SYSTEMATIC REVIEW

OPEN

Adverse Effects Related to Corticosteroid Use in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis

Dipayan Chaudhuri, MD[1]
Lori Israelian, MD[1]
Zbigniew Putowski, MD[2]
Jay Prakash, MBBS[3]
Tyler Pitre, MD[4]
Andrea M. Nei, PharmD[5]
Joanna L. Spencer-Segal, MD, PhD[6,7]
Hayley B. Gershengorn, MD[8,9]
Djillali Annane, MD[10,11]
Stephen M. Pastores, MD[12,13]
Bram Rochwerg, MD[1]

OBJECTIVES: We postulate that corticosteroid-related side effects in critically ill patients are similar across sepsis, acute respiratory distress syndrome (ARDS), and community-acquired pneumonia (CAP). By pooling data across all trials that have examined corticosteroids in these three acute conditions, we aim to examine the side effects of corticosteroid use in critical illness.

DATA SOURCES: We performed a comprehensive search of MEDLINE, Embase, Centers for Disease Control and Prevention library of COVID research, CINAHL, and Cochrane center for trials.

STUDY SELECTION: We included randomized controlled trials (RCTs) that compared corticosteroids to no corticosteroids or placebo in patients with sepsis, ARDS, and CAP.

DATA EXTRACTION: We summarized data addressing the most described side effects of corticosteroid use in critical care: gastrointestinal bleeding, hyperglycemia, hypernatremia, superinfections/secondary infections, neuropsychiatric effects, and neuromuscular weakness.

DATA SYNTHESIS: We included 47 RCTs ($n = 13,893$ patients). Corticosteroids probably have no effect on gastrointestinal bleeding (relative risk [RR], 1.08; 95% CI, 0.87–1.34; absolute risk increase [ARI], 0.3%; moderate certainty) or secondary infections (RR, 0.97; 95% CI, 0.89–1.05; absolute risk reduction, 0.5%; moderate certainty) and may have no effect on neuromuscular weakness (RR, 1.22; 95% CI, 1.03–1.45; ARI, 1.4%; low certainty) or neuropsychiatric events (RR, 1.19; 95% CI, 0.82–1.74; ARI, 0.5%; low certainty). Conversely, they increase the risk of hyperglycemia (RR, 1.21; 95% CI, 1.11–1.31; ARI, 5.4%; high certainty) and probably increase the risk of hypernatremia (RR, 1.59; 95% CI, 1.29–1.96; ARI, 2.3%; moderate certainty).

CONCLUSIONS: In ARDS, sepsis, and CAP, corticosteroids are associated with hyperglycemia and probably with hypernatremia but likely have no effect on gastrointestinal bleeding or secondary infections. More data examining effects of corticosteroids, particularly on neuropsychiatric outcomes and neuromuscular weakness, would clarify the safety of this class of drugs in critical illness.

KEYWORDS: complications; corticosteroids; critical illness; systematic review

Corticosteroids are essential for survival of critical illness, and changes in endogenous corticosteroid signaling involving hypothalamic-pituitary-adrenal axis activity, cortisol metabolism, and glucocorticoid sensitivity may contribute to clinical outcomes (1). Recent guidelines have cautiously recommended corticosteroid administration to critically ill patients with

DOI: 10.1097/CCE.0000000000001071

KEY POINTS

Question: What are the side effects of corticosteroid use in critical illness, specifically in sepsis, acute respiratory distress syndrome, and community-acquired pneumonia?

Findings: Our meta-analysis shows corticosteroids probably have no effect on gastrointestinal bleeding or secondary infections (both moderate certainty) and may have no effect on neuromuscular weakness or neuropsychiatric events (both low certainty). Conversely, they increase the risk of hyperglycemia (high certainty) and probably increase the risk of hypernatremia (moderate certainty).

Meaning: While corticosteroids seem to be safe in critical illness, one must be wary of hyperglycemia and hypernatremia and keep in mind that its effect on weakness and neuropsychiatric events is unclear.

sepsis, acute respiratory distress syndrome (ARDS), and community-acquired pneumonia (CAP) (2, 3). However, the adverse effects associated with corticosteroid use in critically ill patients has not been well studied. Previous systematic reviews have examined corticosteroid-related side effects when administered for specific indications, however, differential reporting across trials and low event rates have resulted in very low-certainty evidence for most of these adverse outcomes (4–6).

We postulate that the underlying pathophysiology leading to corticosteroid-related adverse effects in critically ill patients is similar across sepsis, ARDS, and CAP. By pooling data across all trials that have examined corticosteroid use in these three acute conditions, we aim to increase precision and certainty of evidence and better understand the actual harms associated with this intervention in critically ill patients. The primary objective of this systematic review and meta-analysis was to examine patient-important side effects of corticosteroid use in patients with sepsis, ARDS, and CAP.

MATERIALS AND METHODS

We registered the protocol for this systematic review on PROSPERO (No. 42023421151) and used the PRISMA checklist to report findings (**Supplementary Table 1**, http://links.lww.com/CCX/B327).

Data Sources and Searches

With the help of an experienced medical librarian, we performed a comprehensive search of relevant databases (MEDLINE, Embase, Centers for Disease Control and Prevention library of COVID research, CINAHL, and Cochrane center for trials). The search strategy was based on recently published systematic reviews conducted by authors of this article examining the effects of corticosteroids in patients with ARDS (4), sepsis (5), and CAP (6). We updated the searches for ARDS and CAP to October 2023; the review examining sepsis was just published in October 2023. We limited the search to human studies and set no language restrictions. We screened reference lists of relevant systematic reviews and contacted experts in the field to ensure we were not missing any additional articles. A copy of the search strategy is included in the **Supplementary Materials** (http://links.lww.com/CCX/B327).

Study Selection

Using (Covidence, Melbourne, Australia) a systematic review management software, two reviewers (D.C., T.P.) screened citations independently and in duplicate, in two stages: first, we screened the title and abstract, and then the full text of each abstract selected as potentially relevant in the first stage. We captured reasons for study exclusion at the full-text review stage. A third author (B.R.) adjudicated disagreements, when necessary.

Eligibility Criteria

We included randomized controlled trials (RCTs) that compared corticosteroids to placebo or usual care in patients with ARDS, sepsis, or CAP. Previously published reviews and the Supplementary Materials (http://links.lww.com/CCX/B327) present more detail on the definition of the study conditions (4–6). We excluded any nonrandomized, quasi-randomized, or observational studies. We summarized data addressing the most commonly described side effects of corticosteroid use in critical care: gastrointestinal bleeding, hyperglycemia, hypernatremia,

superinfections/secondary infections, neuropsychiatric effects, and neuromuscular weakness. We did not have a standardized definition for each of these outcomes, given variability of reporting, but rather included them as defined by study authors (**Supplementary Tables 3** and **4** [http://links.lww.com/CCX/B327] for outcome definitions across studies). Further, given that none of these trials were designed for safety, we also collected data on whether trials systematically screened for predefined complications or whether they were self-reported, along with the length of follow-up.

Data Extraction and Quality and Certainty Assessment

Four reviewers (D.C., L.I., Z.P., J.P.) abstracted data independently and in duplicate using a structured data abstraction form. A fifth reviewer (B.R.) resolved any disagreements. We collected study characteristics, patient demographics, intervention, control details, and definitions of the prespecified study outcomes.

We assessed risk of bias (ROB) independently and in duplicate using the (Cochrane Denmark, Odense, Denmark) ROB 2.0 tool for RCTs. We used the tool to assess for ROB in the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We rated each domain as "low," "some concerns," or "high." We determined overall ROB for each trial based on the highest risk attributed to any one domain. We assessed certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (7). We judged the certainty for each outcome as high, moderate, low, or very low, based on considerations of ROB, inconsistency, indirectness, imprecision, and publication bias.

To make judgments regarding imprecision, we used a minimally contextualized approach (8). We used a minimally important absolute difference of 2% for all outcomes based on consensus of the authors. Using updated GRADE guidance, we rated imprecision using the CI method (9).

In keeping with GRADE methods, we use terminology consistent with the overall certainty of evidence. This includes stronger language for high-certainty evidence, and less certain language ("probably" or "may") for moderate- or low-certainty evidence (7).

Data Analysis

Pairwise Meta-Analyses. To generate forest plots and conduct pairwise meta-analysis, we used RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) software. We used the DerSimonian-Laird random-effects model with inverse-variance weighting to generate pooled treatment effects across studies. We assessed statistical heterogeneity between trials using a combination of the chi-square test, the I^2 statistic, and visual inspection of the forest plots. We present results of dichotomous outcomes using relative risk (RR) and continuous outcomes as mean difference, both with 95% CIs. We also provide absolute differences with 95% CIs. If medians and interquartile ranges (IQRs) were reported in included trials instead of mean and SD, we assumed normality in data distribution and converted IQR to SDs using standardized methods (10).

Subgroup Analysis. We planned two a priori subgroup analyses based on: 1) disease etiology (CAP vs. ARDS vs. sepsis—hypothesizing that there would be no difference between groups) and 2) type of corticosteroid used (hypothesizing that there would be no difference between groups). We also performed two post hoc subgroup analyses. First, we examined the outcome of hyperglycemia based on the definition that was used. We grouped hyperglycemia into four categories: glucose greater than 8.3 mmol/L (> 150 mg/dL), glucose greater than 10 mmol/L (> 180 mg/dL), hyperglycemia treated with insulin, and other. Second, we examined outcomes based on whether trials systematically screened for adverse effects or they were self-reported, hypothesizing that we may see a stronger signal for harm in the studies that employed systematic screening.

For all subgroup analyses, if the *p* value for the interaction term was less than 0.05, we used the ICEMAN tool (11) to assess for credible subgroup effects.

Dose-Response Analysis. For each outcome, we performed a dose-response meta-analysis. 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 and Longnecker (12) and Orsini

et al (13) using a one-stage approach (14). For this dose-response analysis, we considered the daily dose of corticosteroids administered during the trial. We used the following corticosteroid conversions for glucocorticoid potency: 1 mg of dexamethasone = 26.7 mg of hydrocortisone = 5.3 mg of methylprednisolone/prednisolone = 6.7 mg of prednisone. For all dose-response 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 (15). 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 associations, we present results from that model. If no statistically significant association was observed, we present only the goodness-of-fit statistic. If both linear and nonlinear dose-response models for an outcome were statistically significant, we presented the more accurate model. We performed analyses using the "dosresmeta" in R (Version 4.03; R Foundation for Statistical Computing, Vienna, Austria).

Trial Sequential Analysis. To help inform our assessment of imprecision, we performed trial sequential analysis (TSA). We conducted TSA (16) using the random-effects model for all included outcomes. For the TSA, we used a statistical significance level of 5%, a power of 80%, and a RR reduction of 15% to represent a clinically important difference. We performed TSA analyses using TSA, Version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark; www.ctu.dk/tsa).

RESULTS

The updated search yielded 6505 unique citations addressing patients with ARDS and 579 citations addressing patients with CAP. After screening, we did not find any new eligible trials beyond those included in the previous reviews (4–6). Overall, we included 47 trials (n = 13,893) (17–61) that reported adverse effects related to corticosteroid use in critically ill patients with ARDS, CAP, and sepsis/septic shock, the details of which are presented in **Supplementary Table 2** (http://links.lww.com/CCX/B327).

Of the included studies, 12 were in patients with ARDS (n = 1739) (17, 18, 29, 40, 51, 56–60), 15 were in patients with CAP (n = 4415) (19–28, 30–33, 61), and 20 trials included patients with sepsis or septic shock (n = 7739) (34–39, 41–50, 52–55). All trials included adult patients except for one that enrolled only children with septic shock (46). For type of corticosteroid molecule, 22 trials used hydrocortisone, 13 used methylprednisolone, six used dexamethasone, and five used prednisone or prednisolone. The dose of corticosteroid varied, although the majority of trials (31/47) used 400 mg/d of hydrocortisone or less. Most studies used corticosteroids for 7 days or fewer (87%, n = 40). Of the 47 studies, 26 systematically screened for adverse effects (17, 18, 22–24, 26–28, 34–39, 45–47, 50, 51, 55–60), 16 self-reported (20, 21, 25, 29–33, 40–43, 48, 52, 59, 61), and five did both depending on outcome (19, 44, 49, 53, 54). Only three trials followed patients for safety outcomes for longer than 30 days (17, 22, 35). Supplementary Tables 2 and 3 (http://links.lww.com/CCX/B327) illustrate how outcomes were defined and collected across studies.

We judged seven RCTs to be at high ROB for all outcomes (19, 25, 27, 32, 40, 47, 49). All seven were at ROB due to concerns regarding randomization, six were at ROB due to deviations from the intended interventions and four were at ROB due to missing outcome data. When examining the specific outcomes of neuropsychiatric adverse effects and neuromuscular weakness, we had concerns regarding measurement of this outcome and selection of the reported result for all included trials. **Supplementary Table 5*A*–*E*** (http://links.lww.com/CCX/B327) presents all ROB assessments.

Supplementary Table 6 (http://links.lww.com/CCX/B327) shows the overall effect estimates and GRADE certainty assessments. We found that corticosteroids probably have no effect on gastrointestinal bleeding (7053 patients in 32 trials; RR, 1.08; 95% CI, 0.87–1.34; absolute risk increase [ARI], 0.3%; 95% CI, 0.5% fewer to 1.4% more; moderate certainty; **Fig. 1**) or secondary infections (11,777 patients in 39 trials; RR, 0.97; 95% CI, 0.89–1.05; absolute risk reduction, 0.5%; 95% CI, 1.9% fewer to 0.9% more; moderate certainty; **Fig. 2**). We found that corticosteroids increase hyperglycemia (11,536 patients in 32 trials; RR, 1.21; 95% CI, 1.11–1.32; ARI, 5.4%; 95% CI, 2.8–7.9% increase; high certainty; **Fig. 3**) and probably increase hypernatremia (5599 patients in seven trials; RR, 1.59; 95% CI, 1.29–1.96; ARI, 2.3%; 95% CI, 1.1–3.8% increase; moderate certainty; **Supplementary Fig. 1**, http://links.lww.com/CCX/B327).

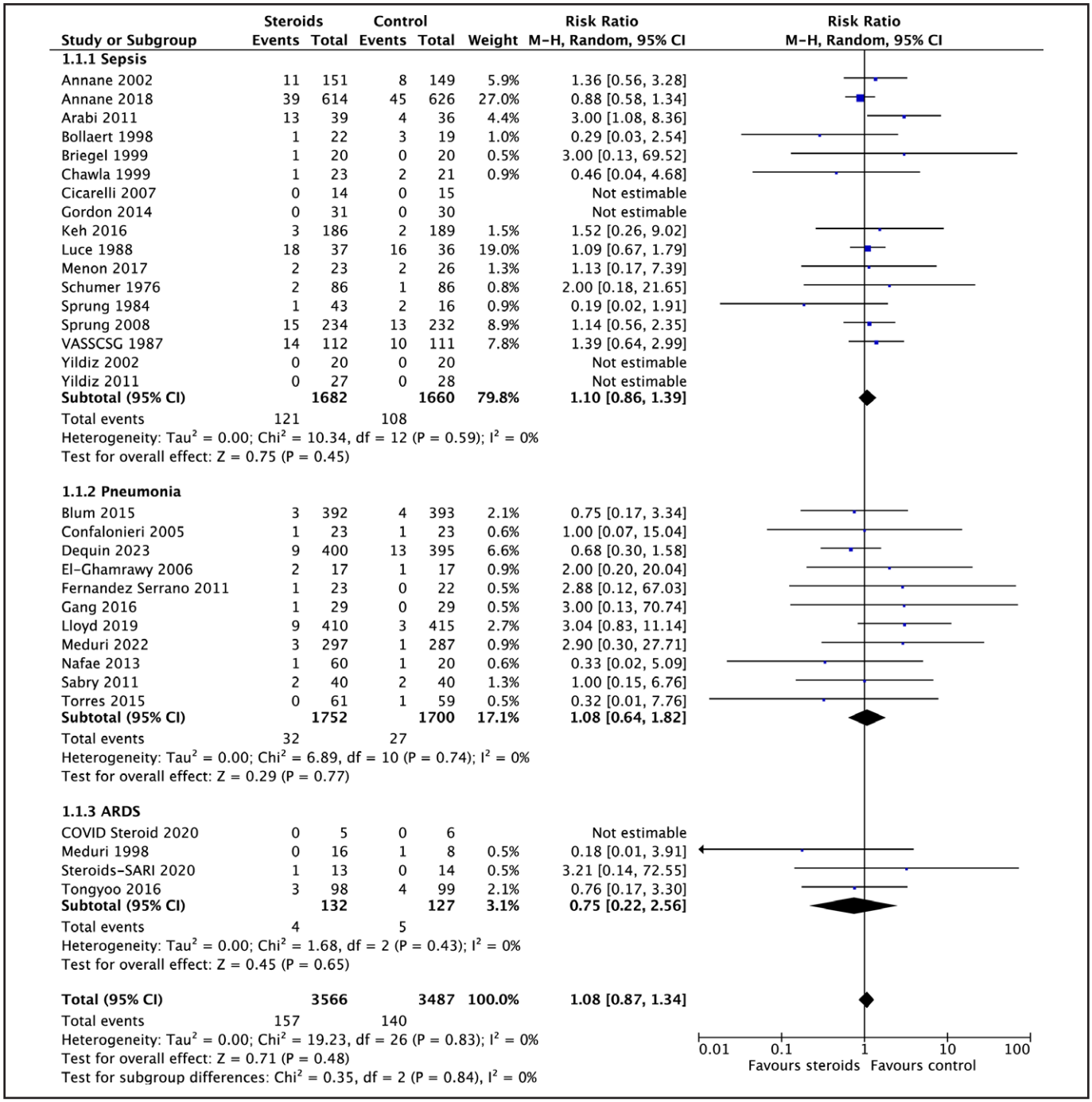

Figure 1. Effect of corticosteroids on gastrointestinal bleeding. Studies are grouped by underlying condition. ARDS = acute respiratory distress syndrome, *df* = degrees of freedom, M-H = Mantel-Haenszel.

Supplementary Table 3 (http://links.lww.com/CCX/B327) shows that studies defined neuromuscular weakness as any combination of muscle weakness or myopathy or neuropathy, and that of the ten studies that reported neuropsychiatric outcomes, most specified delirium and/or psychosis-related side events. Corticosteroids may have no effect on neuromuscular weakness (6361 patients in eight trials; RR, 1.22; 95% CI, 1.03–1.45; ARI, 1.4%; 95% CI, 0.2% more to 2.8% more; low certainty; **Fig. 4**) or neuropsychiatric events (3781 patients in nine trials; RR, 1.19; 95% CI, 0.82–1.74; ARI, 0.5%; 95% CI, 0.5% fewer to 1.9% more; low certainty; **Supplementary Fig. 2**, http://links.lww.com/CCX/B327). TSA showed that optimal information size was only reached for hyperglycemia and secondary infection but was not reached for other outcomes, and

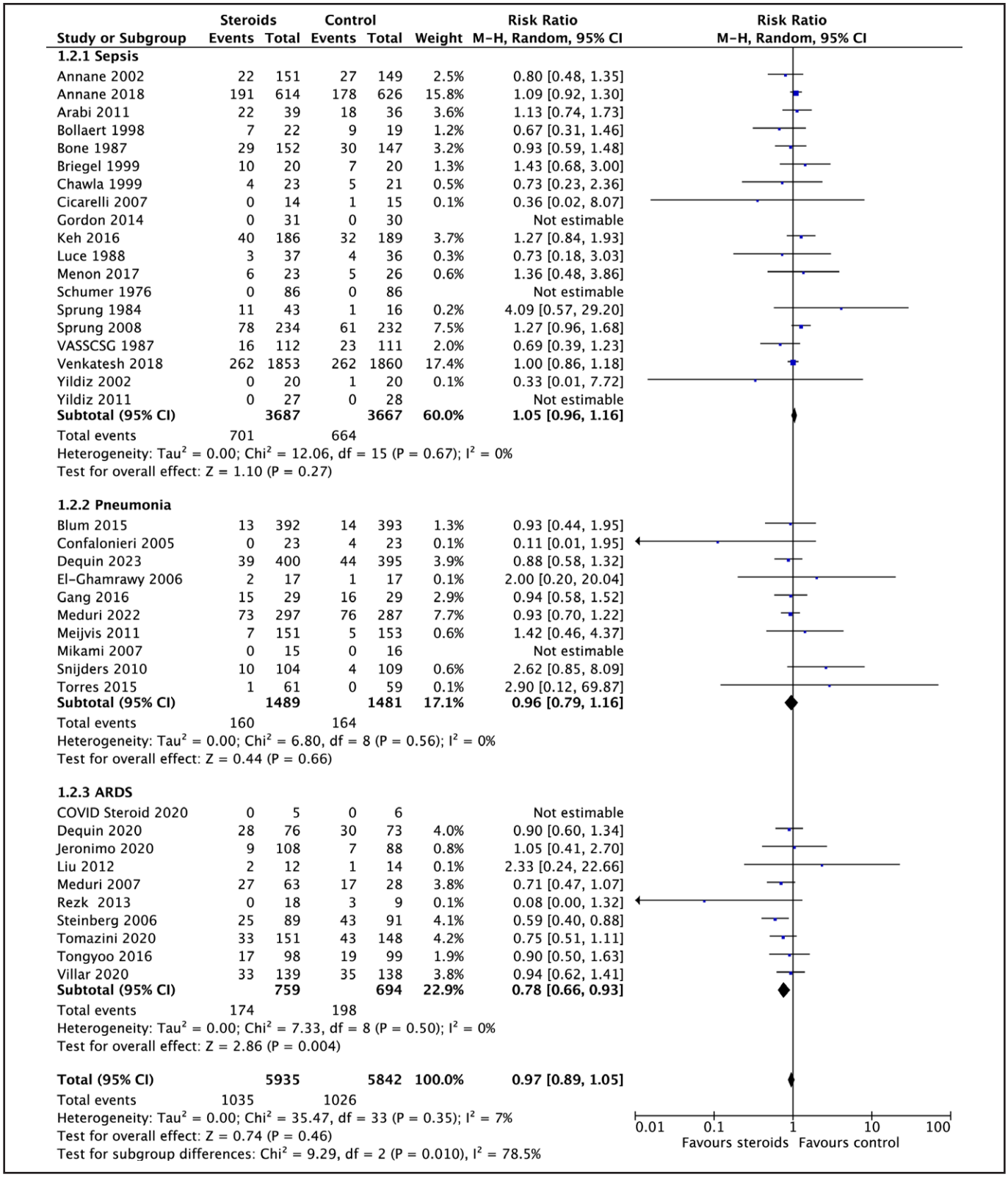

Figure 2. Effect of corticosteroids on superinfections. Studies are grouped by underlying condition. ARDS = acute respiratory distress syndrome, *df* = degrees of freedom, M-H = Mantel-Haenszel.

these findings were incorporated into GRADE assessments (Supplementary Materials, http://links.lww.com/CCX/B327).

Other than the outcome of hyperglycemia, we rated down all outcomes for indirectness as adverse effects were not reported in a standardized fashion across trials,

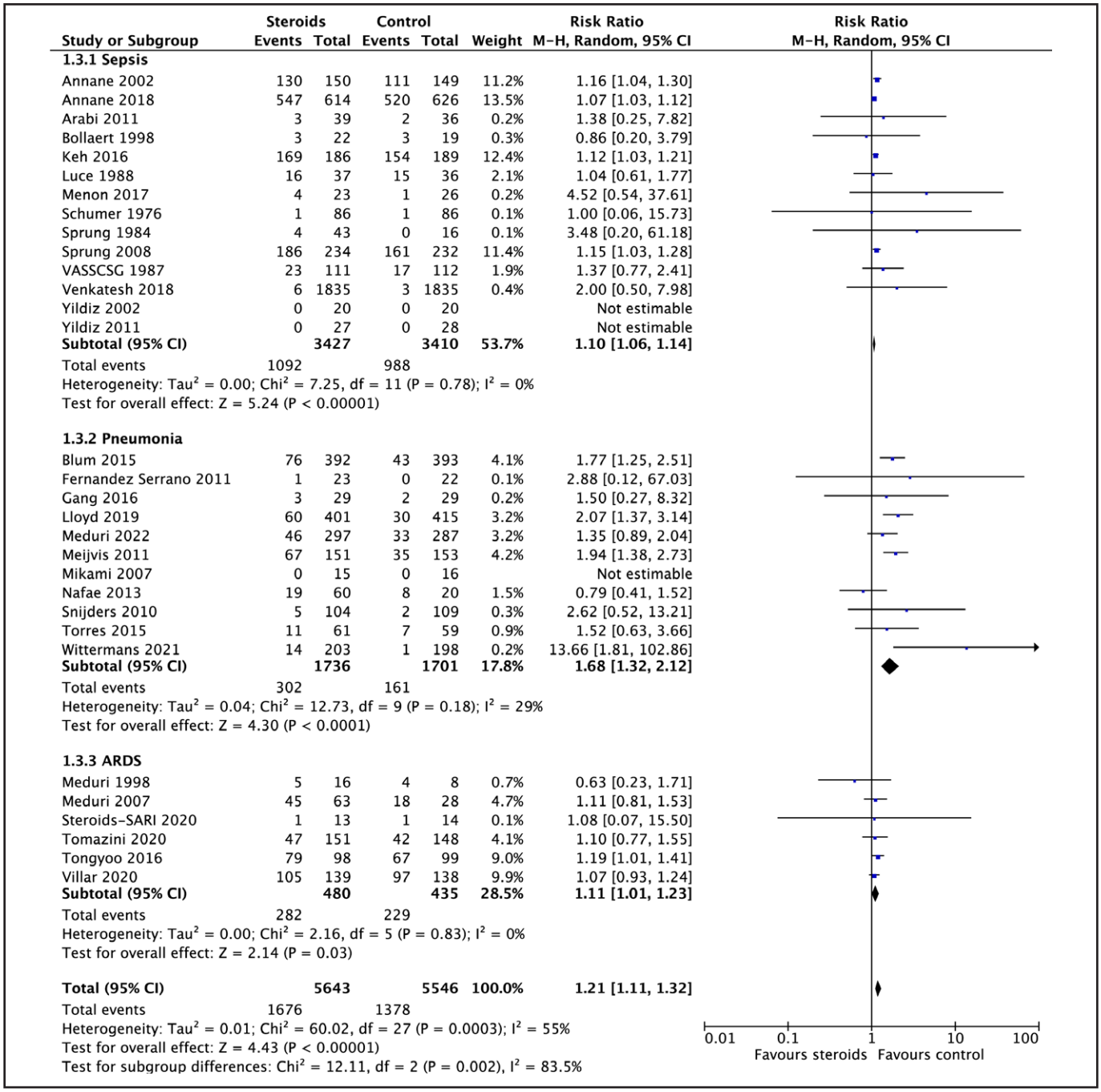

Figure 3. Effect of corticosteroids on hyperglycemia. Studies are grouped by underlying condition. ARDS = acute respiratory distress syndrome, *df* = degrees of freedom, M-H = Mantel-Haenszel.

and the severity and, therefore, the patient-importance of the complication varied. For the outcome of hyperglycemia, we opted not to downgrade for indirectness as regardless of how hyperglycemia was defined, the effect remained the same in both magnitude and certainty (**Supplementary Fig. 3**, http://links.lww.com/CCX/B327). We downgraded the outcome of neuromuscular weakness for imprecision as serious harm could not be excluded and neuropsychiatric effects for the same due to very small total event numbers (< 200 overall) increasing the risk of random error.

Subgroup analysis based on corticosteroid type or on whether adverse events were systematically screened did not demonstrate any credible subgroup effects (**Supplementary Figs. 4–6** and **11–16**, http://links.lww.com/CCX/B327). However, subgroup analysis based on disease type showed patients with ARDS who received corticosteroids had a lower risk

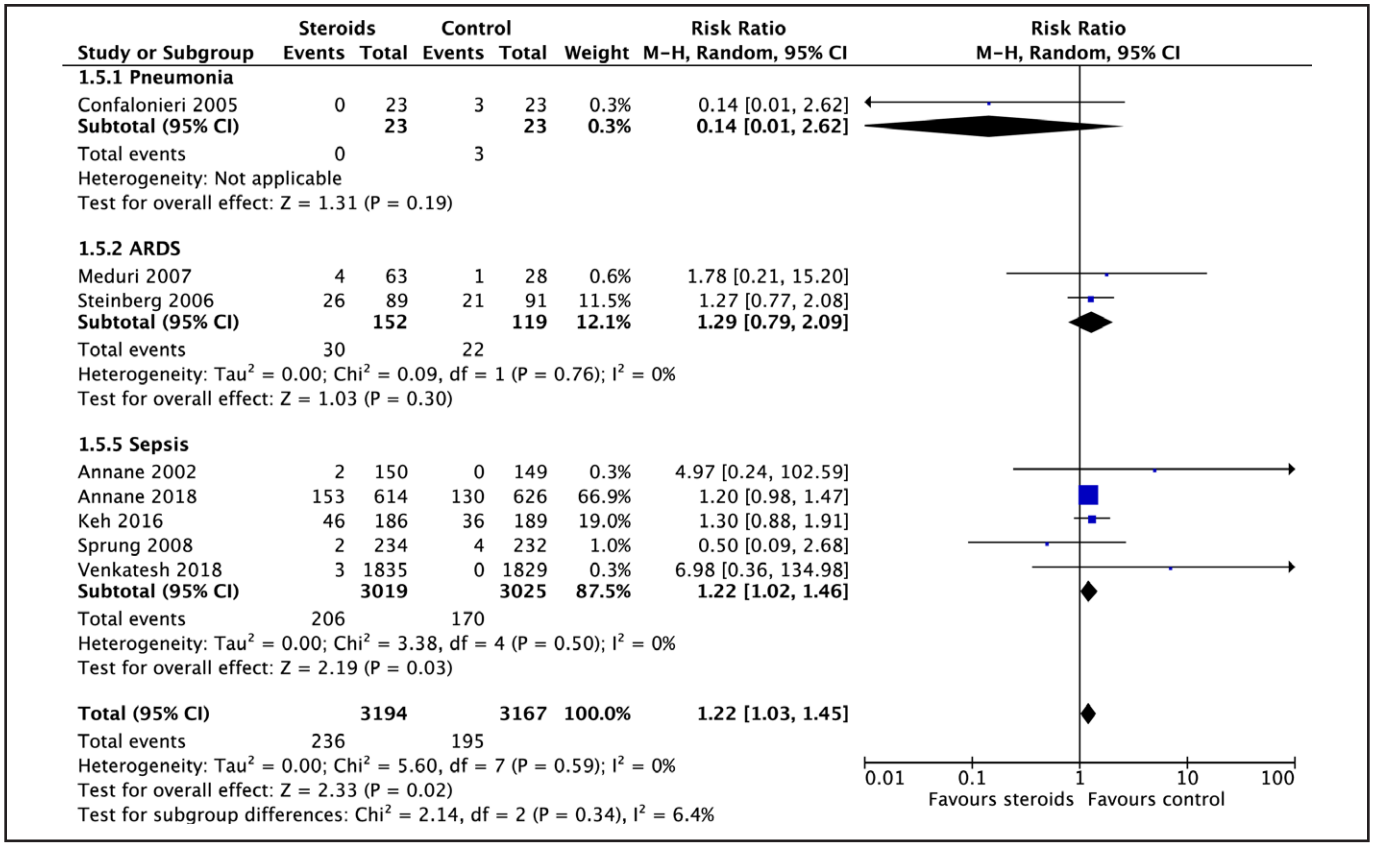

Figure 4. Effect of corticosteroids on neuromuscular weakness. Studies are grouped by underlying condition. ARDS = acute respiratory distress syndrome, *df* = degrees of freedom, M-H = Mantel-Haenszel.

of secondary infections (p = 0.008; moderate credibility; Fig. 2) compared with other indications that demonstrated no effect on secondary infections. The source of secondary infection that was reduced in ARDS patients was ventilator- or hospital-acquired pneumonia (**Supplementary Fig. 7**, http://links.lww.com/CCX/B327), compared with other sources such as bloodstream infections, central line-associated infections, or urinary tract infections (**Supplementary Figs. 8–10**, http://links.lww.com/CCX/B327).

A dose-response analysis showed a nonlinear dose-response relationship for the outcome of hyperglycemia, although the model becomes less certain at doses above 400 mg/d of hydrocortisone. The model suggests increasing harm with higher doses of hydrocortisone. There are no dose-response relationships for any of the other outcomes (Supplementary Materials, http://links.lww.com/CCX/B327).

DISCUSSION

The overall findings of this systematic review and meta-analysis show that corticosteroid use in ARDS, CAP, and sepsis is associated with hyperglycemia and probably with hypernatremia. However, corticosteroid administration for these conditions probably does not increase rates of gastrointestinal bleeding or secondary infections and may not increase neuromuscular weakness and short-term neuropsychiatric sequelae (delirium or psychosis). In addition, other than increasing corticosteroid doses being associated with an increased risk of hyperglycemia and patients with ARDS who receive corticosteroids having a lower rate of secondary infections (primarily pneumonia), there were no credible subgroup findings related to disease/syndrome, corticosteroid type, or dose.

There remains a degree of uncertainty regarding the effect of corticosteroids on neuropsychiatric adverse effects and neuromuscular weakness, especially in the long term (> 30 d). Case reports and case series have indicated an association between corticosteroid use and weakness (62), although more recent data examining this association has demonstrated mixed findings (17, 18, 50), perhaps in part due to better data collection and study design or changes in clinical practice (lower steroid dosing, improvement in mechanical

ventilation). While this review showed that corticosteroids may have no effect on neuromuscular weakness, the lack of consistent definitions of neuromuscular weakness and long-term follow-up across studies limited the certainty of conclusions. This is an area requiring high quality RCT data with a focus on long-term outcomes and careful consideration of the role of potential other factors such as early mobilization and hyperglycemia. Similarly, associations have been made between corticosteroids and delirium (63)—a correlation not observed in larger, well-designed studies (64). While this review did not indicate an association, the rates of delirium that were reported across studies were much lower than expected, with only 2–3% of patients having neuropsychiatric adverse effects, compared with the 20–80% rates of delirium typically reported in ICU studies (65), suggesting likely underreporting. In addition to variation in the definitions of neuropsychiatric effects across studies and serious imprecision, this precluded any definitive conclusions. Further, corticosteroids may have differential effects on short- and long-term neuropsychiatric outcomes. In particular, many prior studies suggest a protective role of corticosteroid treatment against post traumatic stress disorder in long-term critical illness survivors (66, 67), which could not be tested here. Moving forward, specific short- and long-term neuropsychiatric endpoints should be prespecified and collected systematically to address the remaining uncertainties regarding corticosteroid effects on these outcomes (68).

While we found little subgroup effect modification, there was one moderately credible subgroup effect associating corticosteroid use with lower rates of secondary infections in patients with ARDS, specifically secondary pneumonias. This subgroup effect could represent a faster resolution of the underlying ARDS in corticosteroid-treated patients, decreasing the chance of a secondary pneumonia. However, the lack of a clear temporal relationship between corticosteroid use and secondary infections means this correlation must be interpreted with caution and causality cannot be implied. Importantly, despite the known immunosuppressive effects of systemic corticosteroids, there was no indication of increased secondary infections with corticosteroid treatment in the current analysis.

This is a large meta-analysis (over 13,000 patients) comprehensively examining side effects related to corticosteroid use in critical illness. Strengths of this review include the comprehensive search, preregistration of the protocol, meta-regression to evaluate the impact of corticosteroid dose, assessment of ROB using Cochrane 2.0, TSA, and assessment of certainty of evidence using the GRADE approach. This review also has limitations, primarily related to clinical heterogeneity. First, the outcomes we examined were not always collected in a standardized fashion, especially in the case of neuromuscular weakness and neuropsychiatric outcomes. We have attempted to address this by downgrading the certainty of almost all outcomes for indirectness. Furthermore, when using the GRADE methodology to rate outcomes, we rated importance of outcomes through consensus of the coauthor group as opposed to incorporating input from patients or caregivers. Additionally, we were limited by adverse effects commonly reported in clinical trials and thus were unable to assess all complications of corticosteroid use such as impairment of wound healing. With only three trials reporting safety outcomes for longer than 30 days, evidence addressing long-term adverse effects of corticosteroid use during critical illness was also insufficient as was sufficient data specifically examining adverse effects in children. We note that large well-designed observational studies can be complementary to RCTs for outcomes with very low-certainty evidence. While not a part of this review as we a priori decided to only include RCTs, this may prove to be a fruitful focus of future work, particularly for outcomes such as neuromuscular weakness and neuropsychiatric side effects. Finally, this review focused on the most common critical illnesses where corticosteroids are indicated and only examined moderate doses and duration of corticosteroid administration. We were unable to comment on the adverse events associated with the usage of high- or pulse-dose steroids in conditions such as diffuse alveolar hemorrhage, acute transplant rejection, oncologic therapy-associated toxicities, or autoimmune crisis.

CONCLUSIONS

Corticosteroid use in ARDS, sepsis, and CAP is associated with hyperglycemia, probably with hypernatremia but likely has no effect on gastrointestinal bleeding or secondary infections. Further research examining long-term effects of corticosteroid use, particularly on neuropsychiatric outcomes and neuromuscular

weakness, would help further clarify the safety of this class of drugs in critical illness.

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

2 *Centre for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Krakow, Poland.*

3 *Department of Critical Care Medicine, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, India.*

4 *Department of Medicine, University of Toronto, Toronto, ON, Canada.*

5 *Department of Pharmacy, Mayo Clinic Hospital, Rochester, MN.*

6 *Department of Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan, Ann Arbor, MI.*

7 *Michigan Neuroscience Institute, University of Michigan, Ann Arbor, MI.*

8 *Division of Pulmonary, Critical Care, and Sleep Medicine, University of Miami Miller School of Medicine, Miami, FL.*

9 *Division of Critical Care Medicine, Albert Einstein College of Medicine, Bronx, NY.*

10 *Department of Intensive Care, Hôpital Raymond Poincaré, FHU SEPSIS, AP-HP, Garches, France.*

11 *Paris Saclay University, UVSQ, INSERM, Lab of Inflammation & Infection 2I (U1173), Montigny-le-Bretonneux, France.*

12 *Critical Care Center, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY.*

13 *Weill Cornell Medical College, New York, NY.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccejournal).

Dr. Rochwerg is supported by a McMaster Department of Medicine Mid-Career Research Award. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: dipayan.chaudhuri@medportal.ca

REFERENCES

1. Annane D, Pastores SM, Arlt W, et al: Critical illness-related corticosteroid insufficiency (CIRCI): A narrative review from a multispecialty task force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM). *Intensive Care Med* 2017; 43:1781–1792
2. Annane D, Pastores SM, Rochwerg B, et al: Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I). *Crit Care Med* 2017; 45:2078–2088
3. Pastores SM, Annane D, Rochwerg B; Corticosteroid Guideline Task Force of SCCM and ESICM: Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part II): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *Crit Care Med* 2018; 46:146–148
4. Chaudhuri D, Sasaki K, Karkar A, et al: Corticosteroids in COVID-19 and non-COVID-19 ARDS: A systematic review and meta-analysis. *Intensive Care Med* 2021; 47:521–537
5. Rochwerg B, Oczkowski SJ, Siemieniuk RAC, et al: Corticosteroids in sepsis: An updated systematic review and meta-analysis. *Crit Care Med* 2018; 46:1411–1420
6. Pitre T, Abdali D, Chaudhuri D, et al: Corticosteroids in community-acquired bacterial pneumonia: A systematic review, pairwise and dose-response meta-analysis. *J Gen Intern Med* 2023; 38:2593–2606
7. Guyatt GH, Oxman AD, Vist GE, et al: GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–926
8. Brignardello-Petersen R, Bonner A, Alexander PE, et al; GRADE Working Group: Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol* 2018; 93:36–44
9. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al: GRADE guidance 34: Update on rating imprecision using a minimally contextualized approach. *J Clin Epidemiol* 2022; 150:216–224
10. Higgins JPT, Li T, Deeks JJ: Chapter 6: Choosing effect measures and computing estimates of effect. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Higgins JPT, Thomas J, Chandler J (Eds). Cochrane Training, 2020
11. Schandelmaier S, Briel M, Varadhan R, et al: Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020; 192:E901–E906
12. Greenland S, Longnecker MP: Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; 135:1301–1309
13. Orsini N, Bellocco R, Greenland S: Generalized least squares for trend estimation of summarized dose-response data. *Stata J* 2006; 6:40–57
14. Crippa A, Discacciati A, Bottai M, et al: One-stage dose–response meta-analysis for aggregated data. *Stat Methods Med Res* 2019; 28:1579–1596
15. Discacciati A, Crippa A, Orsini N: Goodness of fit tools for dose–response meta-analysis of binary outcomes. *Res Synth Methods* 2017; 8:149–160
16. Wetterslev J, Jakobsen JC, Gluud C: Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017; 17:39
17. Steinberg KP, Hudson LD, Goodman RB, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–1684
18. Meduri GU, Golden E, Freire AX, et al: Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. *Chest* 2007; 131:954–963
19. Nafae RM, Ragab MI, Amany FM, et al: Adjuvant role of corticosteroids in the treatment of community-acquired pneumonia. *Egypt J Chest Dis Tuberc* 2013; 62:439–445

20. Sabry NA, Omar EE-D: Corticosteroids and ICU course of community acquired pneumonia in Egyptian settings. *Pharmacol Pharm* 2011; 2:73–81
21. Fernández-Serrano S, Dorca J, Garcia-Vidal C, et al: Effect of corticosteroids on the clinical course of community-acquired pneumonia: A randomized controlled trial. *Crit Care* 2011; 15:R96
22. Meduri GU, Shih MC, Bridges L, et al; ESCAPe Study Group: Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. *Intensive Care Med* 2022; 48:1009–1023
23. Torres A, Sibila O, Ferrer M, et al: Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: A randomized clinical trial. *JAMA* 2015; 313:677–686
24. Meijvis SCA, Hardeman H, Remmelts HHF, et al: Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: A randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377:2023–2030
25. Li G, Gu C, Zhang S, et al: Value of glucocorticoid steroids in the treatment of patients with severe community-acquired pneumonia complicated with septic shock. *Chin Crit Care Med* 2016; 28:780–784
26. Blum CA, Nigro N, Briel M, et al: Adjunct prednisone therapy for patients with community-acquired pneumonia: A multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2015; 385:1511–1518
27. Lloyd M, Karahalios A, Janus E, et al; Improving Evidence-Based Treatment Gaps and Outcomes in Community-Acquired Pneumonia (IMPROVE-GAP) Implementation Team at Western Health: Effectiveness of a bundled intervention including adjunctive corticosteroids on outcomes of hospitalized patients with community-acquired pneumonia: A stepped-wedge randomized clinical trial. *JAMA Intern Med* 2019; 179:1052–1060
28. Dequin P-F, Meziani F, Quenot J-P, et al: Hydrocortisone in severe community-acquired pneumonia. *N Engl J Med* 2023; 388:1931–1941
29. Ling L, Jia L, Ying-zi H, et al: The effect of stress dose glucocorticoid on patients with acute respiratory distress syndrome combined with critical illness-related corticosteroid insufficiency. *Zhonghua Nei Ke Za Zhi* 2012; 51:599–603
30. Snijders D, Daniels JMA, De Graaff CS, et al: Efficacy of corticosteroids in community-acquired pneumonia: A randomized double-blinded clinical trial. *Am J Respir Crit Care Med* 2010; 181:975–982
31. Wittermans E, Vestjens SMT, Spoorenberg SMC, et al; Santeon-CAP Study Group: Adjunctive treatment with oral dexamethasone in non-ICU patients hospitalised with community-acquired pneumonia: A randomised clinical trial. *Eur Respir J* 2021; 58:2002535
32. Mikami K, Suzuki M, Kitagawa H, et al: Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. *Lung* 2007; 185:249–255
33. El-Ghamrawy A, Shokeir M, Esmat A: Effects of low-dose hydrocortisone in ICU patients with severe community-acquired pneumonia. *Egypt J Chest* 2006; 55:91–99
34. Annane D, Sébille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *J Am Med Assoc* 2002; 288:862–871
35. Annane D, Renault A, Brun-Buisson C, et al; CRICS-TRIGGERSEP Network: Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; 378:809–818
36. Arabi YM, Aljumah A, Dabbagh O, et al: Low-dose hydrocortisone in patients with cirrhosis and septic shock: A randomized controlled trial. *C Can Med Assoc J* 2010; 182:1971–1977
37. Bollaert PE, Charpentier C, Levy B, et al: Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; 26:645–650
38. Bone RC, Fisher CJJ, Clemmer TP, et al: A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317:653–658
39. Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723–732
40. Abdelsalam Rezk N, Mohamed Ibrahim A: Effects of methyl prednisolone in early ARDS. *Egypt J Chest Dis Tuberc* 2013; 62:167–172
41. Chawla K, Kupfer Y, Goldman I, et al: Hydrocortisone reverses refractory septic shock. *Crit Care Med* 1999; 27:33A
42. Cicarelli DD, Vieira JE, Benseñor FEM: Early dexamethasone treatment for septic shock patients: A prospective randomized clinical trial. *Sao Paulo Med J* 2007; 125:237–241
43. Gordon AC, Mason AJ, Perkins GD, et al: The interaction of vasopressin and corticosteroids in septic shock: A pilot randomized controlled trial. *Crit Care Med* 2014; 42:1325–1333
44. Keh D, Trips E, Marx G, et al; SepNet–Critical Care Trials Group: Effect of hydrocortisone on development of shock among patients with severe sepsis the HYPRESS randomized clinical trial. *JAMA* 2016; 316:1775–1785
45. Luce JM, Montgomery AB, Marks JD, et al: Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Respir Dis* 1988; 138:62–68
46. Menon K, McNally D, O'Hearn K, et al: A randomized controlled trial of corticosteroids in pediatric septic shock: A pilot feasibility study. *Pediatr Crit Care Med* 2017; 18:505–512
47. Mirea L, Ungureanu R, Pavelescu D, et al: Continuous administration of corticosteroids in septic shock can reduce risk of hypernatremia. *Crit Care* 2014; 18(Suppl 1):P239
48. Schumer W: Steroids in the treatment of clinical septic shock. *Ann Surg* 1976; 184:333–341
49. Sprung CL, Caralis PV, Marcial EH, et al: The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *Surv Anesthesiol* 1985; 29:238
50. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124
51. Tongyoo S, Permpikul C, Mongkolpun W, et al: Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: Results of a randomized controlled trial. *Crit Care* 2016; 20:329
52. Venkatesh B, Finfer S, Cohen J, et al: Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; 378:797–808

53. Yildiz O, Dǒganay M, Aygen B, et al: Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. *Crit Care* 2002; 6:251–259
54. Yildiz O, Tanriverdi F, Simsek S, et al: The effects of moderate-dose steroid therapy in sepsis: A placebo-controlled, randomized study. *J Res Med Sci* 2011; 16:1410–1421
55. Veterans Administration Systemic Sepsis Cooperative Study Group: Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. *N Engl J Med* 1987; 317:659–665
56. Jeronimo CMP, Farias MEL, Val FFA, et al: Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis* 2020:ciaa1177
57. Villar J, Ferrando C, Martínez D, et al; dexamethasone in ARDS network: Dexamethasone treatment for the acute respiratory distress syndrome: A multicentre, randomised controlled trial. *Lancet Respir Med* 2020; 8:267–276
58. Meduri GU, Headley AS, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 1998; 280:159–165
59. Sterne JAC, Murthy S, et al; WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group: Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. *JAMA* 2020; 324:1330–1341
60. Tomazini BM, Maia IS, Cavalcanti AB, et al: Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA* 2020; 324:1307
61. Confalonieri M, Urbino R, Potena A, et al: Hydrocortisone infusion for severe community-acquired pneumonia: A preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171:242–248
62. Amaya-Villar R, Garnacho-Montero J, Garcia-Garmendia JL, et al: Steroid-induced myopathy in patients intubated due to exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 2005; 31:157–161
63. Schreiber MP, Colantuoni E, Bienvenu OJ, et al: Corticosteroids and transition to delirium in patients with acute lung injury. *Crit Care Med* 2014; 42:1480–1486
64. Hill AR, Spencer-Segal JL: Glucocorticoids and the brain after critical illness. *Endocrinology* 2021; 162:bqaa242
65. Girard TD, Pandharipande PP, Wesley EW: Delirium in the intensive care unit. *Crit Care* 2008; 12(Suppl 3):S3
66. Schelling G, Stoll C, Kapfhammer HP, et al: The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. *Crit Care Med* 1999; 27:2678–2683
67. Schelling G, Briegel J, Roozendaal B, et al: The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. *Biol Psychiatry* 2001; 50:978–985
68. Herridge MS, Azoulay E: Outcomes after critical illness. *N Engl J Med* 2023; 388:913–924