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## Corticosteroids in Sepsis and Septic Shock: A Systematic Review, Pairwise, and Dose-Response Meta-Analysis

**OBJECTIVES:** To perform a systematic review and meta-analysis to assess the efficacy and safety of corticosteroids in patients with sepsis.

**DATA SOURCES:** We searched PubMed, Embase, and the Cochrane Library, up to January 10, 2023.

**STUDY SELECTION:** We included randomized controlled trials (RCTs) comparing corticosteroids with placebo or standard care with sepsis.

**DATA EXTRACTION:** The critical outcomes of interest included mortality, shock reversal, length of stay in the ICU, and adverse events.

**DATA ANALYSIS:** We performed both a pairwise and dose-response metaanalysis to evaluate the effect of different corticosteroid doses on outcomes. We used Grading of Recommendations Assessment, Development and Evaluation to assess certainty in pooled estimates.

**DATA SYNTHESIS:** We included 45 RCTs involving 9563 patients. Corticosteroids probably reduce short-term mortality (risk ratio [RR], 0.93; 95% CI, 0.88–0.99; moderate certainty) and increase shock reversal at 7 days (RR, 1.24; 95% CI, 1.11–1.38; high certainty). Corticosteroids may have no important effect on duration of ICU stay (mean difference, –0.6 fewer days; 95% CI, 1.48 fewer to 0.27 more; low certainty); however, probably increase the risk of hyper-glycemia (RR, 1.13; 95% CI, 1.08–1.18; moderate certainty) and hypernatremia (RR, 1.64; 95% CI, 1.32–2.03; moderate certainty) and may increase the risk of neuromuscular weakness (RR, 1.21; 95% CI, 1.01–1.45; low certainty). The dose-response analysis showed a reduction in mortality with corticosteroids with optimal dosing of approximately 260 mg/d of hydrocortisone (RR, 0.90; 95% CI, 0.83–0.98) or equivalent.

**CONCLUSIONS:** We found that corticosteroids may reduce mortality and increase shock reversal but they may also increase the risk of hyperglycemia, hypernatremia, and neuromuscular weakness. The dose-response analysis indicates optimal dosing is around 260 mg/d of hydrocortisone or equivalent.

KEYWORDS: corticosteroids; critical illness; meta-analysis; sepsis; septic shock

The use of corticosteroids for patients with sepsis and septic shock has been debated for decades and examined in previous randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Despite this, there remains important uncertainty regarding the effects of corticosteroids on patient-centered outcomes in those with sepsis (1, 2).

Previous systematic reviews have found a possible reduction in mortality, albeit based on low certainty evidence (3, 4). Based on higher certainty evidence, corticosteroids have been found to reverse shock and improve organ dysfunction compared with standard care or placebo (3). However, several important questions remain, including whether certain subtypes of patients with sepsis Tyler Pitre, MD, MA<sup>1</sup> Katherine Drover<sup>2</sup> Dipayan Chaudhuri, MD, MSc<sup>3,4</sup> Dena Zeraaktkar, PhD<sup>3,5</sup> Kusum Menon, MD, MSc<sup>6</sup> Hayley B. Gershengorn, MD<sup>78</sup> Namita Jayaprakash, MD<sup>9</sup> Joanna L. Spencer-Segal, MD, PhD<sup>10</sup> Stephen M. Pastores, MD<sup>11</sup> Andrea M. Nei, PharmD<sup>12</sup> Djillali Annane, MD, PhD<sup>13</sup>

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### KEY POINTS

**Question:** What is the efficacy of corticosteroids in severe sepsis and septic shock?

**Findings:** Corticosteroids probably reduce mortality in patients with sepsis and septic shock and reverses shock. The optimal dose is likely around 260 mg/d. There are important adverse effects, including hyperglycemia, hypernatremia, and neuromuscular weakness.

**Meanings:** Clinicians and patients should have more confidence in the effectiveness of corticosteroids in treating sepsis and septic shock.

may benefit more, and whether the corticosteroid regimen (including duration, dose, and the type of corticosteroid) impacts outcomes.

In the past few years, several new RCTs evaluating the use of corticosteroids in patients with sepsis and septic shock have been published. We therefore sought to update the evidence summaries addressing this question incorporating these newer trials with the goal of improving precision and addressing the optimal corticosteroid regimen.

#### METHODS

We registered a protocol on Open Science Framework in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses-protocol checklist on December 28, 2022. We subsequently prepared this article in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (https://osf.io/v5qrz) (5).

#### **Eligibility Criteria**

We included all RCTs examining the use of corticosteroids in critically ill adults and pediatric patients with sepsis or septic shock. We excluded case reports, case series, and observational studies. We did not impose any methodological quality or language restrictions. To provide important information and future research direction, and in keeping with the approach used in the original review, we included studies of adults or children who were diagnosed with sepsis, or septic shock using the sepsis 1, 2, or 3 consensus definitions (6). We included data from trials enrolling any critically ill patients treated with corticosteroids if patients with sepsis or septic shock were reported separately.

We included studies examining any systemic (enteral or parenteral) corticosteroids. We excluded inhaled or topical corticosteroids. We included RCTs that used a placebo or usual care without corticosteroid comparator group. Our primary analysis included studies with corticosteroids or corticosteroids and fludrocortisone alone and did not include cointervention with vitamin C or thiamine. However, we included studies that administered hydrocortisone in combination with ascorbic acid and thiamine, as we planned to include these in a secondary sensitivity analysis.

Outcomes of interest included short-term-mortality (28–31 d or in-hospital), long-term mortality (90-d or longest reported), number of participants with shock reversal at day 7 (stable hemodynamic status over 24 hr after withdrawal of vasopressors), organ dysfunction at day 7 (using Sequential [Sepsis-related] Organ Failure Assessment [SOFA] score), ICU and hospital length of stay, and adverse events associated with corticosteroids, including ICU-acquired neuromuscular weakness, gastrointestinal bleeding, adverse neuropsychiatric events, hypernatremia, superinfection, vascular events (stroke, myocardial infarction), and hyperglycemia requiring intervention. We captured adverse event outcomes as defined by individual study authors.

#### Search Strategy and Study Selection

We updated a search strategy from a previous review (conducted through January 10, 2018) with the help of an experienced medical librarian and included all the existing trials from the previous review (3). We searched Ovid Medline, Embase, Cochrane Clinical Trials Register, and Latin American and Caribbean Health Sciences Literature from January 1, 2018, to January 1, 2023. We only included primary source clinical trial data but reviewed secondary analyses for subgroup data when applicable. **eTable 1** (http://links. lww.com/CCX/B266) presents the search strategy.

Two reviewers worked independently and in duplicate to screen titles and abstracts of citations found with the search. Any study deemed potentially relevant by either reviewer at the title and abstract screening was advanced to the full-text screening. Reviewers resolved discrepancies in full text by discussion or, when necessary, by third party adjudication.

#### **Data Collection**

We collected data describing trial characteristics (author, year published, trial registration, country of enrollment, ethics and funding statements), patient characteristics (age, sex), intervention characteristics (type of corticosteroid, dose, duration), and outcomes of interest.

For dichotomous outcomes, we extracted the number of participants analyzed and the number of events in each arm. For continuous outcomes, we collected the number of participants analyzed, the measure of central tendency (mean or median), and the measure of variability (e.g., sD, interquartile range) for each arm. When studies reported other measures of variability other than sD, we converted them to SDs using methods proposed by Hozo et al (6).

#### **Risks of Bias**

Two reviewers assessed the risk of bias of included studies using the modified Cochrane tool for randomized trials (7–9). We classified trials rated at probably low or low risk of bias across domains as low risk of bias overall. We resolved discrepancies by discussion and, when necessary, with adjudication by a third party.

#### Statistical Methods

We conducted both a pairwise random-effects and a dose-response meta-analysis. For both analyses and for all outcomes, we performed the analysis using the maximum likelihood heterogeneity estimator for the random-effects model to pool effect sizes for each outcome.

We summarized the effects of interventions using relative risks (RRs) and corresponding 95% CIs for dichotomous outcomes and mean differences (MDs) with 95% CI for continuous outcomes. To facilitate interpretation, for dichotomous outcomes, we calculated absolute risk differences per 1000 patients and corresponding 95% CI (10–12) using the baseline risk summarized across the placebo arms of included trials.

We performed prespecified subgroup analyses based on: corticosteroid compound (both type and by weighted mineralocorticoid composition), sepsis comorbidity as defined by study inclusion (sepsis and acute respiratory distress syndrome [ARDS] vs. sepsis and pneumonia vs. not specific to ARDS or pneumonia), sepsis severity (sepsis without shock vs. septic shock), risk of bias (high or probably high vs. low or probably low), children vs. adults (< 18 vs. 18 vr old or older), and duration of corticosteroids (3 d or less vs. more than 3 d). We performed on post hoc subgroup comparing hyperglycemia requiring insulin. We also performed a sensitivity analysis, including hydrocortisone, ascorbic acid, and thiamine (HAT) combination therapy vs. corticosteroid alone. We performed two post hoc analyses using meta-regression based on disease severity (mortality rate in the comparator arm) and year of publication. We hypothesized that there would be a beneficial effect of corticosteroids for patients with septic shock, but no effect for the other moderators. We used the Instrument for assessing the Credibility of Effect Modification Analyses tool to assess credibility of these subgroups if there were statistically significant interaction terms (p < 0.05) (13).

For short-term mortality, we performed an additional dose-response meta-analysis (14, 15). For the dose-response analysis, we conducted a random-effects dose-response meta-analysis using the restricted maximum likelihood heterogeneity estimator and methods proposed by Greenland, Longnecker, Orsini, and colleagues (16, 17) using a one-stage approach (18). Dose-response meta-analysis estimates the association between doses of an exposure and the RR or MD of an outcome. We analyzed the daily dose of corticosteroids administered during the trial.

We used the following corticosteroid conversions: 1 mg of dexamethasone = 26.7 mg of hydrocortisone = 5.3 mg of methylprednisolone/prednisolone = 6.7 mg of prednisone (19–21). To ensure no differences based on molecule, we performed meta-regression using molecule as a moderator.

For analyses with five or more studies, we assessed for nonlinearity by using restricted cubic splines with knots at 10%, 50%, and 90% and a Wald-type test (22). Restricted cubic splines accommodate nonlinear relationships by splitting the independent variable (i.e., dose) at "knots" and fitting separate curves between knots. For analyses in which we observed statistically significant nonlinear associations, we present results from the nonlinear model. For pairwise analyses, we performed all analyses using STATA v.17 (StataCorp LLC, College Station, TX). For the dose-response analysis, we performed all analyses using the *dosresmeta*  and *meta* packages in R (Version 4.03; R Foundation for Statistical Computing, Vienna, Austria) (16, 17). The R code and data for the primary outcome are presented on the registration page (https://osf.io/v5qrz).

#### Certainty of the Evidence

For all outcomes, reviewers, working independently and in duplicate, assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (18, 23). **Supplementary Methods** (http://links.lww.com/ CCX/B266) have more detail on how we assessed the quality of the evidence.

We describe results using guidance from the GRADE Working Group, based on the certainty of evidence and the magnitude of the effect (e.g., corticosteroids reduce mortality [high certainty], corticosteroids probably reduce mortality [moderate certainty], corticosteroids may reduce mortality [low certainty], and the effect of corticosteroids on mortality is uncertain [very low certainty]) (18).

#### RESULTS

#### **Trial Selection and Characteristics**

The search identified 1702 unique citations, of which we identified 11 new eligible RCTs since the previously published review that we were updating. Of these 11, seven RCTs evaluated combination therapy with corticosteroid, ascorbic acid, and thiamine, trials which were not included in the primary analysis. Four of the trials evaluated corticosteroids, including one which was a subgroup analysis of a previously included trial. Thus, we included a total of 45 RCTs in this updated analysis, 42 trials from the previous review and three new RCTs. The seven corticosteroid/ascorbic acid/thiamine trials were included in a secondary sensitivity analysis. **eFigure 1** (http://links.lww.com/CCX/B266) presents more detail on the inclusion and exclusion process.

Of the 45 RCTs, 20 were multicenter and 25 were single center. Twenty-seven RCTs examined patients with septic shock; five included patients with both community-acquired pneumonia (CAP) and sepsis and four enrolled patients with ARDS and sepsis. Six RCTs enrolled only children (24–29) and one enrolled both adults and children but reported the two groups

separately. For steroid compounds, 26 trials used hydrocortisone, seven used methylprednisolone, five used dexamethasone, and three used prednisolone. In addition, two studies used combination hydrocortisone and fludrocortisone, and two used dexamethasone and methylprednisolone.

The dose of corticosteroid varied, although most (n = 40) used a relatively low dose (< 400 mg/d of hydrocortisone or equivalent). **eTable 2** (http://links.lww.com/CCX/B266) presents more details on the included trials. All included studies enrolled patients with sepsis based on previous Sepsis 1 or Sepsis 2 diagnostic criteria.

#### **Risk of Bias**

We judged 22 trials (48.8%) to be at high or probably high risk of bias. Eight were at risk of bias due to issues arising from allocation concealment, eight due to bias arising from lack of blinding, seven due to bias arising from missing data, seven due to bias arising from selective reporting, and seven due to bias arising from deviations from the intended interventions. **eTable 3** (http://links.lww.com/CCX/B266) presents our risk of bias assessments.

#### Mortality

We found that corticosteroids probably reduce shortterm mortality (RR, 0.93; 95% CI, 0.88–0.99; absolute risk reduction, 2.1%; 95% CI, 0.6–3.6% reduction; moderate certainty) (**Fig. 1**; and **eTable 4**, http:// links.lww.com/CCX/B266) and may reduce long-term mortality (RR, 0.94; 95% CI, 0.89–1.00; absolute risk reduction, 1.9%; 95% CI, 0–4.1% reduction; low certainty) (**eFig. 2** and eTable 4, http://links.lww.com/ CCX/B266).

The dose-response meta-analysis found no increased benefit in mortality reduction above 260 mg/d of hydrocortisone or equivalent (RR, 0.93; 95% CI, 0.88– 0.99) as compared with higher or lower doses. **Table 1** and **Figure 2** present the analysis.

#### **Other Efficacy Outcomes**

We found that corticosteroids may not have an important effect on ICU length of stay (MD, 0.60 d shorter; 95% CI, 1.48 d shorter to 0.27 d longer; low certainty) and hospital length of stay (MD, 0.74 d shorter; 95% CI,

| Study     Yes     No     with 95% CL     (%)       Agarwal 2022     22     39     25     34     0.85 [0.54, 1.33]     165       El-Nawawy 2016     14     18     26     38     0.07     108 [0.66, 1.76]     1.38       Annane 2002     82     69     91     58     0.88 [0.73, 1.08]     8.73       Annane 2018     207     407     244     383     0.87 [0.75, 1.00]     15.07       Annane 2018     207     407     244     383     0.87 [0.75, 1.00]     15.07       Boine 1987     65     126     48     142     -     1.55 [0.24, 1.25]     0.48       Charle 1999     3     17     4     16     0.75 [0.19, 2.93]     0.18       Charle 1996     17     10     11     0.55 [0.24, 1.25]     0.48       Cicarelli 2007     7     7     12     3     0.63 [0.35, 1.12]     0.88       Lu 2012     3     9     6     8     1.07 [0.72, 1.60]     2.04       Lv 2017   |  | Cortico   | steroids | Co    | ontrol     |                          | Risk ratio          | Weight |  |  |
|---|--|-----------|----------|-------|------------|--------------------------|---------------------|--------|--|--|
| Ei-Nawawy 2016 14 18 26 38<br>Menon 2017 1 22 3 23<br>Annane 2002 82 69 91 58<br>Annane 2018 207 407 244 383<br>Annane 2018 207 407 244 383<br>Birudariju 2022 9 12 16 6<br>Birudariju 2022 9 12 16 6<br>Chawla 1999 6 17 10 11<br>Chawla 1990 7 7 7 12 3<br>Gordon 2014 7 24 7 23<br>Gordon 2014 7 24 7 23<br>Gordon 2016 62 139 57 150<br>Luce 1988 22 16 20 17<br>Luce 198 22 26 4 27<br>Meijvis 2011 9 142 11 142<br>0.35 [1.35, 9.32] .0.35<br>Josfi [0.52, 1.81] .80<br>0.68 [0.32, 2.81] .80<br>0.68 [0.32, 2.81] .80<br>0.68 [0.32, 2.81] .80<br>0.68 [0.32, 2.81] .80<br>0.68 [0.32, 1.81] .33<br>0.68 [0.32, 1.41] .33<br>0.68 [0.32, 1.41] .33<br>0.68 [0.32, 1.41] .33<br>0.68 [0.42, 1.55] .34<br>1.05 [0.57, 1.58] 1.28<br>Venkatesh 2018 410 1.431 448 1.392<br>Venkatesh 2   | Study  | Yes       | No       | Yes   | No         |                          | with 95% CI         | (%)    |  |  |
| Menon 2017   1   22   3   23     Annane 2002   82   69   91   58     Annane 2018   207   407   244   383     Annane 2018   207   15   12   7     Bolleer 1998   7   15   12   7     Bone 1987   65   126   48   142     Chawla 1999   6   17   10   11   0.55   10,24, 1.25   0.49     Corfalonieri 2005   0   23   6   17   0.68   0.08   0.08   0.01, 1.29   0.04     Gordon 2016   62   139   57   150   1.12   0.83, 1.52   3.60     Hu 2009   4   34   6   33   0.68   0.88   0.88   0.88   0.88   0.88   0.88   0.88   0.88   0.88   0.88   0.88   0.85   | Agarwal 2022   | 22        | 39       | 25    | 34         |                          | 0.85 [ 0.54, 1.33]  | 1.65   |  |  |
| Annane 2002 82 69 91 58<br>Annane 2018 207 407 244 383<br>Arabi 2011 33 6 26 10<br>Birudargu 2022 9 12 16 6<br>Birudargu 2022 9 12 16 7<br>Bone 1987 65 126 48 142<br>Briegel 1999 3 17 4 16<br>Chawla 1999 6 17 10 11<br>Cotarelli 2007 7 7 7 12 3<br>Contalonieri 2005 0 23 6 17<br>Gordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Gordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Gordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Contalonieri 2005 10 23 6 17<br>Gordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Meduri 2007 10 32 8 11<br>Meduri 2005 10 13 11 14<br>Spinug 198 3 10 11 5<br>Sinjders 2010 6 89 6 103<br>Sinjders 2018 54 26 58 22<br>Mainel 21 3 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Menkatesh 2018 410 1,431 44   | El-Nawawy 2016   | 14        | 18       | 26    | 38         |                          | 1.08 [ 0.66, 1.76]  | 1.36   |  |  |
| Annane 2018 207 407 244 383<br>Arabi 2011 33 6 26 10<br>Binudaraju 2022 9 12 16 6<br>Binudaraju 2025 128 48 142<br>Chawla 1999 6 17 10 11<br>Chawla 1990 6 12 139 57 150<br>Hu 2009 4 3 46 6 33<br>Chawla 10 15 155 14 156<br>Luce 1988 22 16 20 17<br>Luce 1988 22 16 20 17<br>Sabry 2011 9 142 11 142<br>Opper 2005 10 13 11 14<br>Copper 2005 10 13 11 14<br>Copper 2005 10 13 11 14<br>Copper 2015 10 13 11 14<br>Copper 2016 6 20 7 19<br>Sabry 2011 2 38 6 34<br>Chawla 130 11 5<br>Shipders 2010 6 88 6 103<br>Spinders 2010 6 88 6 103<br>Spinders 2010 6 88 6 103<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 140] 5.23<br>Talebi Doluee 2018 54 26 58 22<br>O 93 [0.48, 0.99]<br>Heterogeneity: $t^2 = 0.00; t^2 = 0.00; t^2 = 1.00$<br>Test of $\theta = 0; z = -2.47, p = 0.01$<br>$t_{1/28}$   | Menon 2017   | 1         | 22       | 3     | 23         |                          | 0.38 [ 0.04, 3.38]  | 0.07   |  |  |
| Arabi 2011   33   6   26   10   1.17 [0.92, 1.49]   5.60     Birudargiu 2022   9   12   16   6 $0.59 [0.34, 1.03]$ 1.07     Bollaert 1998   7   15   12   7 $0.50 [0.25, 1.02]$ 0.67     Bone 1987   65   126   48   142   1.35 [0.98, 1.48]   3.34     Briegel 1999   3   17   4   16 $0.55 [0.24, 1.25]$ 0.49     Contaloniei 2005   0   23   6   17   10   11 $0.55 [0.24, 1.25]$ 0.49     Contaloniei 2005   0   23   6   17   23   0.08 [0.00, 1.29]   0.40     Gordon 2016   62   139   57   150   1.12 [0.83, 1.52]   3.60     Hu 2009   4   34   6   33   0.55 [0.18, 1.85]   0.25     Luce 1988   22   16   20   17   1.07 [0.72, 1.60]   2.04     Lv 2017   23   35   19   41   0.55 [0.13, 1.5]   0.35   1.38   0.58     Meduri 2007   10  | Annane 2002  | 82        | 69       | 91    | 58         |                          | 0.89 [ 0.73, 1.08]  | 8.73   |  |  |
| Birudaraju 2022 9 12 16 6<br>Birudaraju 2022 9 12 16 6<br>Bone 1987 65 126 48 142<br>Fingel 1999 3 17 4 16 1<br>Dhawla 1999 6 17 10 11<br>Chawla 1999 6 17 10 11<br>Chawla 1999 6 17 10 11<br>Chawla 1999 6 17 10 11<br>Cose 101 2007 7 7 7 12 3<br>Condon 2014 7 24 7 23<br>Gordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Condon 2016 15 156 14 156<br>Liu 2012 3 9 6 8<br>Cose 10 15 156 14 156<br>Liu 2012 3 9 6 8<br>Meduri 2007 10 32 8 11<br>Cose 10 12 007 10 32 8 11<br>Cose 10 12 006 6 20 7 19<br>Schumer 1976 9 77 35 19<br>Ali 12 10 12 3 0 18 3 6<br>Reak 2013 0 18 3 1<br>Reak 2016 0 0 1/2 0 00%, H <sup>2</sup> = 1.00<br>Reak 2018 54 12 12 8<br>Reak 2013 1 1 15 13<br>Reak 2014 10 1/41 148 1,392<br>Reak 2015 16 4, 0 0, 1 <sup>2</sup> 0 00%, H <sup>2</sup> = 1.00<br>Reak 9 0, 10 163, 103 23, 0.99<br>Ridiz 2002 8 12 12 8<br>Reak 2013 1 16 11 15 13<br>Reak 2014 10 1/44 148 1,392<br>Reak 2015 16 7, 0 16 9 0.2 z - 2.47, p = 0.02<br>Reak 2018 16 0, 0, 1 <sup>2</sup> 0 00%, H <sup>2</sup> = 1.00<br>Reak 2018 54 10 0, 1 <sup>2</sup> 0 00%, H <sup>2</sup> = 1.00<br>Reak 2018 54 10 0, 1 <sup>2</sup> 0 00%, H <sup>2</sup> = 1.00<br>Reak 2018 10 0, 1 <sup>2</sup> 0 00%, H <sup>2</sup> = 1.00<br>Reak 200 10 2 z - 2.47, p = 0.02   | Annane 2018  | 207       | 407      | 244   | 383        |                          | 0.87 [ 0.75, 1.00]  | 15.07  |  |  |
| Bollaert 1998 7 15 12 7<br>Bone 1987 65 126 48 142<br>Briegel 1999 3 17 4 16<br>Chawla 1999 6 17 10 11<br>Chawla 1999 6 17 10 11<br>Coarell 2007 7 7 7 12 3<br>Confatonieri 2005 0 23 6 17<br>Gordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Gordon 2016 15 156 14 156<br>Liu 2012 3 9 6 8<br>Liu 2017 10 32 8 11<br>Meduri 2007 10 32 8 11<br>Meduri 2007 10 32 8 11<br>Meduri 2005 10 13 11 14<br>Chawla 1200 6 6 20 7 19<br>Shilp s 2011 9 142 11 142<br>Meduri 2005 10 13 11 14<br>Sprung 1984 33 0 11 5<br>Shilp s 2010 6 98 6 103<br>Sprung 1984 33 0 11 5<br>Shilp s 2010 6 98 6 103<br>Sprung 1984 33 0 11 5<br>Shilp s 2010 6 98 6 103<br>Sprung 1984 33 0 11 5<br>Shilp s 2011 9 142 11 342<br>Meduri 2005 10 13 11 44<br>Chawla 1206 6 20 7 19<br>Shilp s 2011 9 142 11 142<br>Meduri 2006 6 20 7 19<br>Shilp s 2010 6 98 6 103<br>Sprung 1984 33 0 11 5<br>Shilp s 2010 6 98 6 103<br>Sprung 1984 33 0 11 5<br>Shilp s 2010 6 98 6 103<br>Sprung 1984 33 0 11 5<br>Shilp s 2016 22 76 27 72<br>Sprung 1984 33 0 11 5<br>Torres 2015 6 53 9 42<br>Venkatesh 2018 410 1,431 448 1,392<br>Venkatesh 2018 410 1,431 448 1,392<br>Venkatesh 2018 410 1,431 448 1,392<br>Vidiz 2002 8 12 12 8<br>Venkatesh 2018 410 1,431 448 1,392<br>Vidiz 2011 16 11 15 13<br>Corrail<br>Heterogeneity: $r^2 = 0.00^{1^2} = 0.00^{3}$ $r^2 = 1.00$<br>Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$<br>$\frac{1}{1/28}$ $\frac{1}{1/16}$ $\frac{1}{12}$ $\frac{4}{4}$   | Arabi 2011   | 33        | 6        | 26    | 10         | -                        | 1.17 [ 0.92, 1.49]  | 5.60   |  |  |
| Bone 1987 65 126 48 142<br>Briegel 1999 3 17 4 16<br>Chawla 1999 6 17 10 11<br>Chawla 1999 6 17 12 3<br>Confalonier 2005 0 23 6 17<br>Confalonier 2005 0 23 6 17<br>Confalonier 2005 0 23 6 17<br>Confalonier 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Cordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Cordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Cordon 2016 15 156 14 156<br>Hu 2009 4 34 6 8<br>Chawla 22 16 20 17<br>Luce 1988 22 6 4 27<br>Meduri 2007 10 32 8 11<br>Cordon 2011 9 142 11 142<br>Constant 1976 9 77 33 53<br>Shilders 2010 6 98 6 103<br>Shinglers 2010 7 1 3 13 1<br>Shinglers 2015 7 1 3 13 1<br>Shinglers 2015 7 1 3 13 1<br>Shinglers 2016 7 2 7 2<br>Shinglers 2017 7 2<br>Shinglers 2018 54 26 58 22<br>Shinglers 2018 54 26 58 9 22<br>Shinglers 2019<br>Shinglers 2019 7 23 89 24 87<br>Shinglers 2019<br>Shinglers 2   | Birudaraju 2022  | 9         | 12       | 16    | 6          |                          | 0.59 [ 0.34, 1.03]  | 1.07   |  |  |
| Briegel 1999   3   17   4   16   0.75 [0.19, 2.93]   0.18     Chawla 1999   6   17   10   11   0.55 [0.24, 1.25]   0.49     Cicarelli 2007   7   7   12   3   0.68 [0.35, 1.12]   0.98     Confalonieri 2005   0   23   6   17   10   11   0.55 [0.24, 1.25]   0.49     Gordon 2014   7   23   6   17   10   11   0.97 [0.39, 2.43]   0.39     Gordon 2016   62   139   57   150   1.12 [0.83, 1.52]   3.60     Hu 2009   4   34   6   33   0.68 [0.21, 2.23]   0.24     Keh 2016   15   156   14   156   1.07 [0.72, 160]   2.04     Liv 2017   23   35   19   41   1.05 [0.77, 2.04]   1.38     Meduri 2007   10   32   8   11   0.57 [0.27, 1.20]   0.58     Meduri 2009   22   26   4   27   3.55 [1.35, 9.32]   0.35     Meduri 2007   10   32   8   | Bollaert 1998  | 7         | 15       | 12    | 7          |                          | 0.50 [ 0.25, 1.02]  | 0.67   |  |  |
| Chawla 1999 6 17 10 11<br>Cicarelli 2007 7 7 7 12 3<br>Confalonieri 2005 0 23 6 17<br>Gordon 2014 7 24 7 23<br>Gordon 2016 62 139 57 150<br>Hu 2009 4 34 6 33<br>Gordon 2016 15 156 14 156<br>Liu 2012 3 9 6 8<br>Liu 2012 3 9 6 8<br>Liu 2012 3 9 6 8<br>Liu 2017 10 32 8 11<br>Meduri 2007 10 32 8 11<br>Meduri 2007 10 32 8 11<br>Meduri 2005 10 13 11 14<br>Rezk 2013 0 18 3 6<br>Qinger 2005 10 13 11 14<br>Rezk 2013 0 18 3 6<br>Schumer 1976 9 77 33 53<br>Snijders 2010 6 98 6 103<br>Snijders 2016 5 7 19<br>Snijders 2017 7 2<br>Staber 2015 6 5 3 9 52<br>SVASSCS G 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Venkatesh 2018 410 1,411 448 1,392<br>Venkatesh 2018 410 1,411 448 1,392<br>Venkatesh 2018 410 1,411 4   | Bone 1987  | 65        | 126      | 48    | 142        | -                        | 1.35 [ 0.98, 1.84]  | 3.34   |  |  |
| Cicarelli 2007   7   7   12   3     Confalonieri 2005   0   23   6   17     Gordon 2014   7   24   7   23     Gordon 2016   62   139   57   150     Hu 2009   4   34   6   33   0.68   0.021   2.23   0.24     Keh 2016   15   156   14   156   14.12   0.88   0.22   0.24   0.24     Liu 2012   3   9   6   8   0.58   0.18   1.85   0.25     Luce 1988   22   16   20   17   1.07   0.72   1.60   2.04     Lv 2017   23   35   19   41   -0.57   1.07   2.03     Meduri 2007   10   32   8   11   -0.57   1.07   2.04   1.38     Meduri 2007   10   32   8   14   -0.57   0.72   1.03   1.31   1.42   0.38   0.35   1.35   1.92   0.35   1.32   0.04   0.33   0.07 <td>Briegel 1999</td> <td>3</td> <td>17</td> <td>4</td> <td>16</td> <td></td> <td>0.75 [ 0.19, 2.93]</td> <td>0.18</td>  | Briegel 1999   | 3         | 17       | 4     | 16         |                          | 0.75 [ 0.19, 2.93]  | 0.18   |  |  |
| Confalonieri 2005   0   23   6   17   0.08   0.00, 1.29   0.04     Gordon 2016   62   139   57   150   1.12   0.88   0.68   0.21, 2.23   0.24     Keh 2016   15   156   14   156   1.15   1.12   0.83   1.12   0.24   0.88   0.68   0.21, 2.23   0.24     Lue 2016   15   156   14   156   1.07   0.72, 1.60   2.04     Lue 2198   22   16   20   17   1.07   0.72, 1.60   2.04     Lv 2017   23   35   19   41   1.25   0.77, 2.04   1.38     Meduri 2007   10   32   8   11   0.57   0.27, 1.20   0.58     Meigivis 2011   9   142   11   142   0.83   0.35   1.94   0.68   0.08   0.00   1.32   0.94     Rinaldi 2006   6   20   7   19   0.86   0.33   0.07   1.55   0.14     Sprung 1984   33   10   11  | Chawla 1999  | 6         | 17       | 10    | 11         |                          | 0.55 [ 0.24, 1.25]  | 0.49   |  |  |
| Gordon 2014   7   24   7   23   0.97 [0.39, 2.43]   0.39     Gordon 2016   62   139   57   150   1.12 [0.83, 1.52]   3.60     Hu 2009   4   34   6   33   0.68 [0.21, 2.23]   0.24     Liu 2012   3   9   6   8   0.58 [0.81, 1.85]   0.25     Luce 1988   22   16   20   17   1.07 [0.72, 1.60]   2.04     Lv 2017   23   35   19   41   1.25 [0.77, 2.04]   1.38     Meduri 2007   10   32   8   11   0.57 [0.27, 1.20]   0.58     Meduri 2009   22   26   4   27   .355 [1.35, 9.32]   0.35     Meduri 2005   10   13   11   142   0.88 [0.00, 1.32]   0.04     Rinaldi 2006   6   20   7   19   0.88 [0.00, 1.32]   0.44     Sprung 1984   33   10   11   5   1.12 [0.77, 1.61]   2.43     Talebi Doluee 2018   54   26   58   22   0.93 [0.76, 1.14]   5.23 </td <td>Cicarelli 2007</td> <td>7</td> <td>7</td> <td>12</td> <td>3</td> <td></td> <td>0.63 [ 0.35, 1.12]</td> <td>0.98</td>  | Cicarelli 2007   | 7         | 7        | 12    | 3          |                          | 0.63 [ 0.35, 1.12]  | 0.98   |  |  |
| Gordon 2016   62   139   57   150     Hu 2009   4   34   6   33     Keh 2016   15   156   14   156     Liu 2012   3   9   6   8     Liu 2017   23   35   19   41     Lv 2017   23   35   19   41     Meduri 2007   10   32   8   11   0.57 [0.27, 1.20]   0.58     Meduri 2009   22   26   4   27   0.83 [0.35, 1.94]   0.67 [0.27, 1.00]   2.04     Meduri 2009   22   26   4   27   0.83 [0.35, 1.94]   0.65 [0.77, 2.04]   1.38     Meduri 2009   22   26   4   27   0.83 [0.35, 1.94]   0.46     Oppert 2005   10   13   11   142   0.88 [0.00, 1.32]   0.04     Rinaldi 2006   6   20   7   19   0.88 [0.33, 2.21]   0.37     Shrup 1984   33   10   11   5   1.12 [0.77, 1.61]   2.43     Sprung 2008   86   165   78 </td <td>Confalonieri 2005</td> <td>0</td> <td>23</td> <td>6</td> <td>17</td> <td></td> <td>0.08 [ 0.00, 1.29]</td> <td>0.04</td>   | Confalonieri 2005  | 0         | 23       | 6     | 17         |                          | 0.08 [ 0.00, 1.29]  | 0.04   |  |  |
| Hu 2009 4 34 6 33<br>Keh 2016 15 156 14 156<br>Liu 2012 3 9 6 8<br>Liu 2012 3 9 6 8<br>Liu 2012 3 9 6 8<br>Liu 2017 23 35 19 41<br>Meduri 2007 10 32 8 11<br>Meduri 2009 22 26 4 27<br>Mejvis 2011 9 142 11 142<br>Oppert 2005 10 13 11 14<br>Rezk 2013 0 18 3 6<br>Rinaldi 2006 6 20 7 19<br>Sabry 2011 2 38 6 34<br>Schurge 1976 9 77 33 53<br>Snijders 2010 6 98 6 103<br>Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Talebi Doluee 2018 54 26 58 22<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yikiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Madim 2005 11 6 11 15 13<br>Overall<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Madim 2005 11 7<br>Yikiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Medicide 2018 50.16, $p = 0.02$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Medicide 2018 50.16, $p = 0.02$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Metarom-effects ML model  | Gordon 2014  | 7         | 24       | 7     | 23         | _                        | 0.97 [ 0.39, 2.43]  | 0.39   |  |  |
| Keh 2016   15   156   14   156     Liu 2012   3   9   6   8     Liu 2012   3   9   6   8     Luce 1988   22   16   20   17     Lv 2017   23   35   19   41     Meduri 2007   10   32   8   11     Meduri 2009   22   26   4   27     Meijvis 2011   9   142   11   142     Oppert 2005   10   13   11   14     Rezk 2013   0   18   3   6     Schumer 1976   9   77   33   53     Sabry 2011   2   38   6   103     Schumer 1976   9   77   33   53     Sprung 1984   33   10   11   5     Sprung 2008   86   165   78   109   0.85   0.65   0.27     Takeb Doluce 2018   54   26   58   22   0.93   0.76   1.41   7.99     Tandan  | Gordon 2016  | 62        | 139      | 57    | 150        | -                        | 1.12 [ 0.83, 1.52]  | 3.60   |  |  |
| Liu 2012 3 9 6 8<br>Luce 1988 22 16 20 17<br>Lv 2017 23 35 19 41<br>Meduri 2007 10 32 8 11<br>Meduri 2009 22 26 4 27<br>Meijvis 2011 9 142 11 142<br>Oppert 2005 10 13 11 14<br>Rezk 2013 0 18 3 6<br>Rinaldi 2006 6 20 7 19<br>Sabry 2011 2 38 6 34<br>Schumer 1976 9 77 33 53<br>Snjders 2010 6 98 6 103<br>Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Tadeh 2005 11 3 13 1<br>Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Yildiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $r^2 = 0.00$ , $r^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Heterogeneity: $r^2 = 0.00$ , $r^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$  | Hu 2009  | 4         | 34       | 6     | 33         |                          | 0.68 [ 0.21, 2.23]  | 0.24   |  |  |
| Luce 1988 22 16 20 17<br>Lv 2017 23 35 19 41<br>Meduri 2007 10 32 8 11<br>Meduri 2009 22 26 4 27<br>Meijvis 2011 9 142 11 142<br>Oppert 2005 10 13 11 14<br>Rezk 2013 0 18 3 6<br>Rinaldi 2006 6 20 7 19<br>Sabry 2011 2 38 6 34<br>Schumer 1976 9 77 33 53<br>Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Talebi Doluce 2018 54 26 58 22<br>Talebi Doluce 2018 54 26 58 22<br>Meixes 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2011 16 11 15 13<br><b>Overali</b><br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00$ %, $H^2 = 1.00$<br>Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00$ %, $H^2 = 1.00$<br>Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00$ %, $H^2 = 1.00$<br>Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$  | Keh 2016   | 15        | 156      | 14    | 156        | -                        | 1.07 [ 0.53, 2.14]  | 0.68   |  |  |
| Lv 2017 23 35 19 41<br>Meduri 2007 10 32 8 11<br>Meduri 2009 22 26 4 27<br>Meijvis 2011 9 142 11 142<br>Opper 2005 10 13 11 14<br>Rezk 2013 0 18 3 6<br>Rinaldi 2006 6 20 7 19<br>Sabry 2011 2 38 6 34<br>Schumer 1976 9 77 33 53<br>Snijders 2010 6 98 6 103<br>Sprung 1984 33 10 11 5<br>Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Tardan 2005 11 3 13 1<br>Torres 2015 6 53 9 52<br>VASCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2010 16 11 15 13<br>Overall<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$<br>Random-effects ML model   | Liu 2012   | 3         | 9        | 6     | 8          |                          | 0.58 [ 0.18, 1.85]  | 0.25   |  |  |
| Meduri 2007   10   32   8   11     Meduri 2009   22   26   4   27     Meijvis 2011   9   142   11   142     Oppert 2005   10   13   11   14     Rezk 2013   0   18   3   6     Rinaldi 2006   6   20   7   19   0.86 [0.03, 2.21]   0.37     Sabry 2011   2   38   6   34   0.33 [0.07, 1.55]   0.14     Schumer 1976   9   77   33   53   0.27 [0.14, 0.53]   0.73     Sprung 1984   33   10   11   5   1.12 [0.77, 1.61]   2.43     Sprung 2008   86   165   78   170   1.09 [0.85, 1.40]   5.23     Tadebi Doluee 2018   54   26   58   22   0.33 [0.76, 1.14]   7.99     Tadan 2005   11   3   13   1   0.85 [0.62, 1.15]   3.44     Tongyoo 2016   22   76   27   72   0.82 [0.50, 1.34]   1.38     Venkatesh 2018   410   1,431   | Luce 1988  | 22        | 16       | 20    | 17         | -                        | 1.07 [ 0.72, 1.60]  | 2.04   |  |  |
| Meduri 2009   22   26   4   27     Meijvis 2011   9   142   11   142     Oppert 2005   10   13   11   14     Rezk 2013   0   18   3   6     Rinaldi 2006   6   20   7   19   0.86 [0.03, 2.21]   0.37     Sabry 2011   2   38   6   34   0.33 [0.07, 1.55]   0.14     Schumer 1976   9   77   33   53   0.27 [0.14, 0.53]   0.73     Snijders 2010   6   98   6   103   1.05 [0.35, 3.15]   0.27     Sprung 1984   33   10   11   5   1.12 [0.77, 1.61]   2.43     Sprung 2008   86   165   78   170   1.09 [0.85, 1.40]   5.23     Talebi Doluee 2018   54   26   58   22   0.93 [0.76, 1.14]   7.99     Tandan 2005   11   3   13   1   0.82 [0.50, 1.34]   1.38     Tores 2015   6   53   9   52   0.93 [0.76, 1.14]   7.99     Yildiz   | Lv 2017  | 23        | 35       | 19    | 41         |                          | 1.25 [ 0.77, 2.04]  | 1.38   |  |  |
| Meijvis 2011 9 142 11 142<br>Oppert 2005 10 13 11 14<br>Rezk 2013 0 18 3 6<br>Rinaldi 2006 6 20 7 19<br>Sabry 2011 2 38 6 34<br>Schumer 1976 9 77 33 53<br>Snijders 2010 6 98 6 103<br>Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Tarden 2005 11 3 13 1<br>Tardebi Doluee 2018 54 26 58 22<br>Tardebi Doluee 2018 54 26 58 22<br>Tardebi Doluee 2018 54 26 58 22<br>Tardebi Doluee 2018 54 26 58 22<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2011 16 11 15 13<br><b>Overall</b><br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00$ %, $H^2 = 1.00$<br>Test of $\theta_1 = \theta_1$ ; Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$   | Meduri 2007  | 10        | 32       | 8     | 11         |                          | 0.57 [ 0.27, 1.20]  | 0.58   |  |  |
| Oppert 200510131114Rezk 201301836Rinaldi 2006620719Sabry 2011238634Schumer 19769773353Snijders 20106986103Sprung 19843310115Sprung 20088616578170Talebi Doluee 201854265822Tandan 200511313Torres 2015653952VASSCSG 198723892487Venkatesh 20184101,4314481,392Yildiz 2002812128Yildiz 201116111513Otrerall0.93 [0.03, 1.76]1.52Overall0.93 [0.88, 0.99]Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$ Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$ Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$ Test of $\theta = 0$ ; $z = -2.47$ , $p = 0.01$  | Meduri 2009  | 22        | 26       | 4     | 27         |                          | —3.55 [ 1.35, 9.32] | 0.35   |  |  |
| Rezk 201301836Rinaldi 2006620719Sabry 2011238634Schumer 19769773353Snijders 20106986103Sprung 19843310115Sprung 20088616578170Talebi Doluee 201854265822Talebi Doluee 201854265822Tandan 2005113131Torres 2015653952VASSCSG 198723892487Venkatesh 20184101,4314481,392Yildiz 2002812128Yildiz 201116111513Otreall0.93 [0.03]0.91 [0.81, 1.03]23.99Heterogeneity: $r^2 = 0.00$ , $r^2 = 0.00\%$ , $H^2 = 1.00$ 0.93 [0.88, 0.99]Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$ 1/124Random-effects ML model1/161/24   | Meijvis 2011   | 9         | 142      | 11    | 142        |                          | 0.83 [ 0.35, 1.94]  | 0.46   |  |  |
| Rinaldi 2006620719Sabry 2011238634Schumer 19769773353Snijders 20106986103Sprung 19843310115Sprung 20088616578170Talebi Doluee 201854265822Talebi Doluee 201854265822Talebi Doluee 201854265822Tandan 2005113131Torres 2015653952VASSCSG 198723892487Vildiz 2002812128Yildiz 201116111513Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$ 0.93 [0.88, 0.99]Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$ 1/12Aradom-effects ML model4   | Oppert 2005  | 10        | 13       | 11    | 14         |                          | 0.99 [ 0.52, 1.88]  | 0.80   |  |  |
| Sabry 2011 2 38 6 34<br>Schumer 1976 9 77 33 53<br>Snijders 2010 6 98 6 103<br>Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Talebi Doluee 2018 54 26 58 22<br>Talebi Doluee 2018 54 26 58 22<br>Talebi Doluee 2018 54 26 58 22<br>Tandan 2005 11 3 13 1<br>Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = \theta$ : $z = -2.47$ , $p = 0.01$<br>Arrow 2016 20<br>Random-effects ML model  | Rezk 2013  | 0         | 18       | 3     | 6          |                          | 0.08 [ 0.00, 1.32]  | 0.04   |  |  |
| Schumer 1976<br>Schumer 1976<br>9<br>77<br>33<br>53<br>Snijders 2010<br>6<br>98<br>6<br>103<br>Sprung 1984<br>33<br>10<br>11<br>5<br>Sprung 1984<br>33<br>10<br>11<br>5<br>Sprung 2008<br>86<br>165<br>78<br>170<br>Talebi Doluee 2018<br>54<br>26<br>58<br>22<br>11<br>3<br>13<br>1<br>1<br>109<br>10.27<br>1.12<br>10.77, 1.61<br>2.43<br>1.09<br>10.85, 1.40<br>5.23<br>1.09<br>10.85, 1.40<br>5.23<br>1.09<br>10.85, 1.40<br>5.23<br>0.93<br>10.76, 1.14<br>7.99<br>1.085<br>10.62, 1.15]<br>3.44<br>Tongyoo 2016<br>22<br>76<br>27<br>72<br>4<br>0.82<br>10.50, 1.34<br>1.38<br>0.95<br>10.57, 1.58<br>1.28<br>0.95<br>10.57, 1.58<br>1.28<br>0.91<br>10.81, 1.03<br>23.99<br>Yildiz 2002<br>8<br>12<br>12<br>8<br>12<br>12<br>8<br>1.11<br>10<br>1.11<br>10<br>1.12<br>1.11<br>10<br>1.21<br>1.11<br>10<br>1.12<br>1.11<br>10<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.21<br>1.22<br>1.22<br>1.23<br>1.23<br>0.91<br>1.21<br>0.93<br>1.23<br>0.91<br>1.21<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.93<br>1.28<br>0.27<br>0.27<br>0.27<br>0.27<br>0.28<br>0.27<br>0.28<br>0.27<br>0.28<br>0.27<br>0.28<br>0.27<br>0.28<br>0.28<br>0.28<br>0.28<br>0.28<br>0.27<br>0.28<br>0.28<br>0.28 | Rinaldi 2006   | 6         | 20       | 7     | 19         |                          | 0.86 [ 0.33, 2.21]  | 0.37   |  |  |
| Snijders 2010 6 98 6 103<br>Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Talebi Doluee 2018 54 26 58 22<br>Talebi Doluee 2018 54 26 58 22<br>Tandan 2005 11 3 13 1<br>Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Yenkatesh 2018 410 1,431 448 1,392<br>Yildiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $\tau^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Heterogeneity: $\tau^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Arrow and the second secon   | Sabry 2011   | 2         | 38       | 6     | 34         |                          | 0.33 [ 0.07, 1.55]  | 0.14   |  |  |
| Sprung 1984 33 10 11 5<br>Sprung 2008 86 165 78 170<br>Talebi Doluee 2018 54 26 58 22<br>Tandan 2005 11 3 13 1<br>Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Yenkatesh 2018 410 1,431 448 1,392<br>Yildiz 2011 16 11 15 13<br><b>Overall</b><br>Heterogeneity: $\tau^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Arrow 2016 12 12 12 12 12 12 13<br>Torres 2015 16, $p = 0.02$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Arrow 2016 12 12 12 12 11 11 15 13<br><b>Overall</b><br>Heterogeneity: $\tau^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$<br>Arrow 2016 12 12 12 12 12 12 12 12 12 12 12 12 12  | Schumer 1976   | 9         | 77       | 33    | 53         |                          | 0.27 [ 0.14, 0.53]  | 0.73   |  |  |
| Sprung 2008 86 165 78 170<br>Talebi Doluee 2018 54 26 58 22<br>Tandan 2005 11 3 13 1<br>Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $\tau^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_i = \theta_i$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : $z = -2.47$ , p = 0.01<br>Arright of the second se   | Snijders 2010  | 6         | 98       | 6     | 103        |                          | 1.05 [ 0.35, 3.15]  | 0.27   |  |  |
| Talebi Doluee 2018   54   26   58   22   0.93 [0.76, 1.14]   7.99     Tandan 2005   11   3   13   1   0.85 [0.62, 1.15]   3.44     Tongyoo 2016   22   76   27   72   0.93 [0.76, 1.14]   7.99     Torres 2015   6   53   9   52   0.85 [0.62, 1.15]   3.44     VASSCSG 1987   23   89   24   87   0.99 [0.26, 1.82]   0.35     VASSCSG 1987   23   89   24   87   0.95 [0.57, 1.58]   1.28     Venkatesh 2018   410   1,431   448   1,392   0.91 [0.81, 1.03]   23.99     Yildiz 2002   8   12   12   8   0.93 [0.78, 0.127]   0.79     Yildiz 2011   16   11   15   13   0.93 [0.88, 0.99]   0.67 [0.35, 1.27]   0.79     Heterogeneity: $\tau^2 = 0.00$ , $t^2 = 0.00\%$ , $H^2 = 1.00$ 1.11 [0.69, 1.76]   1.52   0.93 [0.88, 0.99]     Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$ 1.12   4   4  | Sprung 1984  | 33        | 10       | 11    | 5          | +                        | 1.12 [ 0.77, 1.61]  | 2.43   |  |  |
| Tandan 2005 11 3 13 1<br>Tandan 2005 11 3 13 1<br>Tongyoo 2016 22 76 27 72<br>Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Yildiz 2011 16 11 15 13<br><b>Overall</b><br>Heterogeneity: $r^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_1 = \theta_1$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : $z = -2.47$ , p = 0.01<br>Arrows and the second seco   | Sprung 2008  | 86        | 165      | 78    | 170        | +                        | 1.09 [ 0.85, 1.40]  | 5.23   |  |  |
| Tongyoo 2016 22 76 27 72<br>Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Yildiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_i = \theta_i$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : $z = -2.47$ , p = 0.01<br>Arrows and the second sec   | Talebi Doluee 2018   | 54        | 26       | 58    | 22         | -                        | 0.93 [ 0.76, 1.14]  | 7.99   |  |  |
| Torres 2015 6 53 9 52<br>VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Overall<br>Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_i = \theta_j$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : z = -2.47, p = 0.01<br>Arrow and a state of the state   | Tandan 2005  | 11        | 3        |       | 1          | -                        | 0.85 [ 0.62, 1.15]  | 3.44   |  |  |
| VASSCSG 1987 23 89 24 87<br>Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Yildiz 2011 16 11 15 13<br>Overall<br>Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_i = \theta_j$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : z = -2.47, p = 0.01<br>Random-effects ML model   | Tongyoo 2016   | 22        | 76       | 27    | 72         |                          | 0.82 [ 0.50, 1.34]  | 1.38   |  |  |
| Venkatesh 2018 410 1,431 448 1,392<br>Yildiz 2002 8 12 12 8<br>Yildiz 2011 16 11 15 13<br><b>Overall</b><br>Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_i = \theta_i$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : z = -2.47, p = 0.01<br>Arrow 11/128 1/16 1/2 4<br>Random-effects ML model   |  | 6         | 53       | 9     | 52         |                          | 0.69 [ 0.26, 1.82]  | 0.35   |  |  |
| Yildiz 2002   8   12   12   8   0.67 [ 0.35, 1.27]   0.79     Yildiz 2011   16   11   15   13   1.11 [ 0.69, 1.76]   1.52     Overall   0.93 [ 0.88, 0.99]   0.93 [ 0.88, 0.99]   0.93 [ 0.88, 0.99]     Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$ 1.11 [ 0.69, 1.76]   1.52     Test of $\theta_i = \theta_i$ : Q(38) = 59.16, p = 0.02   1.11 [ 0.49, 1.76]   1.52     Test of $\theta = 0$ : $z = -2.47$ , $p = 0.01$ 1.12 4   4     Random-effects ML model   Nodel   1.12 4   |  | 23        |          |       |            | <u>+</u>                 |                     |        |  |  |
| Yildiz 2011 16 11 15 13<br><b>Overall</b><br>Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_i = \theta_j$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : z = -2.47, p = 0.01<br>1/128 $1/16$ $1/2$ 4<br>Random-effects ML model   | Venkatesh 2018   | 410       | 1,431    | 448   | 1,392      |                          |                     | 23.99  |  |  |
| Overall   0.93 [ 0.88, 0.99]     Heterogeneity: $\tau^2 = 0.00$ , $l^2 = 0.00\%$ , $H^2 = 1.00$ Test of $\theta_i = \theta_j$ : Q(38) = 59.16, p = 0.02     Test of $\theta = 0$ : z = -2.47, p = 0.01     1/128   1/16     1/12   4  | Yildiz 2002  | 8         | 12       | 12    | 8          |                          | 0.67 [ 0.35, 1.27]  | 0.79   |  |  |
| Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$<br>Test of $\theta_i = \theta_j$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta = 0$ : z = -2.47, p = 0.01<br>1/128 $1/16$ $1/2$ 4<br>Random-effects ML model  | Yildiz 2011  | 16        | 11       | 15    | 13         | -                        | 1.11 [ 0.69, 1.76]  | 1.52   |  |  |
| Test of $\theta_i = \theta_j$ : Q(38) = 59.16, p = 0.02<br>Test of $\theta$ = 0: z = -2.47, p = 0.01<br>Random-effects ML model   | Overall  |           |          |       |            |                          | 0.93 [ 0.88, 0.99]  |        |  |  |
| Test of $\theta$ = 0: z = -2.47, p = 0.01<br>1/128 1/16 1/2 4<br>Random-effects ML model  | Heterogeneity: $\tau^2 = 0.00$ , $I^2 = 0.00\%$ , $H^2 = 1.00$ |           |          |       |            |                          |                     |        |  |  |
| Random-effects ML model   | Test of $\theta_i = \theta_j$ : Q(38) = 59.16, p = 0.02        |           |          |       |            |                          |                     |        |  |  |
| Random-effects ML model   | Test of $\theta$ = 0: z = -2.4                                 | 47, p = 0 | .01      |       |            |                          |                     |        |  |  |
|   |  |           |          |       |            | 1/128 1/16 1/2 4         |                     |        |  |  |
| igure 1. Forest plot for short-term mortality. ML = Maximum likelihood.   | Random-effects ML m  | nodel     |          |       |            |                          |                     |        |  |  |
|   | igure 1. Forest plo  | t for sh  | ort-tern | n moi | rtalitv. I | ML = Maximum likelihood. |                     |        |  |  |

15%; 95% CI, 6.9-23.8% increase; high certainty) and decrease SOFA scores at day 7 (MD, 1.41 points lower; 95% CI, 0.96-1.87 points lower; high certainty) (eFigs. 5 and 6 and eTable 4, http://links.lww. com/CCX/B266).

#### **Adverse Events**

Corticosteroids probably increase hypernatremia (RR, 1.64; 95% CI, 1.32-2.03; absolute risk increase, 2.6%; 95% CI, 1.3-4.2% increase; moderate certainty) and hyperglycemia (RR, 1.13; 95% CI, 1.08-1.18; absolute risk increase, 3.8%; 95% CI, 2.3-5.2% increase; moderate certainty) (eFigs. 7 and 8 and eTable 4, http:// links.lww.com/CCX/B266). Corticosteroids may increase the rate of neuromuscular weakness (RR, 1.21; 95% CI, 1.01-1.45; absolute risk increase, 1.2%; 95% CI, 0.1-2.5% increase; low certainty) and may decrease the rates of neuropsychiatric outcomes (RR, 0.58; 95% CI, 0.33-1.03; absolute risk reduction, 1.2%; 95% CI, 4.0% decrease to 0.2% increase; low certainty) (eFigs. 9 and 10 and eTable 4, http://links.lww. com/CCX/B266).

Corticosteroids had an uncertain effect on other adverse events, including gastrointestinal bleeding

2.06 d shorter to 0.57 d longer; low certainty) (eFigs. 3 and 4 and eTable 4, http://links.lww.com/CCX/B266).

Corticosteroids increase shock reversal at day 7 (RR, 1.24; 95% CI, 1.11-1.38; absolute risk increase,

# **TABLE 1.**Assessments of the Certainty of the Evidence for Each Included Outcome

|                                     | No. of Participants    | Cortointy of                                       |                           | Anticipat            | Anticipated Absolute Effects <sup>d</sup>             |  |  |
|-------------------------------------|------------------------|--|---------------------------|----------------------|---|--|--|
| Outcomes                            | (Studies)<br>Follow-Up | Certainty of<br>the Evidence<br>(GRADE)            | Relative Risk<br>(95% Cl) | Risk With<br>Placebo | Risk Difference With<br>Corticosteroids               |  |  |
| Long-term mortality<br>(90–180 d)   | 6438 (nine RCTs)       | ⊕⊕⊖⊖<br>Low <sup>a,c</sup>                         | RR 0.95 (0.89-1.00)       | 372/1000             | 19 fewer per 1000 (41 fewer to 0 fewer)               |  |  |
| Short-term mor-<br>tality (28–30 d) | 9711 (39 RCTs)         | ⊕⊕⊕⊖<br>Moderate°                                  | RR 0.93 (0.88–0.99)       | 297/1000             | 21 fewer per 1000 (36 fewer to 3 fewer)               |  |  |
| Shock reversal at<br>7 d            | 2922 (13 RCTs)         | ⊕⊕⊕<br>High  | RR 1.24 (1.11–1.38)       | 627/1000             | 150 more per 1000 (69<br>more to 238 more)            |  |  |
| Organ dysfunction<br>at day 7       | 1986 (nine RCTs)       | ⊕⊕⊕<br>High  | -                         | -                    | MD 1.41 points lower<br>(1.87 lower to 0.96<br>lower) |  |  |
| ICU length of stay<br>(d)           | 7626 (22 RCTs)         | $\bigoplus_{Low^{a,c}} \bigcirc$                   | -                         | -                    | MD 0.6 d fewer (1.48 fewer to 0.27 more)              |  |  |
| Hospital length of stay (d)         | 7706 (18 RCTs)         | $\bigoplus_{Low^{a,c}} \bigcirc$                   | -                         | -                    | MD 0.74 d fewer (2.06 fewer to 0.57 more)             |  |  |
| Neuromuscular<br>weakness           | 6178 (seven RCTs)      | ⊕⊕⊖⊖<br>Low <sup>a,c</sup>                         | RR 1.21 (1.01–1.45)       | 57/1000              | 12 more per 1000 (1<br>more to 25 more)               |  |  |
| Gastrointestinal bleeding           | 4355 (24 RCTs)         | ⊕⊖⊖⊖<br>Very low <sup>b,c</sup>                    | RR 1.09 (0.87–1.37)       | 55/1000              | 5 more per 1000 (7<br>fewer to 20 more)               |  |  |
| Neuropsychiatric<br>effects         | 1004 (five RCTs)       | $\underset{Low^{\flat}}{\oplus} \bigcirc \bigcirc$ | RR 0.58 (0.33-1.03)       | 59/1000              | 25 fewer per 1000 (40 fewer to 2 more)                |  |  |
| Hypernatremia                       | 4865 (five RCTs)       | ⊕⊕⊕⊖<br>Moderate <sup>°</sup>                      | RR 1.64 (1.32–2.03)       | 40/1000              | 26 more per 1000 (13<br>more to 42 more)              |  |  |
| Superinfection                      | 4599 (25 RCTs)         | ⊕⊖⊖⊖<br>Very low <sup>b,c</sup>                    | RR 1.05 (0.94–1.17)       | 201/1000             | 10 more per 1000 (12<br>fewer to 34 more)             |  |  |
| Stroke                              | 1225 (four RCTs)       | ⊕⊖⊖⊖<br>Very low <sup>b,c</sup>                    | RR 1.19 (0.42-3.42)       | 10/1000              | 2 more per 1000 (6<br>fewer to 24 more)               |  |  |
| Myocardial infarction               | 1200 (four RCTs)       | ⊕⊖⊖⊖<br>Very low <sup>b,c</sup>                    | RR 1.02 (0.55-1.90)       | 32/1000              | 1 more per 1000 (14<br>fewer to 29 more)              |  |  |
| Hyperglycemia                       | 7683 (18 RCTs)         | ⊕⊕⊕⊖<br>Moderate <sup>ь</sup>                      | RR 1.13 (1.08–1.18)       | 291/1000             | 38 more per 1000 (23<br>more to 52 more)              |  |  |

MD = mean difference, RCTs = randomized controlled trials, RR = risk ratio.

<sup>a</sup>Once for imprecision.

 $^{\rm b}\mbox{Twice}$  for imprecision.

<sup>c</sup>Once for inconsistency.

<sup>d</sup>The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence:

⊕⊕⊕⊕ High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

 $\oplus \oplus \odot$  Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

 $\oplus \oplus \bigcirc \bigcirc$  Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

 $\bigcirc$   $\bigcirc$  Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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**Figure 2.** Dose-response analysis for short-term mortality, with the *line* representing the effect size and the *ribbons* representing the 95% CIs.

decrease to 3.4% increase; very low certainty) (**eFigs. 11** and **12** and eTable 4, http://links.lww.com/CCX/B266), stroke (RR, 1.19; 95% CI, 0.42–3.42; absolute risk increase, 2.0%; 95% CI, 0.6% decrease to 2.4% increase; very low certainty), and myocardial infarction (RR, 1.02; 95% CI, 0.55–1.90; absolute risk increase, 1.0%; 95% CI, 1.4% decrease to 2.9% increase; very low certainty) (**eFigs. 13** and **14** and eTable 4, http://links.lww.com/CCX/B266).

#### **Subgroup Analyses**

Subgroup and sensitivity analyses did not demonstrate a credible effect for any of the predefined analyses and on any of the outcomes of interest, including sepsis vs. septic shock (p > 0.05 for all outcomes). **eFigures 15–26** (http://links.lww.com/CCX/B266) present the results of these subgroups.

#### DISCUSSION

#### Main Findings

We found that corticosteroids probably reduce mortality in adult patients with sepsis, with no difference We also found that corticosteroids increase shock reversal and improve organ dysfunction in 1 week. Furthermore, corticosteroids may increase the risk of hypernatremia, hyperglycemia, and neuromuscular weakness; however, these effects on adverse events were based on low certainty of evidence, limited by imprecision. The dose-response meta-analysis found no increased benefit above 260 mg of hydrocortisone per day (or equivalent). To our knowledge, this is the first dose-response analysis to address this question and provide optimal dosing information for clinicians.

in relative effect between those with or without shock.

Most of the evidence comes from studies that used hydrocortisone with or without fludrocortisone at a relatively low daily dose (under 400 mg/d).

#### In Relation to Other Findings

We found three new trials and one post hoc analysis reporting only on septic shock patients which we included in this updated review. With this new data, we have improved the precision around some of the effect estimates compared with the previous review (3). Most notably, the upper end of the CI around the pooled

effect estimate for short-term mortality now excludes harm (RR, 0.93; 95% CI, 0.88-0.99). Although incremental, the use of corticosteroids in sepsis and septic shock remains quite controversial and improved certainty in treatment effects is important for clinicians, patients, and guideline developers. Although there is still moderate certainty evidence for this outcome, and issues with imprecision persist, this is an important finding as it improves confidence in the effectiveness of corticosteroids in this patient population. A recently published individual patient data meta-analysis (IPDMA) focused only on septic shock found a similar reduction in mortality at 90 days with corticosteroids. The discrepancy in findings is almost certainly due to the included studies. While IPDMA are great at exploring heterogeneity in treatment effect through subgroup analysis, they generally include much less data as fewer trialists are willing to share individual patient data. This is clearly reflected by the referenced IPDMA that included fewer trials and patients as compared with our trial level meta-analysis. Again, while the IPDMA can provide a more nuanced evaluation of subgroups than our trial level Meta-analysis, we believe the precision gained by including more data allows our approach to best address the relative effect of the intervention across patients with sepsis and septic shock (19).

The most recent Surviving Sepsis Campaign international guidelines provide a conditional recommendation for using corticosteroids in adult patients with septic shock who require ongoing support with vasopressors (20). Beyond this expanded population, the increased precision and certainty of findings afforded by the inclusion of new studies, especially for mortality, may support stronger guidance and this will need to be reevaluated in the next iteration of the guideline.

The data addressing the role of corticosteroids in children with sepsis remains less clear. Unfortunately, we did not find many eligible studies examining this population and although there were no signs of relative effect modification based on adults vs. children, the generalizability of these findings to children remains unclear. The ongoing Stress Hydrocortisone In Pediatric Septic Shock trial (NCT03401398) may provide more answers in this specific subset of the population and inform the treatment of children with sepsis. Although there was initial enthusiasm for the HAT combination based on an early uncontrolled observational study (21), subsequent larger RCTs evaluating HAT therapy have shown lack of benefit (22,24,25,30– 33) and maybe even harm. Sensitivity analysis performed as part of this present meta-analysis did not reveal evidence of a differential effect on patient important outcomes with HAT therapy and given more recent data demonstrating the potential harm of vitamin C in sepsis (26), vitamin C should not be given with corticosteroids.

Our dose-response meta-analysis suggests approximately 260 mg/d of hydrocortisone or hydrocortisone equivalent may be the optimal dose; however, our data demonstrated a consistent effect across various corticosteroid compounds and durations of therapy. Notably, most studies evaluated hydrocortisone, with much fewer RCTs examining methylprednisolone, prednisolone, or dexamethasone. This consistent relative effect across corticosteroid compounds is informative as evidence of benefits from dexamethasone (ARDS, COVID) (27) and hydrocortisone (CAP) (28, 29) increases for other overlapping conditions and clinicians must choose an agent when sepsis is present in association with these syndromes.

#### **Strengths and Limitations**

The strengths of this review include a comprehensive search including a prepublished protocol, application of GRADE methodology to assess the certainty of effects, a priori specification of possible effect modifiers, and meta-regression to explore modification and specification of both relative and absolute effects. We also provide a dose-response analysis, which provides a novel insight into optimal dosing for this population, which has previously not been assessed.

Limitations of this review include clinical heterogeneity as studies were conducted over a span of approximately 6 decades. The exploration of the subgroup hypothesis and the failure to identify effect modification based on any factor, including year of publication, decreases this concern.

Although we did not find a statistically significant subgroup effect for patients with septic shock, the included trials mostly focused on this population with few and fewer studies that enrolled patients with sepsis and without shock. All included studies enrolled patients with sepsis based on previous Sepsis 1 or Sepsis 2 diagnostic criteria, although we have no reason to believe that using the new Sepsis 3 criteria would alter the efficacy or risks of corticosteroids.

Based on the dose-response meta-analysis around 260 mg/d of hydrocortisone (or equivalent) appears to be the optimal regime but we were not able to perform a statistical test to compare to other dosing. It is therefore certainly possible that a slightly higher or slightly lower dose would be equally beneficial.

#### **Implications and Future Directions**

This review can help guideline developers and clinicians on several fronts. First, guideline developers can more confidently assess the role of corticosteroids in septic shock and sepsis, due to the more precise estimates of effect, especially evaluating mortality. Second, both clinicians and guideline developers now have a reference for optimal dosing, namely, we found no benefit above the typical standard dosing of approximately 260 mg/d of hydrocortisone or equivalent. Third, this review provides clinicians, patients, and their families with the most up-to-date summary of potential harms (i.e., hyperglycemia, neuromuscular weakness, hypernatremia) and benefits of administering corticosteroids for patients with sepsis. Future studies examining corticosteroids in sepsis should seek to clarify their effect on long-term mortality and should systematically assess gastrointestinal, glycemic, neuromuscular, and neuropsychiatric outcomes to better inform the tradeoff between benefits and risks.

#### CONCLUSIONS

We demonstrate that corticosteroids probably reduce mortality, increase shock reversal, and decrease SOFA scores in patients with sepsis. Corticosteroids probably increase hypernatremia and hyperglycemia and may increase neuromuscular weakness. Dose-response meta-analysis suggested the optimal dosage to be 260 mg/d of hydrocortisone or equivalent.

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