Evaluation of glycemic control in critically ill patients with bacteremia: a retrospective, single-center cohort study

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ABSTRACT

Dysglycemia is a common complication in hospitalized patients and has been suggested to play a significant role in the pathology and virulence of patients with bacteremia. The literature evaluating this relationship in critically ill patients, however, is limited. This retrospective, single-center cohort study aimed to investigate the relationship of glycemic control with 28-day intensive care unit (ICU)-free days in critically ill patients with bacteremia. Glycemic control was evaluated and determined based on time in targeted blood glucose range (TIR) of 70–140 mg/dL. Using a threshold of 80%, patients were then categorized into 2 groups: TIR-lo (<80%) and TIR-hi (≥80%). Unadjusted data identified a significant difference in ICU-free days (TIR-lo 21.29 days vs TIR-hi 24.08 days, p=0.007). However, due to an excess of zero ICU-free days, a zero-inflated Poisson model was used for analysis and demonstrated that patients in the TIR-lo group were 2.57 times more likely to have zero ICU-free days (p=0.033), which was attributed to mortality. Of the survivors, no difference was seen with TIR status and the number of ICU-free days (p=0.780). These findings demonstrate that glycemic control may increase the likelihood of being liberated from the ICU within a 28-day period, which the authors attributed to increased survival. However, of the patients who left the ICU, glycemic control was not associated with a significant difference in the number of ICU-free days.

Significance of this study

What is already known about this subject?

⇒ Dysglycemia is common in hospitalized patients and has been suggested to play a significant role in the pathology and virulence of patients with bacteremia.
⇒ Current guidelines recommend targeting blood glucose levels of 140–180 mg/dL.
⇒ Emerging evidence suggests that stricter glycemic control is associated with lower mortality in patients with bacteremia; however, there is a lack of data involving critically ill patients.

What are the new findings?

⇒ This study suggests that glycemic control during the treatment of bacteremia may significantly impact intensive care unit (ICU) survival, as poor glycemic control was strongly associated with deaths within this group.
⇒ After censoring for ICU deaths, glycemic control was not associated with a difference in the number of ICU-free days.

How might these results change the focus of research or clinical practice?

⇒ The results of this study suggest maintaining blood glucose levels of 140–180 mg/dL may not be generalizable to all patients in the critical ill realm, but rather stricter glycemic control may influence outcomes such as mortality.
⇒ Future research should focus on evaluation of glycemic control in critically ill patients with bacteremia with stratification based on the presence of diabetes mellitus.

INTRODUCTION

Dysglycemia is a common complication in hospitalized patients and includes hypoglycemia, hyperglycemia, and glycemic variability which have all been associated with adverse outcomes.[1–3] The recommendations regarding the level of glycemic control in critically ill patients have fluctuated over the years due to difficulty in determining an ideal range that mitigates the adverse effects associated with dysglycemia. Current guidelines recommend targeting blood glucose (BG) levels of 140–180 mg/dL in all critically ill patients.[4] This recommendation was largely driven by the results of the Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation trial in which intense glycemic control (BG target 81–108 mg/dL) resulted in a higher risk of 90-day mortality (OR 1.14, 95% CI 1.01 to 1.29).[5] Despite the data provided by this landmark trial, there remains an ongoing investigation of the benefit of varying glycemic targets in patients requiring intensive care unit (ICU)-level care. The authors have suggested that glucose variation, rather than absolute values,

may similarly influence critical illness, of which low time in range (TIR-lo), defined as less than 80% of monitoring within the goal range (70–140 mg/dL) in non-diabetic populations, was associated with higher mortality (8.47% vs 15.71%, p<0.001).[6] This difference, however, was not appreciated in patients with diabetes (16.09% vs 14.44%, p>0.99), which introduced the question of the heterogenic importance of glycemic control and variation.

Sepsis remains a major cause of morbidity and mortality in the USA and it has been proposed that dysglycemia may influence outcomes within this pathology. Hyperglycemia contributes to increased susceptibility and clearance of infections due to alterations in cellular and humoral defense mechanisms.[7 8] This is primarily mediated by impaired phagocytosis of bacteria as well as increased adherence of microorganisms to cells. Furthermore, it has been proposed that hyperglycemia may promote the growth and virulence of certain microorganisms.[9] This dysfunction in immunity may be reflected in studies as lower mortality rates have been appreciated in patients with Gram-negative rod bacteremia and initial glycemic values between 150 and 160 mg/dL.[10] Unfortunately, the majority of evidence evaluating the influence of glycemic control in patients with bacteremia has been limited to non-critically ill individuals. To date, it is unknown if this observation would be generalizable to critically ill patients or if the relationship would remain true throughout the course of the illness. Therefore, this retrospective study aimed to investigate the relationship of glycemic control with 28-day ICU-free days in critically ill patients with bacteremia.

MATERIALS AND METHODS

This was a single-center, retrospective cohort study conducted at a 695-bed urban academic medical center in northeast Florida and approved by the facility's institutional review board. Patients were identified using a report generated by the microbiology department consisting of positive blood cultures collected in the emergency department (ED) from January 1, 2012 to December 31, 2019. Inclusion criteria were: 18 years of age or older, direct admission from the ED to the medical intensive care unit (MICU), and a laboratory-confirmed bacteremia. A laboratory-confirmed bacteremia was defined as having at least 1 positive blood culture documented in the electronic medical record warranting treatment with antimicrobial agents as determined by the provider's assessment and evaluation. Patients were excluded if they required treatment with an insulin infusion, had an ICU length of stay (LOS) <1.0 day, active endocarditis, cirrhosis, a history of solid organ or bone marrow transplant, an absolute neutrophil count $<0.5 \times 10^9$/L, pre-existing ventilator dependence, or enrollment in another clinical trial during the documented encounter.

The primary endpoint was to evaluate the relationship between glycemic control and 28-day ICU-free days in critically ill patients with bacteremia. All BG levels measured during the treatment of bacteremia were collected and included for analysis. The institution's standard practice was to obtain BG levels on all MICU patients every 4 hours, with the exception of patients on an insulin infusion. Variance in glycemic changes was not based on nutritional intake and thus readings may have been preprandial or postprandial. Glycemic control was then evaluated using time in targeted blood glucose range (TIR), which was calculated by taking the number of BG levels within the range of 70–140 mg/dL divided by the total number of BG levels collected. Using a threshold of 80%, patients were then stratified into 2 groups for analysis: TIR-lo (<80%) and TIR-hi (≥80%). ICU LOS was calculated by taking the difference (in hours) between the time of admission and the time downgraded from ICU-level care and converted into days. For patients readmitted to the ICU, the same calculation was used for the time readmitted and added to the initial time on the ICU service. The number of ICU-free days was then determined by subtracting the number of days on an ICU service within the initial 28 days of admission from 28.

Secondary endpoints included: in-hospital mortality, hospital LOS, incidence of acute kidney injury (AKI), incidence of hypoglycemic events, time to blood culture clearance, and duration of antimicrobial treatment. AKI was defined as a serum creatinine increase of 1.5 times from baseline or an increase of ≥0.3 mg/dL. Hypoglycemic events were defined as a BG reading <70 mg/dL requiring dextrose intervention, in concordance with institutional guidelines. Time to blood culture clearance was determined by calculating the difference (in hours) between the first positive blood culture and the first negative blood culture after administration of antimicrobial(s). Duration of antimicrobial treatment was calculated (in days) based on antimicrobials administered for the treatment of bacteremia.

Additional data collected included patient demographics, known history of diabetes mellitus (DM), the administration of steroids, insulin requirements, causative organism(s) of bacteremia, and source of bacteremia. A Pitt Bacteremia Score and Charlson Comorbidity Index were then calculated for each patient to assess severity of illness and 10-year mortality, respectively.

A sample size of 198 patients (99 per group) was required to achieve an 80% power to detect an absolute difference of 2 ICU-free days from an estimated ICU LOS of 5.6±5 days at an alpha level of 0.05. Descriptive analyses were represented as frequencies and percentages for categorical variables and means, SDs, medians, and IQRs for numeric variables. Normal distribution was determined using Kolmogorov-Smirnov test. Differences in groups were compared using Pearson's χ^2 test for categorical data and Mann-Whitney U test was used for non-normally distributed continuous data. All data were collected and managed using the Research Electronic Data Capture. Data were analyzed using IBM SPSS Statistics (V.26) and SAS V.9.4.

Due to the skewed distribution observed in the primary outcome, a zero-inflated Poisson (ZIP) model was run to take into account the substantial percentage of patients with zero ICU-free days. Within this model, significant covariates influencing the primary outcome were identified and adjusted for and included Pitt Bacteremia Score and the receipt of corticosteroids. The ZIP model included 2 separate analyses for the interpretation of results. The zero-inflated model categorized patients based on ICU-free days being equal to zero (=0) or greater than zero (>0) to determine the number of patients liberated from the ICU. Of those patients who were downgraded from the ICU,

Table 1 Baseline characteristics

Variable, n (%) (mean±SD or median [IQR])	TIR-lo (n=108)	TIR-hi (n=63)	P value
Age (y)	66.94±12.32	61.01±16.90	0.044
Male sex	61 (56.48)	43 (68.25)	0.146
African American	63 (58.33)	41 (65.08)	0.331
Body mass index (kg/m^2)	26.77 [23.09–31.35]	25.71 [21.15–30.30]	0.221
Diabetes mellitus	53 (49.07)	11 (17.46)	0.001
Hemoglobin A1c (%)	6.05 [5.40–7.33]	5.35 [5.00–5.80]	<0.001
Pitt Bacteremia Score	4.00 [2.75–7.25]	3.00 [2.0–6.00]	0.012
Charlson Comorbidity Index	5.54±2.45	4.62±2.67	0.201
Placed on tube feeds	66 (61)	34 (54)	0.361
Received corticosteroids	43 (39.81)	18 (28.57)	0.139
Total hydrocortisone equivalent dose (mg)	0 [0–412.50]	0 [0–275.00]	0.211
Total insulin requirements (units)	5.5 [0–59.25]	0 [0–0]	<0.001
Causative organisms of bacteremia, n (%)			0.336
Gram negative	54 (50.00)	28 (44.44)	
Gram positive	46 (42.59)	26 (41.27)	
Polymicrobial	8 (7.41)	9 (14.29)	
Source of bacteremia, n (%)			0.744
Urinary	23 (21.30)	15 (23.81)	
Respiratory	14 (12.96)	9 (14.29)	
Central venous catheter	11 (10.19)	4 (6.35)	
Skin and soft tissue	8 (7.41)	7 (11.11)	
Multiple	11 (10.19)	9 (14.29)	
Other	41 (37.96)	19 (30.16)	

TIR, time in targeted blood glucose range.

a positive count model was then run to account for the number of ICU-free days.

As previous evidence has suggested that the presence of DM may influence patient response, a secondary analysis was conducted which stratified patients based on diabetic status. Subsequently, a logistic regression analysis was run to determine the predictors of in-hospital mortality in the non-DM arm.

Patient and public involvement

No patients or members of the public were directly involved in the development, design, implementation, or interpretation of the study or writing of the manuscript. All data are deidentified.

RESULTS

Of the 508 patients screened, a total of 171 were included for analysis with 108 in the TIR-lo group and 63 in the TIR-hi group (online supplemental figure 1). The most common reason for exclusion was a MICU LOS <1.0 day (70%). Included patients were predominantly male and African American. Patients in the TIR-lo group were more likely to be older, have a history of DM, and a higher Pitt Bacteremia Score (table 1).

Evaluation of the unadjusted primary outcome showed that patients in the TIR-lo group had a lower number of ICU-free days (TIR-lo 21.29 days (IQR 0–25.23) vs TIR-hi 24.08 days (IQR 19.71–25.68), p=0.007) (table 2). However, due to the skewed distribution, correlating with a

Table 2 Unadjusted primary and secondary outcomes for all patients

Outcomes, n (%) (mean±SD or median [IQR])	TIR-lo (n=108)	TIR-hi (n=63)	P value
28 d ICU-free days	21.29 [0–25.23]	24.08 [19.71–25.68]	0.007
Hospital LOS (d)*	11.42 [8.16–17.51]	9.66 [5.40–18.51]	0.223
In-hospital mortality	38 (35.19)	9 (14.29)	0.004
Hypoglycemic events	44 (40.74)	17 (26.98)	0.098
Acute kidney injury	81 (75.00)	43 (68.25)	0.377
Time to blood culture clearance (h)	54.17 [46.13–87.96]	62.72 [49.42–86.10]	0.222
Duration of intended antibiotics (d)	16 [14.00–17.81]	15.28 [13.00–23.50]	0.766

*TIR-lo (n=70); TIR-hi (n=54).
ICU, intensive care unit; LOS, length of stay; TIR, time in targeted blood glucose range.

Table 3 Unadjusted primary and secondary outcomes based on diabetic status

Outcomes, n (%) (mean±SD or median [IQR])	History of DM			No known history of DM		
	TIR-lo (n=53)	TIR-hi (n=11)	P value	TIR-lo (n=55)	TIR-hi (n=52)	P value
28 d ICU-free days	23.15 [0–25.34]	23.96 [11.32–24.95]	0.943	20.54 [0.00–24.73]	24.15 [19.71–25.72]	0.004
In-hospital mortality	15 (28.30)	3 (27.27)	>0.99	23 (41.82)	6 (11.54)	0.002
Hypoglycemic events	22 (41.51)	4 (36.36)	>0.99	22 (40.00)	13 (25.00)	0.105
Acute kidney injury	38 (73.08)	9 (81.82)	0.712	43 (78.18)	34 (65.38)	0.196

DM, diabetes mellitus; ICU, intensive care unit; TIR, time in targeted blood glucose range.

higher rate of mortality in the TIR-lo group (online supplemental figure 2), the ZIP model was used, and TIR-hi arm was used as the reference range. Based on the zero-inflated model, patients in the TIR-lo group were 2.57 times less likely to be liberated from the ICU (online supplemental table 1), or in other words, glycemic control was associated with an increased likelihood of being liberated from the ICU within a 28-day period. Patients with greater than zero ICU-free day were subsequently included in the positive count analysis which considered the number of ICU-free days (online supplemental table 2). The average number of ICU-free days was 23.5 days, and the TIR-lo arm was associated with a 1% risk of prolonged ICU stay, which was not significant (p=0.780).

Analysis of secondary outcomes found patients in the TIR-lo group had higher rates of in-hospital mortality (38% vs 9%, p=0.196). There was no difference seen in hospital LOS, incidence of hypoglycemic events, incidence of AKI, time to blood culture clearance, or duration of antimicrobial treatment (table 2).

When stratified based on the presence of DM, there was no difference seen in ICU-free days, in-hospital mortality, incidence of AKI, or incidence of hypoglycemic events in the DM arm (table 3). In the non-DM arm, patients in the TIR-lo group had a lower number of ICU-free days (20.54 days vs 24.15 days, p=0.004) and higher rates of in-hospital mortality (23% vs 6%, p=0.002). There was no difference seen in incidence of AKI or incidence of hypoglycemic events (table 3). A multiple logistic regression analysis of risk factors associated with in-hospital mortality in the non-DM group identified TIR (OR 4.12, 95% CI 1.18 to 14.35) and Pitt Bacteremia Score (OR 1.23, 95% CI 1.04 to 1.46) to be significant covariates (table 4).

Table 4 Multiple logistic regression analysis of mortality risk factors in patients with no known history of DM

Variables	OR (95% CI)	P value
TIR	4.12 (1.18 to 14.35)	0.026
Septic shock	2.21 (0.54 to 9.08)	0.272
Hypoglycemic events	0.67 (0.17 to 2.58)	0.559
Received corticosteroids	1.75 (0.54 to 5.65)	0.352
Pitt Bacteremia Score	1.23 (1.04 to 1.46)	0.018
Total insulin requirements	0.95 (0.90 to 1.01)	0.091
Charlson Comorbidity Index	0.85 (0.65 to 1.11)	0.223

DM, diabetes mellitus; TIR, time in targeted blood glucose range.

DISCUSSION

The theory that glycemic control influences outcomes in patients with bacteremia continues to evolve; however, the evidence is limited in the critically ill realm. Peralta *et al* found lower mortality rates with initial BG concentrations between 150 and 160 mg/dL in patients with community-acquired Gram-negative rod bacteremia and Leung and Liu found lower mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia when glycemic control was maintained within 100–140 and 70–100 mg/dL in patients with and without DM, respectively.[10 11] The intent of this study was to refocus on critically ill patients and evaluate the impact of glycemic control throughout the duration of bacteremia on patient outcomes.

This retrospective, single-center cohort study found that glycemic control, defined as maintaining BG levels between 70 and 140 mg/dL at least 80% of the time during treatment of bacteremia, may significantly impact liberation from the ICU. The authors believe that this finding was secondary to the influence on mortality as glycemic control accounted for all the mortalities within this group. The skewed nature of the data, however, prevented the analysis of the complete cohort and thus the inability to show a difference in ICU-free days may have been secondary to an underpowered cohort, after the elimination of ICU deaths.

The concept that the presence of DM impacts the relationship between glycemic control and mortality in critically ill patients may be explained by the adaptive stress response. Newer literature has shown that hyperglycemia provokes multiple adaptation mechanisms including inflammation and oxidative stress.[12] In a patient without DM, the repeated insult caused by stress-induced hyperglycemia can lead to endothelial damage which may be more pronounced in comparison to patients with DM who have adapted over time. Current literature has found dysglycemia to be associated with an increased risk of mortality in patients without DM compared with patients with DM.[11 13 14] This may have been reflected in the current study as ICU-free days and in-hospital mortality were only significant in the non-DM group. Additionally, TIR and Pitt Bacteremia Score were identified as mortality risk factors in the non-DM group. Overall, these findings warrant a robust prospective study evaluating glycemic control with a focus on critically ill patients with bacteremia with stratification based on the presence of DM.

This study has several limitations. Evaluation of baseline characteristics, such as comorbidities and hemoglobin A1c, may have been inaccurately documented or unavailable.

This subsequently may have impacted the use of scoring tools such as the Charlson Comorbidity Index as well as the ability to stratify patients based on diabetic status. Additionally, although all patients received insulin, glycemic control may have varied between providers in terms of initiating and adjusting insulin regimens.

In conclusion, this study demonstrated that glycemic control during the treatment of bacteremia may significantly impact liberation from the ICU. This association was thought to be secondary to the influence on mortality as poor glycemic control was strongly associated with deaths within this group. After censoring for ICU deaths, however, glycemic control was not associated with a difference in the number of ICU-free days for those that left the ICU. Secondary analyses suggest that the presence of DM may modulate this relationship as ICU-free days and in-hospital mortality were found to be significant only in the non-DM group. Furthermore, TIR and Pitt Bacteremia Score were identified as predictors of in-hospital mortality in the non-DM group. Past studies investigating the relationship between dysglycemia and critical illness have included a heterogeneous patient population and studies focusing on dysglycemia and bacteremia have been limited to 24-hour evaluations of dysglycemia as well as an underrepresentation of critically ill patients. The findings of this study suggest that patients with bacteremia requiring ICU-level care on admission may benefit from stricter glycemic control throughout the course of their illness, primarily in regard to liberation from the ICU. However, this relationship may be modulated based on the presence of preexisting DM.

Contributors AC, RC. VS and JF conceived and planned the design and execution of this project. AC, RC and JC carried out the data structure and extraction. WX contributed to data preparation and analysis as well as interpretation . AC, RC. VS and JF contributed to the interpretation of the results. AC took the lead in writing the manuscript. JF acted as the gurantor. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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