

Guidelines for the diagnosis and management of critical illness related corticosteroid insufficiency (CIRCI) in critically ill adult and pediatric patients (Part I): Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM): 2017

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Guidelines for the diagnosis and management of critical illness related corticosteroid insufficiency (CIRCI) in critically ill adult and pediatric patients: Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM): 2017

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ABSTRACT

OBJECTIVE: To provide an update to the 2008 consensus statements for the diagnosis and management of critical illness related corticosteroid insufficiency (CIRCI) in adult and pediatric patients.

PARTICIPANTS: A multi-specialty task force of 16 international experts in critical care medicine, endocrinology, guideline methods, and members of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.

DESIGN/METHODS: The recommendations were based on the summarized evidence from the 2008 document in addition to more recent literature from an updated systematic review incorporating relevant studies from 2008 to 2017 and formulated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology. The strength of each recommendation was classified as strong or conditional and the quality of evidence was rated from high to very low based on factors that included the individual study design, risk of bias, consistency of the results, and the directness and precision of the evidence. Recommendation approval required agreement from at least 80% of the task force members.

RESULTS: The task force was unable to reach agreement on a single test that can reliably diagnose CIRCI although the delta cortisol (change in baseline cortisol at 60 minutes of < 9 mcg/dL) after cosyntropin (250 mcg) administration and a random plasma cortisol of < 10 mcg/dL may be used most commonly by clinicians. We suggest against using plasma free cortisol or salivary cortisol level over plasma total cortisol (conditional, very low quality of evidence). For treatment of specific conditions, we suggest using intravenous (IV) hydrocortisone < 400 mg/day for at ≥ 3 days at full dose, in patients with septic shock that is not responsive to fluid and moderate to high dose vasopressor therapy (conditional, low quality of

evidence). We suggest against using corticosteroids in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence). We suggest the use of IV methylprednisolone 1 mg/kg/day in patients with early moderate to severe acute respiratory distress syndrome ($\text{PaO}_2/\text{FiO}_2 < 200$ and within 14 days of onset) (conditional, moderate quality of evidence). Corticosteroids are not suggested for patients with major trauma (conditional, low quality of evidence).

CONCLUSIONS: Evidence-based recommendations for the use of corticosteroids in critically ill patients with sepsis and septic shock, acute respiratory distress syndrome, and major trauma have been developed by a multispecialty task force.

Key Words: corticosteroids; glucocorticoids; critical illness; sepsis; septic shock; acute respiratory distress syndrome; major trauma

Introduction

Critical Illness Related Corticosteroid Insufficiency (CIRCI) is a concept that was first introduced in 2008 by an international multidisciplinary task force convened by the Society of Critical Care Medicine (SCCM) to describe impairment of the hypothalamic pituitary axis (stress response) during critical illness (1). CIRCI is characterized by dysregulated systemic inflammation resulting from inadequate intracellular glucocorticoid-mediated anti-inflammatory activity for the severity of the patient's critical illness. The putative symptoms of CIRCI are listed in **Table 1**. CIRCI is associated with increased circulating levels of biological markers of inflammation and coagulation over time, morbidity, length of intensive care unit (ICU) stay and mortality. Given the growing body of evidence that CIRCI occurs across a broad spectrum of critical illness, an understanding of the pathogenesis and treatment of CIRCI is important to all critical care providers.

Two emerging themes required that we revisit the concept, diagnosis and management of CIRCI: (1) The clear recognition of the importance of evidence-based approaches to patient care to enhance quality, improve safety and establish a clear and transparent framework for service development and health-care provision; (2) The widespread use of corticosteroids in critically ill patients, highlighting the need for a valid, reliable and transparent process of evaluation to support key decisions.

Against this background, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) have updated the 2008 guidelines for the diagnosis and treatment of CIRCI. In addition to a rigorous approach in applying GRADE methodology, the recommendations in this document focus on patient-important outcomes and utility for everyday practicing clinicians. It was not intended to define a standard of care, and

should not be interpreted as one. As with any clinical practice guideline, it should not be interpreted as prescribing an exclusive course of management. The guideline covers CIRCI in critically ill children and adults. It does not cover chronic adrenal insufficiency, and does not cover neonates, because the guideline panel felt these areas represented separate areas of expertise. This guideline focuses on the three disorders that most clinicians link CIRCI to: sepsis/septic shock, acute respiratory distress syndrome (ARDS) and major trauma.

Composition of the Guideline Development Group

A multispecialty task force of international experts in critical care medicine, endocrinology and guideline methods was convened from the membership of the SCCM and the ESICM. The first in-person meeting was held during the SCCM Critical Care Congress in San Francisco, CA in January 2014 and was followed by several teleconferences and electronic-based discussion at regular intervals and another three in-person meetings during the annual SCCM Critical Care Congress in January 2015, February 2016, and January 2017. Members who were unable to participate in the in-person meetings were provided opportunity for electronic feedback and meeting updates were circulated.

Conflict of interest policy

We required all guideline task force members to fill out a detailed Declaration of Interest Statement including all current and future financial conflicts of interest (COI) as well as past interest restricted to the two years before joining the guideline development process. No task force members reported any financial COI related to the development and writing of the guideline. All members were allowed to participate in all the discussions and have equal weight in formulating the statements or in voting. All were allowed equal involvement in data extraction and writing the rationales. We also allowed members to exclude themselves from

discussion and voting around specific questions if they felt significant academic COI. There was no input or funding from industry to produce this guideline. The COI forms are available from the SCCM and ESICM and are updated on a regular basis.

Question Development

The task force members developed a list of questions that were structured in Population, Intervention, Comparison, and Outcome (PICO) format regarding the diagnosis and treatment of CIRCI in various clinical conditions (**Appendix 1**). The methods chair (BR) assisted in developing the PICO questions, i.e. framing the clinical questions into a searchable format. This required careful specification of the patient group (P), the intervention (I), the comparator (C) and the outcomes (O) for intervention questions and the patient group, index tests, reference standard and target condition for questions of diagnostic test accuracy. For each question the task force agreed upon explicit review question criteria including study design features. Some of these questions were previously addressed in the 2008 guidelines (**1**) and required updates of the evidence summaries whereas others required *de novo* systematic reviews.

Assessment of the Relative Importance of the Outcomes

For each intervention question, a list of outcomes was compiled, reflecting both benefits and harms of alternative management strategies. Outcomes (as perceived from the perspective of a patient) were ranked from “low” to “critical” importance and agreed upon through consensus of the task force members (**Appendix 2**). Ranking outcomes by their relative clinical importance helps to focus on those that are most relevant to patients and may lead to improved clarification during potential disagreements in decision making.

Searching for Evidence

Sources

The information technologists (based at McMaster University, Hamilton, Ontario) searched The Cochrane Database of Systematic Reviews, DARE, CENTRAL and Medline for all PICO questions on diagnosis and treatment. All searches were updated through May 2017. The search strategies combined subject headings and text words for the patient population, index test and target condition for the diagnostic questions and subject headings and text words for the population and intervention for the intervention questions (**Appendix 1**).

If a previous meta-analysis of high quality was identified which addressed one of the PICO questions, this was used or updated to incorporate new evidence since its publication. Search and screening results were provided to the task force to ensure no important trials were missed or erroneously included.

Reference lists from included publications were screened to identify additional papers. The methods chair also searched guideline databases and organizations including the National Guideline Clearinghouse, Guidelines International Network, Guidelines Finder, Centre for Reviews and Dissemination, National Institute for Health and Care Excellence, and professional critical care and endocrinology societies for guidelines to screen the reference lists.

Selection of studies for inclusion

The information technologists screened all titles and abstracts to discard the clearly irrelevant articles. Task force members completed a second screening. References were allocated to pairs of reviewers for evaluation of eligibility. All abstracts that did not meet the inclusion criteria were discarded. Any discrepancies at this stage were resolved by group consensus. All pairs of reviewers, with help from the methods support team, retrieved full texts of potentially relevant studies and examined them independently for eligibility. Any

discrepancies were resolved by consensus.

Data extraction and critical appraisal of individual studies

For each included study, we collected relevant information on design, conduct, risk of bias, and relevant results. For each question, the methodologist extracted all individual study data and produced (when pooling was judged to be appropriate) forest plots by outcome. All analysis was done using Review Manager (RevMan) [Computer program]. Version 5.3.

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Risk of bias of the included studies was evaluated using various validated checklists, as recommended by the Cochrane Collaboration (2). These were AMSTAR for Systematic Reviews (3), the Cochrane Risk of Bias tool for randomised controlled trials (4), and the Newcastle-Ottawa scale for cohort and case-control studies (5).

Evidence Profiles

Evidence summaries for each question were prepared by the methodologist following the GRADE approach (6) using the GRADEpro Guideline Development Tool online software (www.gradepro.org).

The evidence profiles include the summary – pooled or narrative - outcome data, an absolute measure of intervention effect when appropriate, the importance of the outcome and the summary of quality of evidence for each outcome. Evidence profiles were constructed by the methodologist and reviewed and confirmed with the rest of the task force members.

Rating the Quality of the Evidence for Each Outcome across Studies

In accordance with GRADE, the task force initially categorized the quality of the evidence for each outcome as high if it originated from randomized controlled trials (RCTs) and

low if it originated from observational data. We subsequently downgraded the quality of the evidence one or two levels if results from individual studies were at serious or very serious risk of bias, there were serious inconsistencies in the results across studies, the evidence was indirect, the data were sparse or imprecise or publication bias was thought to be likely. If evidence arose from observational data, but effect sizes were large, there was evidence of a dose-response gradient, or all plausible confounding would either reduce a demonstrated effect or suggest a spurious effect when results showed no effect, we upgraded the quality of the evidence. By repeating this procedure, we obtained an overall quality of the evidence for each outcome and each intervention.

Formulating Statements and Grading Recommendations

Actionable Recommendations

After the evidence summary tables and evidence profiles were prepared, revised and approved by the task force, the recommendations were finalized. All recommendations were developed based on the GRADE evidence profiles for each recommendation. Each of the following factors were considered in recommendation development: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the patient's values and preferences associated with the decision, the implications for resource use and health equity, the acceptability of intervention to stakeholders and the feasibility of implementation. Recommendations and their strength were decided by consensus. Committee members unable to join the face-to-face meetings or teleconferences were provided opportunity for input electronically. The entire committee agreed on the final wording of each recommendation and rationale with further qualifications for each recommendation (e.g., subgroup considerations, justification, implementation considerations).

Each recommendation was designated either “strong” or “conditional” according to the GRADE approach (7). As outlined by GRADE, we used the phrasing “we recommend” for strong recommendations and “we suggest” for conditional (synonymous with the older terminology ‘weak’) recommendations (**Table 2**). The implications of the strength of the recommendations for patients, clinicians, and policy makers are shown in **Table 3**.

Writing Rationale

We collated the actionable recommendations and the clinical advice for each of the clinical questions in separate chapters structured according to a specific format. Each question resulted in one or more specific boxed statements. Within each recommendation the strength was indicated as strong or conditional and the quality of the supporting evidence as high, moderate, low or very low (**Table 2**).

All statements are followed by advice for clinical practice where relevant and the rationale. The rationale contains a brief section on the relevant background and justification of the topic, followed by a short narrative review of the evidence.

External review

External peer review was provided through the Board of Regents of the American College of Critical Care Medicine, the Councils of the SCCM and ESICM, and the editorial boards of *Critical Care Medicine* and *Intensive Care Medicine*. Two international experts in endocrinology (George P Chrousos, MD and Stefan R Bornstein, MD) also reviewed the final draft of the guideline and provided comments.

Recommendations for Diagnosis of CIRCI

1. Is total cortisol response to synthetic adrenocorticotrophic hormone [ACTH] (cosyntropin) superior to random plasma total cortisol for the diagnosis of CIRCI?

Recommendation: The task force makes no recommendation regarding whether to use delta cortisol (change in baseline cortisol at 60 minutes of < 9 µg/dL) after cosyntropin (250 µg) administration or a random plasma cortisol of < 10 µg/dL for the diagnosis of CIRCI.

Rationale:

The 2008 guidelines suggested that the diagnosis of CIRCI is best made by a delta total serum cortisol of < 9 µg/dL after i.v. cosyntropin (250 µg) administration or a random total cortisol of < 10 µg/dL (1). However, to date, clinicians have not adopted these diagnostic criteria in their routine practice. Moreover, the latest Surviving Sepsis Campaign guidelines suggest not using the ACTH stimulation test to select patients with septic shock that may be treated with hydrocortisone (8). Nevertheless, a recent guideline from the Endocrine Society confirmed that the high dose (250 µg) ACTH stimulation test is superior to other existing diagnostic tests to establish the diagnosis of primary adrenal insufficiency with peak cortisol levels below 18 µg/dL (assay dependent) at 30 or 60 minutes indicating adrenal insufficiency (9).

We found one single center randomized trial that compared low dose ACTH (1 µg) stimulation test to total random cortisol to diagnose adrenal insufficiency in 59 adults with septic shock (10). When compared to total random cortisol, the low dose ACTH test was better able to predict a longer duration of vasopressor requirement and hemodynamic response to corticosteroids. Similarly, prospective cohort studies in adults with or without sepsis (11) and in patients with multiple trauma (12) found that patients with CIRCI, i.e. total cortisol levels <10 µg/dl or delta cortisol <9 µg/dl, had poorer outcomes than patients without CIRCI. Likewise, a

large multicenter prospective cohort study found that critically ill children with a delta cortisol $<9 \mu\text{g/dl}$ after the low dose ACTH stimulation test required higher dose and prolonged treatment with catecholamines, higher fluid amount, and had a higher mortality rate (13). **See Appendix 3 for evidence profile.**

Owing to the potential for risk of bias in study design with only one single center unblinded randomized trial and few prospective cohort studies and due to imprecision related to low numbers of patients included, we downgraded the quality of evidence to low. The task force members after two rounds of voting could not reach a consensus ($>80\%$ agreement) on whether the ACTH stimulation test is superior to random cortisol for the routine diagnosis of CIRCI. Due to the broad spectrum of abnormalities that may cause CIRCI, from altered metabolism to tissue resistance, the task force thought it is unlikely that a single test can reliably diagnose CIRCI independent of its mechanisms.

2. Is plasma free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI?

Recommendation: We suggest against using plasma free cortisol level as compared to plasma total cortisol for the diagnosis of CIRCI (conditional recommendation, very low quality of evidence).

Rationale

Free cortisol is the bioactive form of cortisol. Critically ill patients often present with low serum concentrations of cortisol binding globulin (CBG) and hypoalbuminemia. In patients with low serum concentrations of cortisol ligands, serum total cortisol levels may not predict serum free cortisol levels (14).

We found no randomized trial that compared serum total versus free cortisol levels to

diagnose CIRCI. Since the 2008 Task Force recommendations, a prospective study of 112 critically ill adults with treatment-insensitive hypotension, found a good correlation between serum concentrations of free and total cortisol before and after 250 µg ACTH stimulation testing (15). These findings suggested that using total cortisol levels after ACTH testing is sufficient in critically ill adults. Another prospective cohort study of 69 critically ill patients to assess the time course of serum cortisol levels, found that levels of both free and total cortisol predicted clinical outcomes (16). Another prospective cohort study of 29 adults with septic shock found remarkable differences between the serum concentrations of free versus total cortisol levels both over time and in response to 1 µg ACTH (17). **See Appendix 3 for evidence profile.**

Measuring serum free cortisol levels requires cumbersome techniques that are unlikely to be available in all hospital laboratories and unlikely to provide a rapid turnaround time. There were few low quality observational studies with inconsistent findings. Thus, the task force suggested against measuring plasma free cortisol level over plasma total cortisol level in patients with suspected CIRCI.

3. Is salivary free cortisol level superior to plasma total cortisol level for the diagnosis of CIRCI?

Recommendation: We suggest against using salivary as compared to serum cortisol for diagnosing CIRCI (conditional recommendation, very low quality of evidence).

Rationale:

Cortisol levels are used in an attempt to identify septic patients with CIRCI. Most studies have used total serum cortisol levels to evaluate adrenal function. However the disadvantage of using total serum cortisol is that 90% are linked to CBG and albumin. In certain patient populations such as those with cirrhosis, the synthesis of these proteins is reduced and can lead

to an overestimation of the prevalence of adrenal insufficiency (18). Moreover, in critically ill patients, the correlation between free serum and total serum cortisol levels was only 55% to 60% (14).

A few studies evaluated the use of salivary cortisol as a measure for adrenal insufficiency. In one study, free cortisol level was more strongly correlated with salivary than with serum total cortisol in 88 cirrhotic patients (Spearman coefficient =0.91 vs. 0.76, respectively, $p < 0.001$) (19). In contrast, in a study of 57 patients with septic shock, there was no significant difference between free serum cortisol and salivary cortisol levels ($p = .28$) (20). In addition, the correlation between salivary cortisol and total serum cortisol levels was very good (80%). Unbound plasma cortisol can be calculated using total serum cortisol and CBG measurements (21, 22). **See Appendix 3 for evidence profile.**

The evidence demonstrating any benefit of using salivary cortisol over serum cortisol is extremely limited. Although salivary cortisol may be more closely correlated with free cortisol than total cortisol, there is no study that has demonstrated that using salivary cortisol to diagnose CIRCI in critically ill patients leads to improved patient outcomes. Furthermore, the practicality and feasibility of using salivary cortisol is questionable given that it is tested by enzyme immunoassay which may not be routinely available at most centers. Additionally, there are implementation concerns as in the Estrada-Y-Martin study (20) in that of the 57 patients, 19 were excluded as three initial samples did not provide any saliva, and 16 were eliminated because of insufficient saliva or blood contamination. The task force therefore felt that using salivary cortisol would not be cost effective, practical, or feasible.

4. Is the 1 µg ACTH stimulation test superior to the 250 µg ACTH test for the diagnosis of CIRCI?

Recommendation: We suggest that the high dose (250 µg) as compared with the low dose (1 µg) ACTH stimulation test be used for the diagnosis of CIRCI (conditional recommendation, low quality of evidence).

Rationale

The high dose (250 µg) ACTH stimulation test remains the most popular diagnostic test for adrenal insufficiency. However, this supraphysiologic dose of ACTH may result in significant stimulation of the adrenocortical cells in patients with proven adrenal insufficiency. Therefore, to increase the sensitivity of this diagnostic test, low dose (1 µg) ACTH was suggested. The high dose ACTH test is easy to perform and safe. The low dose ACTH test requires some preparation at the bedside as the commercial ampules contain 250 µg of ACTH.

A recent meta-analysis of 30 studies involving 1209 adults and 228 children, found that for secondary adrenal insufficiency, the high and low dose ACTH test had similar diagnostic accuracy (**23**). The likelihood ratio (LR) of a positive test for adults was 9.1 and 5.9 for the high and low dose ACTH test, respectively, and 43.5 and 7.7 respectively, for children. However, both tests had low sensitivity as suggested by the suboptimal LR of a negative test (adults: 0.39 and 0.19 for the high and low dose ACTH test, respectively; children: 0.65 and 0.34, respectively). A prospective cohort study of 74 adults with septic shock found that the delta cortisol using the low and high dose ACTH test was equally accurate in predicting vasopressor dependency and mortality (**24**). Likewise in a prospective multicenter cohort study of critically ill children, the low and high dose ACTH test showed similar accuracy in the prediction of

clinical outcomes (13). **See Appendix 3 for evidence profile.**

Owing to easier practical modalities and the comparable accuracy of the low and high dose ACTH test, the task force suggested using the high dose rather than the low dose ACTH test for the diagnosis of CIRCI.

5. Is hemodynamic response to hydrocortisone (50 to 300 mg) superior to the 250 µg ACTH stimulation test for the diagnosis of CIRCI?

Recommendation: We suggest the use of the 250 µg ACTH stimulation test rather than the hemodynamic response to hydrocortisone (50 to 300 mg) for the diagnosis of CIRCI (conditional recommendation, very low quality of evidence).

Rationale:

First reports on low-dose corticosteroids in human septic shock hypothesized that hemodynamic improvement unmasks adrenocortical insufficiency (25, 26). Hydrocortisone was found to improve the vasopressor response to norepinephrine in septic patients, this effect being more marked in patients with CIRCI (27). Arterial hypotension may serve as a useful marker of inadequate corticosteroid activity, although not all patients with septic shock may have CIRCI (28).

No studies are presently available that directly address this specific question. CIRCI diagnosed with the 250 µg ACTH stimulation was associated with faster shock resolution in two studies (29, 30). In contrast, the CORTICUS trial found a similar hemodynamic response to corticosteroids in patients with or without CIRCI (31). The recent Hydrocortisone for Prevention of Septic Shock (HYPRESS) trial also did not find a difference in the development of septic shock in the presence or absence of CIRCI (32). However, in the HYPRESS trial only a limited number of patients were screened for having CIRCI altering the reliability of these data. **See**

Appendix 3 for evidence profile.

Earlier shock resolution has been shown to lead to lower mortality (33). However, no studies compared the prognostic value of hemodynamic response versus 250 µg ACTH test for the diagnosis of CIRCI. Meta-analyses examined only different mortality rates with corticosteroid treatment between those with and without documented CIRCI (34). Thus, the task force could only recommend the use of the 250 µg ACTH stimulation test to diagnose CIRCI.

6. Is corticotropin level superior to 250 µg ACTH test for the diagnosis of CIRCI?

Recommendation: We suggest against using corticotropin levels for the routine diagnosis of CIRCI (conditional recommendation, low quality of evidence).

Rationale

Plasma corticotropin level is the result of corticotropin release from the anterior pituitary gland into the systemic circulation. Normally, plasma concentrations of corticotropin and cortisol change in opposite directions. In primary adrenal insufficiency, plasma cortisol level is low and plasma corticotropin level is high. In hypopituitarism, plasma cortisol level is low and corticotropin level is low or normal. During critical illness, plasma corticotropin levels have been variably found to be low, normal or high and likely follow a dynamic pattern with transiently elevated levels and subsequent decline over weeks after the initial insult (1). We did not find any study that compared the diagnostic accuracy of corticotropin level as compared to the ACTH stimulation test.

Owing to the complexity of measuring plasma level of corticotropin, the task force deemed that it is not feasible in most institutions to obtain a corticotropin level with a turnaround time to have an impact on the acute management of the critically ill.

Recommendations for Corticosteroid Use in Critical Care Conditions

Sepsis

- A. Among hospitalized adult patients with sepsis without shock, should corticosteroids be administered to improve survival and other clinically relevant endpoints?

Recommendation: We suggest against corticosteroid administration in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence).

Rationale:

Sepsis and septic shock are major healthcare problems, affecting millions of people worldwide annually, and associated with a mortality rate of 25-30% and high direct and indirect costs (35-39). Pro-inflammatory cytokines have been demonstrated to either suppress cortisol response to ACTH or compete with intracellular glucocorticoid function which can result in CIRCI in septic patients. Sepsis-related CIRCI may in turn precipitate organ failure and result in lack of response to vasopressor therapy in these patients (40, 41). Thus, the interest in the potential benefit of corticosteroids for the treatment of sepsis has been tested in dozens of observational studies and trials for several decades.

Analysis of 27 RCTs (n=3176) of patients with sepsis with and without shock revealed a 28-day mortality rate of 29.3% in patients receiving corticosteroids compared to 31.8% in those who received placebo (RR 0.87, 95% CI: 0.76-1.0) (42). The quality of evidence was considered low owing to inconsistency in the results and for imprecision. **See Appendix 4 for evidence profile.**

A separate analysis of 6 RCTs (n=826) of patients with sepsis without shock revealed a 28-day mortality rate of 33.8% in patients receiving corticosteroids compared to 30.6% in those

who received placebo (RR 1.11, 95% CI: 0.91-1.34) (42). Hyperglycemia was the most common adverse event, and corticosteroids did not increase the risk of secondary infections (RR 1.02, 95% CI: 0.87-1.20). The quality of evidence was considered moderate due to imprecision given the wide confidence intervals. **See appendix 4 for evidence profile.**

Most recently, the Hydrocortisone for Prevention of Septic Shock (HYPRESS) multicenter trial, assigned patients with sepsis (excluding those with shock) to either receive a continuous infusion of 200 mg of hydrocortisone for 5 days followed by dose tapering until day 11 (n = 190) or to receive placebo (n = 190) (33). The primary outcome was development of septic shock within 14 days. Patients who received hydrocortisone had no difference in rates of progression to septic shock within 14 days as compared to placebo (difference, -1.8%; 95% CI: -10.7% to 7.2%; P = .70). In addition, there were no significant differences between the hydrocortisone and placebo groups for the use of mechanical ventilation (53.2% vs. 59.9%), mortality at 28 days (8.8% vs. 8.2%) or up to 180 days (26.8% vs. 22.2%), ICU length of stay (median [interquartile range], 8 [5-15] vs. 9 [6-17] days), or hospital length of stay (median [interquartile range], 26 [16-46] vs. 25 [16-40] days). In the hydrocortisone vs. placebo groups, 21.5% vs 16.9% had secondary infections, 8.6% vs 8.5% had ventilation weaning failure, 30.7% vs 23.8% had muscle weakness, and 90.9% vs 81.5% had hyperglycemia. Based on these results, the task force members agreed that corticosteroids may not be beneficial in adult patients with sepsis without shock.

- B. Among hospitalized adult patients with septic shock, should corticosteroids be administered to improve survival and other clinically relevant endpoints?

Recommendation: We suggest using corticosteroids in patients with septic shock that is not

responsive to fluid and moderate to high dose vasopressor therapy (conditional recommendation, low quality of evidence).

C. Among hospitalized adult patients with septic shock treated with corticosteroids, what is the recommended dose and duration of treatment?

Recommendation: If using corticosteroids for septic shock, we suggest using long course and low dose (e.g., IV hydrocortisone <400 mg/day for at ≥ 3 days at full dose) as compared with high dose and short course in adult patients with septic shock (conditional recommendation, low quality of evidence).

Rationale:

The latest Cochrane systematic review of the use of low-dose hydrocortisone for treating septic shock included 33 RCTs involving 4,268 patients (42) showed that corticosteroids significantly reduced the risk of death at 28 days compared to placebo. Three of these RCTs included children and the other 30 trials included only adults. Survival benefits were dependent on the dose of corticosteroids with the lower doses (< 400 mg of hydrocortisone or equivalent per day) for a longer duration of treatment (3 or more days at the full dose) better, and on the severity of the sepsis. Furthermore, corticosteroids did not cause harm except for an increased incidence of hyperglycemia and hypernatremia but no increased risk of superinfection or gastrointestinal bleeding. **See Appendix 4 for evidence profile.**

A network meta-analysis of 22 trials suggested no clear evidence for the superiority of one type of corticosteroids over another in adult patients with septic shock (43). However, hydrocortisone boluses and infusions were more likely than methylprednisolone boluses and placebo to reverse shock.

Given the consistent effect of corticosteroids on shock reversal and low risk for superinfection with low dose corticosteroids, the task force suggests the use of low dose IV hydrocortisone <400 mg/day for at least 3 days at full dose, or longer in adult patients with septic shock that is not responsive to fluid and moderate to high dose (> 0.1 µg/kg/min of norepinephrine or equivalent) vasopressor therapy. The task force panel was unable to comment on pediatric patients with septic shock as the meta-analyses we reviewed did not include enough patients in this age-specific population. A pilot RCT (Steroids in Fluid and/or Vasoactive Infusion Dependent Pediatric Shock, STRIPES) is currently underway to determine the feasibility of a larger RCT to address the role of corticosteroids for the treatment of pediatric shock (44). Since the publication of the Cochrane meta-analysis in 2015, a few small studies of early corticosteroid therapy in patients with pediatric septic shock and adult patients with sepsis-associated ARDS have been published (45-47) but the results are consistent with our current recommendations.

The Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial enrolled 1,241 adult patients with refractory septic shock from 35 centers in France (48). This trial commenced in 2008 and initially included the recombinant form of human activated protein C (APC), drotrecogin alfa-activated. The study featured a 2x2 factorial design with patients assigned to placebo of hydrocortisone, placebo of fludrocortisone, and placebo of APC; hydrocortisone + fludrocortisone and a placebo of APC; placebo of hydrocortisone, placebo of fludrocortisone and APC; or hydrocortisone + fludrocortisone + APC. Hydrocortisone was administered as a 50 mg i.v. bolus every 6 hours and fludrocortisone as a 50 µg tablet via a nasogastric tube once daily. In 2011, APC was withdrawn from the market after failing to demonstrate adequate efficacy in other clinical trials (49). Once APC was no longer available,

the study continued without APC arms but with one arm comprised of placebo corticosteroids (n=627) and the other arm comprised of hydrocortisone and fludrocortisone combined (n=614). Another large RCT (ADRENAL Study) conducted in Australia and New Zealand enrolled 3,800 patients either to hydrocortisone or to a placebo and although enrolment is completed, results are not yet available (50). In this trial, no ACTH stimulation testing was performed. The final results of these two trials are still pending but once available may further define the role of corticosteroids in the setting of sepsis or septic shock. Our recommendations may require re-addressing once these results are available.

Acute Respiratory Distress Syndrome (ARDS)

Among hospitalized adult patients with ARDS, should corticosteroids be administered to improve survival and other clinically relevant endpoints?

Recommendation:

We suggest use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (PaO₂/FiO₂ of < 200 and within 14 days of onset) (conditional recommendation, moderate quality of evidence).

Rationale

Acute respiratory distress syndrome (ARDS) represents an important public health problem globally and despite advances in supportive care, is associated with a high mortality rate (35-45%) (51). ARDS is associated with high costs of inpatient care and significant long-term morbidity and resource utilization (52). In ARDS, prolonged mechanical ventilation is associated with increased risk of disability and mortality at one year (53, 54).

Nine trials have investigated prolonged glucocorticoid treatment in ARDS (46, 55-60). One of these trials was in patients with ARDS due to community-acquired pneumonia (59) and another was a subgroup analysis of the initial corticosteroid trial in septic shock (60). These trials consistently found that glucocorticoid treatment was associated with a significant reduction in markers of systemic inflammation (inflammatory cytokines and/or C-reactive protein levels), reduction in the duration of mechanical ventilation by approximately seven days and probable reduction in hospital mortality by approximately 7% and 11% in patients with mild and severe ARDS, respectively (moderate certainty) (61). All, but two trials (55, 56) investigated treatment initiated in early ARDS. Early (< 72 hours) vs. late (≥7 days) initiation of treatment of

methylprednisolone treatment – when fibroproliferation (62) is still in the early stage of development (cellular with predominant type III procollagen) – responds to a lower daily methylprednisolone dose (1 mg/kg/day vs. 2 mg/kg/day) and is associated with faster disease resolution (61). **See Appendix 4 for evidence profile.**

A recent individual patient data (IPD) analysis of the four largest trials (N=322) investigating prolonged methylprednisolone treatment in early (57, 58) and late (on and after day 7 of onset) (55, 56) ARDS confirmed trial level data demonstrating benefit with corticosteroids for improved survival and decreased duration of mechanical ventilation (61).

With the exception of hyperglycemia (mostly within the 36 hours following an initial bolus), prolonged glucocorticoid treatment was not associated with increased risk for neuromuscular weakness, gastrointestinal bleeding, or nosocomial infections (61). Hyperglycemia was not associated with increased morbidity. Two trials reported a significant risk reduction for developing shock (56, 59).

The task force members believed that the quality of the evidence for the effect of corticosteroids on mortality was moderate given the serious risk of imprecision related to small number of events and confidence interval that approaches no effect. Some of the included trials allowed blinded crossover, two trials were unblinded and four trials had less than 60 patients.

In summary, the task force suggested that methylprednisolone be considered in patients with early (up to day 7 of onset; PaO₂/FiO₂ of < 200) in a dose of 1 mg/kg/day and late (after day 6 of onset) persistent ARDS in a dose of 2 mg/kg/day followed by slow tapering over 13 days (**Appendix 5**). Methylprednisolone is suggested given its greater penetration in lung tissue and longer residence time (63). Furthermore, methylprednisolone should be weaned slowly (6-14 days) and not stopped rapidly (2-4 days) or abruptly as deterioration may occur from the

development of a reconstituted inflammatory response. Finally, glucocorticoid treatment blunts the febrile response; therefore, infection surveillance is recommended to promptly identify and treat hospital-acquired infections.

MAJOR TRAUMA

Among hospitalized adult patients with major trauma, should corticosteroids be administered to improve survival and other clinically relevant endpoints?

Recommendation: We suggest against the use of corticosteroids in major trauma (conditional recommendation, low quality of evidence).

Rationale

Major trauma is the main cause of non-septic systemic inflammatory response syndrome (SIRS). Tissue necrosis, hemorrhage and ischemia-reperfusion injury are the main factors that trigger the inflammatory cascade. CIRCI may be common in severe trauma patients, and is associated with uncontrolled inflammation, vasopressor dependency and poor clinical outcomes (64).

We found 19 trials (n=12269) that investigated the effects of corticosteroids on short-term mortality in adults with multiple trauma. There were 1691/6286 (26.9%) deaths in the corticosteroid group vs. 1401/5983 (23.4%) deaths in the placebo group (RR= 1.00; 95% CI: 0.89 to 1.13). Stratified analysis of mortality based on corticosteroid dose (low vs. high) found no significant dose effect (test for interaction P=0.73). The RR of dying was 1.03 (95% CI: 0.86 to 1.22) in the 10 trials that examined low dose corticosteroid treatment, and 0.98 (95% CI: 0.81 to 1.18) in the 9 trials on high dose corticosteroids. Corticosteroid therapy did not increase the risk of gastroduodenal bleeding (12 trials, RR=1.22; 95% CI: 0.90 to 1.65) or superinfection (n=7 trials; RR=0.93; 95% CI: 0.80 to 1.08). Two trials examined the effects of hydrocortisone (65) and hydrocortisone plus fludrocortisone (66) specifically in trauma-associated CIRCI, as defined by a change in baseline cortisol at 60 minutes of < 9 mcg/dL after cosyntropin (250 mcg) administration. In the first trial (n=113 multi-trauma patients with CIRCI), hydrocortisone

therapy prevented the development of hospital acquired pneumonia by day 28 (HR, 0.47; 95% CI, 0.25-0.86) and increased by 6 days (95% CI, 2-11) the number of mechanical ventilation-free days. In the second trial (n=267 head trauma patients with CIRCI), the HR for hospital-acquired pneumonia with corticosteroids vs. placebo was 0.80 (95% CI 0.56–1.14). In this trial, there was no interaction between response to corticosteroid therapy and CIRCI status. **See Appendix 4 for evidence profile.**

The largest trials which primarily drive the signal for mortality outcome were at low risk of bias, and stratified analysis found no dose effect. Although the type of patients, corticosteroids, dose and duration varied fairly across trials, there was no evidence for significant inconsistency in the results. Although it appears that corticosteroids have no effect on mortality in trauma patients, the imprecision of pooled results does not allow excluding a potential for benefit or harm from corticosteroid therapy. The task force members judged the overall quality of evidence for this question as being low. Given the potential for clinically important side effects with treatment, the task force made a conditional recommendation against corticosteroids for major trauma until further data is available supporting its use.

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