

**INFECTIOUS DISEASES****Hemorrhagic Fever in California**

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Rare and exotic infections caused by Ebola, Marburg, and Lassa viruses used to be confined to distant parts of the world, such as Africa. Many of these infections have high mortality and create a public health alarm. These diseases typically result in a "hemorrhagic fever" syndrome, which relates to the clinical presentation of very high fevers and severe internal and external bleeding from capillary leakage or viral-induced coagulopathy. Transmission occurs with inhalation of airborne particles and direct contact with body secretions. These viruses are hardy and can last for days on hard surfaces such as wood, dirt, and stone. Time from infection to death or recovery may last days, enabling these patients to travel long distances by jet and possibly infect others. Emergency physicians frequently are the first to encounter patients who present with these infections, placing them at high risk. This type of transmission can be best exemplified by the first isolation of Lassa Virus in 1969, in which a nurse missionary in Lassa, Nigeria contracted a high fever and died of massive hemorrhage days later. Of the two nurses caring for her, one died similarly, and the other flew home to New York City and became ill. The virus was identified at that time, but only after two virologists investigating the case also contracted the disease, one of whom died.

Over the past year the number of hemorrhagic fever cases reported in California have increased. A well-known reservoir of infection for hanta virus exists along the eastern slope of the Sierra Nevada mountains. Periodically persons who live or visit this area have acquired hanta virus. In the past year, two persons have been hospitalized at our medical center with hanta virus who had Sierra Nevada exposures, one of whom died. In addition to hanta virus, a new hemorrhagic fever has now surfaced in California: Whitewater Arroyo virus. Three patients have died across California from this virus: in Orange County, Riverside County, and most recently, Alameda County, in Northern California.<sup>1</sup>

**Whitewater Arroyo Virus:** Discovered in New Mexico, wood rats and pack rats serve as a reservoir for the Whitewater Arroyo virus found in several western states including Colorado, Utah, Texas and Oklahoma.<sup>2</sup> Humans acquire the disease after inhalation of rat urine or fecal material. The exact incubation period is unknown. The virus may be similar to other South American hemorrhagic fevers which have an incubation period ranging from a few days to a week.<sup>3</sup> Patients may present with initially with nonspecific symptoms such as fever, weakness and lassitude and may appear no different than a severe case of the flu when first presenting to the ED. As the disease progresses the patient has increasing weakness, fever, dyspnea and develops altered mental status. Lab studies such as CBC, platelets, and coagulation studies may be no different than other patients with severe influenza.

Cardiovascular instability and significant internal hemorrhages usually lead to death. Diagnosis of Whitewater Arroyo virus is through serology and occasionally viral isolation. Currently the University of Texas, Galveston is one of the few labs that can identify Whitewater Arroyo virus.

**Hanta Virus:** Hanta virus was first recognized in the Four-Corner region of the southwest in 1993 and this viral subtype frequently is referred to as Sin Nombre Virus. The deer mouse serves as the reservoir for hanta virus: 8 human cases were reported in 2000 in CA. The author (RD) has personally observed deer mice and their fecal material in Eastern Sierra camping areas. In one area of the Walker River watershed in Eastern California, 60% of deer mice were found to have had evidence of hanta virus infection.<sup>4</sup> The inhalation of mouse fomites such as urine, feces, or other particles may initiate infection. Distribution of this virus is worldwide with many recognized serotypes and genotypes. Patients may present to the ER with viral type symptoms such as headache, fever, myalgias and weakness.<sup>5,6</sup> A finding of a normal chest x-ray and lab test may prompt the physician to send the patient home with a diagnosis of severe influenza. However, patients may progress onward to develop dyspnea, tachypnea, pulmonary edema, and hemorrhage of the hanta virus pulmonary syndrome. The mortality rate in some series exceeds 50%. Hanta virus should be expected when an otherwise healthy adult develops unexplained pulmonary edema or is suspected of adult respiratory distress syndrome (ARDS) without one of the known obvious causes.

Obviously it will be difficult for the emergency department physician to make a final diagnosis of these two hemorrhagic fevers in patients who have only mild or moderate syndromes. However, the clinician should have a high index of suspicion and admit persons who are at high risk to the hospital for supportive care. Additional causes of suspected hemorrhagic fever may be identified as diagnostic studies including DNA-PCR advance.<sup>7</sup> Ribavirin may benefit patients with hanta virus and Whitewater Arroyo virus, but controlled studies demonstrating efficacy are needed. In cases of suspected infection, county and public health, as well as infectious disease experts should be involved as soon as possible.<sup>8</sup> Person-to-person transmission of certain strains of hanta virus have been documented, including from patient to physician. Therefore, appropriate infectious precautions should be employed when caring for patients with suspected infections.

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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.<sup>1</sup>

Before OLT the overall survival rate for patients with fulminant hepatic failure from all causes was less than 20%.<sup>2</sup> With the use of OLT, patient survival rates are approximately 54-74% and are improving.<sup>3,4</sup> 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%.<sup>5</sup> 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.<sup>6,7</sup>

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.<sup>1</sup> Severe metabolic acidosis occurs in 30% of patients with FHF after acetaminophen overdose.<sup>5</sup>

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).<sup>4</sup> 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