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Saline Compared to Balanced Crystalloid in Patients With Diabetic Ketoacidosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Naif Ali Alghamdi, MD[1,2]
Paityn Major, BScH[1]
Dipayan Chaudhuri, MD[1]
Janice Tsui, PharmD, BCPS, MSc[3]
Brent Brown, MD[4]
Wesley H. Self, MD, MPH[5,6]
Matthew W. Semler, MD, MSc[7]
Mahesh Ramanan, MD[8–10]
Bram Rochwerg, MD, MSc[1,11]

OBJECTIVES: This systematic review and meta-analysis compared the use of saline to balanced crystalloid for fluid resuscitation in patients with diabetic ketoacidosis (DKA).

DATA SOURCES: We searched databases including Medline, Embase, and the Cochrane registry.

STUDY SELECTION: We included randomized controlled trials (RCTs) that compared saline to balanced crystalloid in patients with DKA.

DATA EXTRACTION: We pooled estimates of effect using relative risk for dichotomous outcomes and mean differences (MDs) for continuous outcomes, both with 95% CIs. We assessed risk of bias for included RCTs using the modified Cochrane tool and certainty of evidence using Grading of Recommendations, Assessment, Development, and Evaluation methodology.

DATA SYNTHESIS: We included eight RCTs ($n = 482$ patients). Both time to DKA resolution (MD, 3.51 hr longer; 95% CI, 0.90 longer to 6.12 longer; moderate certainty) and length of hospital stay (MD, 0.89 d longer in saline group; 95% CI, 0.34 longer to 1.43 d longer; moderate certainty) are probably longer in the saline group compared with the balanced crystalloid group, although for the latter, the absolute difference (under 1 d) is small. Post-resuscitation serum chloride level may be higher (MD, 1.62 mmol/L higher; 95% CI, 0.40 lower to 3.64 higher; low certainty), and post-resuscitation serum bicarbonate is probably lower (MD, 1.50 mmol/L; 95% CI, 2.33 lower to 0.67 lower; moderate certainty) in those receiving saline.

CONCLUSIONS: In patients with DKA, the use of saline may be associated with longer time to DKA resolution, higher post-resuscitation serum chloride levels, lower post-resuscitation serum bicarbonate levels, and longer hospital stay compared with balanced crystalloids. Pending further data, low to moderate certainty data support using balanced crystalloid over saline for fluid resuscitation in patients with DKA.

KEY WORDS: diabetic ketoacidosis; fluid resuscitation; saline and balanced crystalloids

Diabetic ketoacidosis (DKA) is a metabolic decompensation that occurs due to absolute or relative insulin deficiency (1). Annually, approximately 6.3% of patients with type 1 diabetes experience at least one episode of DKA (2). In addition to insulin, IV fluids are the cornerstone of DKA management as they mitigate fluid loss and improve tissue perfusion (3). Current evidence favors the use of crystalloids rather than colloids for fluid resuscitation in DKA (4, 5), although recommendations regarding type of crystalloid remain variable (4, 6, 7).

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Although widely used for fluid resuscitation, saline has been associated with hyperchloremic metabolic acidosis, reduced smooth muscle contractility, and reduced renal perfusion in preclinical studies (8–11). Balanced crystalloids, on the other hand, such as Ringer's lactate (12), have a composition closer to that of plasma (12). A network meta-analysis examining patients with sepsis and septic shock found low certainty evidence that balanced crystalloids may reduce mortality and need for renal replacement therapy compared with saline (13). Two recent cluster randomized controlled trials (RCTs) demonstrated a reduction in a composite outcome that included death, need for renal replacement therapy, or ongoing acute kidney injury at 30 days in patients receiving balanced crystalloids versus saline in the emergency department and ICU (SMART trial) (14, 15).

DKA is characterized by unique physiology that includes mild to severe metabolic acidosis and a severe fluid deficit. Thus, the comparative effects of balanced crystalloids and saline in DKA patients cannot be extrapolated from other populations. Evidence from observational studies suggests that hyperchloremia in DKA patients is associated with longer time to DKA resolution and longer hospital length of stay (16, 17). A retrospective review of 49,737 pediatric patients found that the use of Ringer's lactate was associated with lower total cost and a lower risk of cerebral edema in patients presenting with DKA (18).

The objective of this systematic review and meta-analysis of RCTs is to examine the role of saline versus balanced crystalloid in the resuscitation of patients with DKA.

MATERIALS AND METHODS

We developed a predefined protocol on July 19, 2019 (See dated protocol in **Supplemental File 1**, http://links.lww.com/CCX/A890).

Data Sources and Searches

We performed a comprehensive search of Medline, Embase, and the Cochrane trial registry from inception to March 19, 2021. A medical librarian helped in designing the search strategy.

We did not apply any language or quality restrictions. We included the following keyword search terms: DKA, fluid resuscitation, saline, and balanced crystalloids. **Figure 1** provides our study flow diagram, and **Supplemental File 2** (http://links.lww.com/CCX/A890) provides details about our search strategy.

Study Selection

Two reviewers (N.A., P.M.) screened all citations independently and in duplicate in two stages, first titles and abstracts, and then full texts to identify eligible studies. A citation identified as potentially eligible by either reviewer at the first stage was advanced to the second stage. In the second stage, disagreements were resolved by discussion or third person (B.R.) adjudication if necessary, and we captured reasons for exclusion.

We included all RCTs that compared saline and balanced crystalloid for fluid resuscitation among patients with DKA. We included studies of both children and adults and those done in hospitalized or critically ill patients. We excluded case reports, case series, and observational studies.

We included the following outcomes: mortality (at the longest time point reported), DKA resolution (as defined by study authors of the primary studies), time to DKA resolution (in hr), post-resuscitation serum chloride and bicarbonate levels, length of stay in ICU or step-down units, and any adverse events. For post-resuscitation electrolyte levels, if there were multiple time points reported, we used the longest follow reported. **Supplemental Table 1** (http://links.lww.com/CCX/A890) illustrates the different definitions used for DKA resolution.

Data Extraction and Quality Assessment

Two reviewers (N.A., P.M.) completed data extraction independently and in duplicate using predefined data abstraction forms (**Supplemental Table 2**, http://links.lww.com/CCX/A890). If necessary, a third reviewer (B.R.) resolved disagreements. We abstracted the following data: study characteristics, demographic data, interventions details, and outcome data. We used graph analyzer (http://plotdigitizer.sourceforge.net) when needed. We contacted individual study authors in cases of missing study data. For those that did not respond, we followed up with a second email approximately 2 weeks later. If we had no reply after two attempts, then we used whatever information was available in the published report and accounted for missing information as part of our risk of bias evaluation.

We assessed risk of bias independently (N.A., D.C.) and in duplicate for each study using a modified Cochrane

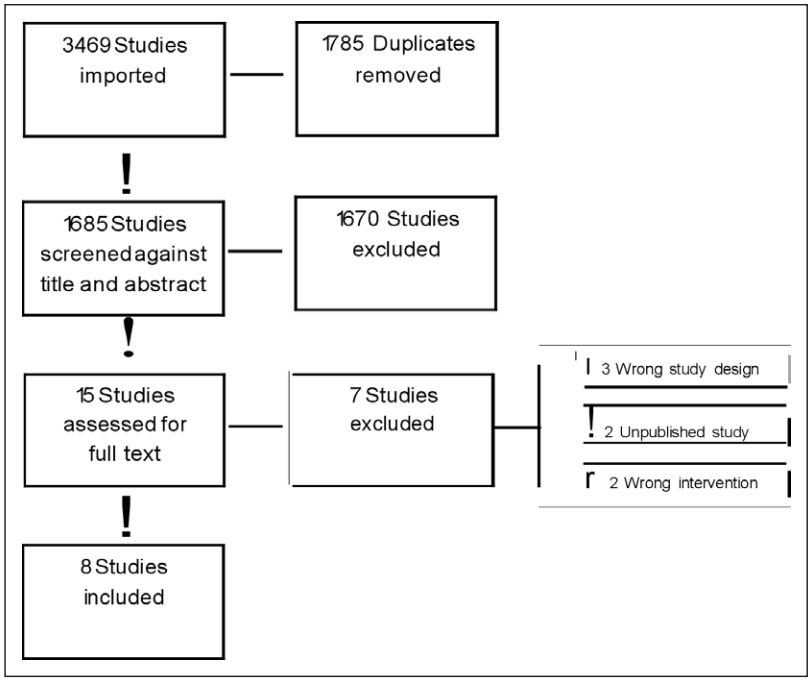

Figure 1. Study flow diagram.

risk of bias tool (19) that classified risk of bias as " low," "probably low," "probably high," or "high" for each of the following items: randomization and sequence generation, allocation sequence concealment, blinding, incomplete data, selective outcome reporting, and other risk of bias. We evaluated the overall risk of bias as the highest risk attributed to any criterion. We appraised the overall certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (20).

Although we planned to assess for publication bias, given we had less than 10 eligible RCTs, this was not possible.

Data Analysis

We performed all analyses using RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) software. We generated study weights using the inverse variance method and used random-effects model. We present results as relative risks (RRs) for dichotomous outcomes and as mean differences (MDs) for continuous outcomes, both with 95% CIs. For continuous outcomes, we assumed a normal distribution (i.e., median = mean) and converted interquartile range to SD using the methods suggested by Cochrane handbook for systematic reviews of interventions (21). For cluster RCTs that met inclusion criteria, we used the intracluster correlation coefficient to calculate the design effect that informed sample size reduction (22).

We assessed for heterogeneity between studies using the chi-square tests for homogeneity, the I^2 statistic (23) and the visual inspection of the forest plots. We considered the magnitude and direction of heterogeneity when considering whether to rate down our certainty in the evidence for inconsistency. Although we had planned for subgroup analysis based on adult versus pediatric patients, this was not possible due to lack of sufficient data.

RESULTS

Search Results and Study Characteristics

Of the 1,685 citations (Fig. 1) identified in our search, we retrieved 15 full texts and included eight RCTs in the review. **Supplemental Table 3** (http://links.lww.com/CCX/A890) shows the details of the eligible trials.

The included RCTs randomized between 30 and 172 patients with DKA. Six of the RCTs were performed in adults (24–29), while two were performed in children (30, 31). One RCT was available only in abstract form (27); however, we were able to acquire more information through contact with study authors.

We found two large RCTs that compared saline to balanced crystalloid in a general critical care population (32, 33). After contacting study authors, one did not collect whether patients had DKA (33) and the other included only three patients with DKA (32), and therefore, neither was included in our analysis.

One study (28) reported the subgroup of DKA patients from two linked cluster RCTs (14, 15) and was treated as a single RCT for the purposes of our analysis. These linked cluster RCTs enrolled a total of 172 patients with DKA; however, after applying the design effect and sample size reduction, we used a functional sample size of 106 patients. Another multicenter cluster study (29) enrolled 90 patients; however, after applying the design effect, we used a sample size of 62.

The RCTs included DKA patients with variable severity of illness except one trial that excluded mild DKA (defined as blood glucose < 200 mg/dL = 11.1 mmol/L, serum bicarbonate above 15 or an anion gap < 16) (24).

Most trials (24–26, 30, 31) excluded patients with end organ failure (defined as cerebral edema or low Glasgow Coma Score, renal failure requiring dialysis, respiratory failure requiring mechanical ventilation, myocardial infarction, or need of vasopressor or inotropic support).

There were a number of different balanced crystalloids examined, including PlasmaLyte (24, 29, 31), Ringer's lactate (25), Ringerfundin (26), and Hartmann's solution (30). One trial (27) used both Ringer's lactate and PlasmaLyte due to a shortage in Ringer's lactate that occurred during the study period. Another trial (28) allowed for the use of either Ringer's lactate or PlasmaLyte at the discretion of the treating clinical team. **Supplemental Table 4** (http://links.lww.com/CCX/A890) presents risk of bias of the included RCTs.

Outcomes

Supplemental Table 5 (http://links.lww.com/CCX/A890) illustrates the GRADE evidence profile for each outcome (20). We found an uncertain effect on mortality (RR, 1.13; 95% CI, 0.32–4.08; very low certainty; **Supplemental Fig. 1**, http://links.lww.com/CCX/A890) with saline compared with balanced crystalloid although mortality was rare in this population (8/370, 2.1%), which contributed to very serious imprecision and the very low certainty of evidence.

DKA resolution was variably defined amongst included trials. Three RCTs used the American Diabetes Association (4) criteria (27–29), two RCTs used a pH equal to or greater than 7.30 and bicarbonate equal to or greater than 15 (25, 30), while one RCT (31) used a pH equal to or greater than 7.30, a bicarbonate equal to or greater than 15 and normal sensorium. Regardless of the definition used, we found there to be likely no difference in DKA resolution (RR, 1.00; 95% CI, 0.97–1.03; moderate certainty; **Supplemental Fig. 2**, http://links.lww.com/CCX/A890) between the fluid types. Importantly, almost all patients achieved resolution of their DKA (380/407, 93%) during the study periods according to the definitions employed. Time to DKA resolution (MD, 3.51 hr longer; 95% CI, 0.90 longer to 6.12 hr longer; moderate certainty; **Fig. 2**) and length of hospital stay (MD, 0.89 d longer in saline group; 95% CI, 0.34 d longer to 1.43 d longer; moderate certainty; **Fig. 3**) were probably longer with saline compared with balanced crystalloids, however, for the latter, the absolute difference (under 1 d) was small. Sensitivity analysis limited to studies of adults found similar results and conclusions (**Supplemental Fig. 3**, http://links.lww.com/CCX/A890).

Post-resuscitation serum chloride may be higher in patients who received saline compared with balanced crystalloids (MD, 1.62 mmol/L higher; 95% CI, 0.4 lower to 3.64 higher; **Supplemental Fig. 4**, http://links.lww.com/CCX/A890); however, this is based on low certainty with serious imprecision due to wide CIs that do not exclude higher serum chloride with balanced crystalloids. The use of saline was associated with a lower post-resuscitation bicarbonate (MD, 1.5 mmol/L; 95% CI, 2.33 lower to 0.67 lower; moderate certainty; **Fig. 4**).

Complications from the administration of different IV fluids were rare, and rates were similar between types of fluid (**Supplemental Table 6**, http://links.lww.com/CCX/A890) with a number of studies not reporting on adverse events. Most of these complications were electrolyte disturbances that were considered easily treatable. Other extremely rare complications included cerebral edema and hypoglycemia.

Only two RCTs (28, 31) reported renal endpoints and even when reported were heterogeneous in how the outcome was captured, and thus, we were unable to pool.

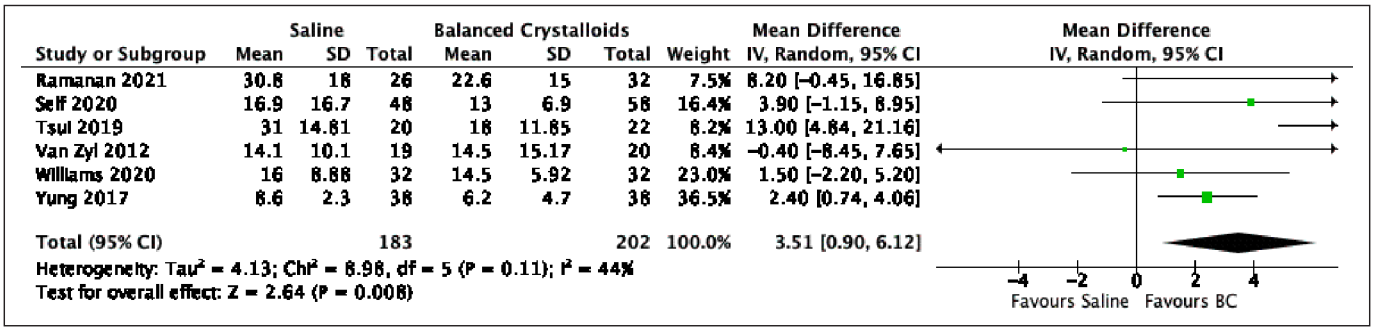

Figure 2. Effect of using either saline or balanced crystalloids (BCs) on time to diabetic ketoacidosis resolution (hr). *df* = degrees of freedom.

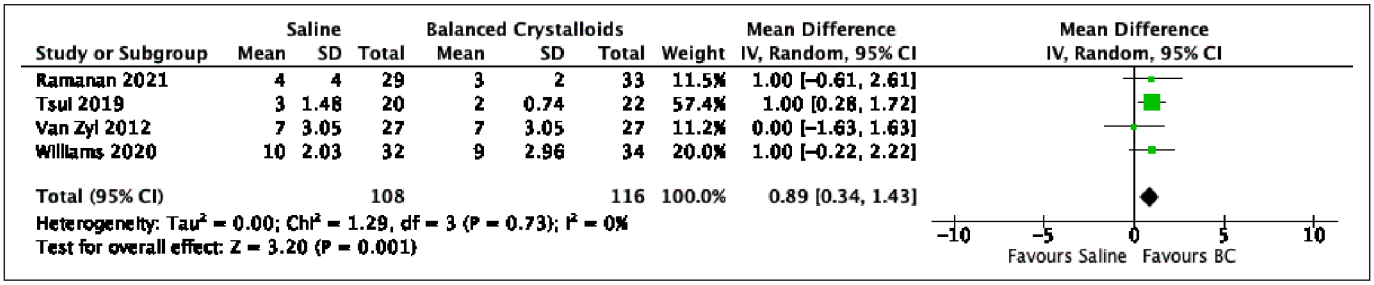

Figure 3. Effect of using either saline or balanced crystalloids (BCs) on length of hospital stay (d). *df* = degrees of freedom.

DISCUSSION

This systematic review and meta-analysis summarize the RCT data examining the effect of saline compared with balanced crystalloid in patients with DKA. Although there was an uncertain effect on mortality and no difference in DKA resolution, patients receiving saline probably had a longer time to DKA resolution and longer hospital length of stay. Also, patients receiving saline may have higher post-resuscitation serum chloride and lower post-resuscitation serum bicarbonate levels. Finally, adverse events were rare, although occurred at similar rates across fluid types.

Although patients with severe DKA often end up being cared for in the ICU, their prognosis is generally good, and their length of stay in ICU short compared with other critically ill patients (2, 34). As such, it is not surprising that there was an uncertain effect on mortality. Of 370 patients included in the mortality pooled estimate, there were only a total of eight deaths (2.1%), and therefore any estimate of effect comparing balanced crystalloid to saline was bound to be imprecise and uninformative. We did not observe any difference in DKA resolution between fluid types. However, of 407 patients reporting on this outcome, almost all (93%) eventually resolved and therefore also not a surprise that no difference was seen. Despite not finding a difference in mortality or DKA resolution, importantly, we found shorter time to DKA resolution in patients receiving balanced crystalloid. This finding was fairly consistent across included trials, observed in five of the six studies reporting on this outcome. Time to DKA resolution is patient-important as a shorter duration of DKA often means leaving the ICU sooner and being discharged from hospital sooner. In fact, we also observed a shorter length of hospital stay in those randomized to balanced crystalloid, which also has an impact on healthcare resource utilization and costs. Although pooled differences in time to DKA resolution and hospital length of stay were relatively short, we still believe these may be important to both patients and healthcare resource utilization as these patients often require admission to high-dependency units for IV insulin and frequent blood testing.

Outcomes including post-resuscitation electrolyte concentrations are less patient-important; however, probably an important surrogate for severity of illness, ongoing requirement for ICU, and increased frequency of blood testing. Patients who received saline had a lower post-resuscitation bicarbonate level and a higher post-resuscitation chloride level. These results are in keeping with previous work that has demonstrated a higher frequency of metabolic abnormalities with high volume saline administration (35, 36). Hyperchloremia has previously been associated with metabolic acidosis, acute kidney injury, and decreased smooth muscle contractility (37–40), all features that may prolong critical illness. Although effects on

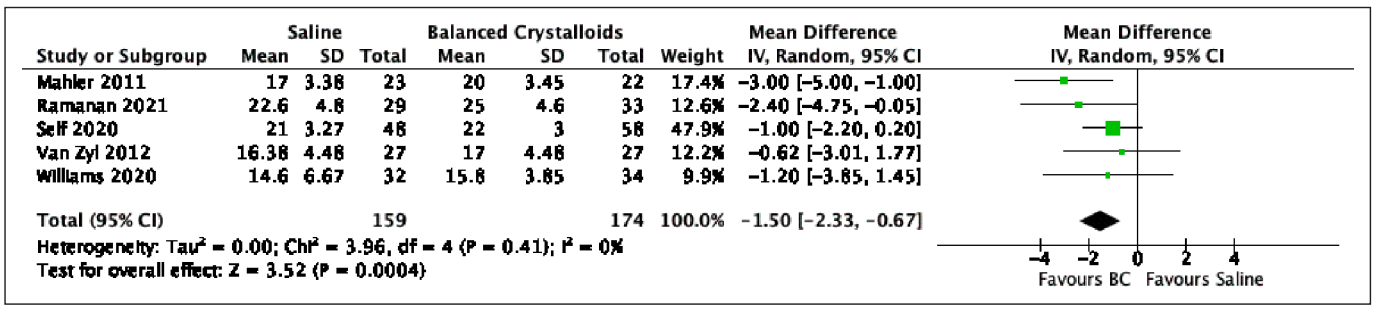

Figure 4. Effect of using either saline or balanced crystalloids (BCs) on post-resuscitation bicarbonate. *df* = degrees of freedom.

potassium levels may also be important, this was not routinely reported in included RCTs. Complications of fluid therapy are likely under-reported. We found these to be relatively rare but to occur at similar frequencies between fluid types. The most common adverse effects reported included electrolyte abnormalities such as hyperkalemia or hypokalemia, which were easily correctable in the ICU setting. Both fluid types are considered standard of care and unlikely to be associated with severe adverse events specifically related to the fluid type chosen.

There are a number of ongoing RCTs (NCT02721654, NCT03777102) and one that was recently published (33), examining the optimal crystalloid to administer to critically ill patients, and we will likely have further information addressing this important question in the near future. Although patients with DKA are not excluded from these ongoing trials, they will likely make up a very small subset of the total population. As such, concerns regarding generalizability will persist, even in the face of emerging data. Until large-scale RCTs specific to DKA patients are performed, the evidence generated by subgroup analysis of larger RCTs and small DKA-specific RCTs will provide the best estimates of effect comparing balanced crystalloids and saline. Based on this review, low to moderate certainty evidence suggests balanced crystalloids may be beneficial compared with saline in critically ill patients with DKA.

Strengths of this study include a comprehensive search, focusing on an important subtype of patients requiring large volume of fluid resuscitation. We relied on rigorous methodology, included various types of RCTs, such as cluster design, and were successful in contacting individual study authors for unpublished data. We used a dated and predeveloped protocol and employed GRADE (20) methodology to assess the certainty of evidence. This review also has limitations. First, the included RCTs were generally small and even using pooled analysis, important issues with imprecision persisted impacting the overall certainty of results. Second, a few of the outcomes were variably defined (e.g., DKA resolution) among the included RCTs, which may have contributed to heterogeneity in treatment effect.

CONCLUSIONS

The use of saline may be associated with longer time to DKA resolution, higher post-resuscitation plasma chloride levels, lower post-resuscitation plasma bicarbonate levels, and longer hospital stay compared with balanced crystalloids. Pending further data, low to moderate certainty data supports using balanced crystalloid over saline for fluid resuscitation in patients with DKA.

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1 *Department of Medicine, McMaster University, Hamilton, ON, Canada.*

2 *Department of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.*

3 *Department of Pharmacy, University of Oklahoma Medical Center, Oklahoma City, OK.*

4 *Pulmonary, Critical Care, and Sleep Medicine Section, Department of Medicine, University of Oklahoma Health Science Center, Oklahoma City, OK.*

5 *Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN.*

6 *Vanderbilt Institute for Clinical and Translational Sciences, Vanderbilt University Medical Center, Nashville, TN.*

7 *Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN.*

8 *ICU, Caboolture and The Prince Charles Hospitals, Metro North Hospital and Health Service, Brisbane, QLD, Australia.*

9 *Critical Care Division, The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia.*

10 *School of Medicine, University of Queensland, St Lucia, QLD, Australia.*

11 *Department of Health Research Methods, Evidence and impact, McMaster University, Hamilton, ON, Canada.*

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Drs. Alghamdi and Rochwerg came up with the study idea. Drs. Alghamdi and Rochwerg coordinated the systematic review and the search strategy. Dr. Alghamdi and Ms. Major screened abstracts, full texts, and extracted the data. Drs. Alghamdi and Chaudhuri assessed risk of bias. Drs. Alghamdi and Rochwerg verified data and performed the analyses. Dr. Alghamdi, Ms. Major, and Dr. Rochwerg created the Grading of Recommendations, Assessment, Development, and Evaluation evidence profiles. All authors interpreted the data analyses. All authors co-wrote and revised the article for intellectual content. All authors approved article submission. Dr. Rochwerg contributed as a senior author. All authors agree to be responsible for all aspects of work.

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Address requests for reprints to: Bram Rochwerg, MD, MSc, Department of Medicine, Division of Critical Care, Juravinski Hospital, 711 Concession St, Hamilton, ON L8V 1C1, Canada. E-mail: rochwerg@mcmaster.ca

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