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Hypoglycemia at admission is associated with inhospital mortality in Ugandan patients with severe sepsis

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Abstract

Objective—Dysglycemia during sepsis is associated with poor outcomes in resource-rich settings. In resource-limited settings, hypoglycemia is often diagnosed clinically without the benefit of laboratory support. We studied the utility of point-of-care glucose monitoring to predict mortality in severely septic patients in Uganda.

Design—Prospective observational study.

Setting—One national and two regional referral hospitals in Uganda.

Patients—We enrolled 532 patients with sepsis at three hospitals in Uganda. The analysis included 418 patients from the three sites with in-hospital mortality data, a documented admission blood glucose concentration, and evidence of organ dysfunction at admission (systolic blood pressure < 100 mm Hg, lactate > 4 mmol/L, platelet number < 100,000/μL, or altered mental status).

Interventions—None.

Measurements and Main Results—We evaluated the association between admission point-of-care blood glucose concentration and in-hospital mortality. We also assessed the accuracy of altered mental status as a predictor of hypoglycemia. Euglycemia occurred in 33.5% (140 of 418) of patients, whereas 16.3% (68 of 418) of patients were hypoglycemic and 50.2% (210 of 418) were hyperglycemic. Univariate Cox regression analyses comparing in-hospital mortality among hypoglycemic (35.3% [24 of 68], hazard ratio 2.0, 95% confidence interval 1.2–3.6, $p = .013$) and hyperglycemic (29.5% [62 of 210], hazard ratio 1.5, 95% confidence interval 0.96–2.4, $p = .08$) patients to euglycemic (19.3% [27 of 140]) patients showed statistically significantly higher rates of in-hospital mortality for patients with hypoglycemia. Hypoglycemia (adjusted hazard ratio 1.9,

95% confidence interval 1.1–3.3, $p = .03$) remained significantly and independently associated with in-hospital mortality in the multivariate model. The sensitivity and specificity of altered mental status for hypoglycemia were 25% and 86%, respectively.

Conclusion—Hypoglycemia is an independent risk factor for in-hospital mortality in patients with severe sepsis and cannot be adequately assessed by clinical examination. Correction of hypoglycemia may improve outcomes of critically ill patients in resource-limited settings.

Keywords

Africa; hypoglycemia; mortality; outcomes; severe sepsis; Uganda

Although infectious diseases contribute to a large proportion of death in sub-Saharan Africa (SSA), there are few data to guide the best approach to evaluate and treat severe sepsis in this region (1, 2). The difficulty in treating severe sepsis in SSA is due in part to the paucity of material and human resources available to treat critical illnesses (3). Clinical diagnoses, such as hypoglycemia, are often made without benefit of supporting clinical laboratory data, which may lead to poor outcomes and increased mortality (4–6). To augment the management of severe sepsis in SSA, emphasis should be placed on applying available technologies that are affordable, simple to use, and easy to interpret in austere settings. This approach includes use of point-of-care (POC) devices that can efficiently differentiate the most critically ill patients and therefore hasten initiation of life-saving therapy (7).

Admission blood glucose abnormalities are associated with in-hospital mortality from severe sepsis in resource-rich settings but have not been specifically studied in SSA (8–12). Although not universally present, POC glucometers are available in many regional and national referral hospitals in SSA and may identify patients with an increased risk of death from severe sepsis. We studied the relationship between admission blood glucose concentration obtained by a POC glucometer and in-hospital mortality in patients admitted with severe sepsis to three hospitals in Uganda. Since current practice at our study sites is to empirically treat hypoglycemia in critically ill patients with altered mental status (AMS), we also evaluated the association between AMS and hypoglycemia in patients with severe sepsis.

MATERIALS AND METHODS

Study Design and Patient Recruitment

We combined data from two prospectively enrolled cohorts of septic patients admitted to three hospitals in Uganda. The first cohort was enrolled at Mulago and Masaka Hospitals from July 2006 until November 2006 and included patients ≥ 18 yrs of age with severe sepsis defined by: 1) a suspected infection; 2) two or more of the following characteristics: axillary temperature of $> 37.5^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$, heart rate of > 90 beats/min, and respiratory rate of > 20 breaths/min; and 3) a systolic blood pressure of < 100 mm Hg (13, 14).

The second cohort was enrolled at Mbarara Hospital from February 2009 until July 2009 and was designed to also include patients with sepsis without organ failure. The same inclusion criteria were applied as in the first cohort, with the exception that a systolic blood pressure of < 100 mm Hg was not required. The white blood cell concentration component of the standard systemic inflammatory response syndrome criteria was not applied at any site because it was not routinely immediately available at the time of enrollment. Patients at all sites were excluded if they had an acute cerebrovascular event or gastrointestinal hemorrhage or needed triage to a surgery or obstetrics and gynecology ward.

The analysis for this study included patients from the three sites with in-hospital mortality data who had a documented admission blood glucose concentration and, for patients enrolled in Mbarara, evidence of organ dysfunction at admission (systolic blood pressure of <100 mm Hg, lactate of >4 mmol/L, platelet number of $<100,000/\mu\text{L}$, or AMS) (13). The primary outcome was in-hospital mortality. We also evaluated the association between AMS and hypoglycemia.

Site Descriptions

Mulago Hospital is a 1,500-bed national referral hospital in Kampala, Uganda. Masaka Regional Referral Hospital is a 330-bed hospital in Masaka, Uganda (125 km southwest of Kampala), and Mbarara Regional Referral Hospital is a 350-bed hospital in Mbarara, Uganda (280 km southwest of Kampala). The three hospitals exist under the auspices of the Uganda Ministry of Health (Kampala, Uganda).

Data Collection and Definitions

At the time of enrollment, consent was obtained from the patient or from a surrogate (a family member or friend) if the patient could not provide consent. The study team observed patients until discharge or death, but the admitting medical team was responsible for clinical management. All clinical and laboratory data were provided to the attending medical team as soon as they were available. We retrieved the following data from each of the three sites: demographics; history of presenting symptoms; examination findings, including axillary temperature, respiratory rate, heart rate, blood pressure, and mental status; human immunodeficiency virus serology status; laboratory findings; in-hospital mortality. Glucose values were obtained before administration of intravenous fluids. Hypoglycemia was defined as a glucose concentration of <4.4 mmol/L (80 mg/dL) (8, 11, 15). Values within the range of 4.4–6.1 mmol/L (80–110 mg/dL) were considered euglycemic (8, 15). Hyperglycemia was defined as a glucose concentration of >6.1 mmol/L (110 mg/dL) (8, 15). AMS was defined as clinical evidence of confusion, reduced Glasgow Coma Scale Score (<14), or convulsions.

Laboratory Evaluation

Laboratory data were obtained at Mulago and Masaka Hospitals as previously described (14). Blood for laboratory evaluation, including POC blood glucose concentrations (Accu-Chek portable glucose analyzer; Roche Diagnostics, Berlin, Germany), was obtained at the time of presentation. POC whole blood lactate concentrations were obtained for a subset of patients at all three hospitals as previously described (7). Complete blood counts were obtained on site at Mbarara (Beckman Coulter, Villepinte, France). Blood cultures at Mbarara Hospital were obtained via aseptic inoculation of 10 mL of blood into two aerobic blood culture bottles. Subculturing and species identification were performed using standard methods. Evaluation of malaria was performed via Field's staining as previously described (16).

Statistical Analysis

SPSS software, version 17.0 (SPSS, Chicago, IL) was used for all statistical analyses. Patient characteristics were reported as frequency with percentage for categorical variables and mean with standard deviation for continuous variables. Cox regression was used to calculate hazard ratios for univariate and adjusted hazard ratios (AHRs) for multivariate analyses. Covariates were included in the multivariate Cox regression model if they met a conservatively set p value of .30 inclusion criterion. Only those variables with a final two-sided p value of $<.05$ were considered independently associated with in-hospital mortality and retained in the final multivariate Cox regression model. Kaplan-Meier estimates were

used to present survival results for each day of follow-up until at least 10% of patients in each glycemic category remained hospitalized. In addition, the predictive value of AMS for hypoglycemia was examined using a simple Pearson's chi-square test. Sensitivity, specificity, and positive and negative predictive values were also calculated.

Ethics Statement

Approval for the study was obtained from the University of Virginia Institutional Review Board (Charlottesville, VA), Makerere University Faculty of Medicine Research Ethics Committee (Kampala, Uganda), Mulago Hospital Office of the Director (Kampala, Uganda), Mbarara University Institutional Review Board (Mbarara, Uganda), Infectious Disease Institute Scientific Research Committee (Makerere University), and Uganda National Council of Science and Technology (Kampala, Uganda).

RESULTS

Background Characteristics

Of the 532 patients enrolled at the three study sites, there were 418 (79%) who met the inclusion criteria for this analysis (Fig. 1). Among these patients, 46% (191 of 418) were from Mulago, 31% (131 of 418) were from Masaka, and 23% (96 of 418) were from Mbarara. Table 1 shows demographic and clinical characteristics of the entire cohort as well as each variable's association with the admission glucose category. The majority of patients were human immunodeficiency virus-infected women, and the average age was 35 yrs. Bacteremia or fungemia was identified in 21% (86 of 418) of patients (Table 2). Parasitemia was detected in 13% (54 of 415) of patients tested for malaria.

Mortality

Total in-hospital mortality was 27% (113 of 418). Patients who survived to discharge were hospitalized for a mean of 7.9 days (SD = 0.37; range 1–55 days). Patients who did not survive died in-hospital an average of 5.6 days postadmission (SD = 0.57; range 1–31 days). The Mbarara site had the highest rate of in-hospital mortality (41.7% [40 of 96]) compared to the other two sites combined (22.7% [73 of 322], $p < .001$). Therefore, enrollment at Mbarara Hospital was included as a covariate for all multivariate models.

Admission Glucose Concentrations

Euglycemia occurred in 33.5% (140 of 418) of patients, whereas 16.3% (68 of 418) of patients were hypoglycemic and 50.2% (210 of 418) were hyperglycemic.

Univariate analyses comparing in-hospital mortality among hypoglycemic (35.3% [24 of 68], hazard ratio 2.0, 95% confidence interval [CI] 1.2–3.6, $p < .013$) and hyperglycemic (29.5% [62 of 210], hazard ratio 1.5, 95% CI 0.96–2.4, $p = .08$) patients to euglycemic (19.3% [27 of 140]) patients showed statistically significant higher rates of in-hospital mortality for patients with abnormally low glucose concentrations (Table 3 and Fig. 2).

Multivariate Predictors of Inpatient Mortality

The admission glucose concentration and covariates with two-sided p values meeting the $p < .30$ criteria (AMS, white blood cell count, heart rate, bacteremia or fungemia, platelet count, and enrollment at Mbarara) were initially included in the Cox regression equation. The final model showed that patients with AMS (AHR 2.2, 95% CI 1.5–3.4, $p < .001$), an abnormal white blood cell count (AHR 1.7, 95% CI 1.1–2.5, $p = .01$), a low platelet count (AHR 1.8, 95% CI 1.2–2.7, $p = .007$), or enrolled at Mbarara (AHR 1.9, 95% CI 1.2–2.9, $p = .004$) had a significantly increased likelihood of in-hospital mortality (Table 3). Even after

these significant covariates were included in the equation, the predictive value of hypoglycemia (AHR 1.9, 95% CI 1.1–3.3, $p = .03$) remained significantly associated with in-hospital mortality. In addition, in a multivariate model for the subset of 260 patients with lactate tested, both lactate of > 4 mmol/L (AHR 2.9, 95% CI 1.8–4.6, $p < .001$) and hypoglycemia remained independent, statistically significant predictors of in-hospital mortality (AHR 1.9, 95% CI 1.0–3.4, $p = .04$).

AMS

Of the total 418 patients, 65 (15.6%) were identified as having AMS at the time of admission. Univariate analysis showed that AMS was significantly associated with in-hospital mortality (hazard ratio 2.5, 95% CI 1.6–3.7, $p = .001$) (Table 3) and hypoglycemia (odds ratio 2.1, 95% CI 1.1–3.9, $p = .002$). However, sensitivity of AMS as a test for hypoglycemia was only 25% with a higher specificity of 86%. The positive predictive value was 26%, and the negative predictive value was 86%.

DISCUSSION

This is the first report from SSA that hypoglycemia is an independent risk factor for in-hospital mortality from severe sepsis. Hypoglycemia is a known risk factor for death in critically ill patients in resource-rich settings and has been associated with an immune-compromised state, a higher illness severity, and a primary septic diagnosis (8–12, 17). These clinical variables are frequently present in patients presenting with severe sepsis in SSA, which increases their risk of hypoglycemia and death (14). For example, approximately 80% of the patients we studied in Uganda were human immunodeficiency virus infected, and 40% had lactate of > 4 mmol/L.

In many settings in SSA, the diagnosis of hypoglycemia can only be made on a clinical basis due to lack of laboratory support (4). Clinicians in SSA often use AMS as a marker of hypoglycemia, but the clinical manifestations of hypoglycemia are nonspecific, and hypoglycemia may occur in the absence of AMS (18, 19). Although AMS may be due to hypoglycemia, other possible causes include severe sepsis with encephalopathy, severe sepsis with a central nervous system focus, or cerebral malaria (20, 21). The specificity of AMS as a predictor of hypoglycemia in our study was high, but its sensitivity and positive predictive value were low. Therefore, hypoglycemia should be suspected in patients with severe sepsis and AMS but should not be ruled out in patients without AMS.

For POC laboratory testing to be useful, it must provide quick and accurate results. In one study from a resource-rich setting, inaccurate POC glucose readings in an intensive care unit setting were most frequently falsely elevated, resulting in misinterpretation of high glucose values with subsequent inappropriate insulin administration or masking of true hypoglycemia (22). However, an evaluation of the Accu-Chek glucometer, which was used in our Ugandan study, revealed that 94% of measurements from an intensive care unit fell within the desired International Organization for Standardization (Geneva, Switzerland) guidelines (23, 24). Prior studies, including one from Uganda, have not revealed a significant influence of the local climate on POC glucose monitor accuracy (25, 26).

Our study does have important limitations. The glucose concentration was only measured at the time of admission to the medical wards. Due to circadian fluctuation in blood glucose control, the glucose concentration at one point in time may not represent a patient's physiologic glucose control over a 24-hr period (27). Furthermore, it is possible that hypoglycemia at admission represents wide glucose variability during severe sepsis, which has been associated with poor outcomes (8, 9, 17, 28, 29). We do not have data to reveal how patients were treated once aberrant glucose concentrations were identified or the

influence of treatment on subsequent glucose concentrations and outcomes. Due to resource constraints, we did not measure cortisol, insulin, or glucagon concentrations, which may have provided a better understanding of the underlying endocrine pathophysiology leading to hypoglycemia in the study patients (18).

There was a statistically significant increased risk of death for patients enrolled at Mbarara. The reasons for this are unclear but could be related to microbiological, ecological, or seasonal differences between this population and patients enrolled at Mulago and Masaka. Mbarara is similar to Mulago and Masaka Hospitals in terms of available resources. However, despite the increased risk of death at the Mbarara site, hypoglycemia remained an independent risk factor for death even when the site of enrollment was included in the multivariate analysis.

CONCLUSIONS

This is the first study of the relationship between admission glucose concentration and in-hospital mortality from severe sepsis in SSA. We used prospective data from a heterogeneous group of patients enrolled at three independent hospitals in Uganda. This represents the largest aggregate of prospectively studied severely septic patients in SSA to date. The benefits of POC glucose monitoring include rapid and reliable results that can be obtained in resource-limited environments without robust clinical laboratory support. On the basis of these strengths and our findings that hypoglycemia is associated with increased mortality from severe sepsis and cannot be accurately diagnosed clinically, we recommend that POC glucose monitoring be incorporated into the evaluation of any patient with severe sepsis in a similar setting. Future studies are needed to determine whether correction of abnormal admission glucose concentrations leads to improved outcomes from severe sepsis in SSA.

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Figure 1.
Flow diagram of the study enrollment and analysis.

Figure 2.
Survival curves including the number of patients at risk according to the admission glucose category.

Table 1

Patient demographics and clinical characteristics in relationship to admission glucose concentration

Variable	Total Sample (n = 418)	Hypoglycemic (<4.4 mmol/L) (n = 68)	Euglycemic (4.4–6.1 mmol/L) (n = 140)	Hyperglycemic (>6.1 mmol/L) (n = 210)
Patient demographic characteristics				
Age, yrs, mean (SD)	35.1 (12.0)	33.7 (11.2)	35.4 (12.6)	35.3 (11.8)
Gender, n (%)				
Female	225 (53.8)	32 (47.1)	64 (45.7)	97 (46.2)
Male	193 (46.2)	36 (52.9)	76 (54.3)	113 (53.8)
Hospital site, n (%)				
Mulago	191 (45.7)	15 (22)	52 (37.1)	124 (59)
Masaka	131 (31.3)	35 (51.5)	48 (34.3)	48 (22.9)
Mbarara	96 (22.9)	18 (26.5)	40 (28.6)	38 (18.1)
Clinical status at admission				
Admission AMS, n (%)				
No AMS	353 (84.4)	51 (75)	126 (90)	176 (83.8)
AMS	65 (15.6)	17 (25)	14 (10)	34 (16.2)
SIRS, ^a n (%)				
<3 SIRS criteria	75 (18)	15 (22.1)	25 (18)	35 (16.7)
3 SIRS criteria	341 (82)	53 (77.9)	114 (82)	174 (83.3)
Heart rate, ^a n (%)				
90 beats/min	21 (5)	2 (3)	6 (4.3)	13 (6.2)
>90 beats/min	395 (95)	65 (97)	133 (95.7)	197 (93.8)
Respiratory rate, ^a n (%)				
20 breaths/min	35 (8.4)	5 (7.5)	13 (9.3)	17 (8.1)
>20 breaths/min	381 (91.6)	62 (92.5)	127 (90.7)	192 (91.9)
Temperature, ^a n (%)				
Normal (35.5°C to 37.5°C)	114 (27.5)	22 (32.8)	38 (27.3)	54 (26)
Abnormal (<35.5°C or >37.5°C)	300 (72.5)	45 (67.2)	101 (72.7)	154 (74)
<35.5°C	44 (10.6)	12 (17.9)	10 (7.2)	22 (10.6)
>37.5°C	256 (61.8)	33 (49.2)	91 (65.5)	132 (63.4)
Systolic blood pressure, ^a n (%)				
90 mm Hg	216 (51.8)	30 (44.8)	79 (56.4)	107 (50.9)
<90 mm Hg	201 (48.2)	37 (55.2)	61 (43.6)	103 (49.1)
Mean arterial pressure, n (%)				
60 mm Hg	269 (64.3)	40 (58.8)	95 (67.9)	134 (63.8)
<60 mm Hg	149 (35.7)	28 (41.2)	45 (32.1)	76 (36.2)
Laboratory results				
Bacteremia or fungemia, n (%)				
Negative	332 (79.4)	54 (79.4)	124 (88.6)	154 (73.3)
Positive	86 (20.6)	14 (20.6)	16 (11.4)	56 (26.7)

Variable	Total Sample (n = 418)	Hypoglycemic (<4.4 mmol/L) (n = 68)	Euglycemic (4.4–6.1 mmol/L) (n = 140)	Hyperglycemic (>6.1 mmol/L) (n = 210)
Human immunodeficiency virus status, ^a n (%)				
Negative	69 (17.2)	4 (6.1)	31 (22.9)	34 (17.1)
Positive	331 (82.8)	62 (93.9)	104 (77.1)	165 (82.9)
White blood cell count, ^a n (%)				
4,000 to 12,000 cells/μL	203 (50)	25 (37.9)	70 (51.1)	108 (53.2)
<4,000 or >12,000 cells/μL	203 (50)	41 (62.1)	67 (48.9)	95 (46.8)
Hemoglobin, g/dL, mean (SD)	9.1 (3.3)	8.9 (2.9)	9.4 (3.1)	8.8 (3.6)
Platelets, ^a n (%)				
100,000 cells/μL	308 (77)	51 (77.3)	106 (79.1)	151 (75.5)
<100,000 cells/μL	92 (23)	15 (22.7)	28 (20.9)	49 (24.5)
Malaria, ^a n (%)				
Negative smear	361 (87)	54 (80.6)	119 (86.2)	188 (89.5)
Positive smear	54 (13)	13 (19.4)	19 (13.8)	22 (10.5)
Lactate, ^a n (%)				
<4 mmol/L	162 (62.3)	36 (62.1)	66 (67.3)	60 (57.7)
>4 mmol/L	98 (37.7)	22 (37.9)	32 (32.6)	44 (42.3)

AMS, altered mental status; SIRS, systemic inflammatory response syndrome.

^aData for some variables were not available for the entire group.

Table 2

Bloodstream isolates

Organism	n (%)
Non-Typhi <i>Salmonella</i>	22 (26)
<i>Staphylococcus aureus</i>	20 (23)
<i>Mycobacterium tuberculosis</i> ^a	19 (22)
<i>Streptococcus pneumoniae</i>	12 (14)
<i>Cryptococcus neoformans</i>	5 (6)
<i>Escherichia coli</i>	4 (5)
<i>Proteus</i> species	1 (1)
<i>Enterobacter</i> species	1 (1)
<i>Haemophilus influenzae</i>	1 (1)
<i>Salmonella</i> Typhi	1 (1)
Total	86 (100)

^aBlood cultures for *Mycobacteria* were only performed for patients enrolled at Mulago Hospital.

Table 3
Univariate predictors of survival meeting 0.30 criteria and final multivariate model results using Cox regression

Outcome	Survived	Died	Univariate	Hazard Ratio (95% Confidence Interval) and <i>p</i>	
				<i>p</i>	Multivariate
Admission glucose concentration, n (%)					
Euglycemia (4.4–6.1 mmol/L)	113 (80.7)	27 (19.3)			
Hypoglycemia (<4.4 mmol/L)	44 (64.7)	24 (35.3)	2.0 (1.2–3.6)	.013	1.9 (1.1–3.3)
Hyperglycemia (>6.1 mmol/L)	148 (70.5)	62 (29.5)	1.5 (0.96–2.4)	.08	1.6 (0.97–2.5)
AMS, n (%)					
No AMS	274 (77.6)	79 (22.4)			
AMS	31 (47.7)	34 (52.3)	2.5 (1.6–3.7)	<.001	2.2 (1.5–3.4)
White blood cell count, n (%)					
4,000 to 12,000 cells/μL	162 (79.8)	41 (20.2)			
<4,000 or >12,000 cells/μL	136 (67.0)	67 (33.0)	1.7 (1.1–2.4)	.01	1.7 (1.1–2.5)
Heart rate, n (%)					
90 beats/min	18 (85.7)	3 (14.3)			
>90 beats/min	286 (72.4)	109 (27.6)	1.9 (0.60–6.0)	.27	—
Bacteremia or fungemia					
Negative	248 (74.7)	84 (25.3)			
Positive	57 (66.3)	29 (33.7)	1.3 (0.88–2.0)	.18	—
Platelets, n (%)					
100,000 cells/μL	245 (79.5)	63 (20.5)			
<100,000 cells/μL	48 (52.2)	44 (47.8)	2.4 (1.6–3.5)	<.001	1.8 (1.2–2.7)
Hospital site, ^a n (%)					
Mulago or Masaka	249 (77.3)	73 (22.7)			
Mbarara	56 (58.3)	40 (41.7)	2.4 (1.6–3.5)	<.001	1.8 (1.2–2.9)
AMS, altered mental status.					.004

^aThe hazard ratio for risk of death by site is calculated by comparing Mbarara to the other two sites combined. There was no difference in mortality between Mulago and Masaka. Dashes indicate covariates that were initially included in the multivariate equation, but did not meet inclusion criteria for the final multivariate model.