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Hemorrhagic Fever continued

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TOPICS IN TOXICOLOGY**Acetaminophen Toxicity: When to Consult the Transplant Surgeon**

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Acetaminophen overdose remains a leading cause of drug-induced toxicity presenting to the Emergency Department. The diagnosis and management of acute acetaminophen ingestions are largely based on patient history and serum drug levels obtained in the ED. While ED physicians should be well versed regarding the management of such cases, it is the patient with a delayed presentation who already exhibits signs and symptoms of hepatic toxicity that is more challenging. Clearly, any patient already manifesting acetaminophen-induced hepatotoxicity should be admitted and receive *N*-acetylcysteine. But when will they need a liver transplant? What are the prognostic indicators of poor outcome in these patients? When should we call the transplant surgeon and arrange early transfer to a hospital with a specialized liver team?

Patients presenting to the ED two or more days after a toxic acetaminophen ingestion may exhibit clinical and laboratory evidence of hepatic injury. Some of these patients will require immediate evaluation by liver transplant specialists. The need for orthotopic liver transplantation (OLT) must be

determined rapidly given the amount of time and effort needed to secure a suitable matched donor. In those selected for transplant, 40 to 50% will die while awaiting a suitable donor.¹

Before OLT the overall survival rate for patients with fulminant hepatic failure from all causes was less than 20%.² With the use of OLT, patient survival rates are approximately 54-74% and are improving.^{3,4} Fulminant hepatic failure (FHF) is defined as acute liver disease occurring in the absence of pre-existing liver disease, leading to encephalopathy within 8 weeks of symptom onset or within 2 weeks of onset of jaundice. Acetaminophen is the most common drug to cause FHF in the United States and in Great Britain. The overall mortality rate from acetaminophen toxicity (including patients without encephalopathy) is 20%.⁵ Given the benefit of OLT in the setting of FHF, it is essential that ED physicians obtain early consultation with liver transplant specialists in cases where certain prognostic indicators are met.^{6,7}

FHF from acetaminophen toxicity presents with a variety of clinical manifestations. Nausea and vomiting predominate early and typically diminish in severity over 24 to 48 hours. Hepatic necrosis with an increase in serum transaminases (AST, ALT), bilirubin and prothrombin time ensues; complaints of right upper quadrant abdominal pain are common. Dehydration, renal insufficiency and oliguria may also occur during this time period. Between 2 to 5 days post-ingestion, jaundice, coagulation defects, hypoglycemia and encephalopathy occur as a result of marked hepatic damage. Cerebral edema is the leading cause of death in FHF and occurs in 75% of patients with high-grade encephalopathy.¹ Severe metabolic acidosis occurs in 30% of patients with FHF after acetaminophen overdose.⁵

Other studies have identified prognostic indicators for FHF, but many of these indicators were either not commonly available in the ED or relied on the development of complications (e.g., cerebral edema, renal failure) which undoubtedly adversely affected outcome. The most widely used early prognostic indicators in FHF are the King's College Criteria, which can be used to determine which patients should be referred to a facility with OLT capabilities (see Table 1).⁸ The authors described "static" variables that were definable at the time of admission, and "dynamic" variables that could be followed sequentially throughout the hospital stay, and studied enough patients to develop separate criteria for acetaminophen and for FHF from other causes.

The static variables were patient age, the etiology of FHF, and grade of encephalopathy at time of admission. Of these, the most important predictor of outcome was etiology: survival to discharge was 44.7% for hepatitis A, 34.4% for acetaminophen, 23.3% for hepatitis B, 13.6% for other drug reactions, and 9.0% for non-A, non-B viral hepatitis. Patient age was not a significant factor in acetaminophen-induced FHF, although older or very young patients from other causes had poorer outcomes. Advanced hepatic encephalopathy at admission was predictive of poor outcome in the acetaminophen patients. Significant

Table 1. KING'S COLLEGE CRITERIA TO SELECT PATIENTS WITH FULMINANT HEPATIC FAILURE FOR LIVER TRANSPLANTATION

Acetaminophen Overdose Patient

Arterial pH <7.3 or the presence of ALL three of the following:

- Prothrombin time >100 seconds (INR >7)
- Creatinine >3.4 mg/dL
- Grade III or IV encephalopathy

Non-Acetaminophen Overdose Patient

Prothrombin time >100 seconds (INR >7) or ANY three of the following:

- Age <10 or >40 years
- Jaundice >7 days before encephalopathy
- Serum bilirubin >17 mg/dL
- Prothrombin time >50 seconds (INR >4)
- Etiology from non-A, non-B hepatitis, halothane, or drug reaction

Adapted from O'Grady JG, et al.: Fulminant hepatic failure. In Shiff L, Schiff E (eds): Diseases of the Liver, 7th Ed. Philadelphia, JB Lippincott, 1993.

dynamic variables for acetaminophen cases were arterial pH <7.3 OR the presence of prothrombin time (PT) >100 seconds plus serum creatinine >3.4 mg/dL, plus grade III or IV encephalopathy (stupor to coma; see Table 2).

In acetaminophen-induced FHF, the positive predictive value (PPV) of a fatal outcome was 0.95 for arterial pH <7.30, with sensitivity of 0.49 and specificity of 0.99. PPV was 0.67 for those meeting the criteria of prolonged PT, elevated creatinine and high-grade encephalopathy, with corresponding sensitivity of 0.45 and specificity of 0.94.⁸ Other studies reported PPV of 0.60–0.92 and negative predictive value of 0.38–0.83 when using the King's College Criteria.^{6,9,10}

Measurements of arterial pH, serum creatinine, and PT should be readily available when patients present to the ED, while determining the presence and grade of hepatic encephalopathy is a fairly straightforward clinical assessment. Changes in arterial pH and creatinine usually occur within the second to third days after ingestion, respectively. The PT usually peaks on the third or fourth day. Abnormalities in these laboratory values generally occur before the onset of grade IV encephalopathy and subsequent cerebral edema, so a reasonable prognostic estimate can be made in patients presenting to the ED within this time frame.

Acetaminophen overdose remains a common problem in the ED and acetaminophen-induced FHF carries a significant mortality risk. Early identification of those individuals who need to be transferred to a facility capable of urgent OLT is essential. By utilizing common and readily available tests in the ED for those patients already manifesting liver toxicity, emergency physicians will be better able to facilitate the intensive management needed for these patients.

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Table 2. CLINICAL STAGES OF HEPATIC ENCEPHALOPATHY

Stage	Clinical Features
I	Slow mentation, disordered sleep, mild confusion, slight asterixis
II	Drowsy, slurred speech, inappropriate behavior, incontinence, asterixis, hypoactive reflexes
III	Stuporous but arousable, marked confusion, incoherence, asterixis, hyperactive reflexes
IV	Comatose, dilated pupils