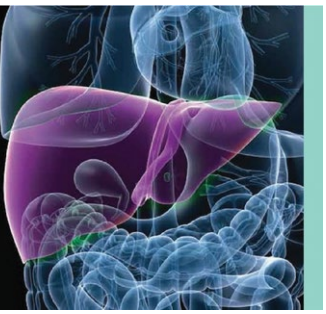

Acute Liver Failure Secondary to Yellow Fever: A Challenging Scenario

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Acute liver failure (ALF) is a clinical syndrome in which there is rapid deterioration of liver function, impaired level of consciousness caused by hepatic encephalopathy (occurring up to 26 weeks after onset of jaundice), and coagulopathy in previously healthy individuals.[1] The overall incidence of ALF in developed countries is 1 to 6 cases per 1 million persons each year,[2] with high mortality and costs. Orthotopic liver transplantation remains the only definitive therapy for patients who are unable to achieve regeneration of hepatocytes to sustain life.[1] Before the advent of transplantation, reported series demonstrated a survival rate of less than 15%. With transplantation, the rates of survival are currently more than 65% in 1 year.

O'Grady et al.[3] classified the syndrome in 1993 according to the interval between onset of jaundice and encephalopathy: hyperacute (7 days), acute (8-28 days), and subacute (5-12 weeks). This classification has been shown to aid in identification of the cause of the liver failure and possible complications. The hyperacute form usually presents with severe coagulopathy, very high transaminases, and low levels of bilirubin. The subacute form presents with moderately elevated transaminases and coagulopathy, with more intense jaundice. Both the hyperacute and the acute forms have a greater chance of recovery, although there is a greater incidence of organ failure and intracranial hypertension because of cerebral edema. The indication of liver transplantation in ALF is based on clinical and laboratory criteria, and the most used are the King's College and Clichy-Villejuif criteria.[4,5]

The main causes of ALF are drug toxicity, viral infections, autoimmune hepatitis, and less commonly, ischemic hepatitis, Budd-Chiari syndrome, malignancies, pregnancy-related liver failure, and hepatic trauma.[1] In South America, viral hepatitis is still one of the main causative factors, although there are lower rates in recent years because of vaccination strategies.[6-9]

Abbreviations: ALF, acute liver failure; YF, yellow fever; YFV, yellow fever virus.

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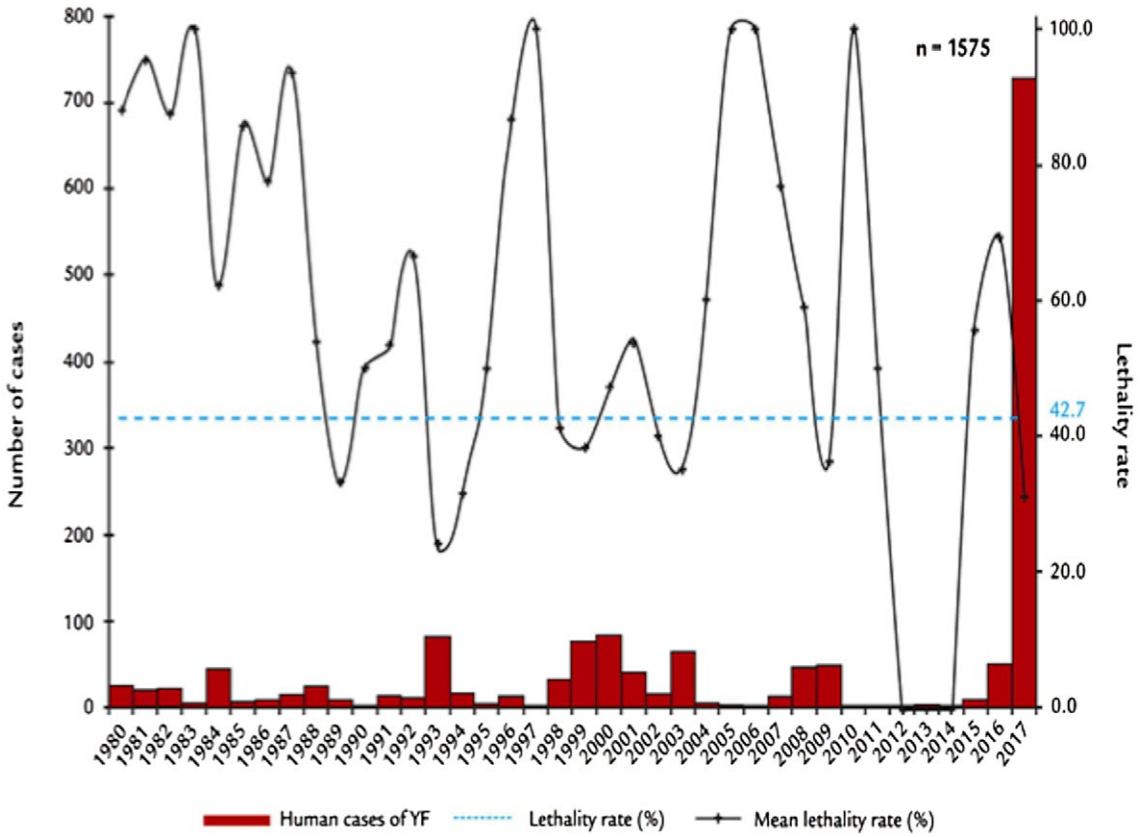

FIG 1 Historical series of the number of confirmed human cases of YF and lethality, 1980-2017. Source: Sinan; GT-Arbo/UVTV/CGDT/DEVIT/SVS/MS. Adapted with permission from the Brazilian Ministry of Health. Copyright 2018, Brazilian Ministry of Health.

One of the infectious causes of ALF is the acute hemorrhagic disease caused by the yellow fever (YF) virus (YFV), a mosquito-borne flavivirus. Despite the availability of an effective vaccine, it continues to pose an important threat to human health. The recent epidemic in Brazil is believed to have begun in December 2016 in the state of Minas Gerais (Fig. 1). From October 2017, epizootics in nonhuman primates were detected in several public parks in the city of São Paulo's suburbs. In January 2018, there were three autochthonous cases of YF in forested areas of Mairiporã, a town adjacent to the north of São Paulo City. There have been 1266 confirmed cases and 415 deaths caused by YF in Brazil from July 2017 to July 2018.[10] (Fig. 2)

The period of incubation ranges from 3 to 15 days. The majority of patients present mild and self-limited disease. Approximately 10% to 15% of infected patients experience severe YF, with high case fatality estimated at 40% to 50%. Clinical manifestations include fever, myalgia, headache, and nausea. Severe forms progress with involvement of various organs and systems, notably severe liver damage with encephalopathy and/or seizures, coagulopathy, cardiovascular dysfunction with bradycardia or rhythm abnormalities, circulatory shock, and acute kidney injury in varying degrees.

For the severe forms of YF, the general treatment in the intensive care unit includes only supportive management. Previous specific treatments have included immune modulators such as interferon-α and antivirals such as high-dose ribavirin in experimental models, but none has proved effective.[11,12] YFV has been recently demonstrated to be susceptible *in vitro* and *in vivo* to the antiviral sofosbuvir,[13] and a randomized clinical trial is currently ongoing in São Paulo, Brazil.

The first successful case of liver transplantation for fulminant hepatitis caused by YF has been performed in our center.[14] (Fig. 3) Cases with similar severity in the 2018 epidemic have all succumbed, except for anecdotal cases in which plasma exchange was used. Several liver transplants were subsequently performed for fulminant YF in

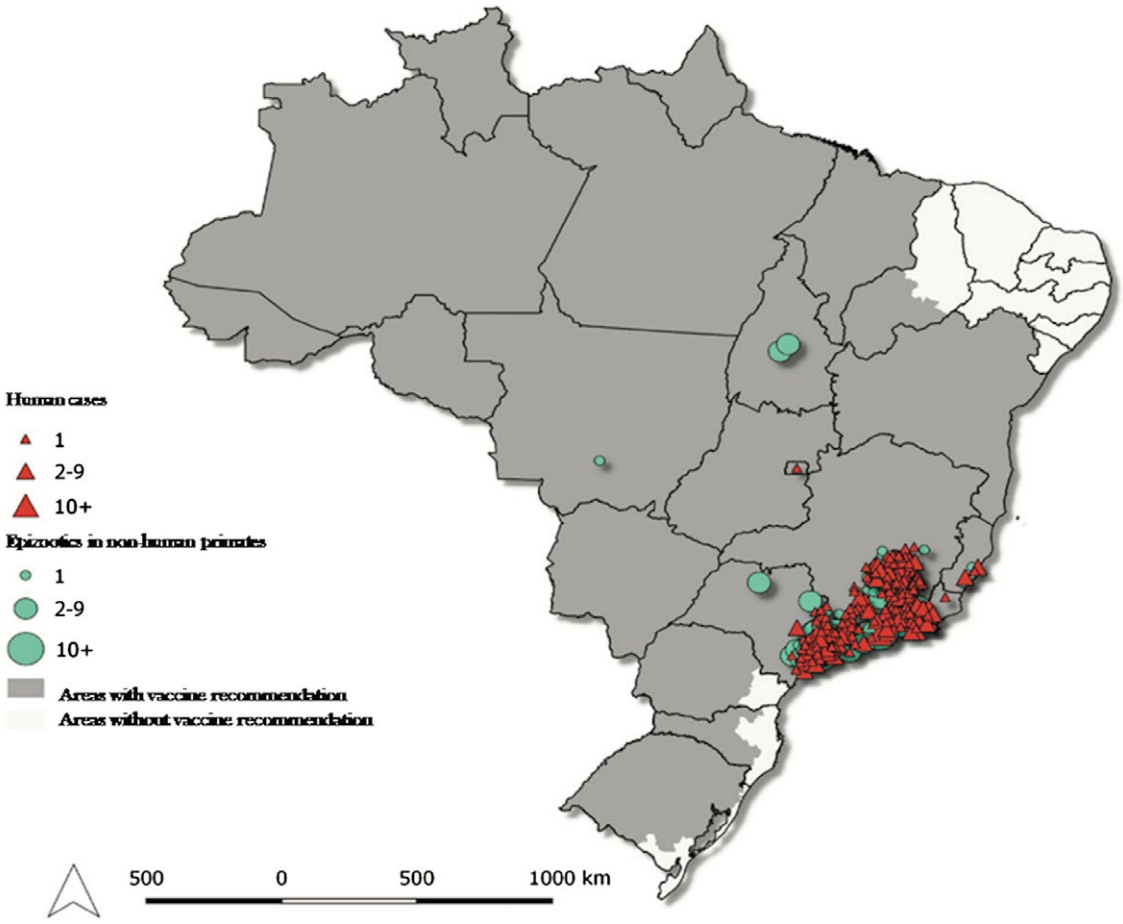

FIG 2 Distribution of confirmed human cases and epizooties of YF, according to the municipality of probable site of infection, surveillance from July 2017 to May 2018, Brazil.[10]

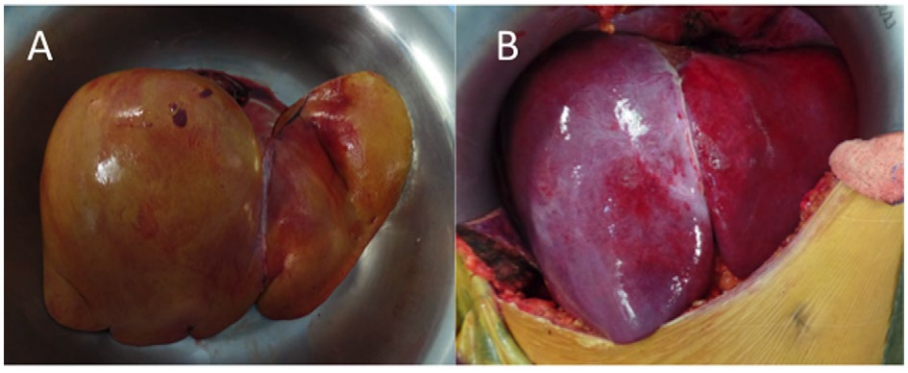

FIG 3 Explant with macroscopic characteristics of (A) YF and the (B) graft of the first liver transplantation performed in a patient with ALF caused by YF.

the Southeast Region of Brazil, with varying survival rates. Plasma exchange, which has been previously reported by Larsen et al.[15] to be a valid procedure in ALF, has been attempted in some centers for these patients. YF fulminant disease presentation is similar to a hyperacute form of ALF, along with other organ diseases, such as hematological disturbances leading to varying degrees of hemorrhage, acute renal failure, and acute pancreatitis. The current

criteria for liver transplantation are not suitable for indication in patients with severe YF. Although precise contraindications are still unclear, in some situations, such as necrotizing pancreatitis, refractory shock and central nervous system bleeding seem to lead to futile transplantation. Studies are under development to attempt to answer these questions.

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