Fluid Management for Critically Unwell Children with Diabetic Ketoacidosis: A Multi-centre Study

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Abstract

Background:

Cerebral oedema in paediatric diabetic ketoacidosis (DKA) can be associated with significant mortality and morbidity. These concerns have led to restrictive fluid management in children presenting with DKA and also led to the revision of guidance by the British Society of Paediatric Endocrinology and Diabetes (BSPED) in 2015.

Methods:

We conducted a multi-centre study of compliance with two BSPED guidelines with liberal (2009) and restrictive fluid management (2015) protocols for children admitted to paediatric critical care units (PCCU) in the UK. We also used univariate and multivariate logistic regressions to study associations with clinical outcomes such as diagnosis of cerebral oedema.

Results:

96 patients with DKA were admitted to eight PCCUs between January 2013 and December 2017. The median age at presentation was 9 years and weight was 32.4kg. Of all admissions, 25% were invasively ventilated, 4% received vasoactive support, 10% received renal replacement therapy and 98% survived to discharge. 42% were suspected to have cerebral oedema with older children being more likely to be diagnosed with cerebral oedema. There was no significant difference in receiving renal replacement therapy, mechanical ventilation, vasoactive support or a clinical diagnosis of cerebral oedema between the two treatment protocols.

Conclusion:

Compliance was lower for the guideline with a more restrictive fluid protocol. The study found no evidence to suggest that differing fluid management across BSPED guidance had any significant impact on clinical outcomes. A larger prospective study is needed to study the impact of the revised 2020 guidance.

What Is Known:

Clinicians remain divided about fluid management in paediatric Diabetic Ketoacidosis and a range of protocols have been used in international studies and guidelines.

The British Society for Paediatric Endocrinology and Diabetes recommended a more restrictive fluid management in 2015 due to concerns regarding cerebral oedema.

What Is New:
In this first multi-centre study from paediatric critical care units across the UK, we compared compliance and outcomes for two guidelines with restrictive and liberal fluid management.

There was no difference in outcomes such as diagnosis of cerebral oedema, receiving renal replacement therapy, mechanical ventilation, or length of stay between the two groups.

**Background:**

The incidence of Type 1 Diabetes Mellitus (T1DM) in paediatric population has increased globally over the last few decades. (1) Approximately 3000 children were newly diagnosed in 2018/19 with T1DM in England and Wales, giving an incidence of 24.5 per 100,000. (2)

One of the major life threatening complications of T1DM; especially, at initial presentation is Diabetic Ketoacidosis (DKA). In a national study from the United Kingdom (UK), 10% of hospital admissions due to DKA required admission to paediatric critical care units (PCCUs). (3)

Cerebral oedema has an incidence of 0.5-1% in paediatric DKA and is associated with significant morbidity and mortality. (4, 5) Children with DKA may present in hypovolemic shock but require careful fluid resuscitation due to concerns regarding possible association with cerebral oedema. (6) A number of international studies and guidelines suggest that a range of fluid infusion protocols are being used in paediatric DKA. (7, 8, 9, 10, 11) Experimental and observational studies have also suggested other causes for cerebral injury and oedema in DKA, such as reperfusion injury and dysfunction of blood brain barrier. (12, 13, 14, 15)

The British Society for Paediatric Endocrinology and Diabetes (BSPED) revised the guidance for hospital management of DKA in 2015 (16) with a more restricted regime for fluid resuscitation and rehydration in comparison to previous guideline published in 2009. (17) The guidance in 2015 suggested giving 10ml/kg of fluid bolus only for shocked patients before discussing with a consultant in comparison to giving up to 30/ml/kg in the guidance from 2009. An objective method to assess dehydration based on initial pH was suggested in 2015, whereas dehydration needed to be clinically evaluated to a maximum of 8% as per the 2009 guidance. Another difference was restriction in maintenance fluid in 2015 compared to the widely used Holiday and Segar formula in 2009 guidance. These changes were made mainly in response to clinical opinion and case reviews of mortality secondary to DKA.

In 2020, the BSPED national working group produced an interim guidance in light of the multi-centre Paediatric Emergency Care Applied Research Network (PECARN) trial that showed a lack of causal association between rapid fluid administration and DKA related brain injury in children presenting with Glasgow coma scale (GCS) score of 11 or more, and concerns raised about the restrictive fluid management potentially leading to increased risk of acute kidney injury and prolonged hospital admissions. (18, 19, 20) Although concerns were raised about the restrictive and liberal fluid management protocols in the UK, (21) no data have been shared and reviewed on multi-centre level.
In collaboration with the Paediatric Critical Care Society, we conducted the first multi-centre study to date for children with DKA admitted to PCCUs across the UK. Our aim was to assess compliance with liberal and restrictive guidance for fluid management and to identify any consequential differences in clinical outcomes such as receiving renal replacement therapy, inotropic support, and the prevalence of cerebral oedema and mortality in PCCU.

**Materials And Methods:**

**Data collection**

The study was advertised to PCCUs across the UK with support from the Paediatric Critical Care Society Trainees’ Audit and Research collaboration (PICSTAR). A pilot audit was conducted in two PCCUs before finalizing the data set and an online survey was designed using ‘onlinesurveys.ac.uk’. This was subsequently modified based on feedback from participating units. The inclusion criteria was defined as all PCCU admissions between January 2013 and December 2017 with primary diagnosis of DKA, reported to Paediatric Intensive Care Audit Network (PICANet), regardless of the level of critical care provided. (22, 23)

The information governance department at Leeds Children's Hospital provided the initial approval for this audit (Supplementary Material 1) and clinicians from each participating unit also gained local approval prior to data collection. Pseudo-anonymised data was then retrospectively collected from clinical notes and nursing charts for every admission which met the inclusion criteria and was entered to the online survey.

All admissions where the patient presented between 8AM and 5PM on weekdays were defined as ‘in-hours’ and all other presentations, including those at any time on a bank holiday were defined as ‘out-of-hours’.

Patients who were treated using the 2009 BSPED guidance were categorised and will hereafter be referred to as the ‘liberal fluid group’ and those who were treated as per the 2015 BSPED guidance as the ‘restrictive fluid group’. There was also a group of patients who were treated following local integrated care pathways (LCPs) that were not included in the liberal or restrictive fluid groups (Supplementary Material 2 and 3). Compliance with guidelines was checked based on the assessment of dehydration and volume of resuscitation fluid given on initial presentation.

**Statistical analysis**

Data was checked for completeness and analysed using Stata 15 (24). We compared data from patients following the restrictive fluid guidance with those following the liberal fluid guidance. Graphical tests of normality were suggestive of a non-normal distribution for most continuous variables. The Wilcoxon-rank sum test was therefore used to test for equality of distributions of continuous variables by BSPED guidelines followed. Chi-square tests of independence were conducted to evaluate differences in the
frequency count distribution of categorical patient demographic and biochemical variables, by guidelines followed.

Chi square test of homogeneity of odds were used to study possible associations between guidelines followed and clinical outcomes such as prevalence of cerebral oedema, use of inotropic support, mechanical ventilation and renal replacement therapy, and odds ratios with 95% confidence intervals (95%CI) calculated. We used intention to treat analysis and included all patients who were treated following either liberal or restrictive fluid guidance even if they were non-compliant (n = 22 patients) in view of possible influence of guideline used on decision making.

Additional subgroup analysis was also performed for the group of patients (n = 40) with a recorded clinical diagnosis of cerebral oedema. Chi-square tests of independence and for categorical variables and Wilcoxon rank sum tests for continuous variables were used to explore differences in the demographic and biochemical profile of patients with and without cerebral oedema. Where these tests were indicative of a significant difference in population distribution for a given variable, univariate logistic regressions were ran to establish directionality of associations. Finally, a multivariate logistic regression model was conducted to model the risk of developing cerebral oedema, adjusting for patient demographic and clinical management factors significant at univariate level.

Results:

Patient demographics:

We received data from eight PCCUs across the UK for 96 admissions during the study period. Of the 96 admissions, 91 had complete data for guideline used and were therefore included in the analysis comparing the two guidelines. The overall median age of children admitted to PCCU was 9 years (IQR: 4-12.5) with slightly more boys (55%). Overall median weight on admission was 30kg (IQR = 16.5–43.9).

Weight was measured in 48 cases, estimated in 39 cases and the method for determining weight was unknown for nine patients. There was equal distribution of patients transferred from a District General Hospital and those admitted from the same Tertiary Hospital and equal numbers presenting in-hours and out-of-hours. Out of the 96 admissions to PCCU, 84% were new diagnoses of T1DM whilst 16% had a known diagnosis of T1DM. There were higher number of admissions in the months of December, January, and July (Fig. 1). Overall median pH at initial presentation was 6.9, HCO3 was 6.0 mmol/L, blood glucose = 32.0 mmol/L and blood ketones = 5.6 mmol/L. Corrected sodium was calculated for 42% of patients.

Differences between liberal and restrictive fluid groups:

Of the 91 included admissions, 30 adhered to the liberal fluid guidance and 32 patients were treated following restrictive fluid guidance. 29 patients were managed according to LCPs. Patient demographics and biochemical profile at initial presentation, by guidance followed are presented in Table 1.
Table 1
Patient demographics and biochemical profile at initial presentation for patients, by BSPED guidelines followed (2009 & 2015)

|                      | Liberal Fluid n = 30 (33%) | Restrictive Fluid n = 32 (35%) | $X^2$/$z$† (p value) |
|----------------------|----------------------------|-------------------------------|---------------------|
| Age (years)          | 10 (2–13)                  | 9 (5.5–12.5)                  | 0.007 0.994         |
| Weight on admission (kg) | 32 (14–40)              | 30 (19–45)                    | -0.303 0.762        |
| Sex (Males)          | 18 (59%)                   | 16 (48%)                      | 0.625 0.429         |
| Out of hours presentation | 14 (47%)                 | 16 (50%)                      | 0.007 0.793         |
| Admission from same hospital | 13 (43%)                | 21 (66%)                      | 3.107 0.078         |
| New diagnosis of diabetes mellitus | 28 (93%)             | 24 (75%)                      | 3.847 0.050         |
| pH                   | 6.9 (6.8-7.0)              | 6.9 (6.9-7.0)                 | -0.070 0.944        |
| pCO2 (kPA)           | 2.5 (1.7–2.9)              | 2.8 (2.0-3.5)                 | -1.256 0.209        |
| HCO3 (mmol/L)        | 5.2 (4.0-6.8)              | 5.7 (2.9–7.8)                 | -0.363 0.716        |
| Lactate (mmol/L)     | 2.3 (1.8–3.2)              | 2.5 (2.1–3.3)                 | -1.178 0.239        |
| Glucose (mmol/L)     | 35(27–48)                   | 28 (24–39)                    | 1.775 0.076         |
| Sodium (mmol/L)      | 137 (131–141)              | 136 (131–141)                 | 0.621 0.535         |
| Corrected Sodium (mmol/L) | 150 (144–158)          | 143 (141–146)                 | 2.499 0.013         |
| Creatinine (mmol/L)  | 75 (34–121)                 | 66 (45.5–89.5)                | 0.838 0.402         |
| Potassium (mmol/L)   | 4.7 (4.2–5.2)              | 4.1 (3.7–4.9)                 | 1.742 0.082         |
| Urea (mmol/L)        | 7.9 (6.3–12.7)             | 6.5 (4.7–9.8)                 | 1.789 0.074         |
| Blood Ketones (mmol/L) | 5.0 (4.5–5.5)            | 5.5 (4.7–6.1)                 | -0.944 0.345        |
| Glasgow Coma Scale (GCS) on presentation | 14 (10–15)             | 13 (11–15)                    | -0.278 0.781        |

Continuous variables presented as median (interquartile range) and categorical variables presented as (n, (%)).

*Results of a Mann-Whitney U (Wilcoxon rank sum) test for continuous variables, in turn, by guidelines followed (2009 vs 2015).

†Results of a chi-square test of independence comparing differences in frequency count distributions of categorical variables in turn, by guidelines followed (2009 vs 2015). Where results are significant (p ≤ 0.05), corresponding $X^2/z$ values are reported.
A higher proportion of patients were non-compliant for estimation of dehydration in the restrictive fluid group, 15% (n = 5) vs 7% (n = 2) in the liberal fluid group. 44% (n = 14) in restrictive group received more resuscitation fluid than advised whereas 20% (n = 6) of patients in the liberal group received initial fluid boluses which exceeded the recommended volume.

Factors affecting compliance with the BSPED guidance included transfer from another hospital, higher urea on admission, and lower GCS on initial presentation. Overall, patients who were non-compliant with the guidance received higher volume of fluid boluses on initial presentation and during the first 24 hours of admission. (Table 2)

|                      | Liberal Fluid (BSPED 2009) | Restrictive Fluid (BSPED 2015) |
|----------------------|-----------------------------|---------------------------------|
|                      | n = 30                      | n = 32                          |
| Compliant            | n = 22 (73%)                | n = 18 (56%)                    |
| Non-compliant        | n = 8 (27%)                 | n = 14 (44%)                    |

**Factors affecting compliance**

- **pH**: 6.9 (6.8-7.0) vs 6.9 (6.8–6.9) vs 7.0 (6.9-7.0) vs 6.9 (6.8-7.0)
- **Urea (mmol/L)**: 7.3 (6.2–10.7) vs 8.4 (7.6–14.4) vs 5.6 (4.6–7.4) vs 8.4 (5.5–12.7)
- **Glasgow Coma Score on presentation**: 14 (10–15) vs 13 (5–14) vs 14 (13–15) vs 13 (9-14.5)
- **Out of hours presentation**: 9 (42.9) vs 5 (62.5) vs 8 (47.1) vs 7 (50.0)
- **Admission from same hospital**: 11 (52.4) vs 2 (25.0) vs 14 (82.4) vs 6 (42.9)

**Fluid variables**

- **Volume of initial fluid bolus (ml/kg)**: 20 (10–30) vs 35.9 (28–241) vs 10 (2–10) vs 20 (20–50)
- **Fluid boluses in 24 hrs (ml/kg)**: 25 (10–30) vs 33.9 (22.5–242.5) vs 10 (5–17) vs 35 (20–45)

Patients in the liberal fluid group received more resuscitation fluid as boluses on initial presentation (median: 20ml/kg, IQR: 20–30) compared to those in restrictive group (median: 10ml/kg, IQR: 9.6–20). Total amount of fluid received in the first 24 hours since initial presentation was also higher in the liberal group (median: 108ml/kg, IQR: 92–122) than the restrictive group (median: 82ml/kg, IQR: 70–95). (Table 3)
### Table 3
Management and clinical outcomes of patients on paediatric critical care units (PCCU) by BSPED guidelines followed (2009 & 2015)

| Management                                                                 | BSPED 2009 |           | BSPED 2015 |           | z*       | p value   |
|----------------------------------------------------------------------------|------------|-----------|------------|-----------|----------|-----------|
| Time to PCCU admission (hours)                                             | 8.3 (4.6–23.1) |           | 6.2 (4–10.3) |           | 0.740   | 0.459     |
| Total amount of fluid in 24 hrs since initial presentation (ml/kg)         | 108 (92–122) |           | 82 (70–95)  |           | 0.552   | 0.581     |
| Total amount of fluid in 24–48 hrs (ml/kg)                                | 79 (74–97)  |           | 74 (60–84)  |           | 0.228   | 0.774     |
| Total amount of fluid boluses on initial presentation (ml/kg)              | 20 (20–30)  |           | 10 (9.6–20) |           | 2.514   | 0.012     |
| Total amount of fluid boluses in 24 hrs since initial presentation (ml/kg)| 30 (20–37)  |           | 17 (10–35)  |           | 1.942   | 0.052     |
| Length of stay in PCCU (days)                                             | 2 (2–3)     |           | 2 (1.5–4)   |           | -0.037  | 0.971     |
| Highest Urea (mmol/L)                                                     | 8.6 (7–13.8) |           | 8.5 (5–12.5) |           | 0.775   | 0.438     |
| Time to starting insulin from initial presentation (hours)                 | 2.2 (1.6–3.2) |           | 2.4 (2–3)   |           | -0.575  | 0.565     |

**Clinical outcomes**

| OR (95%CI) | χ²† | p value |
|------------|-----|---------|

Continuous variables presented tab as median (interquartile range) and categorical variables presented as (n, (%)).

*Results of a Mann-Whitney U (Wilcoxon rank sum) test for continuous variables, in turn, by guidelines followed (2009 vs 2015).

†Results of a chi-square test of homogeneity of odds comparing the 2015 group to 2009 group.

1 Odds ratios for incidence of each clinical outcome, for 2015 compared to 2009 group and corresponding 95% confidence interval.

2 Of those diagnosed with cerebral oedema in each group.
| Clinical Outcome                                      | BSPED 2009 | BSPED 2015 | z*     | p value | Confidence Interval |
|------------------------------------------------------|------------|------------|--------|---------|---------------------|
| Survived to discharge                                | n = 30 (33%) | n = 32 (36%) | 1.94   | 0.164   | -                   |
| Fluid readjusted on admission to PCCU               | 18 (72%)   | 14 (45%)   | 4.00   | 0.045   | 0.32 (0.09–1.04)    |
| Diagnosed with cerebral oedema                       | 11 (37%)   | 16 (50%)   | 1.10   | 0.294   | 1.72 (0.61–4.85)    |
| Treated for cerebral oedema                           | 11 (100%)  | 15 (94%)   | 0.65   | 0.420   | -                   |
| Renal Replacement therapy                            | 6 (21%)    | 2 (6%)     | 2.56   | 0.109   | 0.27 (0.04–1.52)    |
| Mechanical ventilation                               | 8 (26.7%)  | 8 (25.0%)  | 0.02   | 0.881   | 0.91 (0.29–2.89)    |
| Vasoactive agents used                               | 1 (3%)     | 1 (3%)     | 0.00   | 0.962   | 0.93 (0.05–16.02)   |
| Inotropic support received                           | 6 (20%)    | 7 (22%)    | 0.03   | 0.861   | 1.12 (0.32–3.85)    |

Continuous variables presented tab as median (interquartile range) and categorical variables presented as (n, (%)).

*Results of a Mann-Whitney U (Wilcoxon rank sum) test for continuous variables, in turn, by guidelines followed (2009 vs 2015).

†Results of a chi-square test of homogeneity of odds comparing the 2015 group to 2009 group.

1 Odds ratios for incidence of each clinical outcome, for 2015 compared to 2009 group and corresponding 95% confidence interval.

2 Of those diagnosed with cerebral oedema in each group.

There was no difference in highest urea noted during admission and the median length of PCCU admission was 2 days in both groups. There were fewer patients in liberal fluid group (37%, n = 11) with clinical diagnosis of cerebral oedema than in the restrictive group (50%, n = 16). A higher number of patients in liberal group received renal replacement therapy and the proportions of patients who received mechanical ventilation and vasoactive support were similar between the two groups (Table 3).
The two patients, who did not survive to discharge, both adhered to the restrictive fluid guidance. On further detailed review of these cases, one of them was clinically suspected to be in septic shock at presentation with pupillary changes and an initial CT head showing signs of cerebral oedema. The patient developed multi-organ failure and also received renal replacement therapy. The second patient had signs of cerebral oedema on initial presentation and died secondary to brainstem involvement.

**Cerebral Oedema:**

Among all admissions to PCCU, 42% (n = 40/96) were suspected to have cerebral oedema at some point during their admission. The clinical suspicion for cerebral oedema was based on dropping GCS in 90% (n = 36/40) of these cases. Out of these patients, clinical seizures, abnormal pupils, and bradycardia with hypertension were reported for one case each. Cerebral oedema was diagnosed because of developing clinical seizures in one case and the reason for diagnosis of cerebral oedema was unknown in three cases.

Of the 40 admissions who had a clinical diagnosis of cerebral oedema, 85% (n = 34) underwent neuro-radiological imaging with findings suggestive of cerebral oedema in 15% (n = 5) of these cases. Pharmacological interventions such as intravenous mannitol and hypertonic saline were used for 85% (n = 34) of cases of suspected cerebral oedema. Children suspected to have cerebral oedema were older than those without suspicion of cerebral oedema and 77% (n = 31) were newly diagnosed with T1DM at this presentation. The demographic characteristics and biochemical profiles of patients with and without a clinical diagnosis of cerebral oedema, respectively, are summarised in Table 4.
Table 4
Demographic and biochemical profile and fluid boluses for patients with and without a recorded clinical diagnosis of cerebral oedema during single PCCU admission.

| Diagnosis of Cerebral Oedema During PCCU Admission | Clinical diagnosis of cerebral oedema (n = 40 (42%)) | No recorded diagnosis of cerebral oedema (n = 56 (58%)) | X2*/z† p value |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|----------------|
| Age (years)                                       | 12 (9.5–14)                                       | 6 (1-10.5)                                        | -4.417 < 0.001 |
| Sex (Males)                                       | 18 (45%)                                          | 35 (62.5%)                                        | 5.135 0.023    |
| Ketones (mmol/L)                                  | 5.6 (4.7–6.5)                                     | 5.6 (4.8–6.1)                                     | 0.747 0.455    |
| Glucose (mmol/L)                                  | 33 (27–44)                                        | 31 (25–37)                                        | -1.113 0.183   |
| pCO2 (kPA)                                        | 3.0 (2.3–3.7)                                     | 2.7 (2-3.5)                                       | -1.888 0.059   |
| HCO3                                             | 6 (4.0-7.2)                                       | 6.5 (4.4–7.9)                                     | 0.448 0.654    |
| pH                                               | 6.9 (6.8-7.0)                                     | 7.0 (6.9–7.1)                                     | 2.958 0.003    |
| Urea                                             | 9.2 (6.0-14.1)                                    | 6.4 (5.4–8.4)                                     | -2.949 0.002   |
| Sodium (mmol/L)                                   | 136 (129–141)                                     | 136 (132–140)                                     | 1.089 0.276    |
| Corrected Sodium (mmol/L)                         | 150 (144–153)                                     | 145 (141–150)                                     | -0.680 0.497   |
| Volume of initial fluid bolus (ml/kg)             | 20 (17–40)                                        | 20 (10-27.5)                                      | -1.438 0.151   |
| Fluid boluses in 24 hrs (ml/kg)                   | 27 (20–50)                                        | 20 (10–30)                                        | -2.299 0.022   |
| New diagnosis of diabetes mellitus                | 31 (77.5%)                                        | 50 (89%)                                          | 6.690 0.010    |
| Admission from same hospital                      | 13 (32.5%)                                        | 31 (55.4%)                                        | 7.890 0.003    |

Continuous variables presented as median (interquartile range) and categorical variables presented as (n, (%)).

*Results of a Mann-Whitney U (Wilcoxon rank sum) test for continuous variables, in turn, by guidelines followed (2009 vs 2015).

†Results of a chi-square test of homogeneity of odds comparing the 2015 group to 2009 group.

P value to be considered significant if < 0.03
Univariate logistic regression analyses showed significant associations with increasing age (Coef: 0.25, 95% CI: 0.14–0.37, p < 0.001), transfer from a different hospital (OR: 0.39, 95% CI: 0.17–0.90, p = 0.030) and serum urea on initial presentation (Coef: 0.15, 95% CI: 0.06–0.26, p = 0.002), in turn, on risk of cerebral oedema. When these variables were modelled in an adjusted, multivariate model, only serum urea (Coef: 0.18, 95% CI: 0.04–0.30, p = 0.010) and age on admission (Coef: 0.24, 95% CI: 0.12–0.37, p < 0.001) remained significantly associated with risk of cerebral oedema.

Discussion:

In this multi-centre study from PCCUs across the UK, we compared the fluid regimens in 2 guidelines (BSPED 2009 and 2015) with restrictive and liberal fluid management, reflecting a five-year period of practice. Compliance with the guidance was lower in the cohort following the restrictive 2015 guidance, in terms of estimation of dehydration and fluid resuscitation. This could be due to the objective method for estimating dehydration and clinicians’ perception of the acceptability of guidance, compared to their previous practice.

One concern regarding fluid restriction in the 2015 guidance was a possible rise in the prevalence of acute kidney injury and the need for renal replacement therapy. However, we found no evidence to suggest a difference in the use of renal replacement therapy amongst patients who were treated following the restrictive fluid guidance (OR 0.27 (95%CI 0.04–1.52) p > 0.05).

The 2020 interim BSPED guidance recommends estimation of dehydration based on pH but allows a more liberal approach to resuscitation fluid, and uses the Holliday and Segar formula for calculation of maintenance fluid similar to the 2009 guidance. This approach is more in-line with the International Society for Paediatric and Adolescent Diabetes (ISPAD) guidance when replacement volumes are calculated for different ages and weights (9, 25).

Overall, the prevalence for children admitted to PCCU who were clinically diagnosed with cerebral oedema was 42%, which is much higher than the reported incidence of 0.5-1% among children presenting to hospitals with DKA. This could be explained by the inclusion of only critically unwell children in this study who were presumably at higher risk of developing DKA related complications. Also, previous studies have used more specific criteria for the diagnosis of cerebral oedema. (4, 5) The PECARN trial reported an incidence of 0.9% for clinically evident brain injury. However, children at higher risk of cerebral oedema at baseline were excluded from the study and therefore may not be relevant to the high risk population included in this study (26).

In our study population, older children were at higher risk of being diagnosed with cerebral oedema. This is notable as cerebral oedema in DKA has not been previously reported to be associated with increasing age (27, 28). Clinical diagnosis of cerebral oedema was based on low GCS in the majority of cases and only 15% had positive findings on CT brain. The challenges in diagnosis of cerebral oedema in younger patients and validity of GCS for diagnosis of cerebral oedema in DKA should be explored in future studies. There is a need for better guidance to clinically evaluate risks and support a more specific
diagnosis of cerebral oedema to avoid unnecessary investigations and potential risks to targeted management.

Similar to reported evidence, we noted that patients with higher serum Urea were at higher risk of developing cerebral oedema \((27)\). Corrected Sodium has also been shown to be useful as an early warning tool for cerebral oedema and its consistent use needs to be emphasized as only 42% of the patients had corrected sodium calculated on admission. \((29)\)

Due to the retrospective nature of this study, we were unable to include details such as type of fluid used, real time changes in clinical condition including when concerns for cerebral oedema were raised, rationale for management, and long term neurological outcomes. We would have liked to include data from more PCCUs nationally but appreciate the limitations of retrospective audits and the challenges posed by five year data collection. As a result, some units were not able to participate in the study.

The low event rates of some of the clinical outcomes of interest, such as PCCU mortality and vasoactive support hindered the extent to which some associations could be explored. It is possible that due to its relatively small sample size, the present study may be underpowered to detect some present associations. This further emphasises the need for a multicentre audit, with greater numbers of admissions, which would permit more sophisticated, adjusted modelling of clinical outcomes and reduce the likelihood of type II statistical errors.

**Conclusions:**

Recent publications and scientific correspondence suggest that clinicians remain divided about fluid management in paediatric DKA and the association of fluid volumes with brain injury or cerebral oedema. \((21, 27, 30)\) Although this study was not designed or powered to infer causation, our data fails to identify any association between odds of being diagnosed with cerebral oedema or receiving renal replacement therapy and guideline followed for fluid management. There was also no effect on any other outcome measures including mechanical ventilation, inotropic support or length of PCCU stay.

Fluid resuscitation in DKA remains a challenging area and there remains a clear need to develop stronger collaborations between PCCUs in the UK, in order to conduct a comparative effectiveness study. Clinical judgement for individual cases should be exercised with application of implementation science to improve guidelines based on shared experience and knowledge.

**List Of Abbreviations:**
Declarations

Funding:

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of Interests / Competing interests:

The authors declare that they have no competing or conflicting interests

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Code Availability:

Not applicable

Authors’ contributions:

1. KM wrote the audit protocol, designed survey questionnaire, performed statistical analysis, wrote initial draft of the manuscript, revisions, and corresponded with all co-authors
2. KC reviewed statistical plan, performed statistical analysis, contributed to the manuscript and revisions.

3. AF reviewed and contributed to survey questionnaire, collected data, performed literature review, reviewed and contributed to the manuscript and revisions.

4. AB corresponded for PICSTAR and advertised the audit, collected data, performed literature review, reviewed and contributed to the manuscript.

5. MW collected data and corresponding clinician for local unit, performed literature review, reviewed and contributed to the manuscript and revisions.

6. KC collected data and was the corresponding clinician for local unit, performed literature review, reviewed and contributed to the manuscript.

7. OH collected data, performed literature review, supported statistical analysis, contributed to the manuscript and revisions.

8. AH collected data, performed literature review, reviewed and contributed to the manuscript and revisions.

9. JL supervised protocol writing, supported governance approval, reviewed survey questionnaire, analysis, and contributed to the manuscript and revisions.

All co-authors have given final approval of the submitted version of the manuscript and are accountable for all aspects of the work.

**Ethics approval:**

Governance approval was provided by the Caldicott Guardian at Leeds Teaching Hospitals Trust and an ethics approval was not needed as per national legislation. http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf

**Consent to participate:**

All participating hospitals also gained approval from their local governance department. No patient identifiable data was collected or used during analysis.

**Consent for publication:**

Not applicable

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Figures
Figure 1

Number of monthly presentations with DKA for all included admissions over five years (2013-2017) X axis: Month of initial presentation to hospital, y axis: Number of admissions by year

Supplementary Files

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