

Postexposure prophylaxis for Lassa fever: Experience from a recent outbreak in Nigeria

Samson E. Isa, Attah Okwute, Kelly O. Iraoyah, Shehu Y. Nathan, Gomerep S. Simji, Mark O. Okolo¹, Joseph Anejo-Okopi², Daria Spicola³, Daisy E. Isa⁴

Department of Medicine, Infectious Diseases Unit, University of Jos/Jos University Teaching Hospital, ¹Department of Medical Microbiology, University of Jos/Jos University Teaching Hospital, ²Department of Microbiology, University of Jos, Jos, Plateau State, Nigeria, ³Department of Internal Medicine, Infectious Diseases Unit, Armas Civico Di Cristina Benfratelli, Palermo, Italy, ⁴Department of Pharmaceutical Sciences, Aston University, Birmingham, United Kingdom

ABSTRACT

Background: Secondary transmission of Lassa fever (LF) occurs in the community and in health-care facilities, and is associated with high fatality in Nigeria. We investigated the role of oral ribavirin postexposure prophylaxis (orPEP) in preventing LF among the primary contacts of confirmed cases from December 2015 to March 2016. **Materials and Methods:** Epidemiological and clinical data of LF contacts were prospectively collected. However, information regarding ribavirin adverse effects (AEs) were collected retrospectively through a telephone interview. High-risk contacts were clinically monitored ± orPEP. **Results:** Thirty-five (94.6%) out of the 37 individuals enrolled in the study were contacts of confirmed LF cases, and friends and family members (54%) constituted the largest group. However, only 29 (83%) individuals were classified as high-risk contacts. Twenty-one (60%) of contacts were prescribed ribavirin with 6 (28.6%) of them reporting AEs. Body weakness (33%) was the most frequent AE, but there was no incidence of treatment discontinuation due to AE. Furthermore, there were no reported cases of LF among all respondents (0%), whether they had orPEP or not. **Conclusion:** Secondary transmission of LF seems uncommon and the benefit of orPEP is uncertain. Although AEs of ribavirin may not be uncommon, they are rarely serious enough to cause treatment interruption. More emphasis should be on supporting persons looking after LF cases adopt measures that minimize the risks of exposure.

Key words: Lassa fever, Nigeria, oral ribavirin, prophylaxis, secondary transmission

Address for correspondence:

Dr. Samson Ejiji Isa,
Department of Medicine,
Jos University Teaching
Hospital, PMB 2073, Jos,
Plateau State, Nigeria.
E-mail: ejijisa@yahoo.com

INTRODUCTION

Lassa fever (LF) is a viral hemorrhagic disease transmitted by *Mastomys natalensis*, the primary rodent species that carries Lassa virus (LV).¹ The modes of transmission include exposure of broken skin/mucous membranes to contaminated blood/body fluids.² Published data suggest that 4–55% of individuals in West Africa have serological evidence of exposure to LV,^{1,3} with a prevalence of 21% in Nigeria.⁴ Imported cases have been documented in the United States and Europe, and there is global concern that LV can be weaponized.^{5–7} According to the World Health

Organization, the overall mortality rate is 1%, but climbs to 15% among hospitalized patients,⁸ and rates exceeding 40% have been reported in Nigeria.^{9,10} While the Nigerian strains of LV may be more virulent,¹¹ delays in instituting appropriate treatment could also account for the higher mortality.

Timely administration of intravenous ribavirin, a virustatic guanosine analogue, reduces mortality.¹² However, questions regarding the efficacy and appropriate dosages

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Isa SE, Okwute A, Iraoyah KO, Nathan SY, Simji GS, Okolo MO, *et al.* Postexposure prophylaxis for Lassa fever: Experience from a recent outbreak in Nigeria. Niger Med J 2016;57:246-50.

Access this article online

Quick Response Code:



Website:

www.nigeriamedj.com

DOI:

10.4103/0300-1652.188362

of oral ribavirin as postexposure prophylaxis (orPEP) are unresolved.^{5,13} The minimum inhibitory concentration of ribavirin for LV from an *in-vitro* study is in the range of 4–40 $\mu\text{mol/L}$, but a mean peak plasma concentration of only 3.1 $\mu\text{mol/L}$ (range: 1.2–9.6 $\mu\text{mol/L}$) was achieved with oral administration of 1 g/day in three divided doses for 10 days in humans.^{14,15}

Prescription practices for orPEP differ in Nigeria, and systematic studies on their efficacy or adverse effects (AEs) are lacking. In addition, the cost of a 10 day course varies from \$42 to \$1819, depending on the dose prescribed, the manufacturer and the period of purchase.¹³ Given the public health importance of LF and the need for better utilization of scarce resources, we investigated the role of orPEP in the prevention of secondary cases of LF.

MATERIALS AND METHODS

The study was carried out at the Jos University Teaching Hospital (JUTH) from December 2015 to March 2016. The hospital is a major referral center situated in Jos, the capital city of Plateau State.

Epidemiological and clinical data of respondents who had direct contact with suspected LF cases seen at JUTH were prospectively collected. Contact tracing and other aspects of the epidemic response were carried by officials of the State Ministry of Health and JUTH infectious diseases physicians. Contacts were categorized as high- or low-risk as defined by Bausch *et al.*¹³ In brief, high-risk exposure includes: (1) Needlestick injury (2) splashes on mucous membrane/broken skin (3) carrying out emergency procedures without the use of appropriate personal protective equipment (PPE) (4) continuous contact for hours in an enclosed space without the use of appropriate PPE. All contacts were advised to monitor their axillary temperature in the mornings and evenings for 21 days from the last day of exposure, and to report fever ($\geq 38.0^\circ\text{C}$) for further evaluation. According to our usual practice, orPEP was offered to those with high-risk exposure, in whom ribavirin was not contra-indicated. LV-specific reverse-transcriptase polymerase chain reaction test for case confirmation was carried out at two Nigerian reference centers. Oral PEP was discontinued for those whose exposure source tested negative. High-risk contacts of positive cases who enrolled in the study were prescribed different regimens of oral ribavirin (LOT: 141102, Hubei Meibao Pharmaceutical, Tianzshan, China). Data on self-reported orPEP adherence and AEs were collected retrospectively in a telephone interview, approximately 4 weeks after orPEP prescription.

The main outcome measure was the proportion of primary contacts of confirmed LF cases who became ill with LF.

Ethical approval for this study was obtained from the JUTH Ethics Committee. The data set was anonymized by transcribing names into initials and serial numbers.

Statistical analysis was performed using SPSS (version 20, Chicago, IL, USA). Continuous variables were expressed as means \pm standard deviations, or medians with interquartile range (IQR). Categorical variables were presented as proportions and compared using the Chi-squared tests or Fisher's exact test as appropriate. Means were compared using unpaired Student's *t*-tests. The value of $P < 0.05$ was considered statistically significant.

RESULTS

There were 45 primary contacts of suspected LF cases, but only 37 (82.2%) were identified for the study. Their mean age was 40.1 years (± 10.9) and 18 (48.6%) were male. Friends and family members were the most exposed group (54.1%), and most were exposed while nursing the suspected cases. Whereas 35 (94.6%) of the 37 persons had contact with 10 confirmed LF cases, exposure was categorized as high-risk in only 29 (82.9%). Twenty-one individuals had orPEP and the self-reported adherence was 80.9% (17/21). The demographic and epidemiologic characteristics of all primary contacts are shown in Table 1.

The clinical characteristics and outcomes of contacts of confirmed LF cases who took orPEP compared with those who did not are shown in Table 2. There were no significant differences in age, sex, or exposure groups. Of the 21 contacts who were prescribed orPEP, 6 (28.6%) reported AEs during a median follow-up period of 30 (IQR: 29–35) days. While 3 (21.4%) of contacts not prescribed ribavirin also reported symptoms, there was no significant difference between the two groups ($P = 0.58$). None of the exposed individuals were diagnosed with LF.

There were 12 episodes of AEs attributed to orPEP. The median duration from exposure to initiating orPEP was 4 (IQR: 2–9) days while assessment of AEs was carried out 30 (IQR: 29–35) days after Ribavirin prescription. Body weakness was the most frequent AE 4 (33.3%), followed by insomnia 2 (16.7%) and dizziness 2 (16.7%). Diarrhea, malaise, dyspepsia, and palpitation were also reported once, each representing a proportion of 8.3%. Those prescribed 500 mg 4 \times /day for 10 days reported the most AEs 6 (50%). Curiously, there were no AEs with 2 g start, 1 g 3 \times daily \times 10 days prescription. Four (23.5%) individuals on orPEP had been regularly on antacids and hydrochlorothiazide/amiloride. None of those with AEs reported treatment interruption. The distribution of AEs and associated orPEP dosages is shown in Table 3.

Table 1: Demographic, epidemiologic and clinical characteristics of 37 respondents exposed to suspected/confirmed Lassa fever cases

Characteristics	n (%)
Mean age (±SD) years	40.1 (±10.9)
Sex	
Male	18 (48.6)
Female	19 (51.4)
Contact classification	
Doctors	6 (16.2)
Nurses	11 (29.7)
Friends/family members	20 (54.1)
Where exposure occurred	
Hospital	24 (64.9)
Home	13 (34.1)
How exposure occurred*	
Bathing/cleaning/feeding	21 (36.2)
Sharing sleeping space	4 (6.9)
Contact with blood/body fluid	29 (50.0)
Splash on broken skin/MCM	4 (6.9)
Needle stick injury	0 (0)
Exposure risk categorization	
High-risk	29 (78.4)
Low-risk	8 (21.6)
LF test results of exposure source	
Confirmed LF positive contacts	35 (94.6)
Confirmed LF negative contacts	2 (5.4)
Ribavirin prescription	
Prescribed ribavirin [†]	22 (59.5)
Not prescribed	15 (40.5)
Dosages of orPEP	
500 mg 4 × daily × 10 days	3 (14.3)
2 g start, 1 g 3 × daily × 10 days	7 (33.3)
500 mg 3 × daily × 10 days	7 (33.3)
Other [‡]	4 (19.1)

*Some individuals had >1 sources of exposure; [†]1 contact did not take prescribed ribavirin due to pregnancy; [‡]800 mg daily or 800 mg × 2 daily which was not according to prescription. orPEP – Oral ribavirin postexposure prophylaxis; MCM – Muco-cutaneous membrane; SD – Standard deviation; LF – Lassa fever

DISCUSSION

In this study, no secondary transmission of LF occurred with or without orPEP. AEs were reported in 6 (28.6%) individuals who took Ribavirin but curiously, none was reported among those prescribed the highest doses.

The absence of secondary cases of LF in this study suggests that person to person transmission may be uncommon. This is in agreement with a study in the United States in which there was no documented transmission among 188 contacts of an imported case; five of the contacts were considered high risk but were not prescribed ribavirin.⁵ Similarly, there was no secondary transmission, other than one probable asymptomatic infection in a physician, among 30 and 20 high-risk contacts in Germany¹⁶ and Nigeria, respectively.¹⁷ In these two studies, ribavirin prophylaxis was prescribed. However, there are reports of a seemingly secondary community transmission,¹⁸ and of nosocomial transmissions in Nigeria.^{2,18} The risk of transmission

Table 2: Comparison of clinical characteristics and ribavirin prophylaxis outcomes among 35 contacts of confirmed Lassa fever cases

Characteristics	n (%)	Yes orPEP (n=21)	No orPE (n=14)	P
Mean age (±SD) years	35 (100)	41.1 ± 11.7	40.1 ± 11.1	0.69
Sex	35 (100)			
Male	18 (51.4)	12	6	0.46
Female	17 (49.6)	9	8	
Contact classification	35 (100)			
Doctor	5 (14.3)	3	2	0.44
Nurse	10 (28.6)	4	6	
Friends/family members	20 (57.1)	14	6	
Preexisting morbidities*	35 (100)			
Yes	9 (25.7)	5	4	0.17
No	26 (74.3)	16	10	
Concurrent medications [†]	31 (88.6)			
Yes	7 (22.6)	4	3	0.06
No	24 (77.4)	13	11	
AEs/symptoms reported [‡]	31 (96.9)			
Yes	9 (29.0)	6	3	0.58
No	22 (71.0)	11	11	
Developed LF	35 (100)	0	0	
Median follow-up duration (IQR range) days	35 (100)	30 (29-35)	30 (30-38)	0.21

*Hypertension n=5, Acid-peptic disorders n=3, Pregnancy n=1; [†]Hydrochlorothiazide-amiloride n=2, antacids n=5, antibiotics n=2, atermisinin-lumefantrine n=2, multivitamins n=1; [‡]AEs in those who received rPEP and any symptoms in those who did not receive rPEP within the follow-up period; High and low risk exposure. AEs – Adverse effects; rPEP – Ribavirin postexposure prophylaxis; SD – Standard deviation; IQR – Interquartile range

appears low even among nonimmune individuals residing in nonendemic regions.^{5,16} However, the effective use of convalescent human sera for treatment^{19,20} indicates that acquisition of neutralizing antibodies from the previous infection could confer protection in some individuals, and may therefore account for differences in susceptibility in endemic regions. Another possible reason for reported differences in transmission is the severity of illness of the source cases at the time of exposure. Viremia increases as illness progresses, with the risk of transmission increasing in individuals exposed to LF cases with severe disease.^{7,16}

In the current study, we also examined AEs associated with orPEP prescription. Several studies have described the AE profile of ribavirin and reports indicate that they are largely mild and reversible.^{13,16,17} While the Nigerian Federal Ministry of Health recommends a 7 day course of 500 mg 4×/day (unpublished), variations in prescription may partly be a reflection of conflicting data regarding efficacy and AEs. Overall, 6/21 (28.6%) individuals reported AEs in our study, without those prescribed the highest doses. Iroezindu *et al.*¹⁷ reported 12/18 (66.7%) AEs using similarly high dose.¹⁷ They also reported fatigue and dizziness as the most common AEs, which is consistent with our own findings, as body weakness and fatigue may mean the same in Nigeria. The report of symptoms in our comparison group who were not on orPEP and in those concurrently on other medications [Table 2] suggest that

Table 3: Adverse effects reported among contacts of confirmed Lassa fever cases who received oral ribavirin postexposure prophylaxis (N=6)

	n (%)
Adverse effect	
Weakness	4 (33.4)
Insomnia	2 (16.7)
Dizziness	2 (16.7)
Diarrhoea	1 (8.3)
Malaise	1 (8.3)
Dyspepsia	1 (8.3)
Palpitations	1 (8.3)
Total	12 (100)
Dosages	
500 mg 4x/day x10days	6 (50)
500 mg 3x/day x10days	3 (25)
Others	3 (25)
2 g start, 1 g 3x/day x10days	0 (0)
Total	12 (100)

N – Total number of individuals on ribavirin who experienced adverse effects;
n – Number of adverse effects reported; Others – 800 mg daily or 800 mg x2 daily

psychosomatization, AEs from other medications and occurrence of illnesses unrelated to LF can all confound reports of AEs.¹⁷ Although laboratory evidence of Ribavirin AEs has been reported, including increased bilirubin and decreased hemoglobin, they are rarely significant enough to cause treatment interruption.^{16,17}

While our study is the largest evaluation of high-risk contacts of several confirmed LF cases during a single outbreak, it has important limitations. Since we did not assay for LV IgM or IgG antibodies, it was not possible to determine if asymptomatic infection occurred and if administration of ribavirin had any effect on the development of protective immunity in the short or long-term. Ribavirin adherence was self-reported, and as an observational study, we were unable to establish causality with reported AEs. Nonetheless, the inclusion of a control group, although few numbers, indicates that reported AEs can be due to reasons other than ribavirin. Laboratory evidence for AEs was not investigated. However, except perhaps for selected individuals, routine testing may not be necessary or even feasible in endemic regions due to resource constraints.

CONCLUSION

Symptomatic secondary transmission of LF is uncommon. Furthermore, AEs of ribavirin may not be uncommon, but they are rarely serious enough to cause treatment interruption. Although controlled studies for LF would be difficult to conduct, larger prospective studies could improve our understanding of the interactions between host immunity, the risk of infection and the cost-effectiveness of ribavirin prophylaxis. Meanwhile, all persons looking after LF cases, especially friends/relatives,

should be supported to adopt measures that reduce the risks of exposure.

Acknowledgment

We are grateful to the Federal Ministry of Health for providing ribavirin and the Plateau State ministries of health for covering the costs of LF diagnostic tests. We acknowledge all the pharmacists and nursing staff who worked tirelessly to ensure ribavirin was available and promptly administered to the patients and their contacts. Finally, we would like to thank Professor Edmund Banwat, Daniel Egah, Chikaike Ogbonna and Dr. Karshima Jonathan for the administrative and technical support they provided.

Financial support and sponsorship

The ribavirin caplets were provided by the Federal Ministry of Health, Abuja, Nigeria.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Lecompte E, Fichet-Calvet E, Daffis S, Koulemou K, Sylla O, Kourouma F, *et al.* *Mastomys natalensis* and Lassa fever, West Africa. *Emerg Infect Dis* 2006;12:1971-4.
- Fisher-Hoch SP, Tomori O, Nasidi A, Perez-Oroz G, Fakile Y, Hutwagner L, *et al.* Review of cases of nosocomial Lassa fever in Nigeria: The high price of poor medical practice. *BMJ* 1995;311:857-9.
- McCormick JB, Webb PA, Krebs JW, Johnson KM, Smith ES. A prospective study of the epidemiology and ecology of Lassa fever. *J Infect Dis* 1987;155:437-44.
- Tomori O, Fabiyi A, Sorungbe A, Smith A, McCormick JB. Viral hemorrhagic fever antibodies in Nigerian populations. *Am J Trop Med Hyg* 1988;38:407-10.
- Centers for Disease Control and Prevention (CDC). Imported Lassa fever – New Jersey, 2004. *MMWR Morb Mortal Wkly Rep* 2004;53:894-7.
- World Health Organization. Lassa Fever – Sweden. *Emergencies Preparedness, Response*; 2016. Available from: <http://www.who.int/csr/don/8-april-2016-lassa-fever-sweden/en/>. [Downloaded on 2016 Apr 08].
- Peters CJ. Lymphocytic choriomeningitis virus, Lassa virus and the South American haemorrhagic fevers. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. United States: Elsevier; 2010. p. 2295-301.
- World Health Organization. Lassa Fever. Fact Sheet. Available from: <http://www.who.int/mediacentre/factsheets/fs179/en/>. [Downloaded on 2016 Apr 12].
- Carey DE, Kemp GE, White HA, Pinneo L, Addy RF, Fom AL, *et al.* Lassa fever. Epidemiological aspects of the 1970 epidemic, Jos, Nigeria. *Trans R Soc Trop Med Hyg* 1972;66:402-8.
- Adewuyi GM, Fowotade A, Adewuyi BT. Lassa fever: Another infectious menace. *Afr J Clin Exp Microbiol* 2009;10:144-55.
- Jahrling PB, Frame JD, Smith SB, Monson MH. Endemic Lassa fever in Liberia. III. Characterization of Lassa virus isolates. *Trans R Soc Trop Med Hyg* 1985;79:374-9.
- McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, *et al.* Lassa fever. Effective therapy with ribavirin. *N Engl J Med* 1986;314:20-6.

13. Bausch DG, Hadi CM, Khan SH, Lertora JJ. Review of the literature and proposed guidelines for the use of oral ribavirin as postexposure prophylaxis for Lassa fever. *Clin Infect Dis* 2010;51:1435-41.
14. Austin RK, Trefts PE, Hintz M, Connor JD, Kagnoff MF. Sensitive radioimmunoassay for the broad-spectrum antiviral agent ribavirin. *Antimicrob Agents Chemother* 1983;24:696-701.
15. Paroni R, Del Puppo M, Borghi C, Sirtori CR, Galli Kienle M. Pharmacokinetics of ribavirin and urinary excretion of the major metabolite 1,2,4-triazole-3-carboxamide in normal volunteers. *Int J Clin Pharmacol Ther Toxicol* 1989;27:302-7.
16. Haas WH, Breuer T, Pfaff G, Schmitz H, Köhler P, Asper M, *et al.* Imported Lassa fever in Germany: Surveillance and management of contact persons. *Clin Infect Dis* 2003;36:1254-8.
17. Iroezindu MO, Unigwe US, Okwara CC, Ozoh GA, Ndu AC, Ohanu ME, *et al.* Lessons learnt from the management of a case of Lassa fever and follow-up of nosocomial primary contacts in Nigeria during Ebola virus disease outbreak in West Africa. *Trop Med Int Health* 2015;20:1424-30.
18. Achinge IA, Malu OA, Ejeh AB, Mbaave TP, Utoo MP, Bako AI, *et al.* Lassa fever in a physician and his children: A case report. *Highland Med Res J* 2013;13:56-8.
19. Frame JD, Verbrugge GP, Gill RG, Pinneo L. The use of Lassa fever convalescent plasma in Nigeria. *Trans R Soc Trop Med Hyg* 1984;78:319-24.
20. Jahrling PB, Frame JD, Rhoderick JB, Monson MH. Endemic Lassa fever in Liberia. IV. Selection of optimally effective plasma for treatment by passive immunization. *Trans R Soc Trop Med Hyg* 1985;79:380-4.