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Stratifying Sepsis in Uganda Using Rapid Pathogen Diagnostics and Clinical Data: A Prospective Cohort Study

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Abstract. The global burden of sepsis is concentrated in sub-Saharan Africa, where extensive pathogen diversity and limited laboratory capacity challenge targeted antimicrobial management of life-threatening infections. In this context, established and emerging rapid pathogen diagnostics may stratify sepsis patients into subgroups with prognostic and therapeutic relevance. In a prospective cohort of adults (age ≥18 years) hospitalized with suspected sepsis in Uganda, we stratified patients using rapid diagnostics for HIV, tuberculosis (TB), malaria, and influenza, and compared clinical characteristics and 30-day outcomes across these pathogen-driven subgroups. From April 2017 to August 2019, 301 adults were enrolled (median age, 32 years [interquartile range, 26–42 years]; female, n = 178 [59%]). A total of 157 patients (53%) were HIV infected. Sixty-one patients (20%) tested positive for malaria, 52 (17%), for TB (including 49 of 157 [31%] HIV-infected patients), and 17 (6%), for influenza. Co-infection was identified in 33 (11%) patients. The frequency of multi-organ failure, including shock and acute respiratory failure, was greatest among patients with HIV-associated TB. Mortality at 30 days was 19% among patients with malaria, 40% among patients with HIV-associated TB, 32% among HIV-infected patients without microbiological evidence of TB, 6% among patients with influenza, and 11% among patients without a pathogen identified. Despite improvements in anti-retroviral delivery, the burden of sepsis in Uganda remains concentrated among young, HIV-infected adults, with a high incidence of severe HIV-associated TB. In parallel with improvements in acute-care capacity, use of rapid pathogen diagnostics may enhance triage and antimicrobial management during emergency care for sepsis in sub-Saharan Africa, and could be used to enrich study populations when trialing pathogen-specific treatment strategies in the region.

INTRODUCTION

Sepsis is a heterogeneous syndrome of acute organ dysfunction resulting from a complex host response to infection.[1] The global burden of sepsis is substantial, with nearly 50 million cases and 11 million deaths estimated in 2017.[2] Because 85% of sepsis-related deaths occur in low- and middle-income countries (LMICs), the World Health Assembly adopted a resolution in 2017 to improve the prevention, diagnosis, and clinical management of sepsis, with an emphasis on LMICs.[2,3]

Across LMICs, the burden of sepsis is concentrated in sub-Saharan Africa (SSA), where infectious diseases remain the leading cause of hospitalization and death.[2,4–7] Despite a high incidence of infection with diverse pathogens and unique host factors, including epidemic HIV, knowledge of which patients hospitalized with severe infections in SSA are most likely to develop sepsis-associated organ dysfunction and how to triage and manage such patients optimally is poorly understood.[8–11] Although most patients hospitalized with severe infection and sepsis in high-income countries (HICs) are managed with similar antimicrobial and resuscitative interventions regardless of the infecting pathogen, management strategies in SSA may require a more stratified, pathogen-driven approach.[5,8–13] In this context, integration of clinical data with rapid pathogen diagnostics may enable more effective triage and antimicrobial management through earlier, near-point-of-care recognition of sepsis etiologies.[5] Because the diagnostic and prognostic yield of rapid diagnostic platforms among patients with sepsis in SSA remains understudied, related investigations have been highlighted as a research priority.[5]

As part of a prospective cohort study of adults hospitalized with undifferentiated severe infection (i.e., suspected sepsis) at a public district hospital in Uganda, we performed rapid diagnostic testing for HIV, tuberculosis (TB), malaria, and influenza. In this study, we determined the yield of this diagnostic approach and compared clinical characteristics, organ failure profiles, and patient outcomes across pathogen-driven subgroups.

MATERIALS AND METHODS

Study site, capacity, and participants. We conducted a prospective cohort study (Research in the Epidemiology of Severe and Emerging Infections in Uganda [RESERVE-U]) of patients hospitalized with severe undifferentiated infection at Entebbe General Referral Hospital (EGRH) in Uganda from April 2017 to August 2019. EGRH is a 200-bed public district hospital with a surrounding catchment area of approximately 3 million persons. In the primary catchment area, HIV prevalence is approximately 6% and malaria is endemic, with an estimated *Plasmodium falciparum* parasite rate (an index of malaria transmission intensity based on the proportion of the population age 2–10 years that is infected with asexual blood-stage parasites) of 33.8.[14,15] Representative of a general district hospital in SSA, there is no intensive care unit at

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EGRH. No vasopressor or inotropic agents are available on the hospital wards, and intravenous (IV) fluid is typically delivered as 250- to 500-mL infusions of crystalloid, either normal saline or Ringer's lactate solution. Because no piped oxygen is available at EGRH, oxygen concentrators were provided to hospital wards as part of the study program, with the ability to provide 4 to 6 L/min of supplemental oxygen via nasal cannula.

Patients were included in this study if they fulfilled the following criteria: 1) age $\geq$ 18 years, 2) a reported history of fever or a recorded axillary temperature of $\geq$ 37.5°C at presentation, 3) clinical illness at presentation severe enough to warrant hospital admission, and 4) able to provide informed consent or had a surrogate available to do so. Patients were excluded if they presented after trauma or were admitted to a non-medical ward. During the study period, all admissions to the hospital medical wards were screened for eligibility by study staff. Patients were screened on weekdays during daytime hours and were enrolled as close to admission as possible, and no longer than 24 hours afterward. Although patients 5 to 17 years of age were also included in the prospective cohort, given variations in pathogen-specific infection risk and normal vital sign parameters across age groups, for this analysis we included only adults (age $\geq$ 18 years) enrolled in the cohort.

Clinical data collection and rapid pathogen diagnostics. At the time of enrollment, clinical assessments were obtained through patient history and review of medical charts, vital signs were recorded, and a physical examination was performed. If available, results of complete blood counts (performed at the hospital laboratory) were also recorded.

As part of the RESERVE-U study, testing was performed for malaria, influenza, and HIV for all patients; for HIV-infected patients, testing for TB was also performed. Testing for these pathogens was informed by the WHO Integrated Management of Adolescent and Adult Illness (IMAI) *IMAI District Clinician Manual* guidelines for management of patients with sepsis and septic shock. These guidelines emphasize rapid testing for malaria and HIV, a low threshold for TB testing among HIV-infected patients, and consideration of empiric treatment of influenza if it is suspected.[16] Although neuraminidase inhibitors are not widely available in Uganda, EGRH is a longstanding sentinel site for national influenza surveillance, and thus testing for influenza was also performed. For malaria, testing was performed using qualitative detection of histidine-rich protein II and lactate dehydrogenase of *P. falciparum* in whole blood. For all enrolled HIV-infected patients, a single urine sample and a single spontaneously expectorated sputum sample, if obtainable, were tested for *Mycobacterium tuberculosis* (MTB) using the Determine TB-LAM Ag (Alere/Abbott, Abbott Park, IL) and Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA) platforms, respectively. Sputum smear microscopy was performed at the discretion of treating clinicians, as was Xpert MTB/RIF Ultra testing of sputum for non-HIV-infected patients. Nasopharyngeal swab samples were tested for influenza A and B via real-time polymerase chain reaction (PCR), with primers provided by the U.S. CDC. Further details on pathogen diagnostics are available in the supplemental material.

Clinical management and outcomes. Throughout hospitalization, all clinical management decisions were made by ward clinicians independent of the study team. The study team recorded management details until discharge, transfer to another health facility, or death. Specifically, the study team recorded the cumulative volume of IV fluid and antimicrobial agents administered during the first 24 hours of hospitalization, as well as whether patients received blood transfusions. For patients discharged from EGRH alive, functional status at discharge was evaluated using the Karnofsky Performance Status (KPS) score.

The primary outcome of this study was vital status 30 days after discharge (obtained via telephone from patients or their surrogates). Secondary outcomes included a composite measure of in-hospital outcome (death in-hospital or transfer to Uganda's national referral hospital because of progressive severity of illness) and functional status at discharge (among patients who survived and were not transferred). Patients transferred to the national hospital were contacted to assess vital status at 30 days.

Prior to initiating study enrollment, two formal training sessions were conducted with hospital ward clinicians on the emergency management of severe infection and sepsis in resource-limited settings. Training was based on the WHO *IMAI District Clinician Manual*. Specifically, clinicians were educated about the "Quick Check" triage protocol and guidance on the management of sepsis and septic shock, and severe respiratory distress without shock.[16] Notably, in the context of prior clinical trials of protocolized resuscitation among patients hospitalized with severe infection and sepsis in SSA, risks associated with aggressive fluid boluses, particularly in the absence of high-level respiratory support, were highlighted.[17–19] Uganda National Tuberculosis and Leprosy Programme guidelines on the management of inpatient TB suspects were also reviewed.[20] During the subsequent study period, bedside clinical mentoring sessions were conducted ad hoc by study clinicians to review clinical management.

Statistical analysis. Continuous variables were expressed as medians (interquartile range [IQR]); categorical variables were summarized as counts and percentages. Differences in clinical characteristics and outcomes across subgroups were compared using χ^2 or Fisher exact and Kruskal-Wallis H tests, where appropriate. In an exploratory analysis to evaluate the ability of the quick sequential (sepsis-related) organ failure assessment (qSOFA) to discriminate risk of poor in-hospital and 30-day outcomes across pathogen subgroups, we calculated areas under receiver–operating characteristic curves (AUROCs) and corresponding 95% CIs. Analyses were performed using Stata (v. 16; StataCorp, College Station, TX), and data were visualized using the DeepVenn software package.[21]

Ethics statement. In the parent study, each enrolled participant $\geq$18 years or their surrogate provided written informed consent. The study was approved by ethics committees at Columbia University, the Uganda Virus Research Institute, and the Uganda National Council for Science and Technology.

RESULTS

Study participant characteristics. From April 2017 to August 2019, 431 patients were enrolled in the parent cohort study. After excluding 130 patients younger than 18 years,

we analyzed data from 301 adult patients (Supplemental Figure 1). Baseline patient characteristics, results of rapid pathogen diagnostics, and outcomes for this adult cohort are presented in Table 1. Notably, 45% and 87% of patients had a qSOFA score $\geq$ 2 and $\geq$ 1, respectively, and 85% of patients had a modified systemic inflammatory response syndrome score $\geq$ 2.

Clinical management during the first 24 hours of hospitalization. Nearly all patients received IV fluid (91%; median, 1500 mL; IQR, 1,000–2,000 mL) and anti-bacterial agents (95%; most frequently ceftriaxone) during the first 24 hours of admission, and 48% and 19% received anti-malarial and anti-TB agents, respectively (Supplemental Table 1). Only 3% of patients received supplemental oxygen as a result of the limited availability of oxygen at the study site.

Characterization of pathogen-driven subgroups. Of the 301 enrolled patients, 201 (67%) had either malaria, HIV with or without microbiological evidence of TB, or influenza; 100 (33%) did not have a pathogen identified (Supplemental Table 2). Specifically, 61 (21%) had malaria, 49 (16%) had HIV-associated TB, 108 (36%) had HIV without microbiological evidence of TB, and 17 (6%) had influenza (Figure 1). Co-infection was identified in 33 patients: 20 had HIV–malaria co-infection, four had HIV-TB–malaria co-infection, five had HIV–influenza co-infection, two had malaria–influenza co-infection, one had HIV–malaria–influenza co-infection, and another had HIV-TB–influenza co-infection (Figure 1). Illness severity, indicated by higher qSOFA and Modified Early Warning scores, and a greater frequency of multi-organ failure, was greater among patients with pathogens identified, particularly those with HIV-associated TB (Table 2, Supplemental Table 2).

Outcomes. Analysis of the primary outcome showed that 63 of 272 patients with known vital status at 30 days died (23%) (Table 1). Mortality at 30 days was 19% among patients with malaria, 40% among patients with HIV-associated TB, 32% among HIV-infected patients without microbiological evidence of TB, and 6% among patients with influenza (Table 2). Mortality at 30 days in the malaria subgroup was driven largely by those with HIV co-infection (7 of 24 [29%] in malaria with HIV co-infection versus 4 of 35 [11%] in malaria without HIV co-infection). Of the 87 patients for whom no pathogen was identified and 30-day vital status was known, 10 (11%) died (Supplemental Table 2). Forty-two patients (14%) met the composite in-hospital outcome of death or transfer to the national referral hospital. Twenty of 257 patients (8%) who were discharged alive and had known functional status had a KPS score $\leq$ 70, indicating an inability to perform normal activities (Table 1). HIV-infected patients with and without TB met the composite in-hospital outcome more frequently and had worse functional status compared with HIV-uninfected patients (Table 2). Excluding influenza, given the small number of outcome events in this subgroup, discriminatory ability of the qSOFA score to predict poor in-hospital outcome was sub-optimal, ranging from AUROCs of 0.56 to 0.68 across pathogen subgroups for qSOFA $\geq$ 2 and 0.49 to 0.58 for qSOFA $\geq$ 1, with similar ranges observed for 30-day outcomes (Supplemental Table 3).

DISCUSSION

Among a prospective cohort of adults hospitalized with suspected sepsis in Uganda, use of rapid diagnostics identified patients with significantly greater risk of mortality and stratified nearly 70% into actionable, pathogen-driven subgroups. These subgroups had unique clinical characteristics, patterns of organ dysfunction, and outcomes. In conjunction with improvements in acute-care and laboratory capacity, application of rapid pathogen diagnostics, particularly those targeting HIV-associated TB, may enhance triage and antimicrobial management during emergency care for sepsis in SSA.[10,22–24] These platforms could also be used to enrich study populations when trialing pathogen-specific treatment strategies in the region.

In SSA, limited laboratory capacity and an expansive range of endemic pathogens challenge targeted antimicrobial management for patients hospitalized with sepsis. Acknowledging these challenges and the time-critical nature of antimicrobial administration, WHO IMAI guidelines recommend rapid initiation of empiric broad-spectrum anti-bacterial and anti-malarial agents for patients hospitalized with sepsis and septic shock in SSA, as well as consideration of empiric anti-TB therapy for patients with HIV infection.[5,16] Although this syndromic treatment strategy is necessary in settings where laboratory resources are poor, it likely results in administration of ineffective or overly broad antimicrobials given the non-specific clinical presentation of severe HIV- and non-HIV-associated infections.[22] This is reinforced by the relatively high frequency of co-infection (11%) in our cohort. Considering their prognostic yield in identifying patients at greater risk for poor in-hospital and 30-day outcomes, as well as their low cost and near-point-of-care availability, further studies are needed to evaluate integrated use of rapid pathogen diagnostics to guide antimicrobial management for sepsis in SSA.[10,22–24] Given the increasing burden of bacterial antimicrobial resistance (AMR) in SSA, enhanced clinical microbiological capacity is needed to define more fully the epidemiology of AMR and inform development of empiric anti-bacterial regimens in the region.[25]

More than half the patients enrolled in our study were HIV infected. Despite global improvements in anti-retroviral therapy delivery, the final common pathway of advanced HIV infection in SSA remains progressive immunosuppression followed by an acute, often-terminal critical illness event.[7,26] In our study, patients with HIV infection developed more extensive organ dysfunction and had greater mortality and more impaired functional status. There was also a high incidence of severe and often disseminated TB (indicated by positive urine TB-LAM testing) among HIV-infected patients. Because disseminated TB is recognized increasingly as one of the leading causes of sepsis in HIV-infected patients in SSA, our data highlight the importance of severe HIV-associated TB in this context, and reinforce the importance of ongoing clinical trials examining the efficacy of empiric anti-TB treatment in HIV-associated sepsis.[7,27–30]

In contrast to the epidemiology of sepsis in HICs, patients enrolled in our study were young, with a median age of 32 years. The age distribution of our cohort, likely a result of a high prevalence of HIV infection among young adults, is similar to that from other studies of severe infection and sepsis in SSA.[9] The high incidence of severe and critical illness in this population warrants urgent action to define better the functional outcomes among an economically and socially productive age group, and to develop and test sepsis interventions to improve outcomes and enhance survivorship.[9]

Although the global burden of sepsis is concentrated in SSA, understanding of the optimal approach to triage severely infected patients and "diagnose" sepsis in the region is imprecise. The qSOFA score, developed using data from North American and European cohorts to identify infected inpatients at high risk for death, may fail to capture sensitively the spectrum of infection-related organ dysfunction in SSA, where host and pathogen characteristics are

TABLE 1
Patient characteristics, pathogen diagnostics, and outcomes

Patient characteristic	Study population (N = 301)
Female, n (%)	178/301 (59)
Age group, y; n (%)	
18–24	55/301 (18)
25–34	113/301 (38)
35–44	70/301 (23)
45–54	43/301 (14)
55–64	11/301 (4)
≥ 65	9/301 (3)
Age, y; median (IQR)	32 (26–42)
Symptoms reported, n (%)	
Fever	301/301 (100)
Night sweats	236/301 (78)
Cough	188/301 (62)
Headache	238/301 (79)
Diarrhea	102/301 (34)
Shortness of breath	68/301 (23)
Dysuria	40/301 (13)
Duration of illness prior to hospitalization,* d; median (IQR)	4 (3–7)
Received antibacterial or antimalarial agent prior to hospitalization, n (%)	107/301 (36)
Vital signs	
Temperature ≥ 38°C, n (%)	107/301 (36)
Temperature < 36°C, n (%)	87/301 (29)
Heart rate, beats/min; median (IQR)	98 (87–109)
Respiratory rate, breaths/min, median (IQR)	22 (21–26)
Systolic blood pressure, mmHg; median (IQR)	103 (91–117)
Oxygen saturation, %; median (IQR)	97 (95–98)
Altered mental status,† n (%)	58/301 (19)
qSOFA score ≥ 2,‡ n (%)	134/301 (45)
qSOFA score ≥ 1,‡ n (%)	262/301 (87)
Modified SIRS score ≥ 2,§ n (%)	257/301 (85)
MEWS, median (IQR)	3 (2–5)
UVA score, median (IQR)	2 (1–4)
Shock,‖ n (%)	41/301 (14)
Acute respiratory failure,¶ n (%)	65/301 (22)
Severe anemia,# n (%)	60/301 (20)
HIV infected, n (%)	157/299 (53)
WHO clinical stage 3 or 4	126/157 (80)
New diagnosis of HIV infection	21/157 (13)
Taking ART prior to hospitalization**	92/136 (68)
Taking cotrimoxazole prior to hospitalization**	96/136 (71)
Pathogen diagnostics, n (%)	
Malaria RDT positive	61/296 (21)
TB diagnostic positive	52/301 (17)
Sputum Xpert MTB/RIF Ultra or smear positive	23/52 (44)
Urine TB-LAM positive††	41/52 (79)
Influenza PCR positive	17/272 (6)
Patient outcome	
Died in-hospital, n (%)	21/301 (7)
Transferred to national referral hospital, n (%)	21/301 (7)
Duration of hospitalization, d;‡‡ median (IQR)	5 (3–7)
KPS score ≤ 70 if discharged from hospital alive, n (%)	20/257 (8)
Dead at 30 d post-discharge, n (%)	63/272 (23)

ART = anti-retroviral therapy; IQR = interquartile range; KPS = Karnofsky Performance Status; LAM = lipoarabinomannan; MEWS = Modified Early Warning Score; PCR = polymerase chain reaction; qSOFA = quick sequential (sepsis-related) organ failure assessment; RDT = rapid diagnostic test; SIRS = systemic inflammatory response syndrome; TB = tuberculosis; UVA = universal vital assessment.

* Unknown for one patient.

† Anything other than "alert" on the alert, responsive to voice, responsive to pain, unresponsive (AVPU) mental status assessment.

‡ Systolic blood pressure ≤ 100 mmHg, respiratory rate ≥ 22 breaths/min, and altered mental status, with the latter defined using the AVPU scale.

§ Temperature ≥ 38°C or < 36°C, heart rate ≥ 90 beats/min, and respiratory rate ≥ 20 breaths/min.

‖ Systolic blood pressure ≤ 90 mmHg despite administration of ≥ 1 L intravenous fluid.

¶ Oxygen saturation ≤ 90% or respiratory rate ≥ 30 breaths/min.

Hemoglobin < 9 g/dL or administration of blood transfusion.

** Denominator is number with known HIV-infection prior to admission.

†† Urine TB-LAM results available from 124 of 157 HIV-infected patients.

‡‡ Unknown for 11 patients.

highly divergent from those in HICs.[31–34] Conversely, the traditional systemic inflammatory response syndrome criteria may lack specificity to impact triage practices meaningfully and include laboratory values that are often unavailable in LMICs.[31] To improve classification of severely infected patients in SSA into more homogenous clinical and biological subtypes that can be targeted for further investigation, large, multi-national studies incorporating pathogen and AMR diagnostics, and genomic, immunological, and microvascular profiling are needed.[35] In the interim, implementation interventions to enhance vital sign collection and recognition of severe illness using existing guidelines for austere settings should be considered.[36]

Nearly all patients enrolled in our cohort received IV fluid, with a median volume of 1,500 mL administered during the first 24 hours of hospitalization. Estimating an average patient weight of 50 kg, this constitutes administration of approximately 30 mL/kg IV fluid. Although this volume is less than that recommended in guidelines for sepsis and septic shock resuscitation proposed by the WHO IMAI (rapid IV bolus of 1 L of crystalloid; maximum, 60 mL/kg in the first 2 hours) and the Surviving Sepsis Campaign (30 mL/kg IV crystalloid in the first 3 hours), the optimal approach to deliver and assess fluid resuscitation for patients hospitalized with sepsis in SSA is unknown.[10,11,16,37] Although a before-and-after study from Uganda demonstrated improved survival for sepsis among predominantly HIV-infected adults receiving protocol-based resuscitation, three clinical trials in SSA have shown worse survival for pediatric and adult inpatients with severe infection and sepsis managed with early, aggressive fluid resuscitation.[17–19,38] This signal for harm was consistent among subgroups stratified by HIV status, malarial infection, and severity of shock and anemia.[17–19] Because more targeted antimicrobial delivery is unlikely to improve outcomes in the absence of appropriate resuscitation, respiratory support, and monitoring, clinical trials focused on optimizing sepsis resuscitation in SSA, together with improved hospital capacity, remain a global priority.

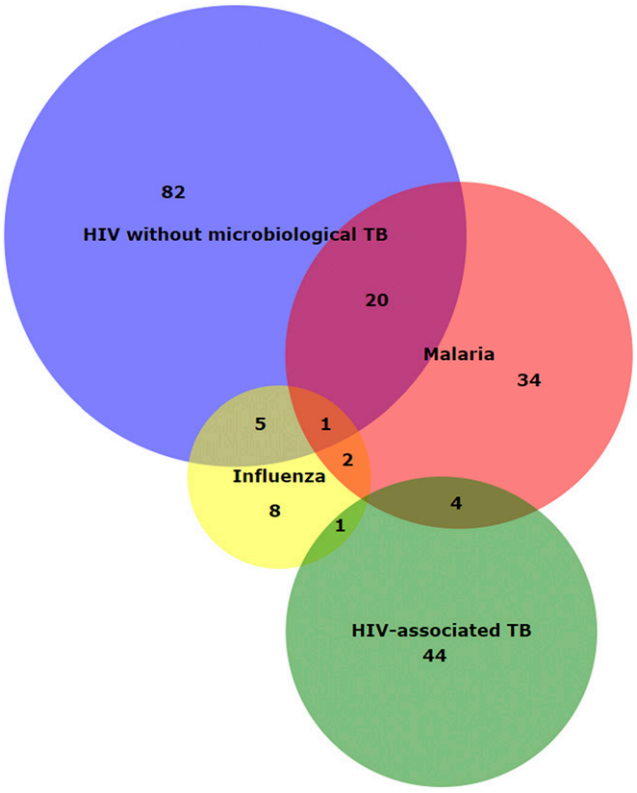

FIGURE 1. Area-proportional Venn diagram demonstrating pathogen subgroups and corresponding co-infections: 20 patients with HIV–malaria co-infection, four with HIV-tuberculosis (TB)–malaria coinfection, five with HIV–influenza co-infection, two with malaria–influenza co-infection, one with HIV–malaria–influenza co-infection, and one with HIV-TB–influenza co-infection. This figure appears in color at www.ajtmh.org.

More than 20% of the patients in our cohort had acute respiratory failure as defined by WHO IMAI guidelines. Despite this, few patients received supplemental oxygen because of the very limited capacity for oxygen delivery at the study site. The burden of acute respiratory failure, including acute respiratory distress syndrome, is poorly understood in SSA as a result of the limited availability of arterial blood gas analysis, chest radiography, and pulse oximetry.[39] However, available data suggest that the burden is likely high, as observational studies from Uganda and Rwanda determined that approximately 5% of adult inpatients met modified criteria for acute hypoxemic respiratory failure and acute respiratory distress syndrome, respectively, with an in-hospital mortality of 50% to 75%.[40,41] Considering implications for resource allocation (i.e., oxygen production and supply) and resuscitation (i.e., conservative fluid administration) and the ongoing coronavirus disease 2019 pandemic, increased recognition and supportive care for acute respiratory failure in SSA, beginning with expanded access to pulse oximetry and supplemental oxygen, are imperative.

Six percent of patients in our cohort were infected with influenza. Increasingly associated with sepsis in high-income settings, both as a primary source of organ dysfunction and as a precipitant for bacterial infection, the incidence of influenza-associated sepsis in SSA and other low-income settings is largely unknown.[42,43] Given the accumulating data identifying influenza as a frequent cause of severe acute respiratory infection in SSA, and the global availability of vaccines and anti-viral agents, further studies are needed to define more completely the incidence, clinical spectrum, and management of severe influenza and bacterial co-infection in the region.[44–46]

Our study has several strengths. First, our analyses were conducted using data available to clinicians in SSA during the first day of hospitalization, and included a standardized approach to rapid pathogen testing using diagnostic platforms largely accessible in the region. Although influenza PCR is not commonly available outside of microbiological reference laboratories in SSA, our results are among the first to report on influenza-associated sepsis in SSA and suggest that further investigation is needed for this preventable and treatable pathogen. Second, although most studies of adult sepsis in SSA have been conducted in urban, national referral hospitals, our cohort was sited at a district general hospital, thereby increasing generalizability to real-life clinical settings in SSA. Third, the prospective nature of our study facilitated performance of rapid diagnostics in nearly

all eligible patients, and we were able to determine in-hospital vital status for the entire cohort.

Our study also has limitations. First, our findings were derived from a single-center cohort. Second, we did not have data on lactate levels or capillary refill time to use as surrogates of organ perfusion, and we defined shock based on volume-unresponsive hypotension. Third, we did not perform blood cultures or testing beyond rapid diagnostic tests for HIV, TB, malaria, and influenza PCR, and likely missed infections with *Streptococcus pneumoniae* and *Cryptococcus neoformans*, high-burden pathogens for which rapid diagnostics are available. Fourth, we missed patients who presented overnight or on weekends. However, we have no reason to believe that this led to selection bias of the cohort because we do not expect the type or severity of infection to vary by day or time. Fifth, 30-day post-discharge outcomes were missing for approximately 10% of patients. Last, the parent study captured the cumulative volume of fluid administered during the first 24 hours of hospitalization, and we were thus unable to record cumulative fluid volumes administered during the first 6 hours of hospitalization, the traditional time period for goal-directed sepsis resuscitation studies and trials in HICs.

CONCLUSION

Using rapid diagnostics, we stratified patients hospitalized with suspected sepsis in Uganda into actionable pathogen-driven subgroups with prognostic and therapeutic relevance. In conjunction with improvements in acute and critical-care

TABLE 2
Demographics, organ dysfunction, and outcomes stratified by pathogen subgroup

Patient characteristic	Malaria (n = 61)*	HIV-associated TB (n = 49)*	HIV, microbiological TB negative (n = 108)*	Influenza (n = 17)*	*P* value†
Female, n (%)	39/61 (64)	26/49 (53)	66/108 (61)	7/17 (41)	0.290
Age, y; median (IQR)	30 (26–40)	32 (27–40)	37 (30–43)	35 (26–40)	0.147
Duration of illness before hospitalization, d;‡ median (IQR)	3 (2–6)	5 (3–7)	5 (3–7)	3 (2–7)	0.009
HIV infected, n (%)	25/61 (41)	49/49 (100)	108/108 (100)	7/17 (41)	–
qSOFA score ≥ 2,§ n (%)	26/61 (43)	33/49 (67)	60/108 (56)	4/17 (24)	0.005
qSOFA score ≥ 1,§ n (%)	53/61 (87)	45/49 (92)	96/108 (89)	15/17 (88)	0.873
Modified SIRS score ≥ 2,‖ n (%)	49/61 (80)	45/49 (92)	94/108 (87)	15/17 (88)	0.391
MEWS, median (IQR)	3 (2–4)	4 (3–6)	4 (3–5)	2 (2–4)	< 0.001
UVA score,¶ median (IQR)	2 (0–4)	4 (3–7)	4 (2–6)	2 (0–5)	< 0.001
Shock,# n (%)	4/61 (7)	12/49 (24)	20/108 (19)	3/17 (18)	0.049
Acute respiratory failure,** n (%)	8/61 (13)	15/49 (31)	24/108 (22)	3/17 (18)	0.159
Altered mental status,†† n (%)	11/61 (18)	12/49 (24)	24/108 (22)	3/17 (18)	0.863
Severe anemia,†† n (%)	8/61 (13)	18/49 (37)	27/108 (25)	1/17 (6)	0.009
In-hospital death or transfer resulting from illness severity, n (%)	11/61 (18)	11/49 (22)	23/108 (21)	2/17 (12)	0.813
Duration of hospitalization,§§ d; median (IQR)	4 (3–6)	8 (5–10)	5 (3–8)	4 (3–5)	< 0.001
KPS score ≤ 70 if discharged from hospital alive, n (%)	1/50 (2)	4/37 (11)	12/85 (14)	0/15 (0)	0.058
Dead at 30 d post-discharge, n (%)	11/59 (19)	19/47 (40)	30/95 (32)	1/16 (6)	0.013

IQR = interquartile range; KPS = Karnofsky Performance Status; MEWS = Modified Early Warning Score; qSOFA = quick sequential (sepsis-related) organ failure assessment; SIRS = systemic inflammatory response syndrome; TB = tuberculosis; UVA = universal vital assessment.

* Twenty patients with HIV–malaria co-infection, four with HIV–TB–malaria coinfection, five with HIV–influenza co-infection, two with malaria–influenza co-infection, one with HIV–malaria–influenza co-infection, and one with HIV-TB–influenza co-infection. Patients with co-infection(s) were included in each subgroup for which they had a positive diagnostic test.

† Fisher exact or Kruskal-Wallis H test.

‡ Unknown for one patient.

§ Systolic blood pressure ≤100 mmHg respiratory rate ≥22 breaths/min, and altered mental status, with the latter defined using the alert, responsive to voice, responsive to pain, unresponsive (AVPU) scale.

‖ Temperature ≥ 38°C or < 36°C, heart rate ≥ 90 beats/min, and respiratory rate ≥ 20 breaths/min.

¶ Altered mental status defined using the AVPU scale.

Systolic blood pressure ≤ 90 mmHg despite administration of ≥1 L intravenous fluid.

** Oxygen saturation ≤ 90% or respiratory rate ≥ 30 breaths/min.

†† Anything other than "alert" on AVPU mental status assessment.

‡‡ Hemoglobin < 9 g/dL or administration of blood transfusion.

§§ Unknown for 11 patients.

capacity, further studies are needed to improve classification of sepsis heterogeneity in SSA with the goal of refining locally relevant definitions and developing more effective sepsis management strategies in the region.

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Note: Supplemental information, tables, and figure appear at www.ajtmh.org.

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