Crit Care Shock (2019) 22:177-188

Corticosteroids and gastrointestinal bleeding in critical care: a systematic review and meta-analysis

Paul E. Marik, Mit P. Patel, Joseph Varon

Abstract

***Background*: Current belief suggests that patients receiving corticosteroids have an increased risk of bleeding from stress ulceration and that these patients should receive stress ulcer prophylaxis. This issue is important as many ICU patients receive corticosteroids and the pharmacologic agents used for stress ulcer prophylaxis are associated with adverse events.**

***Aim*: The goal of this systematic review and meta-analysis was to compare the rate of clinically significant (overt) gastrointestinal (GI) bleeding in critically ill patients receiving corticosteroids versus placebo.**

***Methods*: We searched PubMed, Embase, and the Cochrane database from inception through December 2018. In addition, the bibliographies of selected articles were reviewed for relevant studies and included if inclusion criteria were met. Included studies were randomized, placebo-controlled and blinded studies that compared treatment with corticosteroids for any indication in a patient population that included only ICU patients. Primary outcome of interest was rate of clinically significant GI bleeding in patients treated with corticosteroids versus placebo. Results were expressed as risk ratio (RR) with accompanying 95% confidence interval (CI). Heterogeneity, sensitivity analysis, and risk of bias were explored. In addition, we did a subgroup analysis according to the use of "low-dose" (<400 mg hydrocortisone or equivalent/day) versus "high-dose" corticosteroid.**

***Results*: Thirty-five studies, which enrolled 16,659 patients, met inclusion criteria and were analyzed. Significant GI bleeding was recorded for 355 patients (overall rate of 2.1%). Summary data demonstrated no difference in the risk of GI bleeding between those treated with corticosteroids versus placebo (RR 1.08; 95% CI 0.88-1.33; p=0.46) with minimal heterogeneity between studies (Q statistic p=0.86, I^2=0%). Similarly, there was no significant difference in the risk of GI bleeding in either the low (RR 1.04; 95% CI 0.78-1.38) or the high dose groups (RR 1.13; 95% CI 0.84-1.53) and in those studies at low risk of bias (RR 1.16; 95% CI 0.91-1.49) and those at a high risk of bias (RR 0.88; 95% CI 0.6-1.28).**

***Conclusion*: This meta-analysis did not identify a clinically significant difference in the rate of overt GI bleeding in critically ill patients receiving corticosteroids as compared to placebo. The role of stress ulcer prophylaxis in these patients remains uncertain.**

Key words: Corticosteroids, stress ulcer prophylaxis, gastrointestinal hemorrhage, bleeding, critically ill.

Introduction

The association of corticosteroids and gastrointestinal adverse effects such as gastrointestinal (GI) bleeding has been debated and disputed for decades. (1,2) Furthermore, the use of stress ulcer prophylaxis (SUP) with H2 blockers or proton pump inhibitors (PPIs) to prevent such outcomes has led to further controversy, in relation to not only treating or preventing an unconfirmed disease process, but also, the potential for adverse effects related to PPI use. The use of corticosteroids and its influence on the GI system has been described by several observational studies, (3-5) but uncertainty persists due to the presence of possible confounding factors and the likely multifactorial etiology. In more recent years, the use of PPI has increased enormously, but not without consequences. (6) There has been increasing evidence to suggest a

From Eastern Virginia Medical School, Norfolk, VA, USA (Paul E. Marik and Mit P. Patel), and United Memorial Medical Center/United General Hospital, Houston, TX, USA (Joseph Varon).

Address for correspondence:
Paul Marik, MD
Eastern Virginia Medical School
825 Fairfax Av, Suite 410, Norfolk VA 23507, USA
Email: marikpe@evms.edu

link between the use of PPIs and an increased risk of clostridium difficile infection, nosocomial pneumonia, and acute kidney injury. (7,8) As such, the routine use of SUP in general and specifically for patients on corticosteroids remains controversial. In addition, an association between corticosteroid use and peptic ulcers is considered by many gastroenterologists to be unlikely, as corticosteroids are not believed to possess ulcerogenic properties. (9) However, physician surveys demonstrate that many still consider corticosteroids ulcerogenic and routinely prescribe PPI prophylaxis. (9) This uncertainty is more pronounced in the setting of critically ill patients receiving corticosteroids. The primary goal of this meta-analysis was to review the existing literature and synthesize the evidence to determine the incidence of clinically significant gastrointestinal hemorrhage in critically ill patients receiving corticosteroids.

Methods

Identification of trials

Our goal was to review and include all randomized, blinded, controlled trials in critically ill patients admitted to the ICU who were randomized to receive corticosteroids or placebo for treatment of the underlying principle diagnosis and which reported the rate of clinically important GI bleeding. Clinically important gastrointestinal in the ICU is defined as overt gastrointestinal bleeding and at least one of the following features: a spontaneous decrease blood pressure, a decrease in hemoglobin of at least 2 g per deciliter, or transfusion of two or more units of packed red cells. We excluded studies that included patients who had a history of peptic ulcer disease, those that enrolled patients under the age of 18 years and those that included patients chronically receiving corticosteroids. A literature search was performed using PubMed, Embase, and the Cochrane database from inception through October 2018. The PubMed search strategy is depicted in **Figure S1** (supplementary Figure 1). In addition, the bibliographies of selected articles were reviewed for relevant studies and included if inclusion criteria were met. Articles were reviewed for data on rate of clinically significant gastrointestinal hemorrhage. Studies were sub-grouped according to the use of "low" dose corticosteroid (<400 mg hydrocortisone or equivalent/day) or high dose corticosteroid, and the rate of GI bleeding was compared between the placebo and corticosteroid groups.

Data extraction and quality assessment

The three reviewers independently assessed eligibility of articles identified in the initial search strategy for inclusion. Relevant data was extracted and compiled on a standardized data matrix, which identified each paper with several parameters including: author, year, number of patients, country of origin, underlying principle diagnosis, dose of corticosteroid used, rate of GI bleeding on corticosteroid, rate of GI bleeding on placebo, and the stated use of stress ulcer prophylaxis.

Statistical design

Descriptions of all studies involved in the analysis were compiled and reported. Pooled risk ratio (RR) and its 95% confidence interval (CI) were estimated using a weighted random-effect model DerSimonian-Laird approach. Heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistics. The heterogeneity was considered significant if either the Q statistic had a $p<0.1$ or $I^2>50\%$. All statistical tests for this meta-analysis were performed using Review Manager 5.3.5 (Cochrane Community). The risk of bias was assessed using the Cochrane risk of bias assessment tool. The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Results

Our initial search strategy yielded 106 full text articles for review, of which 32 articles met inclusion criteria. An additional three studies were identified upon review of bibliographies, which met inclusion criteria and were included in the meta-analysis for a total of 35 double blinded, randomized controlled trials, which enrolled a total of 16,659 patients. (10-44) The results of the search strategy are depicted in **Figure S2** (supplementary Figure 2). The included studies are summarized in **Table 1**. The average sample size was 476 (23-7507) patients. The risk of bias assessment of the included studies is depicted in **Figure S3** (supplementary Figure 3). Eight studies (22%) were at high risk for bias for any of the 6 domains. (10,13,16,19,22,25, 32,35)

Significant GI bleeding was recorded for 355 patients (overall rate of 2.1%). Summary data demonstrated no difference in the risk of GI bleeding between those treated with corticosteroids versus placebo (RR 1.08; 95% CI 0.88-1.33; p=0.46) with minimal heterogeneity between studies (Q statistic p=0.86, I^2=0%). Similarly, there was no significant difference in the risk of GI bleeding in either the low (RR 1.04; 95% CI 0.78-1.38) or the high dose groups (RR 1.13; 95% CI 0.84-1.53); the forest plot is depicted in **Figure 1**. There was no

difference in the risk of GI bleeding in those studies with a low risk of bias (RR 1.16; 95% CI 0.91-1.49) and those at a high risk of bias (RR 0.88; 95% CI 0.6-1.28). Three studies reported using PPIs, (20-22) with no difference in risk of bleeding complications (RR 1.14; 95% CI 0.21-6.26; p=0.2) between the corticosteroid and placebo groups. With regards to those studies not reporting on the use of SUP, no difference was once again seen for clinically significant bleeding (RR 1.08; 95% CI 0.88-1.33; p=0.8) between the corticosteroid and placebo groups.

Discussion

The underlying pathophysiology causing stress ulcers or stress related mucosal damage is not completely understood. It is postulated to be consequence of severe physiological stress leading to decreased mucosal blood flow, tissue ischemia and reperfusion injury leading to a compromised integrity of the gut barrier and mucosal defense system. This process ultimately results in inflammation, injury, and ulceration. (45,46) In the 1994 prospective, observational study by Cook et al, which included 2200 critically ill patients, mechanical ventilation for greater than 48 hours and coagulopathy were identified as substantial risk factors for clinically significant GI bleeding, and was subsequently widely adopted as indications for stress ulcer prophylaxis. (47) Over time, this precautionary guideline has become more mainstream as many institutions today routinely engage in SUP in all patients that are admitted to the intensive care unit. More recently, the benefits of stress ulcer prophylaxis have been questioned and the indications for this intervention have become less clear. (48) A recent multicenter, randomized controlled trial, which enrolled 3298 high risk ICU patients failed to demonstrate a benefit from routine stress ulcer prophylaxis. (49) Nevertheless, many clinicians believe that corticosteroids increase the risk of stress ulceration and therefore advocate for the use of stress ulcer prophylaxis in this situation. (50,51)

The meta-analysis reported here demonstrated no evidence of increased incidence of GI bleeding in patients who are critically ill and receiving corticosteroids compared with those receiving placebo. Furthermore, when grouped by high dose and low dose corticosteroid use, there was no significant increase in the rate of GI bleeding for patients on corticosteroids as compared to patients on placebo. If steroids are truly ulcerogenic one would have expected the rate of GI bleeding from stress ulceration to be increased in the group of patients receiving high dose corticosteroids. These findings challenge conventional practice that occurs daily in many intensive care units across the world.

The data presented in this meta-analysis contributes to the heterogeneity of findings that have been reported previously. (1,2,9) Our findings differ from the previously reported meta-analysis by Narum et al, who reported a 40% increase in the odds ratio for GI bleeding or perforation in hospitalized patients receiving corticosteroids. (9) However, the majority of studies reviewed by Narum and colleagues did not report a history of peptic ulcer as an exclusion criterion, which may represent a significant confounding contribution towards the results. (9) Our findings are more consistent with previously published studies by Conn and colleagues, (1,52) who concluded that it was unlikely that corticosteroids increased the risk of bleeding from stress ulceration.

The strengths of this meta-analysis include the fact that we only included randomized, placebo-controlled trials. Furthermore, to our knowledge, this is the first meta-analysis restricted to critically ill patients. In addition, studies that included patients previously on steroids and those who had a history of GI bleeding were excluded, which lead to a more standardized pool of patients to prevent potential confounding. Limitations of our study include a paucity of trials that reported data on the use of stress ulcer prophylaxis. Only three studies, representing 259 patients, reported on the use of stress ulcer prophylaxis. However, due to the ubiquitous use of stress ulcer prophylaxis in ICUs worldwide, (53) it is likely that stress ulcer prophylaxis was used in those studies in which it was not specifically reported. It could therefore be argued that the use of stress ulcer prophylaxis prevented stress ulceration in the patients receiving corticosteroids. However, if such an association existed it would have been expected that the risk of bleeding would be higher in the patients receiving high dose corticosteroids. However, subgroups such as burn victims or patients suffering from traumatic brain injury receiving corticosteroids may derive benefit from stress ulcer prophylaxis as this population may be at an increased risk of bleeding for stress ulceration.

Future directions

The notion of pharmacological interventions to prevent stress ulceration has been challenged in more recent years. (54) As discussed previously, the mechanism of injury is postulated to be related to perfusion abnormalities, and not necessarily gastric acid hypersecretion. In addition, with regard to potential adverse effects of PPI therapy, a substan-

tial interest has been undertaken with alternate strategies, such as enteral nutrition. A meta-analysis, which included 1836 patients reported that in the presence of enteral feeding, pharmacological stress ulcer prophylaxis did not significantly change the rate of stress ulcer related gastrointestinal hemorrhage. (55) Worth noting, is the identification of a subgroup of patients on enteral feeding and PPIs who were at increased risk for pneumonia and increased mortality. (55) A recent, larger meta-analysis confirmed similar findings. (56) Enteral nutrition may lead to more favorable regional gastric mucosal blood flow, leading to optimization of barrier energy utilization and function and intraluminal pH while simultaneously avoiding ischemia and reperfusion related inflammation and injury. (56) Future studies should explore the risk of GI bleeding in patients receiving corticosteroids who are not receiving stress ulcer prophylaxis and the influence of early enteral feeding.

Conclusion

This meta-analysis failed to identify a clinically significant increase in the rate of gastrointestinal bleeding in critically ill patients receiving corticosteroids. The potential confounding of enteral feeding and stress ulcer prophylaxis on corticosteroid induced GI bleeding needs to be further examined.

Competing interests

None of the authors has any competing interests in the manuscript.

Funding

None

Author's contribution

MPP, JV, and PEM independently reviewed the literature and selected relevant studies. PEM performed the statistical analysis. MPP drafted the original version of the manuscript. PEM and JV reviewed and revised the manuscript.

Table 1. A summary of all the studies included in the meta-analysis. Low dose steroids include less than 400 mg hydrocortisone or equivalent per day

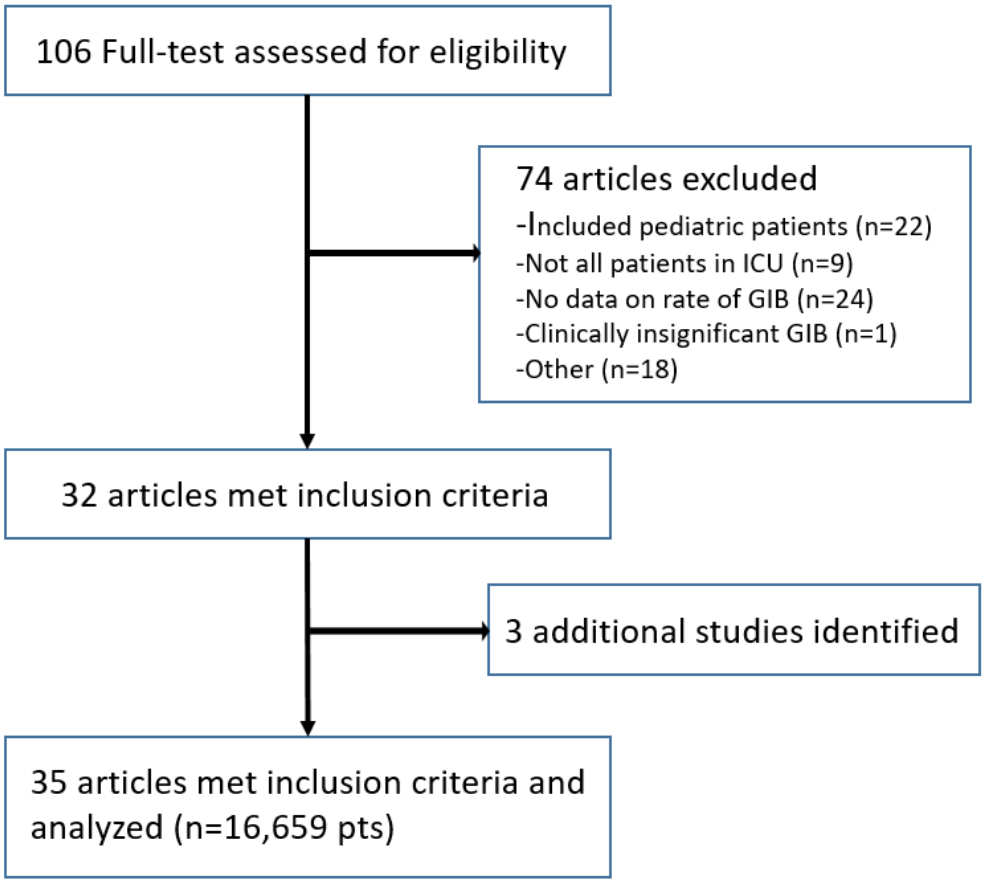
Author	Year	Country	Sample size	Steroid dose	Population
Abroug	2014	Tunisia	217	Low	COPD
Alia	2011	Multiple	83	High	COPD
Annane	2002	France	299	Low	Septic shock
Annane	2018	France	1241	Low	Septic shock
Arabi	2010	Saudi Arabia	75	Low	Cirrhosis and septic shock
Asehnoune	2014	France	328	Low	Traumatic brain injury
Bollaert	1998	France	41	Low	Septic shock
Braakman	1983	Netherlands	161	High	Traumatic brain injury
Bracken	1990	USA	333	High	Spinal cord injury
Briegel	1999	Germany	40	Low	Septic shock
Chaney	1998	USA	60	High	CABG
Confalonieri	2005	Italy	48	Low	Severe CAP
Cooper	1979	USA	76	High	Traumatic brain injury
de Gans	2002	Europe	301	High	Meningitis
Dias Cicarelli	2006	Brazil	29	Low	SIRS syndrome post-op setting
El-Ghamrawy	2006	Egypt	34	Low	Severe CAP
Gagnon	1990	USA	23	Low	Pneumocystis jirovecii
Huang	2014	China	69	Low	Burn patients
Lee	2007	Taiwan	86	Low	MV>48 hrs
Matsumoto	2001	Japan	46	High	Spinal cord injury
Meduri	1998	USA	23	High	ARDS
Meduri	2007	USA	89	Low	ARDS
Mentzelopoulos	2013	Greece	149	Low	In hospital cardiac arrest
Prasongsukarn	2005	Canada	86	High	CABG
Roquilly	2011	France	149	Low	Trauma patients
Sabry	2011	Egypt	80	Low	Severe CAP
Schumer	1976	USA	172	High	Septic shock
Sprung	1984	USA	59	High	Septic shock
Sprung	2008	Europe	499	Low	Septic shock
Thomas	1999	Europe	60	High	Meningitis
Tongyoo	2016	Bangkok	195	Low	ARDS
Torres	2015	Spain	120	Low	Severe CAP
VaSSCSG	1987	USA	223	High	Septic shock
Venkatesh	2018	Australia	3658	Low	Septic shock
Whitlock	2015	Multiple	7507	High	CABG

Legend: COPD=chronic obstructive pulmonary disease; CABG=coronary artery bypass grafting; SIRS=systemic inflammatory response syndrome; ARDS=acute respiratory distress syndrome; CAP=community acquired pneumonia; MV=mechanical ventilation.

Figure S1. The search strategy and keywords used for literature review and identification of relevant studies

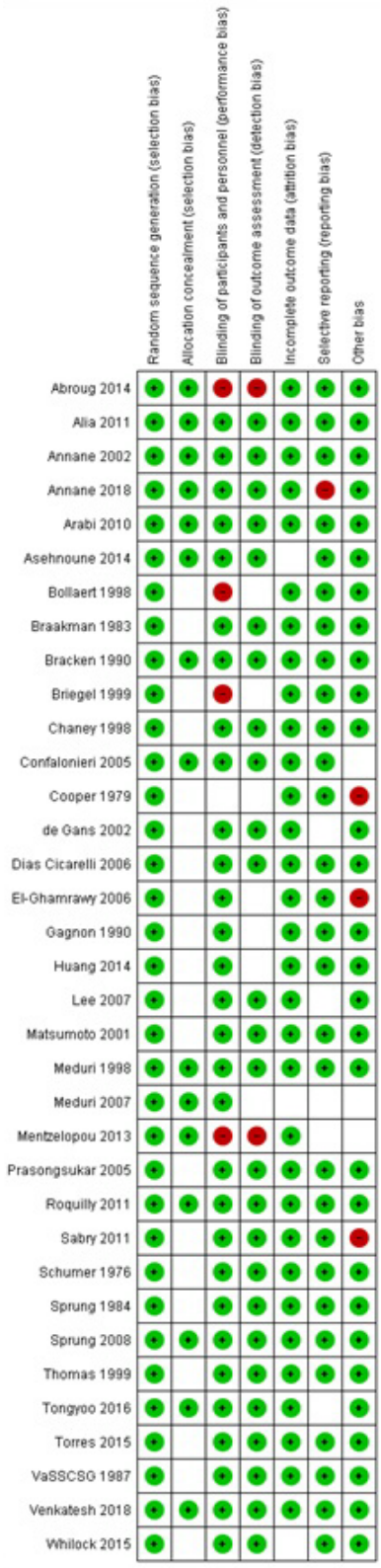
a. Betamethasone
b. Dexamethasone
c. Methylprednisone
d. Cortisone
e. Hydrocortisone
f. Double-blind
g. Randomized controlled trial
h. Pneumonia
i. COPD
j. Pneumocystis
k. ARDS
l. Sepsis
m. Septic shock
n. Mechanical ventilation
o. Traumatic brain injury
p. Spinal cord injury
q. In hospital cardiac arrest
r. Out of hospital cardiac arrest
s. CABG
t. Coronary artery bypass graft
u. Meningitis
v. Critical care
w. ICU
x. Intensive care
y. Critical illness

Figure S2. The selection of relevant studies from search results



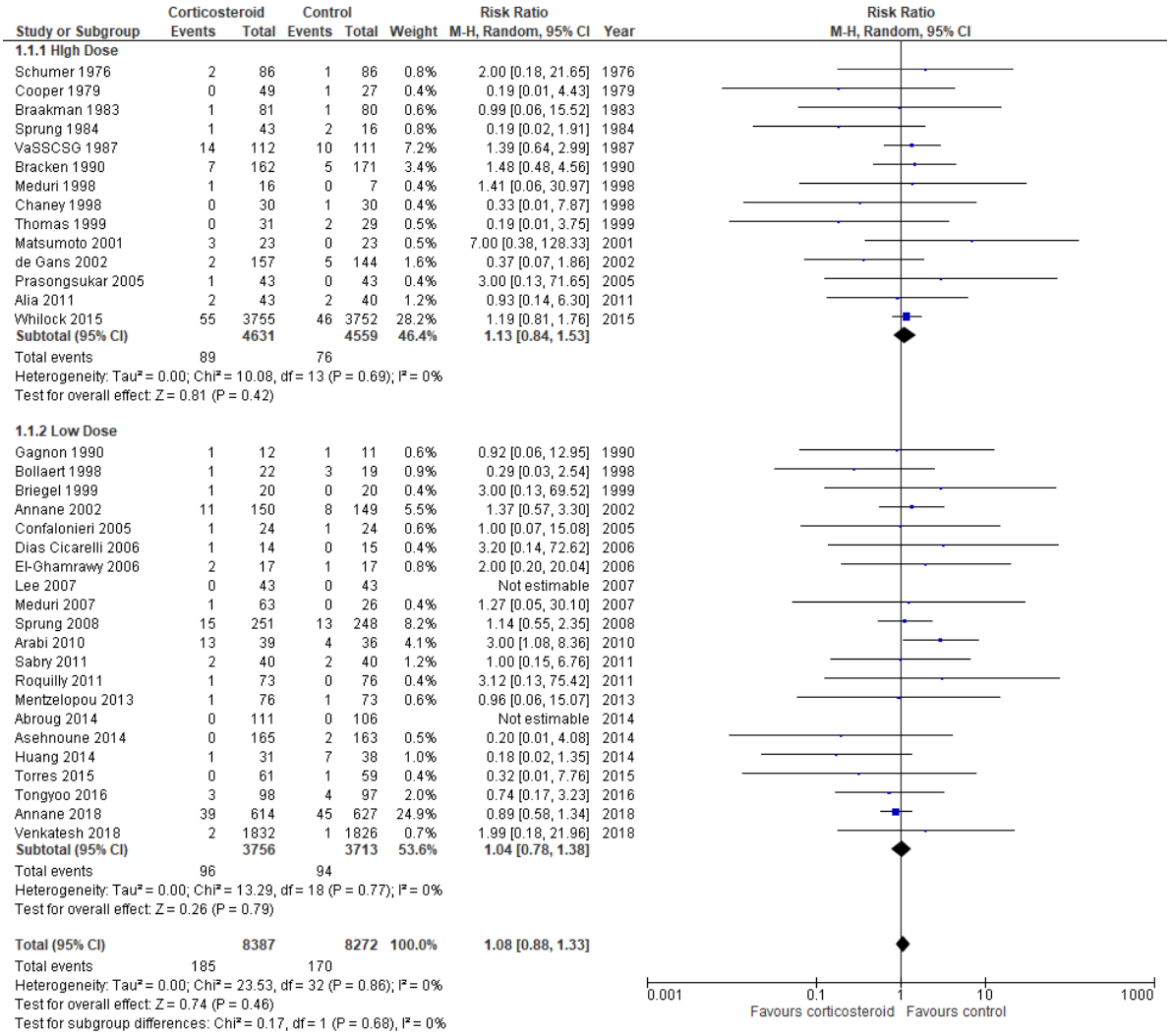
Legend: ICU=intensive care unit; GIB=gastrointestinal bleeding.

Figure S3. Risk of bias assessment



Legend: Green=low risk of bias; clear box=unclear risk of bias; red=high risk of bias.

Figure 1. A summary forest plot of all papers included in systematic analysis stratified by dose of corticosteroids with depicted individual and pooled odds ratio for gastrointestinal hemorrhage



References

1. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994;236: 619-32.
2. Messer J, Reitman D, Sacks HS, Smith H Jr, Chalmers TC. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983;309:21-4.
3. Nielsen GL, Sørensen HT, Mellemkjoer L, Blot WJ, McLaughlin JK, Tage-Jensen U, et al. Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. Am J Med 2001;111:541-5.
4. Hernandez-Diaz S, Rodriguez LA. Steroids and risk of upper gastrointestinal complications. Am J Epidemiol 2001;153:1089-93.
5. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;114:735-40.
6. Johansen ME, Huerta TR, Richardson CR. National use of proton pump inhibitors from 2007 to 2011. JAMA Intern Med 2014;174:1856-8.
7. Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, et al. Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis. World J Gastroenterol 2017;23:6500-15.
8. Yang Y, George KC, Shang WF, Zeng R, Ge SW, Xu G. Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies. Drug Des Devel Ther 2017;11:1291-9.
9. Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open 2014;4:e004587.
10. Abroug F, Ouanes-Besbes L, Fkih-Hassen M, Ouanes I, Ayed S, Dachraoui F, et al. Prednisone in COPD exacerbation requiring ventilatory support: an open-label randomised evaluation. Eur Respir J 2014;43:717-24.
11. Alía I, de la Cal MA, Esteban A, Abella A, Ferrer R, Molina FJ, et al. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. Arch Intern Med 2011;171:1939-46.
12. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.
13. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378: 809-18.
14. Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ 2010;182:1971-7.
15. Asehnoune K, Seguin P, Allary J, Feuillet F, Lasocki S, Cook F, et al. Hydrocortisone and fludrocortisone for prevention of hospital-acquired pneumonia in patients with severe traumatic brain injury (Corti-TC): a double-blind, multicentre phase 3, randomised placebo-controlled trial. Lancet Respir Med 2014; 2:706-16.
16. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. Crit Care Med 1998;26: 645-50.
17. Braakman R, Schouten HJ, Blaauw-van Dishoeck M, Minderhoud JM. Megadose steroids in severe head injury. Results of a prospective double-blind clinical trial. J Neurosurg 1983;58:326-30.
18. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med 1990;322:1405-11.
19. Briegel J, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. Crit Care Med 1999; 27:723-32.
20. Chaney MA, Nikolov MP, Blakeman B, Bakhos M, Slogoff S. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. Anesth Analg 1998;87:27-33.
21. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone

References

infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med 2005;171:242-8.

22. Cooper PR, Moody S, Clark WK, Kirkpatrick J, Maravilla K, Gould AL, et al. Dexamethasone and severe head injury. A prospective double-blind study. J Neurosurg 1979;51:307-16.
23. de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002; 347:1549-56.
24. Cicarelli DD, Bensenor FE, Vieira JE. Effects of single dose of dexamethasone on patients with systemic inflammatory response. Sao Paulo Med J 2006;124:90-5.
25. El-Ghamrawy AH, Shokeir MH, Esmat AA. Effects of low-dose hydrocortiosone in ICU patients with severe community-acquired pneumonia. Egypt J Chest Dis Tuberc 2006; 55:91-9.
26. Gagnon S, Boota AM, Fischl MA, Baier H, Kirksey OW, La Voie L. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med 1990;323:1444-50.
27. Huang G, Liang B, Liu G, Liu K, Ding Z. Low dose glucocorticoid decreases the incidence of complications in severely burned patietns by attenuating systemic inflammation. J Crit Care 2015;30:436.e7-11.
28. Lee CH, Peng MJ, Wu CL. Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomized, double-blind, placebo-controlled study. Crit Care 2007;11:R72.
29. Matsumoto T, Tamaki T, Kawakami M, Yoshida M, Ando M, Yamada H. Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute cervical spinal cord injury. Spine (Phila Pa 1976) 2001;26:426-30.
30. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial. JAMA 1998;280: 159-65.
31. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson SJ, et al. Methyprednisolone infusion in patients with early severe ARDS: results of a randomized controlled trial. Chest 2007;131:954-63.
32. Mentzelopoulos SD, Malachias S, Chamos C, Konstantopoulos D, Ntaidou T, Papastylianou A, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospitalcardiac arrest: a randomized clinical trial. JAMA 2013;310:270-9.
33. Prasongsukarn K, Abel JG, Jamieson WR, Cheung A, Russell JA, Walley KR, et al. The effects of steroids on the occurrence of postoperative atrial fibrillation after coronary artery bypass grafting surgery: a prospective randomized trial. J Thorac Cardiovasc Surg 2005;130: 93-8.
34. Roquilly A, Mahe PJ, Seguin P, Guitton C, Floch H, Tellier AC, et al. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. JAMA 2011;305:1201-9.
35. Sabry NA, Omar EE. Corticosteroids and ICU course of community acquired pneumonia in Egyptian settings. Pharmacol Pharm 2011;2: 73-81.
36. Schumer W. Steroids in the treatment of clinical septic shock. Ann Surg 1976;184:333-41.
37. Sprung CL, Caralis PV, Marcial E et al. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. N Engl J Med 1984;311:1137-43.
38. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-24.
39. Thomas R, Le Tulzo Y, Bouget J, Camus C, Michelet C, Le Corre P, et al. Trial of dexamethasone treatment for severe bacterial meningitis in adults. Adult Meningitis Steroid Group. Intensive Care Med 1999;25:475-80.
40. Tongyoo S, Permpikul C, Mongkolpun W, Vattanavanit V, Udompanturak S, Kocak M, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: Results of a randomized controlled trial. Crit Care 2016;20:329.
41. Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response. A

References

randomized clinical trial. JAMA 2015;313: 677-86.

42. 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;317:659-65.
43. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med 2018;378:797-808.
44. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, et al. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386: 1243-53.
45. Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. J Crit Care 2005;20:35-45.
46. Plummer MP, Blaser AR, Deane AM. Stress ulceration; prevalence, pathology and association with adverse outcomes. Crit Care 2014;18: 213.
47. Cook DJ, Fuller HD, Guyatt GH, Marshall JC, Leasa D, Hall R, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. N Engl J Med 1994;330:377-81.
48. Alhazzani W, Alshamsi F, Belley-Cote E, Heels-Ansdell D, Brignardello-Petersen R, Alquraini M, et al. Efficay and safety of stress ulcer prophylaxis in critically ill patients: a network meta-analysis of randomized trials. Intensive Care Med 2018;44:1-11.
49. Krag M, Marker S, Perner A, Wetterslev J, Wise MP, Schefold JC, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med 2018;379:2199-208.
50. Chanpura T, Yende S. Weighing risks and benefits of stress ulcer prophylaxis in critically ill patients. Crit Care 2012;16:322.
51. Jones MG, Tsega S, Cho HJ. Inappropriate prescription of proton pump inhibitors in the setting of steroid use. A teachable moment. JAMA Intern Med 2016;176:594-5.
52. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976;294:473-9.
53. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, et al. Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. Acta Anaesthesiol Scand 2015;59:576-85.
54. Marik PE, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: A systematic review and meta-analysis. Crit Care Med 2010;38:2222-8.
55. MacLaren R, Jarvis CL, Fish DN. Use of enteral nutrition for stress ulcer prophylaxis. Ann Pharmacother 2001;35:1614-23.
56. Huang HB, Jiang W, Wang CY, Qin HY, Du B. Stress ulcer prophylaxis in intensive care unit patients receiving enteral nutrition: a systematic review and meta-analysis. Crit Care 2018;22:20.