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Observational Cohort Study of Lassa Fever Clinical Course and Prognostic Factors in An Epidemic Context in Nigeria (2018 - Ongoing) - LASCOPE -

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Background – Lassa fever (LF) is one of the WHO priority diseases: its mortality remains high; the efficacy of the recommended treatment, ribavirin, is weakly-evidenced (1); supportive care must be improved. Since available data on LF are often ancient or retrospective (2), we need to gather reliable baseline knowledge to help harmonizing case management guidelines and to inform the design of future therapeutic clinical trials. Hence, we set up a prospective cohort study aiming at: i) depicting the factors associated to a fatal outcome in LF patients, with a focus on pregnancies and acute kidney injury (AKI), ii) building capacities needed for clinical trials.

Figure 1: Infection Control Centre building at Owo FMC (A), Lassa team healthworkers wearing PPEs (B).

Methods – Patients of all ages hospitalized in tertiary facilities in Nigeria for suspected or already confirmed LF are eligible. Lassa suspects with subsequent negative RT-PCR serve as controls. After informed consent, data concerning habits, exposure, disease history and presentation, management and outcomes are collected prospectively starting from admission and during 60 days afterwards. Remnant sera can be stored for further analysis. Patients have access to optimized standard of care (including ribavirin, oxygen and dialysis), routine biology and Lassa RT-PCR. As a cohort, there is no pre-specified sample size. The preliminary results presented here are limited to description of the cohort and exploratory univariate analysis of prognostic factors using Fisher exact test due to the small sample size available. Ethical approval: NHREC/01/01/2007-24/05/2018, Owo FMC ethics committee. Funding: Inserm/REACTing, ALERRT network, University of Oxford. Registration: NCT03655561.

Preliminary results - From April 5th to December 12th 2018, 82 participants were enrolled at Owo FMC, the pilot site. Among the 40 participants with RT-PCR confirmed LF (LF+), 29 had terminated their hospital stay at the time of analysis, of whom 2 died (6.9% in-hospital case fatality rate), 3 were dialyzed (10.3%, of whom 1 died), 5 received oxygen therapy (17.3%) and 4 received total blood transfusion (13.8%). One 6 weeks-old newborn was found to be LF+ and finally survived, as well as his infected mother and grandmother. No woman was pregnant at the time of inclusion. Median values for the duration of hospital stay, delay between symptoms onset and admission and delay between admission and ribavirin start were 14 days (IQR 11-18), 6 days (IQR 4.75-9) and 3 days (IQR 2-4) respectively. Only 33% of LF+ patients received the first dose of ribavirin within 7 days from symptoms onset. Four patients received ribavirin prior to their admission in the Lassa ward. Signs and symptoms present at admission and during hospital stay are summarized in **Table 1**. In univariate analysis, having a pulse oxygen saturation < 92% (p=0.04) or an impaired level of consciousness (C, V, P or U according to ACVPU classification*; p=0.007) at anytime during hospital stay was associated to a fatal outcome.

*ACVPU classification: alert (A), confusion (C), reaction to voice (V), reaction to pain (P), unconscious (U).
**Fisher exact test

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Table 1: signs and symptoms at admission and during hospital stay among participants to the LASCOPE prospective cohort study with RT-PCR confirmed LF, Owo, Ondo State, Nigeria, April to December 2018.

Signs and symptoms	Admission n/N (%)	Hospital stay n/N (%)
Fever ≥ 38°	8/32 (25)	16/29 (55.2)
Heart rate > 100 bpm	4/32 (12.5)	18/29 (62.1)
SpO2 < 92%	2/28 (7,1)	6/27 (22,2)
SBP > 140 mmHg	4/30 (13.3)	13/28 (46.4)
DBP > 90 mmHg	1/30 (3,3)	12/28 (42.9)
SBP ≤ 90 mmHg	4/30 (13.3)	15/28 (53.6)
DBP ≤ 60 mmHg	7/30 (23.3)	24/29 (82.8)
Impaired consciousness (C,V,P or U)*	2/32 (6.3)	3/29 (10.3)
Headache	14/32 (43.8)	13/29 (44.8)
Vertigo/Dizziness	5/32 (15.6)	8/29 (27.6)
Retrosternal pain	2/31 (6.5)	3/27 (11.1)
Dyspnea	0/32 (0)	2/28 (7.1)
Abdominal pain	15/32 (46.9)	14/29 (48.3)
Nausea and/or vomitting	9/31 (29.0)	9/29 (31.0)
Watery diarrhea	8/32 (25.0)	6/29 (20.7)
Bloody diarrhea	1/32 (3.1)	2/29 (6.9)
Hematuria	5/30 (16.7)	7/29 (24.1)
Vaginal bleeding	3/15 (20.0)	3/15 (20.0)
Petechia	1/32 (3.1)	1/29 (3.4)
Hematemesis	0/31 (0)	1/28 (3.6)
Rectorragia	0/32 (0)	2/29 (6.9)

Regarding biological parameters, creatinine was available in 30 LF+ participants and was > 115 µmol/L at least once during follow-up in 14 (46.7%). 6 patients (20.0%) evolved to at least KDIGO stage 2 acute kidney dysfunction (injury) of whom 4 (13.3%) reached KDIGO stage 3 (failure). All stage 3 patients were dialyzed excepted one who died before he could be. Mortality was 50.0 % in stage 3 patients compared to 0 % in others (p=0.01). Transaminitis > 3 times ULN was found in 7 out of 30 patients (23,3%) and was also associated to a fatal outcome (p=0,05).

The main clinical and biological severe features and their association with in-hospital mortality are summarized in **Table 2**.

Table 2: severe clinical and biological features during hospital stay among participants to the LASCOPE prospective cohort study with RT-PCR confirmed LF, Owo, Ondo State, Nigeria, April to December 2018.

Clinical/Biological feature	n/N (%)	Deceased (%)	P**
SpO2 < 92 % anytime	6/27 (22.2)	2 (33.3)	**0.04**
Impaired consciousness (admission)	2/32 (6.3)	1 (50.0)	NS
Impaired consciousness (anytime)	3/29 (10.3)	2 (66.7)	**0.007**
Any neurological feature	20 (69.0)	2 (10.0)	NS
Bleeding	12/29 (41.4)	2 (16.7)	NS
KDIGO stage 3	4/30 (13.3)	2 (50.0)	**0.02**
Transaminases > 3 ULN	7/ (23.3)	2 (28.6)	**0.05**
Sodium < 130 mmol/L	4/31 (12.9)	1 (25.0)	NS
Potassium > 5 mmol/L	2/31 (6.5)	0 (0.0)	NS

The median duration of detectable viremia (delay between the first positive and the first negative Lassa RT-PCR in blood) in LF+ participants was 9 days (IQR 7-18.5, range 4-64).

Regarding capacity building, 2 doctors and 2 nurses have been trained to clinical research. A microbiologist and 4 lab scientists have been trained to working in a new BSL-3 lab offering standard biology capacities (hematology, biochemistry) for Lassa suspected and confirmed patients.

Figure 2: Clinical research training of Owo FMC team in PACCI, Abidjan (A), VHF laboratory team training in Owo (B and C).

Conclusions – Successful recruitment of LF+ patients and controls is ongoing in Owo. We propose to replicate this model in other reference hospitals throughout Nigeria to better reflect the diversity of symptomatic LF as well as to extend clinical research capacities building to other sites. At this point, in-hospital mortality in LF+ patients appears to be low compared to what has been previously reported in the same area, possibly due to the efforts made to improve the standard of care at Owo FMC. The pivotal role of AKI in Lassa disease severity in the Nigerian setting (2) seems to be confirmed by our preliminary results. The role of respiratory distress as well as hepatic involvement in the occurrence of a fatal outcome needs to be confirmed on a greater sample.

Keywords – Lassa fever, cohort studies, Nigeria, prognosis, staff development.

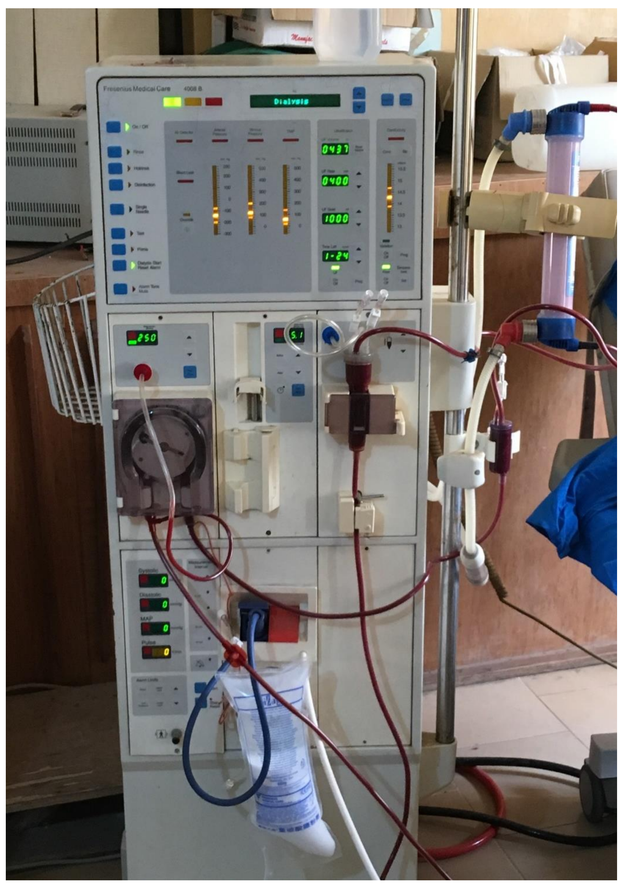

Figure 3: dialysis generator in the dialysis room dedicated to Lassa infected patients at Owo FMC (department of nephrology).

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