Simplified Severe Sepsis Protocol: A Randomized Controlled Trial of Modified Early Goal–Directed Therapy in Zambia*

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Objective: To assess the efficacy of a simple, goal-directed sepsis treatment protocol for reducing mortality in patients with severe sepsis in Zambia.

Design: Single-center nonblinded randomized controlled trial.

Setting: Emergency department, ICU, and medical wards of the national referral hospital in Lusaka, Zambia.

Patients: One hundred twelve patients enrolled within 24 hours of admission with severe sepsis, defined as systemic inflammatory response syndrome with suspected infection and organ dysfunction

Interventions: Simplified Severe Sepsis Protocol consisting of up to 4 L of IV fluids within 6 hours, guided by jugular venous pressure assessment, and dopamine and/or blood transfusion in selected patients. Control group was managed as usual care. Blood cultures were collected and early antibiotics administered for both arms.

Measurements and Main Results: Primary outcome was in-hospital all-cause mortality. One hundred nine patients were included in the final analysis and 88 patients (80.7%) were HIV positive. Pulmonary infections were the most common source of sepsis. In-hospital mortality rate was 64.2% in the intervention group and 60.7% in the control group (relative risk, 1.05; 95% CI, 0.79–1.41). *Mycobacterium tuberculosis* complex was isolated from 31 of 82 HIV-positive patients (37.8%) with available mycobacterial blood culture results. Patients in Simplified Severe Sepsis Protocol received significantly more IV fluids in the first 6 hours (2.7 L vs 1.7 L, $p = 0.002$). The study was stopped early because of high mortality rate among patients with hypoxemic respiratory failure in the intervention arm (8/8, 100%) compared with the control arm (7/10, 70%; relative risk, 1.43; 95% CI, 0.95–2.14).

Conclusion: Factors other than tissue hypoperfusion probably account for much of the end-organ dysfunction in African patients with severe sepsis. Studies of fluid-based interventions should utilize inclusion criteria to accurately capture patients with hypovolemia and tissue hypoperfusion who are most likely to benefit from fluids. Exclusion of patients with severe respiratory distress should be considered when ventilatory support is not readily available. (*Crit Care Med* 2014; 42:2315–2324)

Key Words: Africa; goal-directed therapy; sepsis; tuberculosis; Zambia

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In the United States, 750,000 people die each year from sepsis (1). Although available data are limited, the number of sepsis-related deaths is likely much higher in sub-Saharan Africa, where more than half of all deaths are attributed to infections (2). Cohort studies from the region have found

sepsis to be the third leading cause of death among HIV-infected adults, after tuberculosis (TB) and cryptococcal meningitis (3), and an unpublished audit at the University Teaching Hospital (UTH) in Zambia showed sepsis to be the leading cause of death among hospitalized medical patients. However, optimal management strategies for patients with sepsis in Africa remain controversial (4–7).

Protocol-based management of sepsis has had wide uptake in North America and Europe (8, 9). Studies of early goal–directed therapy have demonstrated that aggressive IV fluid administration, hemodynamic support, and blood transfusion can significantly reduce mortality due to sepsis. Central venous pressure or serum lactate–guided approaches have generally resulted in patients receiving between 4 and 5 L of fluid in the first 6 hours of admission (10, 11). In sub-Saharan Africa, however, uptake has been generally nonexistent due to resource limitations (12). Central venous catheters and lactic acid tests are not widely available, and the use of IV fluids for volume resuscitation has been much more conservative than guidelines recommend (13, 14). There are also questions regarding the generalizability of existing evidence to the sub-Saharan African setting, considering the underrepresentation of resource-limited study sites and patients with HIV/AIDS in most sepsis trials (15). Furthermore, the limited existing evidence from the region is conflicting regarding the potential benefits and harms of aggressive fluid resuscitation (4, 6).

We hypothesized that a novel simplified treatment protocol, based on existing early goal–directed therapy protocols, would reduce mortality compared with usual care in African patients with severe sepsis. The Simplified Severe Sepsis Protocol (SSSP) intervention consisted of early goal–directed fluid administration, plus dopamine and/or blood transfusion when indicated. Patients in both arms received close nurse monitoring with early blood cultures and antibiotics.

METHODS

We conducted a pilot nonblinded randomized controlled trial of patients presenting to the UTH in Lusaka, Zambia, with severe sepsis between February and July 2012. UTH is the national referral hospital for Zambia and is also a major primary care hospital for the city of Lusaka. Ethical approval was obtained from the University of Zambia Biomedical Research Ethics Committee (UNZA BREC) and the Vanderbilt University Institutional Review Board (IRB), and the study was registered with ClinicalTrials.gov (NCT01449916).

Patients

All patients presenting to the emergency department were screened for eligibility. Enrollment occurred 24 hr/d from Monday 7:30 AM to Friday 1:00 PM. Patients were eligible if they were 18 years old or older and met criteria for severe sepsis upon presentation to the emergency department. Additionally, patients who manifested severe sepsis after arrival to the hospital were eligible if they were still in the emergency department less than 24 hours after presentation and were within 6 hours of first meeting severe sepsis criteria. Severe sepsis was defined as the presence of all three of the following: 1) infection suspected by treating doctor, 2) systemic inflammatory response syndrome (SIRS), defined as two or more of the following: heart rate > 90/min, respiratory rate > 20/min, temperature ≥38°C or ≤ 36°C, or WBC > 12,000/mm^3 or < 4,000/mm^3, and 3) one or more signs of organ dysfunction. Organ dysfunction criteria were systolic blood pressure < 90 mm Hg or mean arterial blood pressure (MAP) < 65 mm Hg, altered mentation, creatinine > 1.85 mg/dL, platelet count < 100×10^9/L, respiratory rate > 40/min, or jaundice. Patients were excluded if they had a gastrointestinal bleed, required immediate surgery, or had suspected congestive heart failure exacerbation or end-stage renal disease. Patients with raised jugular venous pressure (JVP) more than 3 cm above the sternal angle, as measured with a level and a ruler, were also excluded. JVP was measured vertically from the sternal angle with the patient positioned between 0° and 45° incline so that the waveform was visible. The normal range for JVP is 1–3 cm above the sternal angle, and JVP over 3 cm is a reliable measure of volume overload by physical examination (16, 17). Study doctors and nurses underwent two half-day training sessions in assessing JVP, followed by regular periodic bedside assessments by the principal investigator until staff members felt confident with the technique.

Randomization

Patients were randomly assigned in a 1:1 ratio to either usual care or the SSSP. Assignments were based on computer-generated permuted blocks of 2, 4, and 6. Randomization assignments were placed in numbered, sealed opaque envelopes, which were opened after written informed consent was obtained. Study staff were not blinded to patient assignments. Emergency department and internal medicine doctors were not informed of patient assignment, although protocol orders were readily visible in the patients' files.

Interventions

Patients in the usual care group received care as per orders written by the emergency department physicians. Usual care consisted of IV fluids, antibiotics, and occasional use of non-titrated dopamine. A dedicated study nurse monitored all patients in both groups, ensured all orders were carried out, and notified emergency department physicians of critical vital signs or changes in condition. Vital signs were monitored every hour for 6 hours. The SSSP (intervention) group received protocol-based care for the first 6 hours following enrollment. Patients in the SSSP group received an initial 2-L bolus of normal saline or lactated Ringer's within 1 hour of assessment. After the initial bolus, an investigator or study nurse reevaluated the patient's JVP. If JVP was less than 3 cm above the sternal angle, patients received an additional 2 L of fluid over 4 hours, for a total of 4 L in the first 5–6 hours of enrollment. The target of 4 L was determined based on previous goal-directed therapy studies (10, 11). Fluids were stopped for any patient who developed worsening respiratory signs or symptoms as determined by the study physician or nonstudy

doctors. If MAP was below 65 mm Hg after 2-L fluid bolus, then a dopamine infusion was started at a rate of 10 μg/kg/min, to be titrated to maintain a MAP greater than or equal to 65 mm Hg. Patients with hemoglobin less than 7 g/dL in SSSP were offered whole blood transfusion. In both groups, blood cultures were drawn and antibiotics were commenced as soon as possible, preferably within 1 hour of recognition of sepsis. One aerobic blood culture was drawn from each patient and incubated in a Bactec FX (BD Diagnostics, Sparks, MD). In HIV-positive patients, an additional mycobacterial blood culture was collected and incubated. Positive mycobacterial cultures were speciated as *Mycobacterium tuberculosis* complex or nontuberculosis complex based on MPT64 rapid antigen test (Standard Diagnostics, Seoul, South Korea) (18). Selection of antibiotics, antimalarials, and tuberculosis therapy was left to the admitting nonstudy physicians, as was the determination of additional investigations, such as malaria blood slides and cerebral spinal fluid studies. Decisions regarding transfer to ICU and initiation of mechanical ventilation or hemodialysis were likewise left to nonstudy physicians. Patients in both arms could receive empiric whole blood transfusion if ordered by the admitting doctors.

Outcomes

The primary outcome was in-hospital all-cause mortality. Secondary mortality outcomes included 28-day all-cause mortality, in-hospital and 28-day mortalities adjusted for the Simplified Acute Physiology Score-3 (SAPS-3), and time to death (19). Process measures included volume of IV fluids administered in the first 6, 24, and 72 hours, proportion of patients receiving antibiotics within 1 hour, and proportion of patients receiving blood transfusion. Patients were monitored for changes in respiratory status, including rise in respiratory rate of 5 or more and decrease in oxyhemoglobin saturation (Spo_2) of 3% or more. Reasons for stopping IV fluids were also recorded.

Statistical Analysis

Our previous data found a 54.9% inpatient mortality rate in patients admitted to our hospital with severe sepsis (14). We used this figure as the expected mortality in the control group. Assuming a 5% two-sided type I error rate and 80% power, we estimated that a sample size of 342 patients would be required to detect a 15% absolute reduction in in-hospital mortality.

Baseline characteristics of patients with severe sepsis were compared by intervention using *t* test for continuous variables and chi-square or Fisher exact tests for categorical variables. Kaplan-Meier estimates and log-rank test were used to compare survival by intervention up to 28 days following admission. All hypothesis testing was two-sided with a level of significance set at 0.05. We assessed in-hospital mortality for the following prespecified subgroups: HIV positive versus negative, MAP ≤ 65 versus > 65 mm Hg, respiratory rate ≥ 40 versus < 40, hemoglobin ≥ 7 versus < 7 g/dL, and above versus below median score for SAPS-3. Post hoc subgroup analyses included patients with hypoxemic respiratory distress, defined as baseline respiratory rate more than 40/min and Spo_2 less than 90%, and patients with tuberculosis. Multivariable log-linear regression was used for subgroup analyses to estimate risk ratios adjusted for baseline SAPS-3 score. We tested for interaction effect between subgroup and intervention group on the risk of in-hospital mortality using Breslow-Day test of homogeneity. Linear regression was used to assess changes in fluid administration in the usual care group as a function of date of study initiation. All analyses were intention to treat, using Stata version 12.1 (StataCorp, College Station, TX) and OpenEpi (http://www.openepi.com) for Breslow-Day calculations.

RESULTS

We enrolled 112 patients in the study (**Fig. 1**). Two patients not meeting the eligibility criteria were excluded within hours of enrollment. One patient was excluded within 1 hour of randomization because informed consent was verbal and not written. The remaining 109 patients were included in intention to treat analysis. In-hospital survival was available for all patients. The 28-day survival outcome was not ascertained in six patients who were lost to follow-up after discharge.

Eighty-eight patients (80.7%) were HIV positive, with median CD4 count of 49 cells/mm^3. Median time from admission to enrollment was 2.5 hours (interquartile range [IQR], 0.9–6.4 hr). In 100 patients for whom JVP was assessable, 88 (88%) had below-normal JVP, including 28 with expiratory JVP at the level of the sternal angle (0 cm) and 60 with a JVP that was below the sternal angle and only visible in the supine position. Mean respiratory rate was very high in both the intervention and control groups, 38.2 and 37.7 breaths/min, respectively. Pulmonary infection was the most commonly suspected source of sepsis, occurring in 63 of 109 participants (57.8%). Eighty-one patients (74.3%) were nonambulatory at the time of admission with a median time of 5 days (IQR, 3–7) since last walking. Baseline characteristics are summarized in **Table 1**.

Management

Treatment of the two groups is summarized in **Table 2**. Slightly over half of patients received a third-generation cephalosporin, either alone or as part of a combination. Antituberculous therapy was given to 21 patients in SSSP (39.6%) and 14 control patients (25.0%). Median time to first dose of antibiotics was 1.4 hours (IQR, 0.5–3.1) from time of admission and 0 hour (IQR, –1.3–2.0) from time of enrolment. Patients in the SSSP group received significantly more IV fluids in the first 6 hours compared with control (2.8 L vs 1.6 L, $p < 0.001$). Of 53 patients in the SSSP group, 30 patients (56.6%) received at least 3 L in the first 6 hours, and 14 of 53 (26.4%) received at least 4 L. The most common reasons for stopping fluids included tachypnea or decreased Spo_2 (in eight patients), raised JVP (7), lost IV access (2), blood transfusion (5), and poor urine output in suspected oliguric renal failure (1). The SSSP group received more fluid in the first 72 hours (5.5 L vs 4.3 L; $p = 0.02$). Regressing 6-hour IV fluid administration on date of admission in the control group resulted in no meaningfully different fluid administration over the study period (–0.005/d; 95% CI, –0.013

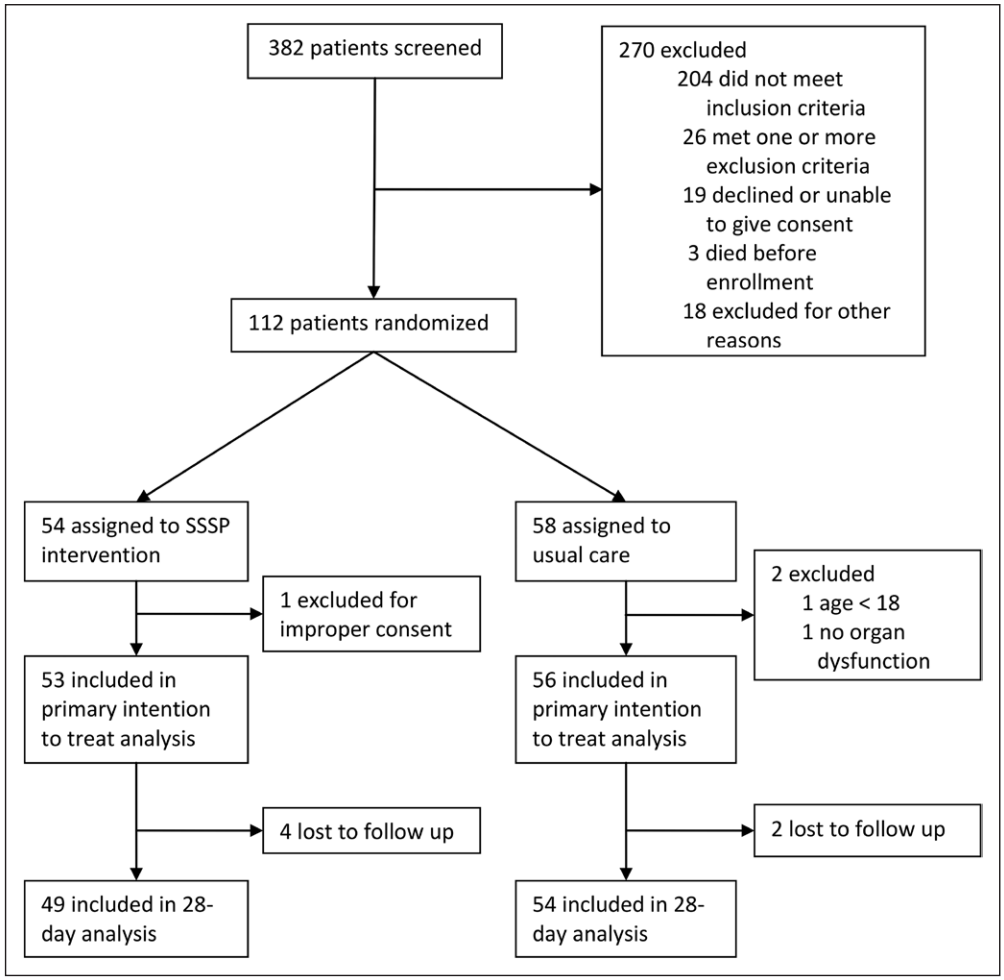

Figure 1. Selection and follow-up of study patients. During the study period, 382 patients presenting to the emergency department were screened for eligibility. Of those, 112 patients with severe sepsis were enrolled and randomized to either Simplified Severe Sepsis Protocol (SSSP) or usual care. Three patients were excluded within hours of randomization due to not meeting all elibility criteria (2) or improper consent (1) and were not included in the final analysis.

to 0.003), suggesting that usual practices were not substantially impacted by a Hawthorne-like effect during the study period.

Only three patients in the SSSP group and one patient in the control group received dopamine. Sixteen patients (30.2%) in the intervention group and 11 control patients (19.6%) received blood transfusion ($p = 0.20$). Median number of units transfused was identical between the two groups (two units). The majority of patients received antibiotics within 1 hour of enrollment, although antibiotics start time was missing for 12 patients. Only two patients, one in each group, were treated in the ICU. For both patients, the indication for ICU transfer was mechanical ventilation. The local conventions for ICU use are described in *Discussion* section.

Clinical Outcomes

Overall, 68 patients (62.4%) died prior to discharge. In-hospital mortality was not significantly different between the two groups. Of 53 patients in the intervention group, 34 patients (64.2%) died in hospital compared with 34 of 56 (60.7%) in controls (relative risk, 1.05; 95% CI, 0.79–1.41; SAPS-3-adjusted risk ratio, 1.01; 95% CI, 0.76–1.33). The 28-day mortality was 71.4% in the intervention group compared with 66.7% for controls (relative risk, 1.07 [0.83–1.39]; adjusted relative risk, 1.03 [0.81–1.32]). We failed to detect differences between intervention and control for the prespecified subgroups (**Table 3**). Because categorizing continuous predictors into intervals may lead to loss of power, models were rerun with continuous exposures (i.e., not categorized into a priori subgroups) with similar results (not shown). Median survival was 4 days in the SSSP group versus 9 days in the control group, but the IQR was 2–28 days in both groups and Kaplan-Meier estimates showed little difference (log-rank $p = 0.57$) (**Fig. 2**).

Bacteriologic Findings

Twenty-six patients (23.9%) had positive aerobic blood cultures. The most common organisms were *Staphylococcus aureus* (seven) and *Streptococcus pneumoniae* and *Salmonella* typhi (three each). Mycobacterial blood cultures were collected from HIV-positive patients only; 31 of 82 patients had tuberculosis mycobacteria (37.8%). Two patients had coinfection with TB and *S. aureus*. The other 29 patients with TB bacteremia had no other identifiable etiology for their sepsis. Among 46 patients with CD4 count less than 75 cells/mm^3, 22 patients (47.8%) had positive TB blood cultures. Four patients, all in the control group, had evidence of *Cryptococcus neoformans* in the cerebrospinal fluid. Two patients, one in each group, had blood-slide-positive malaria.

Decision to Stop Study

The study was stopped early by the investigators prior to the scheduled interim analysis, in communication with UNZA BREC and Vanderbilt IRB, due to the observation that patients with hypoxemic respiratory distress at baseline might be at increased risk from the intervention. Because only two of 109 patients were transferred to ICU for mechanical ventilation, the investigators initiated an unscheduled analysis of participants with baseline respiratory rate above 40/min and oxygen saturation less than 90%. In this group, 15 of 18 patients (83.3%) died during hospitalization, including eight of eight in the intervention group (100%) and seven of 10 in the control group (70%, $p = 0.09$). Based on these findings, the decision was made to stop the study.

TABLE 1. Baseline Characteristics of Zambian Patients With Severe Sepsis

Variable	Simplified Severe Sepsis Protocol (*n* = 53)	Control (*n* = 56)	*p*
Age, yr, mean (SD)	35.2 (1.3)	34.8 (1.4)	0.85
Male, *n* (%)	28 (52.8)	30 (53.6)	0.94
Admission vital signs, mean (SD)			
Systolic blood pressure, mm Hg	102.6 (21.4)	101.6 (24.2)	0.83
Diastolic blood pressure, mm Hg	62.4 (14.4)	65.2 (17.2)	0.35
Mean arterial pressure, mm Hg	75.8 (15.4)	77.3 (18.8)	0.64
Respiratory rate, breaths/min	38.2 (10.9)	37.7 (11.2)	0.81
Heart rate, beats/min	119.2 (15.8)	122.9 (22.3)	0.32
Temperature, °C	37.3 (1.5)	37.9 (1.7)	0.07
Glasgow Coma Scale, median (IQR)	14 (11–15)	14 (10–15)	0.76
HIV positive, *n* (%)	42 (79.2)	46 (82.1)	0.70
CD4 count, median (IQR)	40 (17–107)	70 (24–109)	0.41
On antiretrovirals, *n* (% of HIV positive)	18 (42.9)	16 (35.6)	0.49
Suspected site of infection, *n* (%)			0.86
Pulmonary	31 (58.5)	32 (57.1)	
CNS	19 (35.8)	15 (26.8)	
Abdomen	3 (5.7)	4 (7.1)	
Other[a]	6 (11.3)	7 (12.5)	
Chief complaint, *n* (%)			0.62
Dyspnea	13 (24.5)	15 (26.8)	
Altered mentation	9 (17.0)	10 (17.9)	
Cough	9 (17.0)	8 (14.3)	
Headache	7 (13.2)	10 (17.9)	
Weakness/fatigue	10 (18.9)	4 (7.1)	
Abdominal pain	3 (5.7)	5 (8.9)	
Other[a]	2 (3.8)	4 (7.1)	
Duration of chief complaint, d, median (IQR)	7 (4–30)	14 (3–30)	0.81
Duration of any symptoms,[b] d, median (IQR)	14 (7–30)	30 (14–60)	0.26
Simplified Acute Physiology Score-3, mean (SD)	59.0 (1.6)	56.3 (1.5)	0.23
Acute Physiology and Chronic Health Evaluation II score, mean (SD)	17.8 (0.8)	17.9 (0.9)	0.95

[a]Other chief complaints included fever (3), diarrhea (1), vomiting (1), and seizure (1).
[b]Symptoms include inability to walk or any symptom listed under chief complaint.

DISCUSSION

In this pilot randomized controlled trial in Lusaka, Zambia, a novel goal-directed therapy protocol consisting of early aggressive IV fluids, with dopamine and blood transfusion in selected patients, was not effective in reducing in-hospital mortality compared with usual care. The study was stopped early due to observations that patients with severe respiratory distress were unlikely to benefit from the intervention and were at potential risk of harm. The study intentionally used broad inclusion criteria, defining severe sepsis as probable infection with SIRS and organ dysfunction. End-organ dysfunction was likely unrelated to tissue hypoperfusion in a significant proportion of patients. Patients with confusion due to meningitis or respiratory distress due to pulmonary inflammation have other mechanisms

TABLE 2. Treatments Administered and Adverse Events

Variable	Simplified Severe Sepsis Protocol ($n = 53$)	Control ($n = 56$)	p
Initial antibiotic regimens[a]			–
3rd-generation cephalosporin[b]	22 (41.5)	20 (35.7)	
3rd-generation cephalosporin combination[c]	5 (9.4)	10 (17.9)	
Penicillin G	4 (7.5)	4 (7.2)	
Penicillin G + chloramphenicol	6 (11.3)[d]	7 (12.5)	
Other penicillin G combination[c]	6 (11.3)	3 (5.4)	
Ciprofloxacin ± metronidazole	5 (9.4)	3 (5.4)	
Other[e]	4 (7.5)	7 (12.5)	
Not documented	1 (1.9)	2 (3.6)	
Cotrimoxazole[f]	6 (11.3)	8 (14.3)	0.64
Antituberculous therapy			0.087
Started at admission or before	8 (15.1)	9 (16.1)	
Started after admission	13 (24.5)	5 (8.9)	
Median time to antibiotics, hr (IQR)[g]			
From admission	1.5 (0.5–3.7)	1.3 (0.4–3.0)	0.42
From study enrollment	–0.7 (–2.5 to 0.5)	0 (–1.5 to 0.9)	0.19
Received ≥ 3 L fluid in 6 hr, n (%)	30 (56.6)	11 (20.0)	< 0.001
Fluids administered, L, mean (SD)[h]			
In first 6 hr	2.9 (1.0)	1.6 (1.1)	< 0.001
In first 24 hr	3.9 (1.3)	3.0 (2.1)	0.02
In first 72 hr	5.6 (2.3)	4.3 (2.9)	0.02
Received blood transfusion, n (%)	16 (30.2)	11 (19.6)	0.20
Median time to transfusion, hr (IQR)[g]	16.0 (7.3–32.9)	5.5 (0–13.8)	0.17
Received dopamine, n (%)	1 (1.8)	3 (5.7)	0.28
Stopped IV fluids early, n (%)	25 (49.0)	Not applicable	Not applicable
Reasons for stopping			
Raised jugular venous pressure	7 (13.2)		
Respiratory changes	8 (15.1)		
Lost IV access	2 (3.8)		
Transfuse blood	5 (9.4)		
Oliguria	1 (1.9)		
Other	2 (3.8)		
Increase in respiratory rate or decrease in Spo_2 in first 6 hr, n (%)[i]	18 (34.0)	16 (28.6)	0.54

IQR = interquartile range.
[a]Excludes antituberculous therapy or cotrimoxazole therapy, listed separately.
[b]Includes three patients who received 3rd-generation cephalosporin plus crystalline penicillin.
[c]Includes combinations with ciprofloxacin, erythromycin, metronidazole, and/or cloxacillin.
[d]Includes two patients who received crystalline penicillin + chloramphenicol + metronidazole.
[e]Cloxacillin + metronidazole (1), chloramphenicol (1), erythromycin (3), cotrimoxazole monotherapy (2), and antituberculous therapy only (4).
[f]Includes prophylaxis or treatment doses, used with one of the above combinations in 12 patients; two patients received only cotrimoxazole.
[g]Missing data on time to blood transfusion in two transfused patients and antibiotics start time in 12 patients.
[h]Missing data for fluids in first 6 hr (one patient), 24 hr (eight patients), and 72 hr (15 patients).
[i]Respiratory changes included respiratory rate increase of 5 breaths/min or more or decrease in oxyhemoglobin saturation of 3% or more.
Dash signifies intentional omission (p value was not calculated to compare the initial antibiotic regimens).

TABLE 3. Relative Risk of In-Hospital Death in Patients Managed With Simplified Severe Sepsis Protocol Versus Usual Care: Subgroup Analysis[a]

Subgroups	Simplified Severe Sepsis Protocol[b]	Control[b]	Relative Risk (95% CI)	p[c]
HIV positive	29/42 (69.0)	29/46 (63.0)	1.10 (0.81–1.48)	0.70
HIV negative	5/11 (45.5)	5/10 (50.0)	0.91 (0.37–2.22)	
MAP ≥ 65 mm Hg	26/39 (66.7)	28/46 (60.9)	1.10 (0.79–1.51)	0.72
MAP < 65 mm Hg	8/14 (57.1)	6/10 (60.0)	0.95 (0.48–1.88)	
Respiratory rate > 40[d]	16/20 (80.0)	15/23 (65.2)	1.23 (0.85–1.78)	0.37
Respiratory rate ≤ 40	18/33 (54.5)	18/32 (56.3)	0.97 (0.63–1.50)	
Hemoglobin < 7[e]	8/13 (61.5)	5/8 (62.5)	0.98 (0.50–1.96)	0.83
Hemoglobin ≥ 7	20/33 (60.6)	22/39 (56.4)	1.07 (0.73–1.59)	
SAPS-3 ≥ median	22/28 (78.6)	20/29 (69.0)	1.14 (0.83–1.56)	0.52
SAPS-3 < median	12/25 (48.0)	14/27 (51.9)	0.93 (0.54–1.60)	
Confirmed TB	10/15 (66.7)	12/16 (75.0)	0.89 (0.56–1.40)	0.39
No confirmed TB	24/38 (63.2)	22/40 (55.0)	1.15 (0.79–1.66)	
Hypoxemic respiratory distress[f]	8/8 (100.0)	7/10 (70.0)	1.43 (0.95–2.14)	0.17
No hypoxemic respiratory distress	26/45 (57.8)	27/46 (58.7)	0.98 (0.70–1.39)	
Overall	34/53 (64.2)	34/56 (60.7)	1.06 (0.79–1.41)	

MAP = mean arterial pressure, SAPS-3 = Simplified Acute Physiology Score-3, TB = tuberculosis.
[a]All subgroups were prespecified, except tuberculosis and hypoxemic respiratory distress.
[b]Percent mortality in parentheses.
[c]Test for interaction of risk ratio over subgroups.
[d]Missing respiratory rate in one participant.
[e]Missing hemoglobin in 18 participants.
[f]Hypoxemic respiratory distress defined as respiratory rate > 40 and oxyhemoglobin saturation < 90%.

of organ damage that might be worsened with aggressive fluid administration.

Previous studies from sub-Saharan Africa have shown both harm and benefit with fluid-based interventions. The Fluid Expansion As Supportive Therapy (FEAST) trial in Kenya, Uganda, and Tanzania found increased mortality from fluid boluses in children with severe febrile illness (4). On the other hand, a before-after study in Ugandan adults, by the Promoting Resource-limited Interventions for Sepsis Management in Uganda (PRISM-U) group demonstrated a 12.7% absolute reduction in 30-day mortality (6). There were several key differences between our study and PRISM-U. Their study enrolled only patients with low or low-normal blood pressures. Our median systolic blood pressure of 100 mm Hg was considerably higher than the median of 81–85 mm Hg in PRISM-U. The control group in the PRISM-U study received a median of only 500 mL of fluids in the first 6 hours and 1 L in the first 24 hours. In contrast, median fluid administration in the control arm of the SSSP study was 1.6 L in 6 hours and 3.0 L in the first 24 hours. It is likely that the observational "before" arm of PRISM-U received less nursing attention than the "after" intervention arm. In resource-limited settings, low volumes of fluid administration may be the result of doctors' orders or inadequate nurse staffing. In the SSSP study, both the intervention and control group received one-to-one care in the first 6 hours from a dedicated study nurse. Furthermore, the two groups received equal care and attention except for the use of the SSSP protocol to direct fluid, dopamine, and transfusion administration.

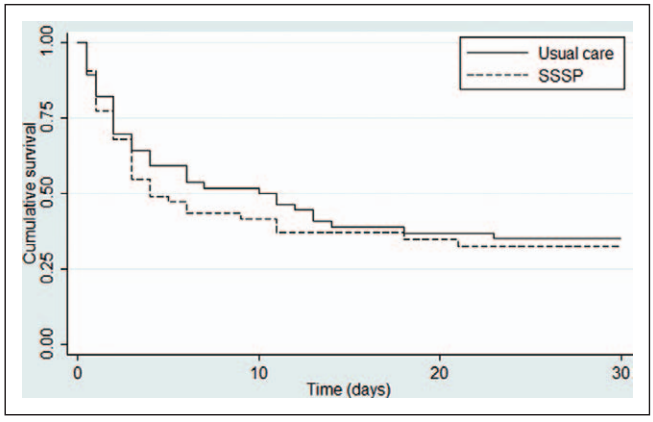

Figure 2. Kaplan-Meier survival estimates for Simplified Severe Sepsis Protocol (SSSP) intervention versus usual care in patients with severe sepsis.

Our intervention was similar in many respects to the protocol-based standard therapy arm in the recently reported

Protocol-Based Care for Early Septic Shock (PROCESS) study, based in the United States (20). Their protocol-based standard therapy also called for 2-L initial fluid bolus within 1 hour, noninvasive monitoring, jugular venous distension and respiratory monitoring for fluid overload, blood pressure triggers for vasopressor initiation, and blood transfusion for severe anemia (< 7.5 g/dL in PROCESS; < 7.0 g/dL in SSSP). Neither study demonstrated a significant mortality difference between the protocolized groups and usual care.

At 62%, our mortality rate was higher than mortality rates seen in PRISM-U and PROCESS. ICU utilization in our study was extremely low. The decision to transfer patients to the ICU was left to nonstudy physicians in order to limit bias in this nonblinded study. The study hospital, UTH, has only 10 ICU beds for a 1,500-bed hospital with catchment population of 13 million, and the majority of ICU beds are usually occupied by surgical patients. The bias of medical staff to transfer to ICU is generally in favor of patients with easily reversible conditions, such as hydrostatic pulmonary edema, status epilepticus, and severe malaria, and against patients with chronic wasting from HIV and/or TB. The low rate of ICU transfer was an important factor in the decision to stop this study early, as appropriate ventilatory support could not be guaranteed in patients with preexisting or fluid-induced severe respiratory distress.

Compared with a previous observational study of septic patients with and without organ dysfunction at our hospital, our study patients had higher mortality rates (62% vs 40%) and baseline respiratory rates (mean respiratory rate, 38/min vs 28/min), and pulmonary source of infection was more common (58% vs 25%) (14). These differences could be attributable to methodologic differences, particularly the SSSP organ failure inclusion criteria, which included respiratory rate more than 40/min, and to a high proportion of unspecified (32.3%) infections in the observational study. Of note, the usual care arm of SSSP received more fluids at 6 hours (median, 1.6 L vs 1 L) and 24 hours (median, 3.0 L vs 1 L) than previously observed. Although usual care did not change appreciably from the beginning to the end of this study, we cannot rule out the possibility that the prestudy training may have impacted usual prescribing practices. We think it is more likely, though, that dedicated study nurses led to more consistent implementation of doctors' orders compared with prestudy periods. However, any study such as ours that compares a new intervention to usual care runs the risk of influencing the usual care control arm toward imitation of an as-yet unproven intervention.

There were several important lessons learned in conducting this study. First and foremost, the use of simplified inclusion criteria that only loosely reflect the pathophysiology of interest should be avoided. As with the FEAST study, SSSP sought to identify hypoperfused severely septic patients without utilizing costly testing such as lactic acid measurement. The intention was to use inclusion criteria that could be generalizable to clinical use in the most resource-limited settings. In FEAST, the majority of patients (70%) qualified as hypoperfused based on severe tachycardia, a nonspecific measure that could reflect hypovolemia, hypoxemia, anemia, high fever, or other distress. Our study made a faulty assumption that organ dysfunction alone was indicative of tissue hypoperfusion in a septic population with a high prevalence of volume depletion. In retrospect, our criteria failed to adequately consider the direct tissue damage attributable to inflammation of the lungs and/or brain. Design of future sepsis studies involving IV fluids should consider more reliable measures of hypoperfusion or fluid responsiveness.

Another important lesson learned regarded the management of patients with respiratory distress. In the absence of available ventilatory support, caution must be exercised when administering IV fluid boluses to such patients. Where ventilatory support is unavailable, the decision to include patients with moderate-to-severe respiratory distress should be scrutinized prior to any study of IV fluid intervention. FEAST and SSSP included severe respiratory distress and severe tachypnea, respectively, as organ dysfunction inclusion criteria, so it should not have been surprising that 83% of participants in FEAST had respiratory distress and 39% of SSSP participants had respiratory rate above 40. Interestingly, the median respiratory rates in SSSP (38/min) were nearly identical to those seen in PRISM-U (36–38/min). However, despite similar volumes of fluid, more patients in SSSP developed worsening respiratory signs. Adjunctive therapies, such as noninvasive positive pressure ventilation (NIV), might be considered for patients with respiratory distress, and studies into the efficacy of NIV are warranted in this setting.

Our study raises the question of the role of hyperacute interventions in the management of chronic or subacute processes. Unlike in North America and Europe, where sepsis is typically an acute process, sepsis in sub-Saharan Africa frequently results from subacute or chronic infection. Over 80% of patients were HIV infected, and the majority had symptoms for at least 2 weeks preceding admission. The leading etiology of sepsis in our study was tuberculosis, with other concomitant pathogens very rarely isolated. Similar prevalence of tuberculous bloodstream infections has been shown in Malawi, Tanzania, and Uganda (13, 21–24). This varies greatly from the literature in high-resource settings, where Gram-positive and Gram-negative bacteria typically account for over 60% of confirmed etiologies (25, 26). Our findings suggest that disseminated tuberculosis infection should be strongly suspected in patients presenting with severe sepsis in sub-Saharan Africa, especially in persons infected with HIV. Because the septic process in these patients may be subacute or chronic, it is reasonable to expect that acute time-dependent interventions like early goal–directed therapy may have limited impact.

The question of an optimal fluid target for patients with sepsis and tissue hypoperfusion in sub-Saharan Africa remains unanswered. The PRISM-U study demonstrated that a "usual care" consisting of less than 1 L of fluids for septic patients with low to low-normal blood pressures was not sufficient. A post hoc observational analysis of PRISM-U suggested that the worst prognosis was in patients receiving less than or equal to 1 L of fluids in the first 6 hours, and the best prognosis was in patients who received more than 1–2.5 L of fluid in the first 6

hours, with similar adjusted outcomes for those who received more than 3.5 L. The mean 6-hour fluid intake in our study was 1.7 L in the control group compared with 2.7 L in the intervention group. We set a cutoff of 4 L of fluid in the first 6 hours, and we used JVP, rather than blood pressure, as the guide to stopping fluids. We intentionally selected JVP because blood pressure may frequently normalize prior to full volume resuscitation. However, we recognize the difficulty in standardizing JVP measurements, particularly among nursing staff and less experienced doctors. Beyond blood pressure and JVP, other methods, such as fluid responsiveness using straight leg raise, warrant investigation in this setting.

Other questions remain with regard to optimal treatment of patients with severe sepsis in sub-Saharan Africa. We must recognize that the sepsis syndrome is a heterogeneous collection of infectious conditions, each with unique physiologic characteristics. Although some patients with sepsis may benefit from early fluid administration, in the absence of mechanical ventilation those with severe respiratory distress clearly do not. Delays in appropriate antituberculous therapy likely contribute to poor outcomes (27), magnifying the importance of clinical algorithms or point-of-care diagnostics to detect TB earlier (28). A study is ongoing to determine the impact of a urine lipoarabinomannan assay for detection of TB in HIV positive hospitalized patients (ClinicalTrials.gov identifier: NCT01770730). Scalable interventions, such as NIV, could be studied as potential therapy for those patients who present with sepsis and severe respiratory distress.

In conclusion, this randomized controlled trial of early goal–directed fluid administration, dopamine, and blood transfusion for Zambian patients with severe sepsis was stopped early due to possible increased risk among patients with hypoxemic respiratory distress. Although the question of optimal fluid administration remains unanswered, any future studies of fluid interventions should carefully consider inclusion criteria to identify patients most likely to benefit from IV fluids and should consider excluding patients with severe respiratory distress when mechanical ventilation is not available.

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