically, persistent bright red emesis, bright red blood per rectum with hypotension), transfusion requirements of greater than 4 units in 6 hours, or suspicion of or known varices. If evaluation of the upper gastrointestinal tract is not diagnostic and indications of persistent bleeding continue, emergent colonoscopy may be considered. Oral purging prior to colonoscopy has been demonstrated to be safe, and increases the yield of diagnostic colonoscopy.11

Findings on EGD indicate the chance of recurrent bleeding. The finding of a “clean” ulcer (ie, without a visible vessel or clot) indicates a less than 5% chance of rebleeding. The presence of active bleeding, an adherent clot, or visible vessel are all consistent with an increased risk of rebleeding.

Endoscopic therapy, with a bipolar electrode, heater probe, laser, or injection of sclerosing agent, can significantly reduce the risk of further bleeding. Endoscopic therapy is able to control hemorrhage in 90% of cases with active bleeding, including those with variceal bleeding.

When the bleeding has been determined to be from a lower gastrointestinal source (ie, EGD is negative), the exact etiology and location may be difficult to ascertain.
Early colonoscopy after oral purging is more likely than EGD to identify a source, although the propensity of the lesions to stop bleeding spontaneously lowers the yield, and pathology that may hemorrhage may not be the source of the current bleeding. Signs indicating that a lesion is the source of the blood include active bleeding, a visible vessel on an appropriate lesion, an adherent clot, a diverticular ulcer with localized fresh blood, and the presence of fresh colonic blood in the absence of ileal blood. If a source of bleeding or possible recurrent bleeding can be localized, methods of coagulation similar to those used with EGD can be used with good results.\textsuperscript{11}

In the event of persistent lower gastrointestinal bleeding that cannot be localized with colonoscopy, technetium Tc 99m–labeled erythrocyte scan and/or arteriography may be used. A technetium-labeled erythrocyte scan can detect bleeding as low as 0.1 to 0.5 mL/min. However, the accuracy in determining the area of bleeding is poor, especially when long delays are used to demonstrate bleeding. Angiography is less sensitive for hemorrhage, but has greater accuracy in localizing the source of bleeding. No studies have been performed comparing technetium-labeled erythrocyte scanning or angiography with colonoscopy.

**TREATMENT FOR PERSISTENT BLEEDING**

Although unusual, gastrointestinal hemorrhage may persist in spite of maximal resuscitation, endoscopic therapy, and its own propensity to stop spontaneously. Or, it may recur in the face of treatment or prophylaxis. In these cases, more definitive invasive procedures are warranted.

**Variceal Bleeding**

There are several options for persistent or recurrent variceal bleeding. Emergent therapy consists of the placement of a gastroesophageal balloon (eg, via a Sengstaken-Blakemore or Minnesota tube). Placement of the tube nearly always requires concomitant endotracheal intubation. Initially the gastric balloon is inflated. If the bleeding persists, than the esophageal balloon is also inflated. The balloons are deflated after 48 hours. Rebleeding is common, and a definitive operation for portal decompression should be undertaken as soon as possible.

Transvenous decompression of the portal system using the TIPS procedure may be performed emergently.\textsuperscript{15} Surgical therapy is also an option, usually involving the placement of a stent from the portal vein to the inferior vena cava. Mortality from the surgical procedure is high, and hepatic function worsens rapidly secondary to decreased liver perfusion. Orthotopic liver transplant is the definitive therapy for varices associated with cirrhosis.

**Bleeding Ulcers**

Emergent surgery for ulcers consists of oversewing the ulcer and pylorotomy and vagotomy. Surgery for non-bleeding but recurrent ulcers unresponsive to therapy may include selective vagotomy and partial gastrectomy.

**Lower Gastrointestinal Bleeding**

Definitive surgery for persistent or recurrent lower gastrointestinal bleeding can be problematic because of difficulty in localizing the source of bleeding. Endoscopic localization in the lower gastrointestinal tract is, at best, 75% sensitive. A tagged erythrocyte scan is not accurate enough alone to guide surgical management, although it can help to guide angiography.\textsuperscript{12} Fortunately, surgical management is not often required to control lower gastrointestinal bleeding.

**FOLLOW-UP TREATMENT AND OUTCOME OF PATIENT 3**

Patient 3 undergoes a TIPS procedure; however, during the procedure he becomes severely hypotensive. His mental status declines significantly, and he dies 24 hours later.
REFERENCES