Upper Gastrointestinal Bleeding, Lower Gastrointestinal Bleeding, and Hepatic Failure

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Objectives:

- To use clinical clues to differentiate between upper and lower gastrointestinal (GI) hemorrhage
- To examine results of vital signs, blood tests, and nasogastric aspirate to assess severity of GI hemorrhage and define immediate resuscitative measures
- To define the common causes of GI hemorrhage in the intensive care unit (ICU)
- To develop a diagnostic strategy and plan of management
- To discuss the advantages and disadvantages of therapeutic options for treatment of GI hemorrhage
- To distinguish between acute hepatitis, acute liver failure, fulminant hepatitic failure, and an acute flare of chronic liver disease
- To assess the clinical features that define poor outcome and need for emergent transplantation
- To define the main causes of acute liver failure in patients presenting to the ICU
- To initiate an appropriate plan for diagnosis and management
- To understand the indications, complications, and utility of intracranial pressure monitoring
- To describe advantages, disadvantages, and outcome of a wide array of treatments, including hepatocyte transplantation, bioartificial liver support, and transplantation (conventional and living donor liver transplantation using the right lobe)

Key words: gastrointestinal hemorrhage, resuscitation, nonsteroidal anti-inflammatory drugs (NSAIDs), hematochezia, melena, hematemesis, varices, diverticulosis coli, peptic ulcer disease, endoscopy, angiography, acute hepatitis, hepatic failure, encephalopathy, cerebral edema, hepatocyte transplantation, liver transplantation, living donor liver transplantation, bioartificial liver, *N*-acetyl cysteine, acetaminophen

Upper Gastrointestinal Hemorrhage

Upper gastrointestinal (UGI) hemorrhage accounts for 0.1% of all admissions to the hospital, occurs twice as frequently in men, is more common in the elderly, and remains a significant cause of ICU morbidity and mortality. For unknown reasons, UGI bleeding from peptic ulcer disease is more common in winter months. Current mortality from transfusion-requiring hemorrhage ranges from 5% to 15%. Mortality increases with age, hemodynamic instability, volume of transfusion requirement ($\geq$ 6 U pRBCs), evidence of organ dysfunction, underlying cardiopulmonary disease, and underlying liver disease. Risk of death increases 3-fold if the patient is already hospitalized at the time of the initial bleed. Three principles underline management: volume and blood product resuscitation, emergent endoscopy for diagnosis, and prompt definition and institution of therapy targeted to the underlying etiology. Surgical consultation should be obtained in the early stages of resuscitation and evaluation.

Case Presentation 1

A 42-yr-old woman experienced sudden hematemesis at work while performing her usual secretarial duties. She was noted by co-workers to be pale, diaphoretic, and faint. Emergency medical technicians started peripheral intravenous lines and administered saline. On arrival at the emergency room, she was alert and oriented, pale, with BP 95/55, P 120, RR 22, T 37°C. She passed a melenic stool and examination revealed only a few scattered spider telangiectasia with mild hepatosplenomegaly. Two units of pRBCs were infused, a nasogastric tube was placed revealing dark blood with clots in the stomach, and she was admitted to the medical ICU. She described recent use of ibuprofen for headaches but denied alcohol or any knowledge of underlying liver disease. Past medical history was unremarkable except for receipt of blood transfusion at age 23 for post-partum hemorrhage.

Resuscitation

Initial assessment of severity of bleeding requires critical evaluation of vital signs. Hematocrit is not a reliable indicator of the degree of hemorrhage because it does not decrease immediately with acute bleeding. The decrease in hematocrit that occurs with bleeding is due to re-equilibration of body fluid and may take 24 to 72 h to manifest.

The patient who has sustained an UGI hemorrhage typically exhibits features of hypovolemia or hypovolemic shock. Immediate measures are focused at restoring intravascular volume and maintaining tissue oxygenation. Two large-bore indwelling intravenous catheters should be placed early in the resuscitation effort and blood pressure immediately corrected with bolus infusion of normal saline. The ideal hematocrit guiding transfusion of blood or packed-RBCs is somewhat controversial, although most recommend a target hematocrit of 25% to 30% (this latter hematocrit is recommended for elderly patients, age > 60 yrs, or in those with underlying ischemic cardiovascular disease). Oxygen delivery to tissues is insured by volume replacement to restore blood pressure, maintenance of RBC volume to restore oxygen-carrying capacity, and administration of nasal oxygen to saturate the carrying capacity of blood. Coagulopathic patients may require platelets, fresh frozen plasma, or cryoprecipitate (to replace fibrinogen). Calcium infusion may be required in those receiving massive units of citrate-treated stored blood since citrate may chelate calcium and lower its plasma concentration.

During resuscitative efforts the patient should be evaluated for underlying organ dysfunction due to the hemorrhage and examined for the presence of chronic liver disease. Lactic acidosis, renal failure, myocardial ischemia and infarction, bowel ischemia, cerebral ischemia, and limb ischemia may all complicate hemorrhagic shock. UGI hemorrhage in the setting of chronic liver disease is related to portal hypertension in approximately 50% of cases (varices or portal hypertensive gastropathy). Management is influenced significantly by the presence of underlying chronic liver disease and its etiology.

Etiology

The causes of UGI bleeding are given in Table 1. Endoscopy or radiologic imaging is required to establish the cause of bleeding. The most common etiology is duodenal ulcer disease, representing 30% to 35% of all cases of UGI bleeding. Bleeding from gastric ulcer is the next most common diagnosis, followed by Mallory-Weiss lesions, portal hypertensive gastropathy, and varices. However, a wide array of conditions may present with UGI hemorrhage (Table 1).

NSAIDs and Risk of Bleeding

The risk of bleeding with use of nonselective NSAIDs is approximately 0.5% after 6 months of ongoing treatment. Risk increases with age, history of ulcer disease, history of cardiovascular disease, and is related to dose of NSAID. Risk is reduced, but not eliminated, by use of the more selective COX-2 inhibitors (celecoxib, rofecoxib). Co-administration of nonselective NSAIDs to patients taking steroids or anticoagulation therapy (heparin or warfarin) increases the relative risk of bleeding up to 12-fold. *Helicobacter pylori*, although proven to increase the risk for ulcer disease, is not an independent risk factor for UGI bleeding.

Diagnosis

Initial findings at physical examination may be useful in providing clues as to the location of the bleeding lesion in the gastrointestinal tract.

Table 1. *Causes of Upper Gastrointestinal Hemorrhage*

Esophageal	**As % of All UGI Bleeds**
Varices	10%
Erosive Esophagitis	2%
Mallory-Weiss lesion	5% to 15%
Medication-induced ulceration	≤ 1%
Caustic ingestion	≤ 1%
Infectious Esophagitis	≤ 1%
Herpes	
CMV	
HIV	
Candida	
Carcinoma	≤ 1%
Gastric	
Peptic Lesions	15% to 20%
Gastric ulcer	
Gastritis	
NSAID ulcers	
Dieulafoy's lesion	≤ 1%
Varices	1% to 3%
Portal Hypertensive Gastropathy	10% to 15%
Vascular malformations	≤ 1%
Neoplastic Lesions	≤ 1%
Carcinoma	
Lymphoma	
Leiomyoma	
Duodenum	
Peptic ulcer	30% to 35%
Vascular malformation	≤ 1%
Aorto-enteric fistula	≤ 1%
Hemobilia	≤ 1%
Hemosuccus pancreatitis	≤ 1%

Evaluation of vital signs, abdominal examination, and appearance of the bowel movement may localize the bleeding site. A patient passing bright red blood per rectum with stable vital signs and a benign abdomen is most likely bleeding from a lower, left-sided colonic lesion. A hemodynamically stable patient passing purplish clots and darker blood may be bleeding from the right colon or small bowel. Mild to moderate UGI bleeding is characterized by loose, black bowel movements (melena). Development of melena requires a minimum bleed of ≥ 100 mL and prolonged residence in the gut (≥ 12 h). Massive bleeding from varices or an artery in an ulcer base, is often characteized by hemodynamic instability or shock, and hematemesis. With brisk bleeding from an UGI source (≥ 1000 mL), one may observe passage of red blood per rectum; almost always mixed with darker blood or clots and characterized by hypotension. Approximately 5% to 15% of cases, initially thought to be bleeding from a lower GI source, are actually bleeding from an UGI source.

Nasogastric (NG) tubes can be helpful diagnostically in some cases, but hemoccult testing of aspirates is not useful and not recommended. If the aspirate lacks blood and contains bile, an UGI source for ongoing active bleeding is less likely. However, 16% of UGI bleeds from duodenal ulcer disease are associated with a clear NG aspirate. The major role for NG tubes is to allow lavage and clearance of blood from the stomach for the purpose of performing endoscopy or other diagnostic studies. Other clues to an UGI source are elevation of BUN, hyperactive bowel sounds, and physical findings (spider telangiectasia, jaundice, hepatosplenomegaly, acanthosis nigricans, pigmented lip lesions, palpable purpura). Some gastroenterologists use the NG tube also to assess the patient for activity of ongoing bleeding and to determine prognosis. A patient admitted for melena, who has a clear NG aspirate, has a predicted mortality of ≤ 5%. In contrast, a patient admitted with hematochezia, who has a red NG aspirate, has a predicted mortality of ~ 30%.

Emergent endoscopy, after resuscitation of the patient and clearance of blood and clots from the stomach, is indicated for nearly all acute UGI bleeders. Not only is endoscopy diagnostic in over 90% of cases, it can also be used to provide definitive therapy (variceal ligation or sclerotherapy, electocautery, alcohol or sclerosant injection, biopsy for *H. pylori* in some cases may lead to antibiotic treatment). In addition, endoscopy is useful in identifying patients at high risk of rebleeding who may benefit from early surgical intervention (visible vessel failing endoscopic management, giant ulcer, diffuse hemorrhagic gastritis, miscellaneous lesions) (Table 2).

Case 1 (continued)

Our patient underwent endoscopy which revealed esophageal varices with stigmata of recent hemorrhage (cherry red spot over varix) and minimal erosive gastritis. She was treated with endoscopic ligation of varices, had no further bleeding, and was discharged from the hospital 72 hours after admission. Subsequent evaluation revealed cirrhosis due to chronic hepatitis C. Varices were eradicated by repeated ligation treatments and she underwent evaluation for liver transplantation.

Imaging studies may also be useful in localizing a bleeding source. If endoscopic studies are nondiagnostic and bleeding persists, a nuclear medicine Tc99m-RBC scan may indicate the site of bleeding. This scan is more sensitive than angiography and when sequential scans are performed the bleeding site may be localized in 60% to 80% of cases. Although the scan can localize bleeding to a site in the bowel, etiology is rarely, if ever, defined from this study. Angiography is used in patients with higher bleeding rates and may be therapeutic if embolization of the bleeding site is performed. Angiography can be diagnostic for vascular lesions of the bowel. Meckel's scan (Technetium pertechnetate) is usually performed only after all

Table 2. *Prediction of Outcome after Upper Gastrointestinal Bleed from Peptic Lesions*

Increased Risk of Mortality is Associated With
• Age > 60 years
• Hemodynamic instability with initial bleed
• Onset of bleeding during hospitalization for unrelated co-morbid condition
• History of cancer
• Underlying co-morbid conditions
• Endoscopic finding of giant ulcer
• Endoscopic finding of visible vessel in base of ulcer
Endoscopic Features Predictive of Rebleeding
• Spurting artery (actively bleeding)
• Nonbleeding but elevated visible vessel
• Adherent clot
• Flat cherry red or black spot with oozing

other studies have failed to provide a diagnosis. Barium studies are not recommended in the initial evaluation of UGI bleeding.

Specific Therapeutic Approaches

Peptic Lesions

Bleeding from peptic lesions of the UGI tract is treated by:

1. Gastric acid suppression (proton pump inhibitors [PPIs] are favored over H2-blockers, but are not effective in the setting of active bleeding)
2. Octreotide, 50 μg bolus followed by 50 μg/h infusion. Use of octreotide for this indication is controversial, but some studies suggest that rebleeding rate is reduced by 30% to 50%.
3. Correction of coagulopathy
4. Therapeutic endoscopy (electocautery, injection of sclerosant) Effectiveness of endoscopic therapy is limited by arterial size. Arterial bleeders with diameter $\geq$ 2 mm usually do not respond and require surgery. Rebleeding after initial control with endoscopic treatment is best managed by repeat endoscopic therapy or radiologic intervention. Surgery is only necessary in ~10% of rebleeds.
5. Surgery, for those who fail endoscopic management
6. After resolution of the acute bleed, all patients with duodenal ulcer should be treated with triple therapy against *H. pylori*. Other peptic lesions may also require this therapy if the patient is *H. pylori*-positive.

Table 3. *Child-Pugh Criteria*

	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged)	1-3	4-6	>6
Ascites	None	slight	moderate
Encephalopathy	None	1-2	3-4

Grades: A = 4-6 points; B = 7-9 points; C = 10-15 points
Pugh's modification of the Child-Turcotte prognostic classification (Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the esophagus for bleeding of esophageal varices. Br J Surg 1973; 60:646)

Varices

Risk of bleeding from esophageal varices is directly related to portal pressure ($\geq$ 12 mm Hg), variceal size and appearance on endoscopy, advanced Child-Pugh score (Table 3), and coincident gastric varices. Mortality from UGI hemorrhage from varices ranges from 30% to 50%. The treatment of bleeding from esophageal varices is aimed at control of portal hypertension using pharmacological agents and direct application of endoscopic treatment to the bleeding variceal channels. A number of pharmacologic agents can lower portal hypertension: beta-blockers, nitroglycerin, vasopressin, and somatostatin. We currently favor use of octreotide or vapreotide since they are effective, well-tolerated, and have few side effects. A loading dose of 50 μg is administered initially, and followed by continuous infusion at 50 μg/h. The majority of patients bleeding from esophageal varices can be controlled by endoscopic ligation, especially if done with co-administration of long-acting somatostatin analogue. Endoscopic

Table 4. *Indications for and Contraindications to Transjugular Intrahepatic Portal-Systemic Shunt (TIPS)*

Indications	Contraindications
Accepted:	Absolute:
Gastroesophageal variceal hemorrhage	Heart failure with elevated CVP
refractory acute variceal bleeding	Polycystic liver disease
refractory recurrent variceal bleeding	Severe hepatic failure
bleeding from intestinal varices	
Cirrhotic Hydrothorax	Relative:
	Active intrahepatic or systemic infection
Promising:	Portal vein occlusion
Refractory Ascites	Hypervascular hepatic neoplasms
Hepatorenal Syndrome	Poorly controlled hepatic encephalopathy
Budd-Chiari Syndrome	Stenosis of celiac trunk

ligation treatment ("banding") is associated with fewer complications than endoscopic sclerotherapy and is currently the preferred modality. Patients bleeding from gastic varices or who rebleed from esophageal varices despite endoscopic treatment may require placement of a Sengstaken-Blakemore tube and performance of either transjugular intrahepatic portal-systemic shunt (TIPS) or surgical shunt (Table 4). TIPS placement is successful in 90% to 95% of cases, but TIPS may thrombose or stenose and require repeated radiological interventions. In addition, TIPS is costly and 15% of 30% of patients undergoing TIPS suffer from post-TIPS encephalopathy. Mortality rates from bleeding varices are directly related to Childs-Pugh score, ongoing alcohol use, and comorbid illness. Mortality is over 50% in Childs class C cirrhotics (Table 5).

Lower Gastrointestinal Hemorrhage

The principles of management for lower GI (LGI) bleeding are similar to those mentioned above for UGI bleeding: resuscitation, diagnosis, and planning for specific therapy. One initial consideration in evaluating the LGI bleeder is to exclude an UGI source. A negative NG lavage may obviate the need for upper endoscopy, but nearly 5% to 15% of patients thought to have LGI bleeding are actually diagnosed with an UGI source, and about 5% are from the small bowel. The average age of LGI bleeders is 65 yr. Causes of LGI bleeding include: hemorrhoids, angiodysplasia, diverticular disease, neoplastic lesions, inflammatory bowel disease, and other vascular lesions or tumors of the LGI tract (Table 6).

Diagnosis

Colonoscopy: The primary diagnostic test in LGI bleeding is colonoscopy after purgation of the bowel by use of Colyte. Studies comparing colonoscopy to air-contrast barium enema (ACBE) indicate that colonoscopy is far superior, identifying the source in ~ 70% of cases compared to only ~30% for ACBE. Another advantage of colonoscopy is the ability to provide treatment (cautery, polypectomy, sclerotherapy). However, there is a 2% risk of perforation with endoscopic treatments when administered in the setting of acute bleeding. Sigmoidoscopy should be reserved for the evaluation of minor LGI bleeding in relatively young patients (≤ 40 yr).

Angiography: Angiography can be diagnostic in up to 75% of cases if the rate of bleeding is ≥ 0.5 mL/min. This diagnostic and therapeutic modality is usually restricted to cases where endoscopy is not possible due to large amounts of blood in the gut lumen or when certain treatments are planned (vasopressin infusion, embolization). Angiography is particularly useful in the diagnosis and management of isolated vascular malformation.

Other Techniques: Technetium-labeled RBC scans are often ordered because of the ease of performance of the test and the perception that valuable information is gained. However, these scans rarely provide definitive information regarding cause or localization of bleeding and cannot provide therapy. The usefulness of RBC scans is quite limited.

Etiology

Diverticular Disease: Diverticuli are the cause of LGI bleeding in 30% of all cases and 50% of those with active hemorrhage undergoing angiography. However, diverticuli are very common and prevalence increases with advancing age. Overall, only 3% of patients with diverticulosis coli ever experience LGI bleeding. When bleeding occurs, it is usually sudden, painless, and often from the right colon (in up to 70% of cases). Acute bleeding stops spontaneously in 80% of cases, but 20% to 25% rebleed. Localization of the site of bleeding is

Table 5. *Risk of Death from Variceal Hemorrhage According to Severity of Liver Disease*

Child-Pugh Class A	≤ 5%
Child-Pugh Class B	≤ 25%
Child-Pugh Class C	> 50%

Table 6. *Causes of Significant Acute Lower Gastrointestinal (LGI) Bleeding*

Diverticulosis	30%
Post-polypectomy	7%
Ischemic colitis	6%
Colonic ulcerations	6%
Neoplasm (cancer and polyps)	5%
Angiodysplasia	4%
Radiation proctitis	2%
Inflammatory bowel disease	2%
Miscellaneous lesions	12%
Undiagnosed LGI bleeding	26%

essential to plan appropriately for treatment, which may include segmental colonic resection or even subtotal colectomy.

The list of other relatively common causes of LGI bleeding is given in Table 6. Additional rare causes of LGI bleeding include infectious colitis, NSAID ulcers, rectal varices, vasculitis, and juvenile polyps. As with other causes of GI bleeding, treatment is directed at the underlying etiology.

Acute Hepatic Failure

Definitions

Acute Hepatitis: The standard definition of acute hepatitis is the development of acute liver parenchymal injury from exposure to hepatotoxins or infectious agents, such as viral hepatitis, toxins, or medications. Typical patients with self-limited disease exhibit variable elevations in transaminases (AST and ALT 100 to 1000 IU/L), limited elevations in bilirubin (< 5 mg/dL), have normal serum albumin, and no coagulopathy (prothrombin time or INR is normal). Most patients with acute hepatitis recover uneventfully, but approximately 1% will experience severe injury with evidence of liver failure. Patients with chronic liver disease, such as chronic hepatitis C, who experience intercurrent acute hepatitis, such as acute hepatitis A, may experience hepatic decompensation and signs of liver failure.

Acute Liver Failure: Acute liver failure is defined by the development of coagulopathy (prothrombin time > 2 sec prolonged, INR > 1.5) in a patient with acute hepatitis who lacks underlying chronic liver disease. Patients with acute liver failure usually have greater elevations of AST and ALT levels with the initial injury (1000 to 5000 IU/L), often are jaundiced, and exhibit more constitutional symptoms. These patients are at risk for fulminant hepatic failure (FHF), although most recover uneventfully.

Fulminant Hepatic Failure: The classification of fulminant liver failure requires evidence of hepatic encephalopathy within 8 weeks of the onset of jaundice related to acute liver injury. One criterion for this diagnosis is the absence of underlying chronic liver disease, the only exception being Wilson's disease. There are approximately 2000 cases of FHF in the US each year.

Case Presentation 2

A 38-yr-old businessman presented with a 3-day history of progressive malaise, myalgia, and anorexia. In the last 24 hours he has noted dark urine and jaundice. His wife reports that the patient has been mildly confused. He and his family deny a past history of underlying medical illness, intravenous drug use, or other exposure to blood or blood products. He described his usual alcohol intake as 2 to 4 mixed drinks each day. In the week prior to the onset of his illness he drank from 5 to 8 mixed drinks each day and frequently skipped meals. In addition, he described taking 8 to10 50-mg tablets of acetaminophen per day for the last 10 days for headaches. Physical examination revealed jaundice, mild hepatomegaly with tenderness to palpation, with no other features of cirrhosis. He was an icteric man who was unaware of the date and had mild asterixis. Laboratory values were as follows: ALT 6250 IU/L, AST 9,765 IU/L, total bilirubin 6.5 mg/dL, albumin 3.8 g/dL, prothrombin time 21.5 sec (INR 2.3), creatinine 2.2 mg/dL, and arterial pH 7.25.

Etiology

The main causes of acute hepatitis are viral hepatitis, drug-induced liver injury, and alcoholic hepatitis. Fulminant liver failure, defined by severe hepatocellular injury, coagulopathy and hepatic encephalopathy, is most often due, in order, to acetaminophen, drug toxicity, hepatitis B, and hepatitis A. However, the second leading diagnostic category for FHF is cryptogenic, cause unknown (Table 7). Recent data, since 1998, indicate that over 50% of

Table 7. *Causes of Acute Liver Failure*

Acetaminophen	20%
Cryptogenic	15%
Non-acetaminophen drug toxicity	12%
Hepatitis B	10%
Hepatitis A	7%
Autoimmune hepatitis	6%
Wilson's disease	6%
Miscellaneous*	24%

* Budd-Chiari syndrome, herpes simplex, paramyxovirus, Epstein-Barr virus, amanita poisoning, ischemia, malignant infiltration

Adapted from Schiodt FV, Atillasoy E, Shakil O, et al. Etiologic factors and outcome for 295 patients with acute liver failure in the United States. Liver Transplant Surg 1999; 5:29-34

cases of FHF in the US are due to acetaminophen (38%) or other idiosyncratic drug reactions (~14%). Sporadic cases of FHF due to both cocaine and Ecstacy have recently been described. FHF from mushroom poisoning occasionally occurs among inexperienced amateur mushroom fanciers. Infiltration of the liver with rapid progression of tumor growth can lead to FHF and has been described for breast carcinoma, lymphoma, and melanoma. Biopsy of the liver is required to establish the latter diagnoses. FHF may also occur in the third trimester of pregnancy related to acute fatty liver of pregnancy, HELLP syndrome, or disseminated Herpes infection.

Acetaminophen-induced acute liver failure occurs in the setting of intentional overdose (majority of cases), but a substantial portion occur as a "therapeutic misadventure." In these cases injury occurs despite taking doses of acetaminophen within the recommended therapeutic range, as little as 4 gm/day for several days, in the setting of moderate alcohol intake and fasting. Enhanced toxicity is due to induction of metabolizing enzymes by alcohol which increase formation of the toxic intermediate of acetaminophen and lead to depletion of hepatic glutathione. Liver injury in this circumstance is associated with towering AST levels, often > 5,000 IU/dL, and mortality may exceed 20%. This high mortality rate contrasts with mortality of <1% after acetaminophen overdose among non-alcoholics. Recognition of the association of alcohol use with higher risk of FHF and death after acetaminophen use has led to labeling changes of over-the-counter acetaminophen preparations (Table 8).

Table 8. *Labeling of Acetaminophen*

Alcohol Warning:
- If you drink 3 or more alcoholic beverages every day, ask your doctor if you should take TYLENOL® or other pain relievers. Chronic heavy alcohol users may be at increased risk of liver damage when taking more than the recommended dose (overdose) of TYLENOL.®

Directions:
- Adults and children 12 years of age and older: Take 2 geltabs (500mg/geltab) every 4 to 6 hours as needed. Do not take more than 8 geltabs in 24 hours, or as directed by a doctor.
- Do not use:
  - with any other product containing acetaminophen
  - for more than 10 days for pain unless directed by a doctor
  - for more than 3 days for fever unless directed by a doctor

Prognosis

A major determinant of prognosis is the level of encephalopathy (Table 9). Patients with FHF who have progressed to higher stages of encephalopathy (Stage III or IV) have the worst prognosis. Additional clinical features that indicate a poor prognosis include: metabolic acidosis, renal failure, severe jaundice, or markedly prolonged prothrombin time. The likelihood of survival varies with the cause of acute liver injury. Patients with acetaminophen overdose have a relatively favorable outcome, over 50% survive. Patients with fulminant hepatitis-A virus and hepatitis-B virus infection have an intermediate prognosis in the range of 30% to 50%. In contrast, patients with a fulminant presentation of Wilson's disease or severe sporadic non-A, non-B, non-C hepatitis have a survival rate of less than 10%.

Clinical Management

Once recognized, patients with fulminant liver failure should be transferred to a center with expertise in managing FHF and which can offer liver transplantation.

Table 9. *Grades of Encephalopathy in Patients with Fulminant Hepatic Failure*

Grade 0:	No alteration of mental status
Grade I:	Awake and responsive
	Mild confusion and disorientation
	Altered personality
	Asterixis may or may not be present
Grade II:	Awake, but agitated
	Increasingly confused and disoriented
	Hallucinations
Grade III:	Increasing suppression of mental status
	Stuporous but arousable to vocal or tactile stimuli
	May require endotracheal tube for airway protection
Grade IV:	Unresponsive to vocal or tactile stimulation
	Essentially comatose but with intact pupillary reflexes
	Usually still withdraw to painful stimuli

Irreversible Brain Injury (Guidelines only):
1. Cerebral edema on brain imaging (CT or MRI) with ischemic necrosis, hemorrhage, and compromised perfusion
2. Sustained elevation of intracranial pressure by intracranial pressure (ICP) monitoring with cerebral perfusion pressure (mean arterial pressure [MAP] – ICP) of < 40 mm Hg for more than 4 hours
3. Lack of brainstem function on neurologic examination (absent pupillary response, corneal reflex, gag reflex, and lack of any physiologic response or withdrawal to painful stimuli)

Case 2 (continued)

The patient described above had acute liver failure with encephalopathy and was transferred to a liver transplantation center. After transfer, the patient's neurological status, coagulation profile, and liver chemistries were carefully monitored. He underwent evaluation for liver transplantation, including living donation, but concern was raised about his chronic excessive alcohol use. Over the next 48 hours, his mental status deteriorated, and his INR increased, despite a precipitous decline in aminotransferases. He was listed at status 1 and received a cadaveric liver transplant and his clinical state, including neurologic condition, completely resolved.

General Measures: Indications for hospitalization include nausea and vomiting severe enough to result in dehydration, or severe impairment of liver function resulting in en≠cepha≠lopathy, ascites, GI bleed, or rising prothrombin time. All admitted patients should be placed on needle (HB, NANB) and stool (HA) precautions but not in isolation. Gloves should be worn when handling biological specimens and specimens should be clearly labeled (Hepatitis patient). All used instru≠ments should be auto≠claved or appropriately disposed. No effective antiviral therapy exists for acute viral hepatitis or FHF; cor≠ticosteroids are contraindicated as they may increase the risk of developing chronic hepatitis. Removal of the offending drug, toxin, or alcohol is the mainstay of therapy of drug-induced and alcoholic hepatitis, respectively. *N*-acetyl cysteine is an effective primary intervention for hepatic injury related to acetaminophen and is currently under investigation in the treatment of FHF due to other etiologies (Table 10).

Upper Gastrointestinal Bleed: By definition, patients with FHF have acute liver disease and, therefore, lack manifestations of cirrhosis, such as esophageal varices. Upper GI bleeding in the setting of FHF is typically not due to varices or portal hypertension. Upper GI bleeding in this setting is usually mild, controlled by correction of coagulopathy, and is usually due to either erosive gastritis or peptic ulcer disease. Emergent endoscopy is indicated to identify the bleeding lesion, plan management, and possibly to apply therapy. The key management issue is prevention of UGI bleeding by acid suppression with either H2-blockers (intravenously or orally) or PPIs (orally) or by use of sucralfate via the NG tube in patients who cannot take oral medications and in whom an adverse effect of H2 blockers (thrombocytopenia) is to be avoided. Doses of the first two agents are adjusted to achieve maximum acid suppression and optimum prophylaxis by monitoring gastric pH (target is pH $\geq$ 5) via an NG tube. Sucralfate is dosed at 1 g q6h, irrespective of gastric pH.

Encephalopathy: Encephalopathy is a hallmark of FHF and is also observed in patients with underlying chronic liver disease who sustain a superimposed acute liver injury. The mechanisms of encephalopathy differ but share some common features. Encephalopathy in the setting of chronic liver disease is linked to ammonia production (and several other factors) and responds to measures that effectively reduce blood ammonia levels: protein restriction, lactulose, and nonabsorbable oral antibiotics, such as neomycin.

In contrast, the encephalopathy of acute hepatic failure is usually related to cerebral edema. The exact mechanisms causing cerebral edema are unknown, however experiments with animal models suggest a role for brain ammonia, production of glutamine, retention of glutamine in astrocytes, and astrocyte swelling. Progressively worsening encephalopathy in patients with acute liver failure

Table 10. *Use of N-Acetyl Cysteine in Treatment of Acetaminophen Overdose*

Oral Dosing Schedule

1. Avoid use of activated charcoal since it will bind *N*-acetyl cysteine, reducing its efficacy
2. Place nasogastric (NG) tube for administration of *N*-acetyl cysteine. *N*-acetyl cysteine is highly unpalatable; most patients cannot tolerate its oral administration. The NG tube is necessary to insure dosing of the medication.
3. Dosage: 140 mg/kg initially, followed by 70 mg/kg q 4 h, to a total of 17 doses of *N*-acetyl cysteine.
4. Toxicity: nausea, vomiting

Intravenous Dosing Schedule (Limited Availability in Research Centers)

1. Intravenous access for administration
2. Obtain informed consent
3. Dosage: Dilute in crystalloid solution to final concentration of 3%. Doses are infused over one hour through a 0.22 micron filter. Loading dose is 140 mg/kg initially, followed by 70 mg/kg q 4 h, to a total of 12 doses of *N*-acetyl cysteine.
4. Adverse reactions occur in approximately 15%: flushing and transient skin rash (usually responds to diphenhydramine), wheezing, nausea, vomiting. Patient should be monitored for anaphlyaxis (Rx with epinephrine, H1 and H2 blockers, supportive care).

is an ominous clincal feature; development of grade III or IV encephalopathy may herald the death of the patient due to central herniation of the brain. Efforts to control the encephalopathy of acute liver failure are directed at preventing or resolving cerebral edema (Table 11). Because emerging evidence suggests that ammonia may play a role in the development of cerebral edema, we recommend limited use of protein (< 40 g/d) and lactulose to purge the bowel. However, one must exercise caution in using lactulose in the setting of FHF; dosing should be monitored carefully and adjusted to avoid alterations in electrolytes and volume depletion. If lactulose (PO) is given simultaneously with IV mannitol, marked loss of free water may occur, inducing severe hypernatremia. Rapid shifts in sodium concentration have been associated with central pontine myelinolysis.

Table 11. *Measures Used to Monitor and Control Cerebral Edema due to Fulminant Hepatic Failure*

1. Correction of metabolic abnormalities
   - Electrolytes (Na, K, Cl, HCO_3)
   - Acid-Base (if patient is on mechanical ventilation, induce mild respiratory alkalosis)
   - Glucose (maintenance intravenous glucose infusion)
2. Avoid over-transfusion or over-hydration
   - Carefully match intake and output once patient is euvolemic
   - Daily weights
   - Avoid use of blood products unless indicated for ongoing bleeding and correction of coagulopathy or to maintain hemostasis when intracranial monitor has been placed. In the latter circumstance, you may need to diurese the patient to avoid an excess intravascular volume, especially from plasma.
3. Institute dialysis in patients in renal failure
   - Continuous arteriovenous or venovenous hemodialysis is preferred over standard hemodialysis
   - Avoid severe volume shifts, stabilize blood pressure, maintain euvolemia, correct electrolyte and acid-base abnormalities
4. Mechanical ventilation (worsening encephalopathy, ≥ Grade II)
   - Main indication in liver failure is airway protection to prevent aspiration pneumonia
   - Induce mild respiratory alkalosis (pH 7.45 to 7.50, P_{CO_2} 20 to 30 mm Hg)
   - Elevate the head of the bed 15 to 30 degrees
   - Use sedation to avoid having the patient "fight the ET tube"
5. Consider placement of intracranial pressure (ICP) monitor in the epidural space
   - Should be considered when patients evolve from stage II (agitated confusion) to stage III (stuporous) encephalopathy.
   - Maintain adequate platelet count (> 60,000 cells/mm^3) with platelet transfusions and INR ≤ 1.5 with fresh frozen plasma, if necessary.
   - Mannitol is used to control ICP in patients with intact renal function or in those on dialysis. Mannitol is given in 0.5 to 1.0 g/kg doses. Serum electrolytes, glucose, and osmolarity should be checked every 4 to 6 hours. If ICP elevated, osmolarity < 310 mOsm/L H_2O, and Na <145 mEq/L, then give mannitol. Mannitol should be held if the patient has excessive serum osmolarity or significant hypernatremia.

Coagulopathy: In general, the coagulopathy of acute liver failure is due to depletion of clotting factors related to inadequate hepatic production. Some patients exhibit features of disseminated intravascular coagulation or primary fibrinolysis. Once the patient is diagnosed with severe acute liver failure or FHF, we recommend administration of mephyton (vitamin K) 10 mg/d SQ. Prophylactic infusions of clotting factors are not of proven benefit. Use of clotting factors, such as blood, fresh frozen plasma and fresh platelets, should be restricted to ongoing bleeding, such as GI hemorrhage.

Sepsis: Prophylactic antibiotics are not recommended. Blood, urine and sputum should be cultured frequently (even in absence of fever or other signs of infection) and antibiotic therapy directed toward specific organisms. Development of fever usually signifies intercurrent infection and should not be attributed to the liver injury, *per se*. Febrile patients should be fully cultured and treated empirically with antibiotics. The most common sources of infection are respiratory, urinary, and line sepsis. Currently we use vancomycin with a fluroquinolone in initial treatment and then tailor antibiotic use once results of cultures are known.

Glucose: Glycogen in the liver represents a main storage supply of glucose during periods of stress or fasting. Hepatic failure impairs glycogenolysis, and depletes the liver of its glycogen stores, resulting in severe, potentially life-threatening hypoglycemia. It is imperative that all patients with acute liver failure or FHF be treated with glucose infusions and that blood glucose levels are checked every 4 to 6 hours.

Liver Support Systems: Several methods have been used in FHF: exchange blood trans≠fusion, plasmapheresis, cross circulation with human and baboon donors, hemoper≠fusion through isolated human or animal liver, hemodialysis (conventional and poly≠acrylonitrate), and column hemoperfusion (microencapsulated charcoal, albumin-covered amberlite XAD-7 Resin). Only exchange transfusion and charcoal hemoperfusion have been evaluated by controlled trial, and the mortality was either

similar or greater in the treated group. Since none of these techniques has been demonstrated to improve survival, their use in FHF is not currently recommended (unless under IRB-approved protocols in major liver centers).

Bioartificial Liver: Extracorporeal liver assist devices (ELAD) or bioartificial liver machines (BAL) have recently emerged as potential therapeutic interventions in the treatment of FHF. However, their use currently is experimental and none has yet been conclusively shown, in randomized controlled trials, to improve outcome for patients with FHF. The major principle behind these devices is the use of a "bioreactor" which contains liver cells in a dialysis cartridge, external to the capillary luminae through which blood or plasma flows. The liver cells used in these reactors vary from primary porcine hepatocytes to transformed cells (subclones of HepG2 cells). "Toxins" or metabolites diffuse across the capillary membrane where the liver cells can remove, metabolize, or inactivate them. Experimental models suggest that removal of toxins and metabolites may reduce the neurotoxicity of FHF by inhibiting the formation of cerebral edema. In clinical terms, the goal is stabilization of neurological function to allow for hepatic regeneration or to bridge the patient to liver transplantation. Randomized controlled trials in the US are currently examining the efficacy of two different bioartificial livers in treatment of FHF.

Stange and colleagues recently reported use of a bioartificial liver (MARS) in 26 patients with chronic liver disease who had either acute or chronic liver failure. The treatments lowered plasma bilirubin and bile acids but effect on clinical outcome was unclear: nine patients with advanced liver disease (equivalent to UNOS 2A) died within an average of 15 days but the remainder survived and were thought to have benefited. Further studies will be needed to define benefit and overall utility.

Hepatocyte Transplantation

The principles guiding use of hepatocyte transplantation are similar to those of the bioartificial liver: provide support during a period of critical need so that the patient can be bridged to recovery or transplantation. One potential advantage of hepatocyte transplantation is the ability of liver stem cells to regenerate, raising the potential for repopulation of a dying or dead liver by allogeneic donor hepatocytes. The latter theoretical consideration has not been proven. Experience with hepatocyte transplantation in FHF is limited. We have used this technique in 6 patients who were not candidates for liver transplantation due to active substance abuse or who had prohibitive underlying medical illness and 1 patient listed for transplantation who had disseminated herpes infection. Despite a suggestion of improvement in neurologic status after hepatocyte transplantation, all 7 died. Difficulties with this approach include: inadequacy of the supply of human hepatocytes, need for arterial puncture in a coagulopathic patient to access either splenic artery for intrasplenic infusion of hepatocytes or hepatic artery for intrahepatic infusion, need for transjugular approach to portal vein if intraportal infusion of hepatocytes is to be performed, compromise of arterial circulation to spleen or liver during infusion, and use of immunosuppression to prevent hepatocyte rejection in setting of severe hepatic failure. Clearly, at this point hepatocyte transplantation for FHF should be viewed as unproven and experimental.

Liver Transplantation

Liver transplantation is the only treatment that has been proven to improve survival in patients with FHF and grade III or IV encephalopathy. Survival of this group of patients without transplantation is 10% to 20%. Survival increases to 60% to 80% with liver transplantation. Patients with FHF are listed at status 1 and given top priority for transplantation. The major limitation in performance of liver transplantation is inadequate availability of donor organs. As of May 1, 2001, there were greater than 18,000 patients on the US waiting list for liver transplantation. In the last 4 years, the number of liver transplants performed has ranged from 4000 to 4500 annually. Although most UNOS regions in the US currently "share" livers between organ procurement organizations (OPO) within each region for status 1 patients, this practice does not increase total donor organ availability. Available organs from patients with more stable chronic liver disease are simply shifted to those with acute liver failure and in greatest immediate need. Expansion of the donor pool is essential to resolve the donor-recipient mismatch.

Adult Living Donor Liver Transplantation Using the Right Lobe: There are currently two major ap-

proaches to expanding the donor pool: splitting cadaveric donor livers and use of living donors. Split livers are used primarily in the setting of an adult and pediatric recipient simultaneously in need of urgent transplantation. The left lateral segment is transplanted into the child and the remaining liver is used for the adult. Splitting livers into right and left hemi-livers for implantation into two adult recipients is under investigation.

Living donor liver transplantation (LDLT) has been performed successfully in approximately 1500 pediatric cases, typically from parent to child using the lateral segment of the left lobe, and in over 800 adults, typically using either full left lobe or, more recently the right lobe. Donor safety is a major concern in the performance of LDLT. Current statistics suggest that donor mortality is approximately 0.13% for adult-to-pediatric cases and 0.25% for adult-to-adult cases. Recent surveys indicate that donors have been satisfied with their decision to donate and in one survey from our institution all indicated a willingness to donate again, if they could.

In adults with FHF, survival is dependent upon an adequate functional hepatic mass. The left lateral segment is not thought to have sufficient hepatocellular mass to support an adult patient. For this reason, living-donation of the left lateral segment for adults with FHF has not been actively pursued. In contrast, an increasing number of liver transplant centers have begun to use the right lobe from living donors to perform hepatic transplantation. Experience with this approach in FHF, however, is limited. At a recent NIH-sponsored workshop (December 2000), outcome after LDLT for FHF was reviewed. Fourteen patients had undergone LDLT for FHF, of these all survived the surgical procedure and the 1-yr survival rate was 90%. These favorable results are encouraging, since results with cadaveric transplantation have yielded 1-yr survival rates of 60% to 80%.

Examination of a single case is instructive. We used LDLT in a young woman with fulminant hepatitis who was in coma, on mechanical ventilation and dialysis, with CT evidence of cerebral edema. There was no cadaveric donor available in our region and her brother inquired into the feasibility of performing living donor transplantation. It should be noted that our center was already experienced with adult-to-adult, right lobe, living donor transplantation in patients with chronic liver disease. The patient sustained complete clinical and neurological recovery following the living-donor transplant. The donor was discharged from the hospital within one week of surgery. Liver volume in both recipient and donor regenerates rapidly after resection and implantation; within 2 to 12 weeks liver volume normalized. Increasing availability of surgical expertise to perform this procedure may allow more widespread application and timely transplantation of patients with FHF.

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