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Epidemiology and Outcome of Sepsis in Adults and Children in a Rural, Sub-Sahara African Setting

OBJECTIVES: To identify the epidemiology and outcome of adults and children with and without sepsis in a rural sub-Sahara African setting.

DESIGN: A priori planned substudy of a prospective, before-and-after trial.

SETTING: Rural, sub-Sahara African hospital.

PATIENTS: One-thousand four-hundred twelve patients (adults, $n = 491$; children, $n = 921$) who were admitted to hospital because of an acute infection.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Demographic, clinical, laboratory data, danger signs, and the presence of sepsis (defined as a quick Sequential Organ Failure Assessment score count ≥ 2) at admission were extracted. Sepsis was observed in 69 adults (14.1%) and 248 children (26.9%). Sepsis patients differed from subjects without sepsis in several demographic and clinical aspects. Malaria was the most frequent type of infection in adults (66.7%) and children (63.7%) with sepsis, followed by suspected bacterial and parasitic infections other than malaria. Adults with sepsis more frequently developed respiratory failure (8.7% vs 2.1%; $p = 0.01$), had a higher in-hospital mortality (17.4% vs 8.3%; $p < 0.001$), were less often discharged home (81.2% vs 92.2%; $p = 0.007$), and had higher median (interquartile range) costs of care (30,300 [19,400–49,900] vs 42,500 Rwandan Francs [27,000–64,400 Rwandan Francs]; $p = 0.004$) than adults without sepsis. Children with sepsis were less frequently discharged home than children without sepsis (93.1% vs 96.4%; $p = 0.046$). Malaria and respiratory tract infections claimed the highest absolute numbers of lives. The duration of symptoms before hospital admission did not differ between survivors and nonsurvivors in adults (72 [24–168] vs 96 hr [72–168 hr]; $p = 0.27$) or children (48 [24–72] vs 36 [24–108 hr]; $p = 0.8$). Respiratory failure and coma were the most common causes of in-hospital death.

CONCLUSIONS: In addition to suspected bacterial, viral, and fungal infections, malaria and other parasitic infections are common and important causes of sepsis in adults and children admitted to a rural hospital in sub-Sahara Africa. The in-hospital mortality associated with sepsis is substantial, primarily in adults.

KEY WORDS: Africa; epidemiology; malaria; outcome; Rwanda; sepsis

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Sepsis is defined as life-threatening organ dysfunction induced by a dysregulated immune response to acute infection (1). An analysis from the Global Burden of Disease Study revealed that 48.9 million incident cases of sepsis and 11 million sepsis-related deaths occurred worldwide in 2017. They additionally observed that sepsis-related deaths accounted for 19.7% of all global deaths during the observation period. Finally, the highest burden of sepsis was recorded in low- or lower-middle-income countries (LMICs), that is, in sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia (2).

Although the epidemiology and outcomes of sepsis in high-income countries have widely been reported (3, 4), only limited data from LMICs are available (5). Given that bacterial pathogens prevail as a cause of sepsis in high-income countries (3, 4), the largest part of the current scientific evidence on sepsis care originates from studies including patients suffering from bacterial infections. Accordingly, international guidelines strongly focus on the management of sepsis caused by bacterial infections (6). Many LMICs are geographically located in tropical regions where pathogens other than bacteria commonly cause infectious diseases (7). Furthermore, and as a consequence of the high prevalence of HIV in many LMICs, tuberculosis and opportunistic infections are also frequently encountered (8, 9). Since tuberculosis and tropical infections, particularly malaria and some viral infections such as Dengue, require specific management principles (10), it is important to describe the epidemiology of sepsis in LMICs (11). This knowledge will guide sepsis research in LMICs and could inform future international sepsis guidelines and thus improve applicability for all sepsis patients around the globe.

In this analysis, we sought to identify the epidemiology and outcome of adults and children who were admitted to a rural hospital in sub-Sahara Africa because of an acute infection with or without sepsis.

MATERIALS AND METHODS

This is an a priori planned substudy of an investigator-initiated, single-center, prospective, before-and-after feasibility trial that was conducted at the emergency department of the Gitwe District Hospital in the Ruhango district in Rwanda between March 2016 and March 2017 (12). The trial protocol was prepublished (www.clinicaltrials.gov; NCT02697513), reviewed, and approved by the National Health and Research Committee as well as the Rwanda National Ethics Committee (No. 007/RNEC/2016). Written informed consent was obtained from all study patients or parents/next of kin in children or those unable to give written informed consent themselves.

Setting

Details about the study site have previously been published (12). Briefly, the Gitwe District Hospital serves a regional population of approximately 160,000 inhabitants, includes 200 inpatient beds and one emergency department with a separate adult and a pediatric admission room. No intensive care or high dependency unit and therefore no mechanical organ support modality such as mechanical ventilation or renal replacement therapy is available. Similarly, collaborative services such as the laboratory and radiology departments face significant resource restrictions. The hospital laboratory cannot provide chemical analyses to systematically evaluate organ functions (e.g., according to the Sequential Organ Failure Assessment [SOFA] score [13]) and cannot process microbiological samples. Microscopy, staining, and rapid diagnostic tests are, however, routinely available.

Study Population

All patients who were hospitalized because of a suspected acute infection were enrolled into the original trial. Exclusion criteria were age less than 28 days of life, limited therapy due to a terminal disease, and refusal to provide written informed consent. All subjects in whom the initial suspicion of an acute infection had been confirmed clinically, radiologically (x-ray, sonography), or by laboratory means as well as by the response to therapy until hospital discharge was included into this subanalysis.

Data Collection and Extraction

Trial data were collected by dedicated research assistants using a standardized documentation sheet at hospital admission, 24, 48, and 72 hours thereafter, as well as at hospital discharge. Anonymized data were entered into an electronic database (REDCap; REDCap Systems, Vanderbilt University, Nashville, TN) and securely stored at the University of Nebraska Medical Center in Omaha, NE. Before data analysis, the database records underwent repeated checks to detect documentation and/or entry errors.

The following variables were extracted from this trial database: demographic data, comorbidities including HIV carrier status and malnutrition, duration of symptoms before hospital admission, clinical history, cause and site of infection as documented in the discharge notes, physical examination findings, vital signs (heart rate, respiratory rate, systolic blood pressure, capillary refill time, temperature), and available laboratory values (blood sugar, white cell count,

hemoglobin levels) at study enrollment. Additionally, "danger signs" including altered mental status, acute respiratory distress, evidence of systemic hypoperfusion at admission, medical complications, abnormal vital signs variables and laboratory values during the first 72 hours after admission, length of hospital stay, costs of care (as determined by the hospital's accounting service), discharge location, and in-hospital mortality were recorded. In patients succumbing during their hospital stay, the cause of death as determined by the attending physician using clinical acumen and whenever available laboratory results was documented. The quick SOFA (qSOFA) score count (14) and pediatric sepsis definitions were determined at hospital admission and 24 hourly during the first 72 hours thereafter.

Determination of the Etiology of Infection

Given the inconsistent laboratory and inexistent microbiological capacities at the study center, determination of the etiology of infection, in many instances, relied on the clinical acumen of the attending physician, availability of radiological services, and the response to therapy. Certain infectious diseases could be diagnosed by clinical means (e.g., abdominal or puerperal infections during surgery or clinical examination), staining and microscopy (e.g., urinary tract infections, meningitis), or routinely available rapid diagnostic or serology tests (e.g., malaria, tuberculosis, HIV, hepatitis, some parasitic gastrointestinal infections).

Definitions

In adult study patients, sepsis was considered to be present when the qSOFA score count as determined at hospital admission was 2 or greater points (14, 15). In children (< 15 yr), sepsis was diagnosed if any one of the following criteria were fulfilled at hospital admission: body temperature less than 36°C, body temperature greater than 38°C plus altered mental status, body temperature greater than 38°C plus respiratory distress, body temperature greater than 38°C plus a history of not feeding, or body temperature greater than 38°C plus convulsions (16). Respiratory failure was defined as the presence of two or more of the following symptoms: respiratory rate greater than 20 beats/min, subjective dyspnea, SpO_2 less than 90% or central cyanosis, nasal flaring, grunting respirations, use of accessory muscles, subcostal/intercostal retractions, or

paradoxical breathing. Acute renal failure was defined as urine output less than 200 mL/24 hr (in adults) and less than 3 mL/kg/24 hr (in children). Given the burden of infectious diarrheal diseases in both adults and children in sub-Sahara Africa, we specified the site of infection in patients with infectious diarrheal diseases as "gastrointestinal." In all other abdominal infections, the site of infection was defined as "abdominal." The decision to transfuse blood was not standardized in this study cohort, as it varied with patient age, disease severity, and first of all the availability of blood products.

Study Endpoints and Statistical Analysis

The primary endpoint of this analysis was to report epidemiologic and outcome data of adults and children with sepsis. Secondary study endpoints were to: 1) compare these data between adults and children with and without sepsis, 2) identify causes of death in adults and children, and 3) define independent risk factors for death in the two populations.

The statistical analysis was performed using a statistical software package (IBM SPSS Statistics 20; IBM, Vienna, Austria). Descriptive statistical methods were used to address the primary study endpoint. For the analysis of the secondary study endpoints, the chi-square, Fisher exact, and the Mann-Whitney U tests were used to compare categorical and continuous variables between groups, as appropriate. Risk factors for in-hospital death were determined using a multivariate logistic regression model. This model used in-hospital death as the dependent variable and study variables which differed between survivors and nonsurvivors at an alpha-level less than 0.05 as independent variables. Collinearity between independent variables was excluded by calculating correlation coefficients and excluding one of the two variables exhibiting a correlation coefficient greater than 0.5. Since all datasets for primary and secondary outcome measures were complete, no statistical methods were used to compensate for missing values. A two-sided p value of less than 0.05 was considered to indicate statistical significance. All data are given as median values with interquartile ranges, if not otherwise stated.

RESULTS

In 1,412 of 1,594 patients included into the original trial, the initial suspicion of an acute infection was confirmed clinically, radiologically, or by laboratory

means, as well as by the response to therapy until hospital discharge (**Supplemental Digital Content - Fig. 1**, http://links.lww.com/CCX/A871). These patients were enrolled into the present analysis. Four-hundred ninety-one and 921 patients were adults and children, respectively. Sepsis criteria were fulfilled in 69 adults (14.1%) and 248 children (26.9%) at hospital admission. Characteristics including epidemiologic data of the study population are displayed in **Supplemental Digital Content - Table 1** (http://links.lww.com/CCX/A871). Adults with sepsis were more frequently male (52.2 vs 33.6%; $p = 0.002$); more often had a history of convulsions (14.5 vs 3.3%; $p = 0.001$) or not feeding (63.8 vs 32.7%; $p < 0.001$); were less frequently ambulant (69.6 vs 28.4%; $p < 0.001$); more often had an altered mental state (46.4 vs 4.7%; $p < 0.001$), respiratory distress (15.9 vs 5.2%; $p = 0.003$), systemic hypoperfusion (76.8 vs 22.5%, $p < 0.001$), or jaundice (7.2 vs 2.4%; $p = 0.047$); and had higher heart (103 [79–108] vs 93 beats/min [79–108 beats/min]; $p = 0.02$) and respiratory rates (22 [22–26] vs 20 beats/min [19–20 beats/min]; $p < 0.001$) and higher qSOFA scores, as well as lower systolic (94 [85–99] vs 110 mm Hg [100–122 mm Hg]; $p < 0.001$) and diastolic (56 [49–63] vs 67 mm Hg [59–75 mm Hg]; $p < 0.001$) blood pressures at hospital admission than adults without sepsis. Children with sepsis were older (3 [1–7] vs 2 [1–5]; $p = 0.006$), more frequently presented with malaria (63.7% vs 50.7%; $p < 0.001$), an altered mental state (32.3% vs 13.8%; $p < 0.001$), a history of convulsions (46.4% vs 4.7%; $p < 0.001$), and failure to feed (61.3% vs. 37.9%, $p < 0.001$), were less frequently ambulant (44% vs 30.3%; $p < 0.001$), or suffered from respiratory tract infection (21.4% vs 31.5%; $p = 0.002$), and had a higher temperature (38.9 [38.4–39.5] vs 37 [36.7–37.7]; $p < 0.001$) at hospital admission than children without sepsis. Malaria was the most frequent type of infection in adults and children with sepsis, followed by suspected bacterial and parasitic infections other than malaria (**Fig. 1**).

In-hospital mortality of patients with sepsis was higher than of those without sepsis in adults (12/69 [17.4%] vs 18/422 [4.3%]; $p < 0.001$) but not children (6/248 [2.4%] vs 8/673 [1.2%]; $p = 0.22$). Additionally, in-hospital mortality significantly differed between age groups in patients with sepsis (**Fig. 2**). Complications and outcomes of study patients are summarized in **Table 1**. Adults with sepsis more frequently developed respiratory failure during the first 24 hours following admission, were less often discharged home, and had higher costs of care than adults without sepsis. Children with sepsis were less frequently discharged home compared with children without sepsis. In-hospital mortality significantly differed between foci of infection in adults but not children (**Fig. 3***A*). Malaria and respiratory tract infections claimed the highest absolute number of lives (**Fig. 3***B*). The duration of symptoms before hospital admission did not differ between survivors and nonsurvivors in adults (72 [24–168] vs 96 hr [72–168 hr]; $p = 0.27$) or children (48 [24–72] vs 36 hr [24–108 hr]; $p = 0.8$).

Respiratory failure and coma were the most common causes of death in adults and children, respectively (**Table 2**). Older age (odds ratio [OR], 1.03/yr (95% CI, 1.01–1.06), $p = 0.008$), tuberculosis (OR, 25.3 [95% CI, 1.7–372.2]; $p = 0.02$), respiratory tract infection (OR, 3.4 [95% CI, 1.05–11.2]; $p = 0.04$), an altered mental state (OR, 8.3 [95% CI, 2.7–24.9]; $p < 0.001$), and a lower systolic blood pressure (OR, 0.97/mm Hg (95% CI, 0.94–0.99]; $p = 0.02$) at admission were independent risk factors for in-hospital death in adults (**Supplemental Digital Content - Table 2**, http://links.lww.com/CCX/A871). In children, a
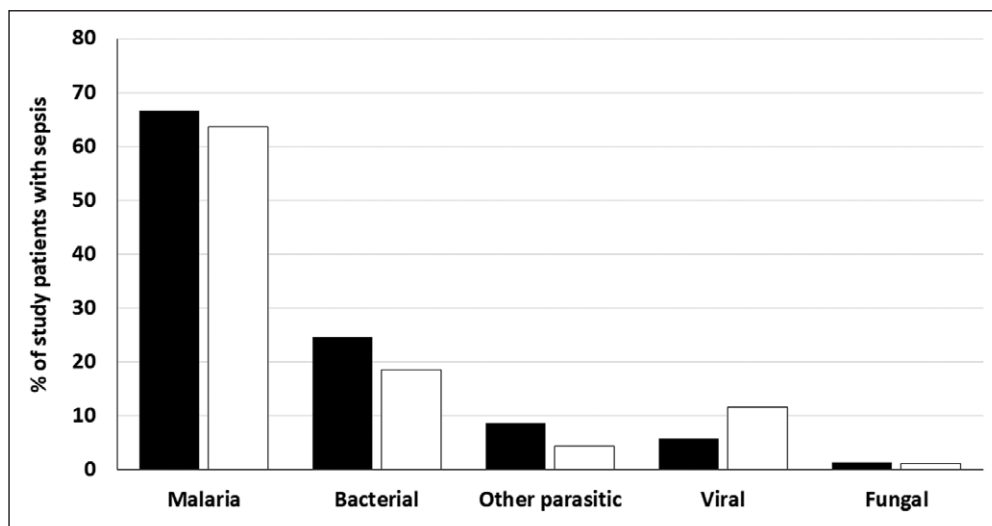

Figure 1. Suspected type of infection in adults (*black bars*) and children (*white bars*) with sepsis.

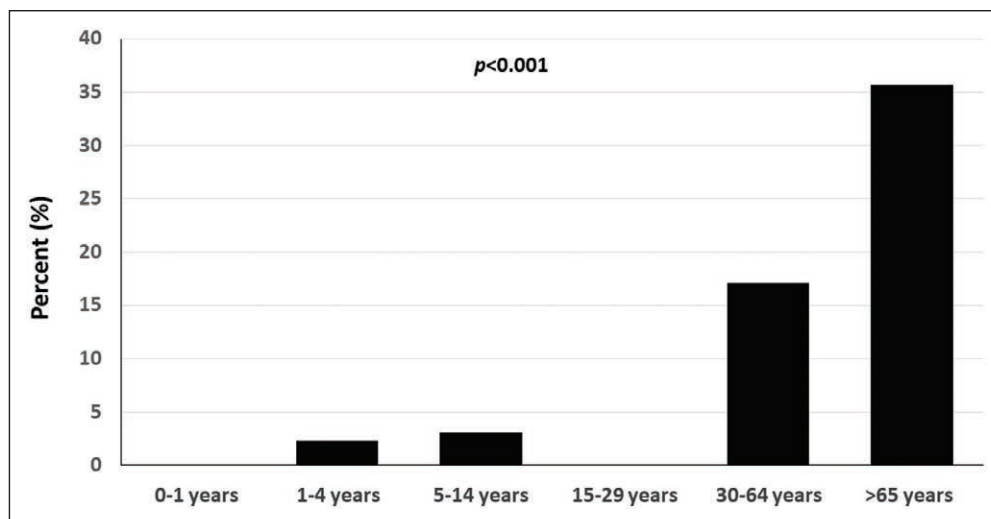**Figure 2.** Mortality rates of patients with sepsis in different age groups.

deranged vital variables at hospital admission, as well as worse outcomes both in adults and children compared with patients with acute infection but no sepsis. Furthermore, malaria was found to be the leading cause of sepsis and death from acute infection both in adults and children.

Because of the lack of laboratory resources required to diagnose organ dysfunction and calculate the SOFA score, we instead used the qSOFA score as an indicator of an increased risk of death from an acute infection and therefore sepsis in adults. In other published studies, patients with suspected infection outside of the ICU, the qSOFA score had a greater predictive validity for in-hospital mortality than the SOFA score and former sepsis criteria supporting its use as a tool to identify patients with sepsis (14). This observation has also been confirmed in LMICs (15). Accordingly, in our study population, a qSOFA score count of 2 points or higher identified adults with a higher disease severity and in-hospital mortality compared with those with a qSOFA score count of 0 or 1 point. The criteria used in our study to define pediatric sepsis similarly

history of not feeding (OR, 11.5 [95% CI, 1.4–91.6]; $p = 0.02$), respiratory tract infection (OR, 4.5 [95% CI, 1.3–15.4]; $p = 0.02$), and a longer capillary refill time (OR, 2.5/s [95% CI, 1.6–4]; $p < 0.001$) at hospital admission were independently associated with in-hospital mortality (Supplemental Digital Content - Table 2, http://links.lww.com/CCX/A871).

DISCUSSION

The main results of this analysis were that in a rural sub-Sahara African study population, sepsis was associated with an impaired physical state and more

TABLE 1.
Complications and Outcomes of Adults and Children With and Without Sepsis

Variable	Unit n	Adults			Children		
		No Sepsis 422	Sepsis 69	p	No Sepsis 673	Sepsis 248	p
Respiratory failure during first 24 hr	n (%)	9 (2.1)	6 (8.7)	0.01[a]	10 (1.5)	5 (2)	0.56
Acute renal failure during first 24 hr	n (%)	18 (4.3)	3 (4.3)	1	0	1 (0.4)	0.27
Transfer to higher level hospital	n (%)	10 (2.4)	1 (1.4)	1	11 (1.6)	9 (3.6)	0.08
Need for blood transfusion	n (%)	23 (5.5)	3 (4.3)	1	49 (7.3)	13 (5.2)	0.3
Length of hospital stay	median (interquartile range), d	4 (2–6)	5 (3–9)	0.14	3 (2–4)	3 (2–4)	0.1
Discharge to home	n (%)	389 (92.2)	56 (81.2)	0.007[a]	649 (96.4)	231 (93.1)	0.046[a]
Costs of care	1,000 Rwandan Francs	30.3 (19.4-49.9)	42.5 (27-64.4)	0.004[a]	23.3 (15.2-35.9)	26.1 (17.9-40.2)	0.16

[a]Significant group difference at $p < 0.05$.

TABLE 2.

Clinical Causes of In-Hospital Death in Adults and Children With Acute Infection

Adults		Children	
	n		*n*
Respiratory failure	9	Coma	4
Coma	5	Respiratory failure	1
Multiple organ failure	5	Cardiovascular failure/shock	1
Cardiovascular failure/shock	2	Multiple organ failure	1
Indeterminate	9	Bleeding	1
		Indeterminate	6

identified children with a poorer functional state at hospital admission and a lower likelihood to be discharged home. However, compared with the qSOFA score in adults, pediatric sepsis criteria appeared to be less accurate for the identification of patients with an increased disease severity or in-hospital mortality. This observation mirrors the current controversies regarding the most appropriate definition of sepsis in a pediatric population (17).

One key finding of this analysis was that malaria was the leading cause of sepsis and in-hospital death in both adults and children. Although one study from Uganda reported malaria as an uncommon cause of sepsis (4% of patients with sepsis) (18), a recent observational study from Thailand found that 52.3% of patients with malaria presented with sepsis (19). A meta-analysis of study including patients with community-acquired sepsis in sub-Sahara Africa reported a pooled prevalence of malaria of 10% (5). These results are particularly relevant as therapeutic strategies in patients with

malaria relevantly differ from those in patients with bacterial sepsis (10). Apart from the management of cerebral complications of malaria, a fluid resuscitation strategy as recommended for patients with bacterial sepsis may be deleterious in both adults and children with severe malaria (20, 21). Future international recommendations for the management of sepsis should highlight these differences in epidemiology as well as the optimal management of sepsis caused by bacterial and malarial infections.

Bacterial infections were suspected to be the second most common type of infection in both adults and children with sepsis in this cohort. Notably, other parasitic infections, such as *Entamoeba histolytica*, *Giardia lamblia*, and intestinal worms, were the third most common forms of infection causing sepsis in both adults and children. This has so far only rarely been reported from sub-Sahara Africa and is another remarkable difference compared with the epidemiology from high-income countries (3, 4). In line with this finding, the gastrointestinal tract was the third most frequent infectious focus following malaria and the respiratory tract in this analysis. Finally, in an analysis from the Global Burden of Disease Study, diarrheal diseases, lower respiratory tract infections, and malaria were the three most frequent infections causing sepsis (2). These results do not only have relevant implications for the clinical management of patients with acute infections but also for preventive strategies including public healthcare planning and campaigns.

In-hospital mortality of patients with sepsis in this patient population was substantial (17.4% in adults and 2.4% in children). The highest in-mortality was observed in patients 65 years old or older (35.7%), as well as those suffering from tuberculosis (50%). Although
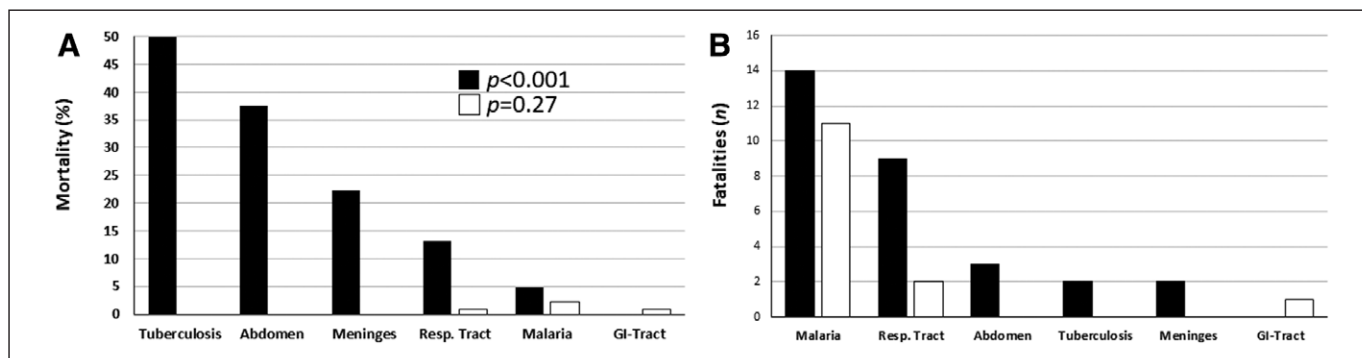

Figure 3. In-hospital mortality rates in percent (**A**) and absolute numbers of in-hospital fatalities (**B**) due to acute infection in adults (*black bars*) and children (*white bars*) as per focus of infection. Please note that tuberculosis was counted as a respiratory infection in the remaining analyses of this study. GI = gastrointestinal, Resp. = respiratory (other than tuberculosis).

the in-hospital mortality rate in our study patients is similar to that reported by a meta-analysis including studies from sub-Sahara Africa (5), sepsis mortalities were lower than those reported from other sub-Sahara African centers (22–25). This difference might be explained by the low HIV prevalence rate as compared with other sub-Sahara African regions (5, 22, 26) and, for pediatric cases, by the fact that our study excluded newborns known to have the highest fatality rate from sepsis among children (2). Furthermore, in our original trial, a focused educational program and an infection treatment bundle were implemented at the study site. These interventions increased the rate of early evidence-based therapies in the study population (12). As indicated in our original trial results, we speculate that this might also have contributed to the lower observed in-hospital mortality rates.

Based on the observed causes of death in our cohort as well as limited access to life-saving interventions, we postulate that the majority of fatalities might have been preventable if advanced organ support modalities (e.g., mechanical ventilation, advanced hemodynamic management, renal replacement therapy) had been available. This speculation is supported by the observation that respiratory tract infections and physiologic derangements such as an altered mental state, low systolic blood pressure, or a prolonged capillary refill time were identified as independent risk factors for death in both adults and children in this cohort. Our contention of improved survival is supported by a recent large study from Uganda which suggested that intensive care medicine in combination with adequate staff training and availability of basic equipment helped to save lives even under difficult conditions when only limited resources are available (25).

Another striking finding from our analysis was that the duration of symptoms before hospital admission was not different between patients with and without sepsis as well as between hospital survivors and nonsurvivors. This result was observed in both adults as well as children and may well represent a result specific to the study centre, as distances to the hospital and therefore time delays to hospital presentation were rather short. This finding, however, contradicts our original trial hypothesis that early initiation of therapy in patients with acute infections could reduce the frequency of sepsis-associated morbidity and mortality (27). It appears that, even in a resource-limited setting such as rural sub-Sahara Africa, the pathophysiology and course of sepsis may depend more on other factors (e.g., age, type and severity of infection, premorbid conditions, and individual genotypes) than the time elapsed between the onset of symptoms and hospital admission. A study analysing biomarkers from patients with sepsis in Uganda identified possible subgroups of patients with distinct host-response profiles (28).

One key limitation of our study is the fact that no microbiological laboratory facilities were available at the study center. This is likely to have influenced the ability of the attending medical teams to reliably diagnose bacterial infections and differentiate them from fungal or certain viral infections. However, many infections could be confirmed by clinical means, radiologically, rapid diagnostic tests including serology testing, staining, and microscopy, as well as by the patient's response to therapy. In addition, the single-center design of this study implies that our results cannot be extrapolated to other LMIC settings, particularly not those in other geographic areas, with a higher prevalence of HIV infection or other tropical infectious diseases. Finally, we did not collect information on the course of patients who suffered from an acute infection but did not reach the hospital for various reasons, including a high disease severity.

CONCLUSIONS

The results of this study suggest that in addition to suspected bacterial, viral, and fungal infections, malaria and other parasitic infectious diseases are common and the important causes of sepsis in both adults and children admitted to a rural hospital in sub-Sahara Africa. The in-hospital mortality associated with sepsis was substantial, primarily in adults.

ACKNWOLEDGMENTS

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