

Failure of the King's College Hospital Criteria to Predict Outcome in a Patient with Acetaminophen Toxicity and Fulminant Hepatic Failure

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Acetaminophen toxicity, secondary to both intentional and accidental ingestion, is a leading cause of hepatic failure, accounting for approximately 20% of cases in the United States and 50% to 70% of cases in Great Britain.¹ The effects of hepatotoxic doses are often unpredictable, especially in patients taking hepatocellular enzyme-inducing drugs such as alcohol, phenytoin, carbamazepine, rifampin, isoniazid, and cimetidine.^{2,3} When the normal route of acetaminophen metabolism (ie, to sulfate and glucuronide) becomes saturated, the hepatic cytochrome P-450 system breaks acetaminophen down to *N*-acetyl-*p*-benzoquinone imine (NAPQI), a toxic compound that requires glutathione for neutralization. With glutathione already depleted, NAPQI binds to hepatocytes and other local cells, causing cell damage.⁴

The prognosis for patients with hepatic failure caused by acetaminophen toxicity is variable, depending on such factors as serum concentrations of acetaminophen and creatinine, the level of encephalopathy, the degree of acidosis and liver enzyme elevation, the extent of coagulopathy, and the time elapsed before treatment. When left untreated, 2% of patients with toxic plasma acetaminophen levels progress to fatal hepatic failure.⁵ In those patients fulfilling the King's College Hospital criteria,⁶ the projected prognosis remains dismal if orthotopic liver transplantation is not performed expeditiously.⁷ This article presents the case of a man whose condition fulfilled all 4 of the King's College Hospital prognostic criteria for patients with fulminant hepatic

failure. Despite a predicted mortality of 95%, the patient survived without emergent transplantation. The article details the patient's clinical course and outcome in light of the King's College Hospital criteria. The pathophysiology of acetaminophen toxicity and pharmacologic management of the condition are also discussed.

CASE PRESENTATION

Patient Presentation and History

A 37-year-old man with a medical history of cervical spine disease was brought to the emergency department of a university-based tertiary care medical center in an unresponsive state. The patient's parents reported that he had been unconscious for a period not exceeding 6 hours. The patient had a history of excessive use of acetaminophen combined with either codeine or hydrocodone, first prescribed to treat cervical radiculopathy. After a brief period of abstinence, the patient resumed use of acetaminophen and hydrocodone, taking approximately 30 to 40 pills a day during the week prior to his hospital admission. The review of systems was significant for a weight loss of 40 pounds over the

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Table 1. Case Patient's Initial Laboratory Values

Hematologic values	
Leukocyte count	31.3 × 10 ³ /mm ³
Platelet count	425 × 10 ³ /mm ³
Hemoglobin	12.5 g/dL
Prothrombin time	> 100 s
Serum chemistry	
Sodium	136 mEq/L
Potassium	4.6 mEq/L
Carbon dioxide content	5 mEq/L
Chloride	95 mEq/L
Glucose	56 mg/dL
Creatinine	2.4 mg/dL
Total bilirubin	2.7 mg/dL
Direct bilirubin	1.9 mg/dL
Alkaline phosphatase	171 U/L
Aspartate aminotransferase (AST, SGOT)	2878 U/L
Alanine aminotransferase (ALT, SGPT)	1926 U/L
Blood urea nitrogen	4 mg/dL
Arterial blood gas results*	
pH	6.84
PCO ₂	17.4 mm Hg
PO ₂	97 mm Hg
Bicarbonate	17.4 mEq/L
Oxygen saturation	99.5%
Base excess	−30

*On 40% fraction of inspired oxygen.

past 3 months and mild, intermittent nausea and vomiting. The patient's parents reported no additional drug or alcohol use by the patient. No other significant medical or surgical problems were present.

Physical Examination and Laboratory Evaluation

Physical examination revealed an unconscious man with a score of 7 on the Glasgow Coma Scale (eye opening, 2; verbal responsiveness, 1; motor responsiveness, 4). The patient's temperature was 34.7°C, blood pressure was 124/54 mm Hg, and pulse was 98 bpm.

Results of the patient's initial laboratory evaluation are shown in **Table 1**. The patient's acetaminophen level was 156 mg/L. Twelve hours after admission, the patient's factor V level showed less than 5% activity. Computed tomography (CT) scan of the head showed no evidence of intracranial bleeding, edema, or masses.

Treatment and Outcome

The patient was intubated in the emergency department for airway control and later was admitted to the surgical intensive care unit. *N*-acetylcysteine was administered via a nasogastric tube, and the patient was given 2 ampules of dextrose. After evaluation, the patient was placed on the transplantation list, but after 48 hours, a suitable donor had not become available. During this period, the patient progressed to stage IV encephalopathy and became hemodynamically unstable, requiring pressor support. A blood culture grew methicillin-resistant *Staphylococcus aureus*. Vancomycin treatment was initiated. Repeat CT scans showed effacement of the sulci and loss of the gray/white-matter demarcation, consistent with impending herniation. The patient's serum creatinine level peaked at 3.6 mg/dL. In addition, chest radiography was consistent with the onset of acute respiratory distress syndrome (ARDS), for which the patient was treated with aggressive ventilatory support.

The patient was no longer felt to be a candidate for transplantation. His family requested that mannitol and vancomycin therapies be withheld and that only endotracheal intubation with ventilatory support and comfort measures be continued. After 36 hours, the patient's encephalopathy and hemodynamic instability began to resolve. *N*-acetylcysteine and vancomycin therapies were restarted. Over the next 14 days, the patient's ARDS resolved, his liver enzyme levels and mental status returned to baseline, and his blood cultures grew no organisms. The patient was discharged home on hospital day 17.

DISCUSSION

Pathophysiology of Acetaminophen Toxicity

Acetaminophen toxicity, caused by intentional and accidental ingestion of acetaminophen, is a common cause of hepatic failure in the United States. Ellenhorn and colleagues⁵ have described 4 phases of acetaminophen toxicity. Phase 1, occurring within the first 24 to 36 hours after ingestion, is characterized by symptoms that include anorexia, nausea, and vomiting. The second phase, which occurs 24 to 48 hours after ingestion, is characterized by oliguria due to acute tubular necrosis and dehydration, pain in the right upper quadrant, and increasing prothrombin time and transaminase and bilirubin levels. Phase 3 occurs 96 hours after ingestion. In this phase, functional abnormalities of the liver peak, and the patient experiences malaise, jaundice, and dysfunction of the central nervous system. In phase 4, seen 7 days after ingestion, the symptoms resolve. Patients who do not recover at this point

may progress to irreversible, and possibly fatal, liver damage.

King's College Hospital Criteria

Those patients who do not recover from acetaminophen toxicity after experiencing phase 4 often have improved outcomes with orthotopic liver transplantation. In the acute phases of acetaminophen toxicity, 1-year survival rates following liver transplantation are approximately 60% overall.⁸ Early transplantation is ideal, with survival rates for patients with stage I or II encephalopathy approaching 80%. In encephalopathy stages III or IV, the survival rate diminishes to 56%.⁸ Without transplantation, the chance for survival is only 10% to 20%.⁹

In determining which patients will likely require liver transplantation, several parameters are examined. Although some physicians advocate the use of factor V levels in determining prognosis,¹⁰ the King's College Hospital criteria (**Table 2**) predict mortality in patients suffering from acetaminophen toxicity with greater accuracy.¹¹ The King's College Hospital criteria predict a 95% mortality for patients fulfilling all 4 criteria who do not undergo liver transplantation.

Patients not fulfilling the King's College Hospital criteria have a much more optimistic prognosis when given adequate treatment. Moreover, certain positive prognostic factors, such as younger age and early presentation to the hospital (both of which characterized the case presentation), can favorably affect patient outcome.

Pharmacologic Management

In addition to appropriate fluid management, *N*-acetylcysteine should be administered to patients with acetaminophen toxicity. This compound helps replenish hepatic glutathione reserves, thus allowing the liver to neutralize NAPQI, the toxic metabolite of acetaminophen. Additionally, *N*-acetylcysteine has been shown to increase cerebral blood flow and cerebral oxygen use in patients with grade IV encephalopathy.¹² Mannitol also decreases intracranial pressure, increasing cerebral blood flow. These therapies lead to fewer incidences of cerebral edema and lessen brain injury.

CONCLUSION

There have been many attempts to analyze additional clinical indicators that could serve as prognosticators in patients with acetaminophen toxicity. However, at this time, there is no single test or group of tests that can determine unequivocally which patients will survive with or without transplantation. The case patient survived, despite fulfilling all of the King's College Hos-

Table 2. King's College Hospital Criteria

pH < 7.3 24 hours after ingestion
Prothrombin time > 100 s
Serum creatinine > 3.4 mg/dL
Grade III or IV encephalopathy

Data from O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439–45.

pital criteria. This case serves as a reminder that adequate and expeditious medical treatment with *N*-acetylcysteine and fluid resuscitation greatly improves survival, even in the face of dire predictive measures. A case report such as this does not repudiate the King's College Hospital criteria; rather, it reminds physicians that they are merely guidelines and that each case should be addressed individually.

With increasing understanding of the mechanisms of hepatic injury from acetaminophen toxicity, new technologies will likely be developed to treat patients with this condition. Such novel instruments as the bio-artificial liver may serve to bridge the time between acute injury and hepatic rejuvenation, thereby decreasing the need for liver transplantation.¹³ The earlier and more aggressive use of *N*-acetylcysteine will also help ameliorate outcomes, as fewer patients proceed to irreversible fulminant hepatic failure. **HP**

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