ABSTRACT

Background: Lassa fever is an acute viral zoonotic disease caused by the Lassa virus. Nosocomial infection has been described in many West African countries. It can be prevented by use of simple universal precaution techniques. Aim: To describe Lassa fever cases and contact tracing and outcome of Health Care Workers (HCWs) who came in contact with two cases. Methods: This study was carried out among the healthcare workers who came in contact with the cases. They were categorized into high and low risk and followed up for a period of 21 days after the last contact with a case. Results: While 71 hospital staff came in contact with both patients only 60 [84.5%] responded to follow up. A total of 34 [47.9%] collected ribavirin prophylaxis out of which 32 [94%] were high risk. Throughout the follow up period, two contacts reported having fever, headaches and body aches. They both tested negative for Lassa virus. They were given antimalarial and antibacterial and both improved. Conclusion: Lassa fever can be difficult to diagnose and the use of simple universal precautions during patient care was sufficient to prevent the nosocomial transmission of Lassa fever and should continue to be encouraged among HCWs.

Key words: Lassa fever, nosocomial transmission, contact tracing, Health Care Workers, ribavirin prophylaxis, biosafety
asymptomatically harbouring the organism in their bodies and excreting it throughout their lives without showing any signs of ill health.\[5\]

Man to man transmission occurs through faecal-oral route, or respiratory tract by inhaling contaminated air containing the virus, or when infected blood touches bruised skin or by sexual intercourse.\[5\] Person-to-person transmission of Lassa fever can also occur through contaminated medical equipment, such as reused needles or when a person comes into contact with virus in blood, tissue, secretions, or excretions of an infected ill individual in a hospital setting.\[6\] The Lassa virus cannot be spread through casual contact [including skin-to-skin contact without exchange of body fluids].\[7\] The virus can be isolated in the blood, faeces, urine, throat swab, vomit, semen and saliva of infected persons and secretion of the virus from infected individuals can continue for 30 days or more.\[8\]

Persons at greatest risk are those living in rural areas where the M. natalensis is usually found, especially in areas of poor sanitation or crowded living conditions.\[4\] However, health care workers are at particular risk if proper barrier nursing and infection control are not maintained.\[9\]

The clinical features of Lassa Fever are initially non-specific\[10,11\] and in areas endemic for these diseases like Nigeria, Malaria and Typhoid fevers are differentials that are first ruled out.\[12\] The incubation period is 6-21 days and symptoms include gradual onset of fever, weakness, pain, and arthralgias. Chest and back pain, exudative pharyngitis, cough, abdominal pain, vomiting and diarrhoea also occur quite commonly.\[13\] Less common features include facial and pulmonary oedema, mucosal bleeding, pleural effusions, neurological involvement, ascites and shock.\[13\] In pregnant women, Lassa fever leads to abortion. Lassa virus infection also leads to a high rate of foetal and neonatal death.\[10\] Recovery generally begins around day 10 but may be accompanied by prolonged weakness and fatigue and 8th cranial nerve damage leading to temporary or permanent deafness in one or both ears occurs as a sequela in 29% of Lassa fever patients.\[10\]

The symptoms of Lassa fever are so varied, nonspecific and similar to those of other diseases common in the tropics, therefore clinical diagnosis is usually difficult particularly in the early course of the illness. Hence, to make accurate diagnosis of Lassa fever, clinical manifestation, epidemiological data, and result of laboratory findings ought to be taken into consideration.\[7\]

In the laboratory, Lassa fever is diagnosed by detection of Lassa antigen, antibodies, or by virus isolation techniques.\[7\] The classical method to detect Lassa virus is inoculation of Vero cells with serum, cerebrospinal fluid [CSF], throat washing, pleural fluid or urine of the patient.\[7\] At the Irrua Specialist Teaching Hospital [ISTH], the foremost Lassa fever diagnostic laboratory in Nigeria, the diagnosis is by the use of Lassa virus specific reverse-transcriptase PCR [RT-PCR].\[12\]

The antiviral drug ribavirin has been confirmed by a study to be effective in the treatment of Lassa fever particularly if administered within six days of onset of clinical illness.\[14\] However, according to the World Health Organisation [WHO], There is no evidence to support the role of ribavirin as post-exposure prophylactic treatment for Lassa fever.\[9\]

In Nigeria, Lassa fever outbreaks has a seasonal variation with peaks in the dry season of the year and is most pronounced from December to April when burning of bush is at its peak.\[13\] These outbreaks became heightened in the last decade and in 2012, there were 70 deaths which included three medical officers and four nurses.\[15\] A number of outbreaks of Lassa virus infection have been regularly reported in more than 23 of the 36 states of Nigeria including Ondo state and Edo state which is a hot spot for the disease.\[16\]

Apart from Nigeria, Lassa fever outbreaks also occur equally frequently in other West Africa countries like Sierra Leone, Guinea and Liberia, Mali and Senegal.\[17\] All these outbreaks are usually associated with nosocomial spreads.\[3\]

Nosocomial infection with high case fatality rate has been described primarily in the hospital settings in many West African countries.\[3,17,18\]
However, as the virus is transmitted through bodily fluids and contaminated medical equipment, most outbreaks are associated with poor pathogen containment through barrier nursing, inadequate disinfection and direct contact with infected blood and contaminated needles.\textsuperscript{[6]} Many documented instances of nosocomial transmission of viral diseases have been attributable to clear deficiencies in infection control.\textsuperscript{[5]} Also, increasing and indiscriminate use of needles for intravenous therapy, or intramuscular injections in West African rural hospitals along with inadequate needle and syringe sterilization can lead to large scale epidemics.\textsuperscript{[19]} These epidemics can be devastating, resulting in the deaths not only of patients but also medical staff, surgeons, nurses and other scarce trained personnel.\textsuperscript{[19]} While studies have proven that simple universal precaution techniques such as appropriate use of gloves, masks, and gowns can prevent transmission, in many limited-resource settings, however, even rudimentary barrier and sterilization methods are beyond local budgets and the nosocomial spread in these settings is due to the current state of the health system, leading to poor medical practice.\textsuperscript{[19]}

Prevention of primary transmission of the Lassa virus from its host to humans can be achieved by avoiding contact with Mastomys rodents.\textsuperscript{[9]} However, in healthcare settings, nosocomial transmission can be avoided by taking preventive precautions against contact with patient secretions by instituting strict barrier nursing.\textsuperscript{[9]} Such precautions include wearing protective clothing, such as masks, gloves, gowns and goggles; using infection control measures and isolating infected patients from contact with unprotected persons until the disease has run its course.\textsuperscript{[7,9]} Also correct procedure for transporting materials suspected to contain highly virulent virus or microorganisms must be observed.\textsuperscript{[9]} In the laboratory, precautionary measures must be taken while carrying out tests on the body fluid and tissue samples of suspected cases and such tests must be done in biosafety chambers.\textsuperscript{[7]}

This study aims to describe the clinical presentation of Lassa fever, to demonstrate the difficulties faced in reaching an early diagnosis especially when presentation is not during an on-going epidemic and also to describe the procedure of contact tracing of HCWs that came in contact with the cases and their outcome.

**CASE PRESENTATION**

**Case 1**

The first patient was a 44-year old man who presented at the Accident and Emergency department of the State Specialist Hospital, Akure [SSHA] at 4:30am on the 5th of January 2016 with 15 episodes of watery diarrhoea, each episode was accompanied by vomiting and associated fever, all of a day’s duration. There was no abdominal pain, no blood or mucus in the stool. He admitted to having eaten out during the preceding days as it was a festive period. The only other significant complain he had was that of joint pains, duration of which was not established.

Examination revealed a conscious and alert man, not pale, afebrile and moderately dehydrated. Temperature was not taken [neither was it taken through the duration of his stay in the hospital because he did not have his own thermometer and thermometers are not shared between patients]. BP was 115/80mmHg and pulse rate was 80bpm.No abnormalities were discovered in the chest and abdomen.

A diagnosis of acute gastroenteritis with moderate dehydration was made and he was admitted and treated as such. He was placed on IV metronidazole 500mg 8hrly, IV ciprofloxacin 200mg b.d, intravenous fluids [IVF] and oral rehydration solution as tolerated.

Hepatitis B surface antigen, Hepatitis C screening and Human Immunodeficiency Virus [HIV] screening were requested for and all were negative. Full Blood Count [FBC] however revealed marked leucopenia of 2.4x 10\(^9\)/ L and a packed cell volume [PCV] of 43%. Blood film for malaria parasite was not done, neither were IgM or IgG for Salmonella Typhi requested.

Patient kept on deteriorating while on treatment, became uncooperative, started refusing medications and agitating to be discharged. He was eventually discharged against medical advice on 8th January, 2016.
On discharge, he went to the Federal Medical Centre [FMC], Owo, where he gave similar complaints and in addition, cough of three days' duration and altered sensorium of four days' duration. He however failed to mention he had been to another hospital before presentation. Haemorrhagic fever and septicaemia were queried as possible diagnosis by the medical team on call. He was admitted at the Accident and Emergency unit of the FMC, placed on diazepam, IV antibiotics, dexamethasone, intranasal oxygen and IVF.

His temperature on admission was 36.7°C. His blood was positive for malaria parasites and his PCV was 40%. He subsequently developed recurrent generalized tonic-clonic seizures along with irrational speech. He was then referred to ISTH the following day on account of suspicion of Viral Haemorrhagic Fever [VHF] where he was confirmed to have Lassa fever the same day. The hospital continued with his management but he eventually died 4 days after.

**Case 2**
The second case was a 13-year old boy who presented at the hospital in the afternoon with a 10-day history of fever, 5-day history of cough and 3-day history of profuse and worsening epistaxis. History revealed that he had previous episodes of epistaxis. During presentation, he started vomiting. No history of diarrhoea, haematuria or abdominal pain. No bleeding from any other orifice or site. Prior to presentation, he had self-medicated with chloroquine, chloramphenicol, amoxyl and vitamin B complex tablets, without improvement.

On examination, he was acutely ill looking and breathless. Pulse rate was 160 bpm and temperature was 36.8°C. An initial assessment of septicaemia with epistaxis was made. He was admitted into the male medical ward, placed on intranasal oxygen, IVF, IV cefuroxime 750mg 12hrly, cmaquine tablets 600mg daily and artesunate tablets 150mg daily for 3 days. HIV screening, blood film for malaria parasite and serial PCV were requested for by the team on call and his nostrils packed with adrenaline soaked gauze. PCV was 24% and blood film for malaria parasite was negative. He was later seen by the Paediatric team on call during which review his temperature was noted to be 37.8°C, bedside clotting time was 25 minutes and a repeat PCV was 21%. In addition to initial impressions, an assessment of poorly treated malaria was also made. He started passing blood with his stool, and subsequently received 2 pints of blood. The haematology team was called at which time his temperature was noted to be 39.5°C and an impression of bleeding disorder to keep in view a VHF was made. He was then placed on IM Vitamin K.

Patient's condition worsened despite all and he started to bleed from IV access site in addition to the profuse epistaxis. He was eventually pronounced dead about 36 hours after admission.

**METHODOLOGY**

This follow up study was carried out at the SSHA, Ondo State Nigeria, among the healthcare workers who came in contact with either or both of the above cases described. The SSHA is a secondary and referral health facility located in the capital of the State and about two hours’ drive from ISTH.

Once the diagnosis of Lassa fever was made [post mortem for case 2], a list of all hospital staff that worked in the wards and clinics where the cases were seen or admitted was gotten from either the most senior nurse or the head of the affected department/unit. The two laboratories in the hospital were also visited and lists of only the laboratory scientists that worked on the patients’ blood samples were collected from the head of each laboratory.

Messages were sent to the official phone numbers of all the contacts on the list. The first was to schedule a meeting with them informing them of the diagnosis and the implications to them. The second and third was to inform them each time to come to a designated location for their information to be entered into the line listing form.

At the sessions, all contacts were separated by which case they had contact with. Their basic demographic details were entered into the
contact listing form and contact follow up forms were opened for each contact.

Contacts were categorized into high risk if they either touched the body fluids of the patient or had direct physical contact with the body of the patient either dead or alive and low risk if they only touched or cleaned the linens cloths or dishes of the patient or only stayed in the same clinic or ward with the patient whether they claimed they used gloves or not. This is because gloves are not used consistently or reliably and infection control procedures in the hospital are far below acceptable standards.

Digital thermometers were given out and they were taught how to use the thermometers. A Community Medicine physician was assigned to each of the two groups. The mobile phone number of the physician was given to everyone in his/her assigned group. The contacts were informed to take their axillary temperature on waking up and when going to bed daily and send the reading to the assigned physician either as a text message, through a phone call, or take it to physician the following morning. They were also told to look out for the development of the following symptoms: malaise, muscle pains, headaches, sore throat, vomiting, diarrhoea, rashes and bleeding from anywhere. Development of any should be reported immediately. In addition, the assigned physicians called all the contacts in their follow up group daily to ascertain the temperature recording and the presence, if any of any of the symptoms listed above. The temperatures reported and the absence or presence of symptoms were documented in the contact follow up forms.

Follow up was for a period of 21 days after the last contact with the case for each contact. The day it started and ended differed for each contact and was dependent on the day of last contact. 500mg of ribavirin six hourly for five days was given to high risk contacts as soon as it became available.

RESULTS

A total of 71 hospital staff came in contact with both patients while they were on admission at the hospital. They were all contacted by phone. Only 60 [84.5%] responded, the remaining refused to give information and to be followed up. Those that refused follow up gave various reasons ranging from simple lack of interest to the fact that they were not ill and therefore did not need follow up. There was no attrition among the respondents throughout the follow up period, though the reporting of temperatures readings was not regular.

Among the 60 that responded, the median age was 37.5 years [range-19-56 years], 38 [63.3%] were females and the highest number, 28 [39.4%] were from the Accident and Emergency Department [table 1].The highest proportion of people were nurses, they constituted 24 (33.8%) of exposed. This was followed by laboratory technicians who constituted 20 (28.2%) and the least was student nurses who constituted only 3(4.2%). There was no association between response to follow up and sex (P=0.31), staff cadre (P=0.68) and department (P=0.87).

Out of the 60, 40[56.3%] came in contact with only the second case, 7[9.9%] came in contact with both and the rest came in contact with only the first case, 46 [64.8%] were classified as high risk contacts, the rest low risk. Being classified as high risk contact was associated with staff cadre (P=0.01) and the department (P=0.02) but not sex (P=0.11).

The median day after exposure that follow up was started for all contacts was 5 days [range-11 days].

A total of 34 [47.9%] collected ribavirin prophylaxis out of which 32 [94%] were high risk. The 32 represents 69.6% of those classified as high risk and therefore contacted to come for prophylaxis. Some contacts that refused prophylaxis gave the reason that they heard the medicine was too toxic. Two high risk didn’t collect ribavirin because they were pregnant [Table 2].

However, ribavirin was offered to and collected by 2 low risk contacts because they were wrongly contacted. The median number of days between the last exposure and onset of prophylaxis was 15.5 days [range 12-19 days].
Table 1: Basic demographic details of hospital contacts of the two Lassa fever cases, SSHA, 2016

<table>
<thead>
<tr>
<th></th>
<th>Contacts that responded N=60, n[%]</th>
<th>Contacts that did not respond N=11, n[%]</th>
<th>Total N=71 n[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median =37.5 years [range=37 years]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 [36.7]</td>
<td>2[18.2]</td>
<td>24 [33.8]</td>
</tr>
<tr>
<td>Female</td>
<td>38 [63.3]</td>
<td>9[81.8]</td>
<td>57 [66.2]</td>
</tr>
<tr>
<td><strong>Staff Cadre</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultants/Medical Officers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Assistants</td>
<td>13 [18.3]</td>
<td>3 [27.3]</td>
<td>16 [22.5]</td>
</tr>
<tr>
<td>Student nurses</td>
<td>3 [4.2]</td>
<td>0 [0]</td>
<td>3 [4.2]</td>
</tr>
<tr>
<td><strong>Department</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paediatrics</td>
<td>5 [7.0]</td>
<td>1 [19.1]</td>
<td>6 [8.5]</td>
</tr>
<tr>
<td>Haematology</td>
<td>2 [2.8]</td>
<td>2 [18.2]</td>
<td>4 [5.6]</td>
</tr>
<tr>
<td>Male medical ward</td>
<td>13 [18.3]</td>
<td>0 [0]</td>
<td>13 [18.3]</td>
</tr>
<tr>
<td>Children’s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Department</td>
<td>4 [5.6]</td>
<td>0 [0]</td>
<td>4 [5.6]</td>
</tr>
<tr>
<td>Main Hospital Laboratory</td>
<td>17 [23.9]</td>
<td>2 [18.2]</td>
<td>19 [26.8]</td>
</tr>
<tr>
<td>Accident and Emergency Department</td>
<td>28 [39.4]</td>
<td>6 [54.5]</td>
<td>34 [47.9]</td>
</tr>
<tr>
<td>Others1</td>
<td>2 [2.8]</td>
<td>0 [0]</td>
<td>2 [2.9]</td>
</tr>
</tbody>
</table>

1 Male surgical ward and Ear Nose and Throat department

Table 2: Proportion of contacts classified as high risk and those that collected Ribavirin, SSHA, 2016

<table>
<thead>
<tr>
<th>Staff cadre</th>
<th>Number of high risk contact within each cadre of staff n[%]</th>
<th>Number out of high risk contacts that collected Ribavirin n[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>House officers</td>
<td>3 [37.5]</td>
<td>2 [66.7]</td>
</tr>
<tr>
<td>Consultants and Medical Officers</td>
<td>5 [71.4]</td>
<td>3 [60%]</td>
</tr>
<tr>
<td>Nurses</td>
<td>13 [81.3]</td>
<td>8 [61.5]</td>
</tr>
<tr>
<td>Nursing Students</td>
<td>3 [100]</td>
<td>2 [66.7]</td>
</tr>
<tr>
<td>Laboratory Scientist/Technologist</td>
<td>16 [100]</td>
<td>12 [75.0]</td>
</tr>
<tr>
<td>Health Assistants</td>
<td>6 [60]</td>
<td>5[83.3]</td>
</tr>
</tbody>
</table>
Throughout the follow up period, only two contacts reported any symptoms. One, a 32-year-old female nurse from the Male Medical Ward, who was categorized as high risk, collected ribavirin on day 17 of exposure and developed muscle aches, headache and malaise the same day. Her body temperature also increased from a documented highest of 36.5°C previously to 37.9°C. Blood sample for RT-PCR for Lassa was taken, she was placed on antibiotics and antimalarial, and advised to continue with ribavirin. The RT-PCR for Lassa test came out negative and she improved after 3 days. The second case was a 47-year-old male Consultant Hematologist who was also categorized as high risk. He developed malaise, body aches and headaches 15 days after last contact and three days after he started prophylaxis. His temperature also rose to 37.8°C. He commenced antimalarial and his blood was tested for Lassa using RT-PCR, which came out negative. He subsequently improved. Temperatures of all other contacts remained between normal between 35.5°C-37.4°C.

**DISCUSSION**

While the second case presented with haemorrhage, the first case presented with diarrhoea. Diarrhoea is a common and early but non-specific presentation of Lassa fever\(^1\) while haemorrhage occurs in less than a third of patients and is a sign of poor prognosis.\(^2\)

The first case had already been self-medicating with antibiotics and antimalarial with the assumption that he had malaria or typhoid. This contributed to the delay in his presentation until the onset of haemorrhage. As have been documented, self-medication is a problem in Nigeria and results in late presentation at the hospital.\(^2\)\(^1\) Although the likelihood of early diagnosis being made in the patient, even if he presented early, was low because his initial symptoms were non-specific and the index of suspicion low as exemplified by the fact that even when he presented with fever and haemorrhage, VHF was not suspected. Furthermore, the patient has had previous episodes of epistaxis though not accompanied with fever.

Though only 60 of the contacts subjected themselves to appropriate follow up, the monitoring team was still able to ascertain that none of all the 71 contacts was clinically ill with Lassa fever throughout the period of follow up. Only two contacts had any form of illness and they were the only two that were tested for Lassa fever, using the RT-PCR, due to limited resources. In 80% of cases, Lassa Fever can be asymptomatic or mildly symptomatic\(^3\) therefore, it cannot be definitely said that none of the clients contacted the illness but only that none of the contacts came down with clinical Lassa fever. Moreover, the two cases that were ill, became ill after commencing ribavirin and they recovered improved after a few days on antimalarial and antibiotics. Therefore, their symptoms could have been due to other endemic diseases malaria, side effects of ribavirin or, though less likely, because of a false
positive test as it has been noted that in countries where Lassa fever is endemic like Nigeria, the RT-PCR, assays, which are usually very sensitive, is limited by issues of strain variation, cross contamination, lack of qualified personnel, inadequate facilities and expense.\[7\]

Our findings support the fact that the use of even basic universal precautions, during patient care can prevent the nosocomial transmission of Lassa fever. All the hospital contacts of the cases used only gloves during procedures that involved touching the cases or their body fluids. The nurse who was ill during the follow up period had used gloves only while giving the case a bed bath but had splashes of vomitus on her. Healthcare workers should continue to be encouraged on the proper use of Personal Protective Equipment [PPEs] and the government encouraged to make at least basic PPEs readily available. This finding also supports that the frequency of transmission of Lassa virus is low even among close contacts.\[22-24\]

In conclusion, diagnosing Lassa fever when there is no outbreak ongoing can be difficult. Unfortunately, early diagnosis is crucial in other to prevent nosocomial transmission. However, the frequency of transmission of Lassa fever to contacts seems low and the use of universal precautions offers good protection to health workers. We recommend a high index of suspicion for VHFs in hospital settings. Health workers should also continue to observe universal precautions with all patients they come in contact with.

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