ORIGINAL ARTICLE

Exploring the clinical utility of blood ketone levels in the emergency department assessment of paediatric patients

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Background: Ketonuria (on standard urine testing) is a frequent finding in children presenting to emergency departments. With the advent of hand-held ketone meters, blood ketone levels can now be rapidly quantified.

Hypothesis: Point of care testing (POCT) of blood ketone levels could provide clinically useful information on severity of illness in children and risk of hospital admission.

Methods: A prospective study using POCT of blood ketone levels in a convenience sample of children <13 years old, with a typical case mix of medical problems.

Findings: 186 children were studied. The range of ketone levels varied widely among this study population depending on the presenting complaint. Higher levels were noted in those presenting with anorexia or vomiting and fever. The median ketone level of the total study population was 0.2 (range 0–6.0, interquartile range 0.1–0.9) mmol/l. Ketone levels correlated poorly with discharge destination and duration of admission. However, receiver–operator characteristics for ketones as a predictor of admission were comparable to Pediatric Risk of Admission scores (area under the curve 0.64 and 0.72, respectively) and may represent an independent risk factor for admission. A ketone level >1.2 mmol/l has a positive predictive value of 66.7% for admission. Ketone levels correlated well with decreased oral intake ($R^2=0.25$; $p<0.001$).

Conclusions: A strong association was found between ketone levels, decreased oral intake and fever. Although ketone levels do not correlate well with more traditional markers of illness severity, they can help to predict the requirement for admission to hospital when interpreted in the context of the presenting illness. They may have applications in both the emergency department and primary care settings. Further prospective testing is required to validate these findings.

Determining how sick a child is when he or she attends an emergency department can be challenging. Assessment is usually based on a “snap shot” built on history and examination findings. At the extremes of illness severity, the decision to admit or discharge is usually self-evident. However, there is a group of children in whom this decision is difficult to make on the basis of history and examination findings alone.^{1–3} As clinicians, we are often looking for simple tools or tests that can help us in the assessment of these children.^{3–8} These may include the use of scoring systems, bedside investigations or the judicious use of more sophisticated tests.

Scoring systems for severity of illness or risk of admission include the Paediatric Risk of Mortality Score,⁹ the Yale Observation Scale, Odyrons Score for Sick Children and, more recently, the Pediatric Risk of Admission (PRISA) score.^{1–2 10} These scores are often complicated and time consuming or not easily used prospectively, making their use in the emergency department difficult.^{2 10 11} Bedside or point of care testing (POCT; eg, pulse oximetry, blood glucose testing, electrocardiograms, bedside spirometry and urine analysis) is usually minimally invasive, easy to obtain, provides rapid and relatively accurate results that can influence management, and is cost effective. More sophisticated laboratory tests and imaging modalities are generally expensive and time consuming, and should be reserved for assessment of appropriate patients at the discretion of the attending doctor. Additional information about the scoring system using the PRISA score is available online at <http://www.emj.bmjournals.com/supplemental>.

Anecdotally, we have noticed that ketonuria is a common finding in children who are ill, but have not been able to

quantify this with accuracy. Ketone bodies are produced by fatty acid metabolism in hepatic mitochondria during a range of physiological and pathological conditions associated with either altered glucose metabolism or relative glucose or glycogen deficiency. There are three ketone bodies: acetoacetate (AcAc), acetone and β -hydroxybutyrate (β -HB). Ketones are used primarily by the heart, kidney, central nervous system and skeletal muscle. These tissues produce the enzyme succinyl coenzyme A-oxoacid transferase.¹² This enables the production of acetyl coenzyme A from ketone bodies and ultimately ATP via the tricarboxylic acid cycle. In toddlers and young children, hyperketonaemia becomes apparent within 12–24 h of a fast. Children of this age are more susceptible to ketosis because of their diminished stores of glycogen and their proportionately larger central nervous systems than adults.¹²

Standard dipstick urine analysis using Ketostix or Multistix (Bayer Diagnostics, Berkshire, UK) gives a semi-quantitative measure of AcAc and, to a lesser degree, of acetone.^{12–15} It is, however, commonly assumed that β -HB is quantitatively and clinically the more important ketone body. The ratio of β -HB to AcAc can vary from 1:1 (postprandially) to 10:1 depending on the physiological status of the patient.^{12–15} Urine AcAc levels may underestimate the severity of ketosis.^{12 14 15} Laboratory measurement of β -HB is not routinely available and takes too long to be of practical use in the emergency department setting. The advent of

Abbreviations: AcAc, acetoacetate; β -HB, β -hydroxybutyrate; HDU, high-dependency unit; IQR, interquartile range; ITU, intensive therapy unit; POCT, point of care testing; PRISA, Pediatric Risk of Admission; ROC, receiver–operator characteristic

hand-held blood ketone meters, more commonly used for testing in patients with diabetes, provides a method for rapid and accurate quantification of blood β -HB levels. Using techniques similar to that for bedside glucose estimation, one drop of blood on a test strip can provide a ketone level in about 30 s.

This is a simple test that has been well researched in people with diabetes,^{12 14–17} but also has potential applications in the assessment of a much broader case mix of medical patients in the paediatric emergency department.

Primary aims

- To determine the pattern of blood ketone levels in children attending the emergency department with medical problems.
- To determine whether blood ketone levels can predict risk of admission to hospital or probability of discharge.

Secondary aims

- To assess whether blood ketone levels correlate with illness severity.
- To clarify whether ketone levels are purely a product of reduced oral intake in this group of children.

METHODS

The study population was a convenience sample of children aged <13 years, attending the emergency department of the Royal Hospital for Sick Children, Edinburgh, UK. Children were included in the study if they presented to the emergency department with medical problems that required blood testing as a part of their medical investigation. Exclusion criteria included children with traumatic injuries, diabetes mellitus, pre-existing metabolic abnormalities and those on intentional ketogenic diets.

Participants were approached for consent when medical staff indicated to us their intention to draw blood from these patients. A blood ketone level was tested opportunistically from the sample being drawn. The device used for blood ketone testing was a hand-held MediSense Optium System supplied by Abbott Laboratories, Berkshire, UK, which was checked daily for accuracy using control solutions. The test strip provided was placed into the meter, switched on, and a drop of blood was placed to fill the window of the strip. The blood ketone sensor produces an electrical signal in 30 s, proportional to the whole blood β -HB concentration. The machines are accurate from 0.0 to 6.0 mmol/l.^{13–17} Levels greater than these are displayed as "HI".

Relatives and care providers were blinded to the test results. The decision to admit the child was made by the attending doctor on the basis of clinical details and hospital policies, and was independent of the ketone level.

Blood ketone levels were recorded on a special data collection paper proforma, along with clinical data including recent feeding patterns, vital signs and diagnosis where available. The predominant presenting complaint according to the parent or guardian was recorded. Presenting complaint rather than diagnosis was used for prospective rather than retrospective information. A PRISA score was calculated for each patient and data on outcome measures such as discharge destination (home, general ward admission, high-dependency unit (HDU), intensive therapy unit (ITU) and death) and duration of stay and interventions were recorded.

The data were then entered on to a database in Microsoft Access (V.XP), and data were statistically analysed using SPSS (V.11.5.0). Levene's test was carried out to determine whether the variances of the populations being compared were equal. In case of equal variances parametric t tests were

used, and in cases of unequal variances non-parametric Mann–Whitney U tests were used. Linear regression was used to analyse the relationship between variables, and receiver–operator characteristic (ROC) curves were plotted to compare PRISA and ketone levels. Points on the ROC curve were then used to determine ketone level sensitivity and specificity, and predictive values for admission.

FINDINGS

A convenience sample of 200 patients was entered into the study. Three children were excluded for age >13 years. Six children were excluded as the opportunity to test for ketones was missed after the child was recruited, the age of one child were unknown and in four children, data available for analysis were insufficient. A total of 186 children were included in the study, with an age range of 0–154 (median 35.5, (interquartile range (IQR) 12.0–74.5) months; there were 114 boys and 72 girls.

Pattern of blood ketone levels in the total study population

The median ketone level of patients attending the emergency department was 0.2 (range 0–6.0, IQR 0.1–0.9) mmol/l. Children in whom the presenting complaint was anorexia, vomiting or fever had higher median and distribution of ketone levels than others (fig 1). Supporting data are available online at <http://emj.bmjournals.com/supplemental>.

Blood ketones as a predictor of admission to hospital

In all, 101 children (54.3%) of the study population were discharged home from the emergency department and 91 (48.9%) of them were admitted to hospital. Children who were admitted had a small but significantly higher median ketone level (0.4 mmol/l, IQR 0.3–1.3 mmol/l) than those who were discharged (0.2 mmol/l, IQR 0.1–0.7 mmol/l); $p < 0.001$.

Figure 2 shows the ROC curve for the PRISA score and ketone levels as predictors of admission. The area under the curve was 0.74 for PRISA (95% confidence interval (CI) 0.64 to 0.72) and 0.64 for ketones (95% CI 0.56 to 0.72). Sensitivity and specificity for ketones as a predictor of admission were determined along with positive and negative predictive values (table 1).

Blood ketones as a marker of illness severity

Table 2 shows the coefficients of determination of ketones and measures of illness severity. With respect to destination, 89 children were admitted to general medical wards and two

Figure 1 Ketone level according to presenting complaint. a, respiratory symptoms; b, fever or febrile convulsion; c, reduced intake or vomiting; d, diarrhoea; e, atraumatic pain; f, neurological or afebrile fits; g, rash; h, bleeding, bruising and epistaxis; i, jaundice; j, uncategorised.

Figure 2 Receiver-operator characteristic curves for Paediatric Risk of Admission (PRISA) score and blood ketone levels as predictors of admission.

were admitted to the intensive care unit (median ketone levels 0.6 and 0.8 mmol/l, respectively). One child died on a general medical ward 39 h after admission owing to arrhythmia caused by viral myocarditis (influenza A). The median ketone level of this child when she attended the emergency department was 2.0 mmol/l.

Blood ketone levels and feeding patterns

Children with normal feeding had a significantly lower median ketone level (0.206 mmol/l) than those with less than normal feeding (1.324 mmol/l; fig 3). The correlation of ketones with decreased oral intake showed R^2 (coefficient of determination) = 0.25; $p < 0.001$. Approximately 9.4% of children with normal feeding patterns had median ketone levels > 0.5 mmol/l and 4.7% of this group had levels > 1.0 mmol/l. Supporting data for fig 3 are available online at <http://emj.bmjournals.com/supplemental>.

INTERPRETATION

Pattern of blood ketone levels in the total study population

It was not possible to compare ketone levels in this study population with that in healthy controls. Ethical constraints mandated that only patients in whom blood tests were deemed necessary by the attending doctor be tested for ketone levels. This prevented us from sampling a healthy population, as they would not normally have blood sampled for medical reasons. Reference levels for blood ketones have been quoted as up to 0.27 mmol/l.¹⁸ However, 0.5 mmol/l is more widely accepted as the upper limit of normal.^{12 14 18} Ketosis occurs at levels ≥ 1.0 mmol/l and ketoacidosis at levels ≥ 3.0 mmol/l.¹⁹

Most children studied had low ketone levels. We have, however, shown variation in the distribution of blood ketone levels according to the presenting complaint. The most

Table 2 Coefficients of determination for ketones and measure of illness severity

	R^2	p Value
Pediatric Risk of Admission	0.007	< 0.5
Destination	0.053	< 0.01
Duration of stay	0.006	< 0.01

Figure 3 Ketone levels according to feeding pattern.

notable raise in ketone levels was in those patients presenting with decreased oral intake or vomiting (median 0.6, IQR 0.2–2.9 mmol/l) and in those presenting with fever (median 0.5, IQR 0.2–1.5 mmol/l; fig 1). Notably low levels of ketones were seen in children presenting with bleeding, bruising or epistaxis (all of who had ketone levels of 0.1 mmol/l), jaundice (median 0.2, IQR 0.15–0.2 mmol/l) and diarrhoea (median 0.2, IQR 0.1–0.2 mmol/l). Owing to the relatively small size of these subpopulations, further analysis was not carried out. However, these results do highlight the fact that ketone levels may provide more relevant information when applied in the context of the presenting complaint.

Blood ketones as a predictor of admission to hospital

We found a statistically significant difference between ketone levels in the admitted and discharged groups (0.2 v 0.4 mmol/l), $p < 0.001$. Given that the median level in both of these groups was in the normal reference range (< 0.5 mmol/l), it is reasonable to conclude that it is probably of little clinical importance. The IQR of those admitted spans from the normal to the ketotic range, whereas the IQR of those discharged is below the ketotic range. This reflects the large range of medical problems requiring admission, of which only some affect ketone levels.

There is a distinct difference between the need for admission and the fact of admission.¹¹ Not every child who is admitted to hospital actually requires admission, but the

Table 1 Predictive ability of ketones for admission to hospital

Ketone level (mmol/l)	Frequency (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≥ 0.2	68.2	78	41	55	67
≥ 0.5	34.4	43	72	59	58
≥ 1.2	21.9	32	86	67	58
≥ 2.0	12.5	21	95	79	57

distinction is often difficult to make, especially when the diagnosis has not been established. We have therefore used ketones as a marker of risk rather than the need for admission, and history and examination still remains the mainstay for determining the need for admission. Blood ketone testing provides an objective marker for prediction of admission that is slightly less effective but comparable to the PRISA score, as evidenced by the respective areas under the ROC curves. It has distinct advantages over the PRISA score in terms of its applications. Whereas PRISA scores are largely used retrospectively in the assessment of emergency department admission patterns, ketone levels can be applied prospectively on a case-by-case basis for predicting admission. Ketone levels, independent of their cause or consequences, can aid in determining the risk of admission purely on statistical grounds. A child with a ketone level ≥ 1.2 mmol/l has about 67% chance of admission (positive predictive value 67%, specificity 86%). Predictive values are even higher for levels ≥ 2.0 mmol/l but the frequency of this result is low (24/186) and most of these patients were recognisable as requiring admission purely on clinical grounds. The negative predictive value (58%) and sensitivity (31%) of a ketone level ≥ 1.2 mmol/l again reflect the fact that there are several reasons for admission to hospital, only some of which are related to ketone levels.

Blood ketones as a marker of illness severity

It is difficult to measure illness severity,¹¹ and therefore even more difficult to compare ketones with a criterion standard of illness severity. Consequently, we have used, for comparison, several related outcome measures such as PRISA score, discharge destination and length of admission.

Scoring systems such as the Paediatric Risk of Mortality Score,⁹ designed for intensive care settings, are not applicable to the general population admitted to the emergency department.² In contrast with this, the PRISA score is more useful, but owing to the inclusion of laboratory results and interventions it cannot be used prospectively.^{1 2 10 11} Its authors acknowledge that the PRISA score was developed for making predictions about populations of patients and not for making individual management decisions about individual patients.^{2 11} We used the PRISA score because it was designed with emergency department presentations in mind, from the very well to the very sick, and although it is a retrospective tool it has been well validated.^{2 10 11} Correlations between PRISA and ketone levels were poor. However, they have similar predictive abilities for admission, as suggested by the ROC curves. This suggests that they are independent risk factors for admission.

Discharge destinations included home, general ward, HDU, ITU and death. We found a significant but low correlation with destination ($R^2 = 0.053$; $p < 0.01$). This reflects the low proportion of severely ill patients in this population of emergency department attendees, as there were no admissions to the HDU, only two admissions to the ITU and one death. It is interesting that the child who died had ketosis (2.0 mmol/l) on presentation to the emergency department 39 h prior, but little can be concluded from this sample of one patient.

Duration of stay correlated poorly with ketone level. Length of admission is dependent on many factors, including disease process, illness severity, social circumstances, parental anxiety or educational requirements, and in some instances delays with investigations. These variables were not factored into this analysis and may have contributed to the poor correlation.

Blood ketone levels and feeding patterns

Recent feeding patterns were qualitatively estimated by parents or caregivers. They were asked to describe oral intake

in the 12 h preceding presentation to the emergency department. Four options were given: normal, reduced (greater than half normal intake), poor (less than half normal intake) and none. We found a correlation between reduced oral intake and increased ketone levels, which is not surprising given past research into ketone production during starvation.^{12 18} Interestingly, however, a proportion of patients with "normal" feeding patterns had ketone levels above the normal: 9.4% had ketone levels above the reference range (>0.5 mmol/l) and 4.7% had ketones in the ketotic range (≥ 1.0 mmol/l). This suggests either increased metabolic demands or derangements of glucose metabolism caused by states of relative ill health, and requires further investigation. It may also be related to parents who have not appreciated states of anorexia in their children. Similarly, there were a significant proportion of patients with normal ketone levels in whom the parents stated decreased feeding patterns. These groups of outliers explain the less than perfect correlation between ketones and feeding patterns.

STUDY LIMITATIONS

The study population was a convenience sample that was mostly recruited during the day and early evening and seldom at night. Similarly, when the department was busy, potentially suitable patients were either not recruited or were excluded because the opportunity to test for ketones when blood was drawn was missed. When the department was comparatively quiet, most suitable patients were recruited and successfully tested. This study was conducted over a 3-month period between November and January (around winter), which does not maximise seasonal variation of emergency department presentations but does maximise the number of medical presentations. This may have caused a selection bias.

Owing to ethical constraints, we were able to check ketone levels only in patients who were having blood drawn as part of their medical investigation, causing further selection bias, as the decision to draw blood is not independent from severity of illness. This has produced two limitations. Firstly, there are no controls. However, normal ranges of ketone levels are well documented in the literature.^{12 15 18} Secondly, the size of our study population is limited, which represents $<5\%$ of children attending the emergency department during this period. Despite the study population being biased towards medical problems that require further biochemical or haematological investigation, it did include the patients whom we were most interested in (those in whom the decision to admit had not been made on clinical grounds alone). Patients who were discharged from the department were not followed up, and it is unknown whether discharge with a high ketone level was a predictor of a further attendance, or if it was associated with an adverse outcome.

A cost comparison between laboratory and POCT is difficult, as laboratory assay costs take into consideration staffing, time, overheads, quality control assessment, laboratory space and consumables. Nonetheless, the cost of an Optium Ketone meter at the time of this study was £25 and the cost of each test strip used was £1. The current all-inclusive assay cost of a single laboratory plasma ketone level test at this hospital was £11.52. Although a formal cost-benefit analysis had not been carried out, it would seem that POCT has a considerable cost advantage over laboratory testing.

CONCLUSIONS

POCT for blood ketones is minimally invasive and gives accurate and rapid results that are clinically relevant. It has benefits over testing of urine for several reasons. It detects the more clinically relevant β -HB as opposed to AcAc. It is an

accurate quantitative analysis as opposed to a semiquantitative urine analysis, and is often more easily obtainable than with urine samples. It provides a useful adjunct to clinical assessment, in determining risk of admission in children presenting to emergency departments with medical problems. As a single predictor of admission, regardless of the presenting complaint, ketone levels >1.2 mmol/l correlate with a 66.67% positive predictive value for admission and have a specificity of 85.57%. Ketone levels are increased in patients with anorexia, vomiting and fever. Subpopulation analysis of children presenting to emergency departments with these particular complaints may further refine its clinical relevance. The combination of useful results and ease of administration may also make this test useful in the emergency department and also in a primary care setting. Validation of these findings is required to determine whether they are reproducible and universally applicable to all paediatric emergency departments.

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Contributors: PBO'D planned the study, gained ethical approval, contributed to data collection, collated and analysed the data, and drafted the paper. RK contributed to data collection and drafted the paper. TFB initiated the idea, contacted Abbott Diagnostics, was associated with the ethical approval application process and drafted the paper.

Ethical approval: The Lothian Research Ethics Committee and the National Health Service approved the study.

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