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Association of Hyperchloremia With Unfavorable Clinical Outcomes in Adults With Diabetic Ketoacidosis

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Abstract

Objective: Hyperchloremia is associated with worsened outcomes in various clinical situations; however, data are limited in patients with diabetic ketoacidosis (DKA). The purpose of this study was to determine the effect of hyperchloremia on time to DKA resolution. **Methods:** We conducted a retrospective cohort study of adult patients admitted with incident DKA from January 2013 through October 2017 and stratified by the development of hyperchloremia versus maintaining normochloremia. The primary outcome was time to final DKA resolution. Secondary outcomes included time to initial DKA resolution, incidence of acute kidney injury (AKI) on admission, in-hospital development of AKI, and hospital length of stay (LOS). **Results:** Of the 102 patients included, 52 developed hyperchloremia. Patients with hyperchloremia had longer times to final DKA resolution compared to those with normochloremia (median 22.3 [interquartile range, IQR, 15.2-36.9] vs 14.2 [IQR 8.8-21.1] hours; $P = .001$). Time to initial DKA resolution was also longer in patients who developed hyperchloremia compared to those who did not (median 16.3 vs 10.9 hours; $P = .024$). More patients with hyperchloremia developed in-hospital AKI (26.9% vs 8.0%; $P = .01$). Median hospital LOS was significantly longer in the hyperchloremia cohort ($P < .001$). On Cox regression analysis, time to DKA resolution was significantly longer with each 1 mmol/L increase in serum chloride (HR 0.951; $P < .001$). **Conclusion:** The presence of hyperchloremia in patients with DKA was associated with increased time to DKA resolution, risk of in-hospital AKI, and hospital LOS. Further evaluation of the avoidance or treatment of hyperchloremia in DKA is needed.

Keywords

diabetic ketoacidosis, hyperchloremia, acute kidney injury

Introduction

Diabetic ketoacidosis (DKA) is characterized by hyperglycemia, ketogenesis, and elevated anion gap metabolic acidosis.[1] Volume depletion and electrolyte abnormalities accompany these derangements. Diabetic ketoacidosis management includes volume resuscitation, insulin administration, and correction of electrolyte imbalances.[1] Volume resuscitation, traditionally utilizing saline, has the potential to worsen electrolyte abnormalities in patients with DKA, specifically the development of hyperchloremia.[2-5] While a growing body of evidence suggests hyperchloremia is associated with an increased risk of morbidity and mortality, its implications in DKA are not well defined.[6,7]

Hyperchloremia has been associated with worse renal outcomes in several observational studies of critically ill subpopulations.[8-13] Recently, the administration of chloride-rich 0.9% NaCl has been associated with increased major adverse kidney events compared with balanced, normochloremic fluids in both an emergency department and an intensive care unit (ICU) setting.[6,14] A pediatric study demonstrated receipt of 0.9% NaCl versus 0.45% NaCl led to increased rates of hyperchloremia and nonanion gap acidosis in DKA. This hyperchloremia-related acidosis resulted in a longer duration of insulin infusion and ICU length of stay (LOS).[5] However, data on the development and subsequent clinical impact of hyperchloremia in adults with DKA are lacking. The goal of

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this study was to determine the effect of hyperchloremia on the time to resolution of DKA.

Materials and Methods

Study Design and Participants

We conducted a retrospective cohort study of adult patients admitted with DKA utilizing the electronic medical record (EMR). All study data were collected and maintained using an electronic data capture tool (REDCap, project-redcap.org).[15] This study was approved by the institutional review board of Wake Forest Baptist Medical Center (IRB#00047320). Given the design of this study, informed consent was not required.

A report of all recipients of a DKA order set from January 2013 to October 2017 was used to identify patients for study inclusion. Patients were included if they were ≥18 years of age, admitted to the medical ICU (MICU) or intermediate care unit, and met all the following DKA diagnostic criteria: plasma glucose >250 mg/dL, arterial pH ≤7.3, serum bicarbonate ≤18 mEq/L, positive urine or serum ketones, and anion gap >10 mEq/L.[1] Only the first episode of DKA during the study period was included for each patient. The cause of DKA was recorded as determined by the treating clinician. For all patients with DKA, clinical pharmacists ensured the use of the DKA order set during daily multidisciplinary rounds. Patients were excluded for end-stage renal disease receiving renal replacement therapy, preexisting nonanion gap acidosis within 6 months, septic shock, acute pancreatitis, and transferal from a hospital not affiliated with the primary study site.

Data Collection

Patient demographics including age, sex, weight, and hospital unit were abstracted from the EMR. Additionally, the EMR was utilized to collect laboratory parameters such as serum glucose, creatinine, and chloride, and the volumes of 0.9% NaCl and 0.45% NaCl administered during the management of DKA. The institutional DKA order set at the time of this study only allowed for administration of 0.9% NaCl or 0.45% NaCl for fluid resuscitation. Administration of alternative fluids was expected to be minimal. Risk factors for acute kidney injury (AKI) were collected and included: age > 65 years, sepsis, hypotension defined as 2 consecutive mean arterial pressures of <65 mmHg, or any administration of contrast media, nonsteroidal anti-inflammatory drug, vancomycin, or aminoglycoside.[16]

Cohort Classification

Patients were divided into 2 cohorts, hyperchloremia and normochloremia, based on peak serum chloride level during DKA treatment. Hyperchloremia was defined as a serum chloride greater than 109 mEq/L and normochloremia was defined as a serum chloride less than or equal to 109 mEq/L. This definition of hyperchloremia was selected a priori based on institutional clinical lab criteria prior to any data collection or analysis.

Clinical Outcomes and Definitions

The primary outcome was the time to final DKA resolution defined as final discontinuation of insulin infusion and laboratory resolution of DKA. Secondary outcomes included time to initial DKA resolution, incidence of AKI on admission, development of in-hospital AKI, hospital LOS, in-hospital mortality, and adherence to guideline recommendations. Time to initial DKA resolution was defined as the first occurrence of laboratory resolution of DKA when plasma glucose was <200 mg/dL with 2 or more of the following: serum bicarbonate ≥15 mEq/L, venous pH >7.3, and anion gap ≤12 mEq/L.[1] Acute kidney injury was defined according to the 2012 Kidney Disease: Improving Global Outcomes Acute Kidney Injury Work Group definition of AKI based on serum creatinine (SCr) increase from baseline of ≥0.3mg/dL within 48 hours or ≥50% within the prior 7 days.[16] Baseline SCr was defined as the average of the 3 lowest values documented within 1 year of admission, or the lowest value during admission in the absence of prior documented SCr values. Acute kidney injury on admission was present when criteria were met on initial laboratory collection. Resolution of admission AKI was defined as the time at which criteria were no longer met. In-hospital development of AKI occurred when criteria were met no later than 72 hours after insulin infusion discontinuation and after the resolution of admission AKI if present.

Adherence to American Diabetes Association Consensus Guideline recommendations was assessed and defined for the purposes of this study as avoidance of bicarbonate use with arterial pH ≥6.9, utilization of dextrose-containing intravenous (IV) fluids within 2 hours of the blood glucose reaching 200 to 250 mg/dL, continuation of IV insulin for ≥1 hour after initiation of subcutaneous insulin, and maintenance of serum potassium between 3.5 and 5.3 mEq/L as evidenced by no 2 consecutive out-of-range measurements separated by ≥2 hours.[1]

Statistical Analysis

We calculated 48 patients would be needed in each group to provide 80% power to detect an absolute difference of 4 hours in the primary outcome with a type 1 error rate of 0.05. This difference in the primary outcome was based on findings from a study of pediatric patients with DKA in which patients who received 0.9% NaCl following initial resuscitation had an increased time to DKA resolution by an average of 4.1 hours when compared to those who received 0.45% NaCl (16.8 ± 7.1 vs 12.7 ± 6.9 hours; $P = .02$).[5] Continuous variables were compared using the Student t test or Mann-Whitney U test and nominal variables were compared using the χ^2 test or Fisher exact test, as appropriate. All comparisons were analyzed by 2-tailed tests with a P value <.05 indicating statistical significance. A Cox proportional hazards regression analysis was

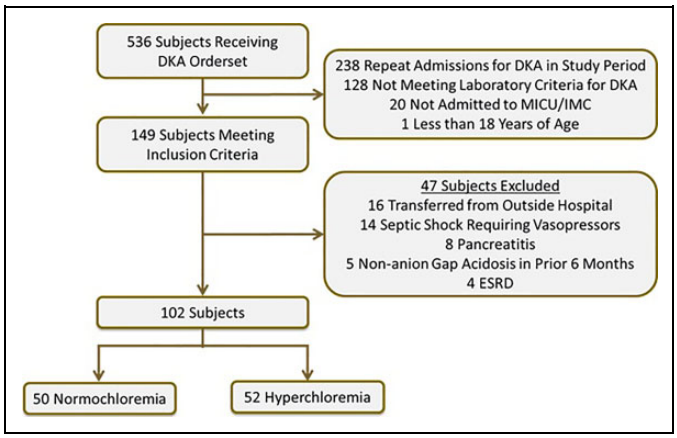

Figure 1. Patient flow diagram of adults admitted for the management of DKA. DKA indicates diabetic ketoacidosis; ESRD, end-stage renal disease; IMC, intermediate care unit; MICU, medical intensive care unit.

conducted for time to final DKA resolution considering risk factors for a prolonged duration of DKA. All plausible variables were initially included in the Cox regression analysis, but only variables associated with time to final DKA resolution with a P value <.2 remained in the model. Individual univariate regression analyses were conducted for each covariate included in the final model. Simple correlation, correlation matrices, and collinearity diagnostics were utilized to test for multicollinearity between variables in the Cox regression model. Statistical analyses were performed using SPSS software, version 25 (SPSS Inc, Chicago, Illinois).

Results

Between January 2013 and October 2017, the DKA order set was utilized 536 times. Patients from this data set were screened for study inclusion (Figure 1). Most excluded cases were for multiple DKA-related admissions during the study period or the absence of qualifying DKA laboratory diagnostic criteria. Overall, 102 patients were included for analysis in the study, of which 52 developed hyperchloremia and 50 maintained normochloremia during DKA management.[17]

Several baseline characteristics differed significantly among the 2 cohorts (Table 1). Patients in the hyperchloremia cohort had higher Acute Physiology, Age, and Chronic Health II (APACHE II) scores (median: 16.0 [interquartile range, IQR: 11.0-23.8] vs 13.5 [IQR 9.0-19.0]; $P = .02$), a higher proportion of MICU admissions (27 [51.9%] vs 12 [24.0%]; $P = .005$), and more severe initial acid–base abnormalities compared to those who maintained normochloremia. No patient in either group died during hospital admission despite predicted mortality of 15% to 25% among the 2 cohorts based on the respective APACHE II scores. The median total volume of fluid resuscitation was significantly larger in the hyperchloremia cohort (5819 [IQR: 4098-8138] mL vs 3915 [IQR: 2939-5230] mL; $P < .001$). The primary fluid used was 0.9% NaCl, with significantly larger volumes administered in the hyperchloremia cohort (3538 [IQR: 2406-5020] mL vs 2675 [IQR: 1825–3913] mL; $P = .008$).[17]

The cause of DKA was known in most patients (93.1%), with noncompliance to home insulin therapy being most prevalent (60.7%). Patients also developed DKA due to infection (39.2%), new-onset diabetes (9.8%), unknown factors (6.9%), or other causes (15.7%) such as myocardial infarction or trauma. Most patients had multiple contributing risk factors for DKA. New onset diabetes occurred more in the hyperchloremia group as compared to those with normochloremia (10 [19.2%] vs 0 [0%]; $P = .001$).[17]

Patients with hyperchloremia had a significantly longer median time to final DKA resolution compared to those with normochloremia (22.3 [IQR: 15.2-36.9] hours vs 14.2 [IQR: 8.8-21.1] hours; $P = .001$; Table 2). The median time to initial DKA resolution was also significantly longer in patients who developed hyperchloremia (16.3 [IQR: 10.2-29.1] hours vs 10.9 [IQR: 7.5-19.7] hours; $P = .02$). Median hospital LOS was significantly longer in the hyperchloremia cohort (97.1 [IQR: 68.8-138.2] hours vs 58.7 [IQR: 43.3-88.2] hours; $P < .001$).[17]

The incidence of AKI present on admission was common, but similar between those with hyperchloremia and normochloremia (47 [90.4%] vs 41 [82.0%]; $P = .22$). The median time to resolution of AKI present on admission was also similar between the 2 cohorts (15.7 [IQR: 8.8-30.0] hours vs 13.1 [IQR: 6.7-29.5] hours; $P = .28$). However, patients with hyperchloremia developed more episodes of in-hospital AKI (14 [26.9%] vs 4 [8.0%]; $P = .01$). The median time to development of in-hospital AKI following final insulin infusion discontinuation was approximately 14 hours (IQR: −21.3 to 98.5) but did not differ significantly between groups ($P = .28$). Risk factors for AKI examined were advanced age >65 years (8.8%), sepsis (5.9%), hypotension (19.6%), and receipt of contrast media (13.7%), nonsteroidal anti-inflammatory agents (7.8%), or vancomycin (14.7%), with no difference in the rates of these risk factors observed between groups. Additionally, 49% of patients had no identified risk factor for AKI.[17]

Covariates of peak serum chloride, APACHE II score, and total fluid volume administered during DKA were included and maintained in the Cox regression analysis predicting time to final DKA resolution (Table 3). Each 1 mmol increase in peak serum chloride (hazard ratio [HR]: 0.95 [95% confidence interval, CI: 0.93-0.98]; $P < .001$) and 1 L increase in total fluid volume administered during time in DKA (HR: 0.72 [95% CI: 0.64-0.80]; $P < .001$) were independently associated with an increase in time to final DKA resolution. The relationship between APACHE II score and time to final DKA resolution was not significant on Cox regression analysis (HR: 0.98 [95% CI: 0.95-1.01]; $P = .20$). Peak serum chloride and total fluid volume administered were demonstrated not to be collinear variables in the Cox regression model through simple correlation ($r = 0.44$), correlation matrix analysis ($r = -0.078$), and collinearity diagnostics (variance inflation factor = 1.24).

Table 1. Baseline Characteristics of the Study Patients.[a]

Characteristic	Normochloremia (n = 50)	Hyperchloremia (n = 52)	*P* Value
Demographics			
Age (years)	42.5 (27.0-55.0)	38.0 (28.3-54.8)	.99
BMI (kg/m^2)	24.6 (20.7-31.7)	24.3 (21.0-31.0)	.95
Type 1 diabetes	34 (68.0%)	35 (67.3%)	1.00
Female sex	21 (42.0%)	32 (61.5%)	.07
Admission to MICU	12 (24.0%)	27 (51.9%)	.005
APACHE II score	13.5 (9.0-19.0)	16.0 (11.0-23.8)	.02
Laboratory values			
First chloride (mEq/L)	92.5 (87.8-95.3)	97.5 (94.0-102.0)	<.001
Peak chloride (mEq/L)	106.0 (105.0-108.3)	114.0 (111.0-118.8)	<.001
First bicarbonate (mEq/L)	14.0 (10.0-17.0)	8.0 (6.0-12.8)	<.001
Baseline creatinine (mg/dL)	0.73 (0.57-0.93)	0.61 (0.53-0.82)	.22
Admission creatinine (mg/dL)	1.24 (0.99-1.64)	1.42 (1.04-1.93)	.15
Peak creatinine (mg/dL)	1.24 (0.99-1.67)	1.46 (1.06-2.01)	.08
First pH	7.24 (7.16-7.28)	7.13 (6.99-7.21)	<.001
Delta gap (mEq/L)	11 (7-17)	15 (8-18)	.11
Secondary NAG metabolic acidosis	10 (20.0%)	22 (42.3%)	.02
Fluid administration			
Total fluid volume (mL)	3915 (2939-5230)	5819 (4098-8138)	<.001
0.9% NaCl volume (mL)	2675 (1825-3913)	3538 (2406-5020)	.008
0.45% NaCl volume (mL)	932 (589-1450)	1400 (756-2075)	.02

Abbreviations: APACHE II, Acute Physiology, Age, and Chronic Health II; BMI, body mass index; MICU, medical intensive care unit; NAG, nonanion gap.
[a]Values expressed as median (interquartile range) or number (%), as appropriate.

Table 2. Clinical Outcomes According to Serum Chloride Cohort.[a]

Outcomes	Normochloremia (n = 50)	Hyperchloremia (n = 52)	*P* Value
Time to final DKA resolution (hours)	14.2 (8.8-21.1)	22.3 (15.2-36.9)	.001
Time to initial DKA resolution (hours)	10.9 (7.5-19.7)	16.3 (10.2-29.1)	.02
AKI on admission	41 (82.0%)	47 (90.4%)	.22
In-hospital AKI	4 (8.0%)	14 (26.9%)	.01
Hospital length of stay (hours)	58.7 (43.3-88.2)	97.1 (68.8-138.2)	<.001

Abbreviations: AKI, acute kidney injury; DKA, diabetic ketoacidosis.
[a]Values expressed as median (interquartile range) or number (%), as appropriate.

Table 3. Cox Regression Analyses of Time to Final DKA Resolution.

Variables	Hazard Ratio (95% CI)	*P* Value
APACHE II	0.98 (0.95-1.01)	.20
Peak chloride (mmol/L)	0.95 (0.93-0.98)	<.001
Total volume (liters)	0.72 (0.64-0.80)	<.001

APACHE II = Acute Physiology, Age, and Chronic Health II; 95% CI, 95% confidence interval.

Adherence to guideline recommendations was not significantly different between groups, except that patients with hyperchloremia did not maintain serum potassium levels within normal range as often as those with normochloremia (61.5% vs 86.0%; $P = .007$). Adherence to guideline recommendations was achieved in most patients regarding avoidance of inappropriate bicarbonate utilization (89.2%), appropriate timing of dextrose initiation (70.6%), and appropriate overlapping of subcutaneous insulin (70.0%).[17]

Discussion

The development of hyperchloremia in this study was associated with worsened clinical outcomes, including longer time to DKA resolution, higher rates of development of in-hospital AKI, and longer hospital LOS. Significant differences in baseline characteristics suggest that patients who developed hyperchloremia were more severely ill at baseline and required larger volumes of IV resuscitative fluids. However, hyperchloremia was found to independently predict a poor outcome after adjusting for these differences between groups. Thus, our results contrast with guideline statements that regard hyperchloremia as a benign consequence of fluid resuscitation in patients with DKA.[1]

Hyperchloremia has been associated with poor renal outcomes in observational studies of various patient populations.[8-12] A plausible mechanism for renal injury caused by hyperchloremia has been suggested from a study of healthy adults.[18] These participants received 2 L infusions of 0.9%

NaCl or a chloride-balanced solution. Sustained hyperchloremia and a reduction in mean renal artery blood flow velocity were observed following 0.9% NaCl administration, but not with the chloride-balanced solution. The authors concluded that the observed reductions in renal perfusion were likely secondary to high concentrations of chloride within the renal tubules and subsequent tubuloglomerular feedback leading to afferent arteriole constriction. This mechanism may explain the approximate 20% increase of in-hospital AKI development observed in patients with hyperchloremia in the present study. Although more patients with hyperchloremia in our study experienced in-hospital AKI, this was not accompanied by differences between groups with regard to AKI present on admission, time to resolution of admission AKI, or time to onset of in-hospital AKI relative to discontinuation of IV insulin. Causality cannot be determined, but the association we observed between hyperchloremia and in-hospital AKI development is strengthened by the temporal relationship between these 2 variables.

Administration of chloride-rich IV resuscitative fluids and subsequent hyperchloremia have resulted in not only worsened kidney function but also poor clinical outcomes in critically ill children with DKA.[5] Basnet and colleagues demonstrated that children who received 0.9% NaCl during DKA following bolus fluid administration experienced a larger average increase in serum chloride of approximately 6 mmol/L and a 20% increase in incidence of hyperchloremic metabolic acidosis compared to patients who received 0.45% NaCl. These metabolic derangements may have resulted in the approximately 4-hour longer duration of insulin infusion observed in patients who received 0.9% NaCl. Our study is unique in that each group received similar types of fluids but appeared to develop hyperchloremia based on the volume of fluid administered. Therefore, the differences in outcomes can be associated with the development of hyperchloremia, irrespective of fluid type. The larger difference in peak serum chlorides between the 2 cohorts in this study (8 mmol/L) may explain the longer 8-hour increase in time to final DKA resolution observed compared to the 4-hour increase in the study of pediatric patients with DKA.

Until recently, randomized controlled trials have not demonstrated greater harm associated with the use of 0.9% NaCl as compared to balanced, "normochloremic" solutions.[7,19] However, a recent large randomized controlled trial demonstrated a higher rate of adverse kidney events from the administration of 0.9% NaCl compared with balanced, or more normochloremic, fluids.[6] The Balanced Crystalloids versus Saline in Critically Ill Adults (SMART) study included over 15 000 ICU patients and demonstrated a 1.1% absolute difference in major adverse kidney events at 30 days in those randomized to receive saline as compared to balanced crystalloids (15.4% vs 14.3%; $P = .04$). The incidence of hyperchloremia in the SMART study was higher in patients who received 0.9% NaCl (35.6% vs 24.5%; $P < .001$), with higher rates of hyperchloremia seen with receipt of larger fluid volumes. Generally, the heterogeneous patient population in the SMART study received relatively small volumes of fluid overall (median 0.9% NaCl volume at 7 days, 1000 mL [IQR: 0-3000]) compared to the patients with DKA in this study (median total fluid volume, 4531 mL [IQR: 3338-6500]). This difference in fluid receipt may explain the nearly 20% difference in the development of in-hospital AKI between groups in this study compared to the smaller difference seen in the SMART trial.

While investigations have demonstrated an association between hyperchloremia and increased hospital mortality, we did not observe any mortality in this analysis despite an APACHE II score of 16 in the hyperchloremia cohort.[9,10] The disparity between predicted and observed mortality in the present study is likely due to 2 main factors. First, patients with DKA commonly present with profound, yet rapidly reversible, metabolic and vital sign abnormalities, accounting for an increase in APACHE II scores. Despite these physiologic aberrations that occur secondary to DKA and a high APACHE II score, the mortality rate in adult patients has been shown to be less than 1%.[1] Second, we excluded patients whose acid–base profile and resuscitation might be confounded by alternative processes (eg septic shock). The absence of patients with these comorbid processes may also have significantly impacted the lack of mortality seen in this analysis. The present results are consistent with historical data regarding in-hospital mortality in adult patients with DKA without additional severe illnesses.[1]

Our study has several strengths. First, we carefully assessed for resolution of the prevalent admission AKI to clearly identify the development of subsequent in-hospital AKI. This was done to establish a temporal relationship between the development of hyperchloremia and successive in-hospital AKI. Second, we attempted to strengthen the validity of our AKI results by comparing potential confounding aspects between groups, including other AKI risk factors and causes of DKA. Third, we assessed compliance with guideline recommendations to ensure no major differences in DKA management between the 2 cohorts existed.

There were several limitations to this study. The retrospective, observational nature limits the determination of causation between serum chloride and adverse clinical outcomes. However, the association between peak chloride and unfavorable outcomes remained after adjusting for other plausible factors that could prolong the duration of DKA. Additionally, the study included patients who developed DKA from a variety of factors but was primarily caused by noncompliance with insulin therapy. It is unclear if the differences in outcomes in this study would be similar if a greater proportion of patients with DKA due to other factors were studied. Lastly, our results may be limited due to the direct relationship between serum chloride concentration and the anion gap. Initial resolution of DKA was defined according to blood glucose and at least 2 of pH, bicarbonate, or anion gap criterion. Acidosis in the setting of hyperchloremia generally presents as a nonanion gap acidosis. One might expect to see a shorter time to initial DKA resolution in

the hyperchloremia cohort if elevated chloride resulted in anion gap normalization. However, we did not observe a shorter time to initial DKA resolution in the presence of hyperchloremia. In the hyperchloremia cohort, our findings were consistent with longer median times to both initial DKA resolution defined by laboratory criteria and final DKA resolution based on cessation of IV insulin.

Conclusion

The development of hyperchloremia in patients with DKA was associated with worse clinical outcomes, including increased time to DKA resolution, hospital LOS, and development of in-hospital AKI. After considering risk factors for a prolonged duration of DKA and insulin infusion in Cox regression analysis, peak serum chloride was independently associated with prolonged time to DKA resolution. Prospective studies of hyperchloremia avoidance in DKA are needed to better define the relationship between chloride and clinical outcomes in this patient population.

Author Note

This study was performed at Wake Forest Baptist Medical Center, Winston-Salem, North Carolina. Notation of Prior Abstract Publication/Presentation: Data from this manuscript have been presented in part at the Society of Critical Care Medicine 48th Critical Care Congress in San Diego, CA on February 17, 2019. Nathan T. Goad is the guarantor of this work, and as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Nathan Goad is now affiliated with Department of Pharmacy, Cabell Huntington Hospital, Huntington, WV, USA.

Authors' Contributions

All authors provided significant contributions to this work, including the development of study design, data collection and analysis, interpretation of data, writing of the manuscript, and approval of the final manuscript version to be submitted for publication.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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