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# Insulin Infusion Dosing in Pediatric Diabetic Ketoacidosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**OBJECTIVES:** In children with diabetic ketoacidosis (DKA), insulin infusions are the mainstay of treatment; however, optimal dosing remains unclear. Our objective was to compare the efficacy and safety of different insulin infusion doses for the treatment of pediatric DKA.

**DATA SOURCES:** We searched MEDLINE, EMBASE, PubMed, and Cochrane from inception to April 1, 2022.

**STUDY SELECTION:** We included randomized controlled trials (RCTs) of children with DKA comparing intravenous insulin infusion administered at 0.05 units/kg/hr (low dose) versus 0.1 units/kg/hr (standard dose).

**DATA EXTRACTION:** We extracted data independently and in duplicate and pooled using a random effects model. We assessed the overall certainty of evidence for each outcome using the Grading Recommendations Assessment, Development and Evaluation approach.

**DATA SYNTHESIS:** We included four RCTs ($n = 190$ participants). In children with DKA, low-dose compared with standard-dose insulin infusion probably has no effect on time to resolution of hyperglycemia (mean difference [MD], 0.22 hr fewer; 95% CI, 1.19 hr fewer to 0.75 hr more; moderate certainty), or time to resolution of acidosis (MD, 0.61 hr more; 95% CI, 1.81 hr fewer to 3.02 hr more; moderate certainty). Low-dose insulin infusion probably decreases the incidence of hypokalemia (relative risk [RR], 0.65; 95% CI, 0.47–0.89; moderate certainty) and hypoglycemia (RR, 0.37; 95% CI, 0.15–0.80; moderate certainty), but may have no effect on rate of change of blood glucose (MD, 0.42 mmol/L/hr slower; 95% CI, 1 mmol/L/hr slower to 0.18 mmol/L/hr faster; low certainty).

**CONCLUSIONS:** In children with DKA, the use of low-dose insulin infusion is probably as efficacious as standard-dose insulin, and probably reduces treatment-related adverse events. Imprecision limited the certainty in the outcomes of interest, and the generalizability of the results is limited by all studies being performed in a single country.

**KEYWORDS:** critical care; diabetes mellitus; diabetic ketoacidosis; drug dosing; insulin

Diabetic ketoacidosis (DKA) remains the most common cause of mortality for children with Type 1 diabetes mellitus (DM) in both developed and developing countries (1). Children with DKA are critically ill and at high risk of DKA-related complications, and may require admission to a PICU for treatment and monitoring (2). One of the most severe complications of DKA is cerebral edema, which occurs in approximately 1% of children and is associated with a 25% mortality rate (3, 4). Insulin therapy is one of the hallmarks of treatment for DKA, lowering glucose and suppressing lipolysis and ketogenesis, thus correcting ketoacidosis. However, insulin therapy can



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## KEY POINTS

**Question:** For children with diabetic ketoacidosis (DKA), what is the safest and most efficacious insulin infusion dose?

**Findings:** A systematic review and meta-analysis of randomized controlled trials comparing low-dose insulin at 0.05 units/kg/hr to standard dose at 0.1 units/kg/hr for children with DKA was performed. Four trials with 190 total patients were included. In children with DKA, the use of low-dose insulin infusion is probably as efficacious and probably reduces treatment-related adverse events.

**Meanings:** Low-dose insulin is probably as efficacious but safer than standard dose for children with DKA, with results limited by imprecision and generalizability to other settings.

cause hypokalemia through promotion of intracellular shift of potassium and hypoglycemia via inhibition of gluconeogenesis and increased peripheral glucose uptake. Furthermore, rapid changes in serum blood glucose during insulin administration may cause a rapid drop in serum osmolality, a possible mechanism exacerbating cerebral edema (5). These adverse effects can be lethal; as a result, children with DKA require close clinical and biochemical monitoring.

The administration of insulin therapy for the treatment of DKA has evolved over the last 50 years. Up until the late 1970s, insulin infusion rates of 1 unit/kg/hr were used for children with DKA (6). More recently, recommendations were for lower insulin infusion rates of 0.1 units/kg/hr (7), based on a single randomized trial reporting this lower dose to be safer with similar efficacy (8). Subsequent observational trials have demonstrated that even lower insulin infusion rates may reduce the incidence of hypoglycemia and hypokalemia in pediatric DKA, while still correcting the underlying acidosis (9, 10). Although a small randomized controlled trial (RCT) reported that 0.05 units/kg/hr was noninferior to 0.1 units/kg/hr (11), there remains controversy on the optimal dosing of IV insulin for children with DKA (2).

We conducted a systematic review and meta-analysis to compare the efficacy and safety of different doses of insulin infusions for children with DKA.

## METHODS AND MATERIALS

We registered the protocol for this systematic review on the International Prospective Register of Systematic Reviews (CRD42021277096) on September 9, 2021. Any deviations from the published protocol are highlighted with an accompanying explanation. The updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used to guide the design and reporting of our systematic review and meta-analysis (12) (see **Supplementary Appendix for PRISMA Checklist, Appendix 8**, http://links.lww.com/CCX/B140). This systematic review did not require Institutional Review Board (IRB) approval given all data reviewed are public and had received IRB approval previously.

### Systematic Search

We conducted a comprehensive search of Medical Literature Analysis and Retrieval System Online, PubMed, Excerpta Medica dataBASE, and unpublished sources including World Health Organization International Clinical Trials Registry Platform, Prospective Register of Systematic Reviews, Clinicaltrials.gov, and the Cochrane trial registry from inception until April 1, 2022. We also searched conference abstracts from the Endocrine Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine from 2019 onward. We searched for RCTs comparing different insulin infusion rates in pediatric DKA. We did not apply language restrictions. We developed the search strategy with the assistance of an expert medical librarian information specialist and included three search terms: "Pediatric," "Diabetic Ketoacidosis," and "Insulin Infusion" (see **Supplementary Appendix for Search Strategy, Appendixes 1–7**, http://links.lww.com/CCX/B140). We used the Medical Subject Headings database for identification of synonyms. We examined the reference list of full-text articles for additional relevant studies.

### Study Selection

We included RCTs that examined patients younger than 18 years old with DKA who were randomized to standard- compared with low-dose insulin infusion. We considered standard-dose insulin infusion to be doses of 0.1 units/kg/hr or higher, and low-dose insulin infusion

to be anything lower than 0.1 units/kg/hr, as 0.1 units/kg/hr of insulin has been the recommended initial dose of IV insulin for children with DKA (6). We excluded studies that examined doses of equal to or higher than 1 unit/kg/hr given this high dose of insulin is no longer considered a clinically appropriate comparator (8). We included studies that reported on any of the following outcomes: time to resolution of hyperglycemia, time to resolution of acidosis, incidence of hypokalemia, incidence of hypoglycemia, incidence of cerebral edema, hospital length of stay (LOS), and PICU LOS. For outcomes reported at multiple timepoints, we used the longest reported follow-up timepoint. After the analysis had been completed, we shared a draft article with content experts in pediatric critical care to review for applicability to their practice in the PICU. They suggested the addition of an additional outcome, rate of change of blood glucose, which we subsequently added to the analysis and discussion.

After implementation of the search strategy, two reviewers screened the title and abstract of all potentially relevant citations independently and in duplicate. Citations deemed potentially relevant by either screener were advanced to second-stage full-text review. Full texts were subsequently reviewed for eligibility independently and in duplicate by two reviewers, with disagreements resolved by consensus, and third-party adjudication if required. We captured reasons for exclusion at the full-text screening stage.

### Data Extraction and Quality Assessment

Two reviewers extracted data independently and in duplicate using prepiloted data abstraction form. We extracted the following information from included studies: study title, first author, demographic data, details of the interventions, outcome data, and risk of bias (RoB) for each study. We contacted study authors for clarification when the population characteristics, method of follow-up, or outcome data were unclear or not reported. We assessed RoB, independently and in duplicate using a modified Cochrane RoB 2 tool for which each domain is rated as "low," "probably low," "high," or "probably high" (13). We examined the following RoB domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of outcome, and bias in selection of reported result. We rated the overall RoB for an individual study close to the highest risk attributed to any domain.

We assessed the overall certainty of evidence for each outcome using the Grading Recommendations Assessment, Development and Evaluation (GRADE) approach (14). We resolved disagreements for RoB and GRADE assessment by consensus and with a third author if required. We used the Guideline Development Tool (www.gradepro.org) to formulate the Summary of Findings table. In accordance with updated GRADE guidance, high certainty effects were characterized as the outcome effect, moderate certainty using "probably," low certainty using "may," and very low certainty as "uncertain" (15).

### Statistical Analysis

We used DerSimonian and Laird random-effects models (16) to conduct the meta-analysis with the RevMan 5.4 (Cochrane Collaboration, Oxford, United Kingdom) software. We generated study weights using the inverse variance method. We present results as relative risks (RRs) and risk difference (RD) for dichotomous outcomes and as mean differences (MDs) for continuous outcomes, all with 95% CIs. We calculated absolute effects using the pooled baseline prevalence from the control arm of included trials. We assessed heterogeneity between trials using visual inspection of the forest plots, the chi-square test for homogeneity (where $p < 0.1$ indicates important heterogeneity), and the $I^2$ statistic (for which a value of 50% or greater was considered reflective of potentially important heterogeneity) (17). Although planned, we did not construct funnel plots to assess for publication bias as these are inaccurate when less than 10 trials are included in the analysis (18). We planned to perform predefined subgroup analyses comparing studies of: 1) malnourished compared with normally nourished children, 2) high RoB studies compared with low RoB studies, 3) first presentation DM compared with known DM, 4) mild-moderate DKA compared with severe DKA, 5) children less than 5 years compared with 5 years old and older, and 6) standard insulin infusion at 0.1 units/kg/hr IV compared with greater than 0.1 units/kg/hr IV. For subgroup findings that were statistically significant, we planned to use the Credibility of Effect Modification Analyses tool to judge subgroup credibility (19).

## RESULTS

Of the 2,198 citations identified in the search (**Fig. 1**), we excluded 347 duplicates and further 1,788 citations after title and abstract screening. We assessed 62 full-text studies and included three RCTs fulfilling study selection criteria, which enrolled a total of 160 patients

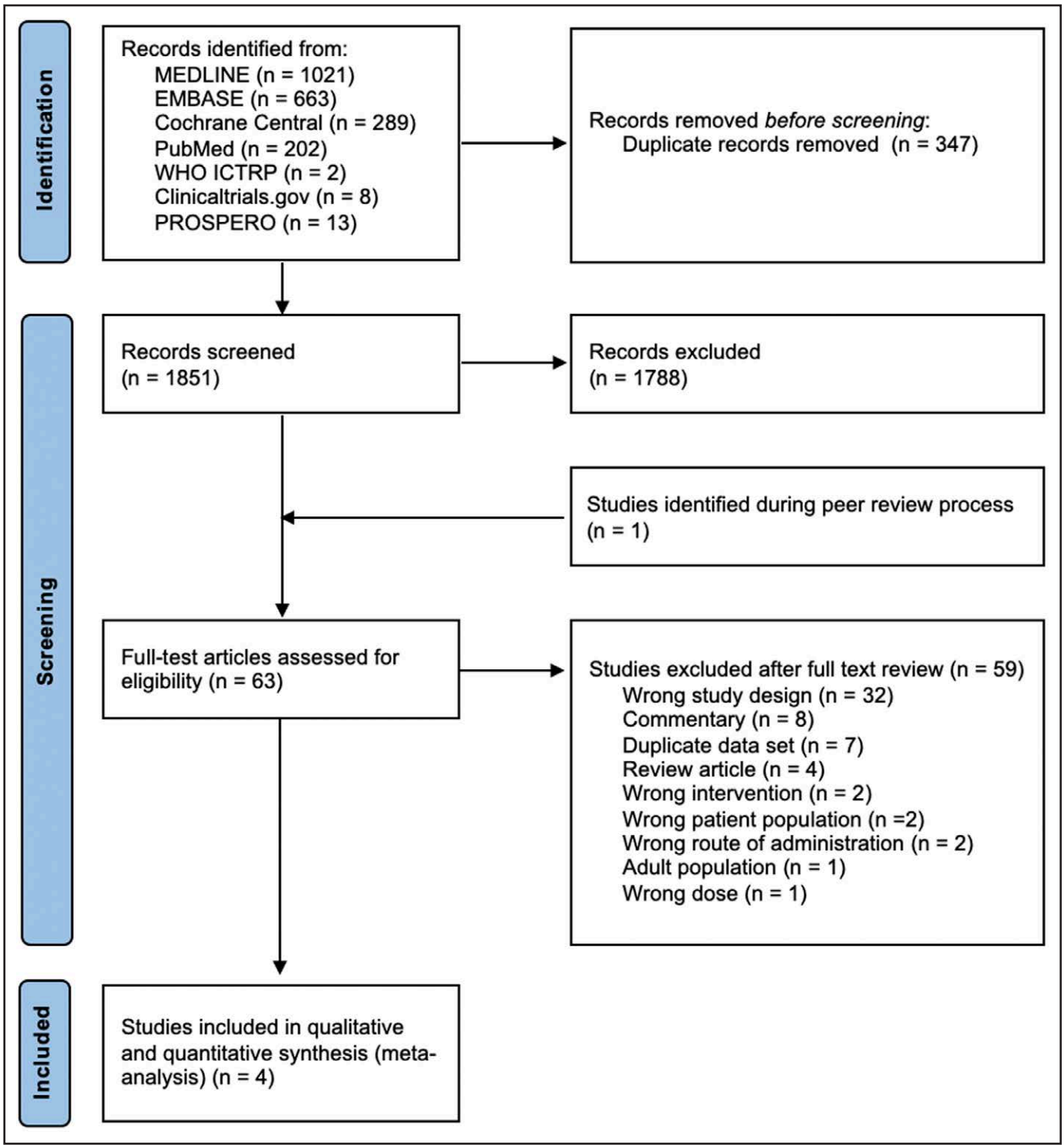


**Figure 1.** Study flowchart. PROSPERO = International Prospective Register of Systematic Reviews, WHO ICTRP = World Health Organization International Clinical Trials Registry Platform.

(11, 20, 21). During the peer-review process, we identified one very recently published RCT, which was also included in our study (22). Baseline characteristics of the included trials are summarized in **eTable 1** (http://links.lww.com/CCX/B140).

## Description of Included Studies

All four included studies were single-center RCTs from emergency departments and PICUs in India. The mean age of participants ranged from 6 to 10 years old; three

**TABLE 1.**
**Risk of Bias Determination of Included Studies**

| Studies | Bias Arising From the Randomization Process | Bias Due to Deviations From Intended Interventions | Bias Due to Missing Outcome Data | Bias in Measurement of the Outcome | Bias in Selection of the Reported Result | Overall ROB |
|---|---|---|---|---|---|---|
| Nallasamy et al (11) | Low | Low | Low | Low | Probably low | Probably low |
| Kaur et al (20) | Low | Low | Low | Low | Probably low | Probably low |
| Rameshkumar et al (21) | Low | Low | Low | Low | Low | Low |
| Saikia et al (22) | Low | Low | Low | Low | Probably low | Probably low |

trials enrolled patients aged 12 years or younger ($n = 140$) (11, 21, 22), whereas the other trial included patients 14 years or younger ($n = 50$) (20). All four trials included patients using similar biochemical criteria for DKA, and excluded patients who had received any insulin treatment prior to admission or were in septic shock. Three trials excluded patients with symptomatic cerebral edema and anuria for more than 6 hours (11, 20, 22). All trials compared 0.05 units/kg/hr of IV insulin (low dose) to 0.1 units/kg/hr of IV insulin (standard dose). The proportion of patients with their first presentation of DM ranged from 40% to 80%. Furthermore, of the included patients, 33–76% had severe DKA (pH < 7.10) on presentation. All four included trials were found to be at low or probably low RoB (**Table 1**). Although three of the trials included were open-label design, there were no deviations from intended interventions in any of the trials and were rated as probably low RoB (11, 20, 22). Further, one of the trials was registered retrospectively (11), and another trial was not registered (22), although this was factored into the RoB assessment, and both trials were ultimately rated as probably low RoB (see RoB in Table 1).

## Efficacy Outcomes

**eTable 2** (http://links.lww.com/CCX/B140) shows the summary of findings for all outcomes including the certainty of evidence. Pooled analysis found that in children with DKA, low-dose insulin infusion compared with standard-dose insulin infusion probably has no effect on time to resolution of hyperglycemia (MD, 0.22 hr fewer; 95% CI, 1.19 hr fewer to 0.75 hr more; moderate certainty) (**Fig. 2*A***; and eTable 2, http://links.lww.com/CCX/B140),

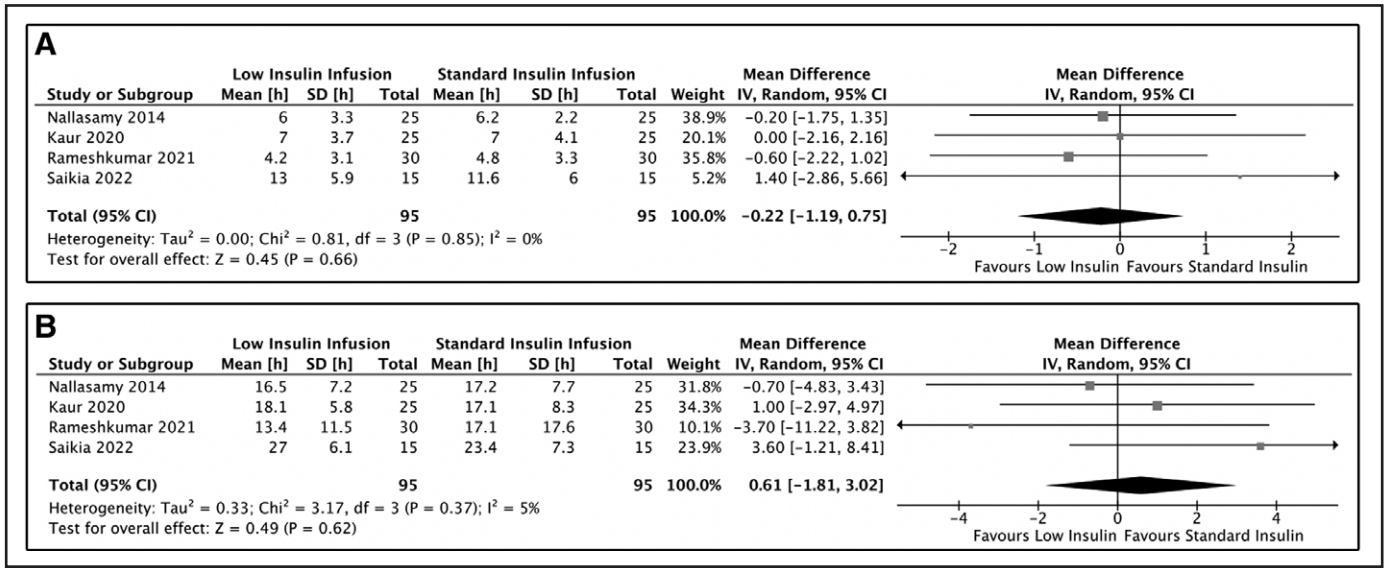


**Figure 2.** Efficacy outcomes comparing low-dose to standard-dose insulin infusions for children with diabetic ketoacidosis. Forest plot comparing low-dose insulin infusion with standard-dose insulin infusion in children with diabetic ketoacidosis for the outcomes of time to resolution hyperglycemia (**A**) and time to resolution acidosis (**B**).

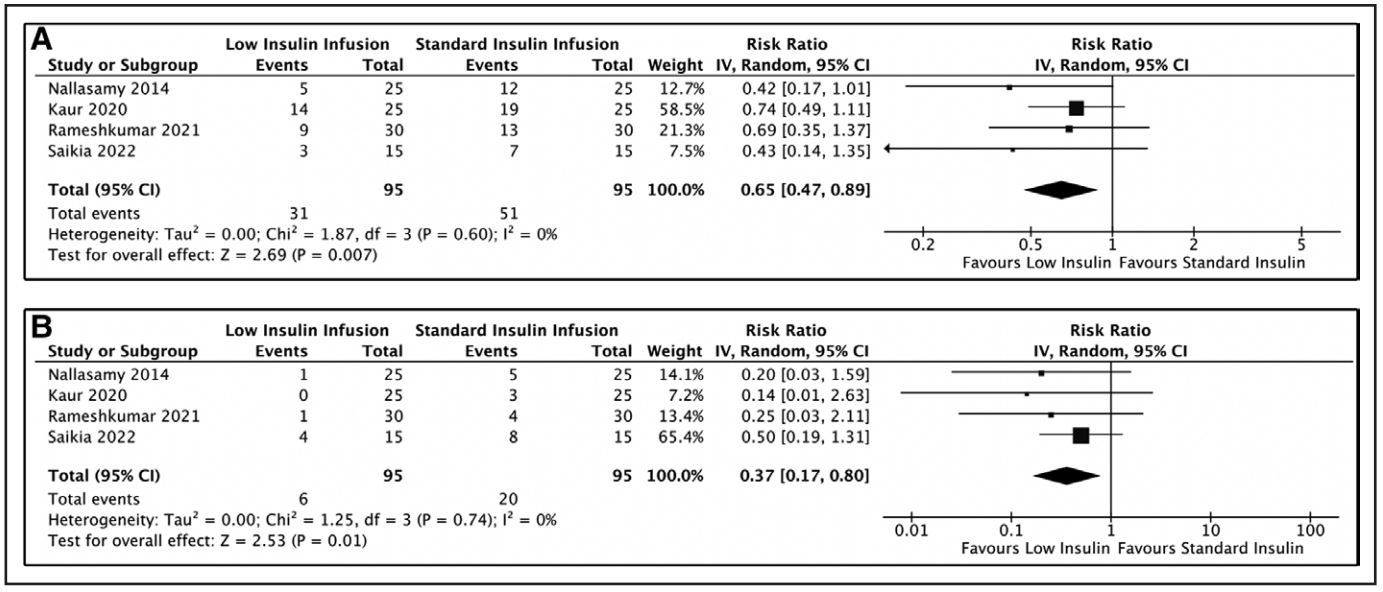


**Figure 3.** Safety outcomes comparing low-dose to standard-dose insulin infusions for children with diabetic ketoacidosis. Forest plot comparing low-dose insulin infusion with standard-dose insulin infusion in children with diabetic ketoacidosis for the outcomes of incidence of hypokalemia (**A**) and incidence of hypoglycemia (**B**).

or time to resolution of acidosis, defined as time until pH greater than 7.3 (MD, 0.61 hr more; 95% CI, 1.81 hr fewer to 3.02 hr more; moderate certainty) (**Fig. 2*B***; and eTable 2, http://links.lww.com/CCX/B140). Although planned, lack of data did not allow for analysis of hospital LOS and PICU LOS.

### Safety Outcomes

Low-dose insulin infusion, compared with standard dose, probably decreases the incidence of hypokalemia (RR, 0.65; 95% CI, 0.47–0.89; RD, 18.8% fewer; 95% CI, 5.9% fewer to 28.5% fewer; moderate certainty) (**Fig. 3*A***; and eTable 2, http://links.lww.com/CCX/B140) and probably decreases the incidence of hypoglycemia (RR, 0.37; 95% CI, 0.17–0.80; RD, 13.3% fewer; 95% CI, 4.2% fewer to 17.5% fewer; RD, 12.0% fewer, 95% CI, 3.6% fewer to 14.3% fewer; moderate certainty) (**Fig. 3*B***; and eTable 2, http://links.lww.com/CCX/B140). Low-dose insulin infusion may have no effect on mean rate of change of serum glucose to a level of 13.9 mmol/L or less (MD, 0.42 mmol/L/hr slower; 95% CI, 1 mmol/L/hr slower to 0.18 mmol/L/hr faster; low certainty) (**Supplementary Appendix, eFig. 1**, and eTable 2, http://links.lww.com/CCX/B140). Compared with standard-dose insulin infusion, low-dose insulin infusion has an uncertain effect on the development of cerebral edema (RR, 0.33; 95% CI, 0.01–0.78; RD, 0.8% fewer; 95% CI, 1.2% fewer to 8.5% more; very low certainty) (**Supplementary Appendix, eFig. 2**, and eTable 2, http://links.lww.com/CCX/B140).

### Subgroup and Sensitivity Analyses

Subgroup analysis comparing high RoB versus low RoB studies was not performed as all included studies were low or probably low RoB (Table 1). Although planned, lack of data did not allow for all other preplanned subgroup analyses.

## DISCUSSION

This systematic review and meta-analysis of RCTs demonstrates that, in children with DKA, the use of low-dose insulin infusion compared with standard-dose insulin is probably as efficacious as standard dose insulin, as it had no effect on time to resolution of hyperglycemia or acidosis. However, low-dose insulin is likely safer and probably decreases the risk of developing hypokalemia and hypoglycemia. The caveat being, however, that residual imprecision lowers the certainty of our conclusions.

One mechanism for no difference in time to resolution acidosis between low and standard doses of insulin infusion is that both doses are within the physiologic range of insulin action on hepatic and peripheral tissues. Circulating insulin levels required to suppress hepatic gluconeogenesis and lipolysis are

around 160 pmol/L, whereas promotion of peripheral glucose uptake occurs at insulin levels of around 400 pmol/L (23, 24). In the setting of pediatric DKA, there is limited evidence that the administration of IV insulin at 0.1 units/kg/hr leads to circulating insulin levels of around 280–560 pmol/L (8). There is no comparable data for circulating insulin levels when insulin is infused at 0.05 units/kg/hr for children with DKA. Although plasma insulin levels were not measured in the studies included in this meta-analysis, the findings of our analysis suggest that low-dose insulin is probably as effective as standard-dose insulin in achieving supraphysiologic levels of insulin sufficient to reverse gluconeogenesis and lipolysis, and promote peripheral glucose uptake.

The presumed differences in plasma insulin levels between low and standard insulin doses may explain our results of low-dose insulin, reducing the incidence of treatment-related adverse events. The higher dose of insulin may cause an increase in peripheral glucose uptake and an increased incidence of hypoglycemia (23). The decreased incidence of hypoglycemia with low-dose insulin is safer and, although low-dose insulin will continue to require closely monitoring, may reduce the incidence of severe symptomatic presentations of hypoglycemia that may occur while treating children with DKA, such as seizures and altered mental status. Further, exogenous insulin promotes hypokalemia through promotion of potassium influx into cells through increased activity of the $Na^+$-$K^+$-ATPase pump (25), and higher insulin doses in DKA may increase risk of hypokalemia. Although the lower frequency of hypokalemia was expected with the lower infusion rates, the reduced need for large volume intravenous potassium replacement may make the low-dose insulin infusion a more appealing and potentially safer choice compared with standard dose. That being said, potassium replacement will be a mainstay of therapy for any patient with DKA, regardless of insulin infusion dose, given the total body potassium deficit associated with this condition. The need for potassium replacement will be influenced by insulin dose but also other factors (25).

Cerebral edema is a rare but deadly complication for children with DKA (26). Although other interventions may also contribute, the rapid lowering of effective serum osmolality has been associated with cerebral edema (27, 28), implicating osmotic mechanisms in the development of cerebral edema. Sudden lowering of serum glucose levels with insulin therapy will decrease serum osmolality (28). Unfortunately, there was only one child with cerebral edema across all four trials included in this review, in part due to the exclusion of children with symptomatic cerebral edema in three of the trials (11, 20, 22), and so, we are unable to make any conclusions in regard to the effect of insulin dose on cerebral edema in children with DKA.

An important limitation of the studies included in this review was all performed in one country, India, which is a developing country where children with DKA are more likely to be malnourished than in developed countries (29). Between 23% and 32% of the patients included in the review were malnourished, and nutritional status is an independent risk factor for treatment related adverse events like hypokalemia and hypoglycemia (29, 30). Furthermore, mortality rates for children with DKA are around 10-fold higher in developing countries compared with developed countries (1), which may be related to delays in diagnosis and insufficient healthcare resources. The lack of randomized data from more developed countries in this systematic review limits the generalizability of the results to a setting with decreased incidence of malnourished patients. However, available observational data comparing low-dose with standard-dose insulin infusions in children with DKA from both Australian and British hospitals are consistent with the results of this systematic review, demonstrating similar efficacy between low and standard insulin infusions (9, 10).

Another limitation of this review is that all of the included studies excluded adolescents, with three trials excluding patients older than 12 years, and one trial excluding patients older than 14 years. As such, it is uncertain whether low-dose insulin infusions are sufficient for adolescents with DKA, who may have increased insulin resistance due to a number of factors. This ongoing uncertainty also applies to other populations with conditions that cause insulin resistance, for example, infection, inflammatory states, and obesity. A third limitation of our systematic review is the serious imprecision, with only 190 participants total in the included trials, leading to very low-to-moderate certainty of evidence.

Given similar efficacy and a more favorable safety profile, low-dose insulin infusion may be a better

alternative than standard-dose insulin, albeit this conclusion is limited by imprecision and moderate certainty evidence. There remains a need for further studies to improve precision and identify the insulin dose that is optimal in terms of safety and effectiveness. Further studies may also examine specific subgroups of children who may benefit from lower and higher doses of insulin. Larger scale studies in both developed and developing countries including children with better baseline nutrition are required to increase the certainty in effect and generalizability of using a low-dose insulin infusion strategy in children with DKA. In the meantime, this systematic review and meta-analysis may inform future guidelines, which will consider the balance of benefits, harms, values, preferences, and costs in developing clinical recommendations.

## CONCLUSIONS

In children with DKA, the use of low-dose insulin infusion is probably as effective as standard-dose insulin. However, low-dose insulin probably decreases the risk of developing hypokalemia and hypoglycemia and, thus, may confer benefits in decreasing complications of therapy. The results are limited by imprecision due to relatively few patients and limited by generalizability as all studies were performed in a single country.

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## CONTRIBUTIONS

Drs. Forestell, Sharif, and Rochwerg designed the study. Drs. Forestell, Eltorki, Samaan, and Choong reviewed the protocol. Drs. Forestell, Battaglia, and Sharif collected the data. Drs. Forestell, Sharif, and Rochwerg analyzed and interpreted the data. Drs. Forestell, Battaglia, and Sharif, Eltorki, Samaan, and Rochwerg contributed to the writing of the article.

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