Journal of Tropical Pediatrics, 2020, 0, 1–12
doi: 10.1093/tropej/fmaa052
Original paper

Altered Mental Status Among Febrile Hospitalized HIV-Infected Children Aged 0–59 Months in Mozambique

Troy D. Moon , MD, MPH,[1,2] Fabião E. Maússe, BSc,[3] Tebeb Gebretsadik, MPH,[4] Darlenne B. Kenga, BSc,[3] Pedro Charles, MD,[5] Mustuafá Agy, MD,[6] Samuel Simbine, BSc,[3] *and* Jahit Sacarlal, MD, PhD[3]

[1]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37203, USA
[2]Vanderbilt Institute for Global Health, Vanderbilt University Medical Center, Nashville, TN 37203, USA
[3]Department of Microbiology, Faculty of Medicine, University Eduardo Mondlane, Maputo, Mozambique
[4]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN 37203, USA
[5]General Hospital Quelimane, Quelimane, Mozambique
[6]General Hospital José Macamo, Maputo, Mozambique
Correspondence: Troy D. Moon, MD, MPH. Department of Pediatrics, Division of Pediatric Infectious Diseases, Vanderbilt Institute for Global Health; 2525 West End Avenue, Suite 750, Nashville, TN 37203, USA. Tel: +615-343-8264. E-mail <troy.moon@vumc.org>.

ABSTRACT

Background: Altered mental status (AMS) is a priority presenting sign that must be assessed in HIV-infected, febrile children, yet diagnosis is difficult in areas with limited diagnostic capacity. Malaria and bacterial meningitis have been reported as the most common causes of AMS in febrile children presenting to the hospital in sub-Saharan Africa. However, in an HIV-infected child, central nervous system manifestations are diverse.

Methods: We conducted a clinical observational study of HIV-infected febrile children, aged 0–59 months, hospitalized in Mozambique and prospectively followed. Within this cohort, a nested study was designed to characterize children admitted with AMS and to assess factors associated with mortality. Univariate and multivariable analysis were performed comparing characteristics of the cohort by AMS status and evaluated demographic and clinical factors by in-hospital mortality outcome.

Results: In total, 727 children were enrolled between April 2016 and February 2019, 16% had AMS at admission. HIV-infected, febrile children, who presented with AMS and who had a diagnosis of bacteremia, had a 4-fold increased relative odds of in-hospital mortality, and children who presented with neurologic symptoms on admission had a roughly 8-fold higher odds of in-hospital mortality relative to children without presenting neurologic findings.

Conclusions: Mozambique has a pressing need to expand local diagnostic capacity. Our results highlight the critical need for clinicians to incorporate a broader differential into their potential causes of AMS, and to develop a Ministry of Health approved diagnostic and management algorithm, which is standardly used, to manage patients for whom reliable and relevant diagnostic services are not available.

KEYWORDS: pediatrics, altered mental status, febrile child, HIV, low-resource setting, Mozambique

INTRODUCTION

Febrile illness remains a major cause of morbidity and mortality in sub-Saharan Africa and a common presenting symptom in children under-5 years of age arriving to the hospital [1–3]. Management of these children is complicated in many low-resource settings due to limitations in diagnostic capacity and the non-specific presentation of a broad variety of symptoms [4]. Since 1990, the World Health Organization (WHO) and United Nations Children Fund have promoted use of the Integrated Management of Childhood Illness (IMCI) guidelines to improve management of these children [5, 6]. In malaria endemic areas, IMCI algorithms have promoted the presumptive treatment of malaria in febrile children, due to its high-associated morbidity and mortality. Despite availability of algorithms for differentiating other causes of fever, presumptive malaria treatment, without a specific diagnosis, frequently delays or inhibits a more thorough exploration of other causes of fever [7]. Furthermore, malaria is frequently over-diagnosed in resource poor environments, even when rapid diagnostic tests are present. Often, children with negative malaria tests will presumptively be treated as if they have malaria, with the clinician foregoing a more complete diagnostic work-up for alternative causes of the febrile illness [8] These challenges are further compounded in areas with high HIV prevalence, due to the large pool of potential opportunistic infections that can contribute to ones symptoms, as well as the severity of presenting symptoms [9]. Delay of both diagnosis and administration of appropriate antibiotic therapy in patients who are ultimately determined to have bacteremia and/or sepsis has been associated with increased hospital stays and increased mortality among pediatric populations [10, 11].

In sub-Saharan Africa, mortality is high for children admitted to hospital and frequently occurs within the first 24 h [12, 13]. Triaging of children at the point of admission is done to identify those who are sickest and in need of early intervention [14]. The WHO's pediatric Emergency Triage Assessment and Treatment (ETAT) guidelines break down the steps to assessing a severely ill child based on the ABCD steps: airway, breathing, circulation, coma, convulsions and dehydration [12, 15]. Altered mental status (AMS) is one of the priority presenting signs that must be assessed in these children, yet the root cause can be difficult to distinguish in areas with limited diagnostic capacity [16] Malaria and bacterial meningitis have been reported as common causes of AMS in febrile children presenting to the hospital in sub-Saharan Africa [16, 17]. However, in an HIV-infected child, central nervous system (CNS) manifestations are diverse and can include (i) HIV encephalopathy; (ii) opportunistic infections such as cytomegalovirus, tuberculosis (TB), toxoplasmosis or cryptococcal meningitis; (iii) primary CNS lymphoma; and (iv) immune reconstitution inflammatory syndrome amongst others [18].

Mozambique is a country of ∼29 million people as of 2017 and has one of the highest HIV prevalence rates in the region (13.2% in 2015) [19, 20]. The number of persons on antiretroviral therapy (ART) in recent years has increased nearly 4-fold, from 309,000 in 2012 to 1.2 million in 2017 [21]. Mozambique is further classified as one of the 30 high TB burden countries. It is estimated that nearly 60% of TB patients are co-infected with HIV [22, 23]. Malnutrition remains a significant problem, with stunting prevalence one of the highest in Africa, roughly 44% in 2015 [24]. Malaria accounted for ∼30% of all deaths in 2017, predominantly occurring in children under 5 years of age [25, 26].

To date, there has been no published data in Mozambique describing the characteristics of HIV-infected children admitted to the hospital with fever and AMS. The aim of this study is to describe the clinical characteristics of HIV-infected febrile children with AMS admitted to hospitals in a predominantly urban area (Maputo) and rural area (Quelimane City) of Mozambique, and to evaluate potential predictors of mortality in this population.

MATERIALS AND METHODS

Study design and population

We conducted a clinical observational study of HIV-infected children, aged 0–59 months, hospitalized in

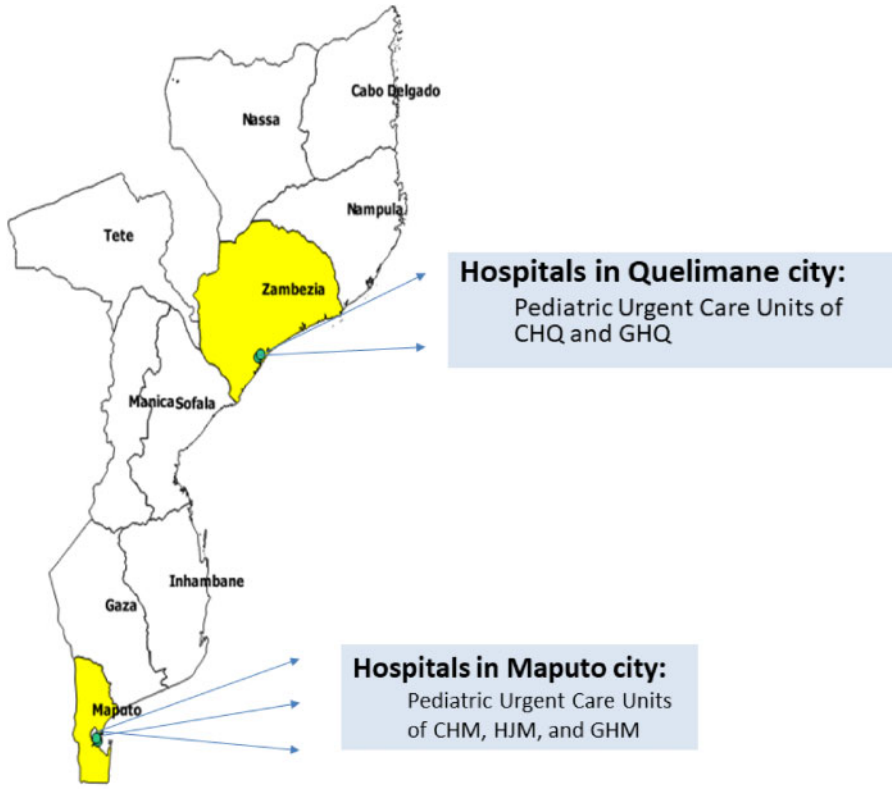

Fig. 1. Map of Mozambique with study hospitals identified for Maputo and Quelimane. *CHQ, Central Hospital Quelimane; GHQ, General Hospital Quelimane; CHM, Central Hospital Maputo; HJM, Hospital José Macamo; GHM, General Hospital Mavalane.

the cities of Maputo and Quelimane, Mozambique, with fever or history of fever, that were prospectively followed during their hospital stay. Within this observational cohort, a nested study was designed to characterize HIV-infected children admitted with AMS and to assess the factors associated with mortality in this age group.

The broader, 'parent' study, was designed to determine the incidence, etiology, antibiotic sensitivity patterns and molecular characterizations of culture confirmed bacteremia in representative rural and urban hospitals in Mozambique. All HIV-infected children aged 0–59 months with a documented axillary temperature of $\geq$37.5°C or rectal temperature $\geq$38.0°C, or history of fever within the 24 h prior to hospitalization between 1 April 2016 and 28 February 2019 were enrolled. Patients were recruited from the pediatric urgent care clinics of three hospitals in Maputo: Central Hospital Maputo, Hospital José Macamo and General Hospital Mavalane; and two hospitals in Quelimane: Central Hospital Quelimane and General Hospital Quelimane. All are tertiary referral hospitals supported by the National Health System (Fig. 1).

Definitions

Children were defined as having AMS if their admitting clinician defined their 'general state' as one of the following responses at admission: (i) somnolent, (ii) unconscious, (iii) agitated or (iv) irritable. Irritable was further characterized as those children who refused to be consoled by their mother or caregiver.

A child was considered HIV-positive if they had documented proof of HIV infection by polymerase chain reaction (PCR) or HIV rapid antibody tests (if $\geq$ 9 months at time of test), or if they were taking ART in the absence of documented HIV test results.

Children admitted with fever, or history of fever, and no documented history of HIV, but with documented maternal HIV exposure by self-report, were offered a PCR (if <9 months old) or an HIV rapid antibody test (if ≥9 months old). A child admitted with fever, or history of fever, and no documented history of HIV and no documented maternal HIV exposure by self-report, though with high clinical suspicion of HIV, were enrolled and offered HIV testing. Those with negative test results were excluded from this analysis.

For all eligible patients, diagnostic testing was performed if there was clinical suspicion based on history or signs/symptoms. Readily available tests included: complete blood count, blood chemistries, dipstick urinalysis, lumbar puncture for chemistries and bacterial culture, stool culture, stool ova and parasites, HIV rapid antibody testing or HIV DNA-PCR and malaria antigen rapid testing. Not all children for whom a lumbar puncture would have been indicated received the procedure. A diagnosis of meningitis could be given based on lumbar puncture results or on clinical suspicion. There was no available laboratory diagnostics for TB in this age group. Although chest X-ray was available, neuroimaging of these children was not.

Anemia was classified as severe, moderate, mild, or no anemia. Severe anemia was defined as a hemoglobin (Hb) concentration of <7 g/dl, moderate anemia as a Hb of 7–9.9 g/dl, mild anemia as a Hb of 10–10.9 g/dl and no anemia if Hb was >11 g/dl. Although weight was collected on nearly all children enrolled in this study, height was inconsistently documented in the medical record. As such, children were counted as being malnourished based on clinician reporting at admission or discharge.

All patients were followed until discharge from the hospital. Possible final disposition included discharged; died during hospitalization; or abandoned treatment, meaning they left the hospital against the wishes of the treating clinician.

Laboratory procedures

In children ≤9 months of age, HIV infection was defined as a HIV-1 DNA-positive result, detected using the Amplicor HIV-1 DNA-PCR kit (Roche Diagnostics, USA) and in older children defined as two positive rapid tests, using the Determine HIV-1/2 Rapid Test (Abbott Laboratories, USA) and the Uni-Gold Rapid Test (Trinity Biotech Co., Ireland). Blood counts including Hb were measured by a Sysmex KX21N^{TM} automated hematology analyzer (Sysmex Long Grove, IL, USA). Blood culture was measured with a single venous blood specimen collected prior to the initiation of antibiotics (Pedibact: Becton-Dickenson, Franklin Lakes, NJ, USA) and incubated within an automatic BACTEC 9050 system (Becton-Dickinson) for 5 days. Malaria was diagnosed through a blood specimen collected in a heparinized capillary tube and tested using the SD Bioline Malaria Antigen test (Standard Diagnostics, Yongin, Republic of Korea). If positive, thick and thin blood films were prepared for confirmation and to quantify *Plasmodium falciparum* parasitemia.

Data collection

Data were collected by study clinicians utilizing a paper-based study instrument and then uploaded into a password protected, tablet-based, on-line database maintained by the Research Electronic Data Capture (REDCap) consortium (www.project-redcap.org). This allowed for the recording of demographic information, medical and medication history, as well as information on clinical course while hospitalized. Data quality control was conducted by study investigators who reviewed all completed paper-based study instruments and confirmed the accuracy of data entered into the electronic database.

Statistical analysis

Descriptive statistics were used to summarize the participants' sociodemographic characteristics using frequencies and proportions (for dichotomous or categorical variables) or medians with interquartile ranges (IQRs) for continuous variables. The analyses were performed in two phases. First, we compared characteristics of the study cohort by AMS status using the χ^2 test. Second, among children with AMS, we compared demographic and clinical factors by in-hospital mortality status. Due to the small number of mortality events ($n = 21$), we a priori specified age, sex, temperature, hemoglobulin, bacteremia and presence of any neurological symptoms (nuchal rigidity, opisthotonos, lack of or abnormal crying or

no response to pain) to explore their association with in-hospital mortality using multivariable logistic regression. We calculated odds ratios and their corresponding 95% CIs, and a forest plot was constructed to examine their adjusted association with in-hospital mortality.

Statistical hypotheses were conducted using two-sided tests, 5% significance levels. Statistical analysis was performed using R version 3.6.3 software (R Core Team, 2015, http://www.r-project.org).

Ethical considerations

The Mozambican National Bioethics Committee for Health (*Comité Nacional de Bioética para Saúde, CNBS*) (404/CNBS/14) and the Institutional Review Board of Vanderbilt University Medical Center (IRB#141167) approved this analysis. Informed consent was obtained from the parent or legal guardian of all children enrolled in this study.

RESULTS

Data from 727 HIV-infected children were used for this analysis. In total, 46% were <12 months of age, 57% were male and 16% were classified as having AMS upon admission. Of those with AMS, 62% came from hospitals in Quelimane, while in contrast, participants from Quelimane represent approximately 46% of those children classified as not having AMS ($p < 0.001$). The most common diagnoses for these HIV-infected, febrile children were acute respiratory infection (ARI; 50%), malnutrition (41%), gastroenteritis/diarrhea (24%), non-cerebral malaria (14%) and bacteremia (10%). Overall, 93% of patients received antibiotic therapy for presumptive bacterial causes of their febrile illness during their hospitalization, with ampicillin + gentamicin being prescribed in slightly >50% of children. Documentation of malaria testing was missing in 90 children; however, of the 637 children with documentation, 77% did receive a malaria test. Twenty-one patients with AMS (18%) vs. 33 patients without AMS (5%) died during their hospitalization (<0.001; Table 1).

Of those HIV-infected children with AMS, 42% had a documented fever of ≥38.5°C. Approximately 77% had fever for <7 days at time of admission [median days 4 (QR : 3,6)]. Ninety-nine percent of children with fever and AMS received antibiotic therapy during their hospitalization. Roughly 57% of patients with AMS showed other neurologic symptoms such as nuchal rigidity, opisthotonos, lack of or abnormal crying or no response to pain. Approximately 33% reportedly they had stopped sucking or drinking and 53% reportedly had difficulty breathing with either dyspnea or retractions on physical exam. Finally, 69% of children with AMS were also anemic, with a median Hb level of 9.5 g/dl [IQR 8.0–11.3] (Table 2).

Table 3 compares demographic and clinical factors for HIV-infected children with AMS by in-hospital mortality using univariable analysis. No statistically significant difference was found by gender, age, duration of fever prior to admission, or median Hb level. However, of patients with AMS who died while hospitalized, 86% were reported as having other neurologic symptoms at admission such as nuchal rigidity, opisthotonos, lack of crying/abnormal cry or no response to pain/poor localization to pain. Due to the small sample size of patients who died with 'other neurologic symptoms' ($n = 18$), we are unable to disaggregate this further to look at each symptom separately.

In multivariable analysis, HIV-infected, febrile children, who presented with AMS and who had a diagnosis of bacteremia, had a roughly 4-fold increased relative odds of in-hospital mortality, and children who presented with neurologic symptoms on admission had a roughly 8-fold higher odds of in-hospital mortality relative to HIV-infected febrile children without presenting neurologic findings (Fig. 2).

DISCUSSION

In this prospective observational study of febrile HIV-infected children admitted to hospitals in either Maputo or Quelimane, Mozambique, we found 16% of our enrolled patients presented with characteristics classified by the admitting clinician as AMS. Furthermore, we found an overall in-hospital mortality of 7%. For those HIV-infected, febrile children with AMS, in-hospital mortality were 18%. The most common diagnoses for our population overall were ARI (50%), malnutrition (41%), gastroenteritis/diarrhea (24%), non-cerebral malaria (14%) and

Table 1. Characteristics of HIV-infected children aged 0–59 months, hospitalized in Mozambique with fever or history of fever, and AMS

Characteristics ($n = 727$)	AMS ($n = 118$)	No AMS ($n = 609$)	p-value[a]
Age			0.990
0–5 months	24 (20%)	116 (19%)	
6–12 months	31 (26%)	163 (27%)	
13–24 months	37 (31%)	191 (31%)	
25–59 months	26 (22%)	139 (23%)	
Sex			0.069
Male	58 (49%)	354 (58%)	
Female	60 (51%)	254 (42%)	
Missing	–	1 (<1%)	
Hospital			<0.001
General Hospital (Quelimane)	4 (3%)	186 (31%)	
Central Hospital (Quelimane)	69 (58%)	124 (20%)	
General Hospital Mavalane (Maputo)	15 (13%)	161 (26%)	
Hospital José Macamo (Maputo)	23 (19%)	130 (21%)	
Central Hospital (Maputo)	7 (6%)	8 (1%)	
Hospital diagnosis[b]			
ARI	59 (50%)	304 (50%)	0.990
Malnutrition	50 (42%)	249 (41%)	0.760
Gastroenteritis/diarrhea	33 (28%)	141 (23%)	0.260
Malaria (non-cerebral)	10 (8%)	94 (15%)	0.048
Cerebral malaria	5 (4%)	4 (1%)	0.001
Bacteremia	18 (15%)	57 (9%)	0.054
Bacterial meningitis	2 (2%)	–	
Tuberculosis (non-meningitis)	6 (5%)	42 (7%)	0.470
Tuberculosis meningitis	–	1 (0%)	
HIV encephalopathy	4 (3%)	–	
Meningoencephalitis	2 (2%)	–	
Hydrocephalus	2 (2%)	–	
Seizures (reason unknown)	2 (2%)	13 (2%)	0.760
Intoxication from a petroleum product	1 (0%)	–	
Intoxication for other traditional medicine	1 (0%)	–	
Cryptococcal meningitis	1 (0%)	–	
Psychomotor Developmental Delay	–	10 (2%)	0.160
Other	36 (31%)	130 (21%)	0.030
Hospital stay			0.620
<7 days	42 (36%)	238 (39%)	
≥7 days	67 (57%)	341 (56%)	
Missing	9 (7%)	30 (5%)	
Tested for malaria ($n = 637$)	91 (82%)	400 (76%)	0.180
Received antibiotics during hospitalization	117 (99%)	557 (91%)	0.003
Death during hospitalization	21 (18%)	33 (5%)	<0.001
Blantyre Coma Score ($n = 502$)	$n = 59$	$n = 443$	<0.001

(continued)

Table 1. (continued)

Characteristics ($n = 727$)	AMS ($n = 118$)	No AMS ($n = 609$)	p-value[a]
0	–	–	
1	1 (2%)	–	
2	3 (5%)	–	
3	11 (19%)	2 (<1%)	
4	16 (27%)	3 (<1%)	
5	28 (47%)	438 (99%)	

[a]A p-value from χ^2 test and included data were present in both groups.
[b]Diagnoses are not mutually exclusive. Values may add up to >100%.

bacteremia (10%). Our results were consistent with findings reported for children admitted to the pediatric intensive care unit at the Central Hospital Maputo (one of our hospital sites) in 2013. They found an overall mortality of 25% and an increased mortality amongst children with sepsis (59%), encephalopathy (56%), non-infectious CNS pathologies (33%) and meningitis/encephalitis (29%) [27]. Beyond, the most common diagnoses described, our patient population did have other diagnoses that could be consistent with causing AMS, including TB meningitis, HIV encephalopathy, meningoencephalitis, cryptococcal meningitis and/or intoxications with either traditional medicines or petroleum products. Most of these diagnoses were reported in very small numbers thus not amenable to carry out proper analysis and draw valid conclusions. Moreover, the vast majority were based on clinician suspicion, without any accompanying confirmatory testing to make a definitive diagnosis.

Infections of the CNS should be high on the differential diagnosis list for any child who presents to a hospital with fever and AMS [28]. Malaria and bacterial meningitis have been reported as the most common causes of AMS in children in sub-Saharan Africa and bacterial meningitis can frequently be caused by hematogenous spread of a bacterial infection elsewhere [16, 17, 28]. The association of AMS and increased risk of mortality has been well described for pediatric hospitalized patients in sub-Saharan Africa, with or without a concurrent bacterial infection/sepsis [16, 29, 30]. This underscores the need for increased recognition of the signs and symptoms of AMS or other neurologic symptoms at the time of admission and then rapid and accurate interventions in order to alleviate the high burden of mortality or other sequalae in these children. In our patients, we were able to do blood culture and malaria testing at the point of triage. However, while malaria rapid diagnostic tests and blood smears are routinely done in Mozambique, microbiologic capacity for blood cultures is fairly limited and most frequently only available as part of a research study protocol [27, 31]. Furthermore, in certain febrile children presenting with AMS, a lumbar puncture for analysis and culture as well as a blood glucose level are indicated to help differentiate some common causes for the AMS. Both tests are theoretically available in Mozambique yet were rarely done in our study population. Unfortunately, it is not possible to determine the reason these tests were not done, though we can speculate based off of experience, that it is most likely due to either a lack of needed supplies, clinician frustration due to slow turn-around times for results from the laboratory, or that the clinician may not have considered it. While we cannot determine, based on the laboratory data available, the true extent of bacterial meningitis as a potential cause of AMS in our cohort of children, we are able to report that 15% of our cohort with AMS had bacteremia, and thus can infer that bacterial meningitis very likely played a significant role.

Our findings further reinforce the difficulty experienced by clinicians in Mozambique in diagnosing and treating febrile children in the absence of a broader array of confirmatory laboratory diagnostics.

Table 2. Clinical characteristics of HIV-infected children aged 0–59 months, hospitalized in Mozambique with fever or history of fever, with AMS

Clinical characteristics ($n = 118$)	*n* (%)
Temperature °C on admission	
<38.5	69 (58%)
≥38.5	49 (42%)
Temperature °C [median, IQR]	38.0 [38,39]
Fever duration at admission ($n = 107$)	
<7 days	82 (77%)
≥7 days	25 (23%)
Fever duration in days at admission [median, IQR]	4[3,6]
Received antibiotics during hospitalization	117 (99%)
General mental state	
Awake	–
Somnolent	46 (39%)
Unconscious	17 (14%)
Agitated	33 (28%)
Irritable	22 (18%)
History of convulsions on admission (with this episode of fever)	
Yes	25 (21%)
No	93 (79%)
Other neurologic symptoms[a] ($n = 114$)	
Yes	65 (57%)
No	49 (43%)
Stopped sucking or drinking ($n = 111$)	
Yes	37 (33%)
No	74 (67%)
Dyspnea or retractions	
Yes	63 (53%)
No	54 (46%)
Anemia status ($n = 113$)	
Non-anemic (Hb >11 g/dl)	35 (31%)
Mild anemia (Hb 10–10.9 g/dl)	15 (13%)
Moderate anemia (Hb 7–9.9 g/dl)	45 (40%)
Severe anemia (Hb <7 g/dl)	18 (16%)
Hb (g/dl) [median, IQR] ($n = 113$)	9.5 [8.0–11.3]

[a]Includes nuchal rigidity, opisthotonos, lack of crying/abnormal cry, or no response to pain/poor localization to pain.

Currently, there is no specific algorithm or protocol for AMS in children that Mozambican clinicians use to guide their management of these patients, but rather, each clinician or in some cases each facility adapts existing international protocols for their context, creating informal norms for themselves and their institutions. Even with strict adherence to guidelines such as WHO ETAT or IMCI, misdiagnosis is common [17, 32]. The consequence of this misdiagnosis early on in the treatment plan, is the

Table 3. Factors associated with mortality in HIV-infected children under-5 years old, hospitalized in Mozambique, with AMS (univariate analysis)

$n = 118$	No death ($n = 97$)	In-hospital death ($n = 21$)	p-value[a]
Sex			0.11
Male	51 (53%)	7 (33%)	
Female	46 (47%)	14 (67%)	
Age			0.092
0–5 months	20 (21%)	4 (19%)	
6–12 months	30 (31%)	2 (10%)	
13–24 months	25 (26%)	11 (52%)	
25–59 months	22 (23%)	4 (19%)	
Age in months [median, IQR]	12 [6, 23]	20 [10, 23]	0.323
Hospital location			0.018
General Hospital (Quelimane)	4 (4%)	0 (0%)	
Central Hospital (Quelimane)	57 (59%)	12 (57%)	
General Hospital Mavalane (Maputo)	11 (11%)	4 (19%)	
Hospital José Macamo (Maputo)	22 (23%)	1 (5%)	
Central Hospital (Maputo)	3 (3%)	4 (19%)	
Fever duration at admission (n=107)			0.640
<7 days	69 (76%)	13 (81%)	
≥7 days	22 (24%)	3 (19%)	
Fever duration in days [median, IQR] ($n = 107$)	4.0 [3.0, 6.0]	4.0 [3.0, 6.0]	0.854
Hb (g/dl) [median, IQR] ($n = 113$)	9.7 [8.0–11.5]	8.8 [7.7–10.2]	0.240
Bacteremia			0.061
No	85 (88%)	15 (71%)	
Yes	12 (12%)	6 (29%)	
Malaria			0.430
No	87 (90%)	20 (95%)	
Yes	10 (10%)	1 (5%)	
ARI			0.810
No	49 (51%)	10 (48%)	
Yes	48 (49%)	11 (52%)	
Malnutrition			0.590
No	57 (59%)	11 (52%)	
Yes	40 (41%)	10 (48%)	
Gastroenteritis/diarrhea			0.950
No	70 (72%)	15 (71%)	
Yes	27 (28%)	6 (29%)	
Convulsions on admission			0.750
Yes	20 (21%)	16 (76%)	
No	77 (79%)	5 (24%)	
Other neurologic symptoms[a] ($n = 114$)			0.003
Yes	47 (51%)	18 (86%)	
No	46 (49%)	3 (14%)	

[a]A p-value from χ^2 test.
[b]Includes nuchal rigidity, opisthotonos, lack of crying/abnormal cry or no response to pain/poor localization to pain.

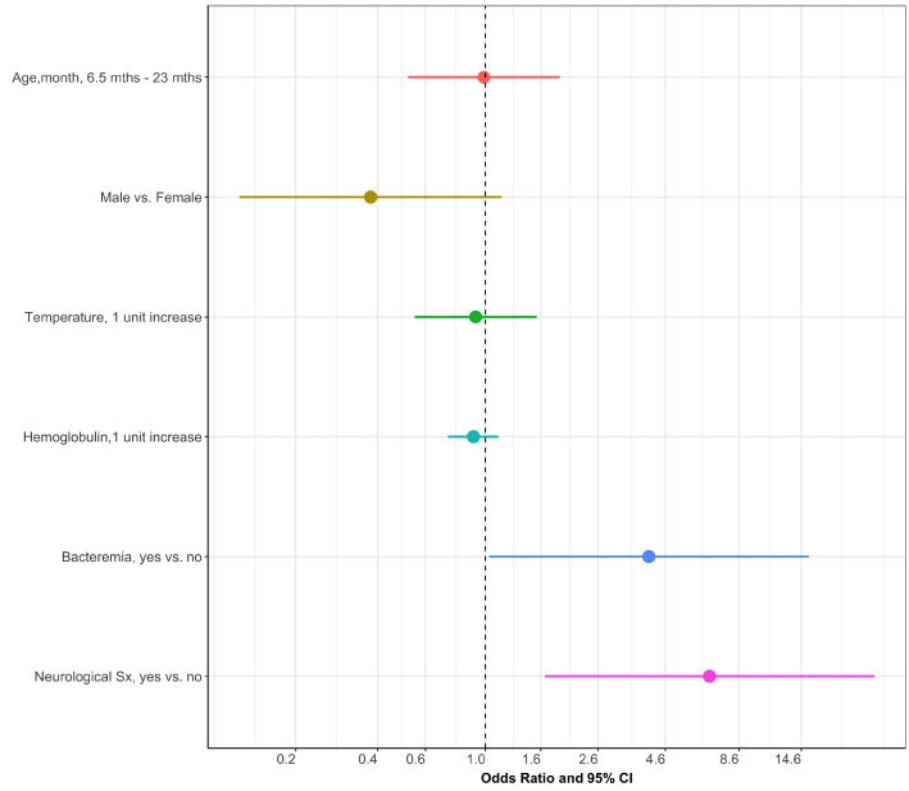

Fig. 2. Forest plot of odds ratios and 95% CIs to explore the relationship of demographic and clinical factors with in-hospital mortality among HIV-infected febrile children aged 0–59 months with altered mental state. *Includes nuchal rigidity, opisthotonos, lack of crying/abnormal cry or no response to pain/poor localization to pain. **An exploratory multivariable logistic regression was performed including only a limited number of demographic and clinical factors as we had only $n = 21$ events (in-hospital mortality).

resultant delay in investigating and treating other life-threatening causes of illness. Ideally, Mozambique would rapidly increase its laboratory capacity for confirmatory diagnostics of many of the opportunistic and other infections common to a febrile HIV-infected child. However, in the immediate absence of this, we highlight the need for clinicians to recognize AMS as a 'red flag' condition when evaluating children at the hospital. Signs of AMS or other neurologic sequelae, especially in children under 2-years of age, should prompt clinicians to conduct a more extensive investigation as to the potential underlying causes of the child's symptoms.

This study has several limitations. First, our study was not specifically designed and powered to identify the clinical characteristics of children with AMS and their in-hospitalization outcomes, as the study's primary objective was to determine the incidence, etiology and other characteristics of blood stream infections in febrile hospitalized children. The definitions and diagnostic testing utilized for determining one's HIV status are based on Mozambican national protocols however, it must be recognized that some children older than 9 months of age with a positive HIV rapid test could represent an HIV-exposed uninfected child with continued presence of maternal HIV antibodies causing the test to be falsely positive. Nonetheless, we feel the likelihood of this to be very low, if any. Our study may have a selection bias as it was performed among hospitalized, febrile, HIV-infected children and our findings likely represent the severe end of the spectrum when it comes to AMS and the high proportion of concomitant morbidity and mortality. Due to the fact that our primary

study objective was not designed to specifically study the underlying factors that are known to be the cause of AMS, our data collection tools did not fully capture events such as hypoxia, hypoglycemia and/or shock, to subsequently correlate these conditions with presentation of children with AMS. Furthermore, we were only able to explore a limited number of potential risk factors of mortality in this population and as an observational study there may be unmeasured confounders that could affect estimates. Overall, our cohort of patients with AMS saw a relatively small number of mortality events ($n = 21$), as such our multiple logistic regression analysis was exploratory and done to generate discussion and hypotheses in order to get a sense of where we should focus future research questions. Finally, our findings cannot be generalized to the general population of children aged 0–59 months in Mozambique and our regional focus on Zambézia and Maputo Provinces may limit generalizability to other regions of Mozambique. Larger sample sizes and a wider catchment area of study cohorts are required to provide a more in-depth understanding of factors associated with mortality and in HIV-infected, febrile children presenting with AMS.

CONCLUSION

Mozambique, like other sub-Saharan African countries, has a pressing need to expand local diagnostic capacity, especially microbiology and blood culture capacity, as well as radiologic capacity. The causes of AMS in HIV-infected febrile children who present to the hospital are diverse and yet to be fully determined. Larger studies need to be replicated with a more comprehensive list of predictors considered. Our results highlight the critical need for clinicians to incorporate a broader differential into their potential causes of AMS, and to develop a Ministry of Health approved diagnostic and management algorithm, which is standardly used, to manage patients for whom reliable and relevant diagnostic services are not available.

ACKNOWLEDGEMENTS

The authors are very grateful to the study subjects for their participation in this study. We would like to thank the laboratory staff of the Microbiology Department of the Faculty of Medicine at UEM as well as the MozBact study team at Central Hospital Maputo, Hospital José Macamo, General Hospital Mavalane, Central Hospital Quelimane, and General Hospital Quelimane.

FUNDING

This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health [grant number R01AI112295]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Herlihy JM, D'Acremont VH, Burgess DC. *et al.* Diagnosis and treatment of the febrile child. In: Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities, 3rd edn, Vol.2. Washington DC: The World Bank, 2016.
2. Reddy M, Bansal A. Febrile child. Indian J Pediatr 2017; 84:782–6.
3. Kiemde F, Tahita MC, Lompo P, *et al.* Treatable causes of fever among children under five years in a seasonal malaria transmission area in Burkina Faso. Infect Dis Poverty 2018;7:60.
4. Maze MJ, Bassat Q, Feasey NA, *et al.* The epidemiology of febrile illness in sub-Saharan Africa: implications for diagnosis and management. Clin Microbiol Infect 2018;24: 808–14.
5. Elfving K, Shakely D, Andersson M, *et al.* Acute uncomplicated febrile illness in children aged 2-59 months in Zanzibar – aetiologies, antibiotic treatment and outcome. PLoS One 2016;11:e0146054.
6. World Health Organization (WHO). Improving Child Health. IMCI: The Integrated Approach. https://apps.who.int/iris/bitstream/handle/10665/66085/WHO_CHD_97.12_Rev.2.pdf? sequence=1 (22 March 2020, date last accessed).
7. Johansson EW, Selling KE, Nsona H, *et al.* Integrated paediatric fever management and antibiotic overtreatment in Malawi health facilities: data mining a national facility census. Malar J 2016;15:12.
8. Smart LR, Orgenes N, Mazigo HD, *et al.* Malaria and HIV among pediatric inpatients in two Tanzanian referral hospitals: a prospective study. Acta Trop 2016;159:36–43.
9. Donald KA, Walker KG, Kilborn T, *et al.* HIV Encephalopathy: pediatric case series description and insights from the clinic coalface. AIDS Res Ther 2015;12:2.
10. Larsen GY, Mecham N, Greenberg R. An emergency department septic shock protocol and care guideline for children initiated at triage. Pediatrics 2011;127:e1585–92.
11. Weiss SL, Fitzgerald JC, Balamuth F, *et al.* Delayed antimicrobial therapy increases mortality and organ

dysfunction duration in pediatric sepsis. Crit Care Med 2014;42:2409–17.
12. World Health Organization (WHO) Guideline: Updates on Paediatric Emergency Triage, Assessment and Treatment: Care of Critically-Ill Children, 2016. https://www.ncbi.nlm.nih.gov/books/NBK350528/ (22 March 2020, date last accessed).
13. Enyuma CO, Anah MU, Pousson A, *et al.* Patterns of paediatric emergency admissions and predictors of prolonged hospital stay at the children emergency room, University of Calabar Teaching Hospital, Calabar, Nigeria. Afr H Sci 2019;19:1910–23.
14. Hansoti B, Jenson A, Keefe D, *et al.* Reliability and validity of pediatric triage tools evaluated in Low resource settings: a systematic review. BMC Pediatr 2017;17:37.
15. World Health Organization (WHO). Emergency Triage Assessment and Treatment (ETAT): Manual for Participants. https://www.who.int/maternal_child_adolescent/documents/9241546875/en/ (22 March 2020, date last accessed).
16. Jumanne S, Meda J, Hokororo A, *et al.* Clinical Predictors of malaria, acute bacterial meningitis and treatment outcomes among febrile children admitted with altered mental status in Northwestern Tanzania. J Trop Pediatr 2018;64:426–33.
17. El-Amin EOH, Elbashir MI, Elamin OE, *et al.* The underlying aetiologies of coma in febrile Sudanese children. Trans R Soc Trop Med Hyg 2013;107:307–12.
18. Donald KA, Hoare J, Eley B, *et al.* Neurologic complications of pediatric human immunodeficiency virus: implications for clinical practice and management challenges in the African setting. Semin Pediatr Neurol 2014;21:3–11.
19. National Institute of Statistics Mozambique. Preliminary Results IV RGPH 2017. http://www.ine.gov.mz/operacoes-estatisticas/censos/censo-2007/censo-2017/resultados-preliminares-iv-rgph-2017/view. (22 March 2020, date last accessed).
20. Mozambique: Survey on the Indicators for Immunizations, Malaria and HIV/AIDS (2015). https://dhsprogram.com/pubs/pdf/AIS12/AIS12.pdf (22 March 2020, date last accessed).
21. Ministry of Health of Mozambique - National Program for the Control of STI and HIV/AIDS. http://www.misau.gov.mz/index.php/its-hiv-sida. (22 March 2020, date last accessed).
22. García-Basteiro AL, Respeito D, Augusto OJ, *et al.* Poor tuberculosis treatment outcomes in Southern Mozambique 2011-2012. BMC Infect. Dis 2016;16:214.
23. Moon TD, Nacarapa E, Verdu ME, *et al.* Tuberculosis treatment outcomes among children in rural Southern Mozambique: a 12-year retrospective study. Pediatr Infect Dis J 2019;38:999–1004.
24. Rose ES, Blevins M, González-Calvo L, *et al.*; for the Ogumaniha-SCIP Zambézia Consortium. Determinants of undernutrition among children aged 6 to 59 months in rural Zambézia Province, Mozambique: results of two population-based serial cross-sectional surveys. BMC Nutr 2015;1:41.
25. Carlucci JG, Blevins Peratikos M, Kipp AM, *et al.*; the Ogumaniha-SCIP Zambézia Consortium. Prevalence and determinants of malaria among children in Zambézia Province, Mozambique. Malar J 2017;16:108.
26. Moon TD, Hayes CB, Blevins M, *et al.*; The Ogumaniha-SCIP Zambézia Consortium. Factors associated with the use of mosquito bed nets: results from two cross-sectional household surveys in Zambézia Province. Malar J 2016;15:196.
27. Punchak M, Hall K, Seni A, *et al.* Epidemiology of Disease and Mortality from a PICU in Mozambique. Pediatr Crit Care Med 2018;19:e603–10.
28. Orman G, Rossi A, Meoded A, *et al.* Children with acute neurological emergency. In: Diseases of the Brain, Head and Neck, Spine 2020–2023: Diagnostic Imaging. New York, NY: Springer, 2020.
29. Secka F, Herberg JA, Sarr I, *et al.* Bacteremia in childhood life-threatening infections in urban Gambia: EUCLIDS in West Africa. Open Forum Infect Dis 2019;6:ofz332.
30. Gwer S, Chacha C, Newton CR, *et al.* Childhood acute non-traumatic coma: aetiology and challenges in management in resource-poor countries of Africa and Asia. Paediatr Int Child Health 2013;33:129–38.
31. Moon TD, Silva WP, Buene M, *et al.* Bacteremia as a cause of fever in ambulatory, HIV-infected Mozambican adults: results and policy implications from a prospective observational study. PLoS One 2013;8:e83591.
32. Reyburn H, Mbatia R, Drakeley C, *et al.* Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ 2004;329:1212.