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RESEARCH ARTICLE

# Children with Diabetic Ketoacidosis Treated with Restricted Fluid Regime in Intensive Care: Risk of Acute Kidney Injury is not Increased and Resolves

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ABSTRACT

**Background:** Children admitted to intensive care with diabetic ketoacidosis are at risk of acute kidney injury. Recent UK guidelines recommends against restricted fluid provision due to a theoretical risk of kidney injury. To date no data has been published that documents this risk in an intensive care cohort.

**Aims:** To describe the natural history of acute kidney injury in patients admitted with diabetic ketoacidosis in whom a restrictive fluid regime was provided.

**Methods:** Retrospective analysis, within a UK Pediatric Intensive Care Unit. Between January 2011 and December 2020 219 patients were referred to the South Thames Retrieval Service with Diabetic Ketoacidosis, of whom 52 were admitted to Evelina PIC. 49 of these records were complete and used for analysis of acute kidney injury stage using Kidney Disease: Improving Global Outcomes criteria measured by serial creatinine. Clinical outcome at discharge from Pediatric Intensive Care was also recorded.

**Results:** 19 out of 49 (38%) patients had acute kidney injury (17 present on admission to pediatric intensive care). Three patients required renal replacement therapy though all of them went on to re-establish their baseline renal function. This compares favourably to published data documenting an acute kidney injury incidence of 43-64% in general paediatric and pediatric intensive care cohorts.

**Conclusion:** In the context of diabetic ketoacidosis, use of a restrictive fluid regime was not associated with higher levels of acute kidney injury than other studies and renal function recovery was observed in all patients followed up.

**Keywords:** Pediatric, Diabetic ketoacidosis, acute kidney injury, guideline

## Introduction

In children suffering with diabetic ketoacidosis (DKA), cerebral oedema is the complication associated with highest risk with a reported incidence of 0.3-0.9% and mortality of 20-25%[1]. In January 2020, new guidance was released by British Society of Paediatric Endocrinology (BSPED), and later supported by National Institute of Clinical Excellence (NICE) that liberalised the fluids advised to treat diabetic ketoacidosis (DKA)[2,3]. In younger patients who are most at risk of cerebral oedema, fluids received could be as much as doubled compared to the previous national guidance[4].

The rationale for changing the fluid regime was a landmark study, the pediatric emergency care applied research network (PECARN) DKA FLUID trial that demonstrated no significant difference in development of cerebral oedema by provision of rapid fluids[5]. Given this equipoise, a preference towards liberalised fluids grew from concerns that previous UK guidance had been too restrictive and could cause acute kidney injury (AKI)[6], a known risk factor for mortality in pediatric intensive care[7].

International and UK guidance are aligned in recommending liberalised fluid provision[8,9]. However, a more restricted approach remains recommended in suspected cerebral edema, raising questions around the risk of potential kidney injury in this subset of patients[8]. Although data published in hospitalised children managed with a liberal fluid regime for DKA reports an AKI incidence of between 43-64%[10,11] no evidence is available for those treated with restricted fluids.

We therefore seek to describe AKI observed in patients admitted to a UK PIC managed with a restrictive fluid regime (RFR) and report patient outcomes.

## Methods

Evelina London Children's Hospital (ELCH)PIC is co-located with South Thames Retrieval Service (STRS), which receives critical care referrals from 20 district general hospitals (DGHs), covering a population of 2.4 million children. STRS and ELCHPIC have employed the same RFR to manage DKA since 2008 which for a 20kg patient would prescribe approximately half of the fluid allowance compared to UK/international guidance[12]. All DGHs received education and were advised to follow the STRS DKA guidance.

The STRS electronic database was searched for all patients with a diagnosis of DKA admitted to ELCHPIC from January 1st 2011-December 31st 2020. Children in whom key data points (e.g. weight) were unavailable were excluded. No children were excluded due to pre-existing illness including prior kidney dysfunction.

Data collected included demographics, time to referral, clinical status, blood gas values, management received and serial laboratory values to assess AKI while the patient was admitted to ELCH.

Patient height was not recorded so the R package *childSDS* was used to generate height data matched for weight centile, age and sex. Blood pressure centiles were calculated using a similar method, though centiles for under 1 year olds were unavailable in the dataset and are therefore not included[13].

Creatinine clearance values were generated based on the Schwartz Equation (k x height/[Creatinine]), with k values adjusted for age and sex. Determination of AKI stage was performed by the Kidney Disease/Improving Global Outcomes (KDIGO) serum creatinine criteria, as urine output data were unavailable[14]. An expected "pre-illness" baseline creatinine value was computed to solve for a clearance of 120mL/min/1.74m$^2$ and used to establish the presence of AKI where serum creatinine was 1.5 (Stage 1), 2 (Stage 2) or 3 times (Stage 3) the calculated baseline. This method was used in two previous pediatric publications describing AKI in DKA[10,11]. Creatinine concentrations were measured using the enzymatic method so were unaffected by raised acetoacetate in DKA.

A fluid conformance index (FCI) was computed based on documented fluid (DF) provision by STRS and compared to calculated fluid requirement (FR) based on the STRS guideline where FCI = DF/FR. Fluid provision data prior to STRS arrival were unavailable, but it was documented if a DGH team did not follow the RFR advised by STRS.

Statistical analysis was performed in R, with chi-squared and Wilcoxen Rank used to compare categorical and continuous, non-parametric, data respectively.

This study was approved by ELCH Audit and Service Evaluation Team with no need for consent (project ID 12056, 2021). As an observational retrospective

study, neither patients nor public were involved in its design.

**Results**

219 children with DKA were discussed with the STRS retrieval service between January 2011 and December 2020, of whom 52 were admitted to ELCHPIC. Three were excluded due to missing data leaving 49 patients for analysis.

| 1a - Presenting Characteristics | |
|---|---|
| On arrival at DGH (n=49) | |
| Age (years) | 10.6 (10.2 - 13.8) |
| Male Sex | 18 (36%) |
| First Presentation of Diabetes | 41 (84%) |
| Systolic Blood Pressure Centile (%) | 96 (74 - 99) |
| GCS | 12 (10 – 14) |
| pH | 6.90 (6.80 - 6.98) |
| $pCO_2$ (kPa) | 2.5 (2.2 - 3.4) |
| Serum Bicarbonate (mmol/L) | 3.4 (2.6 - 5.3) |
| Serum Lactate (mmol/L) | 2.6 (1.6 - 3.5) |
| On Arrival at ELCH (n=49) | |
| Serum Creatinine (mmol/L) | 56 (39 – 84) |
| Creatinine Clearance (mL/min/1.73m$^2$) | 104 (76.8 - 135) |
| Corrected Serum Sodium (mmol/L) | 146 (141 - 152) |
| Serum Chloride (mmol/L) | 121 (113 - 30) |
| PIM2 Mortality (%) | 4 (2.6 - 6) |

| 1b - Patient treatment & Outcomes | |
|---|---|
| Pre STRS Arrival (n=49) | |
| Time at DGH until referral to STRS (mins) | 130 (58 - 252) |
| Time at DGH until STRS arrival (mins) | 504 (244-748) |
| Fluid Bolus (mL/kg) | 20 (10 - 20) |
| Osmotherapy | 39 (80%) |
| Ventilation | 10 (20%) |
| Inotropes | 5 (10%) |
| AKI prevalence | 19 (39%) |
| Fluid regime conformance index by STRS | 1 (0.85 - 1) |
| Post STRS Arrival (n=49) | |
| Additional Fluid Bolus | 7 (14%) |
| PICU stay (days) | 2.9 (1.5 - 4.6) |
| RRT | 3 (6%) |
| Mortality | 0 (0%) |

Therapies received, compliance with RFR and outcomes. Fluid conformance index ([Protocol Fluid Replacement / Administered Fluid]). GCS – Glasgow Coma Scale. PIM – Paediatric Index of Mortality. DGH – District General Hospital. RRT – Renal Replacement Therapy. Values represent number of patients per category with percentage in brackets or median values with interquartile range

**Table 1a –** Presenting Characteristics; Table 1b – Patient treatment & Outcomes

Table 1a demonstrates the presenting characteristics of the STRS cohort with a median pH of 6.9 and a decreased Glasgow coma scale (GCS) of less than 14 in the majority (30/49, 61%). A high proportion (80%, table 1b) of patients required osmotherapy, in-keeping with the GCS scores. All but two cases received a fluid bolus prior to referral with the maximum provided bolus being 40mL/kg. The fluid conformance index had an IQR of 0.85-1 with low variance demonstrating that patients received the correct rate of fluid as prescribed by STRS guidance. Median referral time from admission was 130 minutes with only one DGH team not adopting the STRS regime at time of referral.

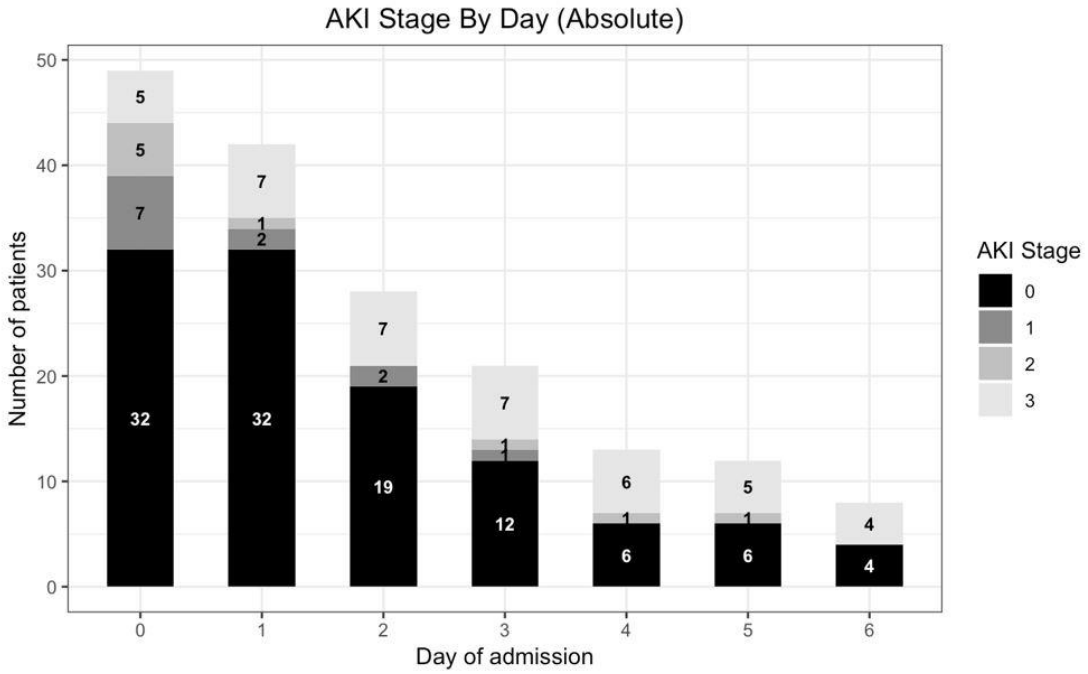


**Figure 1 -** AKI stage of patients by day during admission (absolute numbers).

AKI was seen in 19 patients (39% of patients) with 89% (17/19) of these cases detected at presentation and 11% (2/19) developing AKI after PIC admission (figure 1). The risk of developing AKI was not statistically higher in those with a pre-existing diagnosis of diabetes (50% vs 37%, OR 1.73 (0.3 – 10), p 0.8). Three patients required renal replacement therapy (RRT) in the form of haemofiltration. These three patients all had additional risk factors for developing severe AKI: one suffered a prolonged cardiac arrest due to hypokalaemia, another had septic shock with high vasopressor requirement, and the third had refractory shock on presentation with an unrecordably low blood pressure and GCS of 3.

Eight patients had ongoing AKI at discharge from PIC, of whom six were in stage 3, including the three treated with RRT. Where follow-up data were available (two patients were repatriated and records could not be interrogated) all of these patients returned to their baseline predicted creatinine levels.

**Discussion**

This is the first report focusing on patients with DKA admitted to PIC, monitoring serial creatinine, and demonstrates resolution of AKI in all patients with follow up data available. AKI was observed in the minority of this cohort of PIC children admitted with DKA and treated with RFR. The majority of patients who suffered AKI developed it prior to admission to PIC with only two patients developing AKI on RFR after admission to ICU. There were no deaths. The proportion treated with CVVH was similar to other UK PICs during this epoch (4% vs 6%)[15].

The development of AKI after presentation in two of this group could be attributed to RFR but could also be confounded by the severity of illness with other risk factors for AKI present. Moreover, the incidence of AKI in this cohort was lower than that seen in two previous studies looking at AKI in DKA where more liberal fluid regimes were utilised[10,11]. In all three studies, the majority of AKI was detected at presentation. These findings suggest that AKI is related to dehydration, fluid shifts and other factors related to DKA prior to presentation rather than how much fluid is prescribed in the ongoing management of DKA.

The results of the PECARN FLUID trial precipitated a shift in guidance towards faster fluid administration in children suffering from DKA. However, it did not show a benefit to liberalised

fluids with regards to resolution of pH or AKI and excluded the sickest subset of patients, including those with a reduced GCS. Consequently, only 1% of patients studied had clinical concerns of brain injury and as such it is not known how best to manage this severest group of DKA patients; for example, in patients who develop a reduced GCS, ISPAD recommend avoiding excessive fluids while UK guidance restricts hourly fluid administration by half if cerebral oedema develops[8].

The majority of the cohort in this paper had features of cerebral edema, with a median pH far lower than those in other studies and is representative of a sicker subset of patients[5]. This makes the results demonstrated in our cohort most relevant to clinicians facing the challenge of managing intensive care patients with, or at high risk of, cerebral oedema, where restricting fluid provision may be of benefit. The comparable rates of AKI compared to published data, along with the resolution of kidney injury within this critically ill cohort treated with a RFR are reassuring that a choice to restrict fluid provision in the subset of DKA patients presenting to PIC or with suspected cerebral edema appears to be safe.

**Limitations**

The proportion of patients with AKI was computed from interpolated height data based on matched weight centiles so could be under- or over-estimated. Up to eleven weights may have been estimated by DGHs using a resuscitation formula which can underestimate weight in approximately 60% of healthy children[16]. If children were taller than computed because diabetes-related weight loss had lowered their weight centile compared to height (i.e. BMI) then their baseline GFR would be underestimated, leading to AKI being over-reported in this case series compared to studies where height was recorded. Although less likely in this group, with predominantly new-onset diabetes, if the BMI were conversely higher than the true number with AKI would be greater (further analysis available from authors on request)[17]. As with other studies in this area, creatinine was used as a proxy for AKI and while a reasonable functional marker of renal impairment it is becoming clear that a normal creatinine may mask renal injury.

Fluid boluses received by each patient were documented in case notes but the initial continuous infusion rate prescribed by the DGH was not; some patients may have initially received fluids at a rate greater than the RFR advised by STRS. As the median time from presentation to referral was just over two hours then the extra fluid received is likely to be trivial.

**Conclusion**

The majority of AKI noted in DKA patients admitted to a PIC utilising a restrictive fluid regime, was present at admission and similar to published results in the literature. The risk of developing AKI was small and on follow up, all patients with severe AKI recovered to their predicted baseline creatinine.

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**Competing Interests Statement**

The authors have no competing interests.

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