Sepsis in Sub-Saharan Africa: A Prospective Observational Study of Clinical Characteristics, Management, and Outcomes for Adolescents and Adults with Sepsis in Northern Tanzania

by

John P. Bonnewell

Duke Global Health Institute
Duke University

Date:

Approved:

_____
Matthew P. Rubach, Supervisor

_____
Joseph R. Egger

_____
John A. Crump

_____
Nathan M. Thielman

_____
Lawrence P. Park

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
in the Graduate School of Duke University

2020

ABSTRACT

Sepsis in Sub-Saharan Africa: A Prospective Observational Study of Clinical Characteristics, Management, and Outcomes for Adolescents and Adults with Sepsis in Northern Tanzania

by

John P. Bonnewell

Duke Global Health Institute
Duke University

Date:

Approved:

_____
Matthew P. Rubach, Supervisor

_____
Joseph R. Egger

_____
John A. Crump

_____
Nathan M. Thielman

_____
Lawrence P. Park

An abstract of a thesis submitted in partial
fulfillment of the requirements for the degree
of Master of Science in the Duke Global Health Institute
in the Graduate School of Duke University

2020

Abstract

Background: Sepsis is a leading cause of death and disability globally. Despite a high burden of sepsis in sub-Saharan Africa, clinical data for sepsis in that setting are limited. We sought to describe the clinical characteristics, management, and outcomes in a cohort of adults and adolescents with sepsis in northern Tanzania. We also assessed for associations between clinical factors and in-hospital mortality.

Methods: We carried out a prospective observational cohort study at Kilimanjaro Christian Medical Centre in Moshi, Tanzania. We collected data on demographics, baseline clinical characteristics, and management, with an emphasis on hours 0-6 after arrival to the Emergency Department. Log risk regression was carried out to assess for associations between demographic and clinical factors and our primary outcome of in-hospital death. Separate multivariable regression analyses were conducted for both antimicrobial administration by hour 6 and administration of intravenous (IV) fluids >1L by hour 6 and the outcome of in-hospital mortality.

Results: Fifty-eight participants were included in our analysis. Seventeen (29.3%) participants died in-hospital. Baseline characteristics associated with inpatient mortality included inability to drink unassisted, respiratory rate >30 breaths per minute, hypoxia, and altered mentation. Less than half of participants received any antimicrobial by hour 6, and most participants received <1L of IV fluids. HIV antibody testing was performed

for only one participant in the first 6 hours. On multivariable analysis, neither antimicrobial administration nor IV fluids >1L by hour 6 was associated with inpatient mortality.

Conclusion: Sepsis in northern Tanzania carries a high risk of in-hospital mortality. Further research is urgently needed to establish the highest-yield interventions suited to the unique characteristics of sepsis in sSA.

Dedication

This work is dedicated to my parents, Mark W. Bonnewell and Christina J. Bonnewell. Thank you for all your support throughout my life. This work would not be possible without your love and guidance.

Contents

List of Tables

List of Figures

Acknowledgements

I would like to acknowledge Dr. Matthew P. Rubach and Dr. John A. Crump for their mentorship and guidance both for this project and with my career. They each have been essential in the development of my research skills and career pathway within the past two years. I very much appreciate the collaborative efforts from the faculty at Kilimanjaro Christian Medical Centre, particularly Prof. Venance P. Maro, Dr. Francis Sakita, and Dr. Kajiru Kilonzo. It was an honor to work with the entire KCMC-Duke Collaboration, and I especially want to recognize the efforts of my research staff—clinical officers Jerome Mlangi and Christopher Swai and research assistant Erica Chuwa. I acknowledge Dr. Joseph R. Egger for his guidance in the statistical analysis for the study and for his support as a member of my thesis committee. I also want to acknowledge Dr. Nathan M. Thielman for his mentorship since the beginning of my journey at Duke and for his deep investment in his Global Health Pathway trainees. Further, I want to acknowledge all the support from the Duke Global Health Institute, the faculty and staff of which have contributed greatly to my study and career development along the way. I wish to thank the Fogarty International Center of the U.S. National Institutes of Health for their investment in this project and in me personally. I wish to acknowledge my Global Health Pathway colleagues and Fogarty co-fellows for their friendship and support. Finally, and most importantly, I want to thank all the

participants in the sepsis study for their contributions to science and the betterment of care for future patients in the hospital and the region.

1. Introduction

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, is a leading cause of death and disability globally.[1-3] Despite decades of marked declines in incidence and mortality, it is estimated that there were still nearly 50 million incident cases and 11 million deaths in 2017, accounting for nearly 20% of all global deaths.[3] The burden of sepsis is particularly high in low- and middle-income countries (LMICs), with the highest incidence in sub-Saharan Africa (sSA) and South and Southeast Asia.[3] The early identification and management of sepsis has received considerable focus in high-income settings for decades, but it has drawn limited attention elsewhere, including sSA. To date most research and subsequent guideline development, such as those proposed by the Surviving Sepsis Campaign,[4] have been derived from high-income countries (HICs), where critical care resources are replete and epidemiological patterns of infection differ from those of LMICs. Such research efforts have led to the development of highly effective sepsis bundles focused on certain core interventions, such as intravenous (IV) fluid resuscitation and early antimicrobial administration.[1, 4-9] In addition, a new sepsis definition was recently established from HIC data emphasizing the use of the Sequential Organ Failure Assessment (SOFA) score and a modified "quick SOFA" (qSOFA) score.[1] Unfortunately, this served to widen the gap between sepsis guidelines and reality in LMICs, as components of this new definition are frequently unavailable in such settings.

Despite an ongoing broad focus on control of infectious diseases in LMICs, epidemiological data on sepsis, the final common pathway for many infectious processes, are limited. Studies on the epidemiology and etiologies of severe febrile illness in sSA have demonstrated the differences in underlying infectious etiologies compared with HICs.[10, 11] These include the broad range of pathogens responsible for causing infections requiring hospitalization in sSA, including tropical diseases such as malaria, zoonoses such as leptospirosis, and complications of the higher prevalence of HIV in sSA, including disseminated cryptococcosis and tuberculosis. While descriptive observational work on sepsis has been conducted in several countries in sSA to date, as well as several single-center randomized trials on sepsis interventions, more data are needed.[12-15]

Published trials of sepsis-directed interventions in sSA presently total three. A pre- and post-intervention prospective cohort study from Uganda showed mortality benefit for patients with sepsis receiving an early monitored care approach similar to that used in HICs.[15] Two subsequent studies from Zambia suggested worse survival outcomes among patients receiving sepsis care bundles that emphasized fluid resuscitation.[12, 13] While the results of these studies are mixed, the quasi-experimental design of the Ugandan cohort study could limit the validity of their findings compared to the findings from the controlled trials in Zambia. Taken collectively and considering the quasi-experimental design of the Ugandan study, the current evidence suggests that

protocols emphasizing fluid resuscitation models from HICs could be harmful in sSA. These mixed results highlight the difficulties with directly translating sepsis bundles derived from high-income settings to sSA, where differences such as high prevalence of HIV and malnutrition may interact negatively with established interventions such as higher-volume IV fluids, as may have occurred in the Zambia studies.[12, 13] None of the three trials has fully assessed the impact of shortening time to antimicrobial administration, an intervention that has been important for improving outcomes in HICs.[9, 16]

The aim of our study was to describe the clinical characteristics, current patterns of management, and mortality in a cohort of adults and adolescents with sepsis presenting to a tertiary care hospital in northern Tanzania. Further, we sought to assess for predictors of in-hospital mortality among demographic, clinical, and management characteristics in this cohort.

2. Methods

2.1 Ethics statement

This study was approved by the Kilimanjaro Christian Medical Centre (KCMC) Research Ethics Committee, the United Republic of Tanzania National Institute for Medical Research National Research Ethics Coordinating Committee, and the Duke University Health System Institutional Review Board. All minors <18 years of age had consent provided by a parent or guardian, and those aged 12-17 years were asked to provide written assent. Adults ≥18 years of age provided their own written consent. Those who were initially consented by means of a representative due to alteration in mental status at the time of enrollment were reconsented if he/she regained adequate consciousness to provide consent for him-/herself by the end of the study period.

2.2 Study setting

Moshi is a municipality (population >200,000) and the administrative center of the Kilimanjaro Region (population >1.6 million) in northern Tanzania. The estimated prevalence of HIV in adults >15 years from 2016-2017 in the Kilimanjaro Region was 2.6%, and ranged from 1.9% (Arusha) to 5.0% (Tanga) in adjacent regions.[17] HIV viral suppression in Kilimanjaro was estimated at 67% in 2017.[17] The climate of Moshi is tropical, with rainy seasons from March to May and October to December. The elevation of Moshi is 700 meters above mean sea level at its lowest point. Transmission intensity of

malaria is low in the Kilimanjaro Region[18] with an estimated child prevalence of malaria <1% in 2017.[19]

KCMC is the 630-bed referral hospital for northern Tanzania and the site of a medical college. The hospital has an Emergency Department (ED), medical and surgical inpatient wards, and specialty inpatient wards, including burn and ear, nose, and throat wards. For critically ill patients, intensive care units (ICUs) with capabilities for mechanical ventilation and vasopressor support are available. There are 8 medical, 10 surgical, and 6 pediatric ICU beds. Available vasopressors include dopamine and epinephrine. Supplemental oxygen is available to patients who are hypoxic.

2.3 Study design and procedures

We conducted a prospective observational cohort study at KCMC from 12 September 2019 through 9 January 2020. A study team screened potential participants at the ED triage area at KCMC from Monday through Friday during daytime hours excluding holidays. Due to the primarily descriptive nature of this study, we sought to enroll as many participants as possible within the 4-month study period rather than powering the study based on a specific hypothesis.

Our study included adults and adolescents, defined as persons aged ≥10 years based on guidance from the World Health Organization (WHO) Integrated Management of Adolescent and Adult Illness (IMAI) program.[20-22] All patients ≥10 years of age who presented during the prespecified 8-hour period, from 9:00 am to 5:00 pm, were

screened for eligibility. Our case definition for sepsis was modified from the Systemic Inflammatory Response Syndrome (SIRS) criteria used in the 1991 and 2001 sepsis definitions;[5, 6] the lack of routine availability for certain tests of organ dysfunction precluded the use of the 2016 Sepsis-3 definition.[1] Potential participants met inclusion criteria if they met our case definition for sepsis. Patients were required to meet two of following three SIRS criteria: (1) temperature >38°C or <36°C, (2) heart rate >90 beats per minute, and (3) respiratory rate >20 breaths per minute. The SIRS white blood cell count criterion was not used due to the lack of routine availability of results within the early workup and management window for patients in this setting. Modified SIRS criteria have previously been used in the sSA setting due to the presence of resource-limitations.[14, 15] Patients who met our modified SIRS criteria inclusive of the presence of temperature dysregulation (>38°C or <36°C) were considered to meet inclusion criteria. SIRS inclusive of temperature dysregulation was considered sufficient for inclusion in this observational study given that a large proportion of febrile inpatient admissions in this setting are secondary to infectious causes.[10] In order to increase specificity for sepsis, those with SIRS but without temperature dysregulation were also required to have at least one severe symptom from the WHO IMAI Acute Care manual,[22] which included the following: stiff neck, convulsions, difficulty breathing, severe abdominal pain, lethargy or decline in consciousness, and confusion or agitation. A similar approach was used by Nadjm, *et al.* to classify severe febrile illness cases in northeastern Tanzania.[23]

Finally, those with SIRS but without temperature dysregulation were excluded if his/her treating clinician was confident the presentation was not due to an infectious cause by 2 hours after arrival. This 2-hour window was added two weeks into our 6-week piloting period to better exclude participants with vital signs consistent with SIRS but without infection while maintaining the capability to enroll early after presentation for purposes of data collection. Based on vital signs at presentation, participants were further classified as sepsis without hypotension, defined as systolic blood pressure ≥90 mmHg, and sepsis with hypotension, defined as systolic blood pressure <90 mmHg. These hypotension-based definitions are similar to that used by Andrews, *et al.* in Zambia.[12] Pregnant women, prisoners, refugees, and those unable to speak English or Kiswahili were excluded from the study.

After enrollment, each participant entered the primary period of data collection, which consisted of the first 6 hours of workup and management after arrival to the ED. Trained study staff—two clinical officers and one research assistant—collected data from each participant. A standardized clinical history was taken, and a brief standardized physical examination was performed on each enrolled participant. The history collected data on demographics, presenting symptoms, and prior medical history. As clinical markers of severity of illness in LMICs,[24] the clinical history also assessed inability to walk and inability to drink unassisted for each participant. The physical examination included measurement of vital signs, peripheral oxygen saturation

(SpO_2), mid-upper arm circumference (MUAC) as a measure of nutritional status,[25, 26] and determination of mental status using the Alert-Verbal-Pain-Unconscious (AVPU) scale.[27] A point-of-care StatStrip Lactate test (Nova Biomedical, Billerica, Massachusetts, USA) was collected from each participant, and results were shared with the participant's treating clinician. Data on workup and management of each participant were then collected within the 6-hour period after arrival. These data included information on timing and type of antimicrobials; timing and volume of IV fluids; steroid and vasopressor use; collection of blood cultures and other microbiological specimens; and other laboratory and radiographic evaluations. The performance of either an HIV rapid antibody test or rapid malaria antigen test by the participant's treating clinician was recorded, as were the results of each. Vital signs were rechecked, and a brief examination performed, at hours 3 and 6 after arrival. To collect the above information, study staff followed the participant closely for the duration of the 6-hour time window; this included following the participant's clinical course on the hospital ward if the participant was admitted to the hospital prior to hour 6. After this initial 6-hour period, admitted participants were monitored daily for the duration of the hospitalization to document additional interventions, such as antimicrobial use and ICU utilization, and to ascertain inpatient outcome.

Data were collected using Open Data Kit (ODK Community, 2019) on password-protected Samsung Galaxy Tab A tablets (Samsung Electronics, Suwon, South Korea)

and stored in an Access database (Microsoft Corp., Redmond, Washington, USA) on a secure KCMC-Duke Research Collaboration server on site. This server was compliant with the United States Health Insurance Portability and Accountability Act (HIPAA).

2.4 Definitions

Our primary outcome in this study was all-cause in-hospital mortality. For our analysis, we pre-specified cutoffs for several independent variables of interest in order to assess for associations with the primary outcome. We selected antimicrobial timing of 2 hours as opposed to the HIC standard of 1 hour[4] due to expected delays related to resource-limitations in this setting. A 6-hour cutoff was additionally used given this timeframe is the standard for early sepsis bundles and has been used in prior studies on time-to-antimicrobials.[4, 8] IV fluid timing was analyzed at 3 and 6 hours based on Surviving Sepsis Campaign guidelines,[4] and a primary volume cutoff of 1 liter (L) was selected based on expected lower volume resuscitation overall compared with HICs, as previously described in a Ugandan cohort.[14] MUAC was selected as a primary measure of nutritional status and proxy for BMI[25, 26] given expected difficulties obtaining weights in this acutely ill cohort. A low MUAC-for-age was defined as a Z-score-for-age of -2 or lower for adolescents, based on data from Mramba, *et al*.[25] For adults ≥18 years, low MUAC-for-age was defined as <24 cm, consistent with Food and Nutritional Technical Assistance (FANTA) recommendations for adults, which is also consistent with a Z-score of -2 for 19-year-olds in Mramba, *et al*.[26] Altered mentation was defined as either V,

P, or U on the AVPU scale. Hypoxia was defined as a peripheral oxygen saturation <92% or use of supplemental oxygen. Healthcare-associated infection was defined as hospitalization within 90 days prior to onset of the presenting illness, surgery within 30 days, or prosthetic joint replacement within 1 year with symptoms at the site of joint replacement. While there have been numerous definitions used for healthcare-associated infection,[28] this definition was chosen *a priori* to classify our participants.

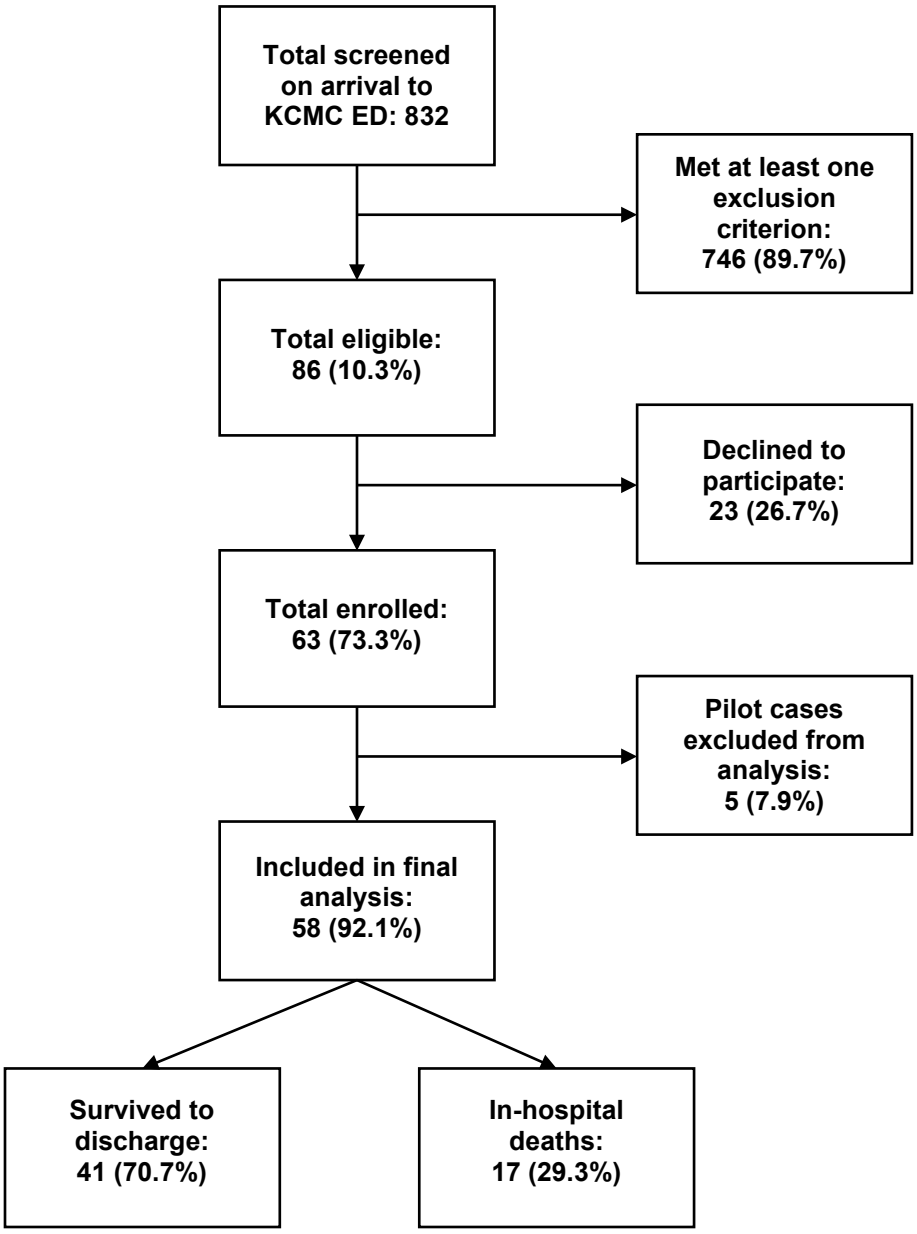
Two clinical prognostic scores for mortality were calculated for the cohort, the qSOFA[1] and Universal Vital Assessment (UVA),[29] and the standard proposed cutoffs for each were used in the analysis. These scores were chosen for their relevance and ease of calculation in resource-limited settings such as Tanzania. For both scores, altered mentation was defined using a score of V, P, or U on the AVPU scale. For UVA, we used our above definition for hypoxia, and we also relied on self-report for HIV-infection status. For our bivariable analysis, we used the following cutoffs for vital sign abnormalities: tachycardia, heart rate >110 beats per minute; tachypnea, respiratory rate >30 breaths per minute; hypotension, systolic blood pressure <100 mmHg; and hypoxia as defined above. These cutoffs were selected *a priori* to explore associations between each variable and in-hospital mortality beyond those used in our other definitions, such as sepsis with hypotension, and also independently from our prognostic scores of interest, while taking cutoffs used in UVA, qSOFA, and other studies in sSA into consideration in establishing these definitions.[1, 12-15, 29]

2.4 Statistical analysis

Descriptive statistics were performed and presented as medians and interquartile ranges (IQR) for continuous variables. Categorical variables were presented as frequencies. Crude risk ratios (RR) with 95% confidence intervals (95%CI) were calculated to assess for associations between demographic and clinical factors and our primary outcome of in-hospital death.

We performed separate multivariable analyses for two independent variables of interest for associations with in-hospital mortality: one analysis for administration of antimicrobials by hour 6 and a separate analysis for administration of IV fluids >1L by hour 6. Covariates in these analyses were selected *a priori* as potential confounders and included the following: age (continuous), sex (binary), insurance status (binary), presence of ≥1 medical comorbidity (binary), and UVA score (ordinal, possible range 0-13) as a marker of acuity of illness (note, UVA includes HIV-infection status). For the multivariable analysis assessing antimicrobials, we adjusted for IV fluids >1 L by hour 6; for the multivariable analysis assessing IV fluids >1L by hour 6, we adjusted for antimicrobials given by hour 6. Sex was also treated as a potential effect modifier in the analysis, and interaction terms were employed for sex and each independent variable of interest in the multivariable analyses. Data were analyzed using Stata16 (StataCorp, College Station, Texas, USA).

Figure 1: Study flow diagram from screening to determination outcome for adults and adolescents with sepsis, northern Tanzania, September 2019 to January 2020.
KCMC: Kilimanjaro Christian Medical Centre; ED: Emergency Department



3. Results

3.1 Participant demographics and medical history

Figure 1 summarizes participant screening, enrollment, and follow-up. There were 832 patients screened on arrival to the KCMC ED, of whom 86 (10.3%) were eligible. Sixty-three (73.3%) were enrolled with the remainder declining to participate. Given that eligibility requirements were changed during piloting to improve specificity for infection among those meeting SIRS criteria, there were 5 (7.9%) enrolled pilot cases excluded from the analysis. These five—from a total of 15 participants (23.8% of the total enrolled) who were enrolled before the changes were introduced—were excluded based on the lack of a preliminary infectious diagnosis recorded at the time of admission. We determined that such an exclusion approach yielded a participant sample that approximated those enrolled after the changes were implemented. Of the 58 participants included in this analysis, 4 (6.9%) were classified as sepsis with hypotension and 54 (93.1%) were sepsis without hypotension. SIRS criteria that were present among included participants were 55 (94.8%) with respiratory rate >20 breaths per minute, 52 (89.7%) with heart rate >90 beats per minute, and 51 (87.9%) with temperature either >38°C or <36°C.

Regarding participant demographics, 20 (34.5%) were female and the median (IQR) age was 52 (32-69) years (Table 1). Six (10.3%) participants were adolescents aged 10-17 years. Forty-nine (84.5%) participants had attained a primary school education or lower. Of ethnic groups, 39 (67.2%) were Chagga, 7 (12.1%) Pare, and 3 (5.2%) Maasai.

Table 1: Baseline demographic, historical, and clinical characteristics for adults and adolescents with sepsis, northern Tanzania, September 2019 to January 2020.

	Total cohort (n=58)	Sepsis without hypotension (n=54)	Sepsis with hypotension (n=4)
Demographics[§]			
Age, median (IQR)	52 (32-69)	52 (32-69)	50 (41-69)
Female, n (%)	20 (34.5)	18 (33.3)	2 (50.0)
Highest level of education completed, n (%)			
None	23 (39.7)	22 (40.7)	1 (25.0)
Primary	26 (44.8)	24 (44.4)	2 (50.0)
Secondary	6 (10.3)	5 (9.3)	1 (25.0)
University	3 (5.2)	3 (5.6)	0
Insured, n (%)	17 (29.3)	16 (29.6)	1 (25.0)
Clinical characteristics			
Duration of illness (days), median (IQR)	6 (3-14)	7 (3-16)	2 (1-5)
Chief complaint by syndrome, n (%)[‡]			
Fever or systemic	12 (20.7)	10 (18.5)	2 (50.0)
Cardiopulmonary	4 (6.9)	4 (7.4)	0
Gastrointestinal	6 (10.3)	5 (9.3)	1 (25.0)
Neurological	30 (51.7)	30 (55.6)	1 (25.0)
Other	6 (10.3)	5 (9.3)	0
Inability to walk unassisted, n (%)[Δ]	48 (82.8)	44 (81.5)	4 (100)
Inability to drink unassisted, n (%)[Δ]	25 (43.1)	22 (40.7)	3 (75.0)
Presence of chronic comorbidity, n (%)[β]	25 (43.1)	23 (43.6)	2 (50.0)
HIV-infected (reported), n (%)	7 (12.0)	6 (11.1)	1 (25.0)
Healthcare-associated infection, n (%)	18 (31.0)	15 (27.8)	3 (75.0)
MUAC (cm), median (IQR)	26.0 (23.0-29.0)	26.0 (23.0-29.0)	26.9 (24.9-27.5)
Temperature (°C), median (IQR)	38.8 (38.4-39.4)	38.9 (38.4-39.4)	38.3 (37.9-39.2)
Heart rate (beats/min), median (IQR)	111 (101-122)	109 (101-121)	126 (116-135)
Respiratory rate (breaths/min), median (IQR)	26 (24-32)	26 (24-33)	24 (23-29)
Systolic blood pressure (mmHg), median (IQR)	119 (107-145)	121 (109-146)	84 (79-87)
Diastolic blood pressure (mmHg), median (IQR)	66 (58-78)	67 (60-82)	48 (43-50)
Hypoxia, n (%)	19 (32.8)	19 (35.2)	0
Altered mentation, n (%)	17 (29.3)	16 (29.6)	1 (25.0)
Lactate (mmol/L), median (IQR)	1.5 (1.1-2.3)	1.4 (1.0-2.2)	3.1 (1.5-3.5)

[§]IQR is interquartile range; MUAC is mid-upper arm circumference.

[‡]Fever or systemic included fever, rigors, night sweats, weight loss, and rash. Cardiopulmonary included cough, hemoptysis, chest pain, and shortness of breath. Gastrointestinal included abdominal pain, severe abdominal pain, vomiting, hematemesis, diarrhea, and blood in stool. Neurological included headache, photophobia, stiff neck, confusion, lethargy, and convulsions. Other included patient-reported symptoms outside of these categories.

[Δ]Participants also included if unable to walk or drink unassisted chronically as a marker of health poorer status.

[β]Presence of chronic comorbidity defined as those reporting a history of hypertension; diabetes mellitus; cancer; or any chronic heart, lung, liver or kidney disease.

Forty-nine (84.5%) participants reported his/her home region as Kilimanjaro. When asked about insurance status, 17 (29.3%) had any type of insurance coverage for medical expenses. Seven (12.0%) participants self-reported HIV-infection, of whom all 7 (100%) reported taking antiretrovirals and 4 (57.1%) reported taking long-term trimethoprim-sulfamethoxazole prophylaxis. Twenty-five (43.1%) had a chronic medical condition other than HIV, most commonly hypertension in 19 (33.3%) and diabetes mellitus in 11 (19.3%). Thirty-four (58.6%) participants had been hospitalized at least once in the past year.

3.1 Participant clinical characteristics

Participants presented to KCMC after a median (IQR) duration of illness of 6 (3-14) days (Table 1). The median (IQR) duration of the first IMAI severe symptom[22] prior to arrival at KCMC was 5 (3-12) days. Of chief complaints by system, 30 (51.7%) were neurologic, of which 22 (73.3%) were reports of lethargy or unconsciousness. Forty-four (75.9%) participants were acutely unable to walk without assistance, with 4 (6.9%) additional unable to do so chronically due to disability or another reason. Twenty-two (37.9%) were unable to drink unassisted, with 3 (5.2%) unable to do so chronically. Eighteen (31.0%) participants had healthcare-associated infections.

Median (IQR) MUAC was 26.0 (23.0-29.0) cm, with 17 (29.3%) low-for-age. Median values for vital signs are reported in Table 1. For those without hypotension, median (IQR) blood pressure was 121/67 (109-146/60-82) mmHg compared with 84/48 (79-87/43-50) mmHg for those with hypotension. Nineteen (32.8%) participants were

Table 2: Management characteristics and outcomes of adults and adolescents with sepsis, northern Tanzania, September 2019 to January 2020.

	Total cohort (n=58)	Sepsis without hypotension (n=54)	Sepsis with hypotension (n=4)
Management characteristics, Hours 0-6§			
Received antimicrobials by 2 hours, n (%)	9 (15.5)	9 (16.7)	0
Received antimicrobials by 6 hours, n (%)	20 (34.5)	20 (37.0)	0
If received, time to antimicrobials by hour 6 (minutes), median (IQR)	163 (102-229)	163 (102-229)	0
Received any IV fluids by 3 hours, n (%)	28 (48.3)	24 (44.4)	4 (100)
Received any IV fluids by 6 hours, n (%)	33 (56.9)	29 (53.7)	4 (100)
<1L IV fluids, n (%)	45 (77.6)	42 (77.8)	3 (75.0)
1-2L IV fluids, n (%)	9 (15.5)	8 (14.8)	1 (25.0)
>2L IV fluids, n (%)	4 (6.9)	4 (7.4)	0
If received, total IV fluids by hour 6 (mL), median (IQR)	500 (500-1000)	500 (500-1000)	500 (350-750)
Blood cultures performed, n (%)	21 (36.2)	20 (37.0)	1 (25.0)
If yes, obtained prior to antimicrobials given, n (%)	19 (90.5)	18 (90.0)	1 (100)
Other investigation for infectious source performed, n (%)‡	47 (81.0)	45 (83.3)	2 (50.0)
Steroid administration, n (%)	2 (3.5)	2 (3.7)	0
Supplemental oxygen given, n (%)	16 (27.6)	16 (29.6)	0
Required emergent surgery, n (%)	1 (1.7)	1 (1.9)	0
Hospital course			
Required vasopressors at any time, n (%)	1 (1.7)	1 (1.9)	0
Required supplemental oxygen at any time, n (%)	20 (34.5)	19 (35.2)	1 (25.0)
Intensive care unit at any time, n (%)	11 (19.0)	10 (18.5)	1 (25.0)
Outcomes			
Inpatient death, n (%)	17 (29.3)	16 (29.6)	1 (25.0)
Length of stay (days), median (range)	5 (1-44)	5 (1-44)	5.5 (1-9)
Deaths by qSOFA and UVA scores:			
qSOFA <2	4 (11.8)	4 (11.8)	n/a
qSOFA ≥2	13 (54.2)	12 (60.0)	1 (25.0)
UVA <2	2 (8.0)	2 (8.0)	n/a
UVA 2-4	5 (27.8)	5 (28.4)	0
UVA >4	10 (66.7)	9 (69.2)	1 (50.0)

§IQR is interquartile range; IV is intravenous; qSOFA is quick Sequential Organ Failure Assessment; UVA is Universal Vital Assessment.

‡Other investigations included any of the following: rapid HIV testing, malaria rapid diagnostic testing, urinalysis, urine culture, sputum culture or AFB smear, mycobacterial molecular testing, lumbar puncture, chest X-ray, or any other imaging.

hypoxic, and 17 (29.3%) had alteration in mental status. Median (IQR) lactate values at baseline were 1.4 (1.0-2.2) mmol/L for those without hypotension and 3.1 (1.5-3.5) mmol/L for those with hypotension.

3.2 Management characteristics and outcomes

Clinical management characteristics and outcomes for participants are summarized in Table 2. Of 58 participants included in the analysis, 17 (29.3%) died in-hospital, including 1 (25.0%) of the 4 who were initially hypotensive. Antimicrobials were given to 3 (5.2%) participants by 1 hour after arrival, 9 (15.5%) by 2 hours, and 20 (34.5%) by hour 6. For those who received an antimicrobial by hour 6, the median (IQR) time to initiation of the first agent was 163 (102-229) minutes. No hypotensive participant received antimicrobials in the initial 6-hour window. The initial empiric antimicrobial regimens given from hours 0-6 were the following: 11 ceftriaxone and metronidazole (55.0%), 7 ceftriaxone monotherapy (35.0%), 1 ampicillin and metronidazole (5.0%), and 1 metronidazole monotherapy (5.0%).

IV fluids were administered to 33 (56.9%) participants within 6 hours after arrival. Forty-five (77.6%) of those received <1L of IV fluids, while 9 (15.5%) received 1-2L, and 4 (6.9%) received >2L. One (25.0%) participant with hypotension received >1L of IV fluids. Those who were administered IV fluids received a median (IQR) of 500 (500-1,000) mL, which did not differ between those with and without hypotension.

Workup for cause of sepsis included at least one standard aerobic blood culture for 21 (36.2%) participants and any other investigation for source of infection, including

Table 3: Clinical characteristics and associations with inpatient mortality in adults and adolescents with sepsis, northern Tanzania, September 2019 to January 2020.

	Survivors (n=41)	In-hospital deaths (n=17)	Crude risk ratio (95%CI)
Demographics[§]			
Age, median (IQR)	47 (30-69)	53 (53-61)	--
Age >60 years	17 (41.5)	5 (29.4)	0.68 (0.28, 1.67)
Female, n (%)	14 (34.2)	6 (35.3)	1.04 (0.45, 2.39)
Education level completed primary or less, n (%)	34 (82.3)	15 (88.2)	1.38 (0.38, 5.02)
Any insurance, n (%)	15 (36.3)	2 (11.8)	0.32 (0.08, 1.26)
Clinical characteristics			
Duration of illness >7 days, n (%)	15 (36.6)	6 (35.3)	0.96 (0.42, 2.22)
Duration since onset of severe symptom >7 days, n (%)	19 (46.3)	4 (23.5)	0.47 (0.17, 1.26)
Presence of chronic comorbidity, n (%)[‡]	16 (39.0)	9 (52.9)	1.49 (0.67, 3.30)
Self-reported HIV-infection, n (%)	5 (12.2)	2 (11.8)	0.97 (0.28, 3.38)
Inability to walk unassisted, n (%)[Δ]	32 (78.1)	16 (94.1)	3.33 (0.50, 22.33)
Inability to drink unassisted, n (%)[Δ]	12 (29.3)	13 (76.5)	4.29 (1.59, 11.58)
Low MUAC-for-age (cm), n (%)	12 (29.3)	5 (29.3)	1.00 (0.42, 2.41)
Temperature >38°C, n (%)	36 (87.8)	14 (92.4)	0.75 (0.27, 2.03)
Temperature <36°C, n (%)	1 (2.44)	0	--
Heart rate >110, n (%)	19 (46.3)	11 (64.7)	1.71 (0.73, 4.01)
Respiratory rate >30, n (%)	10 (24.4)	9 (52.9)	2.31 (1.06, 5.03)
Hypoxia, n (%)	10 (24.4)	9 (52.9)	2.31 (1.06, 5.03)
Systolic blood pressure <100 mmHg, n (%)	6 (14.6)	3 (17.7)	1.17 (0.42, 3.25)
Mean arterial pressure <65 mmHg, n (%)	4 (9.8)	1 (5.9)	0.66 (0.11, 4.01)
Altered mentation, n (%)	6 (14.6)	11 (64.7)	4.42 (1.95, 10.02)
Lactate >2 mmol/L	10 (24.4)	8 (47.1)	1.98 (0.91, 4.23)
qSOFA score ≥2	11 (26.8)	13 (76.5)	4.60 (1.71, 12.40)
UVA score			
UVA score <2	23 (92.0)	2 (8.0)	--
UVA score 2-4	13 (72.2)	5 (27.8)	3.47 (0.76, 15.94)
UVA score >4	5 (33.3)	10 (66.7)	8.33 (2.10, 33.01)

[§]IQR is interquartile range; MUAC is mid-upper arm circumference; qSOFA is quick Sequential Organ Failure Assessment; UVA is Universal Vital Assessment.

[‡]Presence of chronic comorbidity defined as those reporting a history of hypertension; diabetes mellitus; cancer; or any chronic heart, lung, liver or kidney disease.

[Δ]Includes both acute and chronic inability walk or drink unassisted for the respective variables.

other cultures or imaging, for 47 (81.0%). One participant (1.7%) received an HIV rapid antibody test, which resulted positive (100%). Thirteen (22.4%) participants received a rapid malaria antigen test, with 2 (15.4%) of those positive.

Two (3.5%) normotensive participants received steroids in the first 6 hours, and 1 (1.9%) participant, who was initially normotensive on arrival, needed vasopressors during his hospitalization. Supplemental oxygen was used for 20 (34.5%) participants at any time prior to discharge. The ICU was utilized for 11 (19.0%) participants, including 1 (25.0%) participant who was hypotensive on presentation. Of those who died, 7 (41.2%) were in the ICU at any point during their hospitalization. It was noted that 3 (75.0%) of the 4 participants hypotensive on arrival were normotensive with a mean arterial pressure (MAP) >65 by 6 hours, although 2 (50%) remained tachycardic >100 beats per minute.

With respect to prognostic scores, for qSOFA, 13 (52.2%) of those with a score ≥2 died in-hospital, compared to 4 (11.8%) with scores <2. For UVA, compared with the 2 (8.0%) who died with scores <2, there were 5 (27.8%) deaths with scores of 2-4, and 10 (66.7%) deaths for scores >4.

3.3 Clinical and management factors and associations with in-hospital mortality

Crude risk estimates for the associations between demographic and baseline clinical characteristics and the primary outcome of in-hospital death are shown in Table 3. There was no difference in the median age, sex, or educational attainment of those who survived to discharge compared with those who died in-hospital. The risk of mortality was 68% lower among those with medical insurance compared to those without (RR 0.32, 95%CI 0.08, 1.26). Participants who were unable to walk unassisted had a threefold increased risk of inpatient death (RR 3.33, 95%CI 0.50, 22.33), and risk

Table 4: Management factors and associations with inpatient mortality in adults and adolescents with sepsis, northern Tanzania, September 2019 to January 2020.

	Survivors (n=41)	In-hospital deaths (n=17)	Crude risk ratio (95%CI)
Management characteristics, hours 0-6			
Antimicrobials administered by hour 2, n (%)	5 (12.2)	4 (23.5)	1.68 (0.70, 3.98)
Antimicrobials administered by hour 6, n (%)	12 (29.3)	8 (47.1)	1.69 (0.77, 3.70)
Time to antimicrobials (minutes) if received, median (IQR)	163 (90-223)	155 (104-261)	--
Initiation of IV fluid bolus by hour 3, n (%)	19 (46.3)	9 (52.9)	1.21 (0.54, 2.69)
Total IV fluids >1L by hour 6, n (%)	3 (7.3)	4 (23.5)	2.24 (1.01, 4.96)
Total IV fluids (mL) by hour 6, median (IQR)	150 (0-500)	450 (0-1000)	--
Blood cultures performed, n (%)	14 (34.2)	7 (41.2)	1.23 (0.55, 2.78)
Other investigation for infectious source performed, n (%)‡	33 (80.5)	14 (82.3)	1.09 (0.38, 3.15)
Steroid administration, n (%)	0	2 (11.8)	--
Supplemental oxygen given, n (%)	8 (19.5)	8 (47.1)	2.33 (1.09, 4.98)
Required emergent surgery, n (%)	0	1 (5.9)	--
Admission characteristics			
Required vasopressors at any time, n (%)	0	1 (5.8)	--
Required supplemental oxygen at any time, n (%)	8 (19.5)	12 (70.6)	4.56 (1.87, 11.12)
Intensive care unit at any time, n (%)	4 (9.8)	7 (41.2)	2.99 (1.47, 6.07)

§IQR is interquartile range; IV is intravenous.

‡Other investigations included any of the following: rapid HIV testing, malaria rapid diagnostic testing, urinalysis, urine culture, sputum culture or AFB smear, mycobacterial molecular testing, lumbar puncture, chest X-ray, or any other imaging.

was increased fourfold for those unable to drink unassisted (RR 4.29, 95%CI 1.59, 11.58); both estimates are inclusive of those chronically unable to walk or drink unassisted. Alteration in mental status was also more common among those who died than those who survived (RR 4.42, 95%CI 1.95, 10.02). Low MUAC-for-age was not associated with the outcome. With respect to vital signs on presentation, only a respiratory rate >30 breaths per minute and hypoxia were associated with mortality (for each, RR 2.31, 95%CI 1.06, 5.03). Participants with baseline lactate >2 mmol/L were found to have

nearly twice the risk of death compared to those with baseline values ≤2 mmol/L (RR 1.98, 95%CI 0.91, 4.23).

With respect to clinical prognostic scores, participants who had qSOFA scores ≥2 had a fourfold increase in the risk of inpatient death compared with those with scores <2 (RR 4.60, 95%CI 1.71, 12.40). In assessing the proposed thresholds for the UVA score,[29] compared with scores <2, those with scores of 2-4 had a threefold increase risk of death (RR 3.47, 95%CI 0.76, 15.94), and those with scores >4 had an eightfold increase in risk (RR 8.33, 95%CI 2.10, 33.01).

Crude risk estimates for the associations between management factors and in-hospital mortality are shown in Table 4. Regarding timing of antimicrobial administration, our crude risk estimates for in-hospital death were increased at both thresholds of 2 hours (RR 1.68, 95%CI 0.70, 3.98) and 6 hours (RR 1.69, 95%CI 0.77, 3.70). Of those who did receive antimicrobials, time to administration was the same for those who survived to discharge and those who died in-hospital. Risk of death was found to be higher in those who received >1 L of total IV fluids within 6 hours after arrival (RR 2.24, 95%CI 1.01, 4.96). Median (IQR) IV fluid volumes administered by group were similar, with those who died receiving 450 (0-1,000) mL and those who survived receiving 150 (0-500) mL. Those who received any supplemental oxygen during hospitalization had an increased risk of death (RR 4.56, 95%CI 1.87, 11.12), as did those who required ICU care (RR 2.99, 95%CI 1.47, 6.07). Workup for cause of sepsis did not

differ by inpatient outcome status with respect to either blood cultures or other investigations.

In the multivariable analysis (Table 5), the risk ratio for death in those who were not administered antimicrobials by hour 6 was attenuated from a crude estimate of 1.69 (95%CI 0.77, 3.70) to an adjusted risk ratio of 1.14 (95%CI 0.42, 3.05). For those who were administered >1L IV fluids by hour 6, the adjusted risk ratio was attenuated to 1.27 (95%CI 0.47, 3.46) from the crude estimate of 2.24 (95%CI 1.01, 4.96).

Table 5: Multivariable analysis of factors associated with inpatient mortality in adults and adolescents with sepsis, northern Tanzania, September 2019 to January 2020.

	Crude risk ratio	95%CI	Adjusted risk ratio‡	95%CI$^{\Delta}$
Antimicrobials administered by hour 6	1.69	0.77, 3.70	1.14	0.42, 3.05
Intravenous fluid volume >1L by hour 6	2.24	1.01, 4.96	1.27	0.47, 3.46

‡Adjusted for age (continuous), sex (binary), insurance status (binary), presence of ≥1 medical comorbidity (binary), and UVA score (ordinal) as a marker of acuity of illness (note, UVA includes HIV status). Antimicrobial administration by hour 6 was adjusted for intravenous fluid volume >1L by hour 6, and intravenous fluid volume >1L by hour 6 was adjusted for antimicrobial administration by hour 6. Interaction terms for sex and each independent variable of interest were also used in the analyses.
$^{\Delta}$The 95%CI are Huber-White sandwich estimated rather than model-based.

4. Discussion

To our knowledge, our study was the first descriptive study of clinical characteristics, management, and outcomes for adolescents and adults with sepsis in northern Tanzania. The overall mortality for the cohort was 29.3%. Very few participants presented with hypotension. We found that inability to drink unassisted, respiratory rate >30 breaths per minute, hypoxia, and altered mentation at presentation were associated with an increased risk of in-hospital death. Less than half of participants received any antimicrobial by hour 6, and most participants received <1L of IV fluids. On multivariable analysis, neither antimicrobial administration by hour 6 nor IV fluids >1L by hour 6 was associated with inpatient mortality.

In-hospital mortality reported from other sepsis studies in sSA has ranged from 7-40% for non-severe sepsis and 24-61% for severe sepsis, with severe sepsis variably defined but generally using a measure of hypotension or organ dysfunction.[30] Prior sepsis studies in sSA also have shown increasing inpatient mortality with an increasing proportion of HIV-infected participants.[30] Our study was unable to establish the true prevalence of HIV-infection in our sepsis cohort due to both reliance on self-report and testing at clinician discretion, but prior studies at our site have suggested an HIV-infection prevalence of 30-40% in those presenting with severe febrile illness.[10, 31] Our modified Sepsis-2[6] definition was unable to distinguish between sepsis and severe sepsis as defined by organ dysfunction, given certain laboratory and clinical measures of organ dysfunction were not routinely performed; further, there was only one participant that

may have met a Sepsis-2 definition of septic shock. Thus, our cohort likely consisted primarily of a combination of both sepsis and severe sepsis. Overall, the in-hospital mortality in our cohort lies within the reported ranges for the other sepsis cohorts previously studied in sSA.

The baseline clinical factors most strongly associated with inpatient death, which included inability to drink unassisted, respiratory rate >30 breaths per minute, presence of hypoxia, and altered mentation, were all findings that would be expected to indicate an increased severity of illness at presentation. The presence of a chronic comorbidity, inability to walk, and lactate >2 mmol/L on presentation were three other factors indicative of severity of illness with weaker associations with inpatient mortality. Other cohorts in LMICs have reported an increased risk of death with inability to walk unassisted,[32, 33] which is a cost-effective early prognostic measure in resource-limited settings. Of note, while inability to walk was observed frequently among both survivors and among inpatient deaths, inability to drink was a more discriminatory measure associated with mortality in our cohort. Low MUAC-for-age was not found to be associated with in-hospital death in our study. However, nearly all participants classified as low MUAC-for-age were just below the lower limit of our defined cutoff by age, with only one participant below a Z-score of -3. This finding suggests only mild malnutrition was present in the majority characterized as low MUAC-for-age, which may explain the lack of an association with a fatal outcome in this study.

With respect to the two clinical scores calculated for our cohort, qSOFA and UVA, mortality by the proposed cutoffs varied markedly. Notably, for qSOFA, our percentages of scores ≥2 among those who died in-hospital and those who survived were nearly the same as the findings from HIC data presented with the unveiling of the Sepsis-3 definition,[34] suggesting a similar performance of the score in our setting. For the UVA score, we found higher mortality in our cohort than in the initial derivation cohort[29] for each of the proposed cutoffs. Of note, the UVA score was originally derived from a pooled cohort of hospitalized sSA patients in which many, but not all, had a presumptive infectious etiology for presentation. This limits direct comparability between our cohort and the derivation cohort, but our data suggest utility of the UVA score for sepsis in our setting given the marked differences in mortality for each proposed cutoff. Our findings further support findings from Gabon supporting the prognostic performance of these two scores in resource-limited settings.[35] Between both the qSOFA and the UVA clinical scores and the baseline clinical findings associated with a fatal inpatient outcome, it is possible to use routinely available data in our setting to aid in sepsis prognostication.

We make several observations relevant to sepsis management in sSA. Our crude risk estimates both for antimicrobial administration and IV fluids >1L by 6 hours indicate an increased risk for death for each. However, the crude findings are likely confounded by several factors, perhaps most importantly by severity of illness at presentation. Increased severity of illness would be expected to lead to increased and

earlier administration of both antimicrobials and IV fluids—i.e., confounding by indication—and be associated with an increased risk of in-hospital death. We found that our risk estimates for both antimicrobial timing and IV fluid volume were attenuated with adjustment for age, sex, insurance status, key management factors, chronic comorbidities, and acuity of illness. In our small cohort, we were unable to assess adequately the impact of early administration of antimicrobials at the 2-hour timepoint, but our 6-hour adjusted estimate indicates no association between antimicrobial timing and outcome. Timing of antimicrobials has not been studied fully in the sSA setting, and thus it is not clear if early administration is as critical to survival as demonstrated in HICs.[16, 36, 37] Of note, the balance of limited evidence and concerns about antimicrobial overuse recently led to pediatric Surviving Sepsis Campaign recommendations that lengthened the target for antimicrobial administration from 1 to 3 hours for patients without septic shock.[38] It is plausible that increased duration of illness, the varied etiologies of severe febrile illness,[10, 11] the higher prevalence of HIV, and other factors unique to the sSA setting may mitigate the benefits of early antimicrobials compared with HICs. However, our findings on antimicrobials are to be interpreted with caution, as studies to date demonstrating the benefits of early administration have come from large cohorts with modest effect sizes for risk of death with increasing delays in administration.[16, 39] Consequently, we are underpowered to demonstrate small relative benefits of early antimicrobials. Nonetheless, given that overall antimicrobial

administration by hour 6 was low across the cohort, improving antimicrobial timing likely remains a reasonable approach until more data are available.

IV fluid resuscitation is an area of ongoing interest in both HIC and LMIC settings. In the 2000s, there was an emphasis on higher-volume resuscitation with Early Goal Directed Therapy (EGDT) initiatives leading to large volume administration in HIC settings.[7] However, the benefits of EGDT have not been reproduced in three large randomized trials and the pre-specified meta-analysis of those trials,[40-43] and studies including higher-volume resuscitation in sSA showed mixed results, importantly including two studies from Zambia reporting increased mortality with higher-volume IV fluid administration.[12, 13, 15] As a result, it has been suggested that a restrictive IV fluid approach may be a focus for future research, including in HICs.[44] The recently published pediatric Surviving Sepsis Campaign guidelines also recognize that fluid resuscitation may put certain patients at risk, limiting the recommended fluid volume to be given in areas without ICU support.[38] Most of our participants received <1L of IV fluids in the first 6 hours, and there was no clear association between receiving >1L of IV fluids and in-hospital mortality. However, based on the total fluid volumes received, there were too few participants receiving higher than the recommended 30 mL/kg initial fluid bolus for patients with sepsis[4] (approximately 2.1L for the average male of 70kg) to determine if volumes in excess of that target are harmful. Both our sample size and lack of variation in total volume administered limit interpretation of our risk estimate for the

cohort. Further studies on IV fluid resuscitation are urgently needed to better clarify the benefit or risk in the sSA setting.

With respect to workup, we found areas for improvement in sepsis care at our institution. While most participants had at least one investigation performed to identify a source of infection, only a third had blood cultures collected. While the causes of severe febrile illness in sSA vary considerably compared with HICs, bloodstream infections remain a prominent contributor to febrile hospitalizations in this setting.[10, 11] Improving collection of blood cultures is a key measure to improve management of sepsis at our site for the purposes of diagnosis and administration of appropriate therapy. Another notable finding was that only one participant received HIV testing within the first 6 hours of management. If prior estimates of HIV prevalence in those with severe febrile illness in our setting[10, 31] translate to our sepsis cohort, it is likely there were at least another 9 (15%) participants undiagnosed on presentation. HIV testing is recommended for all patients presenting with acute illness in sSA,[22, 45] and knowledge of HIV-infection status can help determine risk for opportunistic infections such as disseminated cryptococcosis. Though some of our cohort may have received HIV testing later in his/her hospitalization, there is a need to improve early testing practices, particularly to determine the need for additional testing and empiric treatment for opportunistic pathogens related to HIV-infection.

Our study has several limitations. First, our sample size limits our ability to detect relatively small differences for both baseline clinical findings and interventions,

particularly with respect to IV fluids and antimicrobial administration, as mentioned. Further, our reliance on provider-ordered HIV, malaria, and other testing limits our ability to describe many clinical characteristics of sepsis, such as markers of organ dysfunction or infectious etiology. Our cohort was also Emergency Department-based, and we were unable to describe sepsis with in-hospital onset. However, it is notable that nearly a third of participants met our definition for hospital-associated infection. Future research is needed to describe the sepsis syndrome in sSA, including onset in-hospital, and assess the impact of key interventions on outcome.

Another potential limitation is our use of an incidence proportion as a measure of risk as opposed to an incidence density. We chose to report the incidence proportion because it is the most often reported measure of occurrence and allowed us to compare our results to similar studies.[30] However, an incidence proportion assumes that all participants were followed for the same length of time (i.e., hospital stay), which we recognize was not the case. If the length of hospitalization among participants experiencing the exposures of interest was significantly different from those who did not experience the exposures of interest, our risk ratio estimates of incidence proportion could be biased.

Our modified SIRS-based sepsis definition is another limitation. While intended to improve the specificity of the sepsis definition and align with an updated understanding of the pathophysiological basis of the syndrome, using a strict Sepsis-3-based definition[1] would require the availability of laboratory results that are often

unavailable or delayed in the sSA setting. Thus, we were required to use an older definition that may have characterized participants with evidence of SIRS, but without infection, as sepsis. While we attempted to improve our eligibility criteria to exclude such patients, it is likely that some enrolled participants did not in fact have sepsis. Until markers of organ dysfunction become more readily available in a timely fashion in LMICs, the current sepsis definition remains of difficult to employ. Additionally, there remains a need to study the performance of the full SOFA-based definition on LMIC cohorts. Despite the limitations of our study, until additional research in larger cohorts is performed in this setting, our data have substantial descriptive value as one of a limited group of studies on sepsis in adults and adolescents in sSA.

5. Conclusions

In our observational study of sepsis at a single tertiary referral medical center in northern Tanzania, we found sepsis was a common reason for presenting to the Emergency Department and that in-hospital mortality for sepsis was high. Simple clinical scores, such as qSOFA and UVA, as well as key clinical findings such as altered mentation or inability to drink unassisted represent feasible means for identifying sepsis patients at increased risk of in-hospital death. While questions remain about key interventions to improve outcomes, we identified areas for improvement, such as timely antimicrobial administration and the need for routine provider-initiated HIV testing in Emergency Department. Further research is urgently needed to improve early identification of sepsis in resource-limited settings and establish the highest-yield interventions suited to the unique characteristics of sepsis in sSA.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.

2. Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Global burden of sepsis: a systematic review. 2015. p. P21-P.

3. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-11.

4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Crit Care Med. 2017;45(3):486-552.

5. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55.

6. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29(4):530-8.

7. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368-77.

8. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014;42(8):1749-55.

9. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96.

10. Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, et al. Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study. PLoS Negl Trop Dis. 2013;7(7):e2324.

11. Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10(6):417-32.

12. Andrews B, Semler MW, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, et al. Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension: A Randomized Clinical Trial. JAMA. 2017;318(13):1233-40.

13. Andrews B, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Bernard GR. Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. Crit Care Med. 2014;42(11):2315-24.

14. Jacob ST, Moore CC, Banura P, Pinkerton R, Meya D, Opendi P, et al. Severe sepsis in two Ugandan hospitals: a prospective observational study of management and outcomes in a predominantly HIV-1 infected population. PLoS One. 2009;4(11):e7782.

15. Jacob ST, Banura P, Baeten JM, Moore CC, Meya D, Nakiyingi L, et al. The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study*. Crit Care Med. 2012;40(7):2050-8.

16. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med. 2017;376(23):2235-44.

17. Population Based HIV Impact Assessment (PHIA). Tanzania HIV Impact Survey (THIS) 2016-2017. New York: Columbia University; 2017.

18. Gething PW, Patil AP, Smith DL, Guerra CA, Elyazar IR, Johnston GL, et al. A new world malaria map: Plasmodium falciparum endemicity in 2010. Malar J. 2011;10:378.

19. United Republic of Tanzania Ministry of Health CD, Gender, Elderly and Children,. Tanzania: Malaria Indicator Survey 2017. Dar es Salaam; 2018.

20. World Health Organization. IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of illnesses with limited-resources. Geneva 2011.

21. World Health Organization. IMAI district clinician manual: hospital care for adolescents and adults: guidelines for the management of illnesses with limited-resources. Geneva 2011.

22. World Health Organization. Integrated Management of Adolescent and Adult Illness: Acute Care: Guidelines for first-level facility health workers athealth centre and district outpatient clinic. Geneva; 2009.

23. Nadjm B, Mtove G, Amos B, Walker NF, Diefendal H, Reyburn H, et al. Severe febrile illness in adult hospital admissions in Tanzania: a prospective study in an area of high malaria transmission. Trans R Soc Trop Med Hyg. 2012;106(11):688-95.

24. Griesel R, Stewart A, van der Plas H, Sikhondze W, Mendelson M, Maartens G. Prognostic indicators in the World Health Organization's algorithm for seriously ill HIV-infected inpatients with suspected tuberculosis. AIDS Res Ther. 2018;15(1):5.

25. Mramba L, Ngari M, Mwangome M, Muchai L, Bauni E, Walker AS, et al. A growth reference for mid upper arm circumference for age among school age children and adolescents, and validation for mortality: growth curve construction and longitudinal cohort study. BMJ. 2017;358:j3423.

26. FANTA. Global MUAC Cutoffs for Adults: A Technical Consultation. Durham, NC: FHI360; 2018.

27. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors. Chicago; 1997.

28. Cardoso T, Almeida M, Friedman ND, Aragao I, Costa-Pereira A, Sarmento AE, et al. Classification of healthcare-associated infection: a systematic review 10 years after the first proposal. BMC Med. 2014;12:40.

29. Moore CC, Hazard R, Saulters KJ, Ainsworth J, Adakun SA, Amir A, et al. Derivation and validation of a universal vital assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub-Saharan Africa. BMJ Glob Health. 2017;2(2):e000344.

30. Lewis JM, Feasey NA, Rylance J. Aetiology and outcomes of sepsis in adults in sub-Saharan Africa: a systematic review and meta-analysis. Crit Care. 2019;23(1):212.

31. Madut DB, Rubach MP, Kalengo N, Carugati M, Maze MJ, Morrissey AB, et al. A prospective study of Escherichia coli bloodstream infection among adolescents and adults in northern Tanzania. Trans R Soc Trop Med Hyg. 2019.

32. Rylance J, Baker T, Mushi E, Mashaga D. Use of an early warning score and ability to walk predicts mortality in medical patients admitted to hospitals in Tanzania. Trans R Soc Trop Med Hyg. 2009;103(8):790-4.

33. Kayambankadzanja RK, Schell CO, Nsanjama G, Mbingwani I, Kwazizira Mndolo S, Rylance J, et al. Inability to Walk Predicts Death among Adult Patients in Hospitals in Malawi. Emerg Med Int. 2019;2019:6586891.

34. Freund Y, Lemachatti N, Krastinova E, Van Laer M, Claessens YE, Avondo A, et al. Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department. Jama. 2017;317(3):301-8.

35. Schmedding M, Adegbite BR, Gould S, Beyeme JO, Adegnika AA, Grobusch MP, et al. A Prospective Comparison of Quick Sequential Organ Failure Assessment, Systemic Inflammatory Response Syndrome Criteria, Universal Vital Assessment, and Modified Early Warning Score to Predict Mortality in Patients with Suspected Infection in Gabon. Am J Trop Med Hyg. 2019;100(1):202-8.

36. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med. 2004;164(6):637-44.

37. Sterling SA, Miller WR, Pryor J, Puskarich MA, Jones AE. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. Crit Care Med. 2015;43(9):1907-15.

38. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020;46(Suppl 1):10-67.

39. Liu VX, Fielding-Singh V, Greene JD, Baker JM, Iwashyna TJ, Bhattacharya J, et al. The Timing of Early Antibiotics and Hospital Mortality in Sepsis. Am J Respir Crit Care Med. 2017;196(7):856-63.

40. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301-11.

41. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496-506.

42. PRISM Investigators, Rowan KM, Angus DC, Bailey M, Barnato AE, Bellomo R, et al. Early, Goal-Directed Therapy for Septic Shock - A Patient-Level Meta-Analysis. N Engl J Med. 2017;376(23):2223-34.

43. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683-93.

44. Corl KA, Prodromou M, Merchant RC, Gareen I, Marks S, Banerjee D, et al. The Restrictive IV Fluid Trial in Severe Sepsis and Septic Shock (RIFTS): A Randomized Pilot Study. Crit Care Med. 2019;47(7):951-9.

45. World Health Organization. Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities. Geneva; 2007.