Biomarkers for Lassa fever outcome?

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Geographically, Lassa virus (LASV), the causative agent of Lassa fever (LF), is endemic to the countries of West Africa. It is thought to infect up to half a million people annually (1), although it is hard to estimate because there has never been a uniform surveillance performed across the region. Although human to human transmission occurs, particularly in nosocomial settings, LASV infection is thought to predominantly occur through interactions with a peridomestic rodent, the *Mastomys natalensis* (2,3). These rodents are abundant across sub-Saharan Africa living in and around homes scavenging for food, particularly in the dry season when food becomes hard to find. LASV infection is thought to occur through direct contact or ingestion of rodent excreta or saliva shed by an infected rodent.

There have been a limited number of published clinical studies on LF over the last 30 years and most are focused on epidemiology and included little information on human disease symptoms and progression. In Nigeria, the country where LASV is thought to have originated and the circulating virus population is most diverse, no large-scale studies have occurred. In a recent article published in *The Lancet Infectious Diseases*, Okokhere and colleagues have described a rather unique clinical study on LF patients treated at the Irrua Specialist Teaching Hospital in Nigeria over nearly 5 years that followed 284 patients and matched known clinical outcomes to biomarkers (4).

In most cases, LASV causes subclinical infections or mild LF with general symptoms that include fever, headache and malaise. Pharyngitis may occur with cough, vomiting or gastrointestinal symptoms. A small proportion of LASV infections progresses beyond these general symptoms to an acute, life threatening illness. Severe cases of LF may display bleeding from mucosal surfaces, conjunctivitis, a petechial rash, swelling around the head and neck and shock. Death occurs from multi-organ failure approximately two weeks after the onset of symptoms (5-7). LF is particularly lethal during pregnancy and it is estimated that 95% of fetuses will not survive if infection occurs during the 3rd trimester (8). The study in Irrua reported a case fatality rate (CFR) of 24%. Mortality increased with age, as nearly 50% of patients over 50 years of age died. Clinical symptoms pertaining to the central nervous system (CNS) were also indicative of higher mortality rates, and those that developed encephalopathy only had a 25% chance of survival. This data correlates well with historical reports of CFRs of hospitalized cases of approximately 15–25%. Recent outbreaks in Nigeria, Liberia and Benin also reported CFR of 25% or greater (9,10) but a study in Sierra Leone reported a CFR of almost 70% in LF confirmed cases (11). However, most of those studies do not describe clinical biomarkers in association with disease outcome that Okokhere and colleagues report in their current study (4).

In the Irrua study, clinical biomarkers were found to be a more reliable marker of survival than clinical presentation of LF. Two biomarkers associated with kidney function were most indictive of fatal outcome; patients with increases in blood urea nitrogen (BUN) and creatine (CRE) were twice as likely to succumb to disease compared to those patients

who did not show signs of renal damage (4). Although this is the first report in humans, the cynomolgus macaque model of LF shows similar changes in blood markers with BUN levels increasing significantly near the terminal stages of disease (12). Corresponding with the increase in BUN levels, high levels of LASV are found in the kidneys and consequently, LASV replication is the likely cause of the tissue damage and subsequent renal failure in infected macaques.

Establishing biomarkers associated with severe or lethal outcome is an important step in learning how best to manage LF patients. Apart from intensive care, the treatment of LF is still largely reliant on the broad-spectrum antiviral drug ribavirin. This nucleoside analog has been used to treat LF since the early 1980's with varying results of efficacy. The effect of ribavirin is controversially discussed (13,14), but it is most effective when treatment is started in the first six days of illness (11,15-17). Recently, another broad-spectrum antiviral drug, favipiravir, has been successfully used to treat lethal LASV infections in mice, guinea pigs and cynomolgus macaques (18-20). This drug has received clearance in Japan to treat influenza and is in clinical trials in the United States for the same purpose. It has seen limited use for treating LF thus far (21), but the promising results in these studies suggest favipiravir use should expand in the clinic setting to further evaluate its efficacy in treating LF.

LASV load is an established diagnostic and laboratory marker for disease outcome. Unfortunately, Okokhere and colleagues (4) were unable to obtain viral load data and thus, future studies need to show the value of these newly identified biomarkers over viral load data for case patient management and disease outcome. Furthermore, viral sequencing data from the patients is not included in this study. Molecular characterization may link certain LASV clades with more severe renal or CNS complications, a finding of importance for public health.

In their study, Okokhere and colleagues have clearly expanded on the clinical aspects of LF and highlighted the significance of renal failure and to a lesser extent, CNS complications for LF outcome. Importantly, this study also serves to illustrate how much of the disease is still unknown and how much work is still needed to understand the mechanisms of LASV pathogenesis. New treatment options should continue to be developed, tested and advanced to the clinics, but moving favipiravir into clinical trials as a single treatment or combined with ribavirin seems a prudent next step. Vaccine development has taken a big step forward with support of the Coalition for Epidemic Preparedness (CEPI) and should continue to be improved until an efficacious universal LF vaccine is produced and distributed in West Africa. Finally, wildlife control measures need to be addressed and targeted towards the reservoir, the *Mastomys natalensis*.

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