Intensive Care Med (2019) 45:1540–1549
https://doi.org/10.1007/s00134-019-05754-3

SYSTEMATIC REVIEW

The effect of systemic corticosteroids on the incidence of gastrointestinal bleeding in critically ill adults: a systematic review with meta-analysis

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Abstract

Purpose: To assess the effect of systemic corticosteroids on the incidence of gastrointestinal bleeding in adult critically ill patients.

Methods: We systematically reviewed randomised clinical trials comparing systemic corticosteroids administered for more than 24 h with placebo/no treatment in adult critically ill patients. Trial selection, data abstraction and risk of bias assessments were performed in duplicate. We used trial sequential analysis (TSA) to assess the risk of random errors and the grading of recommendations, assessment, development, and evaluations (GRADE) approach to assess the quality of evidence. The primary outcome was the incidence of clinically important gastrointestinal bleeding within 90 days. The secondary outcome was the incidence of gastrointestinal bleeding of any severity within 90 days.

Results: Twenty-five trials ($n = 14{,}615$) reported data for the primary outcome and 55 trials ($n = 21{,}792$) for the secondary outcome. The pooled incidence of clinically important gastrointestinal bleeding was 2.3% in the corticosteroid group and 1.8% in the control group (RR, 1.26; 95% CI, 1.01–1.57; $I^2 = 0\%$, TSA-adjusted CI 0.51–3.14). We observed no difference in the risk of gastrointestinal bleeding of any severity (RR, 1.10; 95% CI, 0.92–1.32; $I^2 = 0\%$, TSA-adjusted CI 0.87–1.38). The GRADE quality of evidence was low (risk of bias and imprecision).

Conclusions: We observed an overall low incidence of clinically important gastrointestinal bleeding among adult critically ill patients. Corticosteroids may slightly increase the incidence of clinically important gastrointestinal bleeding, but not bleeding of any severity. Rarity of events, infrequent trial reporting and high risk of bias reduced the quality of evidence.

Keywords: Gastrointestinal bleeding, Peptic ulcer disease, Corticosteroids, Steroids, Critical illness, Intensive care unit, Systematic review

Introduction

Gastrointestinal (GI) bleeding may complicate critical illness. The incidence of clinically important GI bleeding in critically ill patients is 2–3% [1], with use of mechanical ventilation [2], coagulopathy [1–3], chronic liver disease [1, 3] and acute kidney injury [3, 4] associated with

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increased risk of GI bleeding. In the intensive care unit (ICU), GI bleeding has been associated with increased morbidity and mortality [1, 5] and prophylactic use of acid suppressants is very frequent [1].

Corticosteroids are used in the management of critically ill patients for a variety of reasons, including bacterial meningitis [6], septic shock [7, 8], acute respiratory distress syndrome [8] and chronic pulmonary obstructive disease (COPD) [9]. A potentially serious adverse effect to the use of corticosteroids is GI bleeding. A recent meta-analysis has suggested a significantly increased risk of GI bleeding among hospitalised patients receiving corticosteroids. However, as highlighted previously [10], there is equipoise regarding the magnitude or even existence of any risk increase and important methodological limitations with the previous meta-analysis. Hence, the aim of this updated systematic review and meta-analysis was to compare the incidence of GI bleeding in adult critically ill patients allocated to corticosteroids versus placebo or no treatment. We hypothesised that use of corticosteroids does not increase the risk of GI bleeding in these patients.

Take-home message

The incidence of gastrointestinal bleeding among adult critically ill patients is low. Corticosteroids may slightly increase the incidence of clinically important gastrointestinal bleeding, but not gastrointestinal bleeding of any severity.

Methods

We conducted a systematic review of randomised clinical trials (RCTs) with meta-analysis and trial sequential analysis (TSA) [11] in accordance with the recommendations by the Cochrane Handbook [12] and the preferred reporting items for systematic review and meta-analysis (PRISMA) statement (completed checklist included in the electronic supplementary material [ESM]) [13]. The protocol for this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/prospero/; registration number: CRD42018083519) and pre-published [10] following the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) statement [14].

Eligibility criteria

We included all RCTs involving adult (as defined in the included trials) critically ill patients in which any systemic corticosteroid (excluding topical and inhalational) versus placebo/no treatment was administered for more than 24 h; we excluded quasi-RCTs and cross-over trials. We defined critically ill patients as patients cared for in a high-dependency setting, including an ICU or intermediate care unit, and including but not limited to patients requiring mechanical ventilation; acute blood transfusion; renal replacement therapy, inotropic or vasopressor support and cardiopulmonary resuscitation. Trials including both critically ill and non-critically ill patients, or both children and adults, were excluded unless data could be adequately separated or obtained from authors.

Search strategy

We systematically searched EMBASE, MEDLINE, Medline In-Process, Cochrane Library, and Epistemonikos from inception through December 20, 2018. The complete electronic search strategy for each database is presented in the ESM. No language restrictions were imposed. Ongoing trials were identified by searching trial registries according to the pre-published protocol [10]. A hand search through reference lists of relevant primary and review articles was also performed for completeness.

Trial selection

Two review authors (EB and JP) independently and in duplicate screened articles for inclusion based on title and abstract and reviewed relevant articles as full text. Disagreement during the review process was resolved by consensus through involvement of a third review author (MHM).

Data extraction

Two review authors (EB, OC or JC) independently and in duplicate extracted information from each included trial according to the protocol [10]. We contacted corresponding authors of the included trials with incomplete data, including unclear risk of bias ratings, for additional information.

Outcomes

The primary outcome was the proportion of patients with at least one episode of clinically important GI bleeding (as defined in the original trials) from any location (i.e. mouth to anus) within 90 days of allocation (including in-hospital).

The secondary outcome was the proportion of patients with at least one episode of GI bleeding, of any severity, within 90 days of allocation (including in-hospital). Trials reporting all cases of GI bleeding together, regardless of clinical importance, had data included under this outcome.

Risk of bias

Two authors (AG and SLR) not involved in any of the included trials and blinded to the results of the

meta-analyses, independently assessed the risk of systematic errors (bias) of trials included in the meta-analysis according to the Cochrane Handbook, version 5.1.0. [12] and additional pre-defined criteria [10]. Disagreement during the review process was resolved by consensus through involvement of a third review author (MHM). Risk of bias was rated according to the following domains (1) sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting; and (7) other sources of bias (specifically including baseline imbalance, early stopping and financial bias). Trials adjudicated as low risk of bias for all seven domains were classified as having an overall low risk of bias. Trials adjudicated as unclear or high risk of bias for one or more domains were classified as having an overall high risk of bias. Publication bias was assessed by inspecting funnel plots and the Harbord test (with a $p < 0.05$ considered significant evidence of publication bias).

Statistical analysis

Statistical analyses were performed using Review Manager Software 5 (Review Manager (RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and R version 3.5.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the meta package version 4.9-5. The risk of random errors was assessed using TSA (TSA software version 0.9.5.10 beta; http://www.ctu.dk/tsa/).

For each included trial, we calculated the relative risks (RRs) with 95% conventional confidence intervals (CIs) for all outcome measures. Heterogeneity among trials was explored by inspecting forest plots and calculating I^2 statistics [12]. We performed both fixed effect and random effects analyses, reporting the most conservative summary estimate with the broadest confidence interval [15]. Subgroup analyses were performed as standard using RevMan 5 software.

Trial sequential analysis

Meta-analyses including very few participants are at risk of overestimating an effect difference due to chance (type I error) or missing a true difference due to insufficient power (type II error). TSA estimates the required information size for credible results in a meta-analysis by calculating the number of participants that would be included in a single adequately powered trial and increasing this number according to the heterogeneity in the meta-analysis. Before the required information size has been included in a meta-analysis, the results are less certain, and TSA consequently widens the confidence intervals [11]. In this meta-analysis, we applied trial sequential monitoring boundaries according to an a priori 15% relative risk increase, α of 5%, power of 90% (β of 10%), and a control event proportion suggested by all included trials. We planned to use the control event proportion suggested by low risk of bias trials only [10], however there were too few trials adjudicated as overall low risk of bias and the only trial with low risk of bias for the primary outcome contained zero events. We estimated TSA-adjusted CIs and the required information size (RIS; total included patients within the meta-analysis) necessary to detect or reject a 15% relative risk increase. Model variance-based heterogeneity correction was applied to monitoring boundaries. Empirical continuity correction factors were applied for trials with zero events in one arm [16]. Post-hoc sensitivity analyses were performed on TSA parameters. Alternate relative risk increases of GI bleeding (10% and 20%) were explored and empirical correction factors (0.01) were used to assess the effect of including zero-event trials [17, 18].

Subgroup analyses

We conducted the following pre-planned subgroup analyses: (1) overall 'low risk' of bias compared to overall 'high risk' of bias trials; (2) lower dose corticosteroids (< 400 mg of hydrocortisone equivalents per day) compared to higher dose corticosteroids (≥ 400 mg of hydrocortisone equivalents per day); (3) separated according to underlying disease type; (4) critically ill patients managed in the ICU compared to those managed outside the ICU (including intermediate care units); (5) administration (≥ 10% of patients in either trial arm) of NSAIDs, aspirin, or anticoagulant/antiplatelet drugs compared to no administration (< 10% of patients in both study arms); (6) administration (≥ 10% of patients in either trial arm) of proton pump inhibitors (PPIs), H2 receptor antagonists, or antacids compared to no administration (< 10% of patients in both study arms).

Missing outcome data

For studies with patients lost to follow up, sensitivity analyses were conducted for the primary outcome in (1) best–worst and (2) worst–best case scenarios, whereby: (1) all patients lost to follow up (outcome assessment) in the intervention group were assumed to not have had GI bleeding and all patients lost to follow in the control group up were assumed to have had GI bleeding; (2) all patients lost to follow up (outcome assessment) in the intervention group were assumed to have had GI bleeding and all patients in the control group lost to follow up were assumed to not have had GI bleeding [10].

GRADE assessment

Two authors (AG and SLR) not involved in any included trial independently assessed the quality of evidence

Table 1 Summary characteristics of included trials

	Number of trials $n=55$	Number of participants $n=21,792$
Trial characteristics		
Multicentre study	29	19,566
Single-centre study	26	2226
Placebo used	52	21,349
No placebo used	3	443
Patient admission status		
Intensive care unit	35	9059
Other critically ill[a]	20	12,733
Patient disease type		
Sepsis/septic shock	19	7542
Respiratory diseases (including ARDS and COPD)	12	838
Trauma (including traumatic brain injury)	6	11,021
Miscellaneous[b]	6	552
Meningitis	5	1329
Liver diseases	5	233
Post-surgical	2	277
Patient characteristics		
Mean age (years) of trial arms, median [IQR]	Control: 60 [42–66] Intervention: 60 [46–65]	
Percentage of female patients in trial arms, median [IQR]	Control: 40 [28–48] Intervention: 41 [33–53]	
Corticosteroid type		
Hydrocortisone	21	6516
Methylprednisolone	12	10,411
Dexamethasone	10	2017
Prednisone/prednisolone	8	562
Hydrocortisone + fludrocortisone	4	1890
Triamconolone	1	396
Corticosteroid regime[c]		
Bolus administration	44	7128
Continuous infusion	4	4254
Bolus + infusion	8	10,464
Duration of steroids (days), median [IQR]	7 [5–10]	

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *IQR* interquartile range

[a] Other critically ill patients: critically ill patients admitted to a high dependency unit (HDU) or emergency department, or mixed population of ICU/HDU patients, or patients not in ICU but requiring renal replacement therapy or ventilatory support or inotropic support

[b] Miscellaneous disease types: ischemic stroke, severe tetanus, severe pre-eclampsia, burns patients, spinal cord compression, intracerebral haemorrhage

[c] Trials = 56 ($n=21,846$) as one trial (Mirea 2014) had both bolus and infusion experimental arms

across trials at an outcome level according to the grading of recommendations, assessment, development, and evaluations (GRADE) approach [19]. In brief, the quality of evidence could be downgraded for identified risk of bias, inconsistency (unexplained heterogeneity), indirectness of evidence, imprecision of results, and high probability of publication bias. Accordingly, the quality of evidence could be classified as high, moderate, low or very low. Disagreement was resolved through consensus by involving a third review author (MHM).

Results

ESM Fig. 1 shows the trial selection process. The initial search on the 3rd February 2018 identified 4594 unique articles. Following preliminary screening 322 articles were selected for full-text review, of which 51 satisfied the eligibility criteria of this review. Four additional studies were included in the meta-analysis (two studies [20, 21] were found during hand-searching and another two [22, 23] following the updated database search on 20th December 2018) resulting in 55 trials being included in total.

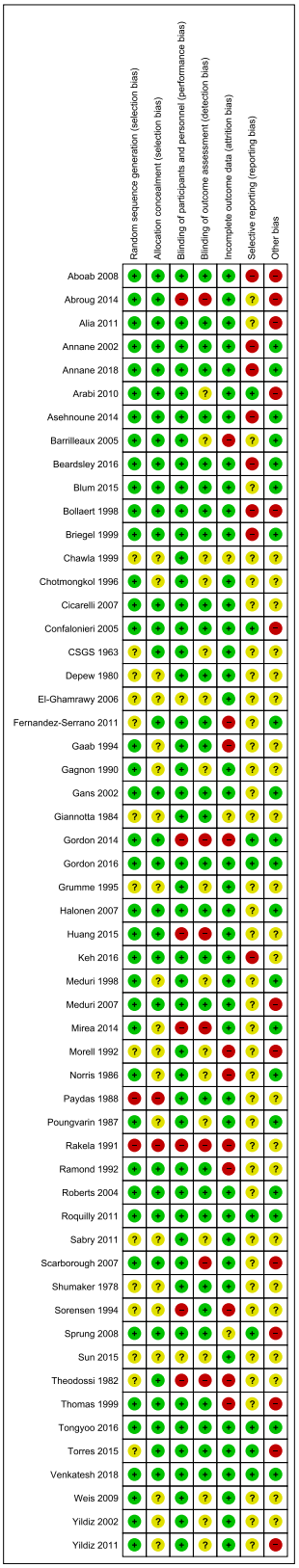

Fig. 1 Summary of risk of bias assessments for studies included in the meta-analyses

Characteristics of included studies

An overview of the characteristics of the included trials is presented in Table 1 and a summary of the risk of bias assessments is presented in Fig. 1. The definition of GI bleeding used for included trials, methods of monitoring and duration of follow up are summarised in ESM eTable 1. Detailed trial characteristics and full risk of bias assessments including justifications for all included trials are presented in the ESM. Only four trials [23–26] were adjudicated to be low risk of bias across all seven domains, of which only one trial reported our primary outcome. We obtained additional information/clarifications from authors of 26 trials included in this review (outlined in the ESM).

Clinically important gastrointestinal bleeding

Our primary outcome, clinically important GI bleeding within 90 days, was reported in 25 trials ($n = 14{,}615$). The pooled incidence of clinically important GI bleeding was 2.3% in the corticosteroid group vs. 1.8% in the control group (RR, 1.26; 95% CI, 1.01–1.57; $I^2 = 0\%$, TSA-adjusted CI 0.51–3.14) (Fig. 2). This result was stable for both fixed effect and random effects statistical models (Table 2) and we observed no evidence of publication bias when inspecting the funnel plot (ESM Fig. 5) or via the Harbord test ($p = 0.54$). TSA indicated that only 13% of the required information size ($n = 109{,}402$) had been reached to detect or reject a 15% relative risk increase in clinically important GI bleeding (ESM Fig. 6) using a control event rate of 1.8%. The quality of the evidence was adjudicated low due to risk of bias and imprecision (Table 3). There was no interaction in the subgroup analyses stratified by location in the hospital, disease type, dosage of steroid, or use of gastroprotective drugs (Table 2). High risk of bias trials and trials not reporting use of anticoagulants/NSAIDs demonstrated an increased incidence of GI bleeding for patients receiving corticosteroids (Table 2).

Gastrointestinal bleeding of any severity

Our secondary outcome, GI bleeding of any severity within 90 days, was reported in 55 trials ($n = 21{,}792$). The pooled incidence of GI bleeding was 2.1% in the corticosteroid group vs. 1.9% in the control group (RR, 1.10; 95% CI, 0.92–1.32; $I^2 = 0\%$, TSA-adjusted CI 0.87–1.38). TSA indicated that only 22% of the required information size ($n = 100{,}111$) had been reached to exclude a 15% relative risk increase in GI bleeding of any severity (ESM Fig. 18) using a control event rate of 1.9%. There was no evidence of publication bias when inspecting the funnel plot (ESM Fig. 17) or via the Harbord test ($p = 0.98$). The quality of the evidence was

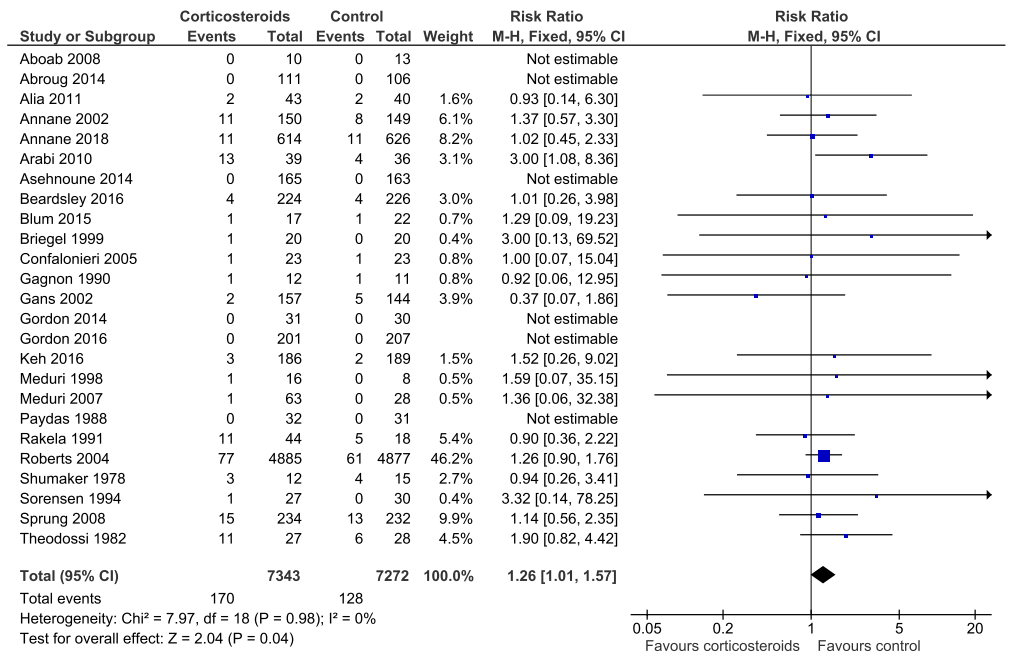

Fig. 2 Forest plot of primary outcome

adjudicated low due to risk of bias and imprecision (Table 3), and there were no subgroup effects evident (ESM Table 2).

Post-hoc sensitivity analyses

Inclusion of trials with zero events did not significantly alter the results of the primary (RR, 1.27; 95% CI, 1.01–1.58; $I^2 = 0\%$, TSA-adjusted CI 0.51–3.14) or secondary outcome (RR, 1.11; 95% CI, 0.93–1.34; $I^2 = 0\%$, TSA-adjusted CI 0.90–1.37).

Exploring a 10% RRI of GI bleeding results in a broadened TSA-adjusted confidence interval (0.57–3.14 and 0.53, 2.34) and increased RIS ($n = 240{,}540$; $n = 227{,}636$) for the primary and secondary outcome respectively.

Exploring a 20% RRI of GI bleeding results in a narrowed TSA-adjusted confidence interval (1.02–1.58 and 0.94–1.32) and decreased RIS ($n = 62{,}941$; $n = 59{,}562$) for the primary and secondary outcome, respectively. The RIS remains unmet.

Discussion

In this large systematic review with meta-analysis of RCTs involving adult critically ill patients, we observed that corticosteroids versus placebo or no treatment, may have increased the risk of clinically important gastrointestinal bleeding slightly, but not GI bleeding of any severity. However, uncertainty remains, because the required information size has not been met, most trials were adjudicated as overall high risk of bias and TSA-adjusted confidence intervals for both outcomes indicate possibility for both benefit and harm. The uncertainty found in our results were supported by sensitivity analyses and those of subgroups including the location in hospital, the use of gastroprotective drugs, and the disease type of the patients.

There are multiple possible explanations for the difference observed in our primary and secondary outcomes. First, critically ill patients are already at increased risk of developing stress ulcers [27]. Hence, the assessment of non-clinically important GI bleeding (e.g. melena in the stool without a significant decline in haemoglobin) may be insensitive to assess the additional effect of corticosteroids in this population, as many critically ill patients may have minor GI bleeds secondary to stress ulcers [1]. Second, the difference in sample size ($n = 21{,}792$ vs $n = 14{,}615$), with the secondary outcome being closer to that of the estimated required information size, which reduces the risk of spurious findings. Third, GI bleeding of any severity (e.g. melaena in the stool) may be more subjective and thus easily influenced by high risk of bias trials.

In a previous systematic review with meta-analysis of trials including both ambulant and hospitalised patients, an increased incidence of GI bleeding of any severity (odds ratio (OR) 1.42, 95% CI 1.22–1.66) was observed amongst the hospitalised adult and paediatric patients [28]. In that systematic review, bronchopulmonary dysplasia (a disease

Table 2 Subgroup and sensitivity analyses for the primary outcome, i.e. clinically important GI bleeding (excluding data from zero event trials)

	Number of trials	Number of participants	Relative risk	95% CI	*p*	I^2	Test of subgroup difference	
Sensitivity analyses for primary outcome								
Fixed-effect model	19	13,515	1.26	1.01–1.57	0.04	0%	NA	
Random-effects model	19	13,515	1.26	1.01–1.57	0.04	0%	NA	
Best–worse case scenario	24	14,878	0.82	0.57–1.19	NA	49%	NA	
Worst–best case scenario	24	14,878	1.86	1.38–2.51	< 0.001	24%	NA	
Subgroup analyses for primary outcome								
Overall risk of bias								
Low risk of bias trials	0	0	NA	NA	NA	NA	NA	
High risk of bias trials	19	13,515	1.26	1.01–1.57	0.04	0%		
Dose of corticosteroid (hydrocortisone equivalents per 24 h)								
Higher dose (≥ 400 mg) corticosteroids	12	10,981	1.20	0.92–1.57	0.18	0%	0.53	
Lower dose (< 400 mg) corticosteroids	7	2534	1.39	0.93–2.07	0.11	0%		
Patient admission status								
ICU patients	11<	2778	1.37	0.94–1.99	0.10	0%	0.59	
Other critically ill patients[a]	8	10,737	1.20	0.92–1.59	0.17	0%		
Patient disease type								
Meningitis	2	751	0.64	0.23–1.89	0.44	0%	0.80	
Sepsis/septic shock	6	2495	1.39	0.92–2.08	0.11	0%		
Trauma (including traumatic brain injury)	1	9762	1.26	0.90–1.76	0.17	NA		
Respiratory diseases (including ARDS and COPD)	6	306	1.10	0.38–3.17	0.85	0%		
Liver diseases	3	144	1.26	0.72–2.19	0.42	0%		
Post-surgical patients	NA	NA	NA	NA	NA	NA		
Miscellaneous[b]	1	57	3.32	0.14–78.25	0.46	NA		
Use of gastroprotective drugs (e.g. proton pump inhibitors)								
≥ 10% population	4	611	1.97	0.92–4.21	0.08	NA	0.75[c]	0.37
< 10% population	1	57	3.32	0.14–78.25	0.56	NA		
Unknown	14	12,847	1.19	0.95–1.51	0.14	0%	–	
Use of anticoagulant or antiplatelet drugs or NSAIDs								
≥ 10% population	2	86	1.60	0.21–12.45	0.65	0%	0.68[c]	0.92
< 10% population	1	450	1.01	0.26–3.98	0.99	NA		
Unknown/not specified	16	12,979	1.26	1.01–1.58	0.04	0%	–	

Subgroup analyses were performed as standard using RevMan 5 software

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *IQR* interquartile range

[a] Other critically ill patients: critically ill patients admitted to a high dependency unit (HDU) or emergency department, or mixed population of ICU/HDU patients, or patients not in ICU but requiring renal replacement therapy or ventilatory support or inotropic support

[b] Miscellaneous disease types: severe tetanus, spinal cord compressionn

[c] Subgroup analyses performed excluding "missing strata" (i.e. data with unknown/not specified information)

confined to premature infants) was included; excluding these trials resulted in a more conservative estimate (OR 1.29, 95% CI 1.07–1.55). In addition, the use of language and time restrictions in the search strategy, lack of protocol registration or publication, systematic assessment of risk of random errors or bias and lack of quality of evidence assessments according to the GRADE approach, all reduce the trustworthiness of these findings.

Our review has strengths including publication of the protocol, detailed and pre-defined sensitivity and subgroup analyses, comprehensive assessment of the risk of systematic and random errors, and assessment of the quality of evidence. Our review also incorporates the results of several, recent large RCTs [22, 23, 29–31] on corticosteroids in the critical care setting, markedly increasing the sample size.

Table 3 GRADE summary of findings table

Certainty assessment							No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Corticosteroids	placebo/no treatment	Relative (conventional 95% CI)	Absolute (conventional 95% CI)	
Clinically important GI bleeding											
25	Randomised trials	Serious[a]	Not serious	Not serious	Serious[b]	None[c]	170/7343 (2.3%)	128/7272 (1.8%)	RR 1.26 (1.01–1.57)	5 more per 1.000 (from zero fewer to ten more)	⊕⊕◯◯ Low
Any GI bleeding											
55	Randomised trials	Serious[a]	Not serious	Not serious	Serious[d]	None[c]	236/10,993 (2.1%)	205/10799 (1.9%)	RR 1.10 (0.92–1.32)	2 more per 1.000 (from two fewer to six more)	⊕⊕◯◯ Low

Question: corticosteroids compared to placebo/no treatment in critically ill adults

CI confidence interval, *GI* gastrointestinal, *RIS* required information size, *RR* risk ratio, *TSA* trial sequential analysis

[a] Almost all trials were adjudicated as overall high risk of bias, this may affect the interpretation of the results. GI bleeding was not the primary outcome in most trials, and we have no strong suspicion that this outcome is highly subjective or affected by the present risk of bias

[b] TSA-adjusted CI: 0.51–3.14; 13% of RIS included (14,532/109,402). This difference equals an absolute difference from nine fewer to 37 more events per 1.000 patients (TSA-adjusted CI for the absolute difference). The conventional 95% CI is significant, but as only a small proportion of the RIS has been included and the TSA-adjusted CI covers substantial relative benefits and harms, this domain has been downgraded 1 level despite the large sample size

[c] No publication bias detected by inspection of funnel plot or the Harbord test

[d] TSA-adjusted CI: 0.87–1.38; 21.8% of RIS included (21,792/100,111). This difference equals an absolute difference from two fewer to seven more events per 1.000 patients (TSA-adjusted CI for the absolute difference). As both the conventional and TSA-adjusted CIs cover both some relative benefits and harms and only a small portion of the RIS has been included, this domain has been downgraded 1 level despite the large sample size

However, our review also has some limitations. First, all adult critically ill patients were included in this meta-analysis. While this significantly increased the pooled population size, which is necessary for analysis of rare events, it also introduced clinical heterogeneity. However, we conducted detailed pre-planned subgroup and sensitivity analyses according to disease type and admission status and results were consistent. Second, we could not assess the use of gastroprotective drugs and antiplatelet/anticoagulant drugs in most of the trials. In particular, proton pump inhibitors are commonly used in the ICU for stress ulcer prophylaxis and may partially explain the low overall incidence of GI bleeding observed in this meta-analysis [1]. Third, the definition of GI bleeding and the methods of assessment/follow-up was scarcely reported and differed between trials. In fact, most trials did not report incidences of GI bleeding, making underreporting likely. Fourth, this study did not assess the benefit of corticosteroids, as this was beyond the scope of this analysis. Hence, it is important to consider these findings in the context of any disease specific benefits of corticosteroids. Fifth, we were not accurately able to assess the effect of duration of corticosteroids on the incidence of GI bleeding due to limitations in available data. Further, aspects of this pragmatic trial level meta-analysis, including subgroup analyses assessing duration of corticosteroid therapy or medications such as NSAIDs or PPIs, may be better assessed in an individual-patient data meta-analysis. Last, most of the included RCTs were adjudicated as unclear or high risk in at least one key domain of bias; the results of our meta-analysis must be considered in light of these findings.

Implications for clinicians

We have demonstrated that the incidence of GI bleeding is uncommon in critically ill patients and that there is low quality of evidence to suggest that GI bleeding is more common in critically ill patients receiving systemic corticosteroids for greater than 24 h than those not receiving corticosteroids. Given the uncertain effects of corticosteroids on GI bleeding found in this review, it also appears uncertain whether prophylactic acid suppressants would be of benefit to critically ill patients not at risk of GI bleeding but receiving corticosteroids.

Conclusions

We observed an overall low incidence of clinically important GI bleeding among adult critically ill patients. Use of corticosteroids may have increased the incidence of clinically important GI bleeding slightly, but not GI bleeding events of any severity. The rarity of bleeding events, infrequent trial reporting and high risk of bias reduced the overall quality of evidence.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05754-3) contains supplementary material, which is available to authorized users.

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Acknowledgements
We are indebted to the numerous authors who have provided additional information and clarifications regarding their studies including Professors Ananne, Arabi, Ashenoune, Briegel, Christ-Crain, Chotmongkol, Cicarelli, Day, Edwards, Gordon, Hoffman, Keh, Kerr, Martin Jr, Meduri, Mirea, Paydas, Payen, Sawanyawisuth, Scarborough, Sorensen, Sprung, Thwaites, Venkatesh and Weigelt and Dr's Alía, Blum, Fernandez-Serrano and Plassais. We are also grateful for the assistance with translations of non-English studies from Mr Chris Chui, Dr Peter Biesenbach and Dr Fernando Zampieri. We apologise if in the process of transcribing we have accidently left out authors who have aided this study and we offer our utmost gratitude. .

Funding
No funding was received for any aspect of this study.

Data availability

All data are freely available in the study and ESM.

Compliance with ethical standards

Conflicts of interest
EB, MHM, OC, AG, JP, SLR, AA: none to declare. AP: the ICU at Rigshospitalet, where AP chairs the Research Unit, receives funds for research from Ferring Pharmaceuticals and the Novo Nordisk Foundation.

Publisher's Note

Received: 6 May 2019 Accepted: 19 August 2019
Published online: 9 September 2019

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