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MAJOR ARTICLE

Sepsis in Northern Tanzania: A Prospective Observational Study of Clinical Characteristics, Management, and Outcomes for Adolescents and Adults With Sepsis

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Background. Despite a high burden of sepsis in Sub-Saharan Africa, clinical data for adolescent and adult sepsis in this setting are limited. We sought to describe clinical characteristics, management, and outcomes in adolescents and adults with sepsis in northern Tanzania. We also assessed for clinical associations with in-hospital mortality.

Methods. We conducted a prospective observational cohort study at Kilimanjaro Christian Medical Centre in Moshi, Tanzania, 2019–2020. Data were collected on demographics, clinical characteristics, and management primarily from hours 0–6 after arrival at the emergency department. We calculated bivariable risk ratios (RRs) for associations between demographic and clinical factors and in-hospital death. A multivariable-adjusted analysis was performed for associations between antimicrobial and intravenous fluid administration and in-hospital death.

Results. Of 86 participants with sepsis, 25 (29.1%) died in the hospital. Baseline characteristics associated with in-hospital mortality included inability to drink unassisted (RR, 3.15; 95% CI, 1.58–6.30), altered mentation (RR, 3.94; 95% CI, 2.12–7.33), quick Sequential Organ Failure Assessment (qSOFA) score ≥2 (RR, 2.86; 95% CI, 1.42–5.72), and Universal Vital Assessment score ≥5 (RR, 6.33; 95% CI, 2.36–17.02). Twenty-nine (33.7%) received an antimicrobial by hour 6. HIV antibody testing was performed for 4 (4.7%) participants by hour 6. On multivariable analysis, neither antimicrobial administration nor intravenous fluids >1L by hour 6 was associated with in-hospital mortality.

Conclusions. Sepsis at our center in northern Tanzania carried a high risk of in-hospital mortality. Further research is needed to establish the highest-yield interventions suited to the unique characteristics of sepsis in Sub-Saharan Africa.

Keywords. global health; sepsis; Sub-Saharan Africa; Tanzania.

Sepsis, life-threatening organ dysfunction caused by a dysregulated host response to infection, is a leading cause of death globally [1–3]. The burden of sepsis is high in low- and middle-income countries (LMICs) [3]. Most research and subsequent guideline development relating to sepsis originate from high-income countries (HICs), where medical resources are substantial and etiologies for infection differ from LMICs [4–7]. Such research efforts have led to the development of sepsis bundles focused on certain core interventions, such as intravenous (IV) fluid resuscitation and early antimicrobial administration, but these interventions may not be readily translated to LMIC settings [1, 8–13].

Epidemiological data on sepsis in LMICs are limited. Studies on the epidemiology of febrile illness in Sub-Saharan Africa (SSA) have demonstrated the differences in underlying infectious etiologies compared with HICs, such as rickettsioses or tuberculosis [14, 15]. While descriptive observational work on sepsis has been conducted in several countries in SSA, as well as several single-center randomized trials on sepsis interventions, more data are needed to better define sepsis and identify effective interventions, including those of greater relevance to SSA [5, 16–18].

To our knowledge, published trials of sepsis-directed interventions in SSA presently total 3. A pre- and postintervention prospective cohort study from Uganda demonstrated a mortality

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benefit for patients with sepsis receiving an early monitored care approach similar to that used in HICs [4]. Two subsequent studies from Zambia suggested worse survival outcomes among patients receiving sepsis care bundles that emphasized fluid resuscitation [16, 17]. Taken collectively, and considering the limitations 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 fluid resuscitation [16, 17]. None of the 3 trials has fully assessed the impact of shortening time to antimicrobial administration, a key intervention in HIC-derived guidelines [13, 19].

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

METHODS

Patient Consent

This study was approved by the Kilimanjaro Christian Medical University College Research Ethics Committee (#2426), the United Republic of Tanzania National Institute for Medical Research National Health Research Ethics Coordinating Committee (NIMR/HQ/R.8a/Vol. IX/3132), and the Duke University Health System Institutional Review Board (Pro00101917). Minors <18 years of age had written consent provided by a parent or guardian, those aged 12–17 were required to provide written assent, and adults age ≥18 years provided their own written consent. Those initially consented by means of a representative due to alteration in mental status were reconsented if they regained adequate consciousness by the end of the study period.

Study Setting

The city of Moshi (population >200 000) is the administrative center of the Kilimanjaro Region (population >1.6 million) in northern Tanzania. The estimated prevalence of HIV in adults age 15–64 years from 2016 to 2017 in the Kilimanjaro Region was 2.6% [20]. HIV viral suppression in Kilimanjaro was estimated at 67% in 2017 [20]. The transmission intensity of malaria is low in the Kilimanjaro Region [21], with an estimated child prevalence of malaria <1% in 2017 [22]. Kiswahili is the most commonly spoken language in the region, though English and tribal languages are also common.

Kilimanjaro Christian Medical Centre (KCMC) is the 630-bed zonal referral hospital for northern Tanzania. The hospital has an emergency department (ED), medical and surgical inpatient wards, and intensive care units (ICUs) with capabilities for mechanical ventilation and vasopressor support available. Supplemental oxygen is available for hypoxic patients.

Study Design and Procedures

We conducted a prospective observational cohort study at KCMC from September 12, 2019, through April 17, 2020. Enrollment was prematurely halted due to the severe acute respiratory syndrome coronavirus 2 pandemic. A study team screened potential participants at the ED triage area from Monday through Friday from 9 am to 5 pm, excluding holidays, and we attempted to enroll as many participants as possible during the study period.

Our study included adolescents and adults, with adolescent defined as 10 to 17 and adults ≥18 years of age based on standards from the World Health Organization (WHO) [23, 24]. All adults and adolescents who presented during the prespecified period were screened for eligibility. Our case definition for sepsis was modified from the Systemic Inflammatory Response Syndrome (SIRS) criteria [9, 10]; certain tests of organ dysfunction were unavailable routinely and precluded the use of the 2016 Sepsis-3 definition [1]. Patients met inclusion criteria if they met our case definition for sepsis. Patients had to meet 2 of 3 SIRS criteria: (1) temperature dysregulation (>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 and $PaCO_2$ criteria were not used, as in other studies in SSA [4, 5], as results were not routinely available. Patients who met our modified SIRS criteria with presence of temperature dysregulation were considered to meet inclusion criteria given the high likelihood of an infectious etiology in our study setting [14]. In order to increase specificity for sepsis, given known limitations as described in Sepsis-3 [1], those with SIRS but without temperature dysregulation were also required to have at least 1 severe symptom from the WHO Integrated Management of Adolescent and Adult Illness (IMAI) Acute Care manual per self-report or staff assessment [23], which included stiff neck, convulsions, difficulty breathing, severe abdominal pain, lethargy or decline in consciousness, and confusion or agitation [25]. Finally, those with SIRS but without temperature dysregulation were excluded if the treating clinician reported confidence by 2 hours after arrival that the presentation was due to a noninfectious cause, regardless of presence of an IMAI severe symptom. This exclusion approach was added 2 weeks into our 6-week pilot period to increase the specificity of our case definition. While this real-time clinical adjudication approach in addition to a modified score was a novel approach, we felt that this process would address known specificity limitations with SIRS while preserving the ability to collect time-critical data points. Participants were classified as sepsis with or without hypotension (systolic blood pressure

≥90 mmHg or <90 mmHg, respectively). Pregnant women, prisoners, refugees, and those unable to speak English or Kiswahili were excluded from the study.

Our primary data collection occurred during the first 6 hours of workup and management after participant arrival to the ED. Trained study staff—2 clinical officers and 1 research assistant—collected the data. A standardized clinical history and physical examination were performed for each participant and included data on demographics, presenting symptoms, and medical history. As markers of severity of illness in LMICs [26], the history also assessed for ability to walk and drink unassisted. The physical examination by research staff included measurement of vital signs, peripheral oxygen saturation (SpO_2), mid-upper arm circumference (MUAC) as a measure of nutritional status [27, 28], and determination of mental status using the Alert-Verbal-Pain-Unconscious (AVPU) scale [29]. A point-of-care StatStrip Lactate test (Nova Biomedical, Billerica, MA, USA) was collected from each participant, and results were shared with the participant's treating clinician. Data on the workup and management of each participant were then collected within the initial 6-hour period, including information on use of antimicrobials, IV fluids, steroids, and vasopressors; collection of blood cultures and other microbiological specimens; and other laboratory and radiographic evaluations. The performance and results of either an HIV rapid antibody test or rapid malaria antigen test by the participant's treating clinician were recorded. We did not collect results of other microbiological studies, as etiological data were largely outside the scope of our study. Vital signs were rechecked, and an examination performed, at hours 3 and 6 after arrival. If a participant was admitted to the hospital before hour 6, their course was followed on the hospital ward until the 6-hour mark. If a patient was admitted to the hospital, limited data, including antimicrobials and vasopressor use, ICU admission, and outcomes, were collected. The study team had no direct involvement in sepsis diagnosis or management other than provision of a lactate result to the managing provider.

Data were collected using Open Data Kit (ODK Community, San Diego, CA, USA) on password-protected Samsung Galaxy Tab A tablets (Samsung Electronics, Suwon, South Korea) and stored in an Access database (Microsoft Corp., Redmond, WA, USA) on a secure server at KCMC.

Definitions

Our primary outcome was all-cause in-hospital death at any time after presentation. For our analysis, we prespecified cutoffs for several independent variables of interest to assess for associations with the primary outcome. We selected antimicrobial timing of 2 hours as opposed to the Surviving Sepsis Campaign standard of 1 hour due to possible delays related to resource limitations in the study setting [8]. A 6-hour cutoff was additionally used given that this time frame is the standard for early sepsis bundles and has been used in prior studies on time-to-antimicrobials [8, 12]. IV fluid administration was recorded and analyzed at 3 and 6 hours based on Surviving Sepsis Campaign 2016 guidelines [8]; a threshold of >1L was selected for analysis based on expected lower-volume resuscitation compared with HICs, as previously described [5]. MUAC was selected as a measure of nutritional status and a proxy for body mass index [26, 27] given expected difficulties obtaining weights in this acutely ill cohort. For adolescents, a low MUAC-for-age was defined as a Z-score-for-age of −2 or lower [27]. For adults, low MUAC-for-age was defined as <24 cm [28]. Altered mentation was defined as either Verbal (V), Pain (P), or Unconscious (U) on the AVPU scale. Hypoxia was defined as an SpO_2 <92% or use of supplemental oxygen. Health care–associated infection was defined as hospitalization within 90 days before onset of the presenting illness, surgery within 30 days, or prosthetic joint replacement within 1 year with symptoms at the site of joint replacement [30].

Two clinical prognostic scores for in-hospital death were calculated for each participant, qSOFA [1] and the Universal Vital Assessment (UVA) [31], and the standard proposed cutoffs for each were used in the analysis. For both scores, altered mentation was defined using a score of V, P, or U on the AVPU scale. For UVA, hypoxia was defined as above and 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 previously defined. Acknowledging that prognostic scoring systems and clinical definitions use varying cutoffs for each of these vital signs, we adopted each cutoff a priori to reflect thresholds that our team hypothesized to be of greater discriminatory capacity for outcomes.

Statistical Analysis

Descriptive statistics were performed and presented as medians and interquartile ranges (IQRs) for continuous variables. Categorical variables were presented as frequencies. Crude risk ratios (RRs) with 95% CIs were calculated using modified Poisson regression to assess for associations between demographic and clinical factors and incidence of all-cause, in-hospital mortality. We defined statistical significance as $P \leq .05$ with a 2-tailed test.

We performed separate multivariable analyses for 2 independent variables of interest for associations with in-hospital death: 1 analysis for administration of antimicrobials by hour 6 and another 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. For the multivariable analysis assessing

antimicrobials, we adjusted for IV fluids >1L 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 Stata 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Enrollment, Demographic, and Clinical Characteristics

Figure 1 summarizes participant screening, enrollment, and follow-up. Because eligibility requirements were changed during piloting to improve specificity for infection among those with SIRS, there were 5 (5.6%) enrolled pilot participants excluded from the analysis based on lack of an infectious diagnosis at time of admission. Of the 86 (94.5%) participants included in the final analysis, 4 (4.7%) were classified as sepsis with hypotension.

Table 1 depicts the baseline demographic and clinical characteristics of the patients.

Six (7.0%) participants were adolescents, and 27 (31.4%) were female. Of 13 (15.3%) participants who self-reported HIV infection, all 13 (100%) were on antiretroviral therapy and 6 (46.2%) were taking trimethoprim-sulfamethoxazole.

Management Characteristics and Outcomes

Clinical management characteristics and outcomes are summarized in Table 2. There were 25 (29.1%) in-hospital deaths. Sixteen (55.2%) of the 57 participants who did not receive antimicrobials within 6 hours reported having taken antimicrobials for this illness before hospitalization. For those who received antimicrobials by hour 6, the median (IQR) time to administration was 129 (97–203) minutes. Twenty-nine (33.7%) participants received antimicrobials during the first 6 hours: 26 (30.2%) ceftriaxone, 17 (19.8%) metronidazole, 1 (1.2%) ciprofloxacin, and 1 (1.2%) ampicillin. Thirty-six (41.9%) additional patients received antimicrobials after admission. All participants with hypotension received IV fluids by hour 3, and 1 (25.0%) received >1L. The median (IQR) IV fluids for the total cohort was 1000 (500–1500) mL. Four (4.7%) participants had rapid HIV tests performed, and all were negative. Malaria rapid diagnostic testing was performed for 20 (23.3%), of whom 3 (15.0%) were positive.

Clinical and Management Factors and Associations With In-hospital Death

Crude risk estimates for the associations between demographic and baseline clinical characteristics and the risk of in-hospital death are shown in Table 3. Clinical factors associated with increased risk of in-hospital death were inability to drink unassisted (RR, 3.15; 95% CI, 1.58–6.30), respiratory rate >30

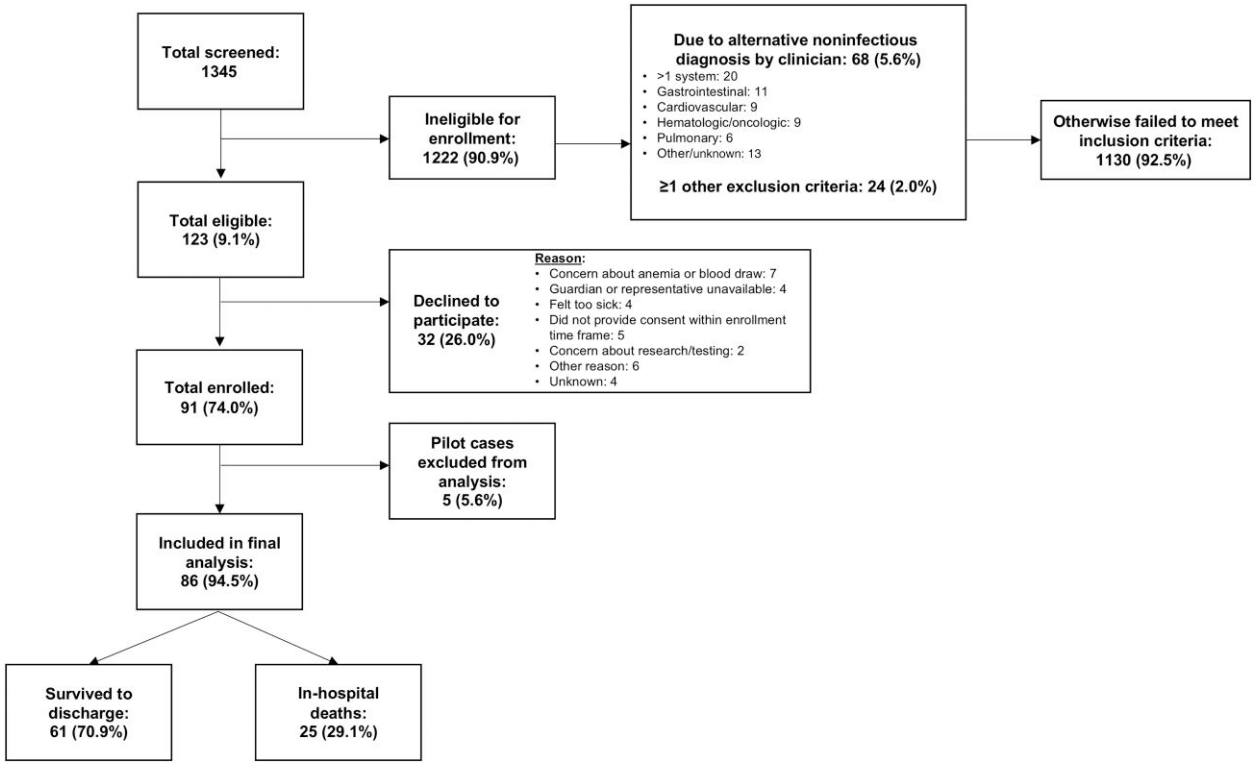

Figure 1. Flowchart of screening, enrollment, and inclusion in final analysis for adolescents and adults with sepsis, northern Tanzania, September 2019–April 2020.

Table 1. Baseline Demographic, Clinical History, Physical Examination, and Laboratory Characteristics for Adolescents and Adults With Sepsis, Northern Tanzania, September 2019–April 2020

	Total Cohort (n = 86)	Sepsis Without Hypotension (n = 82)	Sepsis With Hypotension (n = 4)
Demographics			
Age, median (IQR), y	46.5 (32–60)	46.5 (32–60)	49.5 (40.5–69)
Female	27 (31.4)	25 (30.5)	2 (50.0)
Highest level of education completed	…	…	…
None	26 (30.2)	25 (30.5)	1 (25.0)
Primary	43 (50.0)	41 (50.0)	2 (50.0)
Secondary	10 (11.6)	9 (11.0)	1 (25.0)
University	7 (8.1)	7 (8.5)	0
Insured	27 (31.4)	26 (31.7)	1 (25.0)
Clinical characteristics			
Duration of illness, median (IQR), d	5 (3–14)	5 (3–14)	2 (1–4.5)
Chief complaint by syndrome[a]	…	…	…
Neurological	36 (41.9)	36 (43.9)	0
Fever or systemic	21 (24.4)	19 (23.2)	2 (50.0)
Gastrointestinal	7 (8.1)	6 (7.3)	1 (25.0)
Cardiopulmonary	7 (8.1)	7 (8.5)	0
Other	15 (17.4)	14 (17.1)	1 (25.0)
Inability to walk unassisted	62 (72.1)	58 (70.7)	4 (100.0)
Inability to drink unassisted	31 (36.1)	28 (34.1)	3 (75.0)
Presence of chronic comorbidity[b]	48 (56.5)	45 (54.9)	3 (75.0)
HIV-infected by self-report	13 (15.3)	12 (14.6)	1 (25.0)
Health care–associated infection[c]	24 (27.9)	21 (25.6)	3 (75.0)
MUAC, median (IQR), cm	26.0 (24.0–29.0)	26.0 (24.0–29.0)	26.9 (24.9–27.5)
Temperature, median (IQR), °C	38.8 (38.4–39.4)	38.9 (38.4–39.4)	38.3 (37.9–39.2)
Heart rate, median (IQR), beats/min	111 (100–122)	109 (100–121)	125 (116–134)
Respiratory rate, median (IQR), breaths/min	26 (23–30)	26 (23–30)	24 (22–28)
Systolic blood pressure, median (IQR), mmHg	118.5 (105–145)	119 (107–145)	83 (78–86)
Diastolic blood pressure, median (IQR), mmHg	68 (60–82)	68 (61–84)	48 (43–50)
Hypoxia[d]	26 (30.2)	26 (31.7)	0
Altered mentation[e]	21 (24.4)	20 (24.4)	1 (25.0)
Lactate, median (IQR), mmol/L	1.5 (1.2–2.3)	1.4 (1.1–2.2)	3.1 (1.5–3.5)

Data are presented as No. (%) unless otherwise noted.

Abbreviations: AVPU, Alert-Verbal-Pain-Unconscious; IQR, interquartile range; MUAC, mid-upper arm circumference.

[a]Fever or systemic includes fever, rigors, night sweats, weight loss; Cardiopulmonary includes cough, hemoptysis, shortness of breath, chest pain; Gastrointestinal includes vomiting, vomiting of blood, abdominal pain or severe abdominal pain, diarrhea, blood in stool; Neurological includes headache, photophobia, neck stiffness, convulsions, lethargy, confusion; Other includes all other symptoms.

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

[c]Health care–associated infection was defined as hospitalization within 90 days before onset of the presenting illness, surgery within 30 days, or prosthetic joint replacement within 1 year with symptoms at the site of joint replacement.

[d]Hypoxia was defined as peripheral oxygen saturation <92% or use of supplemental oxygen.

[e]Altered mentation was defined as either V, P, or U on the AVPU scale.

breaths per minute (RR, 2.20; 95% CI, 1.17–4.12), hypoxia (RR, 2.13; 95% CI, 1.12–4.04), and altered mentation (RR, 3.94; 95% CI, 2.12–7.33). Participants with qSOFA ≥2, compared with <2, had an RR of in-hospital death of 2.86 (95% CI, 1.42–5.72), and those with a UVA ≥5, compared with <2, had an RR of 6.33 (95% CI, 2.36–17.02) for in-hospital death. There was no statistical difference in those with UVA scores of 2–4 compared with <2.

Regarding sepsis management factors, crude risk estimates for administration and timing of antimicrobials and IV fluids were not associated with in-hospital death. Among management factors, only the requirement for supplemental oxygen both within the first 6 hours (RR, 2.71; 95% CI, 1.48–4.94) and during hospitalization (RR, 3.88; 95% CI, 1.96–7.68) and admission to the intensive care unit (RR, 2.71; 95% CI, 1.48–4.94) were associated with in-hospital death.

In a multivariable analysis (Table 4), the adjusted RR for in-hospital death for those who received antimicrobials by hour 6 was 1.22 (95% CI, 0.69–2.17). The adjusted RR for risk of death in those who received IV fluids by hour 6 was 1.10 (95% CI, 0.59–2.07).

DISCUSSION

To our knowledge, this was the first study to describe clinical characteristics, management, and outcomes for adolescents

Table 2. Management Characteristics and Outcomes of Adolescents and Adults With Sepsis, Northern Tanzania, September 2019–April 2020

	Total Cohort (n = 86)	Sepsis Without Hypotension (n = 82)	Sepsis With Hypotension (n = 4)
Management characteristics, h 0–6			
Received antimicrobials by 2 h	14 (16.3)	14 (17.1)	0
Received antimicrobials by 6 h	29 (33.7)	29 (35.4)	0
If received, time to antimicrobials by h 6, median (IQR), min	129 (97–203)	129 (97–203)	n/a
Received any IV fluids by 3 h	42 (51.2)	38 (46.3)	4 (100)
Received any IV fluids by 6 h	49 (57.0)	45 (54.9)	4 (100)
<1L IV fluids	23 (46.9)	20 (44.4)	3 (75.0)
1–2L IV fluids	21 (42.9)	20 (44.4)	1 (25.0)
>2L IV fluids	5 (10.2)	5 (11.1)	0
If received, total IV fluids by h 6, median (IQR), mL	1000 (500–1500)	1000 (500–1500)	500 (350–750)
Blood cultures performed	26 (30.2)	25 (30.5)	1 (25.0)
If performed, obtained before antimicrobials given	24 (92.3)	23 (92.0)	1 (100)
Other investigation for infectious source performed[a]	65 (75.6)	63 (76.8)	2 (50.0)
Steroid administration	3 (3.5)	3 (3.7)	0
Supplemental oxygen given	17 (19.8)	17 (20.7)	0
Required emergent surgery	1 (1.2)	1 (1.2)	0
Hospital course			
Received ≥1 antimicrobial after admission	48 (55.8)	45 (54.9)	3 (75.0)
Required vasopressors at any time	2 (2.3)	2 (2.4)	0
Required supplemental oxygen at any time	27 (31.4)	26 (31.7)	1 (25.0)
Intensive care unit at any time	17 (19.8)	16 (19.5)	1 (25.0)
Outcomes			
In-hospital death	25 (29.1)	24 (29.3)	1 (25.0)
Length of stay, median (range), d	4.5 (1–8)	4.5 (1–8)	5.5 (2.5–8)
Deaths by qSOFA and UVA scores[b]	…	…	…
qSOFA <2	9 (17.0) of 53	9 (17.0) of 53	0 of 0
qSOFA ≥2	16 (48.5) of 33	15 (51.7) of 29	1 (25.0) of 4
UVA <2	4 (10.5) of 38	4 (10.8) of 37	0 (0) of 1
UVA 2–4	9 (30.0) of 30	9 (31.0) of 29	0 (0) of 1
UVA ≥5	12 (66.7) of 18	11 (68.8) of 16	1 (50.0) of 2

Data are presented as No. (%) unless otherwise noted.

Abbreviations: IQR, interquartile range; IV, intravenous; qSOFA, quick Sequential Organ Failure Assessment; UVA, Universal Vital Assessment.

[a]Includes rapid HIV test, malaria rapid diagnostic test, urinalysis, urine culture, lumbar puncture, sputum culture, or any sputum acid-fast bacilli test, or any method of imaging.

[b]Given as [# deaths] (%) of [# of cohort or subgroup in score category].

and adults with sepsis in Tanzania. We found that the incidence of in-hospital death was high despite few presenting with hypotension. We also found that several clinical factors were strongly associated with in-hospital death: inability to drink unassisted, respiratory rate >30 breaths per minute, hypoxia, requirement for supplemental oxygen, altered mentation, ICU admission, qSOFA scores ≥2 compared with <2, and UVA scores ≥5 compared with <2. Neither antimicrobial nor IV fluid administration was associated with in-hospital death.

In our cohort, in-hospital death occurred in 29.1%. Very few participants presented with hypotension. The mortality in our cohort is consistent with other sepsis studies in SSA [32]. Our modified Sepsis-2 definition [10] was unable to distinguish between sepsis and severe sepsis as defined by organ dysfunction.

The clinical factors most strongly associated with in-hospital death were inability to drink unassisted, requirement for supplemental oxygen, hypoxia, respiratory rate >30 breaths per minute, and altered mentation. Other cohorts in LMICs have reported an increased risk of death with inability to walk unassisted [33, 34], a low-cost early prognostic measure well-suited for LMICs. While participants frequently reported the inability to walk in our cohort, a participant's reported inability to drink was more strongly associated with death.

We make several observations relevant to sepsis management in SSA. Neither antimicrobial administration nor >1L IV fluid administration by 6 hours was associated with increased risk of death, including in the adjusted analysis. Timing of antimicrobials has not been studied fully in the SSA setting, and thus it is not clear if early administration is as closely linked to survival as demonstrated in HICs [19, 35, 36]. It is plausible that the increased duration of illness, varied etiologies of severe febrile illness [14, 15], delays from onset of severe symptoms to presentation to health care [37], preceding antimicrobial administration, and other factors unique to the SSA setting may mitigate the benefits of early antimicrobials compared with HICs. However, the lack of impact of antimicrobial timing on

Table 3. Clinical Characteristics and Associations With Inpatient Mortality in Adolescents and Adults With Sepsis, Northern Tanzania, September 2019–April 2020

	Survivors (n = 61)	In-hospital Deaths (n = 25)	Risk Ratio (95% CI)
Demographics			
Age, median (IQR), y	45 (31–60)	50 (38–56)	…
Age >60 y	15 (24.6)	6 (24.0)	0.98 (0.45–2.13)
Female	19 (31.2)	8 (32.0)	1.03 (0.51–2.09)
Education level completed primary or less	46 (75.4)	23 (92.0)	2.83 (0.73–10.95)
Any insurance	23 (37.7)	4 (16.0)	0.42 (0.16–1.10)
Clinical characteristics			
Duration of illness ≥7 d	29 (47.5)	10 (40.0)	0.80 (0.41–1.59)
Duration since onset of severe symptom ≥7 d	18 (29.5)	6 (24.0)	0.58 (0.26–1.30)
Presence of chronic comorbidity[a]	31 (51.7)	17 (68.0)	1.64 (0.79–3.39)
HIV-infection (self-reported)	10 (16.7)	3 (12.0)	0.76 (0.26–2.18)
Inability to walk unassisted	40 (65.6)	22 (88.0)	2.83 (0.93–8.67)
Inability to drink unassisted	15 (24.6)	16 (64.0)	3.15 (1.58–6.30)
Low MUAC-for-age, cm	14 (23.0)	8 (32.0)	1.37 (0.69–2.73)
Temperature >38°C	55 (90.2)	21 (84.0)	0.69 (0.30–1.61)
Temperature <36°C	1 (1.64)	1 (4.0)	…
Heart rate >110	29 (47.5)	15 (60.0)	1.43 (0.72–2.84)
Respiratory rate >30	10 (16.4)	10 (40.0)	2.20 (1.17–4.12)
Hypoxia[b]	14 (23.0)	12 (48.0)	2.13 (1.12–4.04)
Systolic blood pressure <100 mmHg	12 (19.7)	5 (20.0)	1.01 (0.44–2.32)
Mean arterial pressure <65 mmHg	4 (6.6)	1 (4.0)	…
Altered mentation[c]	7 (11.5)	14 (56.0)	3.94 (2.12–7.33)
Lactate >2 mmol/L	17 (27.9)	9 (36.0)	1.30 (0.66–2.56)
qSOFA score ≥2	17 (27.9)	16 (64.0)	2.86 (1.42–5.72)
UVA score	…	…	…
UVA score <2	34 (55.7)	4 (16.0)	1
UVA score 2–4	21 (34.4)	9 (36.0)	2.85 (0.97–8.41)
UVA score ≥5	6 (9.8)	12 (48.0)	6.33 (2.36–17.02)
Management characteristics, h 0–6			
Antimicrobials administered by h 2	9 (14.8)	5 (20.0)	1.29 (0.58–2.86)
Antimicrobials administered by h 6	19 (31.2)	10 (40.0)	1.31 (0.67–2.55)
Time to antimicrobials if received, median (IQR), min	129 (80–193)	133.5 (103–206)	…
Initiation of IV fluid bolus by h 3	29 (47.5)	13 (52.0)	1.13 (0.58–2.21)
Total IV fluids >1L by h 6	37 (60.7)	17 (68.0)	1.26 (0.61–2.59)
Total IV fluids by h 6, median (IQR), mL	550 (500–1500)	1000 (500–2000)	…
Blood cultures performed	19 (31.2)	7 (28.0)	0.90 (0.43–1.89)
Other investigation for infectious source performed[d]	45 (73.8)	20 (80.0)	1.29 (0.55–3.03)
Steroid administration	1 (1.64)	2 (8.0)	…
Supplemental oxygen given	7 (11.5)	10 (40.0)	2.71 (1.48–4.94)
Required emergent surgery	0	1 (4.0)	…
Admission characteristics			
Received ≥1 antimicrobial after admission	30 (49.2)	18 (72.0)	2.04 (0.85–4.87)
Required vasopressors at any time	0	2 (8.0)	…
Required supplemental oxygen at any time	11 (18.0)	16 (64.0)	3.88 (1.96–7.68)
Intensive care unit at any time	7 (11.5)	10 (40.0)	2.71 (1.48–4.94)

Data are presented as No. (%) unless noted otherwise.

Abbreviations: AVPU, Alert-Verbal-Pain-Unconscious; IQR, interquartile range; IV, intravenous; MUAC, mid-upper arm circumference; qSOFA, quick Sequential Organ Failure Assessment; UVA, Universal Vital Assessment.

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

[b]Hypoxia was defined as peripheral oxygen saturation <92% or use of supplemental oxygen.

[c]Altered mentation was defined as either V, P, or U on the AVPU scale.

[d]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.

outcomes in our study is to be interpreted with substantial caution—studies to date demonstrating the benefits of early administration have come from considerably larger cohorts with modest effect sizes for risk of death with increasing delays in administration [19, 38]. Further, we had few patients with shock and were not able to ultimately adjudicate the presence of

Table 4. Multivariable Analysis of Factors Associated With Inpatient Mortality in Adolescents and Adults With Sepsis, Northern Tanzania, September 2019–April 2020

	Crude Risk Ratio	95% CI	Adjusted Risk Ratio[a]	95% CI
Antimicrobials administered by h 6	1.31	0.67–2.55	1.22	0.69–2.17
Intravenous fluid volume >1L by h 6	1.26	0.61–2.59	1.10	0.59–2.07

Antimicrobial administration by h 6 was adjusted for intravenous fluid volume >1L by h 6, and intravenous fluid volume >1L by h 6 was adjusted for antimicrobial administration by h 6. Interaction terms for sex and each independent variable of interest were also used in the analyses.

Abbreviation: UVA, Universal Vital Assessment.

[a]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).

infection in our cohort; thus our capacity to evaluate impacts of antimicrobials was quite limited. Nonetheless, given that overall antimicrobial administration by hour 6 was low across the cohort, improving early administration of antimicrobials likely remains a reasonable target for sepsis management in SSA until more data are available.

IV fluid resuscitation is an area of ongoing interest in both HIC and LMIC settings. In the early 2000s, Early Goal Directed Therapy (EGDT) initiatives led to large IV fluid volume administration in HIC settings. However, studies from SSA later demonstrated potential harm of this approach [4, 16, 17], and large EGDT trials failed to reproduce the mortality benefit seen in the original study [39]. Further, a recent study in an HIC setting demonstrated the safety of a fluid-restrictive approach [7]. 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 death. 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 needed to better clarify patients likely to be fluid-responsive in the SSA setting.

With respect to workup, we also found opportunities for improvement. Only a third of participants had blood cultures collected. Though the causes of severe febrile illness in SSA differ considerably compared with HICs, bloodstream infections remain a prominent contributor to febrile hospitalizations at KCMC [11, 12, 14]. Another notable finding was that only 4 participants received HIV testing within the first 6 hours. HIV testing is recommended for all patients presenting with acute illness in SSA [23, 40], as HIV-associated infections, such as disseminated cryptococcosis, can lead to sepsis.

Our study has several limitations. Of course, our small sample size with few participants with shock, use of a convenience sample, and single-center nature limited our power to estimate associations between interventions and mortality, may have introduced bias, and limited generalizability, respectively. We may have also introduced bias via the Hawthorne effect, in which treating clinicians may have changed their management due to observation. Our modified SIRS-based sepsis definition is another limitation. We attempted to compensate for specificity issues with a novel real-time clinical adjudication approach, but our study was not able to make final adjudications of whether an infectious cause was present, and we likely characterized some patients with noninfectious diagnoses as sepsis. We believe practical sepsis definitions in LMIC settings remain a considerable challenge for future study. Finally, our use of an incidence proportion as a measure of risk as opposed to a proportional hazards analysis is a limitation. While a survival model would have accounted for nonlinear rates of death over time and differing lengths of follow-up by exposure strata, sepsis literature frequently uses in-hospital death as a key, if flawed, outcome measure. For the purposes of this study, our team opted to follow an analysis approach that would be more comparable to existing literature despite the potential advantages of the survival model.

Overall, despite the limitations of our study, until additional research in larger cohorts is performed in this setting, our results have substantial descriptive value as one of a limited group of studies on sepsis in adolescents and adults in SSA.

CONCLUSIONS

In our observational study of sepsis at a tertiary referral medical center in northern Tanzania, we found that sepsis carried a high risk of in-hospital death. Clinical findings of altered mentation or inability to drink unassisted represent feasible means for identifying sepsis patients at increased risk of in-hospital death. We identified improvement opportunities, such as timely antimicrobial administration, collection of blood cultures, and early HIV testing. Further research is needed to improve identification of sepsis and establish the highest-yield interventions suited to the unique characteristics of SSA.

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Data availability. Data may be obtained upon request to the corresponding author.

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