Intensive Care Med (2018) 44:474–477
DOI 10.1007/s00134-017-4951-5

WHAT'S NEW IN INTENSIVE CARE

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

Stephen M. Pastores[1*], Djillali Annane[2*], Bram Rochwerg[3] and The Corticosteroid Guideline Task Force of SCCM and ESICM

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 (see Appendix 1 in Supplementary material), 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 i.v. hydrocortisone or equivalent in hospitalized patients with CAP (conditional recommendation, moderate quality of evidence)

*Correspondence: pastores@mskcc.org; djillali.annane@aphp.fr
[1] Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, C-1179, New York, NY 10065, USA
[2] General ICU Department, Raymond Poincaré Hospital (APHP), Health Science Centre Simone Veil, Université Versailles SQY-Paris Saclay, Garches, France
Full author information and disclosures are available at the end of the article.

A full list of the Corticosteroid Guideline Task Force of SCCM and ESICM investigators is presented in the supplementary material (ESM3).

Stephen M. Pastores and Djillali Annane are the co-chairs and co-first authors who have contributed equally to this work.

This article is being simultaneously published in *Critical Care Medicine* (DOI:10.1097/CCM.0000000000002840) and *Intensive Care Medicine*.

The article is linked to two other articles entitled "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)" (DOI: 10.1007/s00134-017-4914-x) and "Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part 1): Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM): 2017" (DOI: 10.1007/s00134-017-4919-5). © 2017 ESICM and SCCM.

Rationale

Lower respiratory infections, the most deadly communicable disease [1], may be characterized by persistent systemic inflammation [2]. Thirteen trials (n = 2005) have investigated varying daily doses (80–400 mg of hydrocortisone-equivalent; i.v. or orally), agents (prednisone, methylprednisolone, dexamethasone, hydrocortisone), and length of treatment (4–10 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 to 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 Appendix 2 in Supplementary material 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 = 1917 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 low risk of bias revealed consistent findings (OR 2.82, 95% CI 1.61–4.92), and increased risk of superinfection. See Appendix 2 in Supplementary material 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 = 4121 patients including 2511 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 Appendix 2 in Supplementary material 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 0.70–9.92) 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 i.v. 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 = 4494), 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 Appendix 2 in Supplementary material for evidence profile.

We believed 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 Appendix 2 in Supplementary material 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.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-017-4951-5) contains supplementary material, which is available to authorized users.

Author details

[1] Department of Anesthesiology and Critical Care Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, C-1179, New York, NY 10065, USA. [2] General ICU Department, Raymond Poincaré Hospital (APHP), Health Science Centre Simone Veil, Université Versailles SQY-Paris Saclay, Garches, France. [3] Division of Critical Care, Department of Medicine, McMaster University, Hamilton, ON, Canada.

Acknowledgements

We acknowledge the assistance of Jean S. Maragno, Director, Library Services, Sherman Library, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Lois Cottrell, Librarian, Library Services, Sherman Library, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, and the SCCM staff during the process of developing these guidelines, particularly Lori A. Harmon, RRT, MBA, Director, Quality; and Sylvia Quintanilla, Guidelines Manager.

Compliance with ethical standards

Conflicts of interest

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 (EISCM) (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. Rochwerg disclosed he is a methodologist for ATS, CBS, ESCIM, and ASH.

Received: 16 August 2017 Accepted: 25 September 2017
Published online: 31 October 2017

References

1. WHO Global Health Observatory Data. Top 10 causes of death. http://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/. Accessed 8 Aug 2017
2. Martinez R, Menendez R, Reyes S et al (2011) Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. Eur Respir J 37(2):393–399
3. Siemieniuk RA, Meade MO, Alonso-Coello P et al (2015) Corticosteroid therapy for patients hospitalized with community acquired pneumonia: a systematic review and meta-analysis. Ann Intern Med 163(7):519–528
4. Bautista E, Chotpitayasunondh T, Gao Z et al (2010) Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 362(18):1708–1719

5. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS (2016) Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev 3:CD010406
6. Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D (2011) Pathogenesis and pathophysiology of pneumococcal meningitis. Clin Microbiol Rev 24(3):557–591
7. Brouwer MC, McIntyre P, Prasad K, van de Beek D (2015) Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 9:CD004405
8. Paparella D, Yau TM, Young E (2002) Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 21(2):232–244
9. Whitlock RP, Devereaux PJ, Teoh KH et al (2015) SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 386(10000):1243–1253
10. Dieleman JM, Nierich AP, Rosseel PM et al (2012) Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. JAMA 308:1761–1767
11. Pene F, Hyvernat H, Mallet V et al (2005) Prognostic value of relative adrenal insufficiency after out-of-hospital cardiac arrest. Intensive Care Med 31(5):627–633
12. Paris PM, Stewart RD, Deggler F (1984) Prehospital use of dexamethasone in pulseless idioventricular rhythm. Ann Emerg Med 13(11):1008–1010
13. Tsai MS, Huang CH, Chang WT et al (2007) The effect of hydrocortisone on the outcome of out-of-hospital cardiac arrest patients: a pilot study. Am J Emerg Med 25(3):318–325
14. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M et al (2009) Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med 169(1):15–24
15. Mentzelopoulos SD, Malachias S, Chamos C et al (2013) Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. JAMA 310(3):270–279