Title Page

Ketones in non-diabetic children with vomiting, diarrhoea or reduced intake: a prospective cohort study

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What is already known on this topic
>> Clinical tests for the assessment and stratification of children with dehydration are lacking to help guide decision making in the Emergency Department.
>> Previous studies had suggested that point-of care ketones may be a useful tool to inform triage management decisions in evaluating children with gastroenteritis and dehydration.

What this study adds
>> This cohort study does not demonstrate a benefit of the use of ketones in non-diabetic children at triage and at 4-hours to predict discharge disposition.
>> The study has shown the profile and change in serum ketones in response to fluid administration in children presenting to the Emergency Department.
>> Our results suggest that there is a weak correlation between ketone elevation and clinical dehydration. The utility of ketones in this population warrants further research.

Ketones in non-diabetic children with vomiting, diarrhoea or reduced intake: a prospective cohort study

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ABSTRACT

Objective To establish the relationship between serum point-of-care (POC) ketones at triage with clinical dehydration based on the validated Gorelick scales.

Design, setting and patients Prospective unblinded exploratory study from April 2016 to February 2017 in a tertiary paediatric Emergency Department. Patients aged 1 month to 5 years, with vomiting and/or diarrhoea and/or decreased intake with signs of dehydration or clinical concern for hypoglycaemia were eligible.

Main outcome measures POC ketones were analysed at triage and 4-hours later or upon discharge if earlier. Secondary outcomes were to examine the response of ketone levels to fluid/glucose administration and patient disposition.

Results Two-hundred and one attendances were included (198 patients); median age 1.8 years. The median triage ketones were 4.4 (interquartile range (IQR) 2.8–5.6) mmol/L. A weak correlation was identified between triage ketones and 10-point Gorelick scale (Pearson r=0.215), however the 4-point Gorelick scale was non-significant. Those admitted to hospital had median triage ketones of 5.2 (IQR 5-6) mmol/L and repeat ketones of 4.6 (IQR 3.3-5.7) mmol/L compared to 4.2 (IQR 2.4–5.2) mmol/L and 2.9 (IQR 1.6–4.2) mmol/L in those discharged home.

Conclusion Elevated POC ketones were demonstrated in non-diabetic children with acute illness. A weak correlation was demonstrated between triage POC ketones and the 10-point Gorelick scale, however, this was not demonstrated with the 4-point Gorelick scale. The use of POC ketones, at triage and at 4-hours, to predict the patient's disposition had poor and fair accuracy respectively. Ketosis and the potential impact of tailored treatments in paediatric acute illness warrants further research.

Abstract Word count: 255/250

INTRODUCTION

Many acute infective illnesses present to the Emergency Department (ED) due to concerns about increased losses and/or decreased intake. This can lead to ketosis. Ketones are produced in starvation due to limited glucose availability resulting in metabolism of lipids to triglycerides and fatty acids.[1] Ketosis symptoms include abdominal pain, anorexia, nausea and vomiting with or without acidosis. A point-of-care (POC) ketone level <0.6 mmol/L is regarded as normal and >1 mmol/L represent hyperketonaemia, and levels >3 mmol/L are indicative of diabetic ketoacidosis (DKA) in diabetic patients.[2]

The relationship between POC ketones to dehydration assessment in the ED has yet to be established. POC serum ketones have been shown to be a useful adjunct in the evaluation of DKA in adults[3] and children[4] and also in hyperemesis gravidarum[5]. There is limited research looking at the usage of POC ketone testing in children without diabetes.[6-10] O'Donohoe et al. reported that POC ketones were useful in determining the risk of admission based on a cohort of 186 pediatric ED patients (0 to 13 years) who required blood testing.[7] O'Donohoe et al. proposed that ketone levels >1.2 mmol/L as a predictor for admission based on a specificity of 86%, a sensitivity of 32% and a positive predicted value of 67%.[7] Levy et al. studied rapid intravenous (IV) rehydration using

dextrose in 188 children with gastroenteritis aged 6 months to 6 years. In the secondary analysis, Levy et al. suggested that elevated serum ketones correlated with the degree of dehydration and magnitude of metabolic acidosis.[8] Janet et al. demonstrated a reduction in median ketone level from 1.5 to 0.8 mmol/L in 56 children aged 6 months to 16 years with mild to moderate dehydration who had rapid IV rehydration with 2.5% dextrose and normal saline for 2 hours.[6] Futatani et al. described the potential usefulness of POC ketones in breastfeeding infants in the early postnatal period as an indicator of dehydration, energy depletion and acid-base imbalance.[10]

The clinical assessment of dehydration in children is challenging. Studies reveal that clinical symptoms are inexact in discerning the degree of dehydration and in predicting the clinical course in the ED.[11] The 4-point Gorelick scale is a validated tool to predict significant dehydration for children aged 1 month to 5 years.[12] It is based on 4 parameters of ill general appearance, absent tears, dry mucous membranes and capillary refill over 2 seconds. A 4-point Gorelick scale of 2 approximates with 5-10% dehydration and 3 or more approximates with dehydration over 10%. A score of 2 or more has a sensitivity of 0.79, specificity of 0.87, and accuracy of 85% for predicting 5% dehydration.[12] The 10-point Gorelick scale requires a more detailed assessment and categorises dehydration with mild, moderate and severe dehydration. Other scales considered included the Clinical Dehydration scale and the World Health Organisation scale but the Gorelick scales were chosen due to the validated age range, the attributes included and the accuracy.[12-14]

There is a paucity of literature on POC ketones in children with acute illness and studies have focussed on children requiring blood tests or IV rehydration. Their role in predicting the need for admission and in children who are rehydrated enterally needs to be explored. In this study, we sought to clarify the relationship between POC ketones at triage with clinical dehydration based on the validated 4-point and 10-point Gorelick scales. We hypothesised that triage POC ketones may predict hospital admission from the ED in children with signs of dehydration. We also examined the response of ketone levels to fluid and glucose administration in the ED.

METHODS

Study design

A single-centre prospective exploratory cohort study was conducted from April 2016 to February 2017 at our urban, university affiliated, tertiary pediatric ED. This ED is without an affiliated short stay observational unit with a 2016 ED census of 38,079 with an overall admission rate of 14% and 20% for the ED diagnosis of gastroenteritis.

Study population

Patients aged 1 month to 5 years who presented with vomiting and/or diarrhoea and/or decreased intake with a 4-point Gorelick scale[12] of 2 or more or concern at triage of possible hypoglycaemia were screened for enrolment. The study clinician subsequently assessed the child using the 10-point Gorelick scale.[12]

Exclusion criteria included gastrointestinal obstruction, conditions that could interfere with dehydration assessment including complex cardiac conditions, chronic renal impairment, known metabolic, gastrointestinal or endocrine patients and patients receiving beta-blocker therapy or tube feeding. All eligible children were identified by the triage nurse and were approached for consent by the treating clinician.

At triage, POC finger prick blood glucose and ketone concentrations were obtained. The Abbott Precision Xceed Pro® blood glucose and ketone monitoring system (Libertyville, IL) was used which measures beta-hydroxybutyrate from 0.0012 mL of blood. Triage category assignment used the Irish Children's Triage System which incorporates vital signs with presenting condition to determine the category (1 = critical to 5 = least critical).[15] Treatments were informed by established guidelines, which included commencement of oral trial after triage as appropriate. Repeat POC ketone and blood sugar were performed at 4-hours after triage or upon discharge.

The primary outcome was to describe the relationship between POC ketones at triage to the Gorelick scales. The a priori secondary outcomes were to describe the relationship:

1. Between POC ketones and presenting symptoms.
2. Between the rate of change of ketones and fluid/glucose intake in ED.
3. Between initial POC ketones and ED disposition.
4. Between the rate of change in ketones on ED disposition.

Data was presented as frequency (percent) or median with interquartile range (IQR). Outcome variables not normally distributed were analysed using non-parametric Wilcoxon-Mann-Whitney and Pearson's correlations. Receiver operating characteristic (ROC) curves including the area under curve (AUC) for the initial and repeat ketone levels were generated. The optimal cut-off points were elicited using Youden's index to maximise both sensitivity and specificity. Statistical significance was defined as a p value <0.05. Data were analysed using IBM SPSS Statistics for Windows (V.25, IBM, Armonk, New York, USA). A sample size of 200 patients was selected based on a previous relevant study.[8] This study was approved by the hospital's research ethics committee. Written informed consent was obtained from the parents or guardians of all participants.

RESULTS

A total of 355 patient visits were screened for inclusion (figure 1). There were 28 patients who met one or more exclusion criteria. Study availability prevented 116 visits from being recruited due to lack of study clinician availability. A total of 198 children were recruited who had 201 presentations meeting the eligibility criteria. Twelve patients did not have repeat POC ketone level recorded at 4-hours or discharge. Patient characteristics are outlined in table 1. The median age was 1.8 years (range 2 months to 4.99 years). There was an admission rate of 32%.

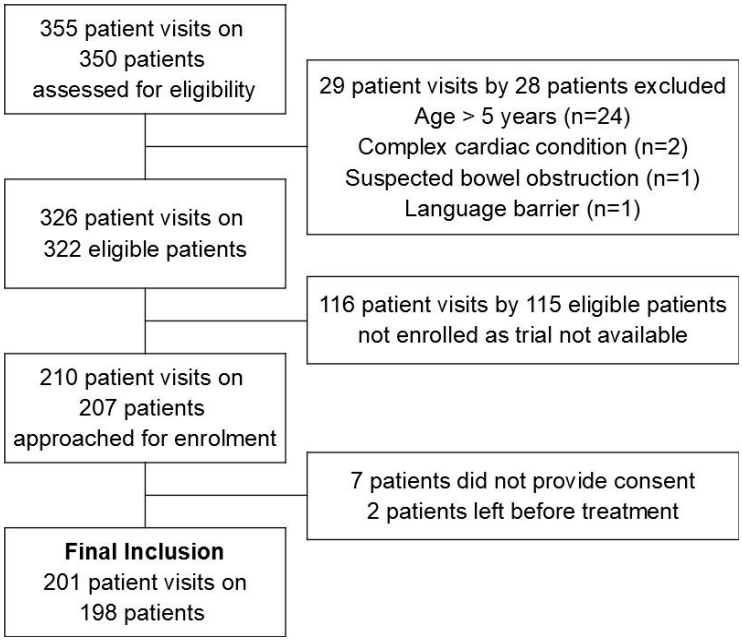


Figure 1 Consolidated Standards of Reporting Trials flow diagram.

The median 4-point Gorelick scale at triage was 2 (IQR 2-3) consistent with moderate dehydration. The median triage ketone level was 4.4 mmol/L (IQR 2.8-5.6 mmol/L) and the median triage glucose level was 3.6 mmol/L (range 1.6–7.9 mmol/L). Hyperketonaemia at triage (ketones >1 mmol/L) was present in 93% of recruits. No correlation was identified between triage ketone level and 4-point Gorelick scale (Pearson's r=0.117) (table 2). The median 10-point Gorelick scale assessment was 3 out of 10 (IQR 2-5; range 0-8). The median time interval from triage to clinician assessment was 25 minutes (IQR 13-61 minutes). Secondary analysis revealed a weak correlation between triage ketone level and severity of dehydration using the 10-point Gorelick scale (Pearson's r=0.215).

Table 1 Patient characteristics stratified by discharge destination (n=201)

Characteristics, n (%)	Admitted (n=64)	Discharged (n=137)
Median age, (IQR)	2.1 (1.1-3.1)	2.2 (1.3-2.9)
Female	36 (56)	66 (48)
Race		
White	53 (83)	125 (91)
Asian	3 (5)	3 (2)
Black	0	3 (2)
Other	8 (12)	6 (5)
Triage assessment[15]		
Triage category 1, most critical	1 (2)	0
Triage category 2	43 (67)	46 (33)
Triage category 3	16 (25)	78 (57)
Triage category 4	4 (6)	13 (10)
Median triage glucose level mmol/L (IQR)	3.2 (2.6-4.2)	3.7 (3-4.3)
4-point Gorelick scale at triage		
Mild dehydration	4 (6)	28 (20)
Moderate dehydration	32 (50)	81 (59)
Severe dehydration	28 (44)	28 (20)
10-point Gorelick scale by clinician		
Mild dehydration	13 (20)	62 (45)
Moderate dehydration	45 (70)	69 (50)
Severe dehydration	6 (10)	6 (5)
Routes fluid administered		
Intravenous (IV)	61 (95)	52 (38)
Oral/nasogastric (NG)	37 (58)	114 (83)
Both oral/NG and IV	34 (53)	29 (21)
Failed oral fluid trial	33 (52)	24 (18)
ED diagnosis		
Gastroenteritis	57 (89)	129 (94)
Bronchiolitis	4 (6)	0
Upper respiratory tract infection	1 (2)	6 (4)
Urinary tract infection	2 (3)	1 (1)
Primary varicella	0	1(1)
Outcomes		
Ondansetron	17 (27)	48 (35)
Vomited	23 (36)	24 (18)
Reattendance within 7 days	5 (8)	17 (12)

Table 2 Relationship between ketone levels at triage and Gorelick scale for predicting significant dehydration (n=201)

4-point Gorelick scale	n	Median ketone level (IQR) mmol/L
0	6	1.7 (0.6-4.2)
1	26	4.2 (3.1-5.3)
2	113	4.4 (3.2-5.3)
3	42	4.9 (2.1-5.8)
4	14	5.2 (3.9-5.6)

Children with symptoms <1 day had median ketone levels of 3.7 mmol/L (IQR 1.1-4.4 mmol/L), compared those with symptoms lasting 1-2 days with median levels of 4.3 mmol/L (IQR 2.2-5.7 mmol/L). Those with symptoms >3 days had median ketone levels of 4.6 mmol/L (IQR 3.3-5.4 mmol/L). The association between elevated triage ketone levels and duration of symptoms was statistically significant comparing symptoms >1 day to symptoms 1 day or over (Mann-Whitney U=748, p=0.019).

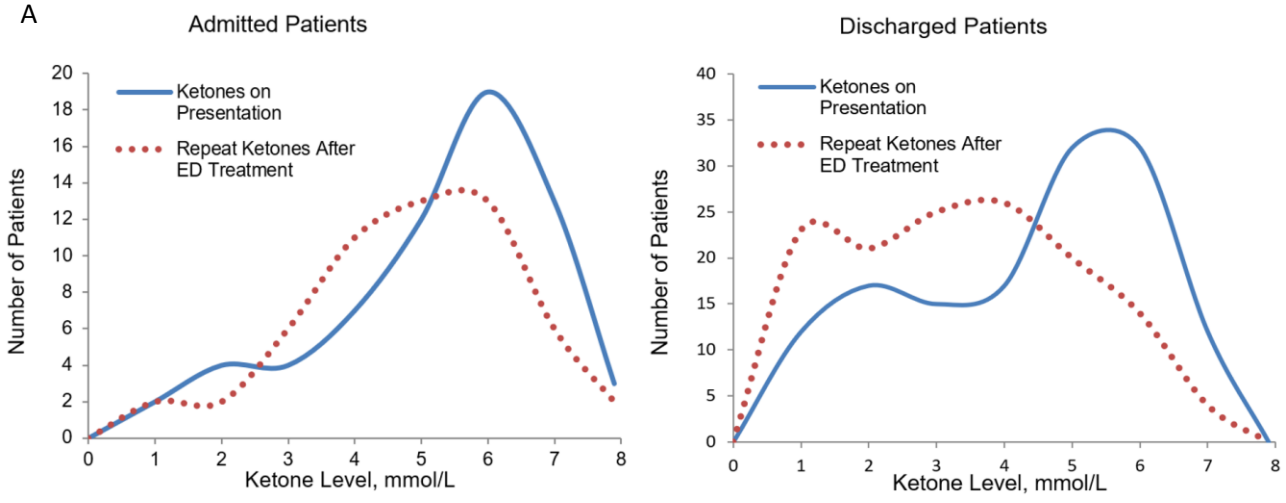
Table 3 Secondary outcome measures

	All	n	Admitted	n	Discharged	P value†
Triage ketones, mmol/L (n=201) *	4.4 (2.8-5.6)	64	5.2 (4-6)	137	4.2 (2.4-5.2)	0.001
4-hour ketones, mmol/L (n=188) *	3.4 (2-4.8)	55	4.6 (3.3-5.7)	133	2.9 (1.6-4.2)	<0.001
Change in ketone, mmol/L (n=188) *	-0.6 (-1.5-0.2)	55	-0.5 (-1.5-+0.6)	133	-1.0 (-1.9-0)	0.052
Change in ketone per hour, mmol/L (n=188) *	-0.15 (-0.4-0)	55	-0.08 (-0.3-+0.1)	133	-0.18 (-0.5-0)	0.010
Total IV/PO/NG fluid, mL/kg (n=188) *	25.9 (17.4-36.3)	55	30.3 (26.1-39.2)	133	22.5 (15-34)	<0.001
Total IV/PO/NG fluid, mL/kg/hr (n=188) *	6.2 (4.4-8.4)	55	6.7 (5.3-8.3)	133	5.8 (4.2-8.3)	0.099
Total glucose, g/kg (n=188) *	0.56 (0.3-1)	55	0.6 (0.4-0.8)	133	0.6 (0.3-1.2)	0.85

* All median values are given with an interquartile range.
† Wilcoxon-Mann-Whitney test two-tailed.

The admission rate was 32%. Patients admitted had median triage ketones of 5.2 mmol/L (IQR 4-6 mmol/L) compared to 4.2 mmol/L (IQR 2.4-5.2 mmol/L) in those discharged home (p=0.001) see table 3. Median ketones at 4-hours were 4.6 mmol/L (IQR 3.3-5.7 mmol/L) amongst patients admitted compared to 2.9 mmol/L (IQR 1.6-4.2 mmol/L) for those who were discharged (p<0.001). There was a median reduction of 0.6 mmol/L (range +2.3 to -6.2 mmol/L) in ketones after rehydration across both groups. Children admitted to the hospital received more fluid than children discharged 6.7 mL/kg/hr compared to 5.8 mL/kg/hr.

A



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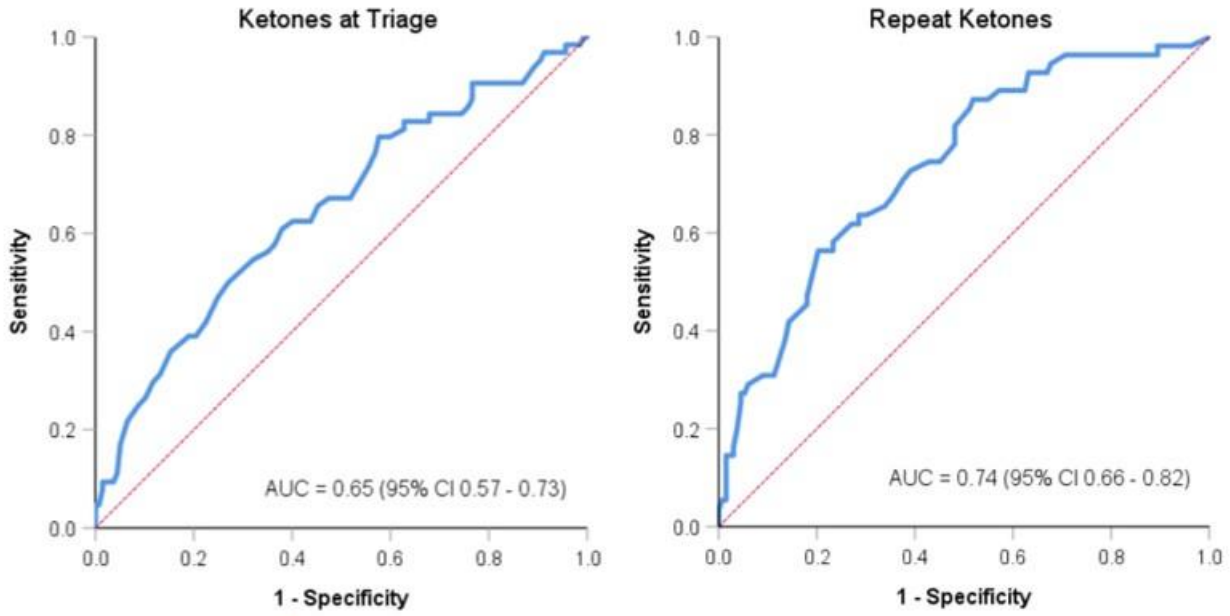

Figure 2 Change in ketones during study period and Receiver Operator Characteristic (ROC) curves (A) Comparison of POC Ketone levels on presentation versus ketone levels after ED treatment broken down by discharge destination. (B) ROC curves for the use of ketone level at triage and repeat ketones level as a predictor of the need for admission.

The discharged cohort had a greater proportion whose POC ketones decreased after rehydration than the cohort who were admitted (figure 2A). The AUC of POC ketone level at triage was 0.65 (95% confidence interval [CI] 0.57-0.73) (optimal cut-off 4.8 mmol/L; sensitivity 61%, specificity 62%) for predicting the need for admission is shown in figure 2B. The AUC of POC repeat ketone level was 0.74 (95% CI 0.66-0.82) (optimal cut-off 4 mmol/L; sensitivity 64%, specificity 71%).

During the ED encounter, laboratory testing was carried out in 58% (n=117) on clinical grounds or clinician preference. There was no case of hypernatraemia (sodium ≥146 mmol/L), 12% (n=14/114) had hyponatraemia (sodium ≤130 mmol/L), 30% (n=35/116) had raised urea (>6 mmol/L), 49% (n=38/78) had bicarbonate <18 mmol/L and 16% (n=13/83) had pH <7.3. Thirty percent (n=61/201) had urinary ketones performed. Children with low urinary ketones (negative, trace or +) had median triage ketones of 1.3 mmol/L (IQR 0.7-2.1 mmol/L) and 4-hour ketones of 0.6 mmol/L (IQR 0.2-1.5 mmol/L). Children with elevated urinary ketones (++, +++ and ++++) had median triage ketones of 4.8 mmol/L (IQR 4.1-5.8 mmol/L) and 4-hour ketones of 3.8 mmol/L (IQR 2.8-4.8 mmol/L).

DISCUSSION

This ED-based prospective cohort study identified a lack of correlation between triage POC ketones and the level of clinical dehydration measured, at triage, on the 4-point Gorelick scale and a weak correlation was demonstrated with the 10-point Gorelick scale at clinician assessment. The 4-point Gorelick scale classified 28% of patients with severe dehydration compared to the 10-point Gorelick scale utilised by the treating clinician which classified 6% of with severe dehydration. The clinician assessment was performed after initiating rehydration and occurred at a median interval of 24 minutes after triage. A minor part of the disparity between the two assessments may relate to the timing of assessment but the authors acknowledge that most likely over one quarter of the patients did not have greater than 10% dehydration as described by the 4-point Gorelick scale. A study by Pringle et al.[14] demonstrated this oversensitivity of the 4-point scale for severe dehydration.

Currently, there is no test to help predict the need for admission in children with acute illness and dehydration. Current UK guidance advises against routinely perform blood biochemical testing in gastroenteritis.[16] We demonstrated the poor accuracy by an AUC of POC ketone level at triage of 0.65 for predicting hospital admission. We demonstrate the more promising yet, fair accuracy with

an AUC of POC repeat ketone level was 0.74 for predicting hospital admission. This study does not support the clinical use of POC ketones in isolation to make disposition determinations in this study population.

This study demonstrates the elevation in POC ketone levels in children at triage with symptoms including vomiting, diarrhoea or decreased intake. This population is generalisable to western emergency and primary care settings that assess pediatric patients. Levy at al. demonstrated that children with gastroenteritis had elevated POC ketone levels above the range considered predictive of DKA in their diabetic counterparts.[8] The median ketone level in our cohort was higher than demonstrated by Levy et al. and Janet et al. (4.4 mmol/L versus 3.1 mmol/L and 1.5 mmol/L, respectively).[6, 9] In our study, 73% of patients had a POC ketone levels >3 mmol/L and blood testing showed features of acidosis in 46% (n=38/83) (blood pH <7.3 or plasma bicarbonate <18 mmol/L). The cohort's hospital admission rate (30%) was noticeably elevated compared to our baseline admission rate for children with the ED diagnosis of gastroenteritis (20%) which reflects the selective inclusion criteria which isolated children with clinically significant manifestation of symptoms. This exploratory study profiled the elevated serum ketones in children with vomiting and/or diarrhoea and/or decreased intake due to acute infective illness, predominantly gastroenteritis.

Our data suggests that children who were given higher volumes of dextrose per kg, regardless of route, had greater reductions in their ketone levels and children who were clinically assessed to be more dehydrated received less glucose per kilogram in their ED treatment. Of note, 92% of admitted children received a fluid bolus without dextrose compared to 36% of discharged children. This different fluid management may explain, in part, the smaller improvement in POC ketone levels between triage and 4-hours in those children admitted to hospital despite receiving a larger fluid intake. The median half-life of beta-hydroxybutyrate ketones is 1.64 hours which informs the anticipated rate of decline of serum levels with adequate glucose availability. Interestingly, Levy et al. previously demonstrated in children with gastroenteritis and dehydration that the administration of larger volumes of IV dextrose was associated with reduced return visits requiring readmission.[17 18] Of the 129 patients (64%), with repeat ketones levels less than triage ketones, the median rate of decrease was 0.3 mmol/L/hr. This decrease is similar to the decrease of 0.2 mmol/L/hr noted by Janet et al. in children rehydrated with 20 mL/kg over 2 hours of normal saline and 2.5% dextrose followed by 120 mL of oral rehydration solution.[6] There is no international consensus for the optimal rehydration fluids in children.[19] We believe that the significance of ketosis in the presentation of acute paediatric illness and the potential for tailored treatments in paediatric acute illness warrants further research.

Limitations

Study subjects were a convenience sample based on study availability. This study was a non-randomised single-centre prospective exploratory cohort study thus the risk of causal inference must be considered. There was robust data collection to describe the profile of the patients and management. Clinical staff were not blinded to the POC ketone levels at triage or post treatment. The pre-existing clinical guidelines did not incorporate any advice in relation to POC ketones and further management. Clinicians were advised to disregard the POC ketones that were unrelated to the standard investigation of hypoglycaemia.

The gold standard for quantifying dehydration by change in body weight was not utilised however, clinical dehydration scales appear to have superior accuracy to unstructured clinical assessment.[13] Past reports revealed that the precision of the Abbott Precision Xceed Pro® ketone meter at high levels (>6 mmol/L) of ketone concentration has been inconsistent by underestimating the true value compared to laboratory values.[20-22] The sample size was based on a previous comparable study based on convenience sampling. An effect size on serum ketones could not be accurately estimated in our population as our population differed from previous studies by inclusion criteria and rehydration methods.

CONCLUSIONS

This study has revealed the elevation in ketone profile of children with symptoms causing dehydration and or starvation. We have identified a weak correlation with between POC ketone

level and dehydration based on the 10-point Gorelick scale, and the association between elevated ketones at triage with the need for admission. We have described the ketone response to fluid administrations. The use of POC ketones to predict the patient's disposition from the ED was not supported by our data. The normalisation of elevated ketones after ED rehydration was also not demonstrated. The role of ketosis in acute illness and its response to tailored treatments in refined clinical groups warrants further research.

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Contributors SD, CB, SOD, SW and MJB conceived and designed the study. MJB supervised the conduct of the study and data collection. JJ, ER, CB and MJB recruited patients. SD, JJ, RH and ER managed the data. SD, ID and MJB provided statistical advice and aided with data analysis. SD drafted the article, and all authors contributed substantially to its revision. MJB takes responsibility for the paper as a whole.

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Competing interests None declared.

Patient consent Obtained.

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