Children's Mercy KANSAS CITY
Evidence Based Practice

Critically Appraised Topic (CAT): DKA Intravenous Fluids

Specific Care Question

For pediatric patients experiencing diabetic ketoacidosis (DKA) is Lactated Ringer's (LR) versus Normal Saline (NS) superior in preventing hyperchloremic metabolic acidosis or cerebral edema?

Recommendations from the DKA Clinical Practice Guideline (CPG) Committe Based on Current Literature (Best Evidence) Only

No recommendation can be made to change the standard of care from use of NS to LR, based on expert opinion and review of current literature by the subject matter experts and the Department of EBP. The overall certainty in the evidence is very low[a]. No studies from the literature search were identified comparing LR to NS in preventing hyperchloremic metabolic acidosis. The literature search identified two cohort studies (Bergmann et al., 2021; Hsia et al., 2015) addressing prevention of cerebral edema. The first study (Bergmann et al., 2021; Hsia et al., 2015) found LR superior to NS in preventing cerebral edema for patients with DKA. The second study (Hsia et al., 2015) found LR to be equivalent to ½ NS in prevention of cerebral edema for patients with DKA.

When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.

Literature Summary

Background

In pediatric patients with established type 1 diabetes, diabetic ketoacidosis (DKA) and its complications are the most common cause of hospitalization, morbidity and mortality, with an overall incidence of 8% in this population. It is estimated that nearly one third of patients present with DKA at time of diagnosis of type 1 diabetes (Levy-Shraga et al., 2017).

Patients with DKA are at risk for adverse outcomes, including hyperchloremic metabolic acidosis and cerebral edema. Hyperchloremic metabolic acidosis may occur from increased chloride load from rehydration with NS and may mask detection of DKA resolution (Badawi et al., 2021). Cerebral edema is one of the most serious adverse outcomes resulting from DKA, with mortality ranges of 20%-90% and neurologic impairment in 25% of survivors (Long & Koyfman, 2017). Fluid management in DKA has been identified as playing a possible role in causation of cerebral edema and hyperchloremic metabolic acidosis (Jayashree et al., 2019). This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on August 9, 2022. R. McDonough, DO and T.Musick, DO reviewed the 69 titles and/or abstracts found in the search and identified[b] 16 single studies believed to answer the question. After an in-depth review of the single studies[b], no studies answered the question for the outcome of hyperchloremic metabolic acidosis and two studies (Bergmann et al., 2021; Hsia et al., 2015) answered the question for the outcome of cerebral edema.

Questions Answered. One cohort study (Bergmann et al., 2021) (*N* = 49,737) looked at patients receiving LR (*n* = 1,762) compared to patients receiving NS (*n* = 43,841) and measured the outcome of cerebral edema. Cerebral edema was defined in this study by ICD-9 coding or coding for parental hyperosmolar solutions (3% saline or mannitol).

A second cohort study (Hsia et al., 2015) (N = 1,868) looked at patients receiving ½ NS (*n* = 604) compared to patients receiving LR (*n* = 1,264) and measured suspected cerebral edema. Suspected cerebral edema was defined in this study as any indication of altered mental status, Glasgow Coma Scale (GCS) of ≤ 8, CT scan of the head, treatment with mannitol or 3% saline, or death.

Summary by Outcome

Cerebral Edema (Actual or Suspected)

For the outcome of cerebral edema, the *OR* indicated that for patients with DKA the intervention of LR was favorable compared to the comparator of NS: 14/1762 LR versus 1578/43841 NS, *OR* = 4.66, 95% CI [2.75, 7.91], *p*-value < .001.

> **Certainty Of The Evidence[a] For Prevention of Cerebral Edema.** The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness nor imprecision however was assessed to have serious risk of bias. The risk of bias was serious due to the potential selection bias of the retrospective cohort study design. As only one study (Hsia et al., 2015) was identified to answer this question, consistency could not be assessed.

Suspected Cerebral Edema

For the outcome of suspected cerebral edema, the *OR* indicated that for patients with DKA the intervention of LR was not different to the comparator of ½ NS: 105/1264 LR versus 58/604 ½ NS, *OR* = 1.17, 95% CI [0.84, 1.64], *p*-value = .35.

> **Certainty Of The Evidence[a] For Prevention of Suspected Cerebral Edema.** The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness risk. However it was assessed to have serious risk of bias and serious imprecision. The risk of bias was serious due to the potential selection bias of the retrospective cohort study design. Imprecision was serious due to the low number of events. As only one study was identified to answer this question consistency could not be assessed.

Identification of Studies

Embase Search Strategy and Results (see Figure 1)

Initial search (included brain edema only)

1) 'diabetic ketoacidosis'/exp OR 'diabetic ketoacidosis':ab,ti,kw OR 'dka':ab,ti,kw
2) 'ringer lactate solution'/exp OR 'ringer lactate solution' OR 'lactated ringers'/exp OR 'lactated ringers' OR 'normal saline'/exp OR 'normal saline' OR 'acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride'/exp OR 'plasma-lyte' OR 'saline solution'/exp OR 'saline solution' OR 'sodium chloride'/exp OR 'sodium chloride' OR 'fluid therapy'/exp OR 'fluid therapy'
3) 'acute kidney failure' OR 'acute kidney injury' OR 'aki':ti,ab,kw OR 'brain edema' OR 'treatment outcome' OR 'outcome'/exp OR outcome OR 'outcome assessment'/exp OR 'hyperchloremia'/exp OR hyperchloremia OR 'hyperchloremic acidosis'/exp OR 'hyperchloremic acidosis' OR 'hyperchloremic metabolic acidosis'/exp OR 'hyperchloremic metabolic acidosis'
4) #1 AND #2 AND #3
5) #4 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim) AND ('article'/it OR 'article in press'/it OR 'review'/it)
6) #4 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim) AND ('article'/it OR 'article in press'/it OR 'review'/it) AND [2012-2022]/py
7) #6 NOT 'case report'/de

   Search dates: 2012-Current
   Records identified through database searching *n* = 64
   Additional records identified through other sources *n* = 0

Second search (expanded to include cerebral edema)

1) 'diabetic ketoacidosis'/exp OR 'diabetic ketoacidosis':ab,ti,kw OR 'dka':ab,ti,kw

2) 'ringer lactate solution'/exp OR 'ringer lactate solution' OR 'lactated ringers'/exp OR 'lactated ringers' OR 'normal saline'/exp OR 'normal saline' OR 'acetic acid plus gluconate sodium plus magnesium chloride plus potassium chloride plus sodium chloride'/exp OR 'plasma-lyte' OR 'saline solution'/exp OR 'saline solution' OR 'sodium chloride'/exp OR 'sodium chloride' OR 'fluid therapy'/exp OR 'fluid therapy'
3) 'cerebral edema' OR 'brain edema' OR 'acute kidney failure' OR 'acute kidney injury' OR 'aki':ti,ab,kw OR 'treatment outcome' OR 'outcome'/exp OR outcome OR 'outcome assessment'/exp OR 'hyperchloremia'/exp OR hyperchloremia OR 'hyperchloremic acidosis'/exp OR 'hyperchloremic acidosis' OR 'hyperchloremic metabolic acidosis'/exp OR 'hyperchloremic metabolic acidosis'
4) #1 AND #2 AND #3
5) #4 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [preschool]/lim OR [school]/li AND ('article'/it OR 'article in press'/it OR 'review'/it) NOT 'case report'/de AND [2012-2022]/py
   Search dates: 2012-Current
   Records identified through database searching *n* = 69
   Additional records identified through other sources *n* = 0

Studies Included in this Review

Citation	Study Type
Bergmann et al. (2021)	Retrospective Cohort
Hsia et al. (2015)	Retrospective Cohort

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Badawi et al. (2021)	Study of NS vs ½ NS
Basnet et al. (2014)	Study of NS vs ½ NS
Böttcher et al. (2020)	Study of other isotonic electrolyte solution
Glaser et al. (2013)	Study design only
Glaser et al. (2021)	Study of NS of ½ NS
Hegab et al. (2022)	Study for outcome of acute kidney injury
Horvat et al. (2018)	DKA pathway for PICU admission
Kuppermann et al. (2018)	Study of NS vs ½ NS
Lehr et al. (2022)	Systematic review includes illnesses other than DKA
Lehtiranta et al. (2021)	Study of plasma-like isotonic fluid
Maurice et al. (2022)	Study of NS vs NS with 5% glucose
Rewers et al. (2021)	Study of NS vs ½ NS
Shafi and Kumar (2018)	Study of 3% saline
Williams et al. (2020)	Study of Plasmalyte

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings (SOF) table(s) for this analysis. Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[d]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

References to Appraisal and Synthesis Methods

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[d]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

Question Originator

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Findings from this review were presented to the DKA CPG committee on September 30, 2022.

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Acronyms Used in this Document

Acronym	Explanation
CAT	Critically Appraised Topic
DKA	Diabetic ketoacidosis
EBP	Evidence Based Practice
ICD-9	International Classification of Diseaes 9th Revision
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
LR	Lactated Ringer's
NS	Normal saline

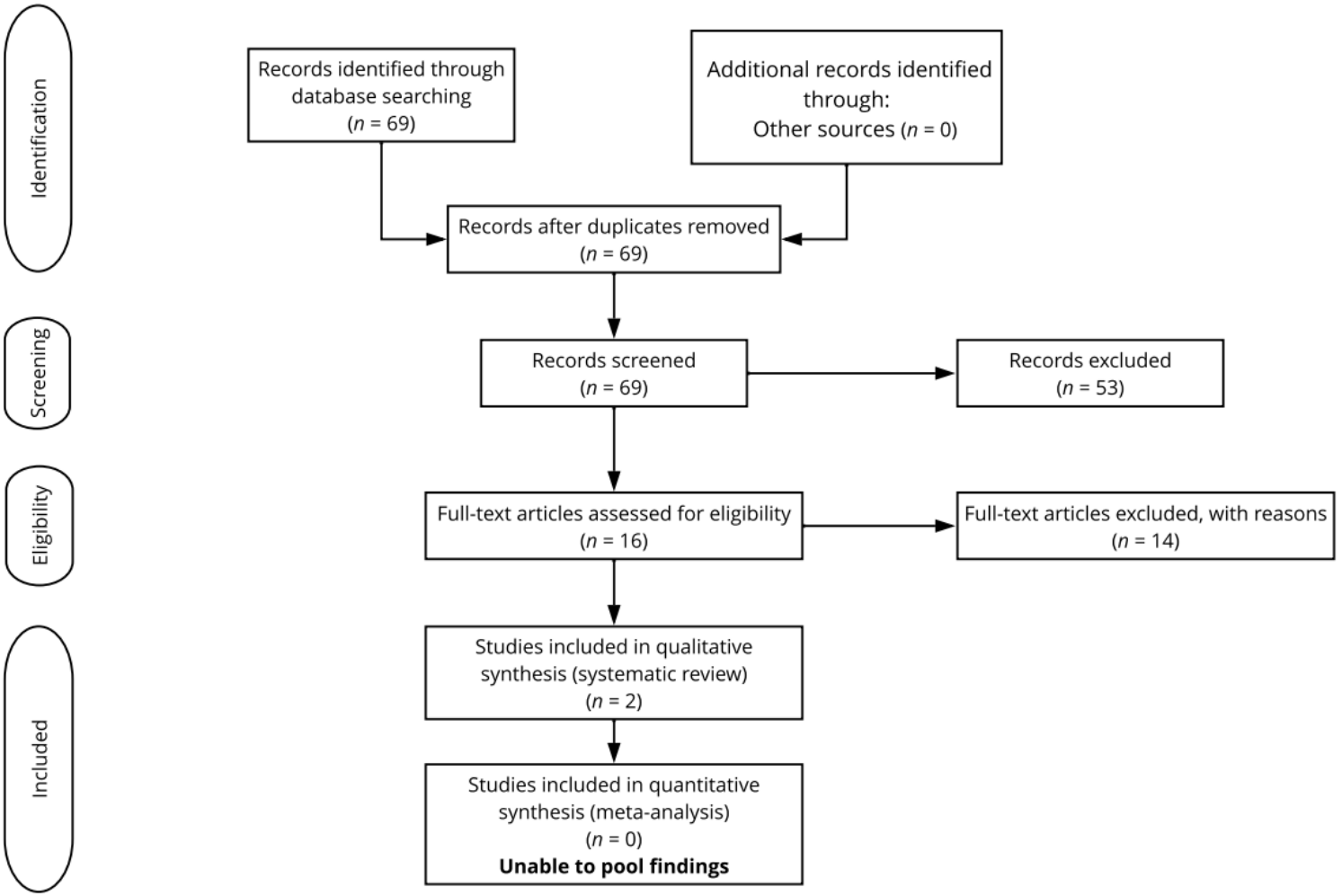
Statistical Acronyms Used in this Document

Statistical Acronym	Explanation

CI	Confidence Interval
I^2	Heterogeneity test
M or $\bar{X}$	Mean
Mdn	Median
n	Number of cases in a subsample
N	Total number in sample
OR	Odds Ratio
P or p	Probability of success in a binary trial
SD	Standard deviation
SR	Systematic Review

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[d]



Characteristics of Intervention Studies

Bergmann et al. (2021)

Methods	Cohort
Participants	**Participant**s: Children aged 0 to 17 years with DKA between January 1, 2005 and September 30, 2015 **Setting:** 48 US Children's Hospitals. Data from Pediatric Health Information System (PHIS) **Number enrolled into study:** *N* = 49,737 • **Group 1, Normal Saline Only (NS):** *n* = 43,841 • **Group 2, Lactated Ringers only (LR):** *n* = 1,762 • **Group 3, Both NS and LR:** *n* = 4,134 **Gender, males (as defined by researchers):** • **Group 1:** *n* = 20,035 (45.7%) • **Group 2:** *n* = 819 (46.5%) • **Group 3:** *n* = 1,881 (45.5%) **Race (as defined by researchers):** [table] **Age, median in years, (IQR)** • **Group 1:** 12 (9 - 15) • **Group 2:** 12 (9 - 15) • **Group 3:** 12 (9 - 15) **Inclusion Criteria:** • Discharged from emergency department, inpatient or observational care with a diagnosis of type 1 diabetes with ketoacidosis **Exclusion Criteria:** • Coding for a bolus of LR or NS • Nonparenteral administration routes • Infusion volumes of less than 50 ml • Saline infusions of concentrations other than 0.9% • Unavailable cost records **Covariates Identified:** • Patient characteristics • Clinical characteristics reflecting illness severity or influence outcome measures • Admission priority • Patient type • All Patient Refined Diagnosis-Related Group severity level • Emergency department • Intensive Care Unit • Infection presence • Mechanical ventilation • Total resuscitation fluid volume • Discharge year • Fixed effects by hospital
Interventions	• **Group 1:** NS Only • **Group 2:** LR Only • **Group 3:** NS and LR
Outcomes	**Primary outcome(s):** • Total intravenous (IV) fluid volume **Secondary outcome(s):** • Total Cost • Length of Stay

	Group 1	Group 2	Group 3
White, non-Hispanic	43.4%	32.6%	33.5%
Black, non-Hispanic	18.1%	15.9%	19.9%
Hispanic	12.1%	17.1%	17.2%
Other	4.6%	2.3%	4.6%
Unknown	21.7%	32.0%	24.9%

<table>
<tr><td></td><td>

- Cerebral edema*

Safety outcome(s):

- Not reported

*Outcomes of interest to the CMH CPG /CAT development team</td></tr>
<tr><td>Results</td><td>

Results:

- Total amount of IV fluid administered was significantly higher in patients treated with both LR and NS but not when comparing patients treated with LR only and NS only
- The rate of cerebral edema was significantly lower in the group that received LR only compared to the groups that received NS only or both LR and NS (*OR* = 4.66; 95% CI [2.75, 7.91], *p* = <.001).

Cerebral Edema

Intervention	**Cerebral Edema**
Normal saline (*n* = 43841)	1578 (3.6%)
Lactated Ringer's (*n* = 1762)	14 (0.8%)

Limitations:

- LR may have been used more often in patients with less risk of cerebral edema
- Unable to determine risk of cerebral edema based on blood urea nitrogen levels due to unavailability of discrete laboratory values in PHIS
- Charge limitations of administrative claim data due to variation in hospital administrative practices (e.g., charge bundling or contractual agreements)</td></tr>
</table>

Hsia et al. (2015)

Methods	Cohort
Participants	**Participant**s: Children presenting with DKA during two time periods (August 1998-July 2004 and August 2004-August 2010) **Setting:** Texas Children's Hospital (TCH) **Number enrolled into study:** *N* = 1,868 • **Group 1, ½ Normal Saline (NS):** *n* = 604 • **Group 2, Lactated Ringers (LR):** *n* = 1,264 **Gender, males (as defined by researchers):** • **Group 1:** 42% • **Group 2:** 45% **Race (as defined by researchers):** • Not reported **Age, mean in years, (SD)** • **Group 1:** 11.4 (6.7 - 16.1) • **Group 2:** 11.9 (6.6 - 16.3) **Inclusion Criteria:** • Admissions for DKA with suspected clinical cerebral edema and adverse outcomes identified by ICD-9 codes for DKA, poorly controlled diabetes, cerebral edema, death records when available, and hospitalizations lasting longer than 5 days. ○ DKA defined by standard criteria: glucose ≥ 200 and HCO_3 ≤ 15 or pH ≤ 7.3 • Considering signs and symptoms of cerebral edema may be subtle and/or not recognized, the criteria were broadened for 'suspected clinical cerebral edema'. Thus, any indication of altered mental status, GCS of ≤ 8, CT scan of the head, treatment with mannitol or 3% saline, or death were recorded as suspected clinical cerebral edema. **Exclusion Criteria:** • Erroneous coding • Hospitalizations for reasons other than DKA and/or not meeting the criteria for DKA • Inadequate laboratory data or clinical record information to determine the presence or absence of DKA or suspected clinical cerebral edema **Covariates Identified:** • New onset diabetes • Length of stay (days) • Transfer from an outside hospital • Suspected clinical cerebral edema
Interventions	• **Group 1:** Initial volume expansion with 10-20 mL/kg of NS; subsequent rehydration with 1/2 NS at a recommended rate of 3500 mL/m^2/d for the first 24 hours; potassium supplement 20mEq/L of K acetate and 20 mEq/L of K_2PO_4 • **Group 2:** Initial volume expansion with 10-20mL/kg of Lactated Ringer's; subsequent rehydration with Lactated Ringer's at a recommended rate of 2500 mL/m^2/d for the first 24 hours; potassium supplement 15 mEq/L of KCl and 30mEq/L of K_2PO_4

<table>
<tr><td>Outcomes</td><td>Primary outcome(s):
Adverse outcomes (neurological impairment or death)*
Secondary outcome(s):
Suspected clinical cerebral edema*
pH
Glucose
BUN
Total fluids in 24 hours
Safety outcome(s):
Not reported
*Outcomes of interest to the CMH CPG /CAT development team</td></tr>
<tr><td>Results</td><td>Results:
Decreasing the intended fluid rate during the initial 24 hours to 2500 mL/m^2/d and increasing the IV fluid sodium content did not significantly decrease the incidence of adverse outcomes in children with DKA.
There was nearly a threefold higher rate of suspected clinical cerebral edema in children who received their initial fluid resuscitation at an outside hospital compared with those initially seen at TCH.
An updated institutional protocol to use higher tonicity fluids for the management of DKA did not lead to a change in morbidity or mortality from cerebral edema.
There was not a significant difference in cases of suspected cerebral edema in the group that received ½ NS vs. the group that received LR (OR = 1.17; 95% CI [0.84, 1.64], p = .35).
Suspected Cerebral Edema<table><tr><th>Intervention</th><th>Suspected Cerebral Edema</th></tr><tr><td>½ Normal saline (n = 604)</td><td>58 (9.6%)</td></tr><tr><td>Lactated Ringer's (n = 1264)</td><td>105 (8.3%)</td></tr></table>Limitations:
Flaws in the complete recovery of medical records
Increased awareness and early intervention for clinical cerebral edema may have improved outcomes
Each admission for patients with more than one admission was included
Group 1: 418 unique patients (1.44 episodes of DKA/patient admitted for documented DKA in the 6-yr period)
Group 2: 942 unique patients (1.34 episodes of DKA/patient admitted for documented DKA in the 6-yr period)</td></tr>
</table>

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