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Resolution of ketoacidosis in children with new onset diabetes: Evaluation of various definitions

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Structured Abstract

Aims—Data are sparse concerning use of serum electrolyte parameters as compared to venous blood gas (VBG) measurements to monitor acid-base status during treatment of diabetic ketoacidosis (DKA). We explored the utility of various parameters to define DKA resolution by investigating the relationship of venous pH (vpH), anion gap (AG), serum bicarbonate (HCO_3^-), and glucose concentration during management of DKA in children with new onset diabetes mellitus (NODM).

Methods—We included all patients with NODM presenting with DKA to Boston Children's Hospital from 10/1/07–7/1/13. DKA was defined as serum glucose ≥ 200 mg/dL (11.1 mmol/L) and $\text{vpH} < 7.30$; severity as mild < 7.30 , moderate < 7.20 , severe < 7.10 ; resolution of DKA as $\text{vpH} \geq 7.30$ and AG ≤ 18 mmol/L. We used Cox regression to determine time to DKA resolution, and logistic regression to evaluate different serum HCO_3^- cut-off values as predictors of DKA resolution.

Results—263 patients (133F, mean age 9.9 ± 4.4 years, 74% White) were included. DKA was mild in 134 (51%), moderate in 75 (28%) and severe in 54 (20%). In mild DKA, AG closed *after* normalization of vpH; in moderate and severe DKA, AG closed *before* normalization of vpH. $\text{HCO}_3^- > 15$ mmol/L correlated with $\text{vpH} \geq 7.30$, and had 76% sensitivity and 85% specificity to predict DKA resolution. Median times to DKA resolution were similar using two different definitions: vpH and AG (8.4 hours [IQR 6.3–11.9]) vs. $\text{HCO}_3^- > 15$ mmol/L (7.9 hours [IQR 5.0–11.8]), $p = 0.42$.

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Contribution of authors

All authors are responsible for the reported research, and all authors have participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript. JVO conceptualized and designed the study, and carried out data collection and data analysis. She drafted the initial manuscript. JW and ER conceptualized and designed the study, and supervised data collection and analysis. They critically reviewed and revised the manuscript. All authors have read and approved the manuscript as submitted.

Conflicts of interest

ER is a Site Principal Investigator for Merck and Astra Zeneca trials related to type 2 diabetes in youth. JVO and JW report no conflicts of interest. JVO wrote the first draft of the manuscript. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

Conclusions—During management of pediatric DKA, $\text{HCO}_3^- > 15$ mmol/L reliably predicts resolution of DKA. In low-resource settings where VBG is unavailable, electrolyte parameters alone may be used to determine DKA resolution.

Keywords

diabetic ketoacidosis; acid-base equilibrium; blood gas analysis; bicarbonate; child

1. Introduction

Diabetic ketoacidosis (DKA) at diagnosis of diabetes is common in children and adolescents; the worldwide incidence varies from approximately 13 to 80% [1]. Risk factors for DKA include younger age, lower pediatric diabetes prevalence, lower socio-economic status and limited access to health care [1,2].

During the management of DKA, acid-base status, glycemia, and serum electrolytes are measured frequently to monitor the efficacy of treatment, detect complications of DKA and its treatment, and to determine resolution of DKA. Although there is some variation in the specific details of treatment protocols [1,3], a common approach includes monitoring blood glucose concentrations every 1–2 hours, and serum electrolytes and venous blood gases (VBG) every 2–4 hours.

Biochemical parameters used to define resolution of DKA include venous pH (vpH), serum bicarbonate concentration (HCO_3^-), anion gap (AG), and 3-hydroxybutyrate (3-OHB) concentration. Urine ketone measurements are still used to monitor ketosis during DKA management when blood 3-OHB measurements are not available; however, it is now well recognized that a significant lag occurs between clearance of ketonuria and resolution of hyperketonemia [4–6]. Several different definitions for DKA resolution have been proposed; e.g., the guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) suggest vpH > 7.3 , $\text{HCO}_3^- > 15$ mmol/L, 3-OHB < 1 mmol/L, and/or closure of the AG [7]. The American Diabetes Association (ADA) guidelines for management of hyperglycemic crises in adults suggest blood glucose < 200 mg/dL (11.1 mmol/L) and two of $\text{HCO}_3^- > 15$ mmol/L, vpH > 7.3 or AG < 12 mmol/L [8]. The guideline of the Joint British Diabetes Societies for the management of DKA uses vpH > 7.3 and 3-OHB < 0.3 mmol/L [9].

Few studies have addressed how these parameters correlate during treatment of DKA. One pediatric study found time to resolution of DKA was significantly reduced when vpH > 7.3 and two bedside 3-OHB measurements < 1 mmol/L was used as the endpoint as compared to vpH > 7.3 and resolution of ketonuria [4]. Another small study in children evaluated the effect of hyperchloremia on acid-base interpretation in DKA and found that the AG decreased more rapidly than serum HCO_3^- concentration increased, but found a tight correlation between the two when serum HCO_3^- was corrected for hyperchloremia [10].

For clinicians to apply any of the above definitions of DKA resolution, frequent measurements of VBG, blood ketones and serum electrolytes are required. However, in many resource-constrained countries and settings, blood gas analyzers and blood ketone measurements may not be available, and expert clinicians with vast experience managing

DKA may not exist. Indeed, many countries have a limited number of trained pediatricians and not a single pediatric endocrinologist. In these circumstances, management of DKA may rely entirely on clinical parameters and measurements of point-of-care blood glucose concentrations with or without availability of urine ketones and serum electrolytes. New point-of-care machines such as i-STAT allow for bedside VBG measurements; however, they may not be available in low-income countries due to the high cost per test and difficulty maintaining a supply of cartridges in countries without local distributors. Decisions about when to stop intravenous (or intramuscular) insulin and switch to subcutaneous insulin administration, when to allow patients to drink and eat, and when to move a patient to a ward with less intensive nursing care and monitoring are typically based on a limited number of objective biochemical parameters.

We have previously confirmed findings by Nadler et al. [11] that serum HCO_3^- concentration and vpH are highly correlated during evaluation of pediatric DKA[12], and we have suggested that serum HCO_3^- levels can be used to diagnose DKA and assess its severity in children with new onset diabetes[12]. To our knowledge, no study has assessed the agreement of vpH with serum HCO_3^- concentrations and AG for defining resolution of DKA, an issue that is particularly relevant for remote or limited resource settings.

Our objectives in this study were 1. to evaluate the relationship of serum HCO_3^- , AG and glucose to vpH during management of DKA; 2. to assess the utility of serum HCO_3^- concentration as a predictor of DKA resolution in children and adolescents with new onset diabetes; and 3. to determine the time to resolution of DKA using three discrete endpoints: vpH , serum HCO_3^- concentration and AG. We compared these parameters to a composite definition of DKA resolution that included both vpH and AG.

2. Patients and Methods

2.1. Study Design and Study Population

This was a retrospective cohort study that included all patients with new onset diabetes mellitus (NODM) and DKA, defined by serum glucose ≥ 200 mg/dL (11.1 mmol/L) and $\text{vpH} < 7.30$, who were admitted to Boston Children's Hospital (BCH) between October 1, 2007 and July 1, 2013, and managed according to the BCH clinical practice guideline for NODM, which is consistent with the ISPAD guidelines for treatment of DKA[7]. To avoid confounding, we excluded patients with a previous diagnosis of diabetes as many such patients have received treatment with insulin, intravenous fluids, or both, prior to arrival at BCH. Further exclusion criteria were a diagnosis of neonatal diabetes mellitus, and patients in whom VBG was not measured. Mild, moderate, and severe DKA were defined as vpH 7.20 – 7.29, 7.10 – 7.19, and < 7.10 , respectively [4]. Anion gap (AG) was defined as the difference between the sum of the serum sodium and potassium concentrations and the sum of the serum chloride and bicarbonate concentrations (reference range 12–18). Resolution of DKA was defined as a composite of both $\text{vpH} \geq 7.30$ and AG closure (< 18 mmol/L).

The BCH treatment protocol for DKA recommends normal saline (NS) administration during the first 4–6 hours of treatment; thereafter, fluid can be switched to three-fourths, two-thirds or half NS, as determined by the individual patient's serum sodium concentration

and effective serum osmolality. Potassium is added when insulin infusion is initiated (typically 1 hour after starting treatment), and dextrose is added when serum glucose decreases to <300 mg/dL. Data were collected throughout the patient's hospitalization. The study was approved by the Institutional Review Board at BCH.

2.2. Data Collection

To identify eligible patients, we used the BCH inpatient Diabetes Quality Improvement Database, which captures all children and adolescents with NODM requiring treatment with insulin, as all are admitted to the hospital at the time of diagnosis. We used Childrens 360, a data extraction tool linked to the hospital's electronic medical record, to obtain baseline demographic and anthropometric information, laboratory results (venous blood glucose concentrations, serum electrolytes, VBG, hemoglobin A1c [HbA1c]), and date and time of laboratory analyses.

2.3. Outcome Measures

Our primary outcome measures were the relationship between serum HCO_3^- , AG, glucose and vpH during management of pediatric DKA, and the value of HCO_3^- that best predicts resolution of DKA defined as vpH ≥ 7.30 and AG ≤ 18 mmol/L. Secondary outcomes were the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of HCO_3^- cut-off values, as well as time to resolution of DKA as defined by these HCO_3^- cut-off values compared to the definition of DKA resolution based on a composite of both vpH and AG.

2.4. Laboratory Analysis

All measurements were performed in the BCH Clinical Chemistry Laboratory, which uses quantitative enzyme-based determination on the Roche/Hitachi cobas c systems platform (Roche Diagnostics, Indianapolis, IN) to determine serum HCO_3^- concentration. The Radiometer ABL 825 (Radiometer, Cleveland, OH) is used to measure VBG, serum glucose and electrolyte concentrations, and the Roche Integra 800 platform (Bayer Healthcare, Whippany, NJ) is used to measure HbA1c. The BCH laboratory undergoes regular quality control assessments and laboratory methods did not change over the time period of our data collection.

2.5. Statistical Analysis

We used standard descriptive statistics to describe the characteristics of patients. These included percentages for categorical variables, and mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, for continuous variables. Analyses of continuous data utilized Student's t-test and Wilcoxon rank sum test for normal and non-normal data, respectively, and chi-square tests to compare categorical variables. We used Pearson correlation coefficients to evaluate the relationships between vpH and electrolyte parameters. We used logistic regression and receiver operating characteristic (ROC) curves to evaluate serum HCO_3^- concentrations as predictors of DKA resolution (vpH ≥ 7.30 and AG ≤ 18 mmol/L). An area under the curve (AUC) of greater than 0.8 was chosen *a priori* as the minimum acceptable goodness-of-fit. The association of predicted probabilities and

observed responses was used to assess how well the model was calibrated; i.e. how well predicted DKA resolution rates matched expected resolution rates. Sensitivity, specificity, PPV and NPV were calculated for HCO_3^- cut-off values used in clinical practice, and an estimate of a best cut-off value of HCO_3^- to predict DKA resolution was determined using the result of [sensitivity – specificity]. We used Cox regression to determine time to resolution of DKA. We compared different HCO_3^- cut-off values as well as serum HCO_3^- and AG closure to the pre-defined composite definition of DKA resolution (vpH ≥ 7.30 and AG ≥ 18 mmol/L). We also evaluated these electrolyte parameters in comparison to a definition of resolution that included serum glucose <200 mg/dL in addition to vpH ≥ 7.30 and AG ≥ 18 mmol/L. We calculated medians and interquartile ranges for vpH, HCO_3^- , AG and vpH at the time of resolution of acidosis, HCO_3^- normalization, AG closure and the composite definition of DKA resolution. Characteristics for different serum HCO_3^- concentration cut-off values to predict resolution of DKA from the model included sensitivity, specificity, PPV and NPV.

For all analyses, p-value <0.05 was considered significant. Analyses were performed using SAS Software Version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.5.1. Sensitivity Analysis—Because all three biochemical parameters (vpH, HCO_3^- and AG) were not available for all patients, we conducted a sensitivity analysis for all the above evaluations that only included 228 patients in whom all three parameters were available.

3. Results

3.1. Patients

We identified 1,264 patients with NODM of whom 60 (4.7%) were excluded because they did not have a VBG measurement at diagnosis. Of the remaining 1,204 patients, we included 263 patients (21.8%) with NODM and DKA in the study. Slightly more than half of the study patients ($n=134$ [51%]) had mild DKA; 75 (28.5%) had moderate DKA, and 54 (20.5%) had severe DKA. The majority of patients (97%) were presumed to have type 1 diabetes based on their clinical and biochemical presentations. Characteristics of the patients are shown in Table 1.

3.2. Relationships between vpH and HCO_3^- , Anion Gap and Serum Glucose

The relationships between vpH and serum HCO_3^- , AG, serum glucose are shown in Figure 1A–C. There was a highly significant positive log-linear relationship between vpH and HCO_3^- ($r=0.84$, $P<.001$). The linear relationships between vpH and AG, and between vpH and glucose were negative ($r=-0.59$ and $r=-0.36$, respectively, both $P<.001$).

Cox regression survival curves show the relationships of all four measures over the course of DKA treatment until resolution (Figure 2A). For all severities of DKA, normalization of HCO_3^- (>15 mmol/L) occurred in parallel with resolution of acidosis (vpH ≥ 7.30) ($P=0.21$). Closure of AG occurred after resolution of acidosis in mild DKA, and before in moderate and severe DKA; and survival curves differed significantly between AG closure and resolution of acidosis (vpH ≥ 7.3) ($P=0.0003$). Survival curves of time to serum glucose <200 mg/dl and acidosis resolution, likewise, were significantly different ($P<.0001$). Time to

serum glucose <200 mg/dl took longest when all severities of DKA were combined, as well as in mild and moderate DKA, but not in severe DKA.

3.3. Evaluation of electrolyte parameters as predictors of DKA resolution

Sensitivity, specificity, NPV and PPV of different serum HCO_3^- concentration cut-off values used to determine resolution of DKA are shown in Table 2. The ROC curve to determine an optimal cut-off for serum HCO_3^- concentration as a predictor of DKA resolution (defined as $\text{vpH} \geq 7.3$ and $\text{AG} \geq 18$ mmol/L) had an area under the curve (AUC) of 0.87 (95% CI: 0.83–0.90, $P < .001$) (Figure 1D). The association of predicted probabilities and observed responses showed a concordance of 84.8 % for serum HCO_3^- concentration to predict DKA resolution, and the optimal cut-point (maximization of sensitivity and specificity) was >15 mmol/L (Table 2a). Sensitivity remained similar and specificity improved to over 90% when closure of AG was added to this serum HCO_3^- cut-off as a criterion for DKA resolution (Table 2b).

Times to DKA resolution as defined by vpH and AG as compared to resolution of acidosis, normalization of serum HCO_3^- concentration, AG closure or the composite definition $\text{HCO}_3^- >15$ mmol/L and closure of AG are shown in Table 3. Median time to DKA resolution was 8.4 hours (interquartile range, IQR: 6.3 – 11.9). Not unexpectedly, mild DKA (median time to resolution 6.9 hours, IQR 5.9–9.6) resolved more quickly than moderate DKA (median time to resolution 8.2 hours, IQR 6.9 – 10.6) and severe DKA (median time to resolution 14.5 hours, IQR 11.6 – 16.3). When compared to resolution times defined by vpH and AG, there were no significant differences in times to resolution of moderate and severe DKA defined by serum $\text{HCO}_3^- >15$ mmol/L; whereas time to resolution of mild DKA was significantly shorter, 5.5 (3.7–7.3) vs. 6.9 (5.6–9.6) hours, respectively.

Survival curves based on three different definitions of DKA resolution: $\text{HCO}_3^- >15$ mmol/L; $\text{HCO}_3^- >15$ mmol/L and $\text{AG} \geq 18$ mmol/L, and $\text{vpH} \geq 7.30$ and $\text{AG} \geq 18$ mmol/L, were similar ($P=0.12$) (Figure 2B). The survival curve showing DKA resolution defined as vpH/AG/ serum glucose differed significantly from the curve defined as vpH/AG ($P=0.13$), $\text{HCO}_3^- >15$ mmol/L ($P=0.02$), and HCO_3^-/AG ($P=0.46$), with resolution occurring later using the $\text{vpH/AG/serum glucose}$ definition.

3.4. Sensitivity Analyses

When we only included patients who had all three parameters measured in the analysis ($n=228$), survival curves showing time to resolution of DKA, median times to resolution, and the comparisons of vpH , HCO_3^- and AG did not change (data not shown).

4. Discussion

The results of our study show that during treatment of DKA, changes in serum HCO_3^- concentrations strongly correlate with vpH , the AG normalizes before vpH reaches 7.30, and serum glucose decreases to <200 mg/dL significantly later. Serum HCO_3^- concentration is a reliable alternative parameter to determine resolution of DKA (defined by $\text{vpH} \geq 7.30$ and AG closure). At a cut-off value of >15 mmol/L, HCO_3^- has acceptable sensitivity, good specificity, an excellent NPV, and a low false positive rate. In moderate and severe DKA, median times to resolution of DKA and survival curves at this cut-off are similar to the

definition based on the composite definition of both vpH and AG. Also, resolution trends based on a composite outcome of both $\text{HCO}_3^- > 15$ mmol/L and AG closure are comparable to those based on a composite outcome of vpH > 7.30 and AG closure. These findings suggest that serum HCO_3^- levels can reliably substitute for vpH to monitor resolution of DKA in pediatric patients with NODM, and that VBG measurements are not routinely required to monitor these patients.

To our knowledge, this is the first study that has systematically investigated correlates of vpH during management and resolution of DKA. Multiple definitions, predominantly based on professional society guidelines[8,13,14], have been used in studies of DKA resolution[15–19]. Dhatariya et al. conducted a national survey of DKA management in the United Kingdom[20] and found that almost all respondents (95%) used blood glucose concentration as a resolution criterion, followed by urine ketones (17%), vpH (11%) and serum HCO_3^- concentration (5.3%). Of five pediatric studies that assessed various DKA treatment protocols[4,21–24], all used vpH to define resolution, one also used either serum or urine ketones[4], and one also used serum HCO_3^- concentration and AG[24]. Only one previous study, however, assessed the relationship between some of the biochemical parameters. In a retrospective study of 18 children, Taylor et al. assessed the relationship of AG vs. venous HCO_3^- , and AG vs. base deficit during treatment of DKA, and showed that the AG decreased more rapidly than the rise in venous HCO_3^- concentration[10]. Our results corroborate this observation. The relationship between AG and HCO_3^- became equimolar when HCO_3^- was corrected for the effect of hyperchloremia[25]. The authors suggested that hyperchloremia is the dominant component of acidosis after 12 hours of treatment and that resolution of DKA may be masked by hyperchloremia. This phenomenon would account for the different times to DKA resolution between AG alone as compared to vpH and serum HCO_3^- concentration. Taylor et al. pointed out that the AG cannot differentiate between a mixed metabolic and hyperchloremic acidosis and pure ketoacidosis, and the degree of hyperchloremic acidosis is not quantifiable using the AG. They suggested that partitioning of the base deficit would possibly help overcome this issue[10]. Indeed, chloride-rich fluids administered during treatment of DKA, typically as normal saline (NS) and potassium chloride, combined with preferential renal excretion of ketone bodies over chloride anions [26], may account for the high frequency of hyperchloremic acidosis developing during treatment of DKA[27,28]. A study in adults compared Plasma-Lyte 148 (a fluid with lower chloride content) to NS and confirmed that patients treated with Plasma-Lyte 148 have stable serum chloride levels, and more rapid resolution of DKA as measured by HCO_3^- and vpH[29]. AG was not reported in this study. Similarly, in a study of 121 children, Basnet et al. found lower rates of hyperchloremia and non-anion gap acidosis and shorter duration of therapy and length of stay in children with DKA who received half-normal saline as compared to those who received NS[30]. While we were unable to extract data on the details of the fluid regimen received by individual patients, all patients were treated according to the BCH DKA treatment protocol that recommends 4–6 hours of NS followed by half to three-fourths NS at 1.5 to 2 times the usual maintenance rate based on either body weight or surface area. Serum chloride levels rose from a median concentration of 97 mmol/L (IQR 92, 104) to a median of 109 mmol/L (IQR 104, 112) suggesting evolving hyperchloremia in at least half of the population. The recently completed (not yet published) prospective Fluid

Therapies Under Investigation in DKA (FLUID) trial conducted by the Pediatric Emergency Care Applied Research Network (PECARN) study group[31] is expected to shed further light on the impact of various fluid regimens, including their chloride content, on biochemical parameters used to indicate resolution of acidosis in children undergoing treatment for DKA.

In our study, at an optimized cut-off value of >15 mmol/L, the venous HCO_3 concentration trended in parallel with vpH during the resolution of DKA, accurately reflecting vpH at all levels of DKA severity. However, it should be noted that during the first 2–3 hours of treatment of mild DKA, the venous HCO_3 concentration over-predicted DKA resolution, likely reflecting that the serum HCO_3 concentration is already at or close to this level at the time of diagnosis of mild DKA. Neither vpH nor HCO_3 are specific for DKA, and both can be affected by the child's respiratory compensation and any underlying respiratory or metabolic acid-base disturbances, as well as antecedent infection and the degree of dehydration. While the vpH, in particular, is sensitive to changes in respiratory status, the venous HCO_3 as a buffer for hydrogen ions can be markedly affected by metabolic conditions causing alkalosis, such as vomiting (common in DKA) and acidosis from increased lactic acid production resulting from poor tissue perfusion. Based on our experience in this cohort of children and adolescents with NODM, such disturbances may either be uncommon or not severe enough to distort the tight relationship of the venous HCO_3 with vpH during treatment and until resolution of DKA. Nonetheless, clinicians must keep basic pathophysiologic principles of acid-base disturbances in mind and use clinical judgment when interpreting vpH and HCO_3 during DKA treatment.

Our survival analyses show that the AG normalizes later than the vpH in mild DKA and earlier in moderate and severe DKA (data not shown). This can be explained by a decrease in serum HCO_3 as chloride concentration rises and the fact that the AG does not reflect the development of hyperchloremia-induced non anion gap acidosis. Thus, the AG does not correlate with the vpH during the course of treatment and resolution of DKA; rather, the AG is a more accurate reflection of ketonemia. Because hyperketonemia is the main cause of an increase in AG during DKA[26], the AG would be expected to most accurately reflect the decrease in blood ketone concentrations with treatment of DKA. Whereas the vpH reflects resolution of acidosis, normalization of the AG reflects reduction of plasma ketone concentrations. The recent increase in the availability of blood 3-OHB measurements, either in commercial laboratories or using point-of-care devices[32], and demonstration of the usefulness of measuring blood 3-OHB concentrations in determining resolution of DKA[4], has highlighted the importance of not only demonstrating resolution of acidosis but also of ketosis. Whereas availability of serum 3-OHB or whole blood point-of-care 3-OHB measurements is often limited in resource-constrained settings, the AG may be more readily available and, therefore, a useful additional measure to evaluate resolution of ketosis in the treatment of DKA. Because measurement methods for the AG may vary widely leading to different values to define AG closure [33,34], clinicians should be aware of the normal reference values for the AG in their laboratory. We have shown that resolution of DKA as defined by vpH >7.30 and AG closure can be reasonably predicted by a composite of serum $\text{HCO}_3 >15$ mmol/L and AG closure.

Our study has several limitations. The study population was limited to a single referral center, raising the possibility that the observed outcomes are specific to this particular patient population. The demographics of our population, however, including race, age distribution and diabetes type, are quite typical of North American and European cohorts with new onset diabetes. The large sample size and significant outcomes support the study's internal validity, and generalizability to populations with similar demographics. Second, because this was a retrospective study, we did not identify preexisting acid base disorders. Third, 3-OHB measurements are not routinely obtained at the time of presentation; therefore, blood 3-OHB levels were unavailable for inclusion in our study. Future studies should verify the hypothesis that AG correlates better with decrease in blood ketone concentrations than with resolution of acidosis. Fourth, we only studied patients with new onset diabetes. While patients with established diabetes represent a smaller fraction of children with DKA, they may present to care partially treated, and during different stages of acid-base derangement. While it is nonetheless likely that HCO_3 would be a reliable correlate of vpH in this population, additional studies should confirm our findings in these patients. Lastly, not all patients had VBG data available to determine resolution, leading to censoring of 29 patients (11%) for the primary outcome, and in 54 patients (25%), serum glucose did not decrease to below 200 mg/dl within 40 hours of commencing DKA treatment. As a result, its addition to the composite resolution outcome could not be reliably evaluated. The vast majority of patients ($n=261$, 99.2%), however, had data available for serum HCO_3 and AG measurements, and our sensitivity analysis did not show any difference between the comparisons based on all patients vs. only those who had VBG, HCO_3 and AG measurements available to compare all three definitions of DKA resolution.

4.1. Conclusion

The results of our study show that during treatment of DKA in children with NODM, serum HCO_3 concentration trends with vpH, and is an acceptable predictor of the composite definition of DKA resolution consisting of vpH ≥ 7.30 and AG closure. When serum $\text{HCO}_3 > 15 \text{ mmol/L}$ is paired with AG closure to define DKA resolution, it trends nearly identically with the composite definition of DKA resolution (vpH and AG closure). In the absence of an underlying renal or respiratory disorder, serum HCO_3 concentration can be used to monitor response to therapy and determine resolution of DKA. Closure of the AG indicates that ketogenesis has been arrested; however, it must be noted that excess chloride will contribute to a non-anion gap acidosis that often develops with DKA treatment (as reflected by both vpH and HCO_3).

These results show that health care professionals in resource-constrained settings (without a blood gas analyzer or the ability to measure 3-OHB concentrations) can confidently rely on the serum electrolyte panel as an alternative to VBG to monitor their management of patients with DKA and determine when it has resolved.

Clinicians should take into account potential metabolic or respiratory acid-base disturbances that may influence the serum HCO_3 and AG values. Future studies should prospectively evaluate the relationship of these parameters to serum 3-OHB concentrations.

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Figure 1. Correlation between vpH and electrolyte parameters and optimal cut points for serum HCO₃ as predictor of DKA Resolution

Linear correlations are shown between vpH and the log of the serum HCO₃ concentration (panel A), vpH and anion gap (panel B), and vpH and serum glucose concentration (panel C). Panel D shows the ROC curve for Serum HCO₃ concentration as a predictor of DKA resolution as defined by vpH and anion gap and B) Anion Gap as a predictor of DKA resolution. Each point on the curve represents a different HCO₃ value, such that sensitivity and specificity vary with the cut-off chosen.

Figure 2. Time to resolution of acidosis, normalization of electrolyte parameters or resolution of DKA

Probability of ongoing DKA (Y-axis) is plotted against time to DKA resolution in hours (X-axis). Panel A shows the resolution curves for all severities of DKA according to individual parameters including resolution of acidosis (defined as $\text{vpH} \geq 7.30$, brown), normalization of serum HCO_3 concentration (defined as $\text{HCO}_3 > 15 \text{ mmol/L}$, red), and anion gap (defined as $\text{AG} \leq 18 \text{ mmol/L}$, blue), and resolution of hyperglycemia (serum glucose $< 200 \text{ mg/dL}$, green). Panel B shows the resolution curve for resolution definition based on $\text{vpH} \geq 7.30$ and anion gap closure (brown) compared to the definition of $\text{HCO}_3 > 15 \text{ mmol/L}$ (blue), $\text{HCO}_3 > 15 \text{ mmol/L}$ and anion gap closure (red), and $\text{vpH} \geq 7.30$, anion gap closure and resolution of hyperglycemia (green).

Figure 2 should be printed in color.

Table 1

Characteristics of Patients (N=263)

Variable	Value	Reference Range
Female No. (%)	133 (50.6)	
Race No. (%)		
White	195 (74.1)	
Asian	5 (1.9)	
African American	18 (6.8)	
Other	25 (9.5)	
Missing	20 (7.6)	
Age, mean (SD), years	9.9 (4.4)	
Weight Z-score, mean (SD)	-0.02 (1.4)	
Venous pH, median (IQR)	7.20 (7.12, 7.26)	7.31 – 7.41
Serum HCO₃, median (IQR), mmol/L	9 (6, 12)	22 – 30
Anion gap, median (IQR)	30 (27, 33)	12 – 18
Glucose, median (IQR), mg/dL	419 (327, 543)	60 – 199
Sodium, median (IQR), mmol/L	133 (129, 137)	135 – 148
Chloride, median (IQR), mmol/L	97 (92, 104)	99 – 111
Potassium, median (IQR), mmol/L	4.3 (3.6, 4.7)	3.2 – 4.5
BUN, median (IQR), mg/dL	14 (11, 19)	5 – 18
Creatinine, median (IQR), mg/dL	0.5 (0.4, 0.6)	0.3 – 1
HbA1c, median (IQR), %	11.7 (10.7, 12.8)	4 – 6
HbA1c, median (IQR), mmol/mol	104 (93, 116)	20 – 43
No. VBG measurements, median (IQR)	3 (2, 5)	

Table 2

Evaluation of Electrolyte Parameters to Predict DKA Resolution

a) HCO₃ vs. (vpH 7.30 and AG 18 mmol/L)					
HCO₃ (mmol/L)	Sensitivity	Specificity	PPV	NPV	
>13	89.6%	69.3%	32.5%	97.6%	
>14	82.5%	76.9%	37.0%	96.4%	
>15	76.0%	84.7%	45%	95.5%	
>16	59.1%	89.4%	47.9%	93.0%	

b) (HCO₃ >15 mmol/L and AG 18 mmol/L) vs. (vpH 7.30 and AG 18 mmol/L)					
	Sensitivity	Specificity	PPV	NPV	
HCO ₃ >15 mmol/L and AG 18 mmol/L	76.0%	90.4%	56.5%	95.8%	

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at different cut-off values of serum HCO₃ concentration are shown in Table 2a. The shaded row reflects the optimal HCO₃ cut-off value. The same evaluation for the composite of the optimal cut-off value and anion closure is shown in Table 2b.

Table 3

Median Time to DKA Resolution

Variable	Severity of DKA				
	All severities	Mild DKA	Moderate DKA	Severe DKA	% censored
vpH 7.30 and AG 18 mmol/L	8.4 (6.3–11.9)	6.9 (5.6–9.6)	8.2 (6.9–10.6)	14.5 (11.6–16.3)	11.3
vpH 7.30	6.8 (4.3–11.0) ^a	4.8 (3.4–6.9) ^a	7.9 (6.0–10.5)	13.4 (11.4–16.3)	11.0
HCO ₃ >15 mmol/L	7.9 (5.0–11.8)	5.3 (3.7–7.3) ^a	9.3 (7.6–11.8)	15.5 (11.9–18.0)	0.4
AG 18 mmol/L	6.7 (5.3–8.8) ^a	6.2 (5.0–8.0)	6.3 (4.6–7.7) ^a	9.2 (6.9–10.8) ^a	1.2
HCO ₃ >15 mmol/L and AG 18 mmol/L	8.9 (6.5–13.2)	6.8 (5.6–8.9)	9.3 (7.8–11.8)	15.5 (11.9–18.0)	1.6

Data are shown in hours (interquartile range). All available data was used for analysis (n=234 for vpH, n=259 for HCO₃, n=252 for AG)

^a $P < .05$ (compared to resolution times defined by the composite outcome of both vpH and anion gap)