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Clinical, epidemiologic, and therapeutic aspects of Lassa fever

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The circumstances surrounding the first recognized case of Lassa fever, 16 years ago in Nigeria, were dramatic. A physician and a nurse died and another person was critically ill. Exclamations of andromeda strain were found in newspapers and magazines. Lassa virus (LV) was isolated at Yale University and subsequently shown to be an arenavirus.

Following its initial identification, the disease was subsequently identified in other areas of Nigeria, and then in the countries of Sierra Leone and Liberia. It was during the investigation of an outbreak of disease in Sierra Leone in 1972 that the virus was isolated from *Mastomys natalensis* caught in homes of patients with Lassa fever. Today, LV and related viruses have been isolated from countries of West, Central and Southern Africa. In other countries of West Africa, such as Senegal, Guinea, and Burkina Faso, persons with antibodies to LV have been identified. The implications to human infection and disease for these parts of Africa remain largely unknown.

A long-term study of Lassa fever was established in the secondary forest area of Sierra Leone's eastern province. A laboratory capable of performing basic serologic and medical laboratory tests was established in two hospitals along with a central laboratory. One of our first studies was of all febrile adult patients admitted to the two hospitals, during which we collected standardized data on patients with Lassa fever and febrile patients not having Lassa fever. We learned that the best diagnostic predictors of Lassa fever were pharyngitis and proteinuria together. Based on a detailed statistical analysis of the clinical course of our patients, we can describe Lassa fever as follows. There is an onset of low-grade fever with an array of symptoms occurring during the 2nd and 3rd days, including sore throat, malaise, weakness, myalgia, back pain, dysuria, joint pain, chest pain, cough, and dizziness. By the end of the 4th day, the patient may have headache, vomiting, diarrhea, and abdominal pain. Hospitalization usually occurs on the 5th to the 8th day. The most important physical findings on admission are pharyngitis, conjunctivitis, abdominal tenderness, and (in 15%–20% of patients) facial edema. The case fatality of hospitalized adult Lassa fever patients in our study was 17%, with no significat differences seen by age group or sex. This observation differs from the early investigations of outbreaks, where 30%–40% fatali-

ty was described. The difference would appear to be due to the completeness in case finding and laboratory confirmation, whereas in early studies primarily the severe cases were identified. We have recently found a case fatality of about 12% in children under the age of 15 years.

The dry season, which normally falls in the months of January to June, is also the time when an increase occurs in hospital admissions due to Lassa fever. The explanation for this is uncertain, but there are cases of Lassa fever in the hospital throughout the year.

We studied the prevalence of antibodies to LV in populations of villages in several different ecological and geographic areas of Sierra Leone. We found a wide range, with a low of less than 10% to a high of 50%, in an eastern province village located in a secondary forest area. Antibodies occur in all age groups, with a lower prevalence in younger children and increasing frequencies in older persons. We established prospective studies of seroconversion rates to LV in villages of Sierra Leone. The incidence in each of four villages ranged from 5% susceptibles per year to about 20% per year.

Extensive studies of rodent distribution were carried out over a 3-year period, including assessments of the effect of trapping on the seroconversion rates. One of the most important observations was that *Mastomys* rodents were significantly more frequently trapped inside houses than in surrounding areas. This may explain why we had been unable to identify groups such as farmers or diamond miners to be more at risk than other members of the population.

We have analyzed many clinical and laboratory variables for their relationship with outcome. Of the symptoms, only vomiting and chest pain were statistically associated with death, and their sensitivity and predictive values are low. Furthermore, it is difficult to quantitate these variables in order to assign specific risk values. Among laboratory measures, two variables have emerged that are quantitatively associated with outcome: the admission viremia and the admission level of aspartate aminotransferase (AST). The mean viremia on admission in patients who eventually succumbed to LV infection was significantly higher than in those who survived. Analysis of these data shows that the risk of death begins to increase at about 10^3 infectious units per ml and enlarges with the level of viremia. Similarly, we have found a relationship between outcome and elevated levels of AST on admission and throughout the course of hospitalization. Survivor analysis similar to that described for viremia shows that an increased risk of death begins to occur at admission levels of 110. We have chosen a level of 150 for our analysis of treatment outcome, which carries an expected fatality of 55%.

Ribavirin is ribonucleoside, which means that it has a ribose moiety and a nucleoside ring. It has a molecular weight of 244 and is water-soluble and extremely stable at ambient temperature, even in tropical areas. It has a broad range of activity in vitro against both RNA and DNA viruses, and has been tested in human trials against many viral diseases, including influenza and illnesses caused by respiratory syncytial virus, against which it has been shown to be active when given as an aerosol. It has activity in animal models against several arboviruses but is not effective in hepatitis B in humans. A limitation in its use in some diseases may be its poor penetration into the central nervous system. Ribavirin is believed to act

as a guanosine analog, and in the case of inhibition of the replication of RNA viruses, it has been shown in several systems to be a competitive inhibitor of the guanylation step in the 5' capping of messenger RNA. Thus its effect on virus replication would be during translation. Specific mechanisms of inhibition of arenaviruses have not been studied.

We began our first study of ribavirin in November 1978. It included any patient with a clinical picture compatible with Lassa fever who was not pregnant. The patients were then randomly assigned to a drug group or plasma group. Those in the drug group were treated with 1 g drug orally as a loading dose, followed by 1 g/day in four separate doses for a period of 10 days. Patients in the plasma group received 250–300 ml plasma taken from a convalescent with an antibody titer determined by immunofluorescence procedure of at least 128; most had titers above 1000. Analysis of the oral trial showed a mortality of 12%, which we felt was not sufficient to warrant use of the drug. However, risk factors had not been taken into account. Therefore, we decided on a trial using a larger dose of ribavirin, this time given intravenously (i.v.). Patients with clinical diesease compatible with Lassa fever were tested on the day of admission for the level of AST. Those with an AST > 150 and who were not pregnant were randomly placed into either a drug or drug and plasma treatment group. The patients in the drug only group were treated with 2 g ribavirin i.v. as a loading dose, followed by 1 g every 6 h for 4 days. The dose was then reduced to 0.5 g i.v. every 8 h for 6 more days for a total of 10 days. Patients in the second group were treated with the same dose of ribavirin as the first group and were given 1 unit of plasma in addition. Pregnant patients received 2 units of plasma, but no drug.

The fatality rates in the groups in which the patients had been treated with ribavirin or with ribavirin and plasma were significantly lower than in the groups in which treatment was with plasma only or in which neither ribavirin nor plasma had been administered. A similar pattern was seen when treated and untreated patients with elevated viremias at admission were compared. Again plasma therapy did not prove to be better than no treatment. A comparison of outcome among patients with lower viremias showed that both types of ribavirin treatment were effective, and again that plasma was ineffective.

We were interested in assessing the effect of early therapy on the outcome. We found that fatality among patients with admission AST > 150 treated i.v. with ribavirin during the first 6 days of illness was significantly less than in patients treated after 6 days. Similar results occurred when patients with elevated viremias were analyzed in the same manner.

The lack of response of Lassa fever to convalescent plasma is different from the clear value of such therapy in Argentinian hemorrhagic fever. In some reports it has been suggested that convalescent plasma might be effective in Lassa fever. However, there were no comparison or control groups, and most diagnoses were made without laboratory confirmation. In addition to the uncertainty of its efficacy, plasma has several disadvantages as compared with the drug. It is expensive to collect, process, and store and is not without its own inherent risk of transmitting other diseases. Ribavirin, while presently somewhat expensive (a treatment course costs US $ 30–40), is cheaper than plasma and has the advantage of being stable, simple to administer, and more easily transported. Further exploration of the effects of higher doses of the drug administered orally and lower doses administered i. v. is in progress.