

Use of Serum Bicarbonate to Substitute for Venous pH in New-Onset Diabetes

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abstract

OBJECTIVE: To investigate whether serum bicarbonate (HCO₃) levels can be used to accurately diagnose diabetic ketoacidosis (DKA) and classify its severity in children with new-onset diabetes mellitus (NODM).

METHODS: Retrospective study of all patients with NODM presenting to Boston Children's Hospital from October 1, 2007, to July 1, 2013. DKA was defined as blood glucose ≥ 200 mg/dL, venous pH (vpH) < 7.3 , and urine ketones $\geq 2+$, and severe DKA as vpH < 7.1 . Linear regression was used to assess serum HCO₃ as a predictor of vpH, and logistic regression to evaluate serum HCO₃ as a predictor of DKA and severe DKA.

RESULTS: Of 690 study cohort subjects (47% girls, age 10.8 ± 4.3 years, 76.7% white), 19.4% presented with DKA. The relationship between serum HCO₃ and vpH was log-linear ($r = 0.87$, 95% CI 0.85–0.89, $P < .001$). HCO₃ predicted vpH ($R^2 0.75$, $P < .001$) using the formula $\text{vpH} = 6.81301 + (0.17823 \cdot \ln[\text{HCO}_3])$ and DKA and severe DKA (c-statistic 0.97 [95% CI 0.96–0.99, $P < .001$] and 0.99 [95% CI 0.991–0.999, $P < .001$], respectively). HCO₃ cutoffs of < 18 and < 8 mmol/L had sensitivities of 91.8% and 95.2%, and specificities of 91.7% and 96.7%, respectively, to diagnose DKA and severe DKA. Findings were similar in a validation cohort of 197 subjects.

CONCLUSIONS: Serum HCO₃ concentration alone can substitute for vpH to diagnose DKA and classify severity in children with NODM. It is suggested as an alternative to reliance on vpH, especially in settings in which access to vpH measurement is limited.



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Dr von Oettingen conceptualized and designed the study, carried out data collection and data analysis, and drafted the initial manuscript; Drs Wolfsdorf and Rhodes conceptualized and designed the study, supervised data collection and analysis, and critically reviewed and revised the manuscript; Dr Feldman supervised data analysis, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

Portions of this study were previously presented in abstract form at the International Society for Pediatric and Adolescent Diabetes, September 3–6, 2014, Toronto, Ontario, Canada, and at the Pediatric Endocrine Society, April 24–28, San Diego, California.

www.pediatrics.org/cgi/doi/10.1542/peds.2015-0156

DOI: 10.1542/peds.2015-0156

Accepted for publication May 21, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Dr Rhodes receives research funding from Merck, and her spouse owned stock in Bristol-Myers Squibb, GlaxoSmithKline, and Sanofi and owns stock in Pfizer and Merck. The other authors have indicated they have no financial relationships relevant to this article to disclose.

WHAT'S KNOWN ON THIS SUBJECT: Diabetic ketoacidosis (DKA) is a common and serious first manifestation of diabetes mellitus in children. During initial evaluation, the venous blood pH is frequently used to make the diagnosis and classify the severity of DKA.

WHAT THIS STUDY ADDS: This study demonstrates that the serum bicarbonate concentration is a simple and accurate predictor of DKA and its severity and can be used in lieu of venous pH measurement, especially in resource-poor settings where access to pH measurement is limited.

Diabetes mellitus in youth is common, with an estimated worldwide annual incidence of 80 000 children younger than 15 years¹ and the incidence is rising.² Diabetic ketoacidosis (DKA) at presentation of new-onset diabetes mellitus (NODM) occurs in approximately 15% to 70% of patients in Europe and North America.³ The incidence of DKA at presentation is higher in younger children, ethnic minorities, families of lower socioeconomic status, and regions with a lower prevalence of diabetes,³⁻⁷ which includes many resource-limited countries.

In many pediatric academic medical centers in the United States, the standard initial diagnostic evaluation for children with NODM and especially those suspected to have DKA includes a panel of laboratory tests to measure venous blood gas (VBG) and the concentrations of plasma glucose, serum electrolytes, serum bicarbonate (HCO₃), serum urea nitrogen (SUN), creatinine, hemoglobin A1c (HbA1c), and serum or urinary ketones. Acidemia is defined as arterial pH <7.35 or venous pH (vpH) <7.3, and traditionally, a vpH <7.3 or a serum HCO₃ <15 mmol/L is used to confirm the diagnosis of DKA, with lower values of both indicating greater severity of the condition. Venous pH <7.1 or serum HCO₃ <5 mmol/L has been used to define severe DKA.^{3,8} These definitions are incorporated into hospital practice guidelines, and emergency department physicians and pediatricians often base management decisions, for example, admission to hospital and use of intravenous versus subcutaneous insulin therapy, on the vpH value. However, in remote or limited resource settings, VBG is not readily available.

A recent study of pediatric patients seen in an emergency department suggested that the venous HCO₃ concentration accurately predicts abnormal vpH in children with DKA.⁹ Similarly, in adults, venous HCO₃ concentrations predicted arterial pH

with a high degree of sensitivity and specificity.¹⁰ The objective of our study was to evaluate the ability of serum HCO₃, measured at presentation, as part of a routine basic metabolic panel, to accurately predict DKA and classify its severity in a large population of youth with NODM.

METHODS

Study Design and Study Population

This was a cross-sectional retrospective review of all patients with NODM presenting to Boston Children's Hospital (BCH) between October 1, 2007, and July 1, 2013. Inclusion criteria were NODM, serum HCO₃ concentration measured within 15 minutes of an initial vpH measurement, and urinary ketone measurement within 4 hours of vpH measurement. These cutoffs were chosen a priori to avoid introduction of effects related to response to therapy. Prespecified exclusion criteria were a previous diagnosis of diabetes and neonatal diabetes. DKA was defined as blood glucose ≥ 200 mg/dL, vpH <7.3, and urine ketones $\geq 2+$. Mild, moderate, and severe DKA were defined as vpH 7.2 to 7.29, 7.1 to 7.19, and <7.1, respectively. Subjects were divided temporally into a study cohort (January 1, 2009–July 1, 2013) and a validation cohort (October 1, 2007–December 31, 2008). The study was approved by the institutional review board at BCH.

Data Collection

We used the BCH inpatient Diabetes Quality Improvement Database to identify eligible subjects. This database includes all patients with diabetes admitted to BCH. Virtually all patients with NODM referred to BCH who require treatment with insulin are admitted to the hospital. We used Childrens 360, a data extraction tool linked to the electronic medical record, to extract subject data. We collected information on patient age at diagnosis, race/ethnicity, anthropometric measures, date and

time of laboratory analyses, and laboratory data, including concentrations of plasma glucose, serum electrolytes and HCO₃, serum and/or urine ketones, HbA1c, and VBG.

Outcome Measures

Our main outcome measure was the correlation between serum HCO₃ concentration and vpH in a population of children and adolescents at the time of their initial diagnosis of diabetes mellitus. Secondary outcomes were the accuracy of serum HCO₃ concentration to diagnose DKA and classify its severity, including a determination of serum HCO₃ cutoffs that would best correlate with the traditionally used vpH cutoffs of <7.3 to define presence of DKA and <7.1 to define severe DKA.

Laboratory Analysis

Serum HCO₃ concentration was measured by using quantitative enzyme-based determination on the Roche/Hitachi cobas c systems platform (Roche Diagnostics, Indianapolis, IN). The VBG, plasma glucose, and serum electrolytes were determined by using the Radiometer ABL 825 (Radiometer, Cleveland, OH). Urine ketone concentrations were measured by using Acetest tablets Bayer Healthcare (Whippany, NJ). HbA1c was measured by immunoassay by using the Roche Integra 800 platform (Roche Diagnostics, Indianapolis, IN). All measurements were performed in the BCH Clinical Chemistry Laboratory.

Statistical Analysis

Standard descriptive statistics were used to describe subject characteristics. These included percentages for categorical variables, and mean and standard deviation (SD) or median and interquartile range as appropriate, for continuous variables. Analyses of continuous data used Student's *t* test and Wilcoxon rank sum test for normal and

non-normal data, respectively, and χ^2 tests to compare categorical variables. The relationship between serum HCO₃ and vpH was assessed by Pearson correlation. Given that the relationship appeared log-linear rather than linear, and because vpH is a log of hydrogen ion concentration, serum HCO₃ was log-transformed for further analyses. Linear regression was used to assess serum HCO₃ as a predictor of vpH, and to create a formula to calculate the vpH as a function of serum HCO₃. A priori, a strong correlation was defined as a Pearson correlation coefficient ≥ 0.7 and a very strong correlation as a coefficient ≥ 0.85 .

For our secondary outcomes, logistic regression and receiver operating characteristic (ROC) curves were used to evaluate serum HCO₃ concentration as a predictor of DKA or severe DKA. An area under the curve (AUC) of greater than 0.9 was chosen a priori as the minimum acceptable value.¹¹ The Hosmer and Lemeshow test was used to assess how well the model was calibrated; that is, how well predicted DKA event rates matched expected event rates. Other variables included in the model by using a purposeful selection approach were age, race/ethnicity, serum osmolality, concentrations of plasma glucose, serum sodium, and SUN, SUN/creatinine ratio, and anion gap. Variables were retained if the c-statistic improved by $>10\%$ or if there was a change in any β coefficient of more than 20%. Characteristics for different serum HCO₃ concentration cutoffs to predict presence of DKA and severe DKA from the model included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The final analysis was then replicated in the validation cohort.

For all analyses, $P < .05$ was considered significant. Analyses were performed by using SAS Software Version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Subjects

The NODM cohort consisted of a total of 987 subjects who had laboratory measurements performed at BCH at the time of diagnosis. Sixty-two subjects were excluded because of missing laboratory data: vpH ($n = 61$), serum HCO₃ ($n = 26$), and/or urine ketones ($n = 8$). Of the remaining 925 subjects, 235 were excluded because VBG and serum HCO₃ were not measured within 15 minutes of each other ($n = 154$), and/or urinary ketones were not measured within 4 hours of the initial VBG measurement ($n = 119$). Thirty-eight subjects did not meet the criteria for either time frame. Overall, 690 subjects met inclusion criteria and were included in the primary study analysis.

Of 284 subjects identified, 197 subjects (48% girls, 85% white, 16.8% DKA) were included in the validation cohort. Reasons for exclusion were similar to the study cohort (data not shown). Baseline characteristics for all subjects are shown in Table 1. There were no significant differences between the study and validation cohorts with respect to demographic characteristics, diabetes type, or severity of presentation. Laboratory

characteristics for the study cohort are shown in Table 2.

Relationship Between Serum HCO₃ Concentration and vpH

Serum HCO₃ concentration correlated with vpH, $r = 0.79$ (95% confidence interval [CI] 0.76–0.82). The relationship appeared to be log-linear, and log transformation of serum HCO₃ values showed a strong correlation between the log of HCO₃ and vpH (Fig 1), $r = 0.87$ (95% CI 0.85–0.89). A linear regression model with serum HCO₃ as the sole predictor of vpH yielded the following formula: $\text{vpH} = 6.81301 + (0.17823 \cdot \ln[\text{HCO}_3])$, $R^2 = 0.75$, $P < .001$. The range of serum HCO₃ concentrations with their corresponding vpH values is shown in Table 3.

Serum HCO₃ Concentration as a Predictor of DKA

The ROC curve derived from the logistic regression model assessing serum HCO₃ concentration as a predictor of DKA showed an AUC of 0.97 (95% CI 0.958–0.987, $P < .001$) (Fig 2A), with a maximum rescaled R^2 of 0.79. The association of predicted probabilities and observed responses showed a concordance of 96.8%. No additional variables met criteria to be included as predictors or confounders. For the prediction of severe DKA, the

TABLE 1 Characteristics of Subjects

Characteristic	Study Cohort, $n = 690$	Validation Cohort, $n = 197$	P^a
Girls, n (%)	324 (47.0)	95 (48.2)	.75
Race/ethnicity, n (%)			.33
White	529 (76.7)	163 (82.7)	
Asian	12 (1.7)	2 (1.0)	
Black	49 (7.1)	11 (5.6)	
Other	55 (8.0)	10 (5.1)	
Missing	45 (6.5)	11 (5.6)	
Age, y	10.8 (4.3)	10.3 (4.0)	.12
BMI, z-score	−0.01 (1.32)	0.02 (1.43)	.76
Diabetes type, n (%)			.66
Type 1	655 (94.9)	186 (94.4)	
Type 2	24 (3.5)	6 (3.1)	
Other	11 (1.6)	5 (2.5)	
DKA severity, n (%)			.53
None	556 (80.6)	164 (83.2)	
Mild	80 (11.6)	19 (9.6)	
Moderate	33 (4.8)	6 (3.1)	
Severe	21 (3.0)	8 (4.1)	

Values are presented as mean (SD), or as n (%) where indicated.

^a Comparison of study versus validation cohorts.

TABLE 2 Biochemical Characteristics of Subjects

Characteristics	All, n = 690	DKA, n = 134	No DKA, n = 556	<i>P</i> ^a
vpH, median (IQR)	7.36 (7.32–7.38)	7.23 (7.15–7.27)	7.37 (7.35–7.39)	<.001
Serum HCO ₃ , mmol/L, median (IQR)	23 (19–26)	11 (8–15)	24 (22–26)	<.001
Serum osmolality, mOsm/kg	309 (13)	321 (17)	306 (10)	<.001
Plasma glucose, mg/dL	425 (167)	470 (172)	414 (168)	<.001
SUN, mg/dL	15 (5)	15 (7)	14 (5)	.03
Creatinine, mg/dL	0.48 (0.19)	0.53 (0.24)	0.46 (0.17)	.0003
Serum SUN/Creat	34 (17)	31 (15)	35 (17)	.04
Anion gap, mmol/L	17 (6)	26 (6)	15 (4)	<.001
HbA _{1c} , %	11.3 (2.3)	12.1 (1.8)	11.1 (2.3)	<.001
Urinary ketones ≥2+, n (%)	464 (67.2)	134 (100)	330 (59.4)	<.001

All values are presented as mean (SD), except where indicated. IQR, interquartile range.

^a Comparison of DKA versus no DKA.

AUC was 0.99 (95% CI 0.991–0.999, $P < .001$) (Fig 2B), with a maximum rescaled R^2 of 0.82 and an association of predicted probabilities and observed responses showed a concordance of 99.4%. The Hosmer and Lemeshow χ^2 statistic was nonsignificant for both DKA ($P = .72$) and severe DKA models ($P = .85$), indicating goodness of fit of both models. Sensitivity, specificity, NPV, and PPV of different serum HCO₃ concentration cutoff values for diagnosis of DKA and for classification of severe DKA are shown in Table 4.

Validation

Using the validation cohort, application of a serum HCO₃ cutoff

value of <15 and <18 mmol/L for the diagnosis of DKA yielded a sensitivity of 84.9% and 100%, specificity of 97% and 89.6%, PPV of 84.9% and 66%, and NPV of 97% and 100%, respectively. For the classification of severe DKA, a cutoff of <5 and <8 mmol/L yielded a sensitivity of 87.5% and 100%, specificity of 98.9% and 96.8%, PPV of 77.8% and 57.1%, and NPV of 99.5% and 100%, respectively.

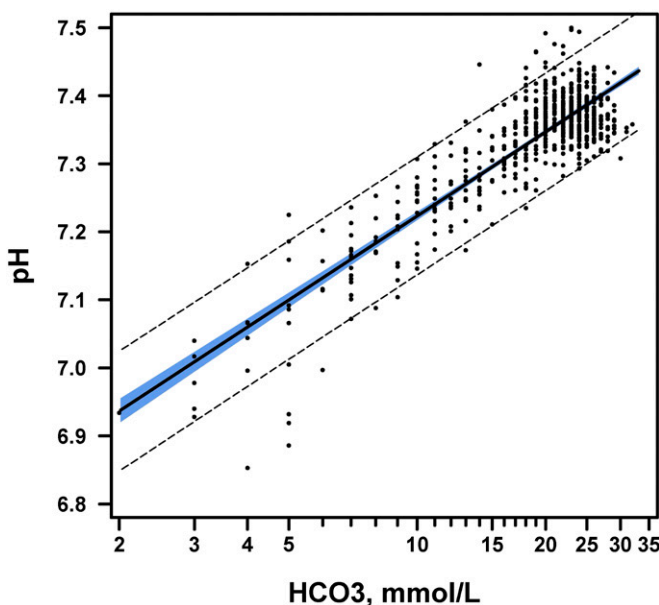
DISCUSSION

The results of our study confirm a very strong log-linear relationship between serum HCO₃ concentration and vpH in patients with NODM. The

findings suggest that serum HCO₃ levels can reliably be used to diagnose and classify DKA in pediatric patients with NODM, and that VBG analysis is not required for the initial evaluation of these patients.

Several other studies have been performed in an attempt to simplify and render more efficient the initial diagnosis and subsequent management of DKA. Sheikh-Ali et al¹² evaluated quantitative serum β -hydroxybutyrate (BOHB) as a diagnostic test for DKA on the basis that pH, HCO₃, and anion gap are relatively nonspecific for the diagnosis of DKA. They suggested a BOHB level >3 mmol/L as a cutoff to diagnose DKA, but found a 20% discordance between BOHB and the conventional criteria by using pH <7.3, HCO₃ <18 mmol/L, and glucose ≥200 mg/dL.¹² At least 3 groups have suggested end-tidal CO₂ as a simpler and less invasive diagnostic or monitoring tool for DKA.^{13–15} Although end-tidal CO₂ had a strong linear correlation with vpH and HCO₃ concentration, the agreement was not narrow enough to confirm DKA, especially in cases of mild acidosis,^{14,15} and its measurement has not been widely adopted. Another attempt to simplify the initial evaluation of patients with DKA has been with the measurement of electrolytes by using a VBG analyzer.¹⁶ Although this approach may be feasible in some settings, many remote and resource-limited settings are not equipped with VBG analyzers and may only have the capacity to measure serum electrolytes.

The attempt to use venous HCO₃ for the prediction of DKA seems intuitive given the Henderson-Hasselbach equation where $\text{pH} = \text{pK} + \log \left(\frac{[\text{HCO}_3^-]}{[\text{CO}_2]} \right)$, establishing the pH as a function of the serum HCO₃ concentration. Any pathophysiological state that affects the serum HCO₃ concentration independent of the derangements

**FIGURE 1**

Correlation between serum HCO₃ and venous pH. The log-linear correlation between serum HCO₃ and venous pH, including 95% CIs, is shown. The x-axis displays the serum HCO₃ concentration on a log scale. Outer band: 95% CI for a single predicted value. Inner band: 95% CI for predicted mean.

TABLE 3 Corresponding Serum HCO₃ and vpH Values

Serum HCO ₃	vpH
1	6.813
2	6.937
3	7.009
4	7.060
5	7.100
6	7.132
7	7.160
8	7.184
9	7.204
10	7.223
11	7.240
12	7.260
13	7.270
14	7.283
15	7.296
16	7.307
17	7.318
18	7.328

caused by DKA poses a risk of misclassification if HCO₃ is used to define DKA. Conditions that raise HCO₃ levels, such as metabolic alkalosis from H⁺ loss caused by vomiting, and, conversely, those that lower HCO₃ levels, such as renal dysfunction or HCO₃ loss with diarrhea, could alter the observed relationship between HCO₃ and vpH.

Only one previous study has assessed the utility of venous HCO₃ for prediction of pH in children.⁹ Similar to our results, this study demonstrated a strong correlation between logarithm serum HCO₃ concentrations and vpH. Whereas a relatively large percentage

of that study population (~39% of 300 patients) presented with DKA, only 8 subjects had severe DKA, thus possibly limiting the accuracy of the classification of severe DKA. The authors suggested the best statistical cutoff of 18.5 mmol/L for serum HCO₃ to define the presence of DKA, and 10.5 mmol/L to define severe DKA. These cutoffs, particularly the latter, are higher than have been suggested in most of the pediatric literature, possibly a result of the small number of subjects with severe DKA.

We have provided a formula to calculate vpH from HCO₃, which suggests HCO₃ values of 15, 9, and 5 correspond to vpH levels of 7.3, 7.2, and 7.1, respectively (Table 3). Although these are consistent with pediatric guideline cutoffs^{3,17} of 15 and 5 mmol/L to diagnose DKA and severe DKA, respectively, these cutoffs had lower sensitivity (82.1% and 52.4%) compared with higher cutoffs, whereas specificity was only slightly higher (Table 4). Thus, HCO₃ values that best correspond to vpH levels of 7.3 and 7.1 may not be the most appropriate cutoffs to use in situations in which a diagnosis of DKA or severe DKA should not be missed, such as in a young child or in settings with limited monitoring capability. We have shown sensitivities and specificities for a range of HCO₃ values both for

diagnosis of DKA and classification of its severity. To minimize the number of false-negatives, clinicians should choose a higher HCO₃ cutoff; alternatively, choosing a lower HCO₃ cutoff will minimize false-positives. The serum HCO₃ range of 15 to 18 mmol/L is also consistent with the most recent American Diabetes Association adult guidelines, which include a bicarbonate range of 15 to 18 mmol/L (in addition to an arterial pH <7.25–7.3 and anion gap >10 mmol/L) for the diagnosis of DKA.¹⁸

Although minor differences exist for the criteria to diagnose DKA,^{3,8,17–19} the most commonly used definition in pediatrics is a combination of pH <7.3, HCO₃ <15–18 mmol/L, ketonuria or ketonemia, and hyperglycemia. Some definitions add the anion gap¹⁸ as a measure of metabolic acidosis. In our study, serum HCO₃ was the strongest predictor of the presence of DKA as defined by vpH <7.3 and presence of hyperglycemia and ketosis. Whereas the anion gap was also a significant predictor of DKA (AUC 0.94 [95% CI 0.926–0.962, *P* < .001]), it did not perform as well as the serum HCO₃ concentration and did not meet the a priori criteria for inclusion in the final statistical model. This is not surprising given that the anion gap, although indicative of acidosis, is affected by several anions that are present in DKA, including lactate, BOHB, acetoacetate, free fatty acids, phosphate, and sulfate. Finally, none of the other measured biochemical parameters added to the value of the HCO₃ to predict DKA. This is likely a reflection of the natural correlation between pH and HCO₃, but supports the use of HCO₃ as the sole predictor of DKA.

Patients had on average 4 VBGs measured, adding significant cost not only to the initial evaluation but to the entire DKA management process. In an era of increasing financial constraints, there is a potential not only for simplification but also for cost-saving in the evaluation of patients with DKA.

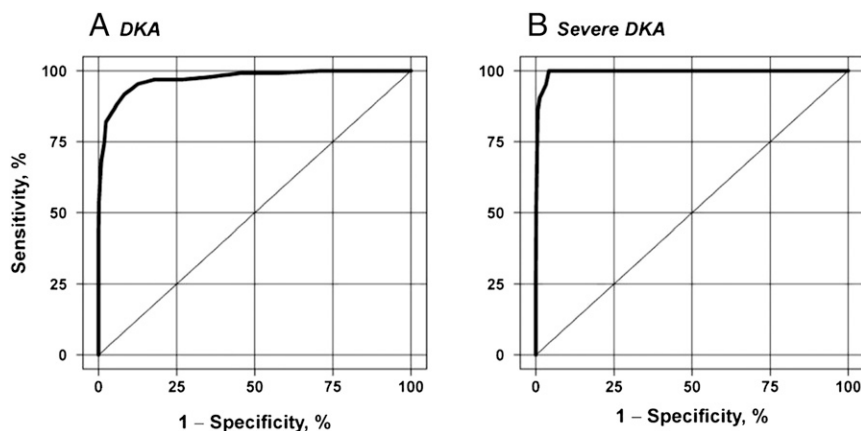


FIGURE 2 ROC curves are shown for (A) serum HCO₃ concentration as a predictor of DKA and (B) serum HCO₃ concentration as a predictor of severe DKA. Each point on the curve represents a different HCO₃ value, such that sensitivity and specificity vary with the HCO₃ cutoff chosen.

TABLE 4 Evaluation of Serum HCO₃ Concentration Cutoff Values

HCO ₃ , mmol/L	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Diagnosis of DKA				
<15	82.1	97.7	89.4	95.8
<16	84.3	96.2	84.3	96.2
<17	88.1	94.2	78.7	97.0
<18	91.8	91.7	72.8	97.9
Classification of Severe DKA				
<5	52.4	99.9	91.2	98.5
<6	85.7	99.4	81.8	99.6
<7	90.5	98.8	70.1	99.7
<8	95.2	96.7	47.6	99.9

Particular strengths of our study include its large number of subjects, highly significant unambiguous results, and their immediate application to clinical practice. Sufficient data were available to develop a precise rule for the most recent time period (2009–2013, study cohort) and to demonstrate that it operated satisfactorily for a previous period (2007–2008, validation cohort). Dividing the data according to time allowed us to confirm the validity of our findings with respect to temporal variation.

Certain limitations of the study merit comment. First, this study was retrospective and limited to a single, large academic referral center. Although the results may be specific to the population studied, our demographics are representative of typical pediatric diabetes populations in the United States and Europe with regard to race/ethnicity, diabetes type, and age distribution. Although the inpatient database used to identify our subjects represents a comprehensive list of all inpatients presenting with NODM requiring insulin therapy, some patients with type 2 diabetes treated with oral antihyperglycemic agents may be treated as outpatients and would not be represented. However, as the focus of the analysis is on the diagnosis and classification of DKA, the composition of the sample as insulin-requiring patients supports the internal validity, and the large sample size and highly significant outcomes supports the generalizability to demographically similar populations.

Second, we could not differentiate between children who had been pretreated with intravenous fluids or insulin and those who had not received any treatment before arriving at BCH. However, a previous study that was able to compare subjects who had received insulin before hospital admission to insulin-naïve subjects did not find a difference with regard to the ability of serum HCO₃ concentration to accurately predict the presence of DKA.¹³ We also could not exclude patients with comorbidities that may have influenced their acid-base status. Clinicians must account for the possible effect of underlying renal and pulmonary disorders when evaluating a patient in DKA.

In addition, we had to exclude a large number of subjects without near-simultaneous measurements of VBG and serum biochemistries, and ketone measurement within a few hours of diagnosis and treatment initiation. The excluded subjects differed from those included in our analyses: they had a higher prevalence of DKA (34.7% vs 19.4%, $P < .001$) and severe DKA (8.9% vs 3%, $P < .001$) and, not surprisingly, a higher frequency of electrolyte derangements and biochemical indicators of dehydration (Supplemental Table 5). These patients may have been sicker, and thus priority was not put on obtaining timely urine ketone measurements, the absence of which accounted for the largest number of patients excluded. However, when we included all patients in the analysis, regardless of the timing of their ketone measurement, none of the

outcomes changed significantly (Supplemental Table 6).

CONCLUSIONS

Serum HCO₃ concentration is a simple, reliable, and effective predictor of the presence and severity of DKA and can be used without the addition of a VBG to diagnose DKA and assess its severity. In clinical practice, a range of HCO₃ cutoff values may be preferable to a single value for the diagnosis of DKA, based on the clinician's priority to maximize either sensitivity or specificity. We suggest that such an approach should be considered in DKA management guidelines for both resource-limited and resource-rich settings. Future prospective, multicenter and, ideally, community-based studies should evaluate the use of these recommendations. It may also be of interest to examine the utility of serial serum HCO₃ relative to BOHB concentrations for monitoring the response to treatment of DKA.

ACKNOWLEDGMENTS

We thank Virginia Coburn and Julie Hosselbarth from the Business Intelligence Group at BCH for assistance with data extraction.

ABBREVIATIONS

AUC: area under the curve
 BCH: Boston Children's Hospital
 BOHB: β -hydroxybutyrate
 CI: confidence interval
 DKA: diabetic ketoacidosis
 HbA1c: hemoglobin A1c
 HCO₃: serum bicarbonate
 NODM: new-onset diabetes mellitus
 NPV: negative predictive value
 PPV: positive predictive value
 ROC: receiver operating characteristics
 SUN: serum urea nitrogen
 VBG: venous blood gas
 vpH: venous pH measurement

FUNDING: This work was conducted with support from Harvard Catalyst, The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102), and financial contributions from Harvard University and its affiliated academic health care centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University, and its affiliated academic health care centers, or the National Institutes of Health. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: Dr Rhodes receives research funding from Merck, and her spouse owned stock in Bristol-Myers Squibb, GlaxoSmithKline, and Sanofi and owns stock in Pfizer and Merck. The other authors have indicated they have no potential conflicts of interest to disclose.

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