

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

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Dr. Pastores participates in the American College of Physicians: Speaker at ACP Critical Care Update Precourse, the American College of Chest Physicians (CHEST) (faculty speaker at Annual Congress), the American Thoracic Society (ATS): Moderator at Annual Meeting, the European Society of Intensive Care Medicine (ESICM) (co-chair of Corticosteroid Guideline in collaboration with SCCM), and the Korean Society of Critical Care Medicine (co-director and speaker at Multiprofessional Critical Care Board Review Course). He has spoken on the topic of corticosteroid use in critical illness and specifically in sepsis at the International Symposium in Critical and Emergency Medicine in March 2017. Dr. Annane has been involved with research relating to this guideline. Dr. Rochwerf disclosed he is a methodologist for ATS, CBS, ESCIM, and ASH.

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This part II of the guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients is related to acute illnesses that may be complicated by CIRCI. We followed strictly the same methodology as for part I (**Supplemental Digital Content 1**, <http://links.lww.com/CCM/C977>), which summarized the guidelines related to CIRCI and sepsis/septic shock, acute respiratory distress syndrome (ARDS), and major trauma. PICOM questions were developed a priori for community-acquired pneumonia, influenza, meningitis, and non-septic systemic inflammatory response syndrome (SIRS) that may be associated with shock, namely burns, cardiac arrest and cardiopulmonary bypass surgery. For all these conditions, we formulated statements for or against the use of exogenous corticosteroids. Recommendations and their strength required the agreement of at least 80% of the task force members. During the editorial process, discussions about the burn condition resulted in the compromise of this question being left out and reconsidered in the next update of these guidelines.

COMMUNITY-ACQUIRED PNEUMONIA

Should corticosteroids be administered to hospitalized adults with community-acquired pneumonia (CAP)?

Recommendation: We suggest the use of corticosteroids for 5–7 days at a daily dose < 400 mg IV hydrocortisone or equivalent in hospitalized patients with CAP (conditional recommendation, moderate quality of evidence).

Rationale: Lower respiratory infections, the most deadly of communicable diseases (1), may be characterized by persistent systemic inflammation (2). Thirteen trials (n = 2005) have investigated varying daily doses (80–400 mg of

hydrocortisone-equivalent; IV or orally), agents (prednisone, methylprednisolone, dexamethasone, hydrocortisone), and length of treatment (4 to 10 days, with and without tapering) with corticosteroids in hospitalized patients with CAP (3). Five additional studies are ongoing. Twelve trials suggested a mortality reduction with corticosteroids, most pronounced in patients with severe rather than mild pneumonia, with some imprecision in the results (relative risk [RR], 0.67; 95% CI, 0.45–1.01) (2). Compared with placebo, corticosteroids, notably, shortened hospital stay (risk difference -2.96 , 95% CI -5.18 – 0.75), reduced the need for mechanical ventilation (RR, 0.45; 95% CI, 0.26–0.79), prevented ARDS (RR, 0.24; 95% CI, 0.10–0.56), and increased the risk for hyperglycemia (RR, 1.49; 95% CI, 1.01–2.19), without other complications. See **Supplemental Digital Content 2** (<http://links.lww.com/CCM/C978>) for evidence profile.

The quality of evidence across outcomes was moderate. Given the consistent signal for benefits across critical outcomes, we agreed that the beneficial effects of treatment with corticosteroids outweighed the risks.

INFLUENZA

Should corticosteroids be administered to hospitalized adults with influenza?

Recommendation: We suggest against the use of corticosteroids in adults with influenza (conditional recommendation, very low quality of evidence).

Rationale: Influenza affects millions of people worldwide annually and is responsible for thousands of deaths, mainly driven by uncontrolled inflammation (4). Analyses from 13 observational studies ($n = 1,917$ patients) found an odds ratio (OR) of dying of 3.06 (95% CI, 1.58–5.92) against corticosteroids (5). Analysis of the four trials with a low risk of bias revealed consistent findings (OR, 2.82; 95% CI, 1.61–4.92), and increased risk of superinfection. See **Supplemental Digital Content 2** (<http://links.lww.com/CCM/C978>) for evidence profile.

The quality of evidence was downgraded to very low because of the absence of a randomized trial and the inconsistent results across studies with regard to indication, type, dose, duration, and timing of corticosteroids. Given the uncertainty in results, and acknowledging that corticosteroids may be unsafe, we made a conditional recommendation against the use of corticosteroids for influenza.

MENINGITIS

Should corticosteroids be administered to hospitalized adults with bacterial meningitis?

Recommendation: We recommend use of corticosteroids in patients with bacterial meningitis (strong recommendation, low quality of evidence).

Rationale: Bacterial meningitis remains associated with unacceptably high morbidity and mortality, partly related to abundant release of cytokines into the subarachnoid spaces (6). Analyses from 25 trials ($n = 4,121$ patients

including 2,511 children) found a RR for dying of 0.90 (95% CI, 0.80–1.01), for severe hearing loss of 0.67 (95% CI, 0.51–0.88), and for neurological sequelae of 0.83 (95% CI, 0.69–1.00) in favor of the use of corticosteroids, with some heterogeneity in the results (7). First, corticosteroids reduced mortality only in *Streptococcus pneumoniae* meningitis (RR, 0.84; 95% CI, 0.72–0.98). Second, corticosteroids reduced severe hearing loss only in *Haemophilus influenzae*-related meningitis (RR, 0.34; 95% CI, 0.20–0.59). Finally, corticosteroids showed reduction in morbidity related to meningitis in trials performed in high-income countries but not in those performed in low-income countries. See **Supplemental Digital Content 2** (<http://links.lww.com/CCM/C978>) for evidence profile.

We agreed that the treatment effects on hearing loss and neurological sequelae were highly relevant and justified a strong recommendation to use corticosteroids in adults with bacterial meningitis, despite the lack of evidence for statistically significant survival benefit. The quality of evidence was downgraded to low because of the inconsistent results across causative organisms or world regions and the imprecision in the results, specifically with regard to the mortality data.

CARDIOPULMONARY BYPASS SURGERY

Should corticosteroids be administered in adults undergoing cardiopulmonary bypass surgery?

Recommendation: We suggest use of corticosteroids in patients undergoing cardiopulmonary bypass surgery (conditional recommendation, moderate quality of evidence).

Rationale: Cardiopulmonary bypass (CPB) may trigger endothelial cell injury, vasoplegic shock, acute lung injury, and eventually multiple organ failure and death (8). Analyses from 14 trials ($n = 13,365$) found a RR of dying of 0.84 (95% CI, 0.70–1.01) and a RR of onset of atrial fibrillation of 0.80 (95% CI, 0.70–0.92) in favor of corticosteroids. In one trial ($n = 7,507$), the RR of dying was 0.87 (95% CI, 0.70–1.07) in favor of methylprednisolone (250 mg IV at anesthesia induction and at onset of CPB) with an increased risk of myocardial injury, i.e., increased in levels of creatine kinase myocardial band (RR, 1.22; 95% CI, 1.07–1.38) (9). In another trial ($n = 4,494$), the RR for mortality was 0.92 (95% CI, 0.57–1.49), for superinfection 0.64 (95% CI, 0.54–0.75), for delirium 0.79 (95% CI, 0.66–0.94), and for respiratory failure 0.69 (95% CI, 0.51–0.94) in favor of dexamethasone (1 mg/kg perioperatively) (10). See **Supplemental Digital Content 2** (<http://links.lww.com/CCM/C978>) for evidence profile.

We believe that there was evidence of benefit, as the direction of the point-estimate for mortality (although non-significant) and for atrial fibrillation favored corticosteroids consistently across studies. Thus, we suggest the use of perioperative corticosteroids in adults undergoing CPB. Owing to the imprecision for mortality outcome and the inconsistency across trials for the atrial fibrillation outcome, the overall quality of evidence was downgraded to moderate.

CARDIAC ARREST

Should corticosteroids be administered to adults who suffer a cardiac arrest?

Recommendation: We suggest use of corticosteroids in the setting of cardiac arrest (conditional recommendation, very low quality of evidence).

Rationale: Studies found that CIRCI may be present in about half of patients admitted to the ICU following cardiac arrest, and may contribute to poor outcomes (11). Analyses from three trials (12–14) showed RR of shock reversal of 1.42 (95% CI, 0.39–5.24), of survival to hospital discharge of 1.96 (95% CI, 0.68–5.64), and of good neurological recovery at hospital discharge of 1.45 (95% CI, 0.41–5.13) in favor of corticosteroids. Another trial of 268 adults with in-hospital cardiac arrest found an OR of return to spontaneous circulation of 2.98 (95% CI, 1.39–6.40) and of survival to hospital discharge with good neurological outcome of 3.28 (95% CI, 1.17–9.20) in favor of methylprednisolone (given during resuscitation), and a OR of survival to hospital discharge with good neurological outcome of 3.74 (95% CI, 1.20–11.62) in favor of hydrocortisone (given for post-resuscitation shock) (15). See Supplemental Digital Content 2 (<http://links.lww.com/CCM/C978>) for evidence profile.

Owing to the benefits in term of shock reversal, survival to hospital discharge, and good neurological outcome and to the absence of evidence for complications, we made a suggestion for corticosteroids in cardiac arrest. The quality of evidence was downgraded to very low owing to imprecision and indirectness, given that corticosteroids were one component of a cardiac arrest cocktail in two trials.

In conclusion, corticosteroids have been considered in the management of numerous acute illnesses. In general, studies suggest potential benefits from this treatment. However, the quality of evidence was most often low, and additional trials are required to ascertain whether the presence or absence of CIRCI may influence responses to corticosteroid therapy in these conditions.

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