GUIDELINE DEVLOPMENT AND EVIDENCE SYNTHESIS IN GASTROINTESTINAL BLEEDING PROPHYALXIS AND CORONAVIRUS DISEASE 2019

Guideline Development and Evidence Synthesis in Gastrointestinal Bleeding Prophylaxis and Coronavirus Disease 2019

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ABSTRACT

The field of guideline development has made considerable progress in the past twenty years, particularly after the introduction of GRADE in 2004. However, there are many shortcomings in current guideline development including failure to use GRADE, low quality systematic reviews, and excessive delays from the publication of practice changing evidence to new recommendations. The objective of this thesis is to describe the development of evidence-based recommendations, to document methodological issues that arose and describe how the research team addressed the questions, and to document how the ultimate guidelines contributed to optimization of treatment in clinical practice. The relevant guidelines address the issues of gastrointestinal bleeding prophylaxis and coronavirus disease 2019 (COVID-19).

The thesis begins by presenting three methodological issues that arose during the planning and implementation of the guideline process and the initial process of how the research team addressed the challenges. The thesis subsequently presents a published paper that documents recommendations regarding gastrointestinal bleeding prophylaxis in critically ill patients. Then, this thesis presents a published systematic review and meta-analysis addressing efficacy and safety of corticosteroids in COVID-19 based on direct evidence from patients with COVID-19, and indirect evidence from acute respiratory distress syndrome, community-acquired pneumonia, severe acute respiratory syndrome, middle east respiratory syndrome and influenza. Further, the thesis includes a published paper describing recommendations regarding corticosteroids,

convalescent plasma and antiviral drugs in COVID-19 on the basis of evidence available very early during the pandemic. This thesis ends by presenting how the methodological issues were ultimately addressed in the relevant guidelines, the importance of the guidelines themselves, and presents perspectives on future research and opportunities in guideline development.

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LIST OF ABBREVIATIONS

ANZICS: Australian and New Zealand Intensive Care Society

ARDS: Acute Respiratory Distress Syndrome

CAP: Community-acquired Pneumonia

CI: Confidence Interval

COVID-19: Coronavirus Disease 2019

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HR: Hazard Ratio

H2RAs: Histamine-2 Receptor Antagonists

ICU: Intensive Care Unit

IDSA: Infectious Diseases Society of America

MERS: Middle East Respiratory Syndrome

MD: Mean Difference

NICE: National Institute for Health and Care Excellence

NR: Not Reported

OR: Odds Ratio

PPI: Proton Pump Inhibitors

RCT: Randomized Controlled Trial

RNA: Ribonucleic Acid

RR: Risk Ratio

SARS: Severe Acute Respiratory Syndrome

SSC: Surviving Sepsis Campaign

WHO: World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is a “sandwich thesis” including five chapters.

Chapter 1 is unpublished. ZY is the sole authors.

Chapter 2 is published in British Medical Journal. ZY led a large team of researchers in producing the guideline. My contributions included conceiving and designing the research; organizing the team; collecting, reviewing, and distributing the evidence to panel members; writing the first draft of the manuscript; and incorporating feedback into the final manuscript. GG, ZY, LL, AB, TA, PV and RS contributed to the conception and design of the work. All authors participated in the teleconferences or email discussions, revising the guideline critically for important intellectual content. They gave final approval of the version to be published and met all authorship criteria.

Chapter 3 is published in Canadian Medical Association Journal. Zhikang Ye and Gordon Guyatt contributed to the conception of the work. Zhikang Ye, Ying Wang, Luis Enrique Colunga-Lozano, Manya Prasad and Gordon Guyatt contributed to the design of the work. Rachel Couban, Zhikang Ye, Ying Wang, Luis Enrique Colunga-Lozano, Manya Prasad, Wimonchat Tangamornsuksan, Liang Yao, Shahrzad Motaghi, Maryam Ghadimi, Malgorzata Bala, Huda Gomaa, Fang Fang and Yingqi Xiao contributed to the acquisition, analysis and interpretation of data. Zhikang Ye, Ying Wang, Luis Enrique Colunga-Lozano and Manya Prasad drafted the manuscript. Zhikang Ye oversaw the integration of contributions of the other authors. All of the authors revised it critically for important intellectual content, gave final approval of the version

to be published and agreed to be accountable for all aspects of the work. Zhikang Ye led the incorporation of feedback and the development of the final manuscript. Zhikang Ye, Ying Wang, Luis Enrique Colunga-Lozano and Manya Prasad are joint primary authors. Chapter 4 is published in Canadian Medical Association Journal. Zhikang Ye, Suodi Zhai, Bin Du, Bram Rochwerg and Gordon Guyatt contributed to the conception and design of the work. Zhikang Ye, Ying Wang, Bram Rochwerg, Haibo Qiu, Mark Loeb, Luis Colunga-Lozano, Bin Du, Fang Liu, Suodi Zhai and Gordon Guyatt contributed to the acquisition of data. Zhikang Ye, Ying Wang, François Lamontagne, Robert Fowler, Neill Adhikari, Li Jiang, Mark Loeb, Haibo Qiu, Li Wei, Ling Sang, Ning Shen, Minhua Huang, Yaseen Arabi, Younsuck Koh, Luis Colunga-Lozano, Dong Liu, Fang Liu, Jason Phua, Aizong Shen, Tianui Huo, Bin Du, Suodi Zhai and Gordon Guyatt contributed to the analysis and interpretation of data. All of the authors drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work. My contributions also included organizing the team; collecting, reviewing, and distributing the evidence to panel members; writing the first draft of the manuscript; and incorporating feedback into the final manuscript.

Chapter 5 is unpublished and ZY is the sole author.

Chapter 1: Introduction of the Thesis

The Institute of Medicine defines clinical practice guidelines as "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (1). The field of guideline development has made considerable progress in the past twenty years, particularly after the introduction of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) in 2004 (2). However, there are many shortcomings in current guideline development including failure to use GRADE, low quality systematic reviews, and excessive delays from the publication of potentially practice changing evidence to new recommendations (3).

The objective of this thesis is to address methodologic issues in developing evidence-based recommendations to inform healthcare providers in making decisions, to lead a systematic review necessary to summarize evidence to inform a guideline, and to develop guidelines in two content areas.

In developing recommendations regarding gastrointestinal bleeding prophylaxis in critically ill patients (4), and in developing recommendations for management of coronavirus disease 2019 (COVID-19) in the very early stages of the pandemic (5), we confronted a number of methodological issues and challenges and explored innovative methods to deal with these challenges.

Indirect evidence

We initiated the COVID-19 guideline in early February 2020 and addressed three categories of clinical questions: corticosteroids, convalescent plasma and antiviral drugs.

At this very early stage of the pandemic when it was largely restricted to China, we anticipated a paucity of direct evidence from studies of patients with COVID-19. Therefore, to facilitate the recommendations addressing corticosteroids in COVID-19, the guideline panel requested a summary of the indirect evidence from related conditions (6).

The issue at hand, the extent of indirectness acceptable to make the comparisons, and whether and how much to rate down for indirectness, presented a methodological challenge. The primary presentation of COVID-19 is respiratory failure, with a clinical picture of pneumonia. In critically ill patients, the presentation of severe COVID-19 appears very similar to the well-recognized clinical syndrome of acute respiratory distress syndrome (ARDS). ARDS represents a severe inflammatory response in the lung, secondary to a wide variety of insults including infection, trauma, pancreatitis, aspiration, and non-pulmonary sepsis.

Because the severe respiratory failure arises from the inflammatory response, corticosteroids have been suggested as a treatment and have indeed proved effective in reducing mortality for ARDS (7). The clinical picture of COVID-19 severe pneumonia is similar to ARDS, and may well share prominent features of pathophysiology. Nevertheless, the panel and review team remained skeptical regarding the application of results from other conditions precipitating ARDS to ARDS-associated COVID-19 based on the extent to which the inflammatory response may differ. As a result, we chose, for evidence regarding effectiveness, to rate down twice for indirectness. The

panel and review team collected and updated the indirect evidence from ARDS summarized in a published systematic review (8).

In the context of ARDS, we believe this indirectness issue differs with regard to possible benefits versus possible harms. There is little reason to think that the adverse events caused by corticosteroids would differ between ARDS caused by COVID-19 versus other conditions. Thus, the panel and review team considered that safety evidence was less indirect than efficacy evidence. Thus the decision was to rate down once for safety evidence because of indirectness, rather than the two levels which we did for efficacy.

Other recommendations addressed severe but not critically ill patients with COVID-19. Relevant evidence for this population included indirect evidence from patients with community acquired pneumonia, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza. Pneumonia represents an inflammatory response in the lung in response to infection caused by bacteria and viruses. Because patients are most commonly infected with COVID-19 in the community, community acquired pneumonia is more related to COVID-19 than hospital acquired pneumonia. Because the inflammatory response contributes to the pulmonary compromise in pneumonia, corticosteroids have been suggested as a treatment and have proved possibly effective in reducing mortality, likely effective in preventing deterioration, and effective in reducing length of hospital stay (9). Thus, the panel and review team collected and updated the indirect evidence from community acquired pneumonia summarized in a systematic review and applied that evidence in the COVID-

19 situation (9). Applying the same rule as for ARDS, the decision was to rate down twice for indirectness for efficacy evidence and once for safety evidence.

SARS and MERS are caused by coronavirus and represented major epidemics; COVID-19 is also caused by coronavirus. The guideline panel postulated that agents with a non-specific action on the inflammatory cascade that follows infection – which is the case with corticosteroids – might have a similar effect in different coronaviruses. Clinicians often administered corticosteroids to patients with SARS and MERS. Thus, on behalf of the panel, I led a systematic review that included collecting and summarizing the indirect evidence from SARS and MERS. In this case, inferring that the response to corticosteroids is likely to be similar across coronavirus infections, we rated down only once for indirectness for both efficacy and safety.

Influenza is also caused by a virus, but not a coronavirus. Whether one should seek indirect evidence under these circumstances is open to question – the generalization to a coronavirus is very uncertain. Nevertheless, clinicians have often administered corticosteroids to patients with influenza with the same rationale of reducing the inflammatory response associated with other infection. The panel decided this was sufficient rationale to review the evidence of steroid use in influenza. Once again, the panel and review team rated down twice for efficacy evidence and once for safety evidence.

Baseline risk calculation

I turn now to the guideline addressing gastrointestinal bleeding prophylaxis in critically

ill patients. In such patients, because there are a number of conditions that increase the risk of bleeding and patients may have none, few or many of these risk factors, the risk of clinically important gastrointestinal bleeding varies substantially between patients.

No previous guideline had made different recommendations for patients at different baseline risk. To do so required placing patients in discrete and appreciably different risk categories. The proved a major challenge.

In terms of average baseline risk across a population, one might expect recent (risk is thought to have decreased over time) observational studies to provide the best estimates. We were not, however, able to identify any observational studies of risk of bleeding exclusively in patients who did not receive gastric acid suppression. Therefore, for average baseline risk across a population, we turned to randomized trials focusing on control arms that did not receive prophylaxis. Because it was the largest, lowest risk of bias, and most recent trial, the SUP-ICU trial provided the best resource to estimate the average baseline risk of clinically important gastrointestinal bleeding in patients not receiving prophylaxis (10). The trial, which enrolled only patients with 1 or more risk factor (excluding those with no risk factors) reported a control group clinically important gastrointestinal bleeding rate of 4.2%. The most common risk factors for gastrointestinal bleeding in the SUP-ICU trial were invasive mechanical ventilation (78.7%), use of vasopressors or inotropes (66.7%), use of anticoagulants (30.3%), and coagulopathy (19.8%).

To determine the association between risk factors and clinically important bleeding, we

turned to a systematic review and meta-analysis that was completed as we were conducting our guideline work and generously shared by the authors (11). This review systematically identified predictors of gastrointestinal bleeding in adult intensive care unit patients. The systematic review was not published at the time we were developing the guideline and indeed was not published until after the guideline was completed. As a result, we could not cite the systematic review in the guideline. As an alternative, we cited the primary observational studies on which the guideline was based (Table 1).

The included observational studies reported risk ratios associated with the four risk factors occurring most frequently in SUP-ICU. These risk ratios varied between approximately 2.5 to 4.5. Given these values, we inferred an average relative increase in risk in SUP-ICU patients over patients with no risk factors of 3.5. Given this inference, one may then deduce that the baseline risk of clinically important gastrointestinal bleeding in patients without any risk factor would be 4.2%*1/3.5=1.2%.

Using this value of 1.2%, we then multiplied the risk ratio for each risk factor reported in the systematic review (Table 1). Then we obtained the absolute risk of each risk factor. The baseline risks ranged from 1% to 9.7%. The guideline panel then categorized the baseline risk into low (1-2%), moderate (2-4%), high (4-8%), and highest risk (8-10%). If patients with two or more moderate risk factors, we elevated it to high category.

Table 1: Risk of clinically important gastrointestinal bleeding for each risk factor

Risk factor.	Clinically important bleeding		
	Risk ratio	Risk	GRADE

		(per 1000)	certainty*
Low risk (estimated risk of clinically important bleeding is 10-20 per 1000)			
No risk factor	1.0 (reference)	12	Moderate
Acute hepatic failure	1.6 (12)	19	Very low
Anticoagulants	1.4 (12, 13)	17	Low
Cancer	1.4 (13)	16	Very low
Use of corticosteroids or immune suppressed	1.4 (12, 13)	17	Low
Male	0.9 (13)	10	Moderate
Moderate risk (estimated risk of clinically important bleeding is 21-40 per 1000)			
Acute kidney injury	3.3 (12, 13)	39	Low
Mechanical ventilation without enteral nutrition	2.4 (12-14)	29	Low
Sepsis	2.0 (12)	24	Low
Shock	2.6 (12, 13)	31	Moderate
High risk (estimated risk of clinically important bleeding is 41-80 per 1000)			
Coagulopathy	4.8 (12, 13)	57	Moderate
Highest risk (estimated risk of clinically important bleeding is 81-100 per 1000)			
Chronic liver disease	7.6 (13)	92	Moderate
Mechanical ventilation without enteral nutrition	8.1 (12-14)	97	Low

Values and preferences

I turn now to COVID-19 guideline. Because COVID-19 was a new epidemic – at the time we developed our guideline restricted to China but subsequently worldwide - there were no existing studies directly addressing patients' values and preferences to which we could refer. It thus proved challenging to propose values and preferences in the COVID-19 guideline.

A challenge in such situations is to focus guideline panel members on the choices fully informed patients would make when presented with the options of using or not using an intervention. When they have engaged in shared decision-making with patients and

families, these interactions could inform clinical experts' intuitive judgements.

The key issue for this guideline was choices patients would make with interventions for which there was possible benefit, including mortality reduction, but only low or very low quality/certainty evidence of such benefit. In the face of such uncertainty, how would patients value these speculative benefits in comparison to the much more certain burden and adverse effects? The guideline steering committee chair proposed draft values and preferences and sent it to all panel members by email, panel members gave feedback by email.

Then, at the first guideline meeting, panel members discussed the issue in the perspective of COVID-19 patients. Finally, we determined the following values and preferences: first, when modest harms were present and there was low quality evidence of a small but important difference in an outcome important to patients (e.g., mortality), most patients would choose to receive an intervention. That is, most patients would place a higher value on an uncertain, small but important benefit than in avoiding modest harms. Second, when low-quality evidence suggests little or no benefit, or when only very low-quality evidence exists and effects are therefore very uncertain, most patients would decline the intervention. The key, then, to whether recommendations would be in favor or against an intervention, would depend on the ratings of quality/certainty of evidence as low (in which case a recommendation in favor was likely) or very low (likely mandating a recommendation against).

In the guideline regarding gastrointestinal bleeding prophylaxis in critically ill patients,

the literature review did not find any evidence regarding values and preference in this topic. Therefore, in this case, we conducted a formal survey of panel members to determine what they considered the threshold of reduction of clinically important gastrointestinal bleeding patients would demand before they would choose the interventions (proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs)). In making their choice patients would be trading off benefits against the possible increase in pneumonia with these acid-reducing agents.

All panel members completed the survey based on their experience in shared decision-making with their patients. 52.4% and 57.1% of survey respondents chose an intervention when this intervention reduced clinical important gastrointestinal bleeding by 1.5% and 2% (figure 1 and 2). The guideline steering committee discussed the survey results and initially determined approximately 20 per 1000 patients as the threshold, a threshold which the whole panel agreed to.

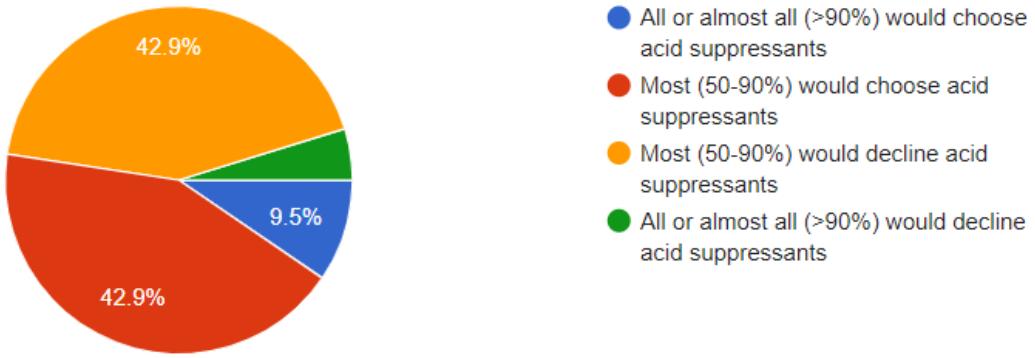

Figure 1. Survey results for bleeding threshold of 1.5%

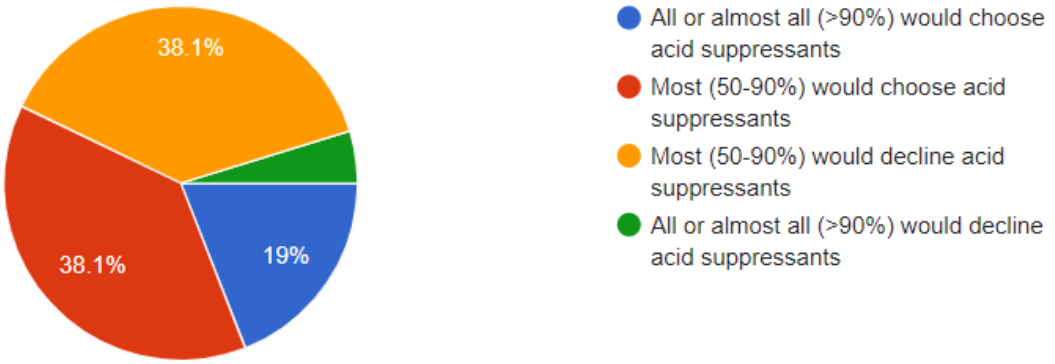

Figure 2. Survey results for bleeding threshold of 2%

Outline of thesis

This is a sandwich thesis of three papers presented in chapters 2 to 4 covering guideline development and evidence synthesis in gastrointestinal bleeding prophylaxis and COVID-19.

Chapter 2 of this thesis addresses recommendations regarding gastrointestinal bleeding prophylaxis in critically ill patients including the optimal agents for prophylaxis, and how the optimal course of action might differ for patients with different bleeding risks.

Chapter 3 is a systematic review and meta-analysis regarding the efficacy and safety of corticosteroids in COVID-19 based on evidence from COVID-19, ARDS, community-acquired pneumonia, SARS, MERS, and influenza, which provide the comprehensive evidence for COVID-19 guideline.

Chapter 4 of COVID-19 guideline that formulates the recommendations about corticosteroids, convalescent plasma and antiviral drugs. This guideline provides valuable and correct recommendations at that time when we lack convincing evidence.

Chapter 5 presents how the guideline panels ultimately dealt with the methodologic

issues presented in this chapter, summarizes the COVID-19 guideline that formulates the recommendations about corticosteroids, convalescent plasma and antiviral drugs, describes the contributions these guidelines made to guideline methods issues in practice and implications for the future.

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Chapter 2: Gastrointestinal Bleeding Prophylaxis for Critically Ill Patients: A Clinical Practice Guideline

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RAPID RECOMMENDATIONS

Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline

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This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

ABSTRACT

Clinical question What is the role of gastrointestinal bleeding prophylaxis (stress ulcer prophylaxis) in critically ill patients? This guideline was prompted by the publication of a new large randomised controlled trial.

Current practice Gastric acid suppression with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) is commonly done to prevent gastrointestinal bleeding in critically ill patients. Existing guidelines vary in their recommendations of which population to treat and which agent to use.

Recommendations This guideline panel makes a weak recommendation for using gastrointestinal bleeding prophylaxis in critically ill patients at high risk (>4%) of clinically important gastrointestinal bleeding, and a weak recommendation for not using prophylaxis in patients at lower risk of clinically important bleeding (≤4%). The panel identified risk categories based on evidence, with variable certainty regarding risk factors. The panel suggests using a PPI rather than a H2RA (weak recommendation) and recommends against using sucralfate (strong recommendation).

How this guideline was created A guideline panel including patients, clinicians, and methodologists produced these recommendations using standards for trustworthy guidelines and the GRADE approach. The recommendations are based on a linked systematic review and network meta-analysis. A weak recommendation means that both options are reasonable.

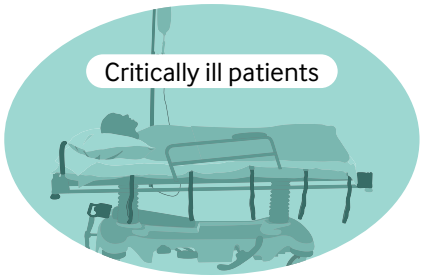
The evidence The linked systematic review and network meta-analysis estimated the benefit and harm of these medications in 12 660 critically ill patients in 72 trials. Both PPIs and H2RAs reduce the risk of clinically important bleeding. The effect is larger in patients at higher bleeding risk (those with a coagulopathy, chronic liver disease, or receiving mechanical ventilation but not enteral nutrition or two or more of mechanical ventilation with enteral nutrition, acute kidney injury, sepsis, and shock) (moderate certainty). PPIs and H2RAs might increase the risk of pneumonia (low certainty). They probably do not have an effect on mortality (moderate certainty), length of hospital stay, or any other important outcomes. PPIs probably reduce the risk of bleeding more than H2RAs (moderate certainty).

Understanding the recommendation In most critically ill patients, the reduction in clinically important gastrointestinal bleeding from gastric acid suppressants is closely balanced with the possibility of pneumonia. Clinicians should consider individual patient values, risk of bleeding, and other factors such as medication availability when deciding whether to use gastrointestinal bleeding prophylaxis. Visual overviews provide the relative and absolute benefits and harms of the options in multilayered evidence summaries and decision aids available on MAGICapp.

RAPID RECOMMENDATIONS

Visual summary of recommendation

Population



Including:

- ✔ Patients admitted to intensive care units

Does not apply to:

- ✖ Patients receiving gastric acid suppression for another therapeutic indication

On average, 4% of critically ill patients develop gastrointestinal bleeding. One cause is physiologic stress leading to stress ulcers in the oesophagus, stomach, or duodenum, but critical illness is also associated with other forms of upper gastrointestinal bleeding.

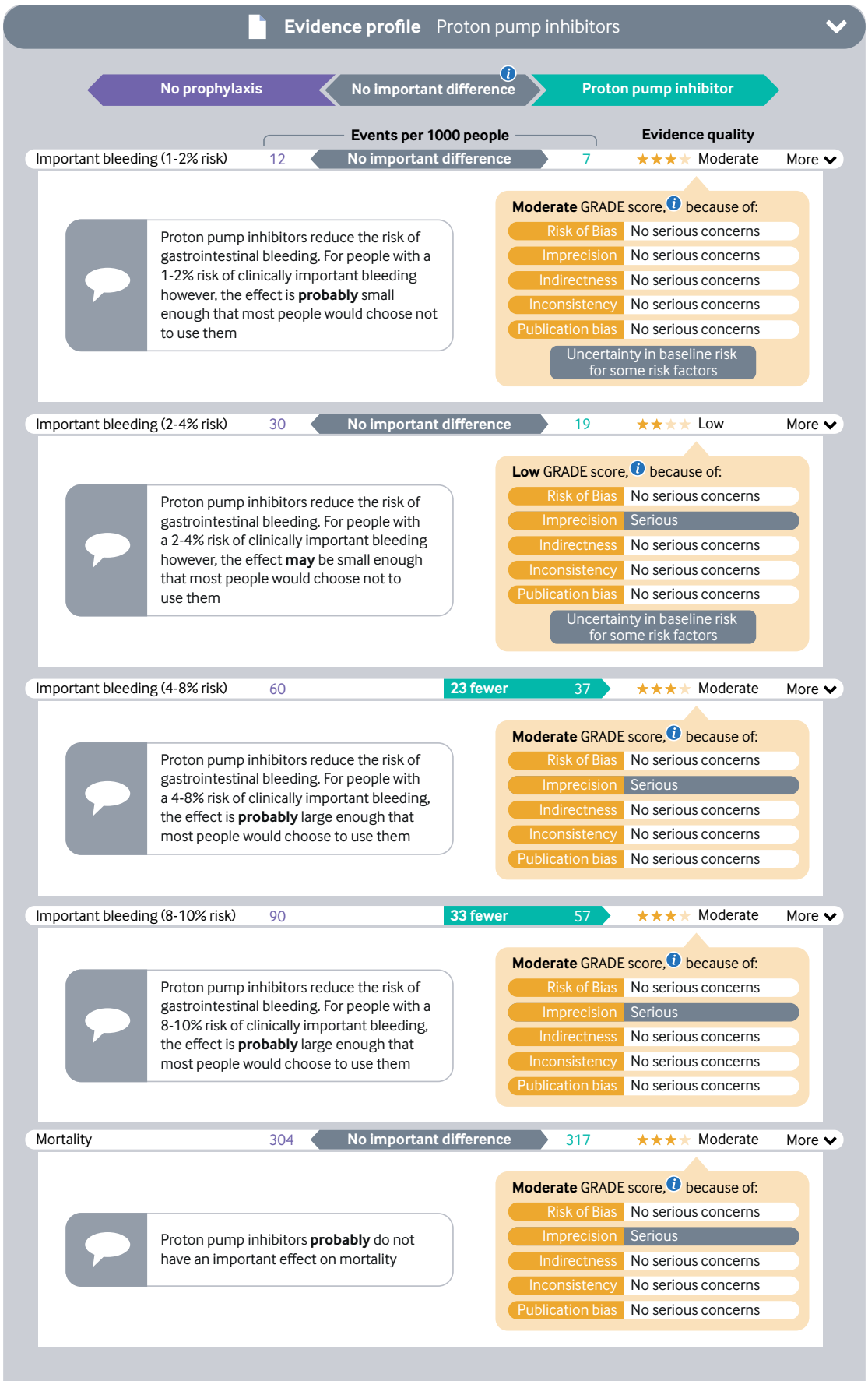
Recommendation 1

No prophylaxis		or	Prophylaxis	
Strong	Weak		Weak	Strong

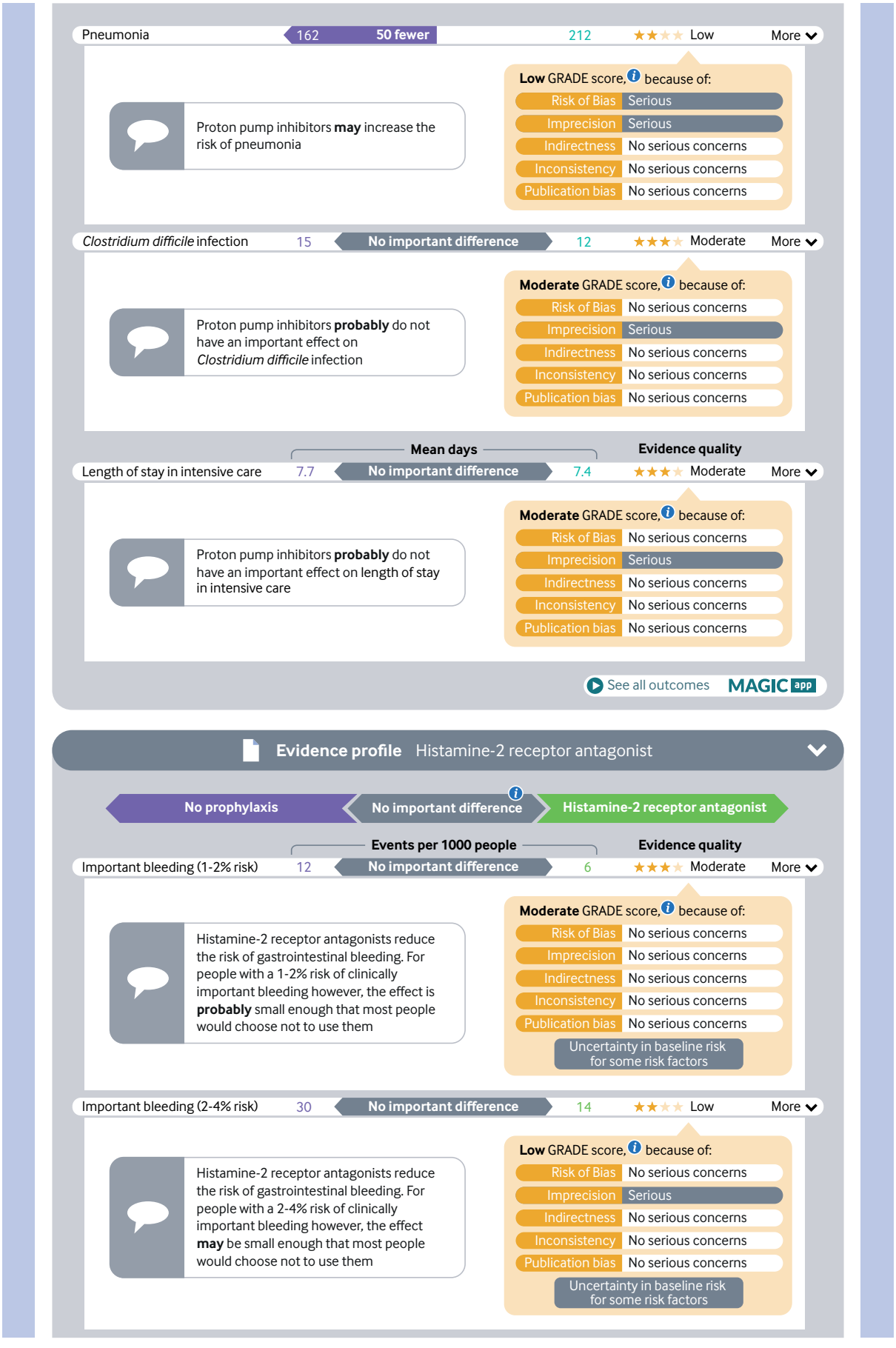
We suggest using acid suppression prophylaxis for people with higher risk of gastrointestinal bleeding (4% or higher)

Calculating bleed risk

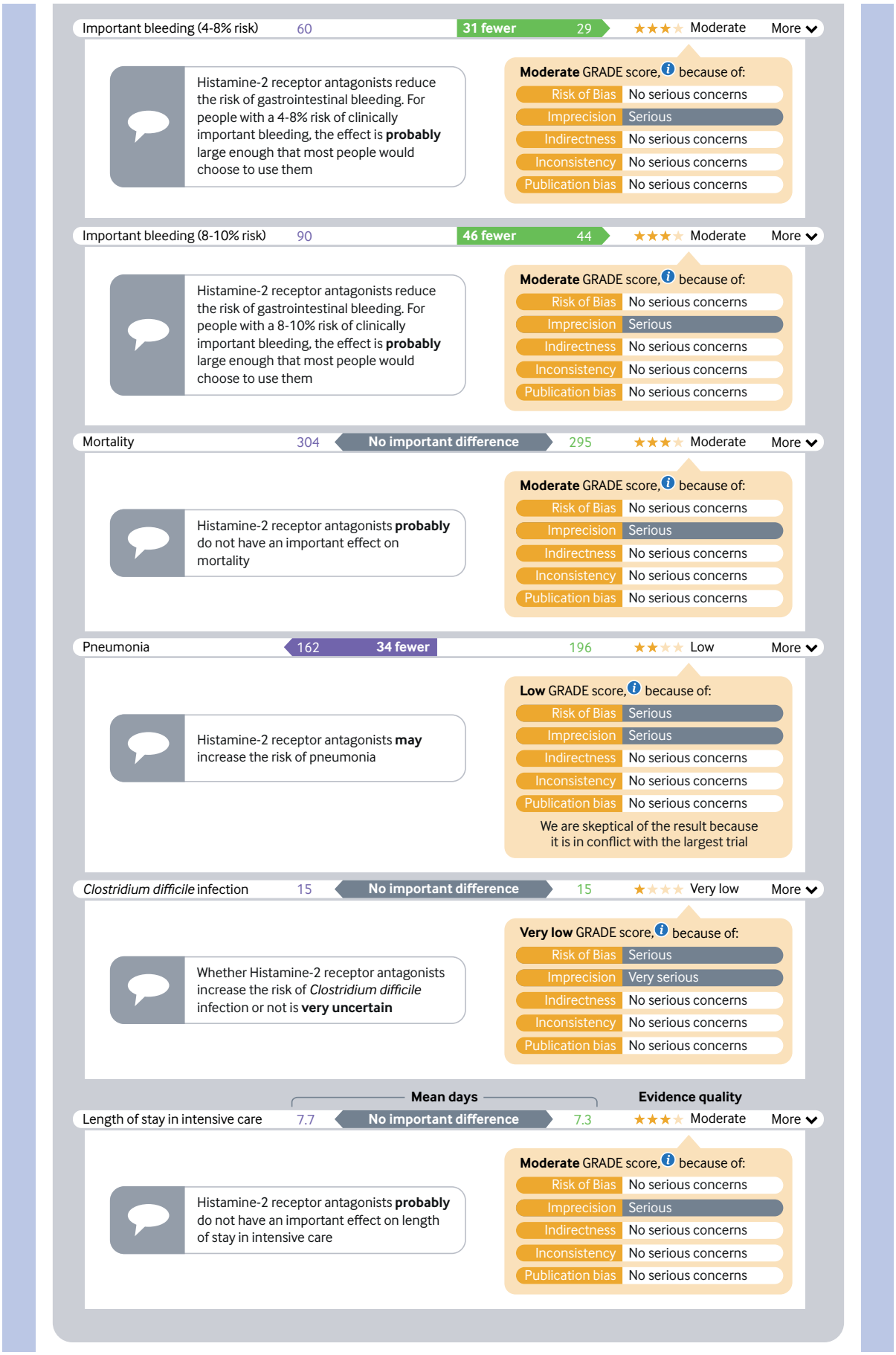
Highest risk	8-10%	Mechanical ventilation without enteral nutrition Chronic liver disease
High risk	4-8%	Concerning coagulopathy 2 or more factors from 2-4% category
		SUGGESTED CUT POINT FOR OFFERING PROPHYLAXIS For patients near this threshold, individual values and preferences become more important
Moderate risk	2-4%	Mechanical ventilation with enteral nutrition Acute kidney injury Sepsis Shock
Low risk	1-2%	Critically ill patients without any risk factor Acute hepatic failure Use of steroids or immunosuppression Use of anticoagulants Cancer Male gender



RAPID RECOMMENDATIONS



RAPID RECOMMENDATIONS



Individual considerations

Key practical issues

No prophylaxis	Proton pump inhibitors	Histamine-2 receptor antagonists
None	Can be administered intravenously or enterally	
	Typically administered once per day	Typically administered two or three times per day

Duration of treatment

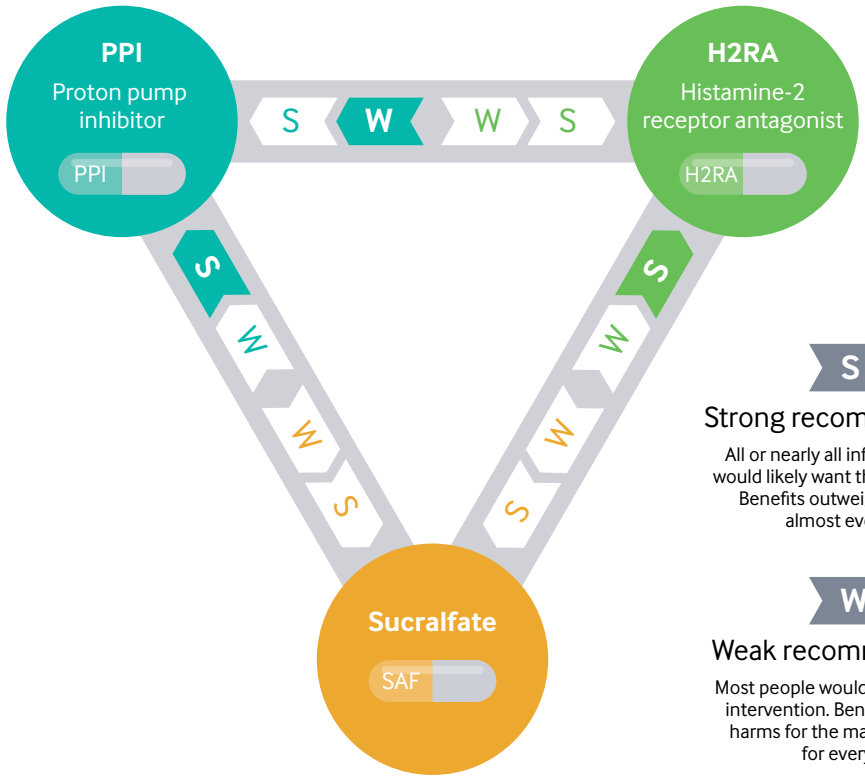
A system should be in place to prevent inadvertent continuation of gastric acid suppression

Values and preferences

It may be challenging to implement shared decision making because there are often many other more important decisions. However, shared decision making should be pursued whenever possible.

Recommendation 2

> In critically ill patients who are going to receive prophylaxis against gastrointestinal bleeding, we suggest a proton pump inhibitor. A histamine-2 receptor antagonist is also a reasonable choice. We recommend not using sucralfate



S

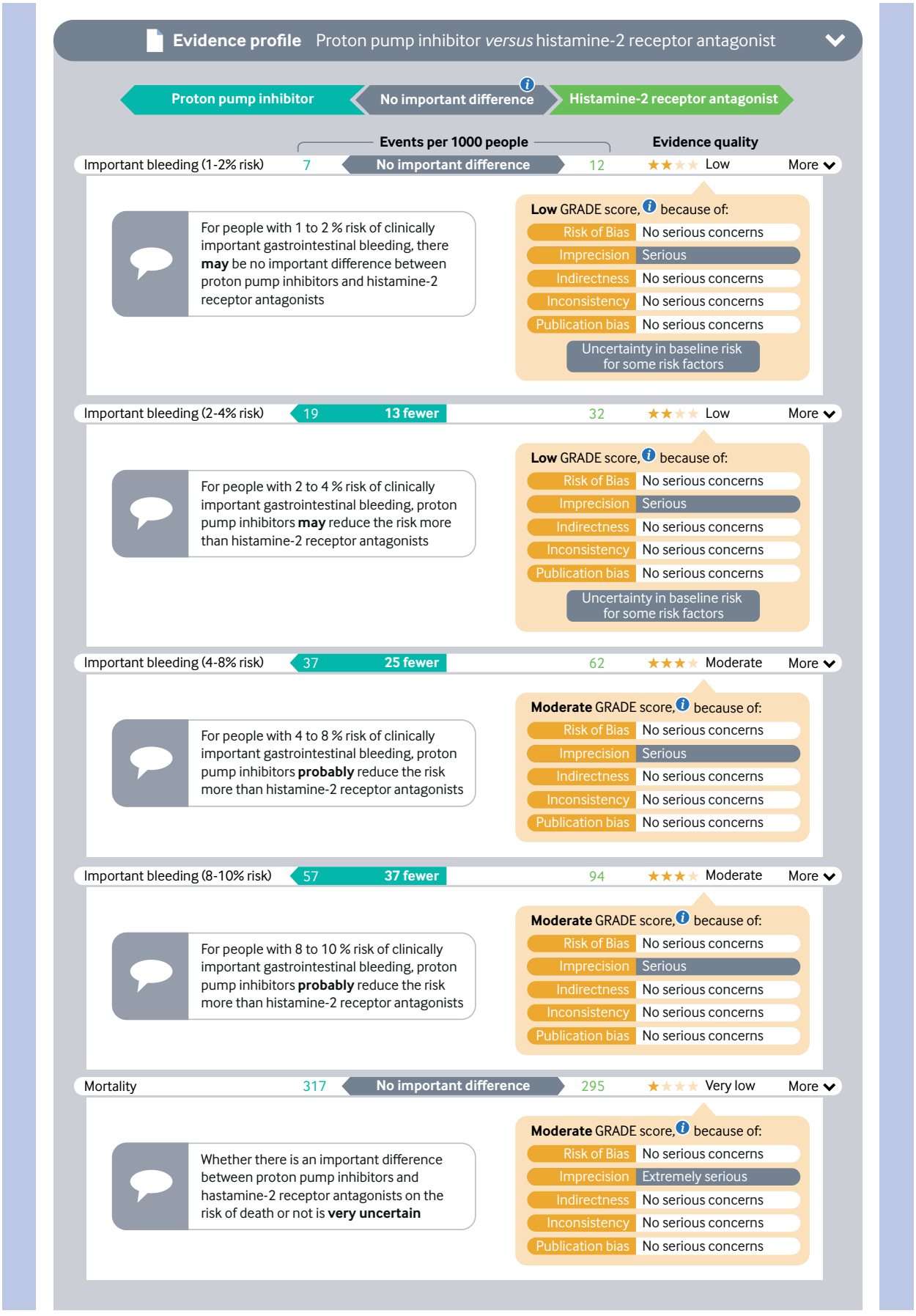
Strong recommendation

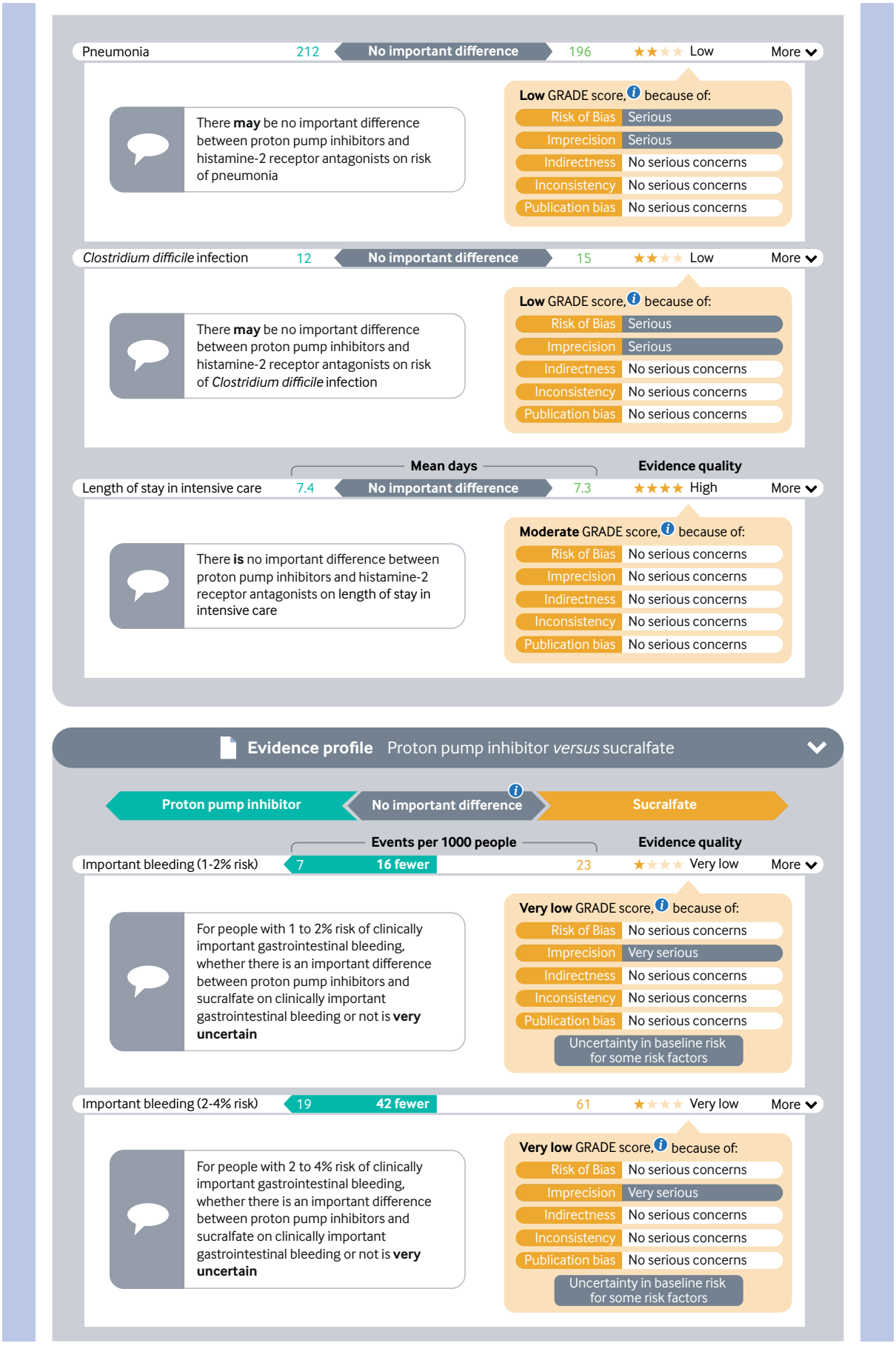
All or nearly all informed people would likely want this intervention. Benefits outweigh harms for almost everyone

W

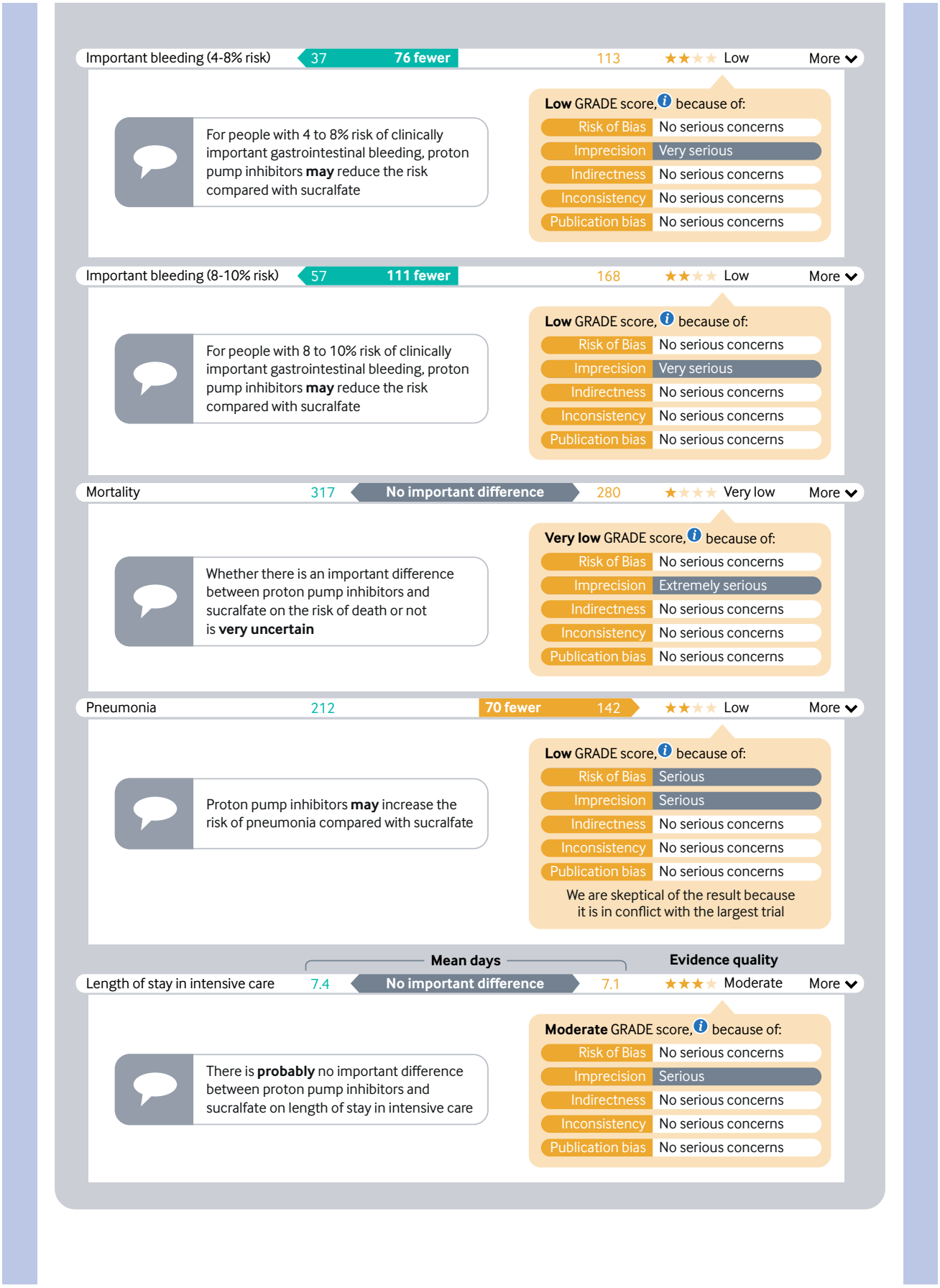
Weak recommendation

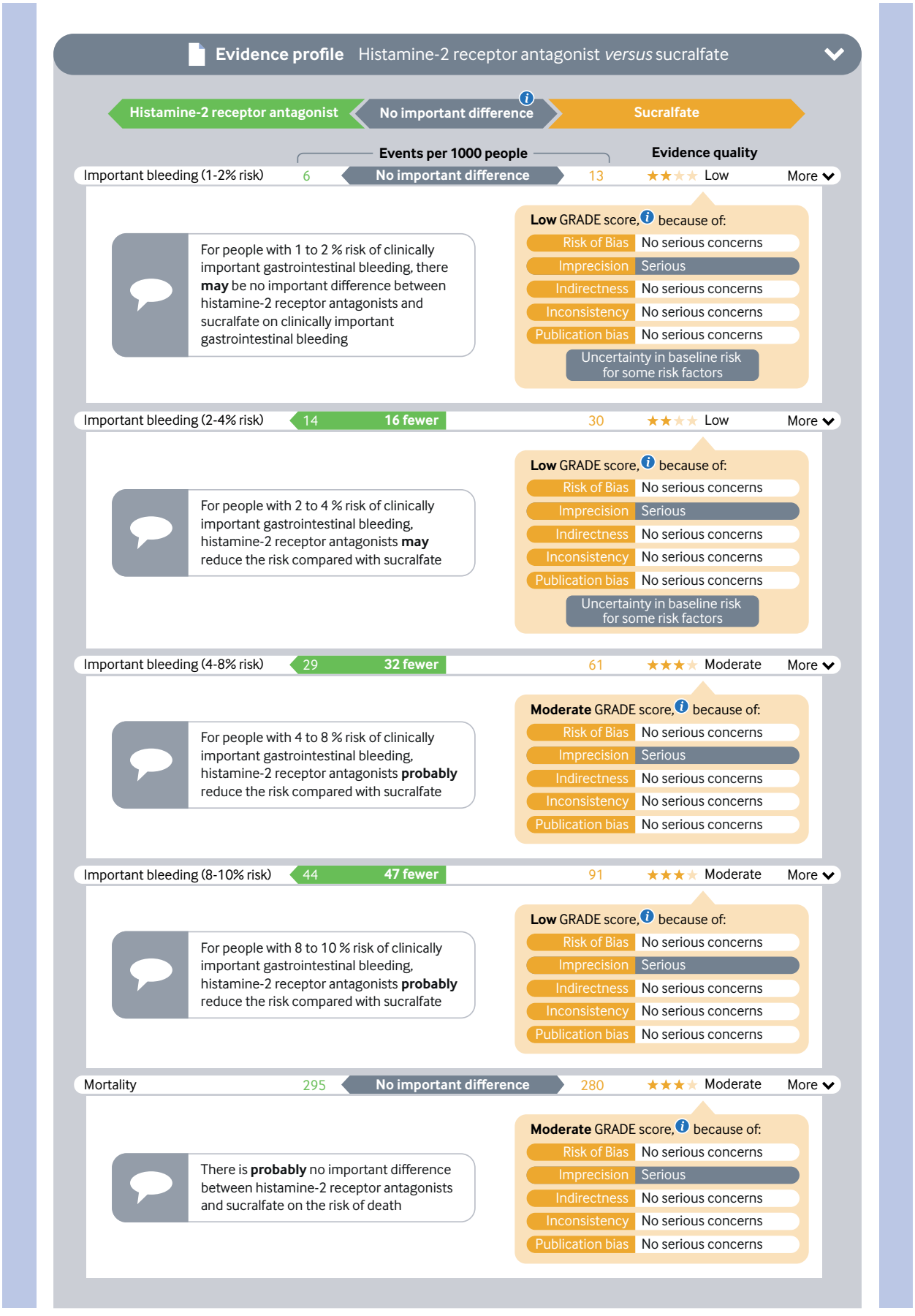
Most people would likely want this intervention. Benefits outweigh harms for the majority, but not for everyone



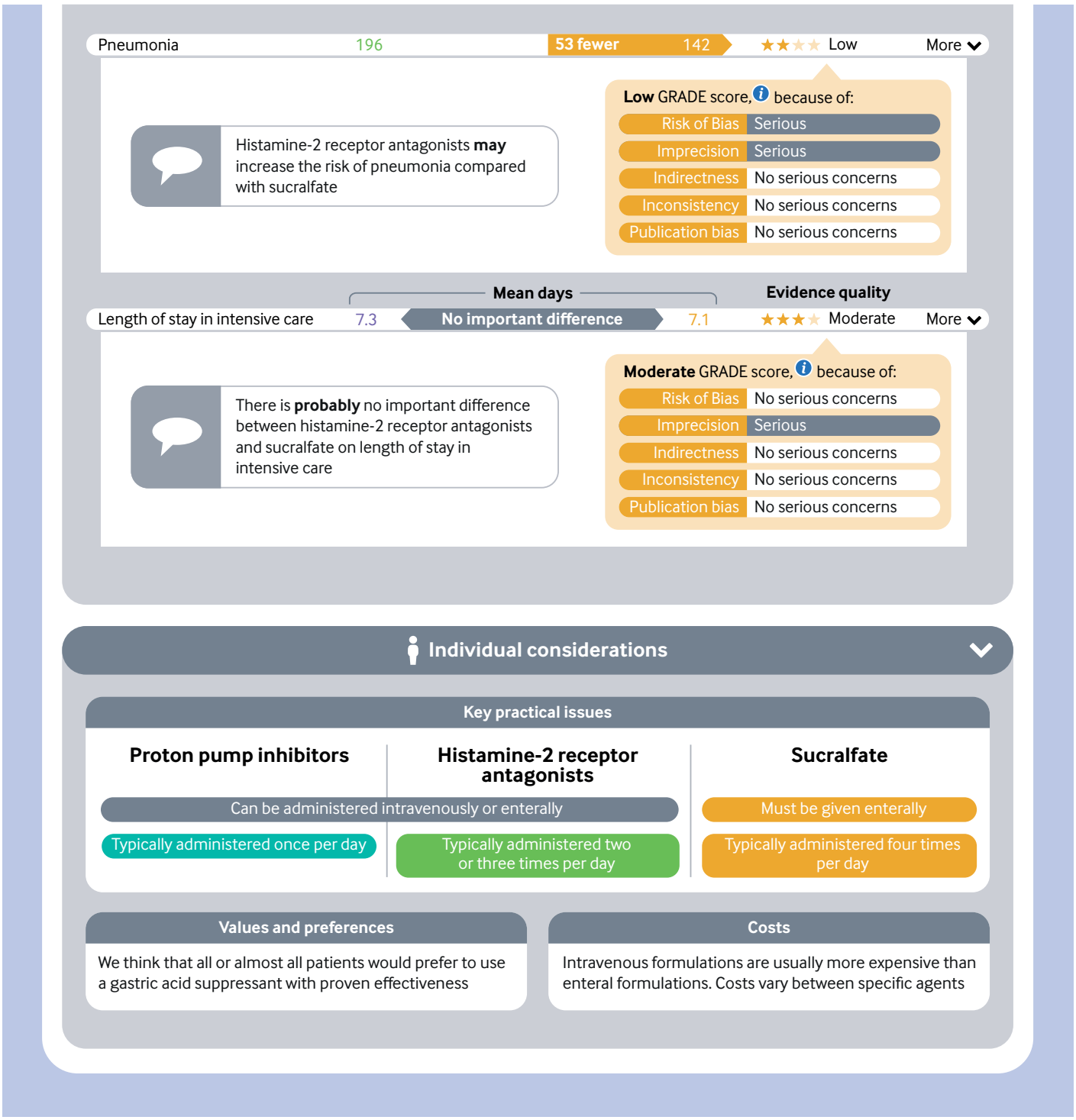


RAPID RECOMMENDATIONS





RAPID RECOMMENDATIONS



Critically ill patients are at risk of gastrointestinal bleeding. The mechanisms vary and include physiologic stress that can lead to stress ulcers in the oesophagus, stomach, or duodenum. Clinicians can prescribe gastric acid suppressants for prophylaxis against clinically important gastrointestinal bleeding in critically ill patients. Clinically important bleeding is overt and has important consequences: about half of affected patients receive endoscopy or surgery, and approximately half of patients receive a transfusion of at least two units of packed red blood cells.[1]

This *BMJ* Rapid Recommendation was triggered by SUP-ICU, a randomised controlled trial published in October 2018.[1] It found no significant net benefit, and raised questions about the widespread use of gastrointestinal bleeding prophylaxis.

We aimed to translate this new evidence for clinicians and patients using the GRADE approach and standards for trustworthy guidelines.[2 3] The guideline committee asked two key questions:

1 In which patients, if any, should gastrointestinal bleeding prophylaxis be used?
2 If gastrointestinal bleeding prophylaxis is used, what agent is best?

The box shows all publications linked in this rapid recommendation package. The main infographic provides an overview of the absolute benefits and harms for four interventions: proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), sucralfate, and no prophylaxis.

Current practice

Existing recommendations vary in the indications for gastrointestinal bleeding prophylaxis (see table 1). There are no recommendations for critically ill patients as a broad target group, and guidelines that apply to specific subgroups of patients (such as those with trauma or sepsis) do not consider differences in importance of individual risk factors. They also do not present the benefits and harms in a way that is usable for individualised decision making. Inappropriate overuse of gastrointestinal bleeding prophylaxis is not only a serious problem in critical care but also general inpatient and outpatient settings.[4 5]

Table 1 | Current recommendations for stress ulcer prophylaxis

Guideline	Agents to be used	Indications for prophylaxis
SCCM and ESICM "Surviving sepsis," 2016[15]	PPIs or H2RAs (weak recommendation)	Patients with sepsis or septic shock with risk factors for gastrointestinal bleeding, which include mechanical ventilation for >48 hours, coagulopathy, pre-existing liver disease, need for RRT, and higher organ failure scores
DASAIM and DSIT, 2014[16]	PPIs rather than H2RAs (weak recommendation)	Insufficient evidence to make any recommendation
Eastern Association for the Surgery of Trauma, 2008[17]	PPIs or H2RAs or cytoprotective agents	Mechanical ventilation; coagulopathy; traumatic brain injury; major burn; ICU patients with multi-trauma, sepsis, or acute renal failure; ICU patients with ISS>15 or receiving high dose corticosteroids

SCCM=Society of Critical Care Medicine; ESICM=European Society of Intensive Care Medicine; DASAIM=Danish Society of Anesthesiology and Intensive Care Medicine; DSIT=Danish Society of Intensive Care Medicine; PPIs=proton pump inhibitors; H2RAs=histamine-2 receptor antagonists; RRT=renal replacement therapy ICU=intensive care unit; ISS=Injury Severity Score.

Linked resources in this *BMJ* Rapid Recommendations cluster

- Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *BMJ* 2019;367:l6722
  - Summary of the results from the Rapid Recommendation process
- Wang Y, Ye Z, Ge L, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: systematic review and network meta-analysis. *BMJ* 2019;367:l6744
  - Review and network meta-analysis of all available randomized trials that assessed prevention of gastrointestinal bleeding in critically ill patients
- MAGICapp (https://app.magicapp.org/public/guideline/j96g2L)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

PPIs are the most commonly used agents, followed by H2RAs; sucralfate and antacids are seldom used.[6 7] Most guidelines recommend using either a PPI or H2RA, but there is some variation in the preferred agent.[8]

The evidence

The SUP-ICU trial was incorporated into a linked systematic review and network meta-analysis comparing PPIs, H2RAs, and sucralfate versus one another or placebo (no prophylaxis). The review included 72 randomised controlled trials and 12 660 patients admitted to intensive care units comparing PPIs, H2RAs, sucralfate versus one another or no prophylaxis. Figure 2 provides an overview of the trials and participants.

How we stratified the risk of bleeding

Prophylaxis cannot reduce the risk of bleeding to zero, but the higher the risk of bleeding, the larger is the expected benefit of prophylaxis. Therefore, we first searched for evidence on risk factors for bleeding; we used evidence from a systematic review of risk factors.[9] Based on studies that we considered low risk of bias, we grouped patients into four categories: low risk, moderate risk, high risk, and highest risk (see table 2 and appendix 1 on bmj.com for details). We had varying degrees of certainty in different risk factors. In particular, the available evidence may underestimate the risk of bleeding for several possible risk factors in the low and moderate risk categories (that is, acute hepatic failure and use of anticoagulation might increase the risk of bleeding more than we estimated).

Gastrointestinal bleeding

Clinically important gastrointestinal bleeding is typically defined as evidence of upper gastrointestinal bleeding with any of the following: significant haemodynamic changes not explained by other causes, need for transfusion of more than two units of blood, significant decrease in haemoglobin level, evidence of bleeding on upper gastrointestinal endoscopy, or need for surgery to control bleeding. Both PPIs and H2RAs reduce the risk of clinically important bleeding compared with no

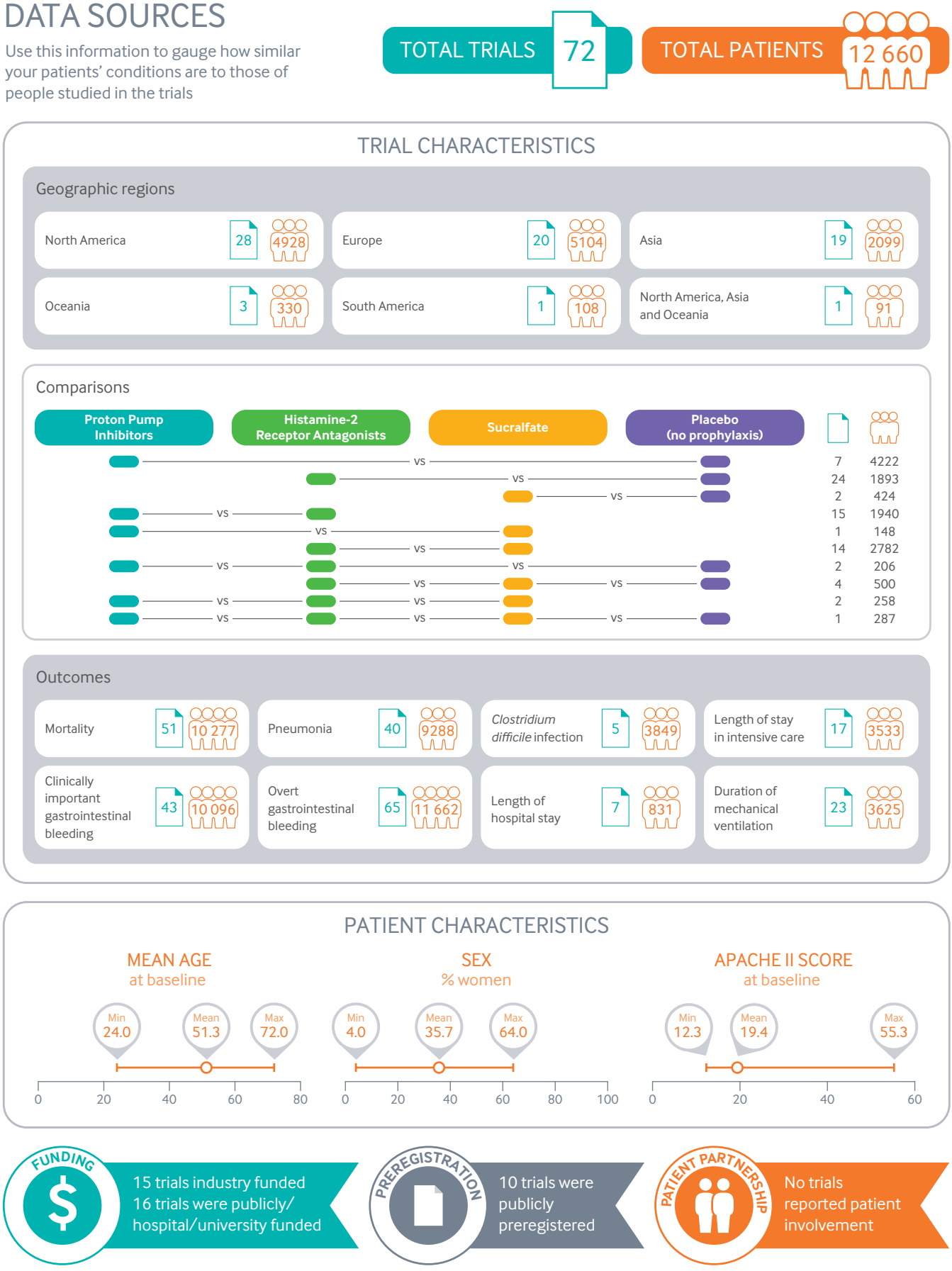


Fig 2| Characteristics of patients and trials included in systematic review of gastrointestinal bleeding prophylaxis in critically ill adults

Table 2 | Baseline risk of clinically important gastrointestinal bleeding for each risk factors

Risk factors	Risk of clinically important gastrointestinal bleeding (per 1000)		Risk of overt gastrointestinal bleeding (per 1000)	
	Baseline risk	Representative risk chosen for evidence profile	Baseline risk	Representative risk chosen for evidence profile
Low risk group*				
Critically ill without any risk factor Acute hepatic failure Use of corticosteroids or immunosuppression Use of anticoagulants† Cancer Male gender	10-20	12	20-60	26
Moderate risk group				
Mechanical ventilation with enteral nutrition Shock‡ Sepsis Acute kidney injury	21-40	30	61-90	75
High risk group				
Coagulopathy§ Two or more of factors in moderate risk group	41-80	60	91-160	125
Highest risk group				
Mechanical ventilation without enteral nutrition Chronic liver disease¶	81-100	90	161-220	190

*Including proposed risk factors without evidence that they substantially increase risk of gastrointestinal bleeding.
†Vitamin K antagonists, direct acting oral anticoagulants, therapeutic doses of unfractionated or low molecular weight heparin, intravenous direct thrombin (II) inhibitors, adenosine diphosphate receptor inhibitor and similar drugs.
‡Continuous infusion with vasopressors or inotropes, systolic blood pressure <90 mm Hg, mean arterial blood pressure <70 mm Hg, plasma lactate level ≥4 mmol/l.
§Platelets $<50\times10^9$/L, international normalised ratio >1.5, or prothrombin time >20 seconds.
¶Portal hypertension, cirrhosis proved by biopsy, computed tomography, ultrasound scan, or medical history of variceal bleeding or hepatic encephalopathy.

prophylaxis, but the magnitude of benefit depends on the baseline risk of bleeding without prophylaxis. In patients at highest risk (>8%), PPIs and H2RAs reduce clinically important bleeding by 3-5%. In critically ill patients at low risk (<2%), PPIs and H2RAs reduce clinically important bleeding by less than 1%.

Overt bleeding (that is visible as haematemesis, haematochezia, or melaena) does not always have important consequences: overt bleeding, which includes important and unimportant bleeding, is more common than clinically important bleeding. The absolute reduction of overt bleeding achieved with prophylaxis is approximately twice that of clinically important bleeding (see full evidence profile in MAGICapp).

In the linked meta-analysis, results from head-to-head clinical trials suggest that PPIs possibly reduce the risk of clinically important bleeding more than H2RAs, but the confidence interval includes no difference (odds ratio 0.58 (95% confidence interval 0.29 to 1.17)). PPIs do reduce the risk of overt bleeding more than H2RAs.

Sucralfate does not seem to reduce the risk of clinically important bleeding compared with placebo (odds ratio 0.76 (0.36 to 1.62)).

Pneumonia

Both PPIs and H2RAs might increase the absolute risk of pneumonia compared with no prophylaxis by approximately 4%, but certainty is low. The credible intervals include no difference, and the most recent and the largest blinded randomised controlled trial suggested that there may not be a difference in risk of pneumonia between the PPI and placebo groups.[1]

Other outcomes

Gastric acid suppression did not seem to affect any other important outcomes, including mortality, length of hospital stay, length of intensive care stay, duration of mechanical ventilation, or *C difficile* infection. Quality of evidence varied across these outcomes; for *C difficile* infection, quality was low.

Understanding the recommendations

Strong recommendations suggest that all or nearly all patients would choose the recommended option. Weak recommendations reflect the uncertainty in the typical patients' preferences, as well as the likely wide variability in preferences between patients.

Who does it apply to?

This guideline applies to critically ill patients. Patients who have a substantial short term risk of dying due to an acute illness are considered critically ill and are commonly treated in an intensive care unit. Accordingly, studies performed in patients admitted to intensive care were considered in the linked systematic review. However, admission practices of intensive care units are variable, and defining critical illness is difficult, so clinical judgment regarding whether this guideline applies to a specific patient may be warranted.

Our recommendations do not apply to patients who have other indications for gastric acid suppression (such as peptic ulcer disease, gastroesophageal reflux disease, Zollinger-Ellison syndrome, or eradication of *Helicobacter pylori*). Patients already taking gastric acid suppressants should probably continue to receive them during an acute illness because abrupt withdrawal may cause rebound acid hypersecretion.[10] However, prolonged use of acid suppressants without clear indication is not advocated.

Values and preferences

We did not find any published evidence addressing patient values and preferences (appendix 2 on bmj.com). Overall,

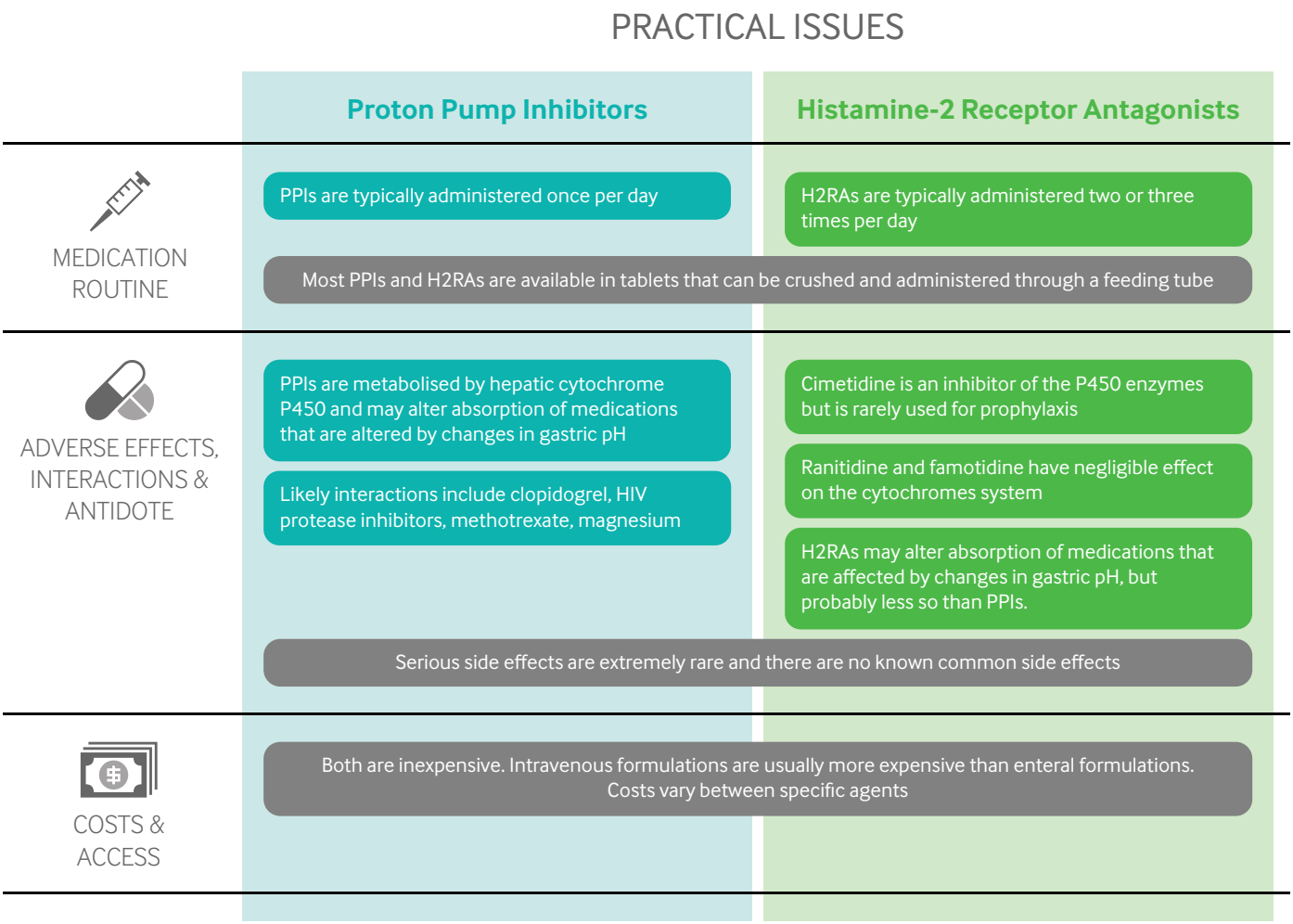


Fig 3| Practical issues about gastrointestinal bleeding prophylaxis for critically ill patients

most of our panellists thought that most patients would consider the benefits, harms, and burdens to be minimal. The panel agreed that there is probably great variability among patients in how much they value bleeding and a possible increased risk of pneumonia. Given the burdens and harms, including a possible increased risk of pneumonia, the panel believed that most patients would require a reduction in clinically important bleeding by at least about 20 per 1000 patients in order to choose acid suppression; the panel was, however, very uncertain about this threshold. The importance of overt bleeding not advancing to clinically important bleeding is questionable and may be altogether unimportant.

Shared decision making

Shared decision making should be pursued whenever possible. This will be challenging with critically ill patients because they are typically not able to have complex discussions about their care. Moreover, the effects of gastric acid suppression are modest, and there are many other more important decisions that often need to be made when caring for critically ill patients (such as probability of survival and/or regaining reasonable quality of life with or without different possible interventions).

Practical considerations

Figure 3 outlines the key practical issues regarding the use of acid suppressants for preventing gastrointestinal bleeding in critically ill patients. For both PPIs and H2RAs, the best specific agent is uncertain and was not addressed by our guideline panel. Pantoprazole, omeprazole, lansoprazole, esomeprazole, and rabeprazole were the most commonly used PPIs in the RCTs and are reasonable choices. Ranitidine and famotidine were the commonly used H2RAs in the RCTs and are reasonable choices.

Dosing and duration

Dose and duration varied between the included studies and were not specifically addressed in this guideline. Typically, PPIs were prescribed once per day and H2RAs two or three times per day. Both can be administered intravenously or enterally, and there is no evidence to suggest that the route of administration alters effectiveness. Unless there is another indication for gastric acid suppression, clinicians should take care to ensure that acid suppression medications are stopped when the patient is no longer critically ill or the risk factor triggering prophylaxis is no longer present. Long term use of gastric acid suppressants confers additional risks, costs, and burdens.[11 12]

Table 3 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

Cost and resources

We did not explicitly consider cost effectiveness of gastric acid suppression. PPIs and H2RAs are generally inexpensive compared with the overall expense of intensive care and are widely available.

Future research

Future research should prioritise several areas:

- Randomised controlled trials to clarify
  - Whether gastric acid suppressants increase the risk of pneumonia
  - Whether gastric acid suppression is less effective in patients receiving enteral nutrition (subgroup analyses)
  - Possible impact on outcomes such as *C difficile* infection
  - Head to head comparison of PPIs and H2RAs.
- Observational studies of risk factors for gastrointestinal bleeding; development of a risk prediction model or score.
- Evidence about patient values and preferences on the importance of bleeding versus possible adverse effects.

HOW THIS RECOMMENDATION WAS CREATED

Our international panel included methodologists, intensivists, pharmacists, a gastroenterologist, a nurse, patient partners who have been hospitalised in intensive care, and a caregiver for a patient who had been hospitalised in intensive care and mechanically ventilated (see appendix 3 on bmj.com for details of panel members). The panel decided the scope of the recommendation and rated the outcome importance to patients.

The panel judged the following as patient-important outcomes for decision making: clinically important bleeding, pneumonia, *Clostridium difficile* infection, mortality, length of hospital stay, length of stay in intensive care, and duration of mechanical ventilation.

The panel met online to discuss the evidence and to formulate recommendations. No panel member had relevant financial conflicts of interest; intellectual and professional conflicts were minimised and transparently described (see appendix 4 on bmj.com).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,[2] including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 5 on bmj.com).[3] The panel considered the benefits, harms and burdens of gastrointestinal bleeding prophylaxis, the certainty (quality) of the evidence for each outcome, variations in patient values and preferences, acceptability, and feasibility.[13] Following the GRADE approach, recommendations can be either strong or weak for or against a specific course of action.[14] The recommendations take a patient-centred perspective. Healthcare systems can adapt these recommendations by including costs and other key issues of relevance, contextualised to national and local circumstances.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The Rapid Recommendation panel included three patients who have experienced intensive care and a family caregiver of a patient.

Updates to this article

Table 3 shows evidence that has emerged since the publication of this article. As new evidence is published, the BMJ Rapid Recommendations collaboration will assess the new evidence and if the new evidence might change the recommendation, we will update the meta-analysis and recommendations (see appendix 5 on bmj.com).

Contributors: All panel members participated in the teleconferences or email discussions and met all authorship criteria. We thank Dr Tessa Richards for providing input as a patient into discussions on selecting and rating patient-important outcomes and subgroups, and values and preferences related to outcomes, during one of the guideline panel meetings.

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Competing interests: All authors have completed the BMJ Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 4 on bmj.com. As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

Transparency: ZY affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

Provenance and peer review: Commissioned; externally peer reviewed

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Appendices

Appendix 1: Estimation of baseline risk of clinically important gastrointestinal bleeding for patients with different risk factors

Appendix 2: A systematic review of literature of critically ill patients' values and preferences on gastrointestinal bleeding

Appendix 3: Details of members of the Rapid Recommendation panel

Appendix 4: Details of panel members' declarations of interests

Appendix 5: Methodology for development of BMJ Rapid Recommendations

Appendix 1

How we estimated baseline risk of clinically important gastrointestinal bleeding for patients with different risk factors

1. We started with the event rate in the placebo group of the SUP-ICU trial[1], because it is the largest and most recent RCT, and we were not able to identify any observational studies of risk of bleeding exclusively in patients who did not receive gastric acid suppression. SUP-ICU included only patients with at least one hypothesised risk factor for bleeding and therefore the patients in this trial had a higher risk of bleeding than patients without risk factors.

   Baseline risk of clinically important bleeding (CIB) with any risk factor = 4.2%

2. The most common risk factors for gastrointestinal bleeding in the SUP-ICU trial were invasive mechanical ventilation (78.7%), vasopressors or inotropes (66.7%), use of anticoagulants (30.3%), and coagulopathy (19.8%). Based on observational studies, the risk ratios (RRs) of these most common risk factors were approximately 2.5 (septic shock and anticoagulation) to approximately 4.5 (mechanical ventilation and coagulopathy). We therefore used the median RR of 3.5 (2.5 to 4.5) of the most common risk factors to estimate the risk of bleeding in patients without these risk factors.

   Baseline risk of CIB without any risk factor =

   risk of CIB with any risk factor * 1 / relative risk increase with risk factor identified from individual observational studies = 4.2% * 1 / (3.5) = 4.2% * 1 / approximately 3.5 = approximately 1.2% (0.9% to 1.7%)

3. We then estimated the risk of bleeding with specific risk factors by applying specific relative risks from observational studies. We only included studies we judged to be low risk of bias, including reporting a multivariable regression analysis. The estimates were obtained from a concurrently performed systematic review and meta-analysis.[2]

Table S1. Estimated risk of clinically important and overt gastrointestinal bleeding in various groups of patients

Risk factor	Clinically important bleeding			Overt bleeding	
	Risk ratio	Risk (per 1000)	GRADE certainty*	Risk ratio	Risk (per 1000)
Low risk (estimated risk of clinically important bleeding is 10-20 per 1000)					
No risk factor	1.0 (reference)	12	Moderate	1.0 (reference)	26
Acute hepatic failure	1.6	19	Very low	3.1	81
Anticoagulants	1.4	17	Low	1.8	47
Cancer	1.4	16	Very low	0.8	22
Use of corticosteroids or immune suppressed	1.4	17	Low	1.5	40
Male	0.9	10	Moderate	0.8	21
Moderate risk (estimated risk of clinically important bleeding is 21-40 per 1000)					
Acute kidney injury	3.3	39	Low	3.5	90
Mechanical ventilation with enteral nutrition	2.4	29	Low	2.5	65
Sepsis	2.0	24	Low	2.0	52
Shock	2.6	31	Moderate	2.6	67
High risk (estimated risk of clinically important bleeding is 41-80 per 1000)					
Coagulopathy	4.8	57	Moderate	4.1	108
Highest risk (estimated risk of clinically important bleeding is 81-100 per 1000)					
Chronic liver disease	7.6	92	Moderate	4.5	117
Mechanical ventilation without enteral nutrition	8.1	97	Low	8.3	216

*GRADE ratings provided for clinically important bleeding only

Enteral nutrition appears to have a large protective effect on GI bleeding in patients who are receiving mechanical ventilation, RR 0.30 (0.13 - 0.67). We therefore estimated the risk of bleeding separately for mechanically ventilated patients who are and are not receiving enteral nutrition. We assumed that approximately 70% of patients received enteral nutrition. The risk of bleeding in patients with mechanical ventilation = approximately 4.9% = (baseline risk with mechanical ventilation with enteral nutrition * 0.7) + (baseline risk with mechanical ventilation without enteral nutrition * 0.3).

We simplified the baseline risk of clinically important bleeding into four natural groupings: low risk (0-20 bleeds per 1000 patients), moderate risk (21-40 bleeds per 1000 patients), high risk (41-80 bleeds per 1000 patients), and highest risk (81-100 bleeds per 1000 patients). Because

there was a lot of uncertainty in many of the estimates and to improve usability of the guideline, we used a single estimate for each of the risk groups: 12 per 1000 for low risk, 30 per 1000 for moderate risk, 60 per 1000 for high risk, and 90 per 1000 for highest risk.

How we estimated the risk for overt gastrointestinal bleeding for patients with different risk factors

We performed the same calculations for overt bleeding that we did for CIB. Patients randomised to the placebo arm of the SUP-ICU trial[1] had a 9.0% risk of overt bleeding. The relative and absolute risks of overt bleeding are reported in table S1, from the same studies.

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Appendix 2

A systematic review of literature of critically ill patients' values and preferences on gastrointestinal bleeding

Summary

We set out to identify literature on how much critically ill patients value avoid gastrointestinal bleeding, and to identify any other relevant qualitative data that might inform the decision to use or not use gastric acid suppressants to prevent gastrointestinal bleeding. Our inclusion criteria included any quantitative or qualitative study on the values and/or preferences of critically ill patients on gastric acid suppression or gastrointestinal bleeding.

Search terms and strategies

We searched MEDLINE, EMBASE, and PsycINFO, using a combination of keywords and MeSH terms for "critically ill" and "gastrointestinal bleeding", and using a search filters for patient values and preferences, which includes terms related to health behaviours, patient values, and patient preferences. We reviewed the references of the included studies for other potentially eligible studies. We searched for grey literature through Google in first five pages.

The following databases were searched on March 1, 2019:
MEDLINE (1946 to February 28, 2019)
EMBASE (1974 to February 28, 2019)
PUBMED (epublications ahead of print only)
PsycInfo (1806 to February Week 1, 2019)
In total 2,196 citations were retrieved.

MEDLINE, EMBASE and PUBMED epublications

Embase <1974 to 2019 February 28>, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Peptic Ulcer/ or Ulcer*.mp. or lesion*.mp.
2 (bleed* or re-bleed* or rebleed* or h?emorrhag*).mp.

3 1 and 2

4 (stress adj3 ulcer*).mp.

5 3 or 4

6 exp Gastrointestinal Hemorrhage/

7 ((gastrointestinal or gastro-intestinal) adj5 (bleed* or re-bleed* or rebleed* or h?emorrhag*)).mp.

8 (h?ematochezia* or h?ematemese* or mel?ena*).mp.

9 exp injury/ and exp gastric mucosa/

10 (mucos* adj5 injur*).tw.

11 (stomach or antrum or antral or pyloric or pylorus or gastri* or gastropathy or epigastr* or duodenal or duodenum or gastro-duodenal or gastroduodenal or oeso*ag* or esp*ag* or "upper GI" or UGI or "upper gastrointestinal" or "upper gastrointestinal").mp.

12 2 and 11

13 exp Gastritis/

14 2 and 13

15 or/5-10,12,14

16 exp Critical Care/

17 exp intensive care/

18 exp Critical Illness/

19 exp Intensive Care Units/

20 ICU*.tw.

21 ((critical or intensive) adj3 (care or illness)).tw.

22 exp Intubation, Gastrointestinal/

23 exp Monitoring, Physiologic/

24 exp Multiple Organ Failure/

25 exp Acid-Base Equilibrium/

26 exp Multiple Trauma/

27 (serious* adj injur*).tw.

28 (severe adj (traum* or shock)).tw.

29 exp Perioperative Care/

30 ((preoperative or intraoperative or perioperative) adj (care or procedure* or period)).tw.
31 exp Resuscitation/
32 exp Shock/
33 exp sepsis/
34 exp Ventilator Weaning/
35 exp Ventilators, Mechanical/
36 exp Ventilators, Negative-Pressure/
37 (protocol* adj weaning).mp.
38 (ventilat* adj weaning).mp.
39 ((artificial or mechanical) adj ventilat*).mp.
40 ventilat*.tw.
41 or/16-40
42 15 and 41
43 Attitude to Health/
44 Patient Participation/
45 Patient Preference/
46 preference*.ti,ab.
47 choice.ti.
48 choices.ti.
49 value*.ti.
50 health state values.ti,ab.
51 valuation*.ti.
52 expectation*.ti,ab.
53 attitude*.ti,ab.
54 acceptab*.ti,ab.
55 knowledge.ti,ab.
56 point of view.ti,ab.
57 user participation.ti,ab.
58 users participation.ti,ab.
59 users' participation.ti,ab.

60 user's participation.ti,ab.
61 patient participation.ti,ab.
62 patients participation.ti,ab.
63 patients' participation.ti,ab.
64 patient's participation.ti,ab.
65 patient perspective*.ti,ab.
66 patients perspective*.ti,ab.
67 patients' perspective.ti,ab.
68 patient's perspective*.ti,ab.
69 user perspective*.ti,ab.
70 users perspective*.ti,ab.
71 users' perspective*.ti,ab.
72 user's perspective*.ti,ab.
73 patient perce*.ti,ab.
74 patients perce*.ti,ab.
75 patients' perce*.ti,ab.
76 patient's perce*.ti,ab.
77 health perception*.ti,ab.
78 user perce*.ti,ab.
79 users perce*.ti,ab.
80 users' perce*.ti,ab.
81 user's perce*.ti,ab.
82 user view*.ti,ab.
83 users view*.ti,ab.
84 users' view*.ti,ab.
85 user's view*.ti,ab.
86 patient view*.ti,ab.
87 patients view*.ti,ab.
88 patients' view*.ti,ab.
89 patient's view*.ti,ab.

90 ((decision* and mak*).ti. or decision mak*.ti,ab. or decisions mak*.ti,ab.) and (patient* or user* or men or women).ti,ab.

91 discrete choic*.ti,ab.

92 decision board*.ti,ab.

93 decision analy*.ti,ab.

94 decision-support.ti,ab.

95 decision tool*.ti,ab.

96 decision aid*.ti,ab.

97 discrete-choice*.ti,ab.

98 Decision Making/ and (patient* or user* or men or women).ti.

99 Decision Support Techniques/

100 (health and utilit*).ti.

101 gamble*.ti,ab.

102 prospect theory.ti,ab.

103 preference score.ti,ab.

104 preference elicitation.ti,ab.

105 health utilit*.ti,ab.

106 utility value*.ti,ab.

107 utility score*.ti,ab.

108 Utility estimate*.ti,ab.

109 health state.ti,ab.

110 feeling thermometer*.ti,ab.

111 best-worst scaling.ti,ab.

112 standard gamble.ti,ab.

113 time trade-off.ti,ab.

114 TTO.ti,ab.

115 probability trade-off.ti,ab.

116 utility score.ti,ab.

117 preference based.ti,ab.

118 preference score*.ti,ab.

119 multiattribute.ti,ab.

120 multi attribute.ti,ab.

121 EuroQol 5D.ti,ab.

122 EuroQol5D.ti,ab.

123 EQ5D.ti,ab.

124 EQ 5D.ti,ab.

125 SF6D.ti,ab.

126 SF 6D.ti,ab.

127 HUI.ti,ab.

128 15D.ti,ab.

129 or/43-128

130 42 and 129

131 remove duplicates from 130

PsycInfo (1806 to February Week 1 2019)

1 exp Gastrointestinal Ulcer/ or Ulcer*.mp. or lesion*.mp.

2 (bleed* or re-bleed* or rebleed* or h?emorrhag*).mp.

3 1 and 2

4 (stress adj3 ulcer*).mp.

5 3 or 4

6 ((gastrointestinal or gastro-intestinal) adj5 (bleed* or re-bleed* or rebleed* or h?emorrhag*)).mp.

7 (h?ematochezia* or h?ematemese* or mel?ena*).mp.

8 (mucos* adj5 injur*).tw.

9 (stomach or antrum or antral or pyloric or pylorus or gastri* or gastropathy or epigastr* or duodenal or duodenum or gastro-duodenal or gastroduodenal or oeso*ag* or esp*ag* or "upper GI" or UGI or "upper gastrointestinal" or "upper gastrointestinal").mp.

10 2 and 9

11 gastritis.tw.

12 2 and 11
13 or/5-8,10,12
14 exp intensive care/
15 ICU*.tw.
16 ((critical or intensive) adj3 (care or illness)).tw.
17 gastrointestinal intubation.tw.
18 (physiologic* adj2 monitoring).tw.
19 organ failure.tw.
20 Acid-Base Equilibrium.tw.
21 exp Trauma/
22 (serious* adj injur*).tw.
23 (severe adj (traum* or shock)).tw.
24 ((preoperative or intraoperative or perioperative) adj (care or procedure* or period)).tw.
25 resuscitation.tw.
26 exp Shock/
27 sepsis.tw.
28 (protocol* adj weaning).mp.
29 (ventilat* adj weaning).mp.
30 ((artificial or mechanical) adj ventilat*).mp.
31 ventilat*.tw.
32 or/14-31
33 13 and 32
34 Health Attitudes/
35 Client Participation/
36 Preferences/
37 preference*.ti,ab.
38 choice.ti.
39 choices.ti.
40 value*.ti.
41 health state values.ti,ab.

42 valuation*.ti.
43 expectation*.ti,ab.
44 attitude*.ti,ab.
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86 decision tool*.ti,ab.

87 decision aid*.ti,ab.

88 discrete-choice*.ti,ab.

89 Decision Making/ and (patient* or user* or men or women).ti.

90 Decision Support Systems/ or Decision Theory/

91 (health and utilit*).ti.

92 gamble*.ti,ab.

93 prospect theory.ti,ab.

94 preference score.ti,ab.

95 preference elicitation.ti,ab.

96 health utilit*.ti,ab.

97 utility value*.ti,ab.

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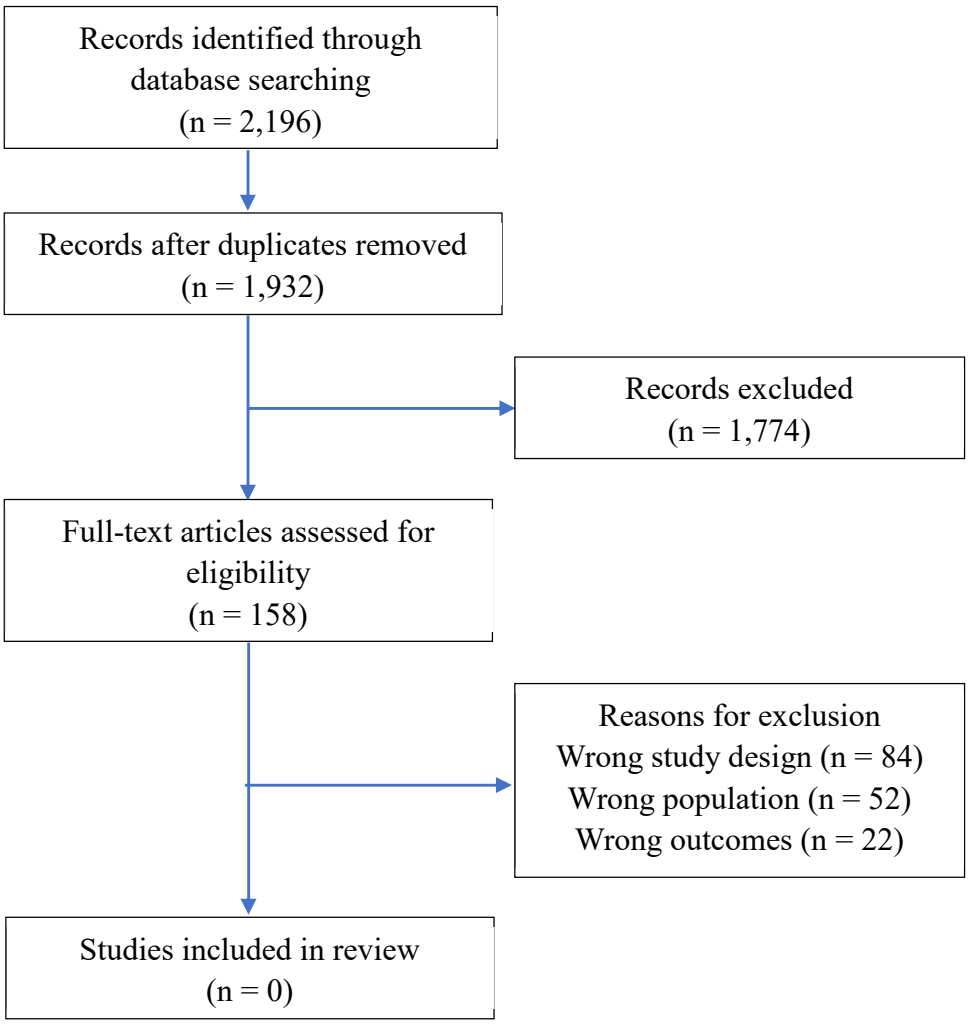
115 EQ 5D.ti,ab.
116 SF6D.ti,ab.
117 SF 6D.ti,ab.
118 HUI.ti,ab.
119 15D.ti,ab.
120 or/34-119
121 33 and 120

Searching results



Appendix 3: Rapid Recommendation panel members
Gastrointestinal bleeding prophylaxis for critically ill patients: a Rapid Recommendation

Clinical co-chair:
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Appendix 4: Full list of authors' declarations of interests

Pre-screening

All panel members were pre-screened for conflicts of interest prior to the guideline process that resulted in the BMJ Rapid Recommendations. The pre-screening was performed by the RapidRecs steering committee, affiliated with the non-profit organisation MAGIC (www.magicproject.org) and with support and approval from at least two unconflicted BMJ editors. No financial conflicts of interest were allowed (specifically, no financial ties to pharmaceutical companies with any stake in gastric acid suppressants) and intellectual and professional conflicts of interest were managed appropriately (see appendix 5: Methods for BMJ Rapid Recommendations). Panel members could not have a conflict for the past three years and do not anticipate a conflict arising in the foreseeable future, which we defined as at least one year.

Disclosures

Financial disclosures: No panel members had any financial conflicts of interest to disclose related to this clinical question.

Professional disclosures: Almost all of the physician panel members routinely see patients to whom this guideline applies, but their practice, rank, and remuneration will be unaffected by these recommendations.

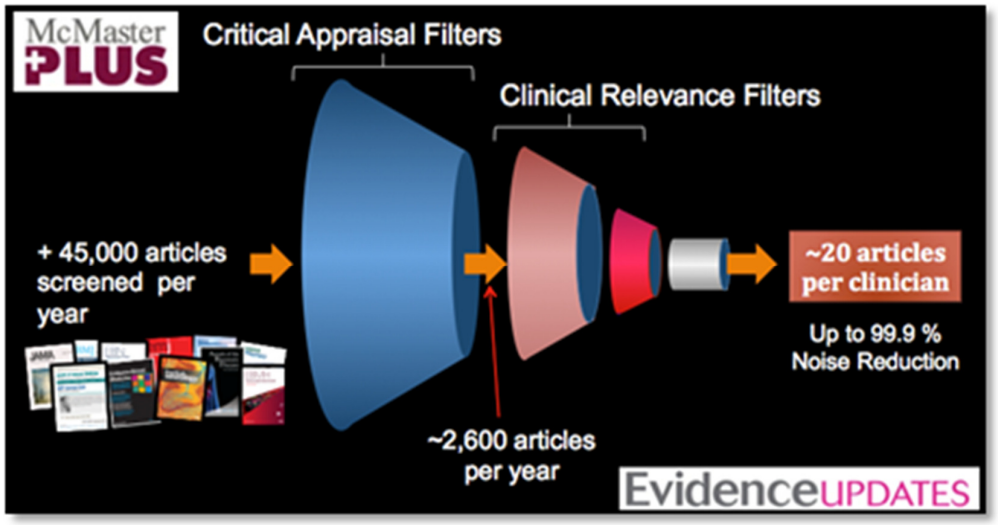
Intellectual disclosures: Zhikang Ye, Reed A.C. Siemieniuk, and Gordon H. Guyatt participated in writing the systematic review that formed the evidence base for this guideline (doi:). Reed A.C. Siemieniuk, Thomas Agoritsas, Per Vandvik, Lyubov Lytvyn, and Gordon H. Guyatt are members of the GRADE Working Group: BMJ Rapid Recommendations adheres to GRADE methods.
Gordon H. Guyatt may be predisposed to weak rather than strong recommendations to justify the necessity of the REVISE trial that compare the benefits and harms of pantoprazole versus placebo (doi: 10.5144/0256-4947.2016.427; NCT02290327). Bin Du is the corresponding author of meta-analysis on stress ulcer prophylaxis in patients receiving enteral feeding, which concluded that gastric acid suppression may be harmful in patients receiving enteral nutrition (doi: 10.1186/s13054-017-1937-1). Julie Camsooksai is a site research nurse coordinator for the ongoing PEPTIC trial that is comparing a proton-pump inhibitor versus a histamine-2 receptor antagonist and may be predisposed to a weak rather than strong recommendation for that recommendation (PMID: 30153780; ANZCTRN 12616000481471).

About *BMJ* Rapid Recommendations

Translating research to clinical practice is challenging. Trustworthy clinical practice recommendations are one useful knowledge translation strategy. Organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence. *BMJ* Rapid Recommendations aims to create trustworthy clinical practice recommendations based on the highest quality evidence in record time. The project is supported by an international network of systematic review and guideline methodologists, people with lived experience of the diseases or conditions, clinical specialists, and front-line clinicians. This overview is one of a package that includes recommendations and one or more systematic reviews published by the *BMJ* group and in MAGICapp (http://www.magicapp.org). The goal is to translate evidence into recommendations for clinical practice in a timely and transparent way, minimising bias and centred around the experience of patients. *BMJ* Rapid Recommendations will consider both new and old evidence that might alter established clinical practice.

Process overview

1. On a daily basis, we monitor the literature for practice-changing evidence:



   a. Formal monitoring through McMaster Premium LiteratUre Service (PLUS)

   b. Informal monitoring the literature by *BMJ* Rapid Recommendations expert groups, including clinician specialists and patients

2. The *Rapid Recommendations* executive team and editors at *The BMJ* choose which clinical questions to pursue among the identified potentially-practice changing evidence, based on relevance to a wide audience, widespread interest, and likelihood to change practice.

3. We incorporate the evidence into the existing body of evidence and broader context of clinical practice via:

    a. a rapid and high-quality systematic review and meta-analysis on the benefits and harms with a focus on the outcomes that matter to patients

    b. parallel rapid recommendations that meet the standards for trustworthy guidelines[1] by an international panel of people with relevant lived experience, front-line clinicians, clinical content experts, and methodologists.

    c. The systematic review and the recommendation panel will apply standards for trustworthy guidelines.[1,2] They use the GRADE approach, which has developed a transparent process to rate the quality (or certainty) of evidence and grade the strength of recommendations.[3,4]

    d. Further research may be conducted including:

        i. A systematic review of observational studies to identify baseline risk estimates that most closely represent the population at the heart of the clinical question, a key component when calculating the estimates of absolute effects of the intervention

        ii. A systematic review on the preferences and values of patients on the topic.

4. Disseminate the rapid recommendations through

    a. publication of the research in *BMJ* journals

    b. short summary of recommendations for clinicians published in *The BMJ*

    c. press release and/or marketing to media outlets and relevant parties such as patient groups

    d. Links to BMJ Group's *Best Practice* point of care resource

    e. MAGICapp which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others who wish to re-examine or consider national or local adaptation of the recommendations.

Who is involved?

Researchers, systematic review and guideline authors, clinicians, and patients often work in silos. Academic journals may publish work from any one or combinations of these groups of people and findings may also be published in the media. But it is rare that these groups work together to produce a comprehensive package. *BMJ-Rapid Recommendations* circumvents organisational barriers in order to provide clinicians with guidance for potentially practice-changing evidence.

Our collaboration involves

a. The *Rapid Recommendations* group with a designated Executive team responsible for recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels.. The *Rapid Recommendations* group is part of MAGIC (www.magicproject.org), a non for profit organization that provides MAGICapp (www.magicapp.org) an authoring and publication platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices.[5]

b. *The BMJ* helps identifiying practice-changing evidence on key clinical questions, coordinates the editorial process and publishes the package of content linking to the MAGICapp that is presented in a user friendly way.

METHODS FOR THE RAPID RECOMMENDATIONS

The formation of these recommendations adheres to standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interests, as well as transparent and systematic processes for assessing the quality of evidence and for moving from evidence to recommendations.[1,2,6]

Guidance on how the panel is picked and how they contribute

Panel members are sought and screened through an informal process.

The following panel members are important

- At least one author of the individual systematic reviews
- At least one patient representative with lived experience of the disease or condition. This person receives patient-oriented documents to explain the process and is allocated a linked panel member to empower their contribution.
- A full spectrum of practicing clinicians involved in the management of the clinical problem and patients it affects, including front-line clinicians with generalist experience and those with deep content clinical and research expertise in the particular topic.
- Methodological experts in health research methodology and guideline development

Any potential conflicts of interest are managed with extreme prudence:

- No panel member can have a financial interest – as assessed by the panel chair, the *Rapid Recommendations* executive team or *The BMJ* editors as relevant to the topic
- No more than two panel members with an intellectual interest on the topic (typically having published statements favouring one of the interventions).

Illustrative example: For the BMJ Rapid Recommendations on corticosteroids for sepsis, no panel member was allowed to have received any financial support from a pharmaceutical company that produces or distributes systemic corticosteroids.

How the panel meets and works

The international panel communicates via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiorecorded, transcribed, and stored for later documentation (available for peer-reviewers on request).

Teleconferences typically occur at three timepoints, with circulated documents by e-mail in advance:

1. At the initiation of the process to provide feedback on the systematic review protocol (for example, on selection of patient-important outcomes and appropriate prespecified analysis of results) before it is performed.
2. At the evidence summary stage with discussion, feedback and agreement on draft evidence (GRADE evidence profile) prepared by the Chair and the methods editor based on the systematic review.
3. At the recommendation formulation phase with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Following the last teleconference the final version of the recommendations is circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission to *The BMJ*. Additional teleconferences are arranged as needed.

How we move from research findings to recommendations

What information is considered?

The panel considers best current evidence from available research. Beyond systematic reviews - performed in the context of the *BMJ* Rapid Recommendations - the panel may also include a number of other research papers to further inform the recommendations.

How is a trustworthy guideline made?

The Institute of Medicine (IOM)'s guidance on out how trustworthy guidelines should be developed and articulated key standards as outlined in the table below.[1] The standards are similar to those developed by the Guideline International Network (G-I-N).[2] These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). The table below lays out how we hope to meet the standards for our rapid recommendations:

1. Establishing transparency **"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"***

- This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content is available.
- We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.

2. Managing conflicts of interest

"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",

- Interests of each panel member are declared prior to involvement and published with the rapid recommendations
- No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ*
- No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic.
- The Chair must have methods expertise, a clinical background and no financial or intellectual interests.
- Funders and pharmaceutical companies have no role in these recommendations.

3. Guideline Development Group Composition

"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"

- *The Rapid Recommendations* group will aim to include representation from most or every major geographic region in the world, with specific efforts made to achieve gender-balance.
- We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available
- Patient-representatives will be given priority during panel meetings and will have an

explicit role in vetting the panel's judgements of values and preferences.

4. Clinical Practice Guideline–Systematic Review Intersection

"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes".

- Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendation.
- The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication and continuity in the process

5. Establishing Evidence Foundations for and Rating Strength of Recommendations

"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"

- The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.[6] For each recommendation systematic and transparent assessments are made across the following key factors:
  - Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables)[4]
  - Quality of the evidence[7]
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)
- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. patophysiology) and clinical experience played into the evidence assessment and

recommendation development.

- Recommendations will be rated either weak or strong, as defined by GRADE.[8]
- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus process customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations

"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats in MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.[9]
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and or with an individual patient.

7. External review

"External reviewers should comprise a full spectrum of relevant stakeholders...., authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for comment.."

- At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy
- A *BMJ* series adviser with methodological and/or statistical expertise will review the *BMJ* Rapid Recommendations publication and the systematic reviews.
- The *Rapid Recommendations* panel will be asked to read and respond to the peer

review comments and make amendments where they judge reasonable

- *The BMJ* and *Rapid Recommendations* executive team may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period of six months after publication.

8. Updating

"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"

- The *Rapid Recommendations* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates of the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

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Chapter 3: Efficacy and Safety of Corticosteroids in COVID-19 based on Evidence for COVID-19, Other Coronavirus Infections, Influenza, Community-acquired Pneumonia and Acute Respiratory Distress Syndrome: A Systematic Review and Meta-analysis

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RESEARCH

Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Very little direct evidence exists on use of corticosteroids in patients with coronavirus disease 2019 (COVID-19). Indirect evidence from related conditions must therefore inform inferences regarding benefits and harms. To support a guideline for managing COVID-19, we conducted systematic reviews examining the impact of corticosteroids in COVID-19 and related severe acute respiratory illnesses.

METHODS: We searched standard international and Chinese biomedical literature databases and prepublication sources for randomized controlled trials (RCTs) and observational studies comparing corticosteroids versus no corticosteroids in patients with COVID-19, severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). For acute respiratory distress syndrome (ARDS), influenza and community-acquired pneumonia (CAP), we updated the most recent rigorous systematic review. We conducted random-effects meta-analyses to pool relative risks and then used baseline risk in patients with COVID-19 to generate absolute effects.

RESULTS: In ARDS, according to 1 small cohort study in patients with COVID-19 and 7 RCTs in non–COVID-19 populations (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.55 to 0.93, mean difference 17.3% fewer; low-quality evidence), corticosteroids may reduce mortality. In patients with severe COVID-19 but without ARDS, direct evidence from 2 observational studies provided very low-quality evidence of an increase in mortality with corticosteroids (hazard ratio [HR] 2.30, 95% CI 1.00 to 5.29, mean difference 11.9% more), as did observational data from influenza studies. Observational data from SARS and MERS studies provided very low-quality evidence of a small or no reduction in mortality. Randomized controlled trials in CAP suggest that corticosteroids may reduce mortality (RR 0.70, 95% CI 0.50 to 0.98, 3.1% lower; very low-quality evidence), and may increase hyperglycemia.

INTERPRETATION: Corticosteroids may reduce mortality for patients with COVID-19 and ARDS. For patients with severe COVID-19 but without ARDS, evidence regarding benefit from different bodies of evidence is inconsistent and of very low quality.

On Mar. 11, 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic.[1] The worldwide spread of COVID-19 represents a profound threat to human health.

Clinicians frequently treat patients with COVID-19 with corticosteroids.[2] Their use is controversial: 2 commentaries published recently in *The Lancet* expressed opposing views based partly on original studies of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and influenza: 1 recommended against using corticosteroids, while the other recommended using corticosteroids in some patients with COVID-19.[3,4]

Formulating recommendations for clinicians regarding use of corticosteroids in patients with COVID-19 requires systematic summaries of the available evidence. Therefore, to support a clinical

practice guideline addressing management of patients with COVID-19,[5] we conducted a series of systematic reviews. Because we anticipated a paucity of direct evidence from patients with COVID-19, we included available evidence addressing corticosteroids in the treatment of acute respiratory distress syndrome (ARDS), SARS, MERS, influenza and community-acquired pneumonia (CAP), all providing indirect evidence that informs the efficacy and safety of corticosteroid use in patients with COVID-19.

Methods

For ARDS, we used definitions in eligible studies. For severe COVID-19, we used the World Health Organization definition of severity: fever or suspected respiratory infection, plus 1 of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or peripheral oxygen saturation (SpO_2) ≤ 93% on room air.[6]

For COVID-19, SARS and MERS, we conducted systematic reviews that sought all eligible primary studies. For ARDS, influenza and CAP, we chose the most recent methodologically rigorous systematic reviews and searched for recent eligible primary studies. Choice of outcomes were informed by our preliminary protocol, by guidance from the guideline panel, and from what authors of eligible studies reported.

Search strategies and selection criteria

Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the protocol we developed before launching these systematic reviews, which follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[7]

COVID-19, SARS and MERS

With the assistance of a medical librarian (R.J.C.), we searched MEDLINE, Embase, PubMed and the Cochrane Central Register of Controlled Trials from the date of their inception to Apr. 19, 2020, and searched medRxiv until Apr. 25, 2020. For studies of patients with COVID-19, we also searched Chinese databases, including China National Knowledge Infrastructure (CNKI), Wanfang, Chongqing VIP Information (CQVIP), and ChinaXiv. Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the complete search strategy.

We included randomized controlled trials (RCTs), cohort and case–control studies comparing corticosteroids versus no corticosteroids in patients with COVID-19, SARS or MERS. For cohort studies and case–control studies, we included only studies that performed adjusted analysis unless all studies failed to conduct an adjusted analysis, in which case we included unadjusted analyses. For overlapping studies (studies that included patients from the same data sources), we included only the larger unless there was a specific additional helpful analysis in the smaller.

ARDS, influenza and CAP

We conducted separate searches for ARDS, influenza and CAP using a 2-stage process (for search strategy, see Appendix 2). First, to identify systematic reviews that examined the effect of corticosteroids on ARDS, influenza or CAP, we searched MEDLINE, Embase, the Cochrane Database of Systematic Reviews and Epistemonikos, and chose the most recent methodologically rigorous one. Second, we searched MEDLINE, Embase and ClinicalTrials.gov for ARDS and CAP, and searched MEDLINE, Embase, PubMed and the Cochrane Central Register of Controlled Trials for influenza, for studies published subsequent to the search of the chosen reviews. For ARDS and CAP, we included only RCTs. For influenza, we included RCTs and cohort studies.

For all searches, 2 reviewers independently screened titles and abstracts and, subsequently, full texts of potentially eligible studies to determine final eligibility. Disagreements were resolved by discussion or, if necessary, referral to a third reviewer. We applied no language restriction.

Data analysis

Two reviewers independently extracted study characteristics, with adjudication by a third reviewer if necessary. Outcomes included mortality, length of intensive care unit (ICU) stay, length of hospital stay, duration of mechanical ventilation, need for mechanical ventilation, viral ribonucleic acid (RNA) clearance, viral shedding time, serious hyperglycemia, superinfection, neuromuscular weakness and gastrointestinal bleeding.

We calculated summary estimates using Stata or Review Manager and calculated relative effects (odds ratios [ORs], risk ratios [RRs] or hazard ratios [HRs]) and 95% confidence intervals (95% CIs) for dichotomous outcomes, and mean differences (MDs) and 95% CIs for continuous outcomes using a random-effects model. For continuous outcomes and adjusted estimates, we used the inverse variance (DerSimonian and Laird) method; for dichotomous outcomes from RCTs, we used the Mantel–Haenszel method. We assessed inconsistency among studies by differences in point estimates and overlap of the confidence intervals, and the I^2 statistic. For dichotomous outcomes, we calculated the absolute treatment effects by applying relative effects to risk in patients not receiving corticosteroids in 2 groups: patients with severe COVID-19 and patients with COVID-19 and ARDS. We chose the baseline mortality risk of patients with COVID-19 and ARDS from an observational study of patients with COVID-19 and ARDS,[8] and the baseline mortality risk of patients with severe COVID-19 from an observational study of patients with severe COVID-19.[2] For other outcomes, we relied for baseline risks on the medians of the groups not receiving corticosteroids in the included studies.

Risk of bias assessment

We used the ROBIS risk of bias tool[9] to choose the most methodologically rigorous systematic review to be updated. We used a modified version of the Cochrane risk of bias tool[10] to assess risk of bias in RCTs, and a revised version of the Newcastle–Ottawa Scale[11,12] for observational studies (details available at www.evidencepartners.com/resources/methodological-resources/). Two reviewers independently assessed risk of bias, resolving disagreements with a third reviewer if necessary.

Rating of evidence quality

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to rate the quality of evidence for each outcome as high, moderate, low or very low.[13] The assessment included judgments addressing risk of bias,[14] imprecision,[15] inconsistency,[16] indirectness[17] and publication bias.[18] If

there were serious concerns in any of these domains (for instance, in risk of bias), we rated down the quality of the evidence. Because the effect of corticosteroids in these diseases might differ from effects in the COVID-19 population, using the GRADE approach, for benefit outcomes in SARS and MERS, we rated down 1 level for indirectness, and for ARDS, influenza and CAP, we rated down 2 levels. Because we considered estimates of harm to be more likely to apply across populations than benefit outcomes, for all populations we rated down 1 level for harms.

Ethics approval

Ethics approval was not required for this systematic review.

Results

Appendix 3 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the study selection process. Our search for COVID-19, SARS and MERS identified 5120 citations. After removing duplicates, screening titles and abstracts, and reviewing full texts, we ultimately included 1 cohort study[8] including 84 patients with COVID-19 and ARDS, 5 cohort studies[19–23] including 679 patients with COVID-19 but without ARDS, 3 studies (2 cohort studies[24,25] and 1 RCT[26]) including 7087 patients with SARS, and 2 cohort studies[27,28] including 623 patients with MERS.

Our search for systematic reviews of ARDS identified 836 citations; we ultimately chose a systematic review published in 2019 as the target for updating.[29] Our search for primary studies identified 1 new eligible RCT published in 2020.[30] Including 6 RCTs identified from the previous review, we included 7 RCTs[30–36] with 851 patients.

Our search for systematic reviews for influenza identified 525 citations; we ultimately chose a systematic review published in 2019 as the target for updating.[37] Our search for primary studies identified 1 new eligible study published in 2020.[38] Including 30 studies identified from the previous review, we identified 31 eligible studies,[39–69] of which 21 with 9536 patients were included in meta-analyses.[41,43–47,50,52,53,55–61,63–65,68,69]

Our search for systematic reviews for CAP identified 346 citations. We ultimately chose a systematic review published in 2015 as the target for updating.[70] Our search for primary studies identified 1 new eligible study published in 2016.[71] With 12 RCTs from the previous review, our systematic review included 13 RCTs[71–83] including 2095 patients.

Appendix 4 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents characteristics of the included studies. Appendix 5 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) presents the risk of bias assessment for each study. Forest plots of the meta-analysis results are shown in Figures 1–5 for mortality and in Appendix 6 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200645/-/DC1) for other outcomes.

ARDS

Evidence for patients with COVID-19 and ARDS was available from a single observational study of 84 patients[8] that suggested corticosteroids may result in a large mortality reduction compared with no corticosteroids (HR 0.41, 95% CI 0.20 to 0.83, MD 29.2% lower; very low-quality evidence) (Table 1).

Evidence for ARDS without COVID-19 was available from 7 RCTs[30–36] including 851 patients (Table 2). We considered the evidence for most outcomes to be high quality for patients with ARDS in general. After rating down 2 levels for indirectness of populations, we considered the evidence to be low quality for COVID-19. These RCTs suggest that corticosteroids may substantially reduce mortality (RR 0.72, 95% CI 0.55 to 0.93, MD 17.3% lower; low-quality evidence) (Figure 1). Very low-quality evidence raised the possibility that corticosteroids may have little or no impact on length of ICU stay[32–34] (MD 0.1 days longer, 95% CI 3.0 days shorter to 3.2 days longer) but may reduce length of hospital stay[33,34,36] (MD 3.6 days shorter, 95% CI 0.02 to 7.2 days shorter). Low-quality evidence shows that corticosteroids may reduce the duration of mechanical ventilation (MD –4.8 days, 95% CI –7.0 to –2.6),[30,31,33–36] but increase serious hyperglycemia (risk increase 8.1%, 95% CI 0.7% to 16.2%),[30,33,35] with few or no adverse effects on neuromuscular weakness,[33,34] gastrointestinal bleeding[35,36] and superinfection.[30,33–36]

Study or subgroup; year	Corticosteroid Events	Corticosteroid Total	Control Events	Control Total	Risk ratio M-H, random, 95% CI
Liu et al., 2012[32]	2	12	7	14	0.33 (0.08 to 1.31)
Meduri et al., 2007[33]	15	63	12	28	0.56 (0.30 to 1.03)
Rezk et al., 2013[31]	0	18	3	9	0.08 (0.00 to 1.32)
Steinberg et al., 2006[34]	28	89	29	91	0.99 (0.64 to 1.52)
Tongyoo et al., 2016[35]	34	98	40	99	0.86 (0.60 to 1.23)
Villar et al., 2020[30]	29	139	50	138	0.58 (0.39 to 0.85)
Zhao et al., 2014[36]	9	24	13	29	0.84 (0.43 to 1.61)
Total (95% CI)		**443**		**408**	**0.72 (0.55 to 0.93)**
Total events	**117**		**154**		
Heterogeneity: I^2 = 32%					

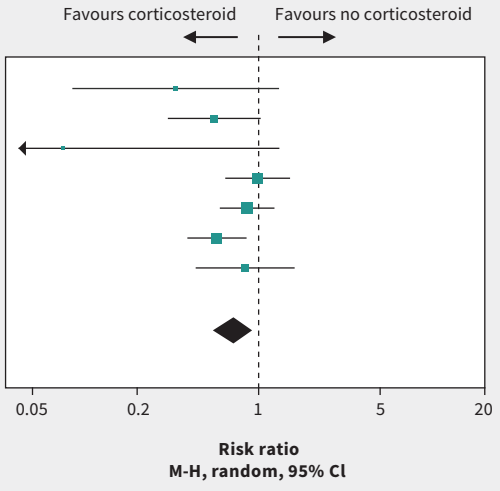

Figure 1: Effect of corticosteroids on mortality in patients with acute respiratory distress syndrome without coronavirus disease 2019. Note: CI = confidence interval, M-H = Mantel–Haenszel.

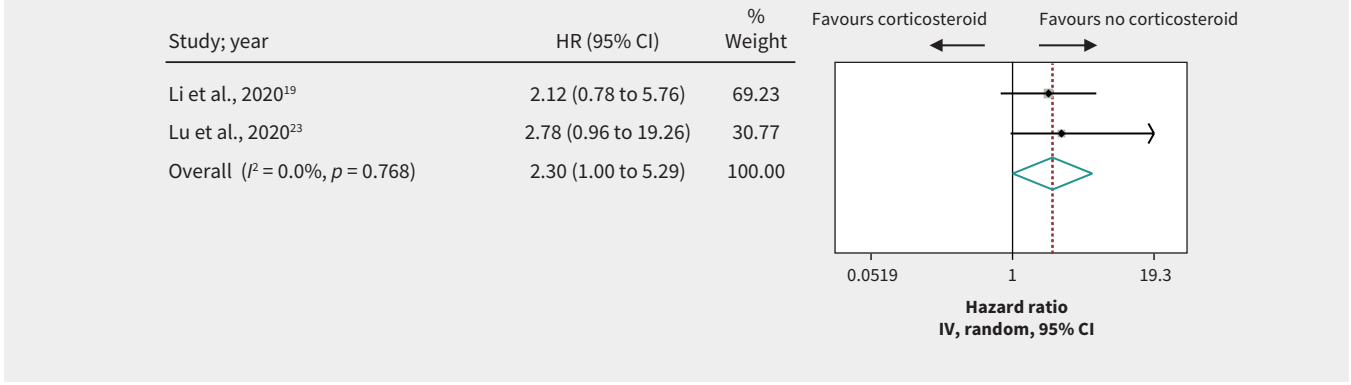

Figure 2: Effect of corticosteroids on mortality in patients with severe coronavirus disease 2019. Weights are from random-effects analysis. Note: CI = confidence interval, HR = hazard ratio, IV = inverse variance.

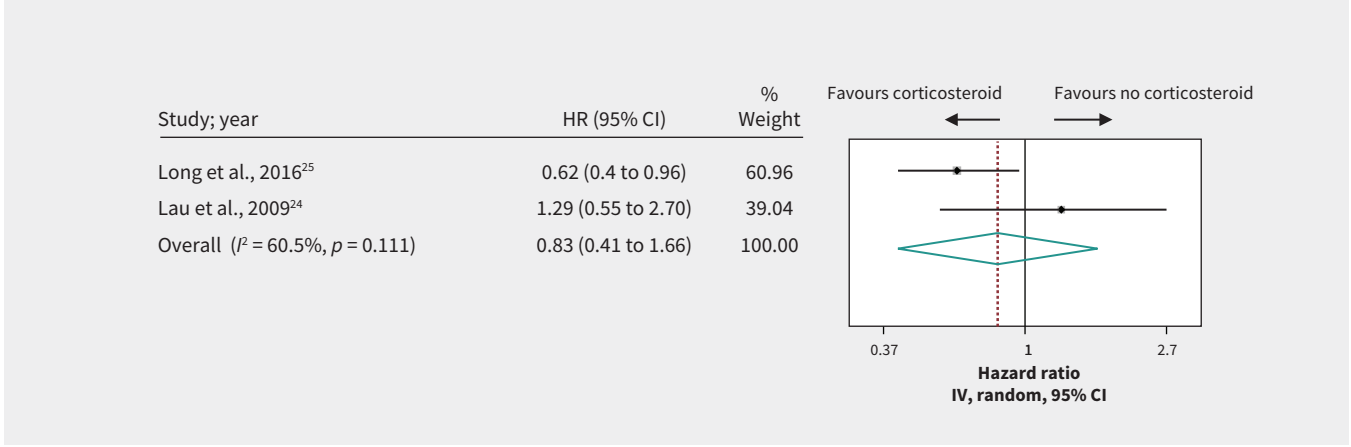

Figure 3: Effect of corticosteroids on mortality in patients with severe acute respiratory syndrome. Weights are from random-effects analysis. Note: CI = confidence interval, HR = hazard ratio, IV = inverse variance.

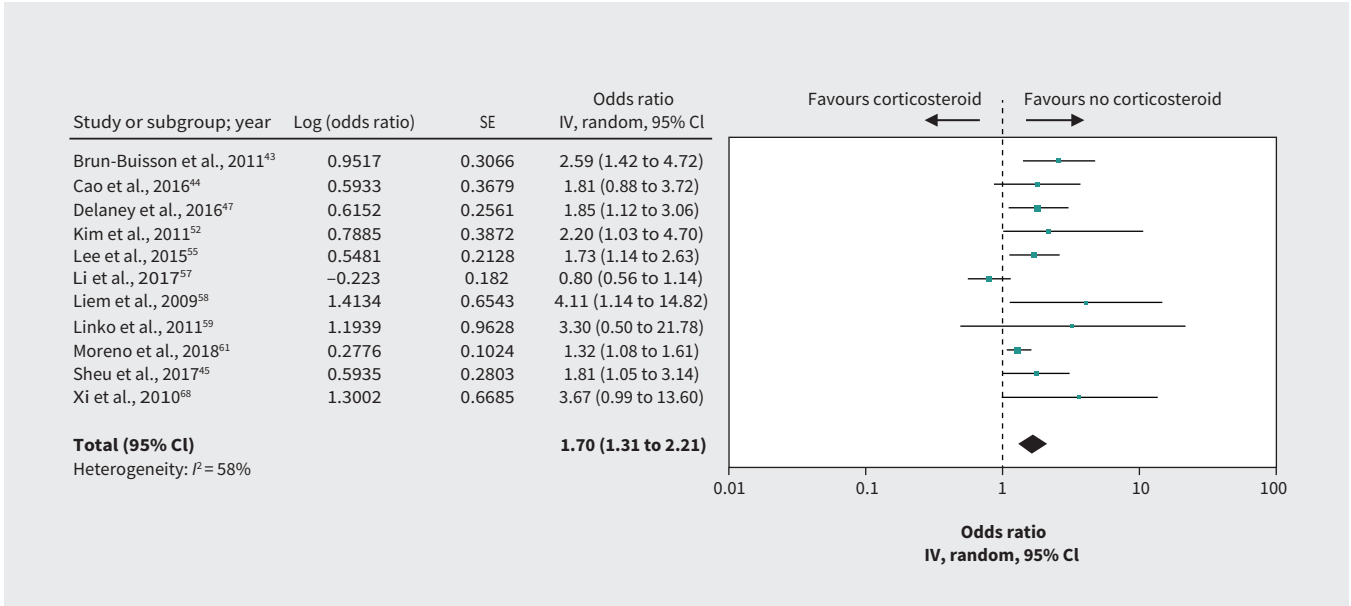

Figure 4: Effect of corticosteroids on mortality in patients with influenza. Note: CI = confidence interval, IV = inverse variance, SE = standard error.

Severe COVID-19: direct evidence from observational studies

Very low-quality evidence from 2 cohort studies[19,23] including 331 patients with severe COVID-19 raised the possibility that corticosteroids may increase mortality compared with no corticosteroids (HR 2.30, 95% CI 1.00 to 5.29, MD 11.9% more) (Table 3, Figure 2). One cohort study[20] reported an increase in the composite outcome of mortality or ICU admission with steroid use. Two cohort studies[21,22] suggested that corticosteroids use was associated with prolonged viral shedding (very low-quality evidence).

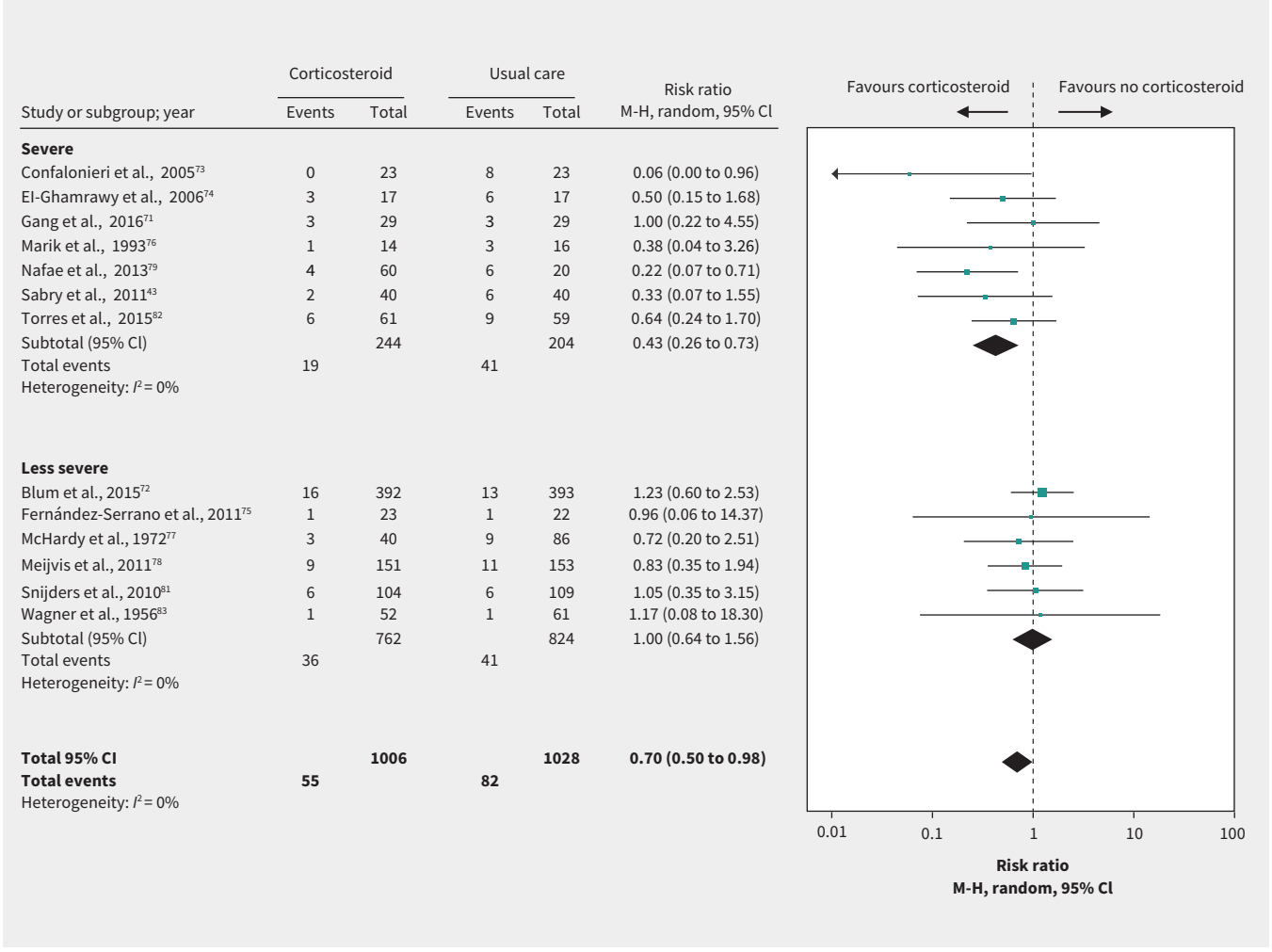

Figure 5: Effect of corticosteroids on mortality in patients with community-acquired pneumonia. Note: CI = confidence interval, M-H = Mantel–Haenszel.

Table 1: GRADE summary of findings: corticosteroids in patients with COVID-19 and ARDS, based on direct evidence from observational studies of patients with COVID-19 and ARDS

		Absolute effect estimates			
Outcomes	**Relative effects**	**Baseline risk for control group,* %**	**Difference (95% CI)%**	**Quality of evidence**	**Plain language summary**
Mortality	HR 0.41 (95% CI 0.20 to 0.83) Based on data from 84 patients with COVID-19 and ARDS in 1 observational study[8]	61.8	−29.2 (−44.3 to −6.8)	Very low (serious imprecision†)	We are very uncertain of the effect of corticosteroids on mortality

Note: ARDS = acute respiratory distress syndrome, CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio.
*Mortality baseline risk from patients with COVID-19 and ARDS without corticosteroid treatment.[8]
†Observational study started at low quality of evidence. Although the CI appears narrow, the small sample size and implausibly large effect led to rating down for imprecision.

Severe COVID-19: indirect evidence from observational studies and a randomized trial of SARS

Two cohort studies[24,25] including 6129 patients with SARS provide low-quality evidence for corticosteroid impact on mortality in these patients, with additional consideration of indirectness in serious COVID-19 pneumonia (HR 0.83, 95% CI 0.41 to 1.66; very low-quality evidence) (Table 4, Figure 3). An RCT[26] in which 16 patients with SARS treated with ribavirin were randomized to corticosteroids or no corticosteroids raised the possibility that early (< 7 days of illness) hydrocortisone therapy may increase the median time for SARS-associated coronavirus (SARS-CoV) RNA to become undetectable in plasma (MD 4.0 days longer, 95% CI 2.0–6.0 days; very low-quality evidence for SARS with additional consideration of indirectness in COVID-19) (Table 4).

Severe COVID-19: indirect evidence from observational studies of MERS

One cohort study[28] that enrolled 290 patients with MERS suggests a possible reduction in mortality with administration of corticosteroids (OR 0.75, 95% CI 0.52 to 1.07; very low-quality evidence

Table 2: GRADE summary of findings: corticosteroids in patients with COVID-19 and ARDS, based on indirect evidence from randomized controlled trials of patients with ARDS but without COVID-19

		Absolute effect estimates			
Outcomes	**Relative effects**	**Baseline risk for control group***	**Difference (95% CI)**	**Quality of evidence**	**Plain language summary**
Mortality	RR 0.72 (95% CI 0.55 to 0.93) Based on data from 851 patients and ARDS in 7 RCTs[30–36]	61.8%	−17.3% (−27.8% to −4.3%)	Low (very serious indirectness†)	Corticosteroids may result in a large reduction in mortality
Length of ICU stay	Based on data from 297 patients in 3 RCTs[32–34]	The median duration of length of ICU stay was 8.0 days	MD 0.1 days (−3.0 to 3.2)	Very low (serious inconsistency, very serious indirectness and serious imprecision‡)	We are very uncertain of the effect of corticosteroids on length of ICU stay
Length of hospital stay	Based on data from 324 patients in 3 RCTs[33,34,36]	The median duration of length of hospital stay was 18.0 days	MD −3.6 days (−7.2 to −0.02)	Very low (very serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on length of hospital stay
Duration of mechanical ventilation	Based on data from 888 patients in 6 RCTs[30,31,33–36]	The median duration of mechanical ventilation was 14.5 days	MD −4.8 days (−7.0 to −2.6)	Low (very serious indirectness†)	Corticosteroids may reduce duration of mechanical ventilation
Serious hyperglycemia	RR 1.12 (95% CI 1.01 to 1.24) Based on data from 565 patients in 3 RCTs[30,33,35]	67.6%	8.1% (0.7% to 16.2%)	Low (serious indirectness and serious imprecision¶)	Corticosteroids may increase serious hyperglycemia events
Neuromuscular weakness	RR 0.85 (95% CI 0.62 to 1.18) Based on data from 271 patients in 2 RCTs[33,34]	26.4%	−3.9% (−10% to 4.7%)	Low (serious indirectness, serious imprecision**)	Corticosteroids may not increase neuromuscular weakness
Gastrointestinal bleeding	RR 0.71 (95% CI 0.30 to 1.73) Based on data from 250 patients in 2 RCTs[35,36]	14.0%	−4.0% (−9.8% to 10.2%)	Low (serious indirectness, serious imprecision**)	Corticosteroids may not increase gastrointestinal bleeding
Superinfection	RR 0.82 (95% CI 0.67 to 1.02) Based on data from 798 patients in 5 RCTs[30,33–36]	33.0%	−5.9% (−10.8% to 0.6%)	Moderate (serious indirectness††)	Corticosteroids probably do not increase superinfection events

Note: ARDS = acute respiratory distress syndrome, CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, ICU = intensive care unit, MD = mean difference, RCTs = randomized controlled trials, RR = risk ratio.
*Mortality baseline risk from patients with COVID-19 and ARDS who do not receive corticosteroid treatment.[8] The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events was obtained from the median estimate from the control group in the included RCTs.
†We rated down 2 levels owing to indirectness; the cause of ARDS across the studies is inconsistent and might not represent the COVID-19 population.
‡We rated down 2 levels owing to indirectness; 1 for inconsistency (I^2 = 73%, heterogeneity p value 0.03) and 1 for imprecision because effect estimate is consistent with benefit or harm.
§We rated down 2 levels owing to indirectness and 1 for imprecision owing to the CI including a trivial reduction in hospital stay.
¶We rated down by 1 level owing to indirectness, as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits; and we rated down by 1 level for imprecision owing to the lower CI, 0.7% representing an unimportant increase in hyperglycemia.
**We rated down by 1 level owing to indirectness as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits; we rated down by 1 level for imprecision, effect estimate consistent with benefit or harm.
††We rated down by 1 level owing to indirectness as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits; we did not rate down owing to imprecision because the largest degree of harm consistent with the evidence is 7 in 1000, which we judge to be unimportant.

for MERS with additional consideration of indirectness in COVID-19) (Table 5). Data from 189 patients in the same study[28] suggest that corticosteroid use may be associated with a delay in Middle East respiratory syndrome coronavirus (MERS-CoV) RNA clearance (HR 0.35, 95% 0.17 to 0.72; very low-quality evidence for MERS with additional consideration of indirectness for COVID-19) (Table 5).

Severe COVID-19: indirect evidence from observational studies of influenza

Evidence in patients with influenza from 11 cohort studies[43–45,47,52,55,57–59,61,68] including 8530 patients with adjusted effect estimates for mortality suggests that corticosteroids may increase mortality (OR 1.70, 95% CI 1.31 to 2.21, MD 6.1% higher; low-quality evidence for influenza rated down to very low for indirectness) (Table 6, Figure 4). Very low-quality evidence for influenza with additional consideration of indirectness when applied to COVID-19 from cohort studies that failed to conduct an adjusted analysis raised the possibility that corticosteroids may increase the rate of superinfection (OR 2.74, 95% CI 1.51 to 4.95)[43,44,47,52,55,57,65] and increase the number of patients requiring mechanical ventilation (OR 5.54, 95% CI 1.83 to 16.80)[52,57,59,61] (Table 6).

Severe COVID-19: indirect evidence from randomized trials of CAP

Thirteen RCTs[71–83] including 2034 patients with CAP addressed a number of important efficacy outcomes. For patients with CAP in general, evidence varied from high to low quality. After we rated down 2 levels for indirectness, all evidence for these outcomes was of low or very low quality. Corticosteroids were associated with reductions in mortality (RR 0.70, 95% CI 0.50 to 0.98, MD 3.1% lower), need for mechanical ventilation[72,75,76,79,82] (risk difference [RD] 10.4%, 95% CI 4.3% to 13.8%), duration of mechanical ventilation[71,73,74,79,80] (MD 3.5 days shorter, 95% CI 1.8 to 5.2 days), length of

Table 3: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on direct evidence from observational studies of patients with severe COVID-19

		Absolute effect estimates			
Outcomes	**Relative effects**	**Baseline risk for control group,* %**	**Difference (95% CI), %**	**Quality of evidence**	**Plain language summary**
Mortality	HR 2.30 (95% CI 1.00 to 5.29) Based on data from 331 patients with severe COVID-19 in 2 observational studies[19,23]	10.4	11.9 (0 to 33.7)	Very low (serious imprecision†)	We are very uncertain of the effect of corticosteroids on mortality

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio.
*Baseline risk from a study of the patients with severe COVID-19 without corticosteroids use.[2]
†Observational study started at low quality of evidence. We rated down 1 level owing to serious imprecision (wide CI).

Table 4: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from randomized controlled trials and observational studies of patients admitted to hospital with SARS

		Absolute effect estimates			
Outcomes	**Relative effects**	**Baseline risk for control group**	**Difference (95% CI)**	**Quality of evidence**	**Plain language summary**
Mortality	HR 0.83 (95% CI 0.41 to 1.66) Based on data from 6129 patients with SARS in 2 observational studies[24,25]	10.4%*	−1.7% (−6.0% to 6.3%)	Very low (serious indirectness and serious imprecision†)	We are very uncertain of the effect of corticosteroids on mortality
Median time for SARS-CoV RNA to become undetectable in plasma	Based on data from 16 patients with SARS in 1 RCT[26]	8.0 days‡	MD 4.0 days (2.0 to 6.0)	Very low (serious risk of bias, serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on time for SARS-CoV RNA to become undetectable in plasma

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio, MD = mean difference, RCT = randomized controlled trial, RNA = ribonucleic acid, SARS = severe acute respiratory syndrome, SARS-CoV = SARS-associated coronavirus.
*Baseline risk from a study of patients with severe COVID-19 without corticosteroid use.[2]
†Observational studies start as low quality of evidence. We rated down 1 level owing to serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with SARS) and 1 level owing to serious imprecision (the CI includes both an important benefit and an important harm).
‡Baseline risk from the RCT that reported median time for SARS-CoV RNA to become undetectable in plasma for the no corticosteroids group.[26]
§Randomized controlled trial started at high quality of evidence. We rated down owing to serious risk of bias, serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with SARS) and serious imprecision (because of small sample size).

ICU stay;[72–76,78,79,82] and length of hospital stay[71–76,78,79,81,82,84] (Table 7, Figure 5). Meta-analysis of 8 RCTs[71,72,75,78,79,81,82,84] showed that corticosteroids may increase the rate of serious hyperglycemia (RD 5.7%, 95% CI 0.18% to 15.3%; moderate-quality evidence for CAP, low quality after rating down 1 level for indirectness).

Mortality results suggested a possible subgroup effect of corticosteroids by pneumonia severity (severe pneumonia, RR 0.43, 95% CI 0.26 to 0.73; less severe pneumonia, RR 1.00, 95% CI 0.64 to 1.56; *p* for interaction 0.02). However, the apparent effect is based on differences between rather than within studies, is driven to a considerable extent by a small study[73] that was stopped early for benefit, almost certainly represents a large overestimate of effect, and does not appear with any other outcome. Thus, the subgroup effect has low credibility.

For other adverse events (neuropsychiatric events;[72,81,82,84] superinfection[71–74,78,81,82,84] and gastrointestinal bleeding[71–75,79,80,82]),

Table 5: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from observational studies of patients admitted to hospital with MERS

		Absolute effect estimates			
Outcomes	**Relative effects**	**Baseline risk for control group, %**	**Difference (95% CI), %**	**Quality of evidence**	**Plain language summary**
Mortality	OR 0.75 (95% CI 0.52 to 1.07) Based on data from 290 patients with MERS in 1 observational study[28]	10.4*	−2.4 (−4.7 to 0.6)	Very low (serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on mortality
MERS-CoV RNA clearance	HR 0.35 (95% CI 0.17 to 0.72) Based on data from 189 patients with MERS in 1 observational study[28]	29.8†	−18.2 (−24.0 to −7.3)	Very low (serious indirectness and serious imprecision¶)	We are very uncertain of the effect of corticosteroids on MERS-CoV RNA clearance

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HR = hazard ratio, MERS = Middle East respiratory syndrome, MERS-CoV = Middle East respiratory syndrome coronavirus, OR = odds ratio, RNA = ribonucleic acid.
*Baseline risk from a study of patients with severe COVID-19 without corticosteroid use.[2]
†Baseline risk from the observational study that reported MERS-CoV RNA clearance for no corticosteroids group.[28]
§Observational studies started at low quality of evidence. We rated down 1 level owing to serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with MERS), and 1 level owing to serious imprecision (the CI includes both a trivial and an important effect).
¶Observational studies started at low quality of evidence. We rated down 1 level owing to serious indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients with MERS), and 1 level owing to serious imprecision because of the small sample size.

Table 6: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from observational studies of patients admitted to hospital with influenza

		Absolute effect estimates			
Outcomes	**Relative effects**	**Baseline risk for control group, %**	**Difference (95% CI), %**	**Quality of evidence**	**Plain language summary**
Mortality	OR 1.70 (95% CI 1.31 to 2.21) Based on data from 8530 participants from 11 observational studies[43–45,47,52,55,57–59,61,68]	10.4*	6.1 (2.8 to 10.0)	Very low (serious indirectness‡)	We are very uncertain of the effect of corticosteroids on mortality
Superinfection	OR 2.74 (95% CI 1.51 to 4.95) Based on data from 6114 participants from 7 observational studies[43,44,47,52,55,57,65]	7.2†	10.3 (3.3 to 20.5)	Very low (serious risk of bias and indirectness§)	We are very uncertain of the effect of corticosteroids on superinfections
Mechanical ventilation	OR 5.54 (95% CI 1.83 to 16.80) Based on data from 4364 participants from 4 observational studies[52,57,59,61]	41.8§	38.1 (15.0 to 50.6)	Very low (serious risk of bias and indirectness†)	We are very uncertain of the effect of corticosteroids on need for mechanical ventilation

Note: CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, OR = odds ratio.
*Baseline risk from a study of patients with severe COVID-19 without corticosteroids use.[2]
†Baseline risk comes from the median effect of the control group in the included studies.
‡Observational studies started at low quality of evidence. Additional concern was indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients admitted to hospital with influenza).
§Observational studies started at low quality of evidence. Additional concerns included high risk of indication bias because unadjusted estimates were included, and indirectness (we applied the results to patients with severe COVID-19, but the relative effect was derived from patients admitted to hospital with influenza).

Table 7: GRADE summary of findings: corticosteroids in patients with severe COVID-19, based on indirect evidence from randomized controlled trials of patients admitted to hospital with community-acquired pneumonia

		Absolute effect estimates			
Outcomes	**Relative effects**	**Baseline risk for control group***	**Difference (95% CI)**	**Quality of evidence**	**Plain language summary**
Mortality	RR 0.70 (95% CI 0.50 to 0.98) Based on data from 2034 patients in 13 RCTs[71–83]	10.4%	–3.1% (–0.2% to –5.2%)	Very low (very serious indirectness† and serious inconsistency)	We are very uncertain of the effect of corticosteroids on mortality
Length of ICU stay	Based on data from 1376 patients in 8 RCTs[72–76,78,79,82]	The median length of ICU stay was 8.3 days	MD –1.7 days (–3.4 to 0.1)	Very low (serious inconsistency, very serious indirectness and serious imprecision‡)	We are very uncertain of the effect of corticosteroids on length of ICU stay
Length of hospital stay	Based on data from 1636 patients in 10 RCTs[71–76,78,79,81,82,84]	The median length of hospital stay was 14.3 days	MD –1.8 days (–2.8 to –0.8)	Very low (serious inconsistency, very serious indirectness and serious imprecision§)	We are very uncertain of the effect of corticosteroids on length of hospital stay
Need for mechanical ventilation	RR 0.42 (95% CI 0.23 to 0.76) Based on data from 1017 patients in 5 RCTs[72,75,76,79,82]	18.0%	–10.4% (–13.8% to –4.3%)	Low (very serious indirectness†)	Corticosteroids may reduce need for mechanical ventilation
Duration of mechanical ventilation	Based on data from 199 patients in 5 RCTs[71,73,74,79,80]	The median duration of mechanical ventilation was 11.3 days	MD –3.5 days (–5.2 to –1.8)	Very low (serious risk of bias and very serious indirectness¶)	We are very uncertain of the effect of corticosteroids on duration of mechanical ventilation
Serious hyperglycemia	RR 1.62 (95% CI 1.02 to 2.67) Based on data from 1476 patients in 8 RCTs[71,72,75,78,79,81,82,84]	9.2%	5.7% (0.18% to 15.3%)	Low (serious indirectness and serious imprecision**)	Corticosteroids may increase serious hyperglycemia events
Gastrointestinal bleeding	RR 0.99 (95% CI 0.43 to 2.24) Based on data from 1228 patients in 8 RCTs[71–75,79,80,82]	3.0%	–0.03% (–1.7% to 3.7%)	Low (serious indirectness and serious imprecision**)	Corticosteroids may have little or no impact on gastrointestinal bleeding
Neuropsychiatric events	RR 1.91 (95% CI 0.68 to 5.39) Based on data from 1142 patients from 4 RCTs[72,81,82,84]	1.6%	1.4% (–0.5% to 7%)	Low (serious indirectness and serious imprecision¶)	Corticosteroids may result in a small increase in neuropsychiatric events
Superinfection	RR 1.31 (95% CI 0.69 to 2.50) Based on data from 1500 patients in 8 RCTs[71–74,78,81,82,84]	3.7%	1.1% (–1.1% to 5.5%)	Low (serious indirectness and serious imprecision¶)	Corticosteroids may result in a small or no increase in superinfection events

Note: CAP = community-acquired pneumonia, CI = confidence interval, COVID-19 = coronavirus disease 2019, GRADE = Grading of Recommendations Assessment, Development and Evaluation, ICU = intensive care unit, MD = mean difference, RCT = randomized controlled trial, RR = risk ratio.
*Mortality baseline risk was obtained from patients with COVID-19 and ARDS without corticosteroid treatment.[2] The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events comes from the median effect of the control group in the included RCTs.
†We rated down 2 levels owing to indirectness; the cause of pneumonia across the studies is inconsistent and might not represent the COVID-19 population. We also rated down for inconsistency because of a possible subgroup effect that suggests mortality benefit was restricted to those with severe pneumonia.
‡We rated down 2 levels owing to indirectness; 1 for inconsistency (I^2 = 76%, heterogeneity p value = 0.0001); and 1 for imprecision because the effect estimates are consistent with important benefit and harm.
§We rated down 2 levels owing to indirectness; 1 for inconsistency (I^2 = 47%, heterogeneity p value = 0.006) and 1 for imprecision because the lower CI includes important benefit and important harm.
¶We rated down 1 level owing to risk of bias and 2 levels owing to indirectness. We did not rate down owing to inconsistency; the effect estimates were in the same direction, despite the I^2 54% and the p value of 0.07.
**We rated down by 1 level owing to indirectness, as we do not expect that the COVID-19 population differs as much from other populations in adverse effects as in benefits, and 1 for imprecision because effect estimates are not consistent with benefit or harm.

evidence was moderate quality for small, no, or uncertain harms of corticosteroids in patients with CAP, and low quality after rating down once for indirectness (Table 7).

Interpretation

This series of systematic reviews informed a guideline addressing management of patients with COVID-19.[5] Direct evidence from 1 observational study[8] of 84 patients with COVID-19 and ARDS was consistent with the findings of our systematic review of RCTs of patients without COVID-19 that suggested corticosteroids may reduce mortality in patients with COVID-19 and ARDS by more than 15% and reduce the duration of mechanical ventilation. The evidence suggested corticosteroids may increase the rate of serious hyperglycemia, although not of other potentially worrisome adverse effects. The evidence for these effects is mostly of low quality.

For patients who have severe COVID-19 but are not critically ill, direct evidence from observational studies provided very low-quality evidence of an increase in mortality with corticosteroids. In SARS and MERS, evidence from observational studies raises the possibility of a modest mortality reduction with corticosteroids, but also of a delay in viral clearance. In CAP, RCT evidence also raises the possibility of a mortality reduction with corticosteroids and other benefits including reduction in length of hospital and ICU stay, and need for and duration of mechanical ventilation. Low-quality evidence suggests a likely increase in hyperglycemia and possible small increases in neuropsychiatric events and superinfection, but not in gastrointestinal bleeding. Observational studies in influenza provide discrepant findings, raising the possibility of substantial increases in mortality, superinfection and mechanical ventilation with corticosteroids.

Strengths of this review include a comprehensive search, independent study selection, data abstraction and risk of bias assessment by 2 reviewers and presentation of absolute effects for dichotomous outcomes. We rated the quality of evidence with the GRADE approach, paying close attention to important methodological issues such as differences in the impact of indirectness of evidence on benefit and harm outcomes. We are more skeptical of making inferences regarding benefits in patients with COVID-19 from other patient populations than we are of making inferences on harms. For observational studies, we included, as far as possible, only those with adjusted analyses. Finally, a particular strength is the presentation of a comprehensive assessment of all the indirect evidence, including from ARDS, SARS, MERS, influenza and CAP, together in a single document.

We compared our review with another published systematic review addressing corticosteroid therapy in COVID-19.[85] Apart from COVID-19, SARS and MERS, our review included 3 additional populations: ARDS, CAP and influenza. We updated our search until Apr. 19, including evidence published more recently than the previous systematic review, which searched until Mar. 15.[8,19–23] Third, we included, as far as possible, only cohort and case–control studies with adjusted effect estimates. Finally, we used GRADE to rate the quality of evidence.

For ARDS, our review showed similar results to the 1 other published systematic review[29] that included the latest published studies. For CAP, the results on which we focus are similar to those of other recent reviews[86–89] that showed that corticosteroids may reduce mortality and length of hospital stay, and increase hyperglycemia.

The findings for influenza are consistent with other previous systematic reviews[90–92] that also found increased mortality associated with corticosteroid use. One review[90] focused on patients with influenza pneumonia only, excluding those with mild illness or those in the ICU. The results showed that corticosteroids were associated with higher mortality. In contrast, another review[92] studied severe forms of influenza and reported that among studies with adjusted estimates, results showed no statistically significant difference between the corticosteroid and control groups.

Limitations

The limitations of this study are largely those of the underlying evidence, which is either of low or, for benefits, very low quality for the most part. One could argue that we should have broadened our consideration of indirect evidence. For instance, we could have included *Pneumocystis jiroveci* pneumonia, in which evidence supports corticosteroid use. Our threshold was based on patients with viral pneumonia being included in the population, which is clearly the case for SARS, MERS and influenza, but also true for ARDS and CAP.

Similarly, with respect to harms, consideration of evidence from RCTs of short-term use of corticosteroids in other conditions might have strengthened our findings. We have, however, moderate-quality evidence in patients with ARDS of no important increase in superinfection, and low-quality evidence of an increase in serious hyperglycemia. Low-quality evidence suggests a possible small increase in neuropsychiatric events. For this outcome, evidence from other conditions might have been particularly helpful.

Conclusion

Given the paucity of direct evidence and the limitations of indirect evidence, it is critical for clinicians and researchers to cooperate in conducting high-quality studies, in particular large and rigorous RCTs, to evaluate the effect of corticosteroids in both patients with COVID-19 and ARDS and patients with severe COVID-19 but who are not critically ill. Fortunately, RCTs, including those that address corticosteroid treatment, are ongoing.

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Appendix 1 (as supplied by the authors): Protocol

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Corticosteroids for COVID-19 related acute respiratory distress syndrome: A rapid review protocol

Background

In December 2019, an outbreak of a new strain of coronavirus (Covid-19) was registered. Since then, the infection has affected more than 26 countries worldwide with more than 70 000 confirmed cases [1]. Covid-19 sometimes results in severe pneumonia and severe acute respiratory distress syndrome (ARDS) that proves fatal in approximately 2% of the total population of infected individuals [2]. Although limited information is available regarding ARDS related to Covid-19, it seems that the clinical behavior is indistinguishable from other etiologies related to ARDS. [3]

ARDS is a rapidly progressive, life-threating disease that occurs in critically ill patients. ARDS is characterized by diffuse inflammation of the alveolar-capillary membrane. [4] Currently, healthcare professionals use the Berlin definition (ARDS Task Force 2012) to make the diagnosis by assessing four dimensions: timing of the symptoms (Within 1 week of clinical insult or worsening respiratory symptoms), chest imaging (bilateral opacities, not explained by effusion, collapses or nodules), origin of the edema (not explained by cardiac failure/fluid overload) and oxygenation (Mild; 200 - 300 mmHg PaO2/Fio2, Moderate; 100 – 200 mmHg PaO2/Fio2 and severe; <100 mmHg PaO2/Fio2; plus, PEEP ≥ 5 cmH20). [5 6]

Several therapeutic strategies may improve outcomes of patients diagnosed with ARDS [7-9]: lung protective strategies using lower tidal volumes (PBW 6 – 8 ml/kg); prone mechanical ventilation; higher dose of positive end-expiratory pressure (PEEP); neuromuscular blocking agents; conservative fluid management; and extra-corporeal membrane oxygenation (ECMO). Current ARDS international guidelines recommend most of these strategies [7 9].

The use of corticosteroids in ARDS has proved controversial. Concerns include that most of the trials were conducted in an era when clinicians used higher tidal volumes and lack of a standardized definition for ARDS diagnosis [10 11]. Current guidelines avoid recommending

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

either for or against the corticosteroid use due to the limitations of the current evidence [7 8]. To clarify the issue to inform a recommendation regarding use of steroids in critically ill patients with Covid19, we reviewed the systematic reviews available addressing impact of corticosteroid therapy in ARDS and updated the most recent review with a subsequently published randomized control trial [12].

Objective

To assess the effectiveness and safety of corticosteroids in adults with ARDS.

Methods

PICO Question

- **Population:** Patients with COVID-19 who develop ARDS
- **Intervention:** Any corticosteroid, intravenous or oral, in moderate to high doses (20 mg. equivalent or more of prednisone).
- **Comparisons:** Management without use of steroids.
- **Outcomes:** Mortality, length of ICU stay, length of hospital stay, days of mechanical ventilation and adverse events.

Because we anticipate finding little or no direct evidence for our target population of patients with COVID-19, we will include studies of patients with any etiology of ARDS. We anticipate such studies will provide indirect evidence for our target population.

In order to conduct our rapid review, we will perform two stages; first, we will identify the most recent most methodologically rigourous systematic review (SR); if there are reviews with important complementary information, we will also include them. Second, we will search for recent randomized controlled trials (RCTs) addressing corticosteroids in ARDS to update the chosen review.

Type of studies

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

First stage: We will search for systematic reviews of randomized controlled trials. Second stage: We will perform a time limited search from the date of the included systematic review to February 20th, 2020 to identify newer randomized controlled trials. We will exclude systematic reviews published before 2000.

Type of participants

We will include adults diagnosed with ARDS admitted to an ICU. We will use authors definition of ARDS.

Type of interventions

We will include studies assessing corticosteroids compared to placebo or no therapy. We will exclude studies reporting on corticosteroids for prophylaxis in mild ARDS.

Type of outcome measurement

Primary outcomes: We will include overall mortality, early mortality (as defined by the authors), ICU mortality and hospital mortality.

Secondary outcomes: We will include:

- Length stay (ICU and hospital)
- Days of mechanical ventilation or free days of mechanical ventilation.
- Adverse events:
    - Serious hyperglycemia (as defined by the authors)
    - Hypernatremia (Number of cases with serum sodium above 145 mmol/l)
    - Neuromuscular weakness (as defined by the authors)
    - Gastrointestinal bleeding.
    - Superinfection (defined as an infection occurring after or on top of an earlier infection, especially following treatment with broad-spectrum antibiotics)

Search methods for identification of studies

Electronic searches

First stage: We will identify the SRs of RCT thought a literature search in the following databases: Ovid (MEDLINE), Embase, Cochrane CDSR and Epistemonikos.

Second stage: We will conduct a time limited search from the time-frame of the included systematic review to February 24th. We will search in the following databases: Ovid (MEDLINE), Embase and ClinicalTrials.gov.

Study selection

First stage: Pairs of reviewers will independently screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies. Disagreements will be resolved by discussion or by referring to a third reviewer.

Second stage: Pairs of reviewers will independently screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies.

Data extraction

First stage: We will assess the most recent SRs with the ROBIS checklist [13]. The summary may thus come from a single review using the best methods and the most recent evidence, or from complementary reviews each providing important information.

For summarizing the included systematic review(s), we will extract the number of included patients and studies for each outcome, the characteristics of the patients included, the formulation and doses of steroids administered, magnitude of steroid effects, and any subgroup analyses reported by the authors. If, for a particular included study, the SR of choice does not report specific information that we suspect may in fact have been reported in the primary study, we will review the primary study seeking that information. Such an instance may arise, for example, for adverse event data.

Pairs of reviewers will extract data. Disagreements will be resolved by discussion or, if necessary, by a third reviewer.

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Second stage: We will extract data from identified individual studies by using a standardized temple. The template will include the following:

- Methods: Settings, time-frame.
- Participants: Number of participants in each group and baseline characteristics.
- Intervention/Comparator: Detail description about doses, timing, duration.
- Outcomes: We will collect all of our relevant outcomes reported by the authors.

Risk of bias assessment

First stage: We will use the risk of bias judgments provided by the SR authors.

Second stage: We will use the modified Cochrane tool to assess the risk of bias in randomized trials [14]. Two review authors will independently asses the study risk of bias with disagreements resolved by involving a third reviewer. We will assess the following domains.

- Sequence generation (selection bias);
- Allocation concealment (selection bias);
- Blinding of participants, personnel, and outcome assessors (performance and detection bias);
- Missing data (Attrition bias).

Data synthesis or analysis

We will use the results of the statistical analysis reported in the included review. We will update the review with new information from the new RCTs. We will collect dichotomous data for mortality outcomes and adverse events. We will collect continuous data for the duration of length of ICU stay, length of hospital stay and mechanical ventilation. We will transform median to mean by the equation published by Hozo 2005 [15].

Measure of treatment effect

We will calculate relative risk (RR) and 95% confidence intervals (95% CI) for dichotomous outcomes. We will calculate mean difference (MD) and 95% CI for continuous outcomes.

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We will use random-effects models to pool study data. We will carry out all statistical analyses using Review Manager 5.3.

Assessment of statistical heterogeneity and inconsistency

We will assess inconsistency between studies by visual inspection of forest plots, in particular extent of overlap of confidence intervals (CI), the Q statistic, and the I^2 value.

Subgroup analysis

We will conduct a subgroup analysis based on the information reported in the included systematic review. If the information allows it, we will explore the effect estimates across the different type of interventions, doses, timing and etiologies, also, we will examine to see if the effect differs in those with mild, moderate or severe disease with the a priori hypothesis that larger effects with steroids will be see in those with more severe disease

Assessment of reporting biases

We will use the judgments reported in the included systematic review.

GRADE assessment of the overall quality in the body of evidence by outcome

We will use the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology to rate the quality in the body of evidence for each outcome as high, moderate, low, or very low. The assessment included judgments addressing risk of bias, imprecision, inconsistency, indirectness, and publication bias. A senior methodologist will check all GRADE ratings of the quality in the body of evidence.

Evidence Summary

We will summarize the evidence both narratively and in GRADE evidence profiles.

Timeline

We will finish this systematic review before March 15.

Study selection	February 15 to 21

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Data extraction and risk of bias	February 22 to 29
Statistical analysis and GRADE assessment	March 1 to 7
Interpreting results and writing manuscript	March 8 to 15

Funding

There is no funding for this systematic review.

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Protocol for systematic review on use of corticosteroids in patients with COVID-19, SARS, MERS

Introduction

The worldwide spread of coronavirus disease-2019 (COVID-19) represents a profound threat to human health. Based on data released by the Chinese government on February 13, the number of diagnosed patients in China is 59907, 8204 of whom experienced critically ill and 1368 of whom died – a toll considerably greater than that exacted by the severe acute respiratory syndrome (SARS).

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Clinicians frequently treat COVID-19 patients with corticosteroids. One published paper by Chinese researchers reported that, of 138 infected patients, 44.9% received corticosteroids to treat this disease.(1) The use of corticosteroids is controversial: two commentaries recently published in the Lancet expressed opposite views.(2, 3) Systematic summaries of the available evidence are needed to inform the discussion.

Therefore, we will conduct a systematic review to summarize the relevant evidence. Because we anticipate a paucity of direct evidence addressing the use of corticosteroids in COVID-19, we will also summarize available evidence addressing steroids in the treatment of SARS and middle east respiratory syndrome (MERS).

Methods

PICO questions

1. The use of corticosteroids in patients infected with SARS

Population: Patients infected with SARS requiring hospitalization

Intervention: Any corticosteroid, intravenous or oral, in moderate to high doses (20 mg. equivalent or more of prednisone)

Comparisons: Management without use of steroids

Outcomes: Mortality, length of ICU stay, length of hospital stay, days of mechanical ventilation and any other patient-important outcomes that included studies report

2. The use of corticosteroids in severe COVID-19 patients

Population: Severe COVID-19 patients

Intervention: Any corticosteroid, intravenous or oral, in moderate to high doses (20 mg. equivalent or more of prednisone)

Comparisons: Management without use of steroids

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Outcomes: Mortality, length of ICU stay, length of hospital stay, days of mechanical ventilation and any other patient-important outcomes that included studies report

3. The use of corticosteroids in patients infected with MERS

Population: Patients infected with MERS requiring hospitalization

Intervention: Any corticosteroid, intravenous or oral, in moderate to high doses (20 mg. equivalent or more of prednisone)

Comparisons: Management without use of steroids

Outcomes: Mortality, length of ICU stay, length of hospital stay, days of mechanical ventilation and any other patient-important outcomes that included studies report

Search strategy

We will develop our literature search in collaboration with a research information specialist. The search will include Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and a PubMed search for studies not yet indexed or not found in Medline. Since COVID-19 outbreaks started in China, the Chinese databases (CNKI, WanFang, and CQVIP) will be searched. We will review reference lists of all included studies and relevant systematic reviews for additional references. Trials registration websites and conference proceedings will not be searched because of urgency considerations in this rapid review. We will search medRxiv previews. Their articles are not peer-reviewed.

We will search the original eligible studies on the use of corticosteroids in patients infected with SARS, MERS, and COVID-19. This search strategy will contain two parts: corticosteroids and diseases (SARS, MERS, and COVID-19).

Eligibility criteria

For SARS, MERS, and COVID-19, we will include randomised controlled trials (RCTs) and observational studies that compared the use of corticosteroids at a dose equivalent of 20 mg. of prednisone daily or greater to no steroid use and reported on at least one of our outcomes

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of interest. We will exclude case series in which all patients, or no patients, received steroids. The primary outcome is mortality, secondary outcomes are length of intensive care unit (ICU) stay, length of hospital stay, duration of mechanical ventilation, need for mechanical ventilation, viral ribonucleic acid (RNA) clearance, viral shedding time, serious hyperglycemia, superinfection, neuromuscular weakness, gastrointestinal bleeding.

Study selection

Pairs of reviewers will independently screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies. Disagreements will be resolved by discussion or by referring to a third reviewer.

Data extraction

Pairs of reviewers will extract data. We will abstract surname of the first author, year of publication, country, region and hospital, population, interventions, and outcomes. For observational studies, we also abstracted covariates adjusted for in the analysis. Disagreements will be resolved by discussion or, if necessary, by a third reviewer.

Risk of bias assessment

Two reviewers will independently assess the risk of bias for each randomized controlled trial using a modified Cochrane Collaboration tool that includes sequence generation, allocation sequence concealment, blinding, and missing outcome data. Each criterion will be judged as definitely or probably low risk of bias, or probably or definitely high risk of bias.(4) Two reviewers will independently assess the risk of bias for each observational study using a modified version of the Newcastle-Ottawa Scale.(5, 6)

Data synthesis or analysis

If the evidence permits, we will conduct meta-analysis for each of SARS, MERS and COVID-19. Since SARS, MERS and COVID-19 are all coronaviruses, we will consider conduct a meta-analysis that combines data form each of the three conditions. We will conduct subgroup analysis or meta-regression analysis based on critically ill or not critically

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

ill patients (critical illness defined by admission to an intensive care unit prior to start of steroids, hypothesis being that steroids will have a greater impact on sicker patients), the dose of steroid given (tentatively up to 40 mg. of prednisone equivalent or greater than 40 mg., the hypothesis that larger doses will have larger effects), and the duration of steroid use (tentatively up to one week or greater than one week, the hypothesis being that longer duration will have larger effects) .

Subgroup Analysis

For each systematic review we will examine to see if the effect differs in those with mild, moderate or severe disease with the a priori hypothesis that larger effects with steroids will be see in those with more severe disease. Categorization may depend on what is specified in the study reports.

Quality of evidence

We will use the GRADE approach to assess the quality of evidence. Randomised controlled trials start as high quality and observational studies start as low quality.(7)

Evidence Summary

We will summarize the evidence both narratively and in GRADE evidence profiles.

Timeline

We will finish this systematic review before March 15.

Study selection	February 15 to 21
Data extraction and risk of bias	February 22 to 29
Statistical analysis and GRADE assessment	March 1 to 7
Interpreting results and writing manuscript	March 8 to 15

Funding

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

There is no funding for this systematic review.

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Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Background

Influenza virus infections are responsible for a large number of hospitalizations and deaths during seasonal peaks and pandemics. Influenza A H1N1 and H7N9 have been implicated in causing widespread outbreaks with serious morbidity. In patients infected with H1N1, the rate of pneumonia has been as high as 40%, 25% of patients were admitted into the intensive care unit (ICU), and 36% of those in the ICU developed Acute Respiratory Distress Syndrome (ARDS) (1). In one series, among patients infected with H7N9 and reporting with symptoms, 97% presented with rapidly progressive pneumonia and the death rate in these patients was as high as 46% (2).

There is evidence that supports the role of corticosteroids in Community Acquired Pneumonia (3) and sepsis (4). The role that corticosteroids play in inhibiting inflammation, via mechanisms such as reducing the overproduction of proinflammatory cytokines/chemokines and an excess of activated lymphocytes, has formed the rationale for testing steroids in respiratory infections and sepsis.

Patients hospitalized with severe forms of influenza are often prescribed corticosteroids, despite uncertainty regarding their potential benefits or harms (5). Some case series have reported improvement in outcomes with corticosteroids in influenza patients (6), while other cohort studies report the opposite (7,8). A recent systematic review reported increased mortality with corticosteroids; however, the evidence was of low quality (9).

In light of these limitations of the current evidence, we will search for and assess the systematic reviews available on the impact of corticosteroid therapy in influenza and update the most recent methodologically rigorous review with subsequently published primary studies.

Objective

To assess the effectiveness and safety of corticosteroids in patients with influenza.

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Methods

PICO Question

- **Population:** Patients with influenza requiring hospitalization.
- **Intervention:** Any corticosteroid, intravenous or oral, in moderate to high doses, for any duration
- **Comparisons:** Management without use of corticosteroids.
- **Outcomes:** Mortality, rate of ICU admission, length of ICU stay, length of hospital stay, days on mechanical ventilation and adverse events (including hospital acquired infection)

We will conduct the rapid review in two steps. First, we will identify the most recent most methodologically rigorous systematic review (SR) addressing the question on corticosteroids in influenza. Second, we will search for recent studies and update the chosen review.

Type of studies

First stage: We will search for systematic reviews of randomized controlled trials (RCTs). Second stage: We will perform a time limited search from the time frame of the included systematic review to March 7th, 2020 to identify newer randomized controlled trials. We will exclude systematic reviews published before 2010.

We intend to include RCTs in the systematic review. However, if enough RCTs are not available to review (fewer than 100 patients in RCTs), we will include quasi-experimental and observational studies.

Type of participants

We will include patients of influenza requiring hospitalization.

Type of interventions

We will include studies assessing corticosteroids compared to placebo or no therapy.

Type of outcomes:

Primary outcome: Overall mortality

Secondary outcomes:

- Rate of ICU admission,
- Hospital readmission rate at 30 days post discharge,
- Number and nature of adverse events secondary to corticosteroid use, such as incidence of gastrointestinal bleeding, hospital-acquired infections, and metabolic complications (e.g. hyperglycaemia, hypernatraemia), neuromuscular weaknesss
- Proportion of participants requiring mechanical ventilation
- Length of stay in hospital

Search methods for identification of studies

Electronic searches

First stage: We will identify the SRs of RCTs through a literature search in the following databases: Medline, Embase, Cochrane CDSR and Epistemonikos.

Second stage: We will conduct a time limited search from the time-frame of the included systematic review to March 7th. We will search in the following databases: Medline (Ovid), Cochrane CENTRAL, Embase, CINHAL and Web of Science.

Study selection

First stage: Pairs of reviewers will independently screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies. Disagreements will be resolved by discussion or by referring to a third reviewer.

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Second stage: Pairs of reviewers will screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies.

Data extraction

First stage: We will assess the most recent SRs with the ROBIS checklist (10). The summary may thus come from a single review using the best methods and the most recent evidence, or from complementary reviews each providing important information.

For summarizing the included systematic review(s), we will extract the number of included patients and studies for each outcome, the characteristics of the patients included, the formulation and doses of steroids administered, magnitude of steroid effects, and any subgroup analyses reported by the authors. If, for a particular included study, the SR of choice does not report specific information that we suspect may in fact have been reported in the primary study, we will review the primary study seeking that information. Such an instance may arise, for example, for adverse event data.

Pairs of reviewers will extract data. Disagreements will be resolved by discussion or, if necessary, by a third reviewer.

Second stage: We will extract data from identified individual studies by using a standardized template. The template will include the following:

- Methods: Study design
- Participants: Number of participants in each group, type of influenza
- Intervention/Comparator: Type of corticosteroid, initial dose
- Outcomes: We will collect all of our relevant outcomes reported by the authors.

Risk of bias assessment

First stage: We will use the risk of bias judgments provided by the SR authors.

Second stage: We will use the modified Cochrane tool to assess the risk of bias in randomized trials (11) and the revised New Castle Ottawa scale for Cohort studies (12). Two review

authors will independently assess the study risk of bias with disagreements resolved by involving a third reviewer. We will assess the following domains.

- Sequence generation (selection bias),
- Allocation concealment (selection bias),
- Baseline prognostic balance,
- Blinding of participants, personnel, and outcome assessors (performance and detection bias),
- Incomplete outcome data (Attrition bias)

Data synthesis or analysis

We will use the results of the statistical analysis reported in the included review. We will update the review with new information from the new RCTs/ cohort studies. We will only include Cohort studies in the systematic review only if there are fewer than 100 patients in RCTs. We will collect dichotomous data for mortality outcomes, ICU admissions, hospital readmission and adverse events. We will collect continuous data for the duration of length of ICU stay, length of hospital stay and days of mechanical ventilation.

Measure of treatment effect

We will calculate pooled relative risk (RR) and 95% confidence intervals (95% CI) for dichotomous outcomes. We will calculate mean difference (MD) and 95% CI for continuous outcomes. We will use random-effects models to pool study data. We will carry out all statistical analyses using Review Manager 5.3

Assessment of statistical heterogeneity

We will assess heterogeneity in the meta-analyses by visual inspection of the forest plot and by the I^2 statistic.

Investigation of heterogeneity

We will attempt to explain heterogeneity by conducting subgroup analyses exploring

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

the following potential effect modifiers, if reported data allows it:

- Daily corticosteroid dose (low versus high, with postulated greater effects in higher doses)
- Timing of corticosteroid use (early versus late with postulated larger effects in earlier)
- Duration of corticosteroid course (shorter versus longer course with postulated larger effects in longer)
- Route of administration (intravenous versus oral with postulated larger effects in intravenous)

Assessment of reporting biases

We will report the assessment of publication bias in the recent systematic review. We will assess publication bias by funnel plot after including any new studies.

GRADE assessment of the overall quality in the body of evidence by outcome

We will use the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology to rate the quality in the body of evidence for each outcome as high, moderate, low, or very low (13). The assessment included judgments addressing risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Evidence Summary

We will summarize the evidence both narratively and in GRADE evidence profiles.

Timeline

We will finish this systematic review before March 21st.

Study selection	March 7th to 11th
Data extraction and risk of bias	March 12th to 15th
Statistical analysis and GRADE assessment	March 16th to 17th

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Interpreting results and writing manuscript	March 18th to 21st

Funding

There is no funding for this systematic review.

References:

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Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

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11. GH Guyatt JB. Modification of Cochrane Tool to assess risk of bias in randomized trials 2015. Available from: https://www.evidencepartners.com/resources/methodological-resources/.
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Corticosteroids for COVID-19 related pneumonia: A rapid review protocol

Background

In December 2019, an outbreak of a new strain of coronavirus (Covid-19) was register and since then, the infection has affected more than 26 countries worldwide with more than 70 000 confirmed cases (1). Covid-19 is a RNA virus belonging to the Coronaviridae family; coronavirus infections is commonly manifested as a mild respiratory disease, however, in the past two decades' other pandemics related to similar virus have manifested with severe community acquired pneumonia (CAP) cases, with the following mortality rates, as MERS-COV 37% and SARS-COV with 10% (2).

In February 2020, two articles were published describing the clinical features for patients with Covid-19 related pneumonia. Huang et al (2). reported 41 hospitalized patients; median age range from 41 to 58 years, men were most affected (73%) and less than half had an underlying disease (Diabetes 20%; Hypertension 15%; Cardiovascular disease 15%). All the patients were classified with CAP with abnormal findings in their chest CT scan. Antimicrobial therapy was based on broad spectrum antibiotics and antiviral (oseltamivir).

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Corticosteroid therapy (40 – 120 mg methylprednisolone) was given if patients presented severe pneumonia (nine patients). The mortality rate was 15% (six patients). Wang et al (3). reported 138 hospitalized patients. Median age range from 42 to 68 years old, men were most affected (54.3%) and less than half had an underlying disease (Hypertension 31.2%; Cardiovascular disease 14.5%; Diabetes 10%). Most of the cases were suspected to by hospital-associated transmission (29%). Antimicrobial therapy was based on antibacterial therapy – moxifloxacin, ceftriaxone, azithromycin – (64.4%, 24.6%, 18.1%) and antiviral therapy – oseltamivir- (89.9%). Corticosteroid therapy was given to 44.9%. The mortality rate was 4.3% (six patients).

Current guidelines do not recommend the routine use of corticosteroids in CAP patients due to the uncertainty of the current evidence (4). However, evidence suggest that patients with severe CAP might benefit from adjunctive glucocorticoids, decision that needs to be consider case-by-case (5-7). To clarify the issue to inform a recommendation regarding use of steroids with patients with Covid19 pneumonia, we reviewed the systematic reviews available addressing impact of corticosteroid therapy in CAP and updated the most recent review with subsequent randomized control trials.

Objective

To assess the effectiveness and safety of corticosteroids in adults with CAP.

Methods

PICO Question

- **Population:** Patients with COVID-19 who develop pneumonia.
- **Intervention:** Any corticosteroid, intravenous or oral, in moderate to high doses (20 mg. equivalent or more of prednisone).
- **Comparisons:** Management without use of steroids.
- **Outcomes:** Mortality, length of ICU stay, length of hospital stay, days of mechanical ventilation and adverse events.

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Because we anticipate finding little or no direct evidence for our target population of patients with COVID-19, we will include studies of patients with any etiology of CAP. We anticipate such studies will provide indirect evidence for our target population.

In order to conduct our rapid review, we will perform two stages; first, we will identify the most recent most methodologically rigourous systematic review (SR); if there are reviews with important complementary information, we will also include them. Second, we will search for recent randomized controlled trials (RCTs) addressing corticosteroids in CAP to update the chosen review.

Type of studies

First stage: We will search for systematic reviews of randomized controlled trials. Second stage: We will perform a time limited search from the date of the included systematic review to February 29th,

Type of participants

We will include adults diagnosed hospitalized with CAP. We will use authors definition of CAP.

Type of interventions

We will include studies assessing corticosteroids compared to placebo or no therapy.

Type of outcome measurement

Primary outcomes: We will include overall mortality, early mortality (as defined by the authors), ICU mortality and hospital mortality.

Secondary outcomes: We will include:

- Length of stay (ICU and Hospital)
- Mechanical ventilation (Need for and days)
- Adverse events
    - Serious hyperglycemia (as defined by the authors)

- Hypernatremia (Number of cases with serum sodium above 145 mmol/l)
- Duration of viral shedding.
- Neuromuscular weakness (as defined by the authors)
- Gastrointestinal bleeding
- Neuropsychiatric events.
- Superinfection (defined as an infection occurring after or on top of an earlier infection, especially following treatment with broad-spectrum antibiotics)

Search methods for identification of studies

Electronic searches

First stage: We will identify the SRs of RCT thought a literature search in the following databases: Ovid (MEDLINE), Embase, Cochrane CDSR and Epistemonikos.

Second stage: We will conduct a time limited search from the time-frame of the included systematic review to February 29th. We will search in the following databases: Ovid (MEDLINE), Embase and clinicaltrials.gov.

Study selection

First stage: Pairs of reviewers will independently screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies. Disagreements will be resolved by discussion or by referring to a third reviewer.

Second stage: Pairs of reviewers will independently screen titles and abstracts, and review the full texts of potential eligible studies to determine the final eligible studies.

Data extraction

First stage: We will assess the SRs with the ROBIS checklist (8). The summary may thus come from a single review using the best methods and the most recent evidence, or from complementary reviews each providing important information.

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

For summarizing the included systematic review(s), we will extract the number of included patients and studies for each outcome, the characteristics of the patients included, the formulation and doses of steroids administered, magnitude of steroid effects, and any subgroup analyses reported by the authors. If, for a particular included study, the SR of choice does not report specific information that we suspect may in fact have been reported in the primary study, we will review the primary study seeking that information. Such an instance may arise, for example, for adverse event data.

Pairs of reviewers will extract data. Disagreements will be resolved by discussion or, if necessary, by a third reviewer.

Second stage: We will extract data from identified individual studies by using a standardized temple. The template will include the following:

- Methods: Settings, time-frame.
- Participants: Number of participants in each group and baseline characteristics.
- Intervention/Comparator: Detail description about doses, timing, duration.
- Outcomes: We will collect all of our relevant outcomes reported by the authors.

Risk of bias assessment

First stage: We will use the risk of bias judgments provided by the SR authors.

Second stage: We will use the modified Cochrane tool to assess the risk of bias in randomized trials (9). Two review authors will independently asses the study risk of bias with disagreements resolved by involving a third reviewer. We will assess the following domains.

- Sequence generation (selection bias);
- Allocation concealment (selection bias);
- Blinding of participants, personnel, and outcome assessors (performance and detection bias);
- Missing data (Attrition bias).

Data synthesis or analysis

We will use the results of the statistical analysis reported in the included review. We will update the review with new information from the new RCTs. We will collect dichotomous data for mortality outcomes and adverse events. We will collect continuous data for the duration of length of ICU stay, length of hospital stay and mechanical ventilation.

Measure of treatment effect

We will calculate relative risk (RR) and 95% confidence intervals (95% CI) for dichotomous outcomes. We will calculate mean difference (MD) and 95% CI for continuous outcomes. We will use random-effects models to pool study data. We will carry out all statistical analyses using Review Manager 5.3.

Assessment of statistical heterogeneity and inconsistency

We will assess inconsistency between studies by visual inspection of forest plots, in particular extent of overlap of confidence intervals (CI), the Q statistic, and the I^2 value.

Subgroup analysis

We will conduct a subgroup analysis based on the information reported in the included systematic review. If the information allows it, we will explore the effect estimates across the different type of interventions, doses and timing, also, we will examine to see if the effect differs in those with mild or severe disease with the a priori hypothesis that larger effects with steroids will be see in those with more severe disease

Assessment of reporting biases

We will use the judgments reported in the included systematic review.

GRADE assessment of the overall quality in the body of evidence by outcome

We will use the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) methodology to rate the quality in the body of evidence for each outcome as high, moderate, low, or very low. The assessment included judgments addressing risk of bias, imprecision, inconsistency, indirectness, and publication bias. A senior methodologist will check all GRADE ratings of the quality in the body of evidence.

Evidence Summary

We will summarize the evidence both narratively and in GRADE evidence profiles.

Timeline

We will finish this systematic review before March 15.

Study selection	March 1 to 5
Data extraction and risk of bias	March 5 to 9
Statistical analysis and GRADE assessment	March 9 to 13
Interpreting results and writing manuscript	March 13 to 15

Funding

There is no funding for this systematic review.

References:

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. The Lancet Infectious diseases. 2020.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
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9. GH Guyatt JB. Modification of Cochrane Tool to assess risk of bias in randomized trials 2015. Available from: https://www.evidencepartners.com/resources/methodological-resources/.

Appendix 2 (as supplied by the authors): Search strategy

1. ARDS

1.1 Search strategy for systematic reviews

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Adrenal Cortex Hormones/ (391670)

2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (556784)

3 1 or 2 (719668)

4 Respiratory Distress Syndrome, Adult/ (18884)

5 Acute Lung Injury/ (5971)

6 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (38224)

7 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (14961)

8 or/4-7 (47700)

9 3 and 8 (3349)

10 systematic review.mp. or "Systematic Review"/ (169706)

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

11 MEDLINE.tw. (113047)

12 meta-analysis.pt. (110665)

13 intervention$.ti. (143782)

14 or/10-13 (403906)

15 9 and 14 (103)

Database: Embase <1974 to 2020 February 14>

Search Strategy:

1 exp corticosteroid/ (902689)

2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (912650)

3 1 or 2 (1232593)

4 adult respiratory distress syndrome/ (34967)

5 respiratory distress syndrome/ (13658)

6 exp acute lung injury/ (14541)

7 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. (70101)

8 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. (24488)

9 or/4-8 (94334)

10 3 and 9 (13577)

11 MEDLINE.tw. (140038)

12 systematic review.mp. (300580)

13 exp meta analysis/ (181123)

14 intervention$.ti. (192248)

15 or/11-14 (605606)

16 10 and 15 (498)

Cochrane Library CDSR

Date Run: 19/02/2020 05:00:38

ID Search Hits

#1 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14145

#2 steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison* 64053

#3 #1 or #2 66038

#4 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees 1238

#5 MeSH descriptor: [Acute Lung Injury] explode all trees 396

#6 (acute or adult) and (respiratory near distress) 3988

#7 (acute near lung near injur*) or (shock near lung) 1334

#8 #4 or #5 or #6 or #7 4576

#9 #3 and #8 in Cochrane Reviews 160

Epistemonikos

https://www.epistemonikos.org/en/matrixes/579ac76cd8307f16de30786a

1.2 Search strategy for RCTs

Database: Ovid MEDLINE(R) <1996 to February 25, 2020>

Search Strategy:

1 exp Respiratory Distress Syndrome, Adult/ or Respiratory Distress Syndrome.mp. (41863)

2 (((acute or adult) and (respiratory adj1 distress)) or ards).mp. (106715)

3 exp Acute Lung Injury/ (6030)

4 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. (39860)

5 1 or 2 or 3 or 4 (141686)

6 ((randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or clinical trials as topic.sh. or trial.ti.) not (exp animals/ not humans.sh.) (1395666)

7 5 and 6 (4909)

8 corticosteroid*.mp. (335634)

9 7 and 8 (315)

10 2019 to February 25, 2020 (25)

Database: Embase <Inception to March 5th, 2020>

Search Strategy:

1. 'adult respiratory distress syndrome'/exp OR 'adult respiratory distress syndrome'
2. adult AND respiratory AND distress AND syndrome:ti,ab
3. acute AND respiratory AND distress AND syndrome:ti,ab
4. ards:ti,ab
5. #1 OR #2 OR #3 OR #4
6. 'steroid'/exp
7. steroid*:ti,ab
8. 'corticosteroid'/exp
9. #6 OR #7 OR #8
10. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
11. #5 AND #9 AND #10 (219)
12. 2018 to March 5, 2020 (27)

Clinicaltrials.gov <Inception to March 5th, 2020>

(Corticosteroids OR steroids) AND Acute Distress Respiratory Syndrome (17)

2. COVID-19, SARS, and MERS

1) search up to March 20, 2020

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/ (11361)

2 exp Coronavirus Infections/ (9639)

3 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word,

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23815)

4 or/1-3 (26162)

5 exp Adrenal Cortex Hormones/ (392727)

6 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (558465)

7 5 or 6 (721635)

8 4 and 7 (485)

Database: Embase <1974 to 2020 March 19>

Search Strategy:

1 exp coronavirinae/ (10978)

2 exp Coronavirus infection/ (11075)

3 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (28593)

4 or/1-3 (32832)

5 exp corticosteroid/ (907250)

6 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (917769)

7 5 or 6 (1239170)

8 4 and 7 (1220)

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Cochrane Library

Date Run: 20/03/2020 19:41:49

ID Search Hits

#1 MeSH descriptor: [Coronavirus] explode all trees 11

#2 MeSH descriptor: [Coronavirus Infections] explode all trees 12

#3 (coronavir* or coronovir* or SARS or MERS or "MERS-COV" or "SARS-COV" or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19"):ti,ab,kw (Word variations have been searched) 1235

#4 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14100

#5 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*):ti,ab,kw (Word variations have been searched) 60429

#6 #4 or #5 62421

#7 #1 or #2 or #3 1235

#8 #6 and #7 in Trials 136

PubMed

Search (((((((coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19))) AND ((steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*)))) AND ((((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)))))) Sort by: PublicationDate 39

Chinese Databases (CNKI, WanFang and CQVIP)

156

medRxiv search March 20, 2020

https://www.medrxiv.org/search/coronavir%252A%252Bor%252Bcoronovir%252A%252Bor%252BSARS%252Bor%252BMERS%252Bor%252BMERS-COV%252Bor%252BSARS-COV%252Bor%252BSARS-COV-2%252B%252Bor%252BCOV%252Bor%252BNCOV%252Bor%252B2019nCOV%

252Bor%252B2019-nCOV%252Bor%252BCOVID%20jcode%3Amedrxiv%20numresults%3A75%20sort%3Arelevance-rank%20format_result%3Astandard?page=1

results= 507

2) search from March, 2020 to April 19, 2020

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Coronavirus/ (12243)

2 exp Coronavirus Infections/ (10626)

3 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (28455)

4 or/1-3 (30798)

5 exp Adrenal Cortex Hormones/ (393430)

6 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (559983)

7 5 or 6 (723346)

8 4 and 7 (554)

9 (coronavir* or coronovir* or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword

heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (20970)

10 1 or 2 or 9 (25514)

11 7 and 10 (470)

12 limit 11 to ed=20200315-20200419 (15)

Database: Embase <1974 to 2020 April 17>

Search Strategy:

1 exp coronavirinae/ (12615)

2 exp Coronavirus infection/ (11918)

3 (coronavir* or coronovir* or SARS or MERS or MERS-COV or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (31767)

4 or/1-3 (36029)

5 (coronavir* or coronovir* or SARS-COV or SARS-COV-2 or COV or NCOV or 2019nCOV or 2019-nCOV or COVID-19).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (24150)

6 exp corticosteroid/ (911020)

7 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. (921603)

8 6 or 7 (1244325)

9 1 or 2 or 5 (30677)

10 8 and 9 (1183)

11 limit 10 to em=202008-202052 (107)

Cochrane Library

Search Strategy:

ID Search Hits

#1 MeSH descriptor: [Coronavirus] explode all trees 11

#2 MeSH descriptor: [Coronavirus Infections] explode all trees 38

#3 ((coronavir* or coronovir* or SARS or MERS or "MERS-COV" or "SARS-COV" or "SARS-COV-2" or COV or NCOV or "2019nCOV" or "2019-nCOV" or "COVID-19")):ti,ab,kw (Word variations have been searched) 1286

#4 #1 or #2 or #3 1286

#5 (coronavir* or coronovir* or "SARS-COV" or "SARS-COV-2" or COV or NCOV or 2019nCOV or "2019-nCOV" or "COVID-19"):ti,ab,kw (Word variations have been searched) 223

#6 #1 or #2 or #4 1286

#7 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14135

#8 steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison* 62705

#9 #7 or #8 64682

#10 #6 and #9 in Trials 138

#11 #10 with Cochrane Library publication date in The last 3 months 8

Chinese Databases

CNKI, WanFang, CQVIP (108)

ChinaXiv (4)

medRxiv

https://connect.medrxiv.org/relate/content/181?page=1

n=2272

3. Influenza

3.1 Search strategy for systematic reviews

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 Influenza, Human/ (48134)

2 exp Influenzavirus A/ (43096)

3 exp Influenzavirus B/ (4199)

4 (influenza* or flu).tw. (120758)

5 (h1n1 or h5n1 or h3n2).tw. (24960)

6 or/1-5 (128402)

7 exp Adrenal Cortex Hormones/ (392230)

8 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (557136)

9 7 or 8 (720173)

10 systematic review.mp. or "Systematic Review"/ (169979)

11 MEDLINE.tw. (113116)

12 meta-analysis.pt. (111566)

13 intervention$.ti. (143893)

14 or/10-13 (404471)

15 6 and 9 and 14 (50)

Database: Embase <1974 to 2020 March 05>

Search Strategy:

1 exp influenza/ (83541)

2 exp Influenza virus A/ (11786)

3 exp influenza b virus/ (1300)

4 (influenza* or flu).tw. (139529)

5 (h1n1 or h5n1 or h3n2).tw. (30744)

6 or/1-5 (159825)

7 exp corticosteroid/ (905900)

8 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, heading word, drug trade

name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (916295)

9 7 or 8 (1237250)

10 MEDLINE.tw. (140913)

11 systematic review.mp. (303491)

12 exp meta analysis/ (182677)

13 intervention$.ti. (193520)

14 or/10-13 (610158)

15 6 and 9 (8235)

16 14 and 15 (294)

Cochrane

Date Run: 07/03/2020 02:23:00

ID Search Hits

#1 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14102

#2 MeSH descriptor: [Hydrocortisone] explode all trees 5872

#3 MeSH descriptor: [Cortisone] explode all trees 143

#4 MeSH descriptor: [Steroids] explode all trees 57349

#5 corticosteroid* or steroid* or cortison* or hydrocortison* 56761

#6 methylprednisolon* or (methyl next prednisolon*) or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid* 26332

#7 #1 or #2 or #3 or #4 or #5 or #6 108317

#8 MeSH descriptor: [Influenza, Human] explode all trees 2595

#9 MeSH descriptor: [Influenzavirus B] explode all trees 274

#10 MeSH descriptor: [Influenzavirus A] explode all trees 840

#11 influenza* or flu 11390

#12 h1n1 or h5n1 or h3n2 1787

#13 #8 or #9 or #10 or #11 or #12 11402

#14 #7 and #13 in Cochrane Reviews 172

Epistemonikos

https://www.epistemonikos.org/advanced_search?q=influenza%20steroids&protocol=no&classification=systematic-review

3.2 Search strategy for primary studies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 Influenza, Human/ (48151)

2 exp influenzavirus a/ or exp influenzavirus b/ (44047)

3 (influenza* or flu).tw. (120977)

4 (h1n1 or h5n1 or h3n2).tw. (25017)

5 or/1-4 (128627)

6 exp Adrenal Cortex Hormones/ (392289)

7 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (557603)

8 6 or 7 (720650)

9 5 and 8 (2090)

10 limit 9 to yr="2018 -Current" (240)

Database: Embase <1974 to 2020 March 09>

Search Strategy:

1 exp influenza/ (83575)

2 exp influenzavirus a/ (11794)

3 exp influenzavirus b/ (1313)

4 (h1n1 or h5n1 or h3n2).tw. (30740)

5 (influenza* or flu).tw. (139504)

6 or/1-5 (159828)

7 exp corticosteroid/ (906248)

8 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. (916575)

9 7 or 8 (1237659)

10 6 and 9 (8239)

11 limit 10 to yr="2018 -Current" (1120)

Central

Date Run: 10/03/2020 19:16:35

ID Search Hits

#1 Adrenal Cortex Hormones 2377

#2 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 14102

#3 MeSH descriptor: [Hydrocortisone] explode all trees 5872

#4 MeSH descriptor: [Cortisone] explode all trees 143

#5 MeSH descriptor: [Steroids] explode all trees 57349

#6 corticosteroid* or steroid* or cortison* or hydrocortison* 56764

#7 methylprednisolon* or (methyl next prednisolon*) or betamethason* or dexamethason* or glucocorticoid* or fludrocortison* or mineralocorticoid* 26333

#8 #1 or #2 or #3 or #4 or #5 or #6 98512

#9 MeSH descriptor: [Influenza, Human] explode all trees 2595

#10 MeSH descriptor: [Influenzavirus B] explode all trees 274

#11 MeSH descriptor: [Influenzavirus A] explode all trees 840

#12 influenza* or flu 11391

#13 h1n1 or h5n1 or h3n2 1787

#14 #9 or #10 or #11 or #12 or #13 11403

#15 #8 and #14 with Cochrane Library publication date Between Jan 2018 and Dec 2020, in Trials 174

PubMed

Search ((((flu or influenza))) AND ((corticosteroid* or steroid* or cortison* or hydrocortison* or methylprednisolon* or betamethason* or dexamethason* or

glucocorticoid* or fludrocortison* or mineralocorticoid*))) AND (((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint))) Sort by: PublicationDate 183

4. CAP

4.1 Search strategy for systematic reviews

Database: Ovid MEDLINE(R) <1996 to February 25, 2020>

Search Strategy:

1. exp Pneumonia/ (90140)
2. meta analysis[Publication Type] (533416)
3. corticosteroid*.tw,nm. (334604)
4. 6 and 7 and 10 (56 studies)

Database: Embase <1996 to February 29, 2020>

Search Strategy:

1. 'pneumonia'/exp OR 'pneumonia' (314,788)
2. 'corticosteroid'/exp OR 'corticosteroid' (990,900)
3. 'meta analysis' (271,175)
4. #1 AND #2 AND #3 (681 studies)

Database: Cochrane CDSR <inception to March 5th>

Search strategy:

"community acquired pneumonia" in All Text AND "corticosteroid" in All Text - (Word variations have been searched) (13 studies)

Database: Epistemonikos < inception to March 5th>

Search strategy

(title:((title:(Pneumonia) OR abstract:(Pneumonia)) AND corticosteroid) OR abstract:((title:(Pneumonia) OR abstract:(Pneumonia)) AND corticosteroid AND Systematic review)) (63 studies)

4.2 Search strategy for RCTs

Database: Ovid MEDLINE <1996 to February 29, 2020>

Search Strategy:

1. exp Pneumonia/ (90135)
2. pneumon*.tw. (469756)
3. bronchopneumon*.tw. (9843)
4. pleuropneumon*.tw. (4341)
5. CAP.tw. (136325)
6. HAP.tw. (10024)
7. Respiratory Distress Syndrome, Adult/ (18933)
8. adult respiratory distress syndrome.tw. (13472)
9. acute respiratory distress syndrome.tw. (42083)
10. ARDS.tw. (33922)
11. or/1-10 (689340)
12. exp Steroids/ (847223)
13. steroid*.tw,nm. (695213)
14. exp Adrenal Cortex Hormones/ (392087)
15. adrenal cortex hormone*.tw,nm. (64420)
16. corticosteroid*.tw,nm. (334508)
17. corticoid*.tw,nm. (11648)
18. glucocorticoid*.tw,nm. (205891)
19. glucocorticosteroid*.tw,nm. (9732)
20. pregnenedione*.tw,nm. (2192)
21. pregnenolone*.tw,nm. (11146)
22. hydrocortisone.tw,nm. (107838)
23. hydroxypregnenolone.tw,nm. (1598)
24. hydroxycorticosteroid*.tw,nm. (7133)
25. tetrahydrocortisol.tw,nm. (888)
26. cortodoxone.tw,nm. (858)
27. cortisone.tw,nm. (33020)

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

28. fludrocortisone.tw,nm. (5744)

29. corticosterone.tw,nm. (52490)

30. triamcinolone.tw,nm. (28528)

31. prednisone.tw,nm. (145872)

32. prednisolone.tw,nm. (111350)

33. paramethasone.tw,nm. (288)

34. methylprednisolone.tw,nm. (77978)

35. dexamethasone.tw,nm. (159549)

36. clobetasol.tw,nm. (6425)

37. beclomethasone.tw,nm. (9816)

38. betamethasone.tw,nm. (19815)

39. budesonide.tw,nm. (19461)

40. (efcortesol or hydrocortone or solu-cortef).tw,nm. (255)

41. (betnelan or betnesol).tw,nm. (172)

42. (deflazacort or calcort).tw,nm. (1626)

43. (medrone or solu-medrone or depo-medrone).tw,nm. (147)

44. kenalog.tw,nm. (1515)

45. (novolizer or pulmicort or symbicort).tw,nm. (1555)

46. (beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or becloforte).tw,nm. (1460)

47. cortisol.tw,nm. (126950)

48. or/12-47 (1965836)

49. 11 and 48 (97926)

50. ((randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or clinical trials as topic.sh. or trial.ti.) not (exp animals/ not humans.sh.) (1173)

51. limit 2015 to current (377)

Database: Embase <1996 to February 29, 2020>

Search Strategy:

#56 #55 AND limit 2015 to current (1576)

#55 #51 AND #54 (4,883)

#54 #52 OR #53

#53 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR assign*:ab,ti OR

allocat*:ab,ti OR volunteer*:ab,ti OR ((singl* OR doubl*) NEAR/2 (blind* OR mask*)):ab,ti

#52 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp

#51 #11 AND #50

#50 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR

#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46

OR #47 OR #48 OR #49

#49 cortisol:ti,ab

#48 beclometasone:ti,ab OR aerobec:ti,ab OR asmabec:ti,ab OR beclazone:ti,ab OR becodisks:ti,ab OR becotide:ti,ab OR clenil:ti,ab AND

modulite:ti,ab OR qvar:ti,ab OR becloforte:ti,ab

#47 novolizer:ti,ab OR pulmicort:ti,ab OR symbicort:ti,ab

#46 kenalog:ti,ab

#45 medrone:ti,ab OR 'solu medrone':ti,ab OR 'depo medrone':ti,ab

#44 deflazacort:ti,ab OR calcort:ti,ab

#43 betnelan:ti,ab OR betnesol:ti,ab

#42 efcortesol:ti,ab OR hydrocortone:ti,ab OR 'solu cortef':ti,ab

#41 budesonide:ti,ab

#40 betamethasone:ti,ab

#39 beclomethasone:ti,ab

#38 clobetasol:ti,ab

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

#37 dexamethasone:ti,ab

#36 methylprednisolone:ti,ab

#35 paramethasone:ti,ab

#34 prednisolone:ti,ab

#33 prednisone:ti,ab

#32 triamcinolone:ti,ab

#31 corticosterone:ti,ab

#30 fludrocortisone:ti,ab

#29 cortisone:ti,ab

#28 'cortodoxone'/de

#27 cortodoxone:ti,ab

#26 tetrahydrocortisol:ti,ab

#25 hydroxycorticosteroid*:ti,ab

#24 hydroxypregnenolone:ti,ab

#23 hydrocortisone:ti,ab

#22 pregnenolone*:ti,ab

#21 pregnenedione*:ti,ab

#20 'pregnane derivative'/de

#19 glucocorticosteroid*:ti,ab

#18 glucocorticoid*:ti,ab

#17 corticoid*:ti,ab

#16 corticosteroid*:ti,ab

#15 'adrenal cortex hormone*':ti,ab

#14 'corticosteroid'/exp

#13 steroid*:ti,ab

#12 'steroid'/exp

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#10 ards:ti,ab

#9 acute AND respiratory AND distress AND syndrome:ti,ab

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

#8 adult AND respiratory AND distress AND syndrome:ti,ab

#7 'adult respiratory distress syndrome'/de

#6 hap:ti,ab

#5 cap:ti,ab

#4 pleuropneumon*:ti,ab

#3 bronchopneumon*:ti,ab

#2 pneumon*:ti,ab

#1 'pneumonia'/ex

Clinicaltrials.gov <inception to March 5th, 2020>

Search strategy

(Corticosteroids OR steroids) AND Community-acquired Pneumonia (17 studies)

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Appendix 3 (as supplied by the authors): Study selection figures

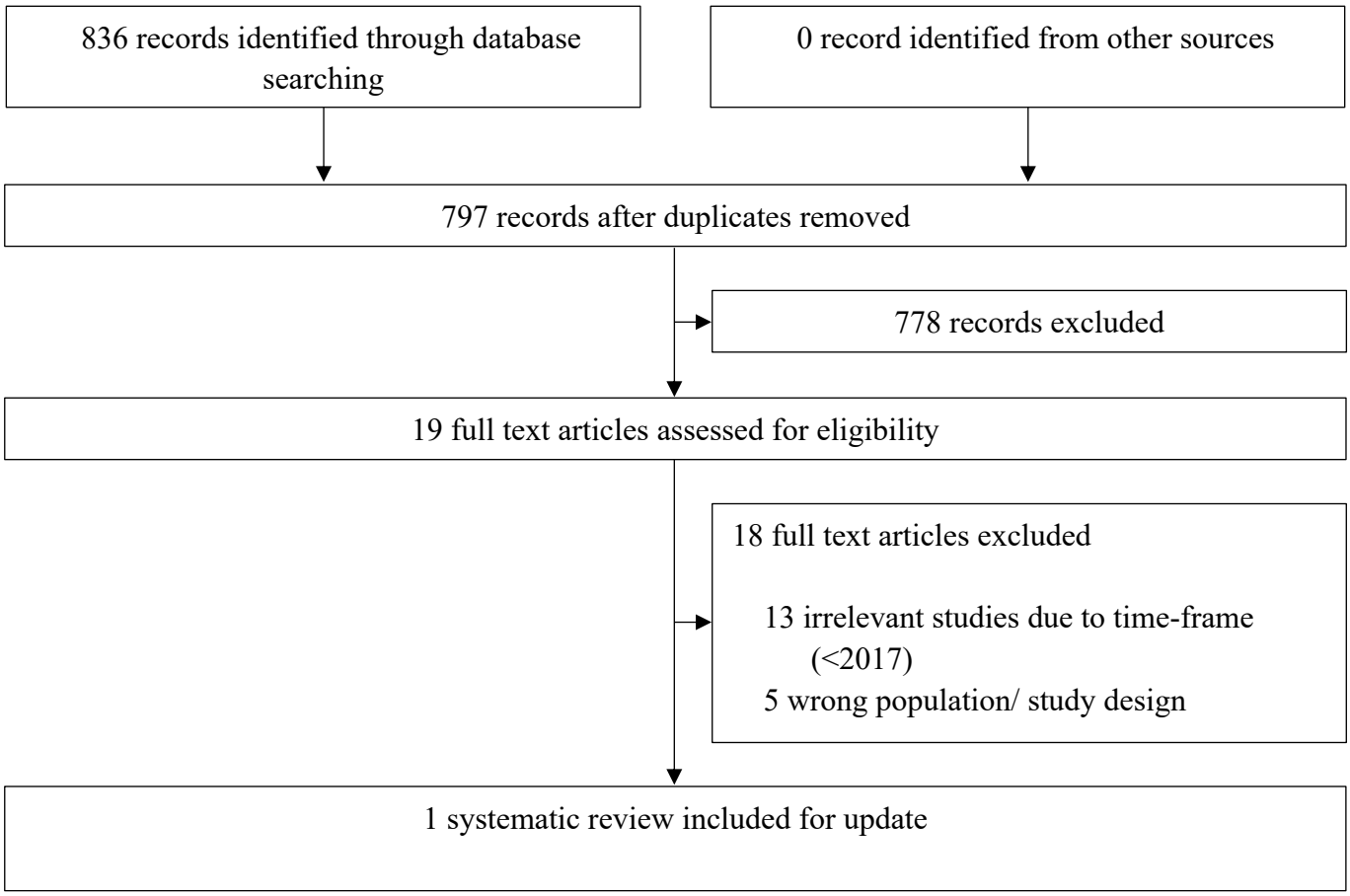


Figure 1: Systematic review identification for ARDS

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

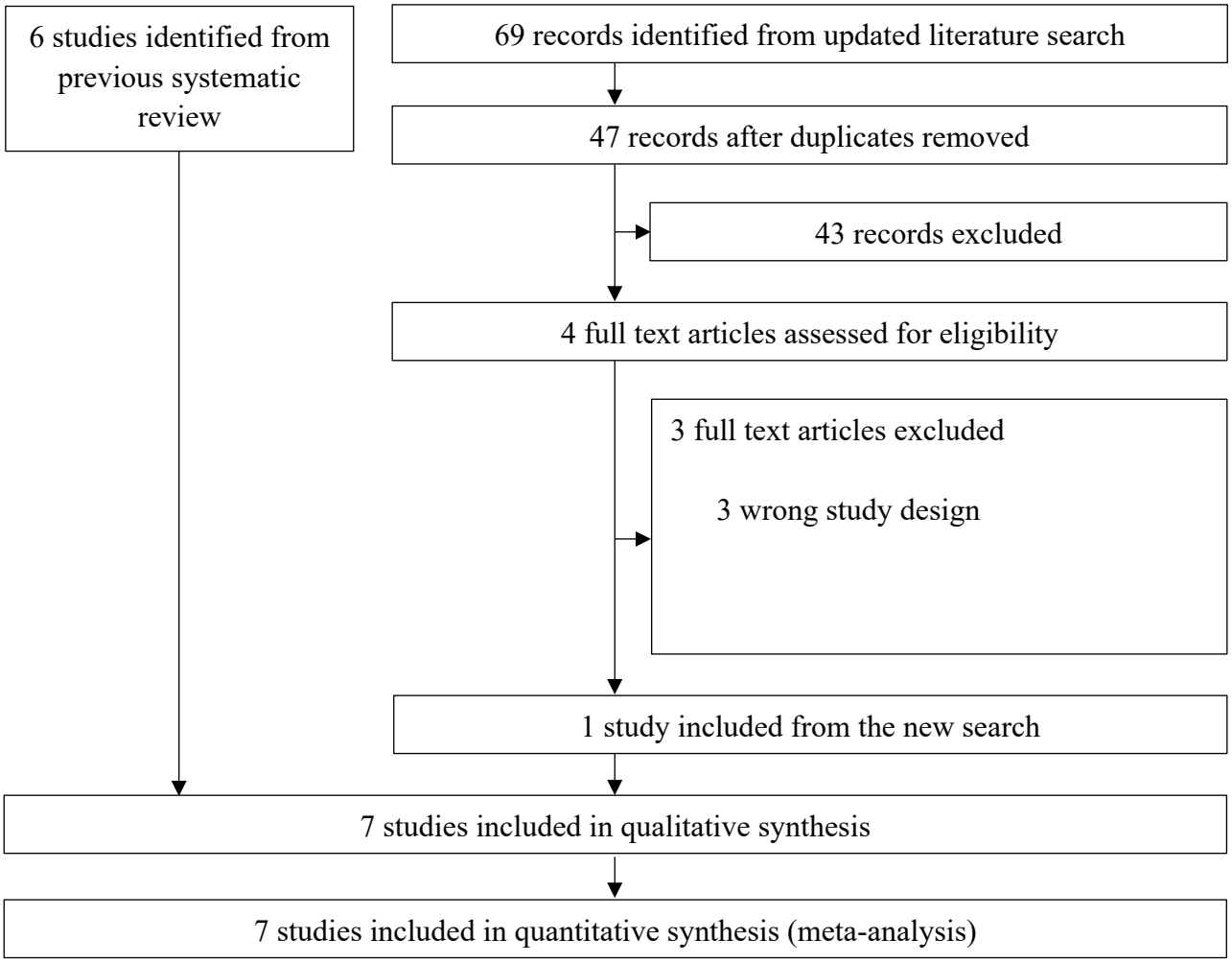


Figure 2: Study selection for ARDS

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

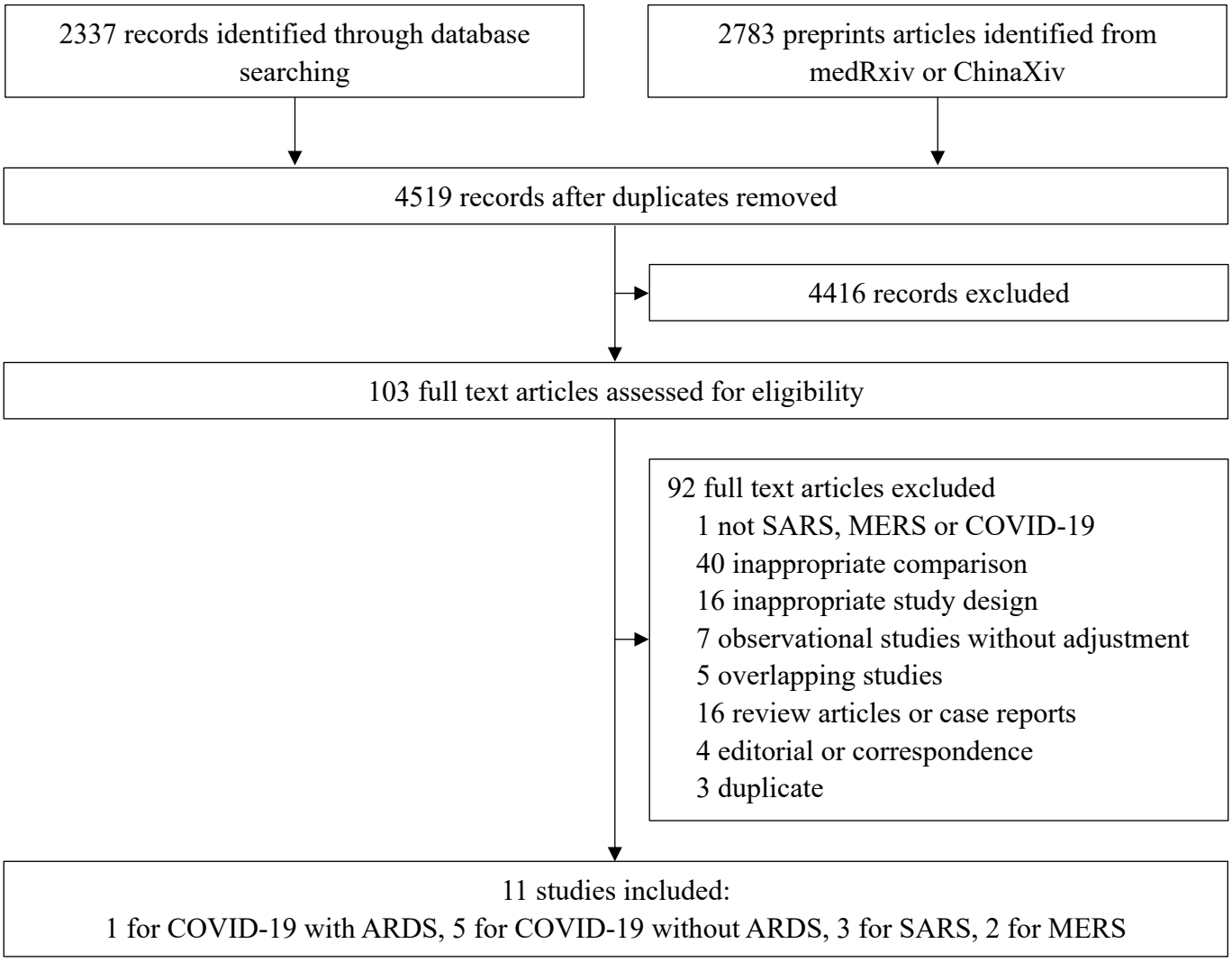


Figure 3: Study selection for COVID-19, SARS and MERS

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

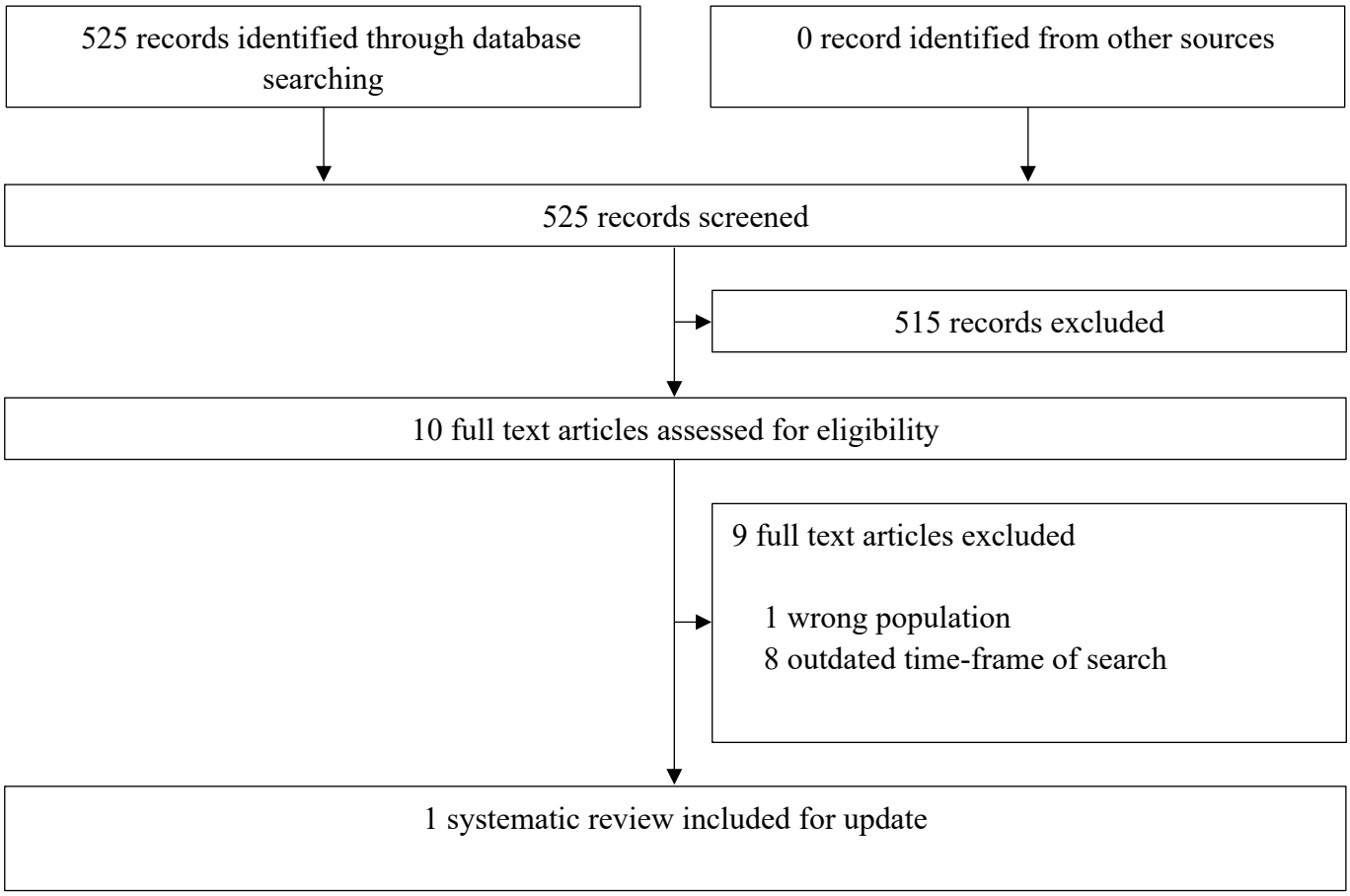


Figure 4: Systematic review identification for influenza

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

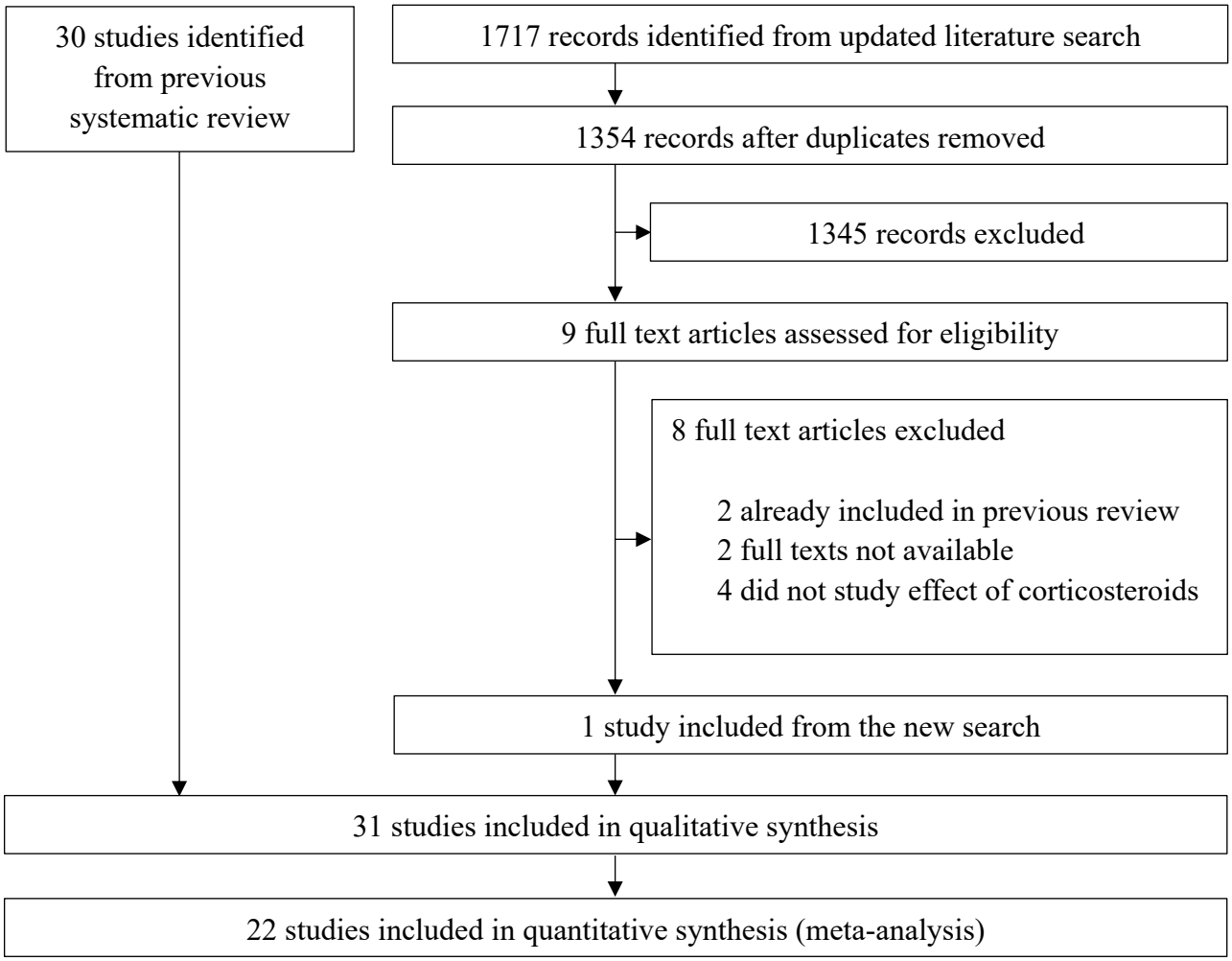


Figure 5: Study selection for influenza

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

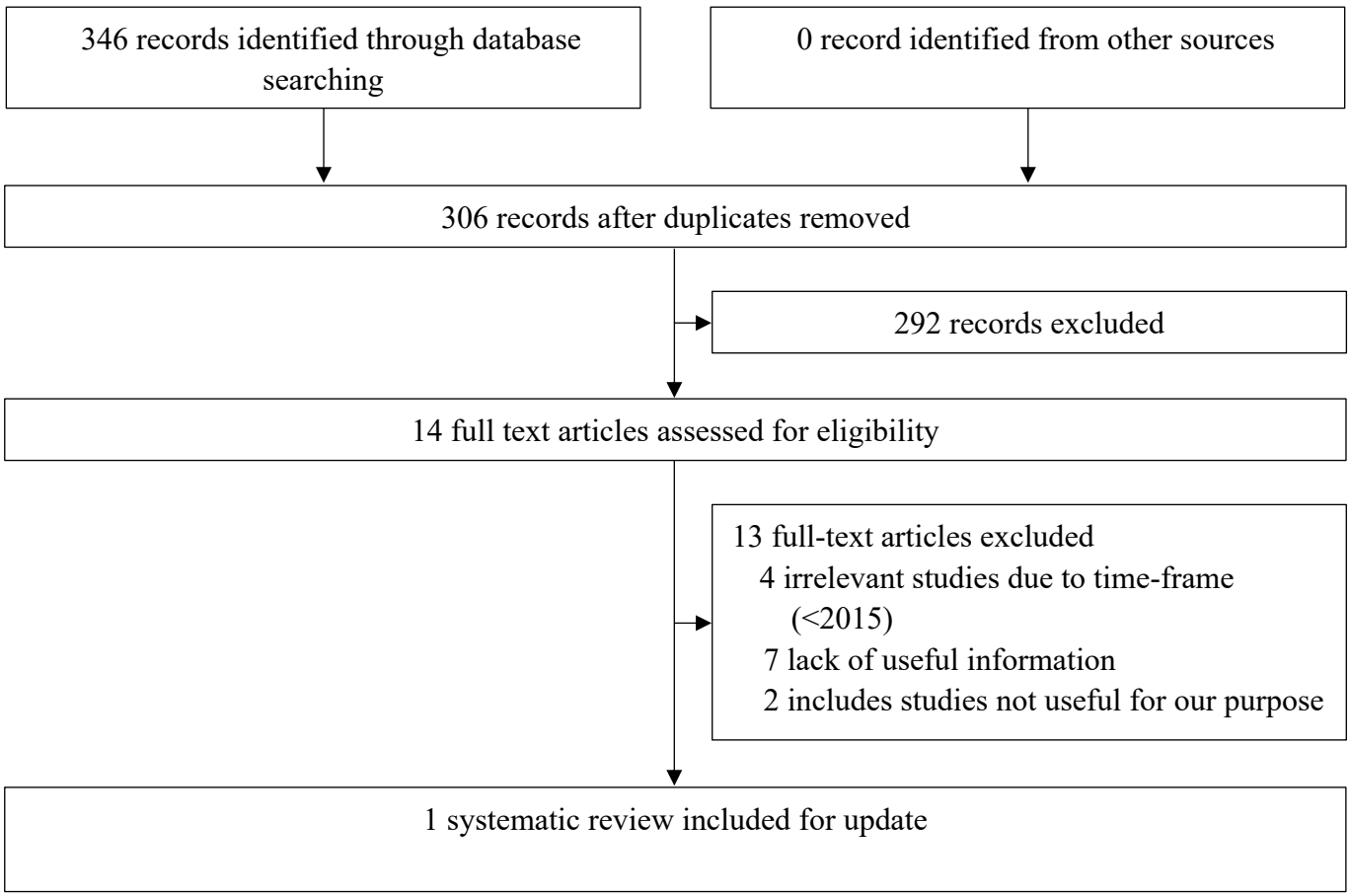


Figure 6: Systematic review identification for CAP

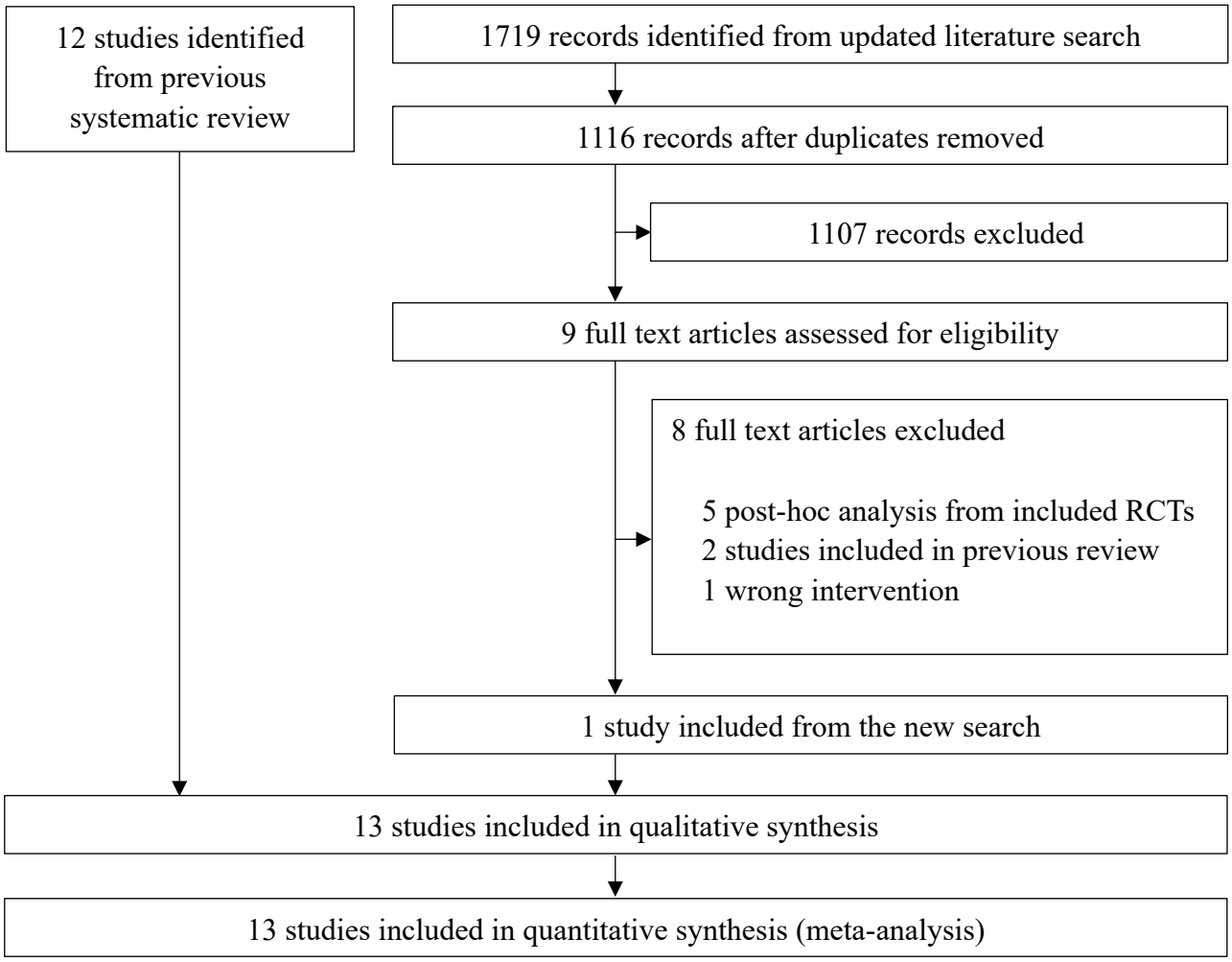


Figure 7: Study selection for CAP

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645. Copyright © 2020 Joule Inc. or its licensors

Appendix 4 (as supplied by the authors): Characteristics of included studies

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Table 1 Characteristics of included studies for COVID-19 with ARDS

Study	Country, region and hospital	Study design	Population	Intervention	Adjustment	Outcomes
Wu 2020	Jinyintan Hospital, Wuhan, China	Retrospective cohort study	Patients with COVID-19 pneumonia with ARDS: according to WHO criteria	Methylprednisolone (n=50) No steroids (n=34)	Cox regression analysis	Mortality

ARDS=acute respiratory distress syndrome; WHO=World Health Organization.

Table 2 Characteristics of included randomized controlled trials for ARDS

Study/year (country) (reference	Setting/ inclusion criteria	Patient characteristics	Disease severity scores	CS Group N	Non-CS group N	Corticosteroid therapy dose /timing/duration	Outcomes reported
Steinberg, 2006 (USA)	25 hospitals of the National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network Intubated and receiving mechanical ventilation; 7 to 28 days after onset of ARDS; on day of study entry PaO2/FiO2 had to be < 200 mmHg	Persistent Acute Respiratory Distress Syndrome	APACHE III score mean 87.6 sd 27.5 placebo mean 84.6 sd 29.4	89	91	Methylprednisolone sodium succinate diluted in 50 mL of 5% dextrose in water; single IV dose of 2 mg/kg of PBW; followed by 0.5 mg/kg of PBW every 6 hours for 14 days; then dose of 0.5 mg/kg of PBW every 12 hours for 7 days, then tapering of dose	Mortality Length of ICU Length of hospital stay Duration of mechanical ventilation Neuromuscular weakness Superinfection
Meduri, 2007 (USA)	5 ICUs Adult intubated patients receiving mechanical ventilation; meeting criteria for ARDS according to AECC (Bernard 1994) within 72 hours	Early ARDS	APACHE III score mean 60.2 sd 20.2 placebo mean 57.9 sd 21.0	63	28	Methylprednisolone;mixed in 240 mL of normal saline and administered daily as an infusion at 10 mL/hour; loading dose of 1 mg/kg, followed by infusion of 1 mg/kg/day from day 1 to day 14; 0.5 mg/kg/day on days 15 to day 21; 0.25 mg/kg/day on days 22 to day 25; then 0.125 mg/kg/day from	Mortality Length of ICU Length of hospital stay Duration of mechanical ventilation Serious hyperglycemia Neuromuscular weakness Superinfection

Liu, 2012 (China)	ICU of Zhongda Hospital Affiliated to Southeast University Adults from 18 to 80 years of age; fulfils criteria of ARDS according to the AECC (Bernard 1994); ARDS diagnosis within 3 days of admission; fulfils CIRCI diagnosis according to Society of Critical Care Medicine of PLAs Guidelines 2006	Early ARDS plus critical illness related corticosteroid insufficiency	APACHE II score mean 20.7 (sd 6.4) mean 21.4 (sd 7.16)	12	14	Stress dose glucocorticoid; hydrocortisone 100 mg IV 3 times a day for 7 days	Mortality Length of ICU
Rezk, 2013 (Kuwait)	ICU of Farwaneya Hospital Kuwait Patients diagnosed with ARDS; mechanically ventilated; start of treatment in first 48 hours	Early ARDS	NR	18	9	Methylprednisolone mixed in 240 mL normal saline; administered daily at infusion of 10 mL/ hour; loading dose of 1 mg/kg followed by infusion of 1 mg/kg/day on days 1 to 14, 0.5 mg/kg/day from day 15 to day 21, 0.25 mg/kg/day from day 22 to day 25, 0.125 mg/kg/day from day 26 to day 28	Mortality Duration of mechanical ventilation
Zhao, 2014 (China)	ICU of Songjiang hospital of shanghai Criteria of ARDS according to AECC (Bernard 1994)	ARDS	NR	24	29	Budesonide plus conventional treatment; inhaled budesonide 2 mg twice a day for 12 days alongside ARDS management algorithm according	Mortality Length of hospital stay Duration of mechanical ventilation Gastrointestinal bleeding

						to the 2006 Chinese Society for Critical Care Medicine Guidelines	Superinfection
Tongyoo, 2016 (Thailand)	ICU of Siriraj Hospital, Bangkok Adults > 18 years of age; with severe sepsis or septic shock; receiving mechanical ventilation for hypoxaemic respiratory failure; within 12 hours of study entry; meeting the diagnostic criteria for ALI/ARDS according to the AECC definition (Bernard 1994)	Early sepsis associated ARDS	APACHE II score mean 21.7, sd 5.7; placebo mean 21.9, sd5.7	98	99	Hydrocortisone; IV bolus, 50 mg in 10 mL of normal saline, every 6 hours for 7 days	Mortality Duration of mechanical ventilation Serious hyperglycemia Gastrointestinal bleeding Superinfection
Villar, 2020 (Spain)	17 ICUs Eligible patients were aged 18 years or older; intubated and mechanically ventilated; had acute onset of ARDS, as defined by the American- European Consensus Conference criteria for ARDS,11 or by the Berlin criteria as moderate-to-severe ARDS,12 which includes having an initiating clinical condition	Moderate-to-severe ARDS	Moderate (100 <PaO2/FiO2 ≤200) 239/277 Severe (PaO2/FiO2 ≤100) 38/277	139	138	Dexamethasone plus conventional treatment; Patients in the dexamethasone group received an intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10.Treatment with dexamethasone was maintained for a maximum of 10 days after randomisation or until extubation (if occurring before day 10).	Mortality Duration of mechanical ventilation Serious hyperglycemia Superinfection

	(eg, pneumonia, aspiration, inhalation injury, sepsis, trauma, or acute pancreatitis) within 1 week of the known clinical insult, or new or worsening respiratory symptoms; bilateral pulmonary infiltrates on chest imaging (x-ray or CT scan); absence of left atrial hypertension, pulmonary capillary wedge pressure of less than 18 mm Hg, or no clinical signs of left heart failure; and hypoxaemia, as defined by a ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO2/FiO2) of 200 mm Hg or less on positive end-expiratory pressure (PEEP) of 5 cm H2O or more, regardless of FiO2.

ALI=Acute lung injury; ARDS=Acute Respiratory Distress Syndrome; PBW=Predicted Body Weight; ICU=Intensive care unit; IV=Intravenous; AECC=American-European Consensus Conference; CS=Corticosteroid; CIRCI=critical illness-related corticosteroid insufficiency.

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Table 3 Characteristics of included studies for COVID-19

Study	Country, region and hospital	Study design	Population	Intervention	Adjustment	Outcomes
Li 2020 (n=269)	Tongji Hospital, Wuhan, China	Retrospective cohort study	Severe COVID-19 patients. Diagnosed based on the WHO interim guidance and Chinese COVID-19 guideline.	Steroid (n=196) No steroid (n=73)	Multivariable Cox proportional hazards regression analysis	Mortality
Lu 2020 (n=62)	Tongji hospital, Wuhan, China	Retrospective cohort study	ICU patients with confirmed SARS-CoV-2 infection	Steroid (n=31) No steroid (n=31)	Propensity score matching analysis	Mortality
Wang 2020 (n=115)	Third People's Hospital of Hubei, China	Retrospective cohort study	Patients with confirmed SARS-CoV-2 infection (mixed severity)	Steroid (n=73) No steroid (n=42)	Multivariable logistic regression analysis	Mortality or intensive care unit (ICU) admission
Xu 2020 (n=113)	First Affiliated Hospital of Zhejiang University, Shenzhen Third People's Hospital,	Retrospective cohort study	Patients with confirmed SARS-CoV-2 infection (mixed severity)	Steroid (n=64) No steroid (n=49)	Multivariable logistic regression analysis	Duration of SARS-CoV-2 Virus RNA detection

	China					
Yan 2020 (n=120)	NO.3 People's hospital of Hubei, China	Retrospective cohort study	Patients with laboratory-confirmed SARS-CoV-2 infection (mixed severity)	Steroid (n=54) No steroid (n=66)	Multivariable logistic regression analysis	Prolonged viral shedding

ARDS=acute respiratory distress syndrome; WHO=World Health Organization.

Table 4 Characteristics of included studies for SARS

Study	Country, region and hospital	Study design	Population	Intervention	Adjustment	Outcomes
Lau 2009 (n=1743)	Hong Kong	Retrospective cohort study	Probable SARS patients: according to the WHO criteria.	Steroid (n=51) No steroid (n=751) Without ribavirin	Multinomial logistic regression	Case fatality
Lee 2004 (n=17)	Two regional hospitals in Hong Kong	Randomized controlled trial	Probable SARS, with or without laboratory confirmation according to the CDC criteria	Early (<7 days of illness) intravenous hydrocortisone 100 mg every 8 hourly (n=9) Normal saline (n=7)	NA	Median time for SARS-CoV RNA to become undetectable in plasma Plasma SARS-CoV RNA concentrations in the second and third week of illness
Long 2016 (n=5327)	Mainland China	Retrospective cohort study	Clinically diagnosed SARS: according to the CDC criteria. Case definitions were as follows: 1) fever (temperature >38 °C); 2) chest radiograph showed evidence of consolidation with or without respiratory symptoms; 3) history of exposure to an index case suspected of having SARS or direct contact with a person who fell ill following exposure to the index case. Severe SARS cases: according to the criteria of Health Ministry of China, with one of the following: 1) breathing of more than 30/min; 2) oxygen partial pressure of more than 70 mmHg; 3) blood oxygen saturation of less than 93%; 4) sternum score of greater than or equal to 2 points.	Steroid (n=NR) No steroid (n=NR)	Multivariate Cox's proportional hazard regression model	Mortality

SARS=severe acute respiratory syndrome; WHO=World Health Organization; CoV=coronavirus; NA=not applicable; CDC=Center for Disease Control and Prevention; RNA=Ribonucleic Acid; NR=not

reported.

Table 5 Characteristics of included studies for MERS

Study	Country, region and hospital	Study design	Population	Intervention	Adjustment	Outcomes
Alfaraj 2019 (n=314)	Prince Mohammed bin Abdulaziz Hospital, Saudi Arabia	Retrospective cohort study	Symptomatic MERS-CoV confirmed patients. All infections were confirmed using real time RT-PCR of respiratory samples.	Steroid (n=NR) No steroid (n=NR)	Logistic regression analysis	Mortality
Arabi 2018 (n=309)	Fourteen Saudi Arabian tertiary care hospitals	Retrospective cohort study	ICU patients with MERS	Steroid (n=151) No steroid (n=158)	Multivariable logistic regression analysis Cox proportional hazards model Marginal structural model	90-day all cause mortality MERS-CoV RNA Clearance Time to MERS-CoV RNA clearance

MERS-CoV=middle east respiratory syndrome coronavirus; PT-PCR=positive reverse transcriptase polymerase chain reaction; NR=not reported; ICU=intensive care unit; RNA=Ribonucleic Acid.

Table 6 Characteristics of included studies for influenza

Study	Country, region and hospital	Study design	Population	Intervention		Adjustment	Outcomes
				Steroid	No steroid		
Al-Busaidi 2016 (n=68)	Oman	Single centre, retrospective cohort	In-hospital patients Median age (years): 23 (range 25 days to 67 years)	11	57	Multivariable regression analysis	Length of stay
Balaganesakumar 2013 (n=1302)	India	Multicentre, prospective cohort study	In-hospital/admissions with influenza Median age (years): 26 (1 to 82)	70	210	Multiple logistic regression analysis	Mortality
Boudreault 2011 (n=143)	USA	Single-centre, retrospective cohort	Non-ICU/HCT recipients with RTI Median age (years): no CS 42 (32 to 51); low-dose CS 42 (28 to 53); high-dose CS 40 (32 to 54)	80 (low-dose 43 and high-dose 37)	63	Cox proportional hazards analysis	MV, time to death
Brun-Buisson 2011 (n=208)	France	Multicentre, retrospective analysis of prospectively collected data	ICU/severe respiratory failure (ARDS or MV) Median age (years): no CS 45 (35 to 55); CS 49 (34 to 56) Immunosuppression: no CS 18.4%; CS 21.7%	83 (early CS 50 and late CS 33)	125	Cox proportional hazards regression analysis	Hospital mortality, length of ICU stay, adverse events
Cao 2016 (n=288)	China	Multicentre, retrospective cohort study	In-hospital patients ≥ 14 years with pneumonia Median age (years): 58 (IQR 45 to 68)	204	84	Cox proportional hazards regression analysis	Mortality, adverse events, viral shedding
Chawla 2013 (n=77)	India	Single-centre, retrospective	ICU/admissions with influenza Mean age (years): 40.9 (± 13.4)	38	39	NA	Mortality

		cohort study					
Delaney 2016 (n=607)	Canada	Multicentre, prospective cohort study	ICU/age ≥ 18 years; critically ill with confirmed, probable or highly suspected influenza Mean age (years): no CS 46.2 (± 15.2); CS 48.8 (± 15.3) Asthma: CS 29.3%; no CS 12.8%; P = < 0.001 COPD: CS 25.0%; no CS 9.2%; P = < 0.001 Immunosuppressed: CS 8.9%; no CS 3.1%; P = 0.002	280	327	Multivariable logistic regression analysis	Mortality, hospital-acquired infections
Delgado-Rodriguez 2012 (n=813)	Spain	Multicentre, prospective cohort	In-hospital/ILI, RTI, septic shock, multi-organ failure Cohort median age (years): 41 (19 to 55)	31	782	Multivariate logistic regression analysis	Poor outcome (ICU admission and in-hospital death), LOS
Han 2011 (n=83)	China-Shenyang City	Multicentre, retrospective cohort	In-hospital/age > 3 years Median age (years): no CS 38 (5 to 75); CS 43 (3 to 70)	46 (early CS 17 and late CS 29)	37	Cox proportional hazards regression analysis	Critical illness
Huang 2017 (n=86)	Taiwan	Single-centre, retrospective cohort study	In-hospital/ age > 18 years Cohort mean age (years): 65.9 (± 19.2) Chronic pulmonary disease: respiratory distress cohort 27.1%	29	19	Multivariable Logistic regression analysis	Mortality
Jain 2009 (n=272, CS data available for 239)	USA	Multicentre, retrospective cohort	In-hospital/ILI with hospital admission ≥ 24 hours Cohort median age: 21 years (21 days to 86 years) Asthma: 28%; COPD: 8% Immunosuppression: 15%	86	153	NA	Death/ICU admission versus survival/no ICU admission
Kim 2011 (n=245)	South Korea	Multicentre, retrospective	ICU/age ≥ 15 years; presence of critical illness	107	138	Multivariable Logistic regression analysis	Mortality (14-day, 30-day and 90-day), LOS, acquired

		cohort/case-control	Mean age (years): no CS 54.1 (± 19.3); CS 56.9 (± 17.2) Asthma: CS 9%; no CS 7% COPD: CS 13%; no CS 4%				infections
Kinikar 2012 (n=92)	India	Single centre, retrospective cohort study	ICU/admissions with influenza < 12 years Cohort median age (years): 2.5 (1.3 to 6) Asthma: 4.3% Congenital heart disease: 6.5%	21	71	NA	In-hospital mortality
Kudo 2012 (n=89)	Japan	Single-centre, retrospective cohort	In-hospital/hospitalised patients with respiratory disorders Cohort median age (years): 8 (0 to 71) Asthma: 29.2%	46	12	NA	LOS
Lee 2015 (n=2649)	China	Multicentre, retrospective analysis of prospectively collected data	In-hospital/age > 17 years Cohort median age (years): 63 (42 to 79)	610	2039	Multivariable regression analysis	Mortality, bacterial superinfection, LOS
Li 2012 (n=46)	China-Anhui province	Multicentre, retrospective cohort study	In-hospital/pregnant, severe disease Median age (years): adults who died 21 (18 to 31) and survivors 21 (18 to 27)	27	19	NA	Mortality

Li 2017 (n=2141)	China	Multicentre, retrospective analysis of prospectively collected data	In-hospital with viral pneumonia > 14 years Median age (years): no CS 33.7 (24.6 to 48.7); CS 35.0 (23.8 to 52.4) Asthma: no CS 1.5%; CS 2.1% COPD: no CS 4.3%; CS 5.6% Immunosuppression: no CS 1.4%; CS 3.2%	1055	1086	Cox proportional hazards regression analysis	Mortality, ICU admission, hospital-acquired infection, MV
Liem 2009 (n=67)	Vietnam	Multicentre, retrospective cohort	In-hospital/hospitalised patients with influenza Cohort median age (years): 25 (16 to 42)	29	38	NA	In-hospital mortality
Linko 2011 (n=132)	Finland	Multicentre, prospective cohort study	ICU/admissions with influenza Median age (years): no CS 44 (25 to 57); CS 51 (40 to 56) COPD: no CS 5%; CS 8% Other obstructive pulmonary disease: no CS 23%; CS 21%	72	60	Multivariable logistic regression analysis	In-hospital mortality, MV, LOS
Mady 2012 (86)	Saudi Arabia	Single-centre, retrospective cohort study	ICU/influenza with respiratory failure Cohort mean age (years): 40.8 Asthma or COPD: 38.3%	43	43	NA	Mortality

Moreno 2018 (n=1846)	Spain	Multicentre, prospective cohort study	ICU/viral pneumonia Median age (years): CS 53 (41 to 62); no CS 51 (39 to 61)	604	1242	Cox proportional hazards regression analysis	ICU mortality
Ono 2016 (n=88054)	Japan	Multicentre retrospective cohort study	Medical insurance database, < 65 years, first episode of hospitalisation with confirmed influenza All < 65 years. Asthma: hospitalised 39.5%; non-hospitalised 23.5% COPD: hospitalised 2.9%; non-hospitalised 0.5% Immunosuppression: hospitalised 0.36%; non-hospitalised 0.13%	804	87250	Cox proportional hazards regression analysis	Rate of hospitalisation
Patel 2013 (n=63)	India-Gujarat	Single-centre, retrospective cohort study	In-hospital/admissions with influenza Cohort median age (years): 34 (3 to 69)	39	24	NA	Mortality
Sertogullarindan 2011 (n=20)	Turkey	Single-centre, prospective cohort study	ICU/severe community-acquired pneumonia and influenza Cohort median age (years): 36 (15 to 72) COPD: 10%	7	13	NA	Mortality
Sheu 2017 (n=192)	Taiwan	Multicentre, retrospective cohort study	ICU admissions with confirmed influenza Cohort mean age (years): 58.3	101	91	NA	Mortality

Viasus 2011 (n=197)	Spain	Multicentre, prospective cohort study	In-hospital/ non-immunosuppressed, admitted > 24 hours Median age (years): no CS 35 (28 to 47); CS 44 (36 to 53) Chronic pulmonary disease: no CS 17.1%; CS 45.9%	37	129	NA	Severe disease (composite outcome of ICU admission/death), acquired infection
Wirz 2016 (n=785)	Switzerland	Multicentre RCT of adjunct prednisone therapy versus placebo in community-acquired pneumonia	Non-ICU with community-acquired pneumonia (influenza subgroup n = 24) All trial participants: mean age (years): CS arm 70.3 (± 17.5); placebo arm 69.0 (± 17) COPD: CS arm 19.3%; placebo 15.4%	11	13		Any-cause mortality at 30 d, hospital readmission at 30 days post discharge, time to effective hospital discharge, time to clinical stability
Wu 2012 (n=206)	Taiwan	Single-centre, prospective cohort	Mixed cohort of out-patients and in-patients Age >= 65 years in cohort: 12.6% Chronic lung disease: 9.7% Malignancy: 8.7%	17	189	Multivariable logistic regression analysis	Complicated influenza (requiring hospitalisation)
Xi 2010 (n=155)	China-Beijing	Multicentre, retrospective	In-hospital/age ≥ 18 years	52	103	Multivariable logistic regression analysis	In-hospital mortality Subgroup analysis of

		cohort study	Cohort mean age (years): 43 (±18.6) COPD: 6.5%				mortality by CS dose
Yu 2011 (n=128)	China-Zhengzhou	Multicentre, retrospective cohort study	Not defined Cohort mean age (years): females 28.5 (± 16.4); males 28.5 (± 20.4) Range 8 months to 79 years	54	74	Multivariable logistic regression analysis	Mortality
Tsai 2020 (n=241)	Taiwan	Multicentre prospective cohort	ICU/Influenza with ARDS Cohort median age 60 (51 to 66) 63.5% male Malignancy12%, diabetes 28.6%	Not reported (85 for sensitivity analysis)	Not reported (156 for sensitivity analysis)	Multivariable logistic regression analysis	Mortality, bacteremia

ARDS=acute respiratory distress syndrome; CS=corticosteroid; HCT=hematopoietic cell transplant; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; MV=mechanical ventilation; PVS=prolonged viral shedding; RTI=respiratory tract infection.

Table 7 Characteristics of included randomized controlled trials for CAP

Study/year (country) (reference	Setting/ inclusion criteria	Patient characteristics	Disease severity scores	CS Group N	Non-CS group N	Corticosteroid therapy dose /timing/duration	Outcomes reported
Wagner, 1956 (US)	Not specified Culture-confirmed pneumococcal pneumonia	Not specified	Not specified	52	61	Hydrocortisone 80–100 mg oral every 6 h tapering dose over 5 days.	Mortality
McHardy, 1972 (Australia)	City Hospital, Edinburgh Age ≥12 y, clinical diagnosis of pneumonia	Inpatient adults and children (aged > 12 years) with pneumonia	Severe (physician judgment), 20/126	40	86	Prednisolone 20 mg daily for 7 days	Mortality
Marik, 1993 (South africa)	ICU of Baragwanath Hospital and Department of Clinical and Experimental Pharmacology (Dr. Havlik), University of the Witwatersrand Age ≥18 and ≤70 y, BTS criteria for severe CAP	Inpatient adults with severe CAP	APACHE II and Lung Injury Score	14	16	Hydrocortisone dose IV 10 mg/kg, 30 minutes prior to starting antibiotic therapy,1 dose;during hospitalisation in ICU	Mortality Length of ICU Need for mechanical ventilation
Confalonieri, 2005 (italy)	ICU or f Respiratory Intermediate Unit (RICU) Ospedale di Trieste, Ospedale Gradenigo (Torino), Ospedale Molinette (Torino),	Inpatient adults with severe community-	American Thoracic	23	23	Hydrocortisone IV 200 mg loading bolus followed by an infusion (hydrocortisone 240 mg in 500	Mortality Length of ICU Length of hospital stay

	Arcispedale S. Anna (Ferrara), Ospedale di Crema, or Ospedale di Paderno Dugnano (Milano). CAP with 1993 ATS criteria severe; Major criteria included (1) requirement of mechanical ventilation; (2) increase in the size of opacities on chest radiograph of 50% or more at 48 hours; (3) requirement of vasopressors for more than 4 hours; or (4) serum creatinine 2 or more mg/dl.	acquired pneumonia	Society criterion for severe pneumonia			cmh 0.9% saline) at a rate of 10 mg/hour; duration 7ds	Need for mechanical ventilation Duration of mechanical ventilation Gastrointestinal bleeding Superinfection
El-Ghamrawy, 2006 (Saudi Arabia)	Not reported Age ≥18 y, severe CAP by ATS criteria requiring ICU admission	Age ≥18 years old with severe CAP	ATS 2001	17	17	Hydrocortisone IV 200 mg bolus followed by maintenance IV dose 240 mg in 500 mL 0.9% saline at a rate of 10 mg/kg/hour	Mortality Length ICU stay Length of hospital stay Duration of mechanical ventilation Gastrointestinal bleeding Superinfection
Mikami, 2007 (Japan)	Kanto Central Hospital (community general hospital),	Inpatient adults with community-	PORT	15	16	Prednisolone IV 40 mg x 1/d; duration 3 days	Length of hospital stay Serious hyperglycemia. Neuropsychiatric events

	Any CAP, non-severe by ATS criteria	acquired pneumonia					Superinfection
Snijders, 2010 (Netherlands)	Medical Centre Alkmaar, a 900-bed teaching hospital Age ≥18 y hospitalized with CAP	Inpatient adults with CAP	Pneumonia Severity Index	104	109	Prednisolone IV or PO 40 mg x 1/d; duration 7 days	Mortality Length of hospital stay Serious hyperglycemia Neuropsychiatric events Superinfection
Fernández-Serrano, 2011 (Spain)	Hospital Universitari de Bellvitge, a 900-bed hospital in Barcelona, Spain Age ≥18 and ≤75 y, severe CAP with consolidation of ≥ 2 lobes and Po2/FIo2 < 300 mmHg	Inpatient adults with CAP	Fine Score	23	22	Methylprednisolone IV 200 mg bolus followed by maintenance IV dose (20 mg/6 hour); duration 10 days	Mortality
Meijvis, 2011 (Netherlands)	2 centers; 880-bed St Antonius Hospital in Nieuwegein and the 00-bed Gelderse Vallei Hospital inEde in the Netherlands Age ≥18 y, CAP by PSI criteria	Inpatient adults with CAP	Pneumonia severity index	151	153	Dexamethasone IV 5 mg x 1/d; duration 4 days	Mortality Length ICU stay Length of hospital stay Serious hyperglycemia Superinfection
Sabry, 2011 (Egypt)	3 centers; Cairo University, and the National Institute of Chest Diseases, and Intensive Care Unit of Ain-Shams Hospital, Ain- Shams University. Adults with ATS criteria for severe CAP	Inpatient adults with severe CAP	ATS 1998	40	40	Hydrocortisone IV (loading dose of 200 mg, followed by 12.5 mg/h); duration 7 days.	Mortality Duration of mechanical ventilation Gastrointestinal bleeding

Nafae, 2013 (Egypt)	Chest Department, Respiratory Intensive Care Unit, General Medicine Department and General Medicine Intensive Care Unit of the Zagazig University Hospitals Age ≥18 y, Patients with clinical and radiographic evidence of CAP (pneumonia diagnosed by clinical signs and symptoms: cough with or without sputum, fever> 38.5, dyspnea, pleuritic chest pain or abnormal breath sounds, and radiographic pulmonary abnormalities that are at least segmental and are not due to preexisting or other known causes) which was acquired at the community or within the first 48 h of hospitalization	Inpatient adults with community-acquired pneumonia	Pneumonia Severity Index	60	20	Hydrocortisone IV 200 mg bolus followed by maintenance IV dose of 10 mg/hour; duration 7 days	Mortality Length ICU stay Length of hospital stay Need for mechanical ventilation Duration of mechanical ventilation Serious hyperglycemia Gastrointestinal bleeding
Blum, 2015 (Switzerland)	7 centers Age ≥18 y, hospital admission with CAP defined by a new infiltrate on chest radiograph and the presence of at least one of the following acute respiratory signs and symptoms: cough, sputum production, dyspnoea, core body temperature	Inpatient adults with CAP	Pneumonia Severity Index	392	393	Prednisone PO 50 mg x 1/d; duration 7 days	Mortality Length ICU stay Length of hospital stay Need for mechanical ventilation Serious hyperglycemia Gastrointestinal bleeding

	of 38·0°C or higher, auscultatory findings of abnormal breathing sounds or rales, leucocyte count higher than 10 000 cells per μL or less than 4000 cells per μL.15						Neuropsychiatric events Superinfection
Torres, 2015 (Spain)	3 centers Age ≥18 y with severe CAP by ATS or PSI criteria and serum CRP level >150 mg/L	Inpatient adults with CAP	PSI, AST	61	59	Methylprednisolone IV 0.5 mg/kg in bolus x 2/d; 5 days	Mortality Length ICU stay Length of hospital stay Need for mechanical ventilation Serious hyperglycemia Gastrointestinal bleeding Neuropsychiatric events Superinfection
Gang, 2016 (China)	China-Japan Friendship Hospital Criteria of Respiratory Disease Branch of Chinese medical association	Inpatient adults with severe CAP and Septic shock	Criteria of Respiratory Disease Branch of Chinese medical association	29	29	Methylprednisolone sodium succinate 80 mg daily, duration 7 days; plus Antibacterial drugs	Mortality Length of hospital stay Duration of mechanical ventilation Serious hyperglycemia

CS=Corticosteroid; CAP=Community acquired pneumonia; ATS=American Thoracic Society; BTS=British Thoracic Society; PSI=Pneumonia Severity Index; PO=Oral administration; CRP=C-Reactive protein; IV=Intravenous.

Appendix 5 (as supplied by the authors): Risk of bias assessment

Table 1: Risk of bias of included studies for COVID-19 with ARDS

Study	From the same population	Assessment of exposure	Outcome not present at start	Adjustment	Assessment of prognostic factors	Assessment of outcome	Adequate follow-up	Co-Interventions similar
Wu 2020	Low	Probably low	Low	Probably low	Probably low	Low	Low	Probably high

Table 2: Risk of bias of included randomized controlled trials for ARDS

Study	Sequence Generation	Allocation Sequence Concealment	Blinding (Performance bias)	Blinding (Outcome measurement)	Missing Outcome Data	Other Bias	Comments
Steinberg, 2006	Low	Low	Low	Low	Low	Low	None
Meduri, 2007	Low	Low	Low	Low	Low	Probably High	Lack of protocol.
Liu, 2012	Low	Probably low	Low	Low	Low	Probably High	Allocation concealment is not reported and lack of protocol.
Rezk, 2013	High	Probably High	Low	Low	Low	Probably High	Baseline characteristics are imbalance and no detail of random sequence generation or allocation concealment and lack of protocol.
Zhao, 2014	Low	Probably low	Low	Low	Low	Probably High	Lack of protocol.
Tongyoo, 2016	Low	Probably low	Low	Low	Low	High	Discrepancies between the clinical trial registry and the study.
Villar, 2020	Low	Low	Low	Low	Low	Probably Low	This trial was stopped early, however, authors reported stopping roles, less than a 100 events, probability of overestimation of the effect estimate.

Table 3: Risk of bias of included studies for COVID-19

Study	From the same population	Assessment of exposure	Outcome not present at start	Adjustment	Assessment of prognostic factors	Assessment of outcome	Adequate follow-up	Co-Interventions similar
Li 2020	Low	Low	Low	Probably low	Probably low	Low	Probably low	Probably high
Lu 2020	Low	Low	Low	Probably low	Probably low	Low	Probably low	Probably high
Wang 2020	Low	Low	Low	Probably high	Probably low	Low	Probably low	Probably high
Xu 2020	Low	Low	Low	Probably low	Probably low	Low	Probably low	Probably high
Yan 2020	Low	Low	Low	Probably high	Probably low	Low	Probably low	Probably high

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Table 4: Risk of bias of included cohort studies for SARS

Study	From the same population	Assessment of exposure	Outcome not present at start	Adjustment	Assessment of prognostic factors	Assessment of outcome	Adequate follow-up	Co-Interventions similar
Lau 2009	Low	Low	Low	Probably low	Low	Low	Low	Probably high
Long 2016	Low	Low	Low	Probably low	Low	Low	Low	Probably high

Table 5: Risk of bias of included randomized controlled trial for SARS

Study	Sequence Generation	Allocation Sequence Concealment	Blinding	Missing Outcome Data	Other Bias
Lee 2004	Probably low	Probably low	Probably low	High	Low

Table 6: Risk of bias of included studies for MERS

Study	From the same population	Assessment of exposure	Outcome not present at start	Adjustment	Assessment of prognostic factors	Assessment of outcome	Adequate follow-up	Co-Interventions similar
Alfaraj 2019	Low	Probably low	Low	Probably high	Probably low	Low	Low	Probably high
Arabi 2018	Low	Probably low	Low	Probably low	Probably low	Low	Probably low	High

Table 7: Risk of bias of included cohort studies for influenza

Study	From the same population	Assessment of exposure	Outcome not present at start	Adjustment	Assessment of prognostic factors	Assessment of outcome	Adequate follow-up	Co-Interventions similar
Al-Busaidi 2016	Yes	Yes	Yes	Probably yes	Probably no	Yes	Yes	No
Balaganesakumar 2013	Yes	Probably yes	Yes	Probably yes	Probably yes	Yes	Yes	No
Boudreault 2011	Yes	Yes	Yes	Probably yes	Probably yes	Yes	Yes	Probably no
Brun-Buisson 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Probably no
Cao 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Probably no
Chawla 2013	Yes	Yes	Yes	No	Probably no	Yes	Yes	No
Delaney 2016	Yes	Yes	Yes	Yes	Probably yes	Yes	Yes	Probably yes
Delgado-Rodriguez 2012	Yes	Probably yes	Probably no	Probably yes	Yes	Yes	Yes	No
Han 2011	Yes	Yes	Probably yes	Probably yes	Yes	Probably yes	Yes	No
Jain 2009	Yes	Yes	Yes	No	Probably yes	Yes	Yes	No
Huang 2017	Yes	Yes	Yes	No	Probably no	Yes	Yes	No
Kim 2011	Yes	Yes	Yes	Probably no	Probably yes	Yes	Yes	No
Kinikar 2012	Yes	Yes	Yes	No	Probably yes	Yes	Yes	No
Kudo 2012	Yes	Yes	Yes	No	Probably no	Yes	Yes	No
Lee 2015	Yes	Yes	Yes	Probably yes	Probably yes	Yes	Yes	Probably yes
Li 2012	Yes	Probably no	Yes	No	Probably no	Yes	Yes	No
Li 2017	Yes	Yes	Yes	Yes	Probably yes	Yes	Yes	Yes
Liem 2009	Yes	Yes	Yes	No	Probably yes	Yes	Yes	No
Linko 2011	Yes	Yes	Yes	Probably yes	Probably yes	Yes	Yes	No

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Mady 2012	Yes	No	Yes	No	No	No	Yes	No
Moreno 2018	Yes	Yes	Yes	Yes	Probably yes	Yes	Yes	No
Ono 2016	Yes	Yes	Yes	Yes	Probably yes	Yes	Yes	Probably no
Patel 2013	Yes	Yes	Yes	No	Probably yes	Yes	Yes	Probably no
Sertogullarindan 2011	Yes	Probably yes	Yes	No	Probably no	Yes	Yes	No
Tsai 2020	Yes	Yes	Yes	Probably yes	Probably yes	Yes	Yes	Probably yes
Viasus 2011	Yes	Probably yes	Yes	No	Probably no	Yes	Yes	No
Wu 2012	Yes	No	No	Probably yes	Probably no	Probably yes	Yes	Probably no
Xi 2010	Yes	Yes	Yes	Probably yes	Probably yes	Yes	Yes	Probably no
Yu 2011	Yes	Yes	Yes	Yes	Probably yes	Yes	Yes	Probably no

Table 8: Risk of bias of included randomized controlled trial for influenza

Study	Sequence Generation	Allocation Sequence Concealment	Blinding	Missing Outcome Data	Other Bias
Wirz 2016	Low	Low	Low	Low	Probably low

Table 9: Risk of bias of included randomized controlled trials for CAP

Study	Sequence Generation	Allocation Sequence Concealment	Blinding (Performance bias)	Blinding (Outcome measurement)	Missing Outcome Data	Other Bias	Comments
Wagner 1956	High	Probably High	Low	Low	Low	Probably High	Quasi-randomized controlled trial and lack of protocol.
McHardy 1972	Probably Low	Low	Probably High	Probably High	Probably High	Probably High	Lack of blinding, drop-out without explanation and lack of protocol.
Marik 1993	Low	Probably low	Probably High	Probably High	Low	Probably High	Lack of blinding and and lack of protocol.
Confalonieri 2005	Low	Low	Low	Low	Low	High	The trial stopped early and stopping role was a surrogate outcome with less of 50 patients included.
El-Ghamrawy, 2006	Probably High	Probably High	Probably High	Probably Low	Low	Probably High	Lack of information about random sequence generation, lack of protocol (sample size calculation) and blinding pf personal.
Mikami 2007	Probably High	Probably High	Probably High	Probably Low	Low	Probably High	Lack of information about random sequence generation, lack of protocol and blinding pf personal.
Snijders 2010	Low	Low	Low	Low	Low	High	Discrepancy between outcome reported in the registry and the published trial.

Fernández-Serrano, 2011	Probably High	Probably High	Low	Low	Low	Low	Lack of information about random sequence generation.
Meijvis 2011	Low	Low	Low	Low	Low	High	Discrepancy between outcome reported in the registry and the published trial.
Sabry 2011	Probably High	Probably High	Low	Low	Low	High	Lack of information about random sequence generation and discrepancy between outcome reported in the registry and the published trial.
Nafae 2013	Probably High	Probably High	Probably low	Probably low	Low	Probably High	Lack of information about random sequence generation and lack of protocol.
Blum 2015	Low	Low	Low	Low	Low	Probably High	Only the primary outcome was reported in the registry.
Torres 2015	Low	Low	Low	Low	Low	Probably Low	None
Gang 2016	Low	Probably Low	Probably High	Low	Low	Probably High	Lack of protocol, sample size calculation and blinding in the personal.

Appendix 6 (as supplied by the authors): Forest plot

ARDS

Figure 1 Effect of corticosteroids on length of ICU stay in ARDS patients

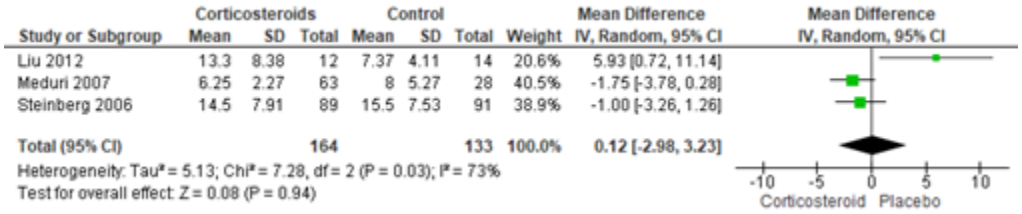


Figure 2 Effect of corticosteroids on length of hospital stay in ARDS patients

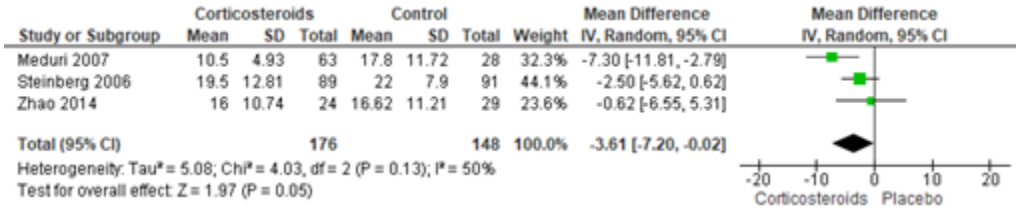


Figure 3 Effect of corticosteroids on duration of mechanical ventilation in ARDS patients

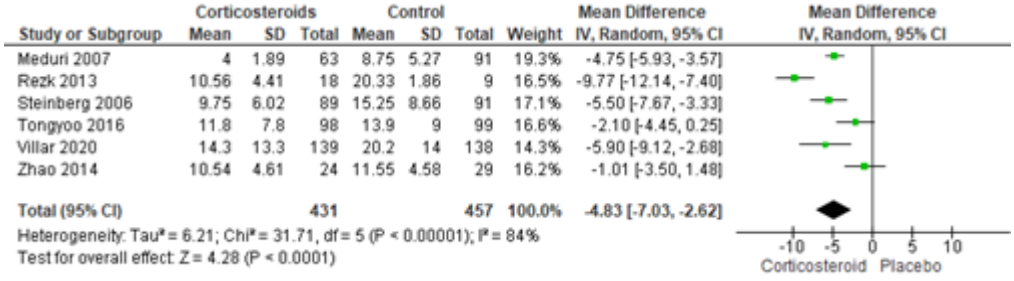
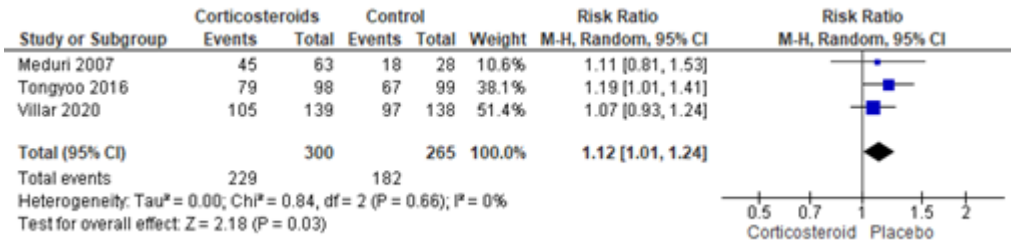


Figure 4 Effect of corticosteroids on serious hyperglycemia in ARDS patients



Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Figure 5 Effect of corticosteroids on neuromuscular weakness in ARDS patients

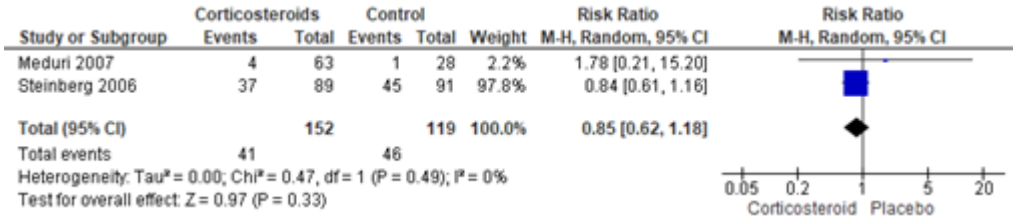


Figure 6 Effect of corticosteroids on gastrointestinal bleeding in ARDS patients

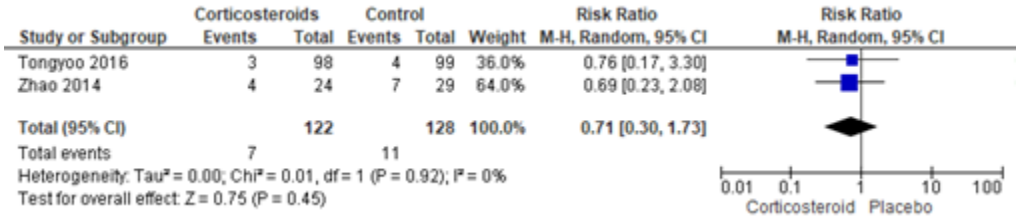
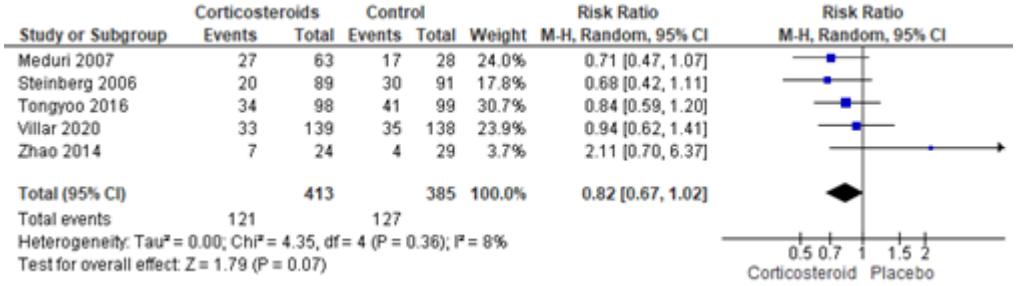
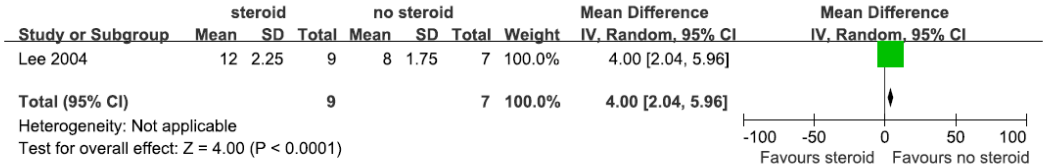


Figure 7 Effect of corticosteroids on super-infection in ARDS patients



SARS

Figure 8 Effect of corticosteroids on Median time for CoV RNA to become undetectable in plasma in SARS patients



Influenza

Figure 9 Effect of corticosteroids on superinfection in influenza patients

Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

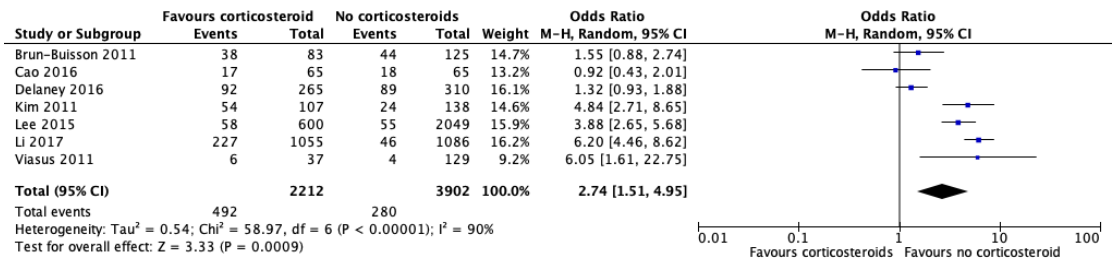
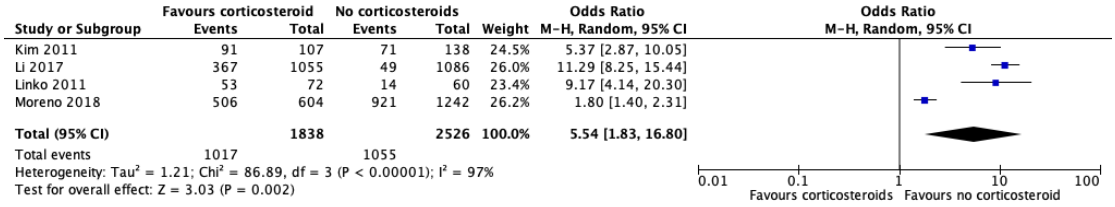


Figure 10 Effect of corticosteroids on rate of mechanical ventilation in influenza patients



CAP

Figure 11 Effect of corticosteroids on length of ICU stay in CAP patients

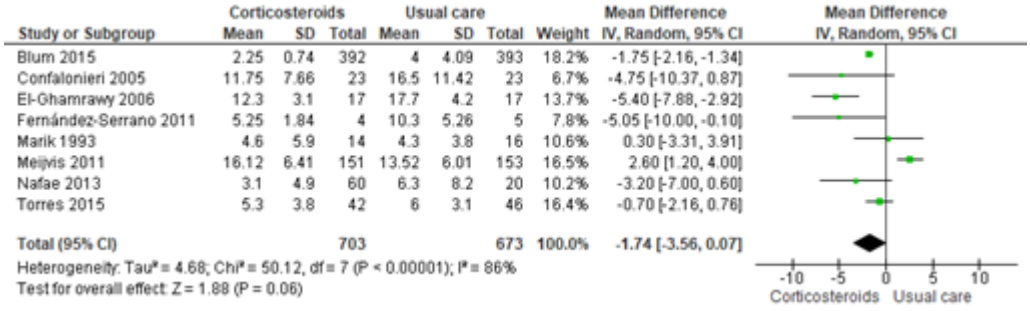


Figure 12 Effect of corticosteroids on length of hospital stay in CAP patients

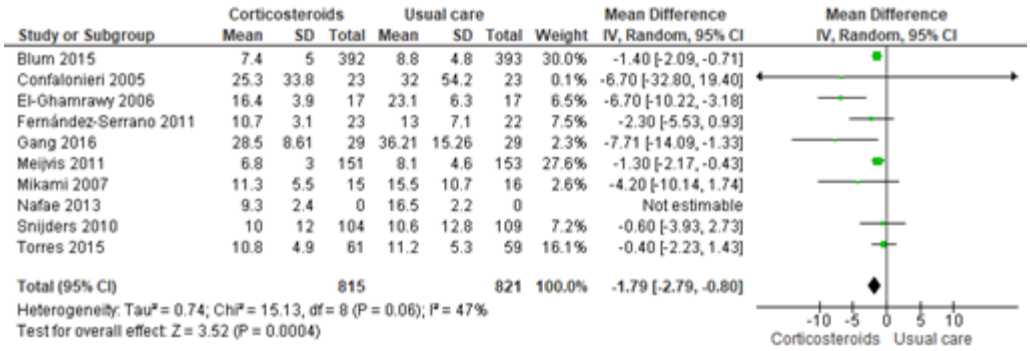


Figure 13 Effect of corticosteroids on the need of mechanical ventilation in CAP

patients

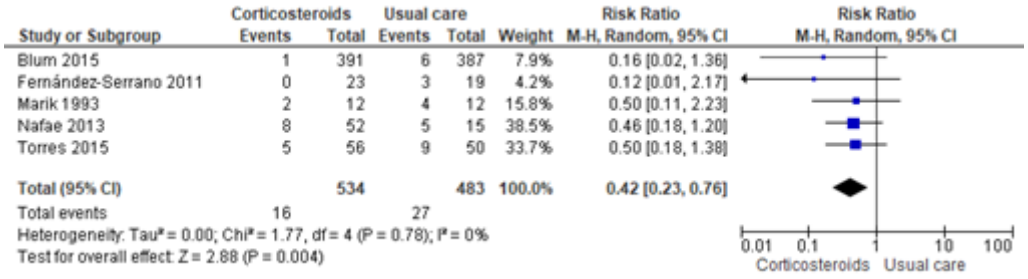


Figure 14 Effect of corticosteroids on duration of mechanical ventilation in CAP patients

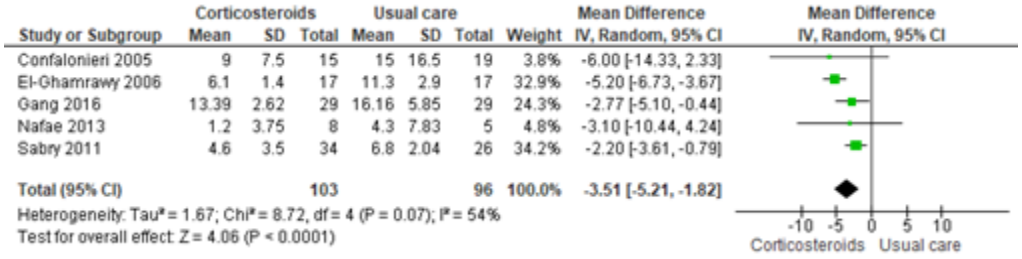


Figure 15 Effect of corticosteroids on serious hyperglycemia in CAP patients

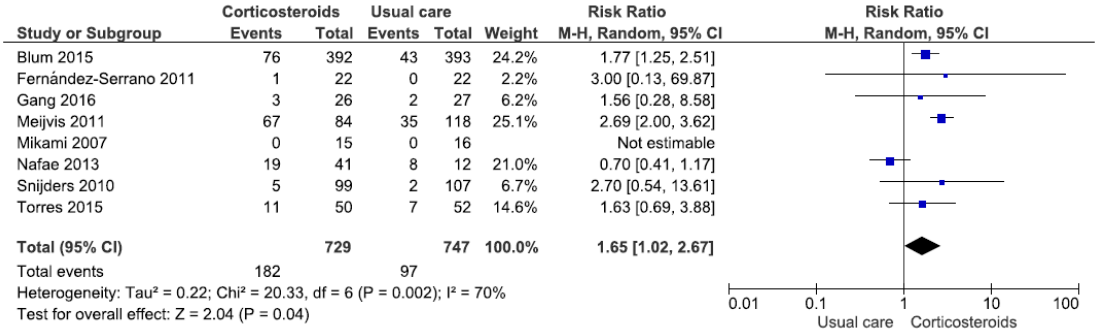


Figure 16 Effect of corticosteroids on gastrointestinal bleeding in CAP patients

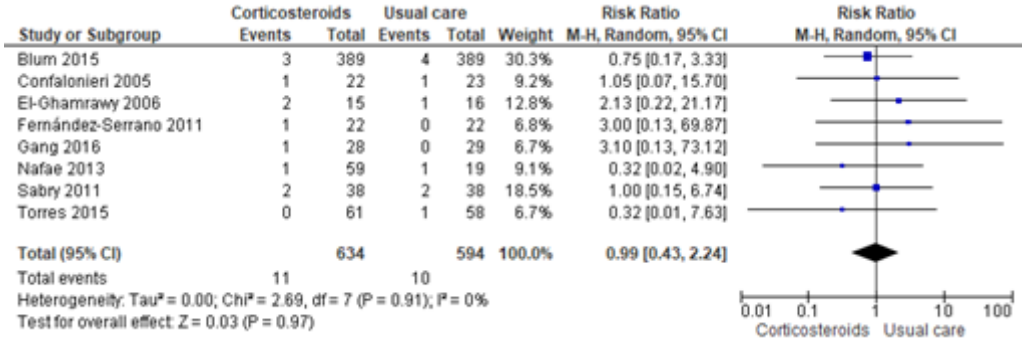


Figure 17 Effect of corticosteroids on neuropsychiatric events in CAP patients

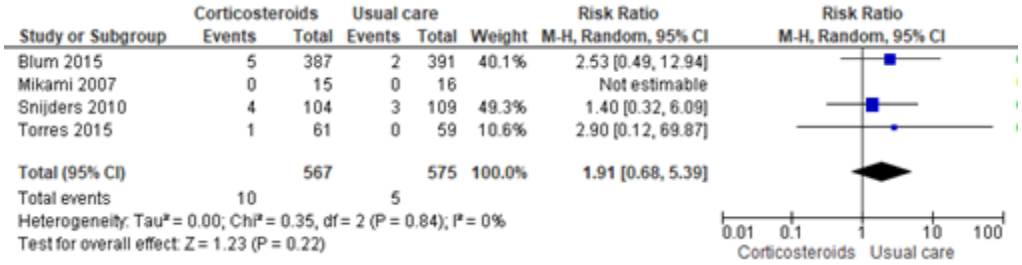
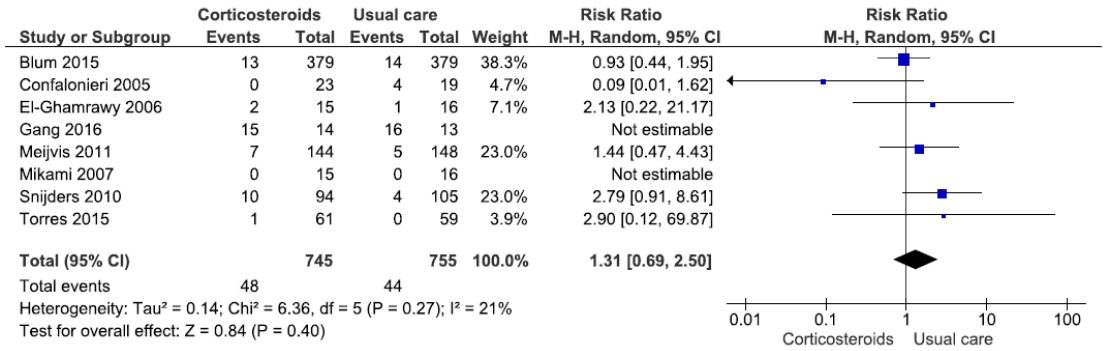


Figure 18 Effect of corticosteroids on super-infection in CAP patients



Appendix to: Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2020. doi: 10.1503/cmaj.200645.

Chapter 4: Treatment of Patients with Nonsevere and Severe Coronavirus Disease 2019: An Evidence-based Guideline

Cited as and reprinted from: Ye Z, Rochwerg B, Wang Y, Adhikari NK, Murthy S, Lamontagne F, et al. Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline. Can Med Assoc J. 2020;192(20):E536-E45.

GUIDELINE CPD

Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline

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CMAJ Podcasts: interview in English at https://soundcloud.com/cmajpodcasts/200648-guide; entrevue en français au https://soundcloud.com/cmajpodcasts/200648-guide-fre

This guideline will be updated at https://app.magicapp.org/#/guideline/EK6W0n as new evidence becomes available.

On Mar. 11, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic. The worldwide spread of COVID-19 represents a profound threat to human health.

Patients with COVID-19 present primarily with fever, cough, and myalgia or fatigue, and sometimes initially with predominantly gastrointestinal symptoms. A minority of patients progress to severe pneumonia, and about 15% of these patients to critical illness characterized by acute respiratory distress syndrome (ARDS), which is associated with mortality of about 50%.[1–3]

The enormity of the adverse health consequences of COVID-19 has understandably left clinicians and patients eager for interventions that can decrease progression, prevent mortality and speed recovery. This eagerness has perhaps contributed to overly sanguine assessments from experts, regulatory authorities and prominent politicians regarding the potential benefits of treatments, with underappreciation of potential harms.[4,5]

Use of medication without established effectiveness can undermine public trust, result in unnecessary harm, compromise investigations that might provide definitive answers and divert resources from truly beneficial interventions. Evidence-based guidelines for treatment of patients with COVID-19 provide one strategy for avoiding overuse of highly touted but unestablished therapies.

Therefore, we have developed an evidence-based guideline that focuses on both patients with nonsevere and severe COVID-19 and, for use of corticosteroids, patients with ARDS. Our guideline process followed standards of trustworthy guidelines,[6] including use of widely adopted Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for rating quality of evidence and grading strength of recommendations.[7] Given the anticipated paucity of evidence from studies enrolling patients with COVID-19, the recommendations hinge on both direct and relevant indirect evidence.

KEY POINTS

- The available evidence for treatment of coronavirus disease 2019 (COVID-19) is either indirect (from studies of influenza, severe acute respiratory syndrome and Middle East respiratory syndrome) or from several observational studies and randomized controlled trials in patients with COVID-19, which are limited in sample size and rigour, permitting only weak recommendations.
- Given the inevitable adverse effects of interventions, the guideline panel (which included 2 patient partners) inferred that most informed patients would decline treatment when only very low-quality evidence of benefits — and, thus, very large uncertainty — is available.
- The panel made only 1 weak recommendation in favour of treatment: use of corticosteroids in patients with acute respiratory distress syndrome (ARDS), based on indirect evidence.
- The panel made weak recommendations against use of corticosteroids in patients without ARDS, against use of convalescent plasma and against several antiviral drugs that have been suggested as potential treatments for COVID-19.
- Rigorous randomized trials are urgently needed to establish the benefits and risk of candidate interventions.

Scope

Health care providers represent the target audience of this guideline. The guideline includes 3 categories of interventions: corticosteroids, convalescent plasma therapy and antiviral drugs. We address the use of these interventions for COVID-19 in patients with nonsevere disease, severe disease and, for corticosteroids, those with ARDS, as the balance of benefits may differ among these groups. For instance, the death rate in patients with nonsevere COVID-19 is estimated to be 1/1000 and in those with severe disease is estimated at more than 100/1000, thus providing much more scope for important benefit in severe COVID-19.[1]

Our definition of severe COVID-19 pneumonia follows that of the WHO: fever or suspected respiratory infection, plus 1 of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or arterial oxygen saturation measured by pulse oximeter (SpO_2) ≤ 93% on room air.[8] The WHO definition of "severe" includes patients admitted to hospital with pneumonia who can be managed on medical wards and are not critically ill. Best evidence suggests that about 85% of such patients will never progress to critical illness such as ARDS.[1]

Because we anticipate that clinicians are unlikely to consider the use of convalescent plasma in patients with nonsevere COVID-19, for this intervention we addressed only patients with severe COVID-19. Similarly, clinicians are unlikely to consider corticosteroids in patients with nonsevere infection; in addressing corticosteroids use, we therefore focused on patients with severe COVID-19 and those with ARDS.

Recommendations

Box 1 summarizes the recommendations. We made 1 weak recommendation in favour of a treatment (corticosteroids in severe COVID-19 with ARDS) and made weak recommendations against use of the other treatments included in this guideline.

Box 1: Summary of recommendations

We suggest using corticosteroids in patients with severe coronavirus disease 2019 (COVID-19) and acute respiratory distress syndrome (ARDS) (weak recommendation).

- The agent, dose and duration of corticosteroid varied in the relevant randomized controlled trials. Methylprednisolone 40 mg intravenously for 10 days represents 1 reasonable regimen used by critical care clinicians on our panel.

We suggest not using corticosteroids in patients with severe COVID-19 who do not have ARDS (weak recommendation).

- If clinicians choose to use corticosteroids in patients who do not have ARDS, lower doses of corticosteroids for short periods may reduce the likelihood of toxicity.

We suggest not using convalescent plasma in patients with severe COVID-19 (weak recommendation).

We suggest not using ribavirin, umifenovir, favipiravir, lopinavir-ritonavir, hydroxychloroquine, interferon-α and interferon-β in patients with nonsevere COVID-19 (weak recommendation).

We suggest not using ribavirin, umifenovir, favipiravir, lopinavir-ritonavir, hydroxychloroquine, interferon-α and interferon-β in patients with severe COVID-19 (weak recommendation).

Corticosteroids

We suggest using corticosteroids in patients with severe COVID-19 and ARDS (weak recommendation).

Comment: The agent, dose and duration of corticosteroid varied in the relevant randomized controlled trials (RCTs). Methylprednisolone 40 mg intravenously for 10 days represents 1 reasonable regimen used by critical care clinicians on our panel.

Direct evidence

In 1 observational study[3] of patients with severe COVID-19 and ARDS, the administration of methylprednisolone reduced the risk of death (adjusted hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.20 to 0.83; very low-quality evidence) (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1).[9]

Indirect evidence

The biological rationale for administering corticosteroids in a variety of conditions causing ARDS — including viral infections, bacterial infections and noninfectious causes — is similar and relates to the effect of corticosteroids on the inflammatory cascade and subsequent alveolitis leading to respiratory compromise. Evidence from 851 patients with ARDS in 7 RCTs suggests that use of corticosteroids results in a reduction in mortality that, applied to patients with COVID-19, may reduce deaths by 17.3% (95% CI –27.8% to –4.3%; low-quality evidence) (Appendix 1).[9]

Corticosteroids may reduce the duration of mechanical ventilation by more than 4 days (low-quality evidence), but we are very uncertain regarding the effect of corticosteroids on length of stay in the intensive care unit (ICU) and length of hospital stay (Appendix 1).[9]

Corticosteroids may increase serious hyperglycemia events by 8.1% (low-quality evidence), may have little or no effect on gastrointestinal bleeding and neuromuscular weakness (low-quality evidence), and probably have little or no effect on superinfection (moderate-quality evidence) (Appendix 1).[9]

Rationale

Use of corticosteroids in patients with severe COVID-19 and ARDS may result in a substantial reduction in mortality, a critical outcome. The harm of short-term use of corticosteroids is limited. Based on our inferences regarding patients' values and preferences, we made a weak recommendation in favour of corticosteroids.

We suggest not using corticosteroids in patients with severe COVID-19 who do not have ARDS (weak recommendation).

Comment: If clinicians choose to use corticosteroids in patients who do not have ARDS, lower doses of corticosteroids for short periods may reduce the likelihood of toxicity.

Direct evidence

Very low-quality evidence from 2 cohort studies[10,11] that included 331 patients with severe COVID-19 raised the possibility that corticosteroids may increase mortality compared with no corticosteroids (HR 2.30, 95% CI 1.00 to 5.29); 1 of these studies[11] is a preprint (Appendix 1).[9]

Indirect evidence

Very low-quality evidence from 6129 patients with severe acute respiratory syndrome (SARS) in 2 observational studies[12,13] raises the possibility that corticosteroids may reduce mortality. Evidence from 290 patients with Middle East respiratory syndrome (MERS) in 1 observational study[14] also suggests that corticosteroids may reduce mortality, but again the evidence is very low quality. Evidence from SARS and MERS provides very low-quality evidence that corticosteroids may delay clearance of coronavirus ribonucleic acid (RNA) (Appendix 1).[9] Efforts should be made to study corticosteroids for viral pneumonia (as distinct from ARDS) in RCTs.

Very low-quality evidence from 8530 patients with influenza in 11 observational studies raises the possibility that corticosteroids may increase mortality. It remains possible that corticosteroids increase superinfection and the need for mechanical ventilation (very low-quality evidence) (Appendix 1).[9]

Very low-quality evidence from 2034 patients with community-acquired pneumonia in 13 RCTs raises the possibility that corticosteroids may reduce mortality. Corticosteroids may reduce the need for mechanical ventilation by 10.4% (95% CI −13.8% to −4.3%; low-quality evidence), while very low-quality evidence raises the possibility of reductions in length of ICU stay, length of hospital stay and duration of mechanical ventilation. Corticosteroids probably increase serious hyperglycemia events by 5.7% (0.18% to 15.3%; low-quality evidence) and may increase neuropsychiatric events and superinfection events (low-quality evidence). Corticosteroids may have little or no effect on gastrointestinal bleeding (low-quality evidence) (Appendix 1).[9]

Rationale

In patients with severe COVID-19 outside the ICU, any benefit of corticosteroids is less than in those with ARDS. The indirect evidence regarding mortality was very low quality and inconsistent among SARS, MERS, influenza and community-acquired pneumonia. Low-quality evidence suggests that corticosteroids, when used over the short term, have modest harm. In this context, when any benefit is very uncertain, our inferences regarding patient values and preferences dictate a weak recommendation against use of corticosteroids in patients with severe COVID-19 who do not have ARDS.

Convalescent plasma

We suggest not using convalescent plasma in patients with severe COVID-19 (weak recommendation).

Indirect evidence

Very low-quality evidence from 40 patients with SARS in 1 observational study[15] raises the possibility that convalescent plasma may reduce mortality (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1).[16]

Four RCTs[17–20] that included 572 patients with influenza contributed to very low-quality evidence suggesting that convalescent plasma may have little to no effect on mortality, may have a small benefit in hastening recovery and may reduce length of hospital stay and duration of mechanical ventilation. Use of convalescent plasma may result in little or no difference in rate of serious adverse events (−1.2%, 95% CI −3.5% to 2.3%; low-quality evidence) (Appendix 2).[16]

Rationale

Very low-quality evidence raised the possibility that convalescent plasma may have some benefit in important outcomes and may be safe. Given the resources associated with preparation and administration of convalescent plasma, we have insufficient evidence to support its use.

Antiviral drugs

We suggest not using ribavirin, umifenovir (Arbidol), favipiravir, lopinavir-ritonavir, hydroxychloroquine, interferon-α and interferon-β in patients with nonsevere COVID-19 (weak recommendation).

Because the likelihood of death from COVID-19 in patients with nonsevere disease is extremely low (in the range of 1/1000), we are very confident that antiviral drugs will have little or no effect on mortality in such patients.[1]

An RCT[21] of umifenovir and lopinavir-ritonavir reported other relevant outcomes in patients with nonsevere COVID-19, including cough, fever and progression to severe disease, but the RCT included only a total of 23 patients treated with umifenovir and 28 patients treated with lopinavir-ritonavir; as a result, the confidence intervals were so wide as to make the evidence uninformative (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1).[22] One observational study[23] in 120 patients with COVID-19 with mixed-severity disease provides very low-quality evidence that lopinavir-ritonavir may increase viral clearance at day 23 (Appendix 3).[22]

With respect to interferon-α, an observational study[24] in 70 patients with mixed-severity COVID-19 provides very low-quality evidence that the addition of interferon-α to umifenovir therapy may not affect time to viral clearance or length of hospital stay relative to umifenovir alone. There is no published evidence regarding benefit or harm of interferon-β or ribavirin in patients with nonsevere COVID-19.

With regard to favipiravir, an RCT[25] in 236 patients with mixed-severity COVID-19 suggested, in comparison with umifenovir, a possible higher incidence of recovery at day 7, but because of risk of bias, imprecision and indirectness, the evidence was only very low quality (Appendix 3).[22] One observational study[26] in 80 patients with nonsevere COVID-19 provides very low-quality evidence that favipiravir may increase viral clearance at day 7 relative to lopinavir-ritonavir. Symptomatic benefit outcomes from patients with nonsevere disease for other agents were unavailable.

Turning to harms, studies of interferon-α did not address symptomatic harms. Observational studies suggested substantial increases in anemia (26%) and bradycardia (15%) with ribavirin, but whether patients experienced symptoms remains uncertain.[27] Evidence regarding adverse effects in umifenovir is very low quality, and for favipiravir is low quality (Appendix 3).[22] An RCT[28] of lopinavir-ritonavir provides moderate-quality evidence of increased diarrhea (6%), nausea (9.5%) and vomiting (6.3%) with this drug combination.

Evidence for hydroxychloroquine came from 3 RCTs[29–31] of 240 patients with nonsevere COVID-19. Because of serious risk of bias (lack of blinding), imprecision (wide confidence intervals) and indirectness (both intervention and control groups included other drugs, limiting inferences regarding the effect of hydroxychloroquine), these studies provided very low-quality evidence

regarding the following possible effects: little or no effect on viral clearance, a small reduction in duration of fever, little or no progression from nonsevere to severe disease, and little or no effect on recovery at day 7 (Appendix 3).[22] Hydroxychloroquine may cause diarrhea in about 10% of patients (low-quality evidence). Very low-quality evidence suggests possible increases in headache, rash, nausea, vomiting and blurred vision (Appendix 3).[22]

Rationale

Because of a very low incidence of death, antiviral drugs cannot result in important mortality reductions in patients with nonsevere disease. We have no persuasive evidence of symptomatic benefit for any drug, with evidence of appreciable harm with ribavirin and lopinavir-ritonavir and high uncertainty regarding adverse effects in other drugs. Efforts should be made to study these agents in RCTs.

For all drugs to this point, the panel reached a consensus. For hydroxychloroquine, there was no suggestion of benefit in patients with nonsevere COVID-19, with possible increases in rash, nausea and vomiting. For hydroxychloroquine, 15 panel members voted for a weak recommendation against the drug, 3 voted for no recommendation, and 7 members had intellectual competing interests and did not vote.

We suggest not using ribavirin, umifenovir, favipiravir, lopinavir-ritonavir, hydroxychloroquine, interferon-α and interferon-β in patients with severe COVID-19 (weak recommendation).

Indirect evidence

Observational studies[12,32–34] of ribavirin and interferon in non–COVID-19 coronaviruses (SARS and MERS) provide point estimates suggesting mortality reductions, but confidence intervals are very wide and include mortality increases; overall, the evidence is very low quality (Appendix 3).[22] As presented in the previous section, an observational study[27] suggests frequent anemia and bradycardia in patients receiving ribavirin, but the effect on patient experience remains uncertain.

Direct evidence

We have no direct evidence for ribavirin or interferon-β in severe COVID-19 disease. For interferon-α, as presented in the previous section, an observational study[24] provides very low-quality evidence that the drug has minimal or no effect on time to viral clearance or length of hospital stay.

For umifenovir, the only RCT[21] enrolled 23 patients with nonsevere COVID-19 disease, leaving (in addition to indirectness of evidence from patients with nonsevere disease) confidence intervals for all outcomes so wide as to be uninformative (Appendix 3).[22] An observational study[35] in 504 patients with mixed-severity COVID-19 provides very low-quality evidence that umifenovir may decrease mortality.

For favipiravir, we noted in the previous section the very low-quality evidence of increased viral clearance relative to lopinavir-ritonavir (Appendix 3). An RCT[36] of lopinavir-ritonavir in 386 patients with influenza suggests the drug may not cause diarrhea (the results of this RCT have not yet been published).

Evidence from 199 patients with severe COVID-19 in 1 RCT[28] suggests that lopinavir-ritonavir may reduce mortality by 2.4% (95% CI –5.7% to 3.1%), length of ICU stay by 5 days (95% CI –9 to 0), and length of hospital stay by 1 day (95% CI –2 to 0), but given the 95% confidence intervals, the results include the possibility of no effect (all low-quality evidence, from imprecision and risk of bias). We found moderate-quality evidence of increases in diarrhea (6%), nausea (9.5%) and vomiting (6.3%) for lopinavir-ritonavir (Appendix 3).[22] As presented in the previous section, 1 observational study[23] in 120 patients with mixed-severity COVID-19 provides very low-quality evidence that lopinavir-ritonavir may increase viral clearance at day 23 (Appendix 3).[22] Very low-quality evidence from 181 patients with severe COVID-19 and 255 patients with mixed-severity disease in 2 observational studies (preprints)[37,38] raised the possibility that hydroxychloroquine may increase mortality and the need for mechanical ventilation (Appendix 3).[22]

Rationale

Very low-quality evidence raised the possibility that ribavirin, umifenovir, favipiravir, interferon-α and interferon-β may have little or no benefit in mortality for patients with severe COVID-19. We are also very uncertain regarding the safety of these drugs in patients with severe disease.

The panel reached consensus on all recommendations regarding antiviral drugs mentioned thus far. As described above, however, for lopinavir-ritonavir, although 1 RCT[28] suggested the combination may reduce mortality, the 95% CI (–5.7% to 3.1%) included a 3.1% increase in mortality, and because of an open-label design, the study was at high risk of bias. Similarly, the 95% CI with respect to estimates of decreased length of ICU and hospital stay included no effect, and the evidence was overall low quality. Considering the uncertainty and the likely increases in diarrhea (best estimate 6%), nausea (9.0%) and vomiting (6.4%), the panel made a weak recommendation against the use of lopinavir-ritonavir. Ultimately, 14 panel members voted to recommend against the drug combination, and 6 were in favour; 5 members had intellectual competing interests and did not vote.

In patients with severe COVID-19, 2 observational studies[37,38] raised the possibility that hydroxychloroquine may increase mortality and the need for mechanical ventilation. Ultimately, 15 panel members voted for a weak recommendation against the drug, 3 voted for no recommendation, and 7 members had intellectual competing interests and did not vote.

Methods

Group composition and process

The guideline steering committee comprised 5 members: the guideline chair (G.G.), the project lead (Z.Y.), a COVID-19 clinical investigator and clinical expert (B.D.), an academic pharmacist investigator (S.Z.) and a critical care physician and methodologist (B.R.). The main roles of the guideline steering committee included defining the scope of the guideline; proposing the initial specific clinical questions addressed by this guideline; choosing guideline panel members, including reviewing competing interests; determining the rules for reaching consensus or voting; overseeing the process of developing all affiliated systematic reviews and the summary of findings tables, and ensuring deadlines were met; and pro-

posing the initial values and preferences that the panel ultimately endorsed for use in this guideline.

The guideline panel comprised 26 members from 6 countries (China, Canada, South Korea, Saudi Arabia, Singapore, Mexico) and included 6 critical care physicians, 5 pharmacists, 3 respiratory physicians, 1 infectious diseases physician, 1 nurse, 1 patient partner who had recovered from mild and 1 from severe COVID-19, and 8 methodologists, all of whom are also involved in clinical care (Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1, contains the full list of guideline panel members).

The guideline panel met 3 times by videoconference (Feb. 28, Mar. 23, and Mar. 24, 2020). Before the first meeting and between the first and second panel meetings, the steering committee also met to discuss issues of scope, population and approaches to summarizing indirect evidence, planning the systematic reviews and formulating recommendations.

Following these meetings, the panel continued with email correspondence; in particular, the panel reviewed a revised summary of findings table on hydroxychloroquine after our identification of new evidence in April 2020 and revoted on the corresponding recommendation on Apr. 25, 2020.

Selection of priority questions

At its first meeting, the guideline panel established the issues to be addressed in the guideline, based on the members' judgment of the questions of foremost concern to clinicians treating patients with nonsevere and severe COVID-19. The earlier section on "Scope" outlines the populations and interventions on which the panel chose to focus. The panel advised the systematic review teams on the priority outcomes of interest.

Summarizing the evidence

Following recommended methods,[39] an independent group of systematic reviewers, with direction from the guideline steering committee and input from the panel, conducted 3 systematic reviews of the evidence relevant to our questions.[9,16,22] These 3 systematic reviews (1 addressing corticosteroids, 1 on antiviral agents and 1 on convalescent plasma) included searches on MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials and medRxiv in March 2020 and applied no restriction on the language of publication. Additional details regarding the searches are available in the systematic reviews.[9,16,22] We included RCTs, cohort and case–control studies, but not single-arm studies. We also updated the direct evidence from COVID-19 to Apr. 25, 2020.

To assess risk of bias in RCTs, we used a modified version of the Cochrane 1.0 risk of bias instrument.[40] To assess risk of bias in cohort and case–control studies, we used instruments developed by the CLARITY (Clinical Advances through Research and Information Translation) research group at McMaster University, Hamilton, Ontario.[41,42]

Using the GRADE approach, bodies of evidence were rated as high, moderate, low or very low quality. Randomized controlled trials began as high quality and observational studies as low quality.[43] Issues of risk of bias,[44] imprecision,[45] inconsistency,[46] indirectness[47] and publication bias[48] could lead to rating down of the quality of the study. The presence of a large magnitude of association or a dose–response gradient could lead to rating up of the quality of an observational study.[49]

We summarized evidence in GRADE summary of findings tables, presenting both relative and absolute effects. We obtained absolute effects by applying estimates of relative effects, sometimes from non–COVID-19 populations, to baseline risks that came from COVID-19 populations. In this document, because these are of most importance to patients, we present only absolute effects.

Because we anticipated a paucity of direct evidence from studies of patients with COVID-19, we summarized related indirect evidence from patients with SARS, MERS, ARDS, influenza, community-acquired pneumonia and, for adverse effects of convalescent plasma, Ebola virus disease. Using the GRADE approach, for efficacy outcomes from patients with SARS or MERS, we rated the evidence down 1 category for indirectness; for efficacy evidence from ARDS, influenza, community-acquired pneumonia and other acute viral infectious diseases, we rated the evidence down 2 categories for very indirect evidence. The panel considered evidence regarding adverse effects as less indirect than efficacy evidence and so rated the evidence down only once, or in some cases not at all, for indirect evidence.

Values and preferences

On the basis of the panel members' experience with patients, input from the 2 patient partners on the panel and knowledge of the limited available evidence, the panel specified the following value and preference judgments that were used to inform the recommendations. First, when modest harms were present and there was low-quality evidence of a small but important difference in an outcome important to patients (e.g., mortality), most patients would choose to receive an intervention. That is, most patients would place a higher value on an uncertain, small but important benefit than in avoiding modest harms. Second, when low-quality evidence suggests little or no benefit, or when only very low-quality evidence exists and effects are therefore very uncertain, most patients would decline the intervention.

Formulation of recommendations

The guideline panel developed the recommendations during the second and third guideline panel meetings and, as mentioned previously, for hydroxychloroquine during subsequent email correspondence. The panel had access to the summary of findings tables before the meetings, and the chair reviewed the details of the tables at the meetings. The recommendations were formulated at the meetings, after review of the evidence, based on magnitude of benefits and harms, quality of supporting evidence, and underlying values and preferences with, when relevant, some consideration of resource expenditure (Box 2).

The aim of the panel discussion was first to achieve consensus, which was successful for most recommendations. If the panel did not achieve consensus, a formal vote occurred, requiring 70% in favour of 1 option to make a recommendation. If the 70% threshold was not achieved, our process was to declare the panel undecided, make no recommendation, and instead report the vote and associated rationale. The chair endeavoured to guide the panel toward consensus without taking a position, and did not participate in the voting.

Box 2: Grading of recommendations

The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[7] to inform the recommendations. It determined the strength of recommendations according to the balance between desirable and undesirable outcomes, with consideration of patient values and preferences, confidence in the estimates of effect and their associated uncertainty or variability, and resource use.

Strong recommendations

The panel made no strong recommendations.

Weak recommendations

The panel made exclusively weak recommendations based on the low or very low quality of the evidence, inferences regarding patient values and preferences and, secondarily, resources consumed by unproven interventions.

Management of competing interests

Our competing interest procedures adhered to Guidelines International Network principles.[50] We collected both direct (financial) and indirect (intellectual) disclosures for all participants at the start of the guideline process and before publication. We excluded from the panel individuals with personal financial competing interests. Panel members completed a declaration of competing interests that steering committee members considered in making final decisions regarding conflicts, on a recommendation-by-recommendation basis (Appendix 5, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1). Members with intellectual conflicts, which included ongoing research addressing the treatments being considered, were permitted to participate in discussion but not in making decisions regarding recommendations for which they had competing interests.

Table 1 (part 1 of 2): International recommendations on the treatment of COVID-19

Intervention	IDSA guideline (Apr. 21, 2020)[51]	SSC guideline (Mar. 23, 2020)[52]	WHO interim guidance (Mar. 13, 2020)[8]	ANZICS guideline (version 1, Mar. 16, 2020)[53]	NICE guideline (Apr. 3, 2020)[54]	This guideline
Corticosteroids*	Among patients who have been admitted to hospital with COVID-19 pneumonia, the IDSA guideline panel suggests against the use of corticosteroids (conditional recommendation, very low-certainty evidence).	In adults on mechanical ventilation with COVID-19 and respiratory failure (without ARDS), the SSC guideline suggests against the routine use of systemic corticosteroids (weak recommendation).	The WHO interim guidance recommends not routinely giving systemic corticosteroids for treatment of viral pneumonia outside clinical trials.	The ANZICS guideline does not recommend corticosteroids for routine use in acute respiratory failure with COVID-19. Some patients will have appropriate alternative clinical indications for the use of corticosteroids, such as the presence of septic shock.	The NICE guideline recommends not routinely offering a corticosteroid unless the patient has other conditions for which these are indicated, such as asthma or chronic obstructive pulmonary disease.	We suggest using corticosteroids in patients with severe COVID-19 and ARDS (weak recommendation).
	Among patients who have been admitted to hospital with ARDS owing to COVID-19, the IDSA guideline panel recommends the use of corticosteroids in the context of a clinical trial (knowledge gap).	In adults on mechanical ventilation with COVID-19 and ARDS, the SSC guideline suggests using systemic corticosteroids, over not using corticosteroids (weak recommendation).				We suggest not using corticosteroids in patients with severe COVID-19 who do not have ARDS (weak recommendation).
Convalescent plasma*	Among patients who have been admitted to hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma in the context of a clinical trial (knowledge gap).	In adults who are critically ill with COVID-19, the SSC guideline suggests against the routine use of convalescent plasma (weak recommendation).	NR	NR	NR	We suggest not using convalescent plasma in patients with severe COVID-19 (weak recommendation).

Table 1 (part 2 of 2): International recommendations on the treatment of COVID-19

Intervention	IDSA guideline (Apr. 21, 2020)[51]	SSC guideline (Mar. 23, 2020)[52]	WHO interim guidance (Mar. 13, 2020)[8]	ANZICS guideline (version 1, Mar. 16, 2020)[53]	NICE guideline (Apr. 3, 2020)[54]	This guideline
Antiviral drugs						
Umifenovir	NR	NR	NR	NR	NR	We suggest not using umifenovir in patients with nonsevere and severe COVID-19 (weak recommendation).
Favipiravir	NR	NR	NR	NR	NR	We suggest not using favipiravir in patients with nonsevere and severe COVID-19 (weak recommendation).
Hydroxychloroquine	Among patients who have been admitted to hospital with COVID-19, the IDSA guideline panel recommends hydroxychloroquine in the context of a clinical trial (knowledge gap).	Insufficient evidence to make a recommendation	NR	NR	NR	We suggest not using hydroxychloroquine in patients with nonsevere and severe COVID-19 (weak recommendation).
Interferon-α	NR	NR	NR	NR	NR	We suggest not using interferon-α in patients with nonsevere and severe COVID-19 (weak recommendation).
Interferon-β	NR	NR	NR	NR	NR	We suggest not using interferon-β in patients with nonsevere and severe COVID-19 (weak recommendation).
Lopinavir-ritonavir	Among patients who have been admitted to hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir-ritonavir only in the context of a clinical trial (knowledge gap).	In critically ill adults with COVID-19, the SSC guideline suggests against the routine use of lopinavir-ritonavir (weak recommendation).	NR	NR	NR	We suggest not using lopinavir-ritonavir in patients with nonsevere and severe COVID-19 (weak recommendation).
Ribavirin	NR	NR	NR	NR	NR	We suggest not using ribavirin in patients with nonsevere and severe COVID-19 (weak recommendation).

Note: ANZICS = Australian and New Zealand Intensive Care Society, ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, IDSA = Infectious Diseases Society of America, NICE = National Institute for Health and Care Excellence, NR = not reported, SSC = Surviving Sepsis Campaign, WHO = World Health Organization.
*These interventions were not considered for use in patients with nonsevere COVID-19 in this guideline.

Implementation

This guideline will be available in user-friendly and multilayered formats for clinicians and patients through MAGICapp (https://app.magicapp.org/#/guideline/EK6W0n). This will include interactive GRADE summary of findings tables and consultation decision aids to facilitate shared decision-making. The guideline will be updated on MAGICapp as new information becomes available.

Additionally, the participants in this guideline anticipate being part of a wider effort to produce new recommendations rapidly when higher-quality practice-confirming or practice-changing evidence from RCTs becomes available.

The recommendations in this guideline should discourage use of interventions for which there is very low-quality evidence, thus decreasing medical waste. However, misleading statements about and advocacy for use of medications for which we were unable to find robust evidence of benefit at this time present the major barriers to this guideline's implementation.

Other guidelines

Table 1 summarizes the recommendations addressing corticosteroids, convalescent plasma and antiviral drugs from 5 guidelines on COVID-19, from the Infectious Diseases Society of America (IDSA),[51] Surviving Sepsis Campaign (SSC),[52] WHO,[8] Australian and New Zealand Intensive Care Society (ANZICS)[53] and UK National Institute for Health and Care Excellence (NICE).[54]

With respect to corticosteroids and ARDS, IDSA recommends use only in the clinical trial context; SSC suggests in favour; and WHO, ANZICS and NICE all recommend against. In patients without ARDS, all guidelines recommend against use of corticosteroids.

Regarding convalescent plasma, IDSA recommends its use only in the context of a clinical trial. The SSC and our guideline suggested not using convalescent plasma. Other guidelines did not address convalescent plasma.

The IDSA recommended use of lopinavir-ritonavir only in the context of a clinical trial, and SSC, like our guideline, suggested against using this drug. The other guidelines did not address lopinavir-ritonavir. The IDSA recommended use of hydroxychloroquine only in the context of a clinical trial, and SSC made no recommendation on hydroxychloroquine; the other guidelines did not address hydroxychloroquine. None of these guidelines addressed any of the other drugs for which our guideline made recommendations.

Gaps in knowledge

The benefits and, to a considerable extent, the harms, associated with the interventions addressed in this guideline remain very uncertain. Although RCT evidence is required for all agents considered, the more promising agents should likely receive higher priority.

Because of the most promising evidence of important benefits at present, we suggest conduct of large, methodologically sophisticated RCTs to address the effect of corticosteroids in patients with severe COVID-19 and particularly those with ARDS, and lopinavir-ritonavir and umifenovir in severe COVID-19. Hydroxychloroquine would be another candidate for further study, not because of current evidentiary support from human studies, but rather because of the results from preclinical studies and the attention the drug has received thus far.

A large number of RCTs are under way to assess interventions in COVID-19, including an important WHO-sponsored initiative, the SOLIDARITY trial.[55]

Limitations

At the time we determined the scope of the guideline, we decided not to include remdesivir because it was not licensed for use anywhere in the world and tocilizumab because there were no studies available regarding its use. Both drugs are now among those being considered for use in COVID-19 and our failure to address them constitutes a limitation of this guideline.

The composition of the guideline panel represents another limitation: our panel included more men than women, and panellists were mainly from China and Canada.

Conclusion

Given the largely very low-quality evidence regarding benefits of the treatments that the panel considered, and given the panel's inferences regarding patient values and preferences, the panel made almost exclusively weak recommendations against use of the interventions included in this guideline. The research community should interpret the weak recommendations that this guideline offers as a call to urgently undertake rigorous RCTs of the candidate interventions.

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Competing interests: Younsuck Koh, Bin Du and Yaseen Arabi report being authors of *Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults With Coronavirus Disease 2019*, which made 1 recommendation relevant to this guideline regarding corticosteroids in acute respiratory distress syndrome. Bin Du reports being the principal investigator of an ongoing prospective randomized controlled trial (RCT) examining the efficacy of corticosteroids in patients with moderate-to-severe coronavirus disease 2019 (COVID-19), which is funded by the research grant 2020YFC0841300 from the Ministry of Science and Technology of the People's Republic of China. Srinivas Murthy and Robert Fowler report being investigators in a trial, supported by a Canadian Institutes of Health Research (CIHR) grant, evaluating the effect of corticosteroids and antiviral drugs (hydroxychloroquine and lopinavir-ritonavir) in patients with COVID-19. Ning Shen reports being an investigator in a trial evaluating the effect of hydroxychloroquine in patients with COVID-19, funded by Peking University Health Science Center. Neill Adhikari reports being a co-investigator of a CIHR-funded grant of antivirals in hospitalized patients with COVID-19 and of a second CIHR-funded grant of a variety of treatments, including corticosteroids, in critically ill patients with COVID-19. Mark Loeb reports receiving a grant and personal fees from the World Health Organization (WHO) for contract work on influenza and antibiotic resistance; consulting fees and a grant from Seqirus for an RCT on influenza; personal fees as a member of the advisory board and non-financial support from Sanofi, for an in-kind vaccine for the influenza RCT; and consulting fees from Pfizer and Medicago. Dr. Loeb also reports being an investigator in a trial evaluating the effect of chloroquine-azithromycin in patients with COVID-19, funded by Ontario Ministry of Health, Bayer and Abbott. François Lamontagne and Bram Rochwerg report being investigators in a trial, supported by a CIHR grant, evaluating the effect of corticosteroids and antiviral drugs (hydroxychloroquine and lopinavir-ritonavir) in patients with COVID-19. No other competing interests were declared.

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Appendix 1 (as supplied by the authors): Summary of findings for corticosteroids

Table 1: GRADE summary of findings: Corticosteroids in COVID-19 with ARDS, direct evidence from observational studies of COVID-19 with ARDS patients

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	HR 0.41 (95% CI 0.20 to 0.83) Based on data from 84 COVID-19 patients with ARDS in 1 observational study	61.8%	-29.2% (-44.3% to -6.8%)	Very low (Serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality

Note: ARDS = acute respiratory distress syndrome, HR = hazard ratio, CI = confidence interval.

1Mortality baseline risk from COVID-19 ARDS patients without corticosteroid treatment – Wu C, et al. doi:10.1001/jamainternmed.2020.0994.

2Observational study started at low quality of evidence. Although confidence interval appears narrow the small sample size and implausibly large effect led to rating down for imprecision.

Appendix to: Ye Z, Rochwerg B, Wang Y, et al. Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline.
CMAJ 2020. doi: 10.1503/cmaj.200648.

Table 2: GRADE summary of findings: Corticosteroids in COVID-19 with ARDS, indirect evidence from randomized controlled trials of patients with ARDS

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	RR 0.72 (95% CI 0.55 to 0.93) Based on data from 851 ARDS patients in 7 RCTs	61.8%	- 17.3% (-27.8% to - 4.3%)	Low (Very serious indirectness[2])	Corticosteroids may result in a large reduction in mortality
Length of ICU stay	Based on data from 297 patients in 3 RCTs	The median duration of length of ICU was 8.0 days	MD 0.1 days (-3.0 to 3.2)	Very Low (Serious inconsistency, very serious indirectness and serious imprecision[3])	We are very uncertain of the effect of corticosteroids on length of ICU stay
Length of hospital stay	Based on data from 324 patients in 3 RCTs	The median duration of length of stay was 18.0 days	MD -3.6 days (-7.2 to - 0.02)	Very Low (Very serious indirectness and serious imprecision[4])	We are very uncertain of the effect of corticosteroids on length of hospital stay
Duration of mechanical ventilation	Based on data from 888 patients in 6 RCTs	The median duration of mechanical ventilation was 14.5 days	MD -4.8 days (-7.0 to - 2.6)	Low (Very serious indirectness[2])	Corticosteroids may reduce duration of mechanical ventilation
Serious hyperglycemia	RR 1.12 (95% CI 1.01 to 1.24) Based on data from 565 patients in 3 RCTs	67.6%	8.1% (0.7% to 16.2%)	Low (Serious indirectness and serious imprecision[5])	Corticosteroids may increase serious hyperglycemia events
Neuromuscular weakness	RR 0.85 (95% CI 0.62 to 1.18) Based on data from 271 patients in 2 RCTs	26.4%	-3.9% (-10% to 4.7%)	Low (Serious indirectness, serious imprecision[6])	Corticosteroids may not increase neuromuscular weakness

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Gastrointestinal bleeding	RR 0.71 (95% CI 0.30 to 1.73) Based on data from 250 patients in 2 RCTs	14.0%	-4.0% (-9.8% to 10.2%)	Low (Serious indirectness, serious imprecision[6])	Corticosteroids may not increase gastrointestinal bleeding
Superinfection	RR 0.82 (95% CI 0.67 to 1.02) Based on data from 798 patients in 5 RCTs	33.0%	-5.9% (-10.8% to 0.6%)	Moderate (Serious indirectness[7])	Corticosteroids probably do not increase superinfection events

Note: RR = risk ratio, CI = confidence interval, RCTs = randomized controlled trials, MD = mean difference, ICU = intensive care unit.

1Mortality baseline risk from COVID-19 ARDS patients without corticosteroid treatment – Wu C, et al. doi:10.1001/jamainternmed.2020.0994. The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events obtained from the median estimate from the control group in the included RCTs.

2We rated down two levels due to indirectness; the ARDS etiology across the studies is inconsistent and might not represent the COVID-19 population.

3We rated down two levels due to indirectness; one for inconsistency (I^2=73%, heterogeneity p-value 0.03) and one for imprecision because effect estimate consistent with benefit or harm.

4We rated down two levels due to indirectness and one for of imprecision due to the confidence interval including a trivial reduction in hospital stay.

5We rated down by one level due to indirectness, as we do not expect the COVID-19 population differs as much from other populations in adverse effects as in benefits; and we rated down by one level for imprecision due to the lower confidence interval, 0.7% representing an unimportant increase in hyperglycemia.

6We rated down by one level due to indirectness as in 4; we rated down by one level for imprecision, effect estimate consistent with benefit or harm.

7We rated down by one level due to indirectness as in 4; we did not rate down due to imprecision because the largest degree of harm consistent with the evidence is 7 in 1,000, which we judge unimportant.

Table 3: GRADE summary of findings: Corticosteroids in severe COVID-19, direct evidence from observational studies of severe COVID-19 patients

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	HR 2.30 (95% CI 1.00 to 5.29) Based on data from 331 severe COVID-19 patients in 2 observational studies	10.4%	11.9% (0 to 33.7%)	Very low (Serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality

Note: HR = hazard ratio, CI = confidence interval.

1Baseline risk from a study of the severe COVID-19 patients without corticosteroids use - Guan W et al. doi: 10.1056/NEJMoa2002032.

2Observational study started at low quality of evidence. We rated down one level due to serious imprecision (wide confidence interval).

Appendix to: Ye Z, Rochwerg B, Wang Y, et al. Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline. *CMAJ* 2020. doi: 10.1503/cmaj.200648.

Table 4: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from randomized controlled trials and observational studies of patients hospitalized with SARS

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group	Difference (95% CI)		
Mortality	HR 0.83 (95% CI 0.41 to 1.66) Based on data from 6129 SARS patients in 2 observational studies	10.4%[1]	-1.7% (-6.0% to 6.3%)	Very low (Serious indirectness and serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality
Median time for CoV RNA to become undetectable in plasma	Based on data from 16 SARS patients in 1 RCT	8.0 days[3]	MD 4.0 days (2.0 to 6.0)	Very low (Serious risk of bias, serious indirectness and serious imprecision[4])	We are very uncertain of the effect of corticosteroids on time for CoV RNA to become undetectable in plasma

Note: SARS = severe acute respiratory syndrome, HR = hazard ratio, CI = confidence interval, RNA = ribonucleic acid, RCT = randomized controlled trial, MD = mean difference.

1Baseline risk from a study of the severe COVID-19 patients without corticosteroids use - Guan W et al. doi: 10.1056/NEJMoa2002032.

2Observational studies start as low quality of evidence. We rated down one level due to serious indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from SARS patients) and one level due to serious imprecision (the confidence interval includes both an important benefit and an important harm).

3Baseline risk from the randomized trial which reported median time for SAR-CoV RNA to become undetectable in plasma for no corticosteroids group - Lee N, et al. doi:10.1016/j.jcv.2004.07.006.

4Randomized trial started at high quality of evidence. We rated down due to serious risk of bias, serious indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from SARS patients) and serious imprecision (because of small sample size).

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CMAJ 2020. doi: 10.1503/cmaj.200648.

Table 5: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from observational studies of patients hospitalized with MERS

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group	Difference (95% CI)		
Mortality	OR 0.75 (95% CI 0.52 to 1.07) Based on data from 290 MERS patients in 1 observational study	10.4%[1]	-2.4% (-4.7% to 0.6%)	Very low (Serious indirectness and serious imprecision[2])	We are very uncertain of the effect of corticosteroids on mortality
CoV RNA clearance	HR 0.35 (95% CI 0.17 to 0.72) Based on data from 189 MERS patients in 1 observational study	29.8%[3]	-18.2% (-24.0% to -7.3%)	Very low (Serious imprecision[4])	We are very uncertain of the effect of corticosteroids on CoV RNA clearance

Note: MERS = middle east respiratory syndrome, OR = odds ratio, RNA = ribonucleic acid, HR = hazard ratio.

1Baseline risk from a study of the severe COVID-19 patients without corticosteroids use: Guan W et al. doi: 10.1056/NEJMoa2002032.

2Observational studies started at low quality of evidence. We rated down one level due to serious indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from MERS patients), and one level due to serious imprecision (the confidence interval includes both a trivial and an important effect).

3Baseline risk from the observational study which reported MERS-CoV RNA clearance for no corticosteroids group: Arabi YM et al. doi: 10.1164/rccm.201706-1172OC.

4Observational studies started at low quality of evidence. We rated down one level due to serious imprecision because of the small sample size.

Appendix to: Ye Z, Rochwerg B, Wang Y, et al. Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline. *CMAJ* 2020. doi: 10.1503/cmaj.200648.

Table 6: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from observational studies of patients hospitalized with influenza

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group	Difference (95% CI)		
Mortality	OR 1.70 (95% CI 1.31 to 2.21) Based on data from 8530 participants in 11 observational studies	10.4%[3]	6.1% (2.8% to 10.0%)	Very Low (Serious indirectness[1])	We are very uncertain of the effect of corticosteroids on mortality
Superinfection	OR 2.74 (95% CI 1.51 to 4.95) Based on data from 6114 participants from 7 observational studies	7.2%[4]	10.3% (3.3% to 20.5%)	Very low (Serious risk of bias and indirectness[2])	We are very uncertain of the effect of corticosteroids on superinfections
Mechanical ventilation	OR 5.54 (95% CI 1.83 to 16.80) Based on data from 4364 participants from 4 observational studies	41.8%[4]	38.1% (15.0% to 50.6%)	Very low (serious risk of bias and indirectness[2])	We are very uncertain of the effect of corticosteroids on need for mechanical ventilation

1Observational studies started at low quality of evidence. Additional concern was indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from hospitalized influenza patients).

2Observational studies started at low quality of evidence. Additional concerns included high risk of indication bias because unadjusted estimates included and indirectness (we applied the results to severe COVID-19 patients, but the relative effect was derived from hospitalized Influenza patients).

3Baseline risk from a study of the severe COVID-19 patients without corticosteroids use: Guan W et al. doi: 10.1056/NEJMoa2002032.

4Baseline risk comes from median effect of the control group in the included studies.

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Table 7: GRADE summary of findings: Corticosteroids in severe COVID-19, indirect evidence from randomized controlled trials of patients hospitalized with CAP

Outcomes	Relative effects	Absolute effect estimates		Quality of evidence	Plain language summary
		Baseline risk for control group[1]	Difference (95% CI)		
Mortality	RR 0.70 (95% CI 0.50 to 0.98) Based on data from 2034 patients in 13 RCTs	10.4%	-3.1% (-0.2% to -5.2%)	Very low (Very serious indirectness[2] and serious inconsistency)	We are very uncertain of the effect of corticosteroids on mortality
Length of ICU stay	Based on data from 1376 patients in 8 RCTs	The median length of ICU stay was 8.3 days	MD -1.7 days (-3.4 to 0.1)	Very low (Serious inconsistency, very serious indirectness and serious imprecision[3])	We are very uncertain of the effect of corticosteroids on length of ICU stay
Length of Hospital stay	Based on data from 1636 patients in 10 RCTs	The median length of hospital stay was 14.3 days	MD -1.8 days (-2.8 to -0.8)	Very low (Serious inconsistency, very serious indirectness and serious imprecision[4])	We are very uncertain of the effect of corticosteroids on length of hospital stay
Need for mechanical ventilation	RR 0.42 (95% CI 0.23 to 0.76) Based on data from 1017 patients in 5 RCTs	18.0%	-10.4% (-13.8% to -4.3%)	Low (Very serious indirectness[2])	Corticosteroids may reduce need for mechanical ventilation
Duration of mechanical ventilation	Based on data from 199 patients in 5 RCTs	The median duration of mechanical ventilation was 11.3 days	MD -3.5 days (-5.2 to -1.8)	Very low (Serious risk of bias and very serious indirectness[5])	We are very uncertain of the effect of corticosteroids on duration of mechanical ventilation

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Serious hyperglycemia	RR 1.62 (95% CI 1.02 to 2.67) Based on data from 1476 patients in 8 RCTs	9.2%	5.7% (0.18% to 15.3%)	Low (Serious indirectness[6])	Corticosteroids probably increase serious hyperglycemia events
Gastrointestinal bleeding	RR 0.99 (95% CI 0.43 to 2.24) Based on data from 1228 patients in 8 RCTs	3.0%	-0.03% (-1.7% to 3.7%)	Low (Serious indirectness and serious imprecison[6])	Corticosteroids may have little or no impact on gastrointestinal bleeding
Neuropsychiatric events	RR 1.91 (95% CI 0.68 to 5.39) Based on data from 1142 patients from 4 RCTs	1.6%	1.4% (-0.5% to 7%)	Low (Serious indirectness and serious imprecison[6])	Corticosteroids may result in a small increase neuropsychiatric events
Superinfection	1.31 (95% CI 0.69 to 2.50) Based on data from 1500 patients in 8 RCTs	3.7%	1.1% (-1.1% to 5.5%)	Low (Serious indirectness and serious imprecison[6])	Corticosteroids may result in a small or no increase superinfection events

Note: RR = risk ratio, CI = confidence interval, RCTs = randomized controlled trials, MD = mean difference.

1Mortality baseline risk was obtained from COVID-19 ARDS patients without corticosteroid treatment – Guan 10.1056/NEJMoa2002032. The baseline risk for the length of ICU stay, hospital stay, duration of mechanical ventilation and adverse events comes from median effect of the control group in the included RCTs.

2We rated down two levels due to indirectness; the pneumonia etiology across the studies is inconsistent and might not represent the COVID-19 population. We also rated down for inconsistency because of a possible subgroup effect that suggests mortality benefit restricted to those with severe pneumonia.

3We rated down two levels due to indirectness; one for inconsistency (I^2=76%, heterogeneity p-value 0.0001); and one for of imprecision because the effect estimates are consistent with important benefit and harm.

4We rated down two levels due to indirectness; one for inconsistency (I^2=47%, heterogeneity p-value 0.006) and one for imprecision because the lower confidence interval includes important benefit and important harm.

5We rated down one level due to risk of bias and two levels due to indirectness. We did not rate down due to inconsistency, the effect estimates were in the same direction, despite the I2 54% and the p value of 0.07.

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6 We rated down by one level due to indirectness, as we do not expect the COVID-19 population differs as much from other populations in adverse effects as it does in benefits, and one for imprecision because effect estimates are not consistent with benefit or harm.

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Appendix 2 (as supplied by the authors): Patient or population: Children or adults with severe COVID-19 infection
Intervention: Convalescent or hyperimmune intravenous immunoglobulin
Comparison: Usual care + placebo (saline or intravenous immunoglobulin)

Outcomes	Relative effects, Source of evidence	Absolute effects		Certainty/Quality of evidence	Plain language summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality (7- 28 days)	RR 0.94 (95%CI 0.49 to 1.80) Based on 572 influenza patients in 4 RCTs	104[1]	-6 (-53, 84)	Very Low ⨁⊖ ⊖⊖ (Very serious indirectness and serious imprecision)[2]	Convalescent plasma may have little to no effect on mortality but the evidence is very uncertain
Mortality (22 days)	RR 0.10 (95% CI 0.01 to 1.70) Based on 40 SARS patients in 1 observational study	104[1]	-94 (-103, 73)	Very Low ⨁⊖ ⊖⊖ (Serious indirectness, very serious risk of bias and serious imprecision)[3]	Convalescent plasma could have an important effect on decreasing or increasing mortality but the evidence is very uncertain
Recovery by 28 days as measured by a 6-point ordinal scale[4]	Proportional odds ratio for recovery[4] OR 1.05 (95% CI 0.67 to 1.64) Based on 438 influenza patients from 2 RCTs	104[1]	5, (-30, 56)	Very Low ⨁⊖ ⊖⊖ (Very serious indirectness and serious imprecision)[2]	Convalescent plasma may have little to no effect on recovery but the evidence is very uncertain
Length of hospital stay in days	Based on 259 influenza patients in 3 RCTs	Median 13 days[5]	MD -1.62 (-3.82, 0.58) days	Very Low ⨁⊖ ⊖⊖ (Very serious indirectness and serious imprecision)[2]	Convalescent plasma may confer a small reduction in hospital length of stay but the evidence is very uncertain
Length of ICU stay in days	Based on 149 influenza patients in 2 RCTs	Median 7 days[6]	MD -0.32 (95% CI -3.20 , 2.56)	Very Low ⨁⊖ ⊖⊖ (Very serious indirectness and serious imprecision)[2]	Convalescent plasma may have little to no effect in reducing duration of ICU stay but the evidence is very uncertain

Days on mechanical ventilation	Based on 83 influenza patients in 2 RCTs	Median 9.25 days[6]	MD -3.67 (95% CI -7.70, 0.36)	Very Low ⨁⊖ ⊖⊖ (Very serious indirectness and serious imprecision)[2]	Convalescent plasma may reduce days of mechanical ventilation but the evidence is very uncertain
Serious adverse events	RR 0.85 (95% CI 0.56, 1.29) Based on 576 patients with influenza in 3 RCTs	80[7]	-12 (-35, 23)	Low ⨁⨁⊖⊖ (Serious indirectness and imprecision)[8]	Convalescent plasma may result in little or no difference in number of serious adverse events.

RCT: randomized controlled trials; ICU: Intensive care unit; MD: Mean Difference;RR: Relative risk; OR: Odds ratio; CI: Confidence interval

1. We chose the baseline risk from hospitalised COVID-19 patients who did not receive convalescent plasma and steroids from the paper by Guan, W. J, 2020, doi:10.1056/NEJMoa2002032.[3] This paper reports 96/173 severe patients did not receive steroids or hyperimmune plasma of which 10 patients died (information obtained from email communication). Hence, the baseline mortality risk is 10/96=10.4%. The median duration of hospitalization was 12.0 days (mean, 12.8).
2. We rated down two levels for indirectness since clinical and epidemiological characteristics of patients with influenza vary from COVID-2. We rated down one level for imprecision because the confidence interval included both important benefit and important harm
3. Evidence from observational studies beigins as low quality evidence We rated one level of indirectness since evidence came from SARS-CoV than COVID-19. Rated one level down for imprecision because the confidence intervals included both important benefit and important harm.
4. Recovery defined by an ordinal outcome (6 mutually exclusive categories) at 28 days: Death, in ICU, in-hospital with O2 support, in-hospital without O2 support, discharged but not normal, discharged and fully recovered. OR of >1 indicates treatment is better than control, interpreted as odds of better recovery is 1.24 times higher among those treated with hyperimmune plasma than control arm. This OR is similar across categories. We also assume the risk differences between treatment groups is same across categories of the outcome.
5. We chose the median duration of hospitalization from hospitalised COVID-19 patients with severe disease from the paper by Guan, W. J, 2020, doi:10.1056/NEJMoa2002032.[3]
6. This is the median days in ICU obtained from the control arm of RCTs including patients with severe influenza.
7. The baseline risk of serious adverse events obtained from control arm of studies including influenza (3 studies)
8. We rated down one level for indirectness for this safety outcome, inferring that the adverse effects are likely to be similar across viral illneses and one level down for imprecison because the confidence intervals included both important benefit and important harm

Appendix 3 (as supplied by the authors)

GRADE summary of findings on antivirals in COVID-19

Table 1. GRADE summary of findings: Ribavirin in non-severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Symptomatic anemia	OR 3.00 (95%CI 1.77 to 5.16) Based on data from 306 SARS patients with mixed severity in 1 observational study	296[1]	262 (131 to 388)	Very low ⊕ O O O (Serious indirectness)[2]	Ribavirin may result in a large increase in anemia, but we are very uncertain about the effect of ribavirin on symptomatic anemia.
Symptomatic bradycardia	OR 2.30 (95%CI 1.21 to 4.20) Based on data from 306 SARS patients with mixed severity in 1 observational study	171[1]	151 (29 to 293)	Very low ⊕ O O O (Serious indirectness)[3]	Ribavirin may result in a large increase in bradycardia, but we are very uncertain about the effect of ribavirin on symptomatic bradycardia.

[1]Baseline risk from non-severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Muller MP. doi: 10.1592/phco.27.4.494).
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic anemia). Anemia was defined as decrease in hemoglobin level of 2 g/dl.
[3]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic bradycardia). Bradycardia was defined as heart rate < 55 bpm.

Table 2. GRADE summary of findings: Ribavirin in severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	OR 0.66 (95%CI 0.04 to 12.36) Based on data from 51 MERS patients with mixed severity in 1 observational study	104[1]	-33 (-99 to 485)	Very low ⊕ O O O (Serious imprecision and indirectness)[2]	We are very uncertain of the effect of ribavirin on mortality
Mortality	OR 0.83 (95%CI 0.49 to 1.41) Based on data from 1334 SARS patients with mixed severity in 2 observational studies	104[1]	-16 (-50 to 37)	Very low ⊕ O O O (Very serious indirectness and serious imprecision)[3]	We are very uncertain of the effect of ribavirin on mortality
Symptomatic anemia	OR 3.00 (95%CI 1.77 to 5.16) Based on data from 306 SARS patients with mixed severity in 1 observational study	296[4]	262 (131 to 388)	Very low ⊕ O O O (Serious indirectness)[5]	Ribavirin may result in a large increase in anemia, but we are very uncertain about the effect of ribavirin on symptomatic anemia.
Symptomatic bradycardia	OR 2.30 (95%CI 1.21 to 4.20) Based on data from 306 SARS patients with mixed severity in 1 observational study	171[4]	151 (29 to 293)	Very low ⊕ O O O (Serious indirectness)[6]	Ribavirin may result in a large increase in bradycardia, but we are very uncertain about the effect of ribavirin in symptomatic bradycardia.

[1]We chose the baseline risk from severe COVID-19 patients in: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: indirectness (MERS patients), and imprecision (Wide confidence interval includes no difference).
[3]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: imprecision (Wide confidence interval includes no difference), and for two issues of indirectness (SARS patients. OR was estimated from HR in one study).
[4]Baseline risk from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Muller MP. doi: 10.1592/phco.27.4.494).
[5]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic anemia). Anemia was defined as decrease in hemoglobin level of 2 g/dl.
[6]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for indirectness (Surrogate outcome for symptomatic bradycardia). Bradycardia was defined as heart rate < 55 bpm.

Table 3. GRADE summary of findings: Hydroxychloroquine in non-severe COVID-19, direct evidence from three RCTs of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Viral clearance at day 14	RR 0.98 (95%CI 0.89 to 1.07) Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	714[1]	-14 (-79 to 50)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on viral clearance at day 14.
Duration of fever (day)	Based on data from 39 non-severe patients in 1 RCT	3.2[3]	-1 (-1.64 to -0.36)	Very low ⊕ O O O (Serious risk of bias, imprecision and indirectness)[4]	We are very uncertain of the effect of hydroxychloroquine on duration of fever.
Progressing from non-severe to severe	RR 0.96 (95%CI 0.10 to 9.66) Based on data from 240 non-severe patients in 3 RCTs	143[1]	-6 (-129 to 857)	Very low ⊕ O O O (Serious risk of bias, indirectness and very serious imprecision)[5]	We are very uncertain of the effect of hydroxychloroquine on progressing from non-severe to severe.
Clinical recovery at day 7	RR 1.10 (95%CI 0.44 to 2.77) Based on data from 117 non-severe patients and 2 severe patients in 1 RCT	127[6]	13 (-71 to 225)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[7]	We are very uncertain of the effect of hydroxychloroquine on clinical recovery at day 7.
Diarrhea	Not applicable, no events in control group Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	0[1]	106 (40 to 171)	Low ⊕ ⊕ O O (Serious risk of bias and indirectness)[8]	Hydroxychloroquine may increase diarrhea.
Headache	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[3]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on headache.
Rash	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[10]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on rash.
Nausea	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[10]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on nausea.
Vomiting	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[10]	29 (0 to 68)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on vomiting.
Blurred vision	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[11]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of hydroxychloroquine on blurred vision.

[1]We chose the baseline risk from non-severe COVID-19 patients in the study from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from the referred study were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.

[2]We rated down three levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference), one for indirectness (Both intervention and control patients used other antiviral agents. Possible synergic effect between hydroxychloroquine and other antiviral agents).

[3]We used the control group of the study itself to serve as baseline risk (Chen Z. doi: 10.1101/2020.03.22.20040758).

[4]We rated down three levels: one for risk of bias (No blinding on patients), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), one for imprecision (Wide confidence interval includes very small benefit).

[5]We rated down for the following: risk of bias (No blinding on patients in one study. Open-label in other studies), indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), and imprecision (Very wide confidence interval includes important benefit and harm).

[6]We used the control group of the study itself to serve as baseline risk. Clinical recovery was defined as: resolving from fever to an axillary temperature of ≤ 36.6; normalization of SpO2 (>94% on room air); disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production and shortness of breath.

[7]We rated down three levels: one for risk of bias (open-label study), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), one for imprecision (Wide confidence interval includes no difference).

[8]We rated down two levels: one for risk of bias (open-label study), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents).

[9]We rated down three levels: one for risk of bias (No blinding on patients), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), and one for imprecision (Wide confidence interval includes no difference).

[10]Baseline risk data from non-severe COVID-19 patients is not available. We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe.

[11]We used the control group of the study itself to serve as baseline risk (Tang W. doi: 10.1101/2020.04.10.20060558).

Table 4. GRADE summary of findings: Hydroxychloroquine in severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	RR 1.48 (95%CI 0.42 to 5.24) Based on data from 181 severe patients and 255 patients with mixed severity in 2 observational studies	104[1]	50 (-60 to 441)	Very low ⊕ O O O (Very serious imprecision, inconsistency and serious indirectness)[2]	We are very uncertain of the effect of hydroxychloroquine on mortality.
Mechanical ventilation	HR 1.43 (95%CI 0.53 to 3.79) Based on data from 255 patients with mixed severity in 1 observational study	387[1]	116 (-159 to 457)	Very low ⊕ O O O (Very serious imprecision and serious indirectness)[3]	We are very uncertain of the effect of hydroxychloroquine on mechanical ventilation.
Viral clearance at day 14	RR 0.98 (95%CI 0.89 to 1.07) Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	563[4]	-11 (-62 to 39)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[5]	We are very uncertain of the effect of hydroxychloroquine on viral clearance at day 14.
Diarrhea	Not applicable, no events in control group Based on data from 178 non-severe patients and 2 severe patients in 2 RCTs	0[4]	106 (40 to 171)	Low ⊕ ⊕ O O (Serious risk of bias and indirectness)[6]	Hydroxychloroquine may increase diarrhea.
Headache	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[7]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[8]	We are very uncertain of the effect of hydroxychloroquine on headache.
Rash	Not applicable, no events in control group Based on data from 62 non-severe patients in 1 RCT	0[4]	32 (0 to 94)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[8]	We are very uncertain of the effect of hydroxychloroquine on rash.
Nausea	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[4]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on nausea.
Vomiting	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[4]	29 (0 to 68)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on vomiting.
Blurred vision	Not applicable, no events in control group Based on data from 148 non-severe patients and 2 severe patients in 1 RCT	0[10]	14 (0 to 42)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[9]	We are very uncertain of the effect of hydroxychloroquine on blurred vision.

[1]We chose the baseline risk from severe COVID-19 patients in the study providing the relative effect estimate: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for imprecision (Very wide confidence interval included important benefit and harm), inconsistency (Two studies reported different directions of mortality), and indirectness (RR was estimated from HR in one study).

[3]Observational studies started at low certainty/quality of evidence. In addition, we rated down for imprecision (Very wide confidence interval included important benefit and harm) and indirectness (Risk difference was estimated from HR).

[4]We chose the baseline risk from severe COVID-19 patients in the study from Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe.
[5]We rated down for the following: risk of bias (Open-label study), imprecision (Wide confidence interval includes no difference), and for two issues of indirectness (Both intervention and control patients used other antiviral agents. Possible synergic effect between hydroxychloroquine and other antiviral agents. Data came from non-severe COVID-19 patients).
[6]We rated down two levels: one for risk of bias (open-label study), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents).
[7]Baseline risk from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Chen Z. doi: 10.1101/2020.03.22.20040758).
[8]We rated down three levels: one for risk of bias (No blinding on patients), one for indirectness (Other antiviral agents used in both intervention and control patients. Possible synergic effect between hydroxychloroquine and other antiviral agents), and one for imprecision (Wide confidence interval includes no difference).
[9]We rated down three levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference), one for indirectness (Both intervention and control patients used other antiviral agents. Possible synergic effect between hydroxychloroquine and other antiviral agents).
[10]Baseline risk data from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Tang W. doi: 10.1101/2020.04.10.20060558).

Table 5. GRADE summary of findings: Umifenovir in non-severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Viral clearance at day 14	RR 1.23 (95%CI 0.74 to 2.03) Based on data from 23 non-severe patients in 1 RCT	714[1]	164 (-186 to 286)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on viral clearance at day 14.
Cough alleviation at day 7	RR 1.33 (95%CI 0.35 to 5.13) Based on data from 15 non-severe patients in 1 RCT	333[1]	110 (-216 to 667)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on cough alleviation at day 7.
Fever at day 7	RR 0.66 (95%CI 0.31 to 1.40) Based on data from 11 non-severe patients in 1 RCT	1000[1]	-340 (-690 to 0)	Very low ⊕ O O O (Very serious imprecision)[3]	We are very uncertain of the effect of umifenovir on fever at day 7.
Progressing from non-severe to severe	RR 0.88 (95%CI 0.09 to 8.14) Based on data from 28 non-severe patients in 1 RCT	143[1]	-17 (-130 to 857)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on progressing from non-severe to severe.
Diarrhea	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[1]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on diarrhea.
Decreased appetite	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[1]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[2]	We are very uncertain of the effect of umifenovir on decreased appetite.

[1]We used the baseline risk from non-severe COVID-19 patients from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from Li's study were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.
[2]We rated down three levels for imprecision (Very wide confidence interval includes important benefit and harm).
[3]We rated down three levels for imprecision (Very wide confidence interval includes important benefit).

Table 6. GRADE summary of findings: Umifenovir in severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	OR 0.18 (95%CI 0.08 to 0.45) Based on data from 504 patients with mixed severity in 1 observational study	104[1]	-84 (-95 to -54)	Very low ⊕ O O O (Serious risk of bias)[2]	We are very uncertain of the effect of umifenovir on mortality.
Viral clearance at day 14	RR 1.23 (95%CI 0.74 to 2.03) Based on data from 23 non-severe patients in 1 RCT	563[3]	129 (-146 to 437)	Very low ⊕ O O O (Very serious imprecision and serious indirectness)[4]	We are very uncertain of the effect of umifenovir on viral clearance at day 14.
Diarrhea	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[3]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[5]	We are very uncertain of the effect of umifenovir on diarrhea.
Decreased appetite	RR not estimable (no event in either group) Based on data from 23 non-severe patients in 1 RCT	0[3]	Not estimable (no event in either group)	Very low ⊕ O O O (Very serious imprecision)[5]	We are very uncertain of the effect of umifenovir on decreased appetite.

[1]We chose the baseline risk from severe COVID-19 patients in: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for risk of bias (Inadequate adjustment for disease severity: failed to adjust for respiratory rate, and cointerventions with oxygen, mechanical ventilation) and ambiguous definition of admission data as a predictor.

[3]We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe.

[4]We rated down three levels: two for imprecision (Very wide confidence interval includes important benefit and harm), one for indirectness (Data came from non-severe COVID-19 patients).

[5]We rated down three levels for imprecision (Very wide confidence interval includes important benefit and harm).

Table 7. GRADE summary of findings: Favipiravir in non-severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Clinical recovery at day 7	RR 1.18 (95%CI 0.95 to 1.48) Based on data from 236 patients with mixed severity (88.6% non-severe) in 1 RCT comparing favipiravir with umifenovir	517[1]	93 (-26 to 248)	Very low ⊕ O O O (Serious risk of bias, indirectness and very serious imprecision)[2]	We are very uncertain of the effect of favipiravir on clinical recovery at day 7.
Viral clearance at day 7	HR 3.43 (95%CI 1.16 to 10.15) Based on data from 80 non-severe patients in 1 observational study comparing favipiravir with lopinavir/ritonavir	714[3]	272 (52 to 286)	Very low ⊕ O O O (Very serious indirectness)[4]	We are very uncertain of the effect of favipiravir on viral clearance at day 7.

[1]The control group of the study itself serves as baseline risk (Chen C. doi: 10.1101/2020.03.17.20037432).
[2]We rated down for the following: risk of bias (open-label study), indirectness (compared with umifenovir), and imprecision (very wide confidence interval includes important benefit and harm). Clinical recovery was defined as: axillary temperature ≤ 36.6 °C; respiratory frequency ≤ 24 times/min; Oxygen saturation ≥ 98% without oxygen inhalation; mild or no cough.
[3]We used the baseline risk from non-severe COVID-19 patients from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from Li et al. were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.
[4]Observational studies started at low certainty/quality of evidence. In addition, we rated down for three issues of indirectness (Both intervention and control patients used interferon. Possible synergic effect between favipiravir and interferon. Favipiravir was compared with lopinavir/ritonavir. Risk difference was estimated from HR).

Table 8. GRADE summary of findings: Favipiravir in severe COVID-19, direct evidence from one observational study of patients with COVID-19

Outcomes	Relative effects	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Viral clearance at day 7	HR 3.43 (95%CI 1.16 to 10.15) Based on data from 80 non-severe patients in 1 observational study comparing favipiravir with lopinavir/ritonavir	324	415 (41 to 657)	Very low ⊕ O O O (Very serious indirectness)[2]	We are very uncertain of the effect of favipiravir on viral clearance at day 7.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe. The baseline risk was viral clearance at day 5 instead of day 7.
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for four issues of indirectness (Both intervention and control patients used interferon. Possible synergic effect between favipiravir and interferon. Favipiravir was compared with lopinavir/ritonavir. Risk difference was estimated from HR. Data came from non-severe COVID-19 patients).

Table 9. GRADE summary of findings: Favipiravir in non-severe COVID-19, indirect evidence from one RCT of patients with influenza

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Diarrhea	RR 0.94 (95%CI 0.39 to 2.26) Based on data from 386 influenza patients with unspecified severity in 1 RCT	51	-3 (-31 to 64)	Low ⊕⊕OO (Serious indirectness and imprecision)[2]	Favipiravir may not increase diarrhea.

[1]We used the control group of the study itself to serve as baseline risk (NCT01068912. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01068912?term=FAVIPIRAVIR&rslt=With&draw=2&rank=1).
[2]We rated down two levels: one for indirectness (Influenza patients), one for imprecision (Wide confidence interval includes no difference).

Table 10. GRADE summary of findings: Favipiravir in severe COVID-19, indirect evidence from one RCT of patients with influenza

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Diarrhea	RR 0.94 (95%CI 0.39 to 2.26) Based on data from 386 influenza patients with unspecified severity in 1 RCT	51	-3 (-31 to 64)	Low ⊕⊕OO (Serious indirectness and imprecision)[2]	Favipiravir may not increase diarrhea.

[1]We used the control group of the study itself to serve as baseline risk (NCT01068912. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01068912?term=FAVIPIRAVIR&rslt=With&draw=2&rank=1).
[2]We rated down two levels: one for indirectness (Influenza patients), one for imprecision (Wide confidence interval includes no difference).

Table 11. GRADE summary of findings: Interferon-α in non-severe COVID-19, direct evidence from one observational study of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Time-to viral clearance (day)	Based on data from 70 patients with mixed severity in 1 observational study	7[1]	-1.1 (-2.32 to 0.11)	Very low ⊕OOO (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on time-to viral clearance.
Length of hospital stay (day)	Based on data from 70 patients with mixed severity in 1 observational study	11[3]	-2.1 (-4.89 to 0.69)	Very low ⊕OOO (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on length of hospital stay.

[1]We chose the baseline risk from non-severe COVID-19 patients in the study from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from Li were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe..
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: indirectness (Patients in both groups used umifenovir. Possibe synergic effect between interferon and umifenovir), and imprecision (Wide confidence interval includes no difference).
[3]We chose the baseline risk from non-severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The non-severe patients from the referred study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of non-severe.

Table 12. GRADE summary of findings: Interferon-α in severe COVID-19, direct evidence from one observational study of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Time-to viral clearance (day)	Based on data from 70 patients with mixed severity in 1 observational study	29[1]	-4.60 (-7 to 0.45)	Very low ⊕OOO (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on time-to viral clearance.
Length of hospital stay (day)	Based on data from 70 patients with mixed severity in 1 observational study	13[3]	-2.48 (-5.78 to 0.82)	Very low ⊕OOO (Serious indirectness and imprecision)[2]	We are very uncertain of the effect of interferon-α on length of hospital stay.

[1]Baseline risk from severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Zhou Q. doi: 2020.04.06.20042580).
[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: indirectness (Patients in both groups used umifenovir. Possible synergic effect between interferon and umifenovir), and imprecision (Wide confidence interval includes no difference).
[3]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from the referred study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

Table 13. GRADE summary of findings: Interferon-α in non-severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Leukopenia requiring G-CSF	RR 0.84 (95%CI 0.45 to 1.56) Based on data from 87 SARS patients with mixed severity in 1 observational study	348[1]	-56 (-191 to 195)	Very low ⊕ O O O (Serious risk of bias and very serious imprecision)[2]	We are very uncertain of the effect of interferon-α on leukopenia requiring G-CSF.

[1]Baseline risk from non-severe COVID-19 patients is not available. The control group of the study itself serves as the baseline risk (Li J. doi: 10.3760/cma.j.issn.1008-6315.2005.02.007).

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: risk of bias (Unadjusted outcome value), and imprecision (Very wide confidence interval includes important benefit and harm).

Table 14. GRADE summary of findings: Interferon-α in severe COVID-19, indirect evidence from observational studies of patients with SARS/MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	OR 0.23 (95%CI 0.04 to 1.32) Based on data from 83 MERS patients with mixed severity in 2 observational studies	104[1]	-78 (-99 to 29)	Very Low ⊕ O O O (Serious imprecision and indirectness)[2]	We are very uncertain of the effect of interferon-α on mortality.
Leukopenia requiring G-CSF	RR 0.84 (95%CI 0.45 to 1.56) Based on data from 87 SARS patients with mixed severity in 1 observational study	348[3]	-56 (-191 to 195)	Very low ⊕ O O O (Serious risk of bias and very serious imprecision)[4]	We are very uncertain of the effect of interferon-α on leukopenia requiring G-CSF.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. We rated down two levels: one for indirectness (MERS patients), one for imprecision (Wide confidence interval includes no difference).

[3]Baseline risk from severe COVID-19 patients is not available. The control group of the study itself serves as the baseline risk (Li J. doi: 10.3760/cma.j.issn.1008-6315.2005.02.007).

[4]Observational studies started at low certainty/quality of evidence. In addition, we rated down for the following: risk of bias (Unadjusted outcome value), and imprecision (Very wide confidence interval includes important benefit and harm).

Table 15. GRADE summary of findings: Interferon-β in severe COVID-19, indirect evidence from observational studies of patients with MERS

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)[1]	Difference (95% CI) (per 1000)		
Mortality	OR 0.37 (95%CI 0.07 to 2.05) Based on data from 83 MERS patients with mixed severity in 2 observational studies	104	-63 (-96 to 88)	Very low ⊕OOO (Serious imprecision and indirectness)[2]	We are very uncertain of the effect of interferon-β on mortality.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.

[2]Observational studies started at low certainty/quality of evidence. In addition, we rated down two levels: one for indirectness (MERS patients), one for imprecision (Wide confidence interval includes no difference).

Table 16. GRADE summary of findings: Lopinavir/ritonavir in non-severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Length of hospital stay (day)	Based on data from 199 severe patients in 1 RCT	11[1]	-0.69 (-1.38 to 0)	Very low ⊕ O O O (Serious risk of bias, indirectness and imprecision)[2]	We are very uncertain of the effect of lopinavir/ritonavir on length of hospital stay
Viral clearance at day 14	RR 0.99 (95%CI 0.76 to 1.29) Based on data from 158 patients (130 severe and 28 non-severe) in 2 RCTs	714[3]	-7 (-171 to 207)	Low ⊕ ⊕ O O (Serious risk of bias and imprecision)[4]	Lopinavir/ritonavir may have little or no impact on viral clearance at day 14.
Viral clearance at day 23	OR 2.42 (95%CI 1.10 to 5.36) Based on data from 120 patients with mixed severity in 1 observational study	366[5]	217 (22 to 390)	Very low ⊕ O O O (Serious risk of bias)[6]	We are very uncertain of the effect of lopinavir/ritonavir on viral clearance at day 23.
Cough alleviation at day 7	RR 1.42 (95%CI 0.42 to 4.85) Based on data from 25 non-severe patients in 1 RCT	333[3]	140 (-193 to 667)	Very low ⊕ O O O (Very serious imprecision)[7]	We are very uncertain of the effect of lopinavir/ritonavir on cough alleviation at day 7.
Progressing from non-severe to severe	RR 2.67 (95%CI 0.40 to 17.74) Based on data from 28 non-severe patients in 1 RCT	143[3]	239 (-86 to 857)	Very low ⊕ O O O (Very serious imprecision)[7]	We are very uncertain of the effect of lopinavir/ritonavir on progressing from non-severe to severe.
Fever at day 7	RR 0.85 (95%CI 0.46 to 1.58) Based on data from 13 non-severe patients in 1 RCT	1000[3]	-150 (-540 to 0)	Very low ⊕ O O O (Very serious imprecision)[8]	We are very uncertain of the effect of lopinavir/ritonavir on fever at day 7.
Diarrhea	Not applicable, no events in control group. Based on data from 222 patients (194 severe and 28 non-severe) in 2 RCTs	0[3]	60 (17 to 104)	Moderate ⊕ ⊕ ⊕ O (Serious risk of bias)[9]	Lopinavir/ritonavir probably increases diarrhea.
Stomach ache	RR 4.17 (95%CI 0.47 to 36.62) Based on data from 194 severe patients in 1 RCT	10[10]	32 (-5 to 356)	Very low ⊕ O O O (Serious risk of bias and very serious imprecision)[11]	We are very uncertain of the effect of lopinavir/ritonavir on stomach ache.
Nausea	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[10]	95 (36 to 154)	Moderate ⊕ ⊕ ⊕ O (Serious risk of bias)[9]	Lopinavir/ritonavir probably increases nausea.
Vomiting	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[10]	63 (14 to 112)	Moderate ⊕ ⊕ ⊕ O (Serious risk of bias)[9]	Lopinavir/ritonavir probably increases vomiting.

[1]We chose the baseline risk from non-severe COVID-19 patients from: Guan WJ. doi: 10.1056/NEJMoa2002032. The non-severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of non-severe.
[2]We rated down three levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference), one for indirectness (Data from severe COVID-19 patients).
[3]We used the baseline risk from non-severe COVID-19 patients from: Li Y. doi: 10.1101/2020.03.19.20038984. The non-severe patients from the referred study were defined as having mild clinical symptoms but no signs of pneumonia on imaging or moderate clinical status, defined as having fever, respiratory symptoms and pneumonia on imaging, but are consistent with WHO definition of non-severe.

[4]We rated down two levels: one for risk of bias (One of the study with 83% weight was an open-label study), one for imprecision (Wide confidence interval includes no difference).
[5]Baseline risk from non-severe COVID-19 patients is not available. We used the study itself to serve as baseline risk (Yan D. doi: 10.1101/2020.03.22.20040832).
[6]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for risk of bias (Did not adjust for disease severity).
[7]We rated down three levels for imprecision (Very wide confidence interval includes important benefit and important harm).
[8]We rated down three levels for imprecision (Very wide confidence interval includes important benefit).
[9]We rated down one level for risk of bias (Open-label study).
[10]Baseline risk from non-severe COVID-19 patients is not available. We used the control group of the study itself to serve as baseline risk (Cao B. doi: 10.1056/NEJMoa2001282). The population of the study from Cao et al. was severe COVID-19 patient.
[11]We rated down three levels: one for risk of bias (Open-label study), two for imprecision (Very wide confidence interval includes important benefit and important harm).

Table 17. GRADE summary of findings: Lopinavir/ritonavir in severe COVID-19, direct evidence from studies of patients with COVID-19

Outcomes	Relative effects and source of evidence	Absolute effect estimates		Certainty/Quality of evidence	Plain languages summary
		Baseline risk for control group (per 1000)	Difference (95% CI) (per 1000)		
Mortality	RR 0.77 (95%CI 0.45 to 1.30) Based on data from 199 severe patients in 1 RCT	104[1]	-24 (-57 to 31)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may reduce mortality.
Mechanical ventilation	RR 0.83 (95%CI 0.52 to 1.34) Based on data from 199 severe patients in 1 RCT	387[1]	-66 (-186 to 132)	Very low ⊕OOO (Serious risk of bias and very serious imprecision)[3]	We are very uncertain of the effect of lopinavir/ritonavir on mechanical ventilation.
ICU length of stay (day)	Based on data from 199 severe patients in 1 RCT	11[4]	-5 (-9 to 0)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may largely decrease ICU length of stay.
Length of hospital stay (day)	Based on data from 199 severe patients in 1 RCT	13[1]	-0.81 (-1.63 to 0)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may reduce length of hospital stay slightly.
Viral clearance at day 14	RR 0.99 (95%CI 0.76 to 1.29) Based on data from 158 patients (130 severe and 28 non-severe) in 2 RCTs	563[4]	-6 (-135 to 163)	Low ⊕⊕OO (Serious risk of bias and imprecision)[2]	Lopinavir/ritonavir may have little or no impact on viral clearance at day 14.
Viral clearance at day 23	OR 2.42 (95%CI 1.10 to 5.36) Based on data from 120 patients with mixed severity in 1 observational study	577[5]	190 (23 to 303)	Very low ⊕OOO (Serious risk of bias)[6]	We are very uncertain of the effect of lopinavir/ritonavir on viral clearance at day 23.
Diarrhea	Not applicable, no events in control group. Based on data from 222 patients (194 severe and 28 non-severe) in 2 RCTs	0[4]	60 (17 to 104)	Moderate ⊕⊕⊕O (Serious risk of bias)[7]	Lopinavir/ritonavir probably increases diarrhea.
Stomach ache	RR 4.17 (95%CI 0.47 to 36.62) Based on data from 194 severe patients in 1 RCT	10[4]	32 (-5 to 356)	Very low ⊕OOO (Serious risk of bias and very serious imprecision)[8]	We are very uncertain of the effect of lopinavir/ritonavir on stomach ache.
Nausea	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[4]	95 (36 to 154)	Moderate ⊕⊕⊕O (Serious risk of bias)[7]	Lopinavir/ritonavir probably increases nausea.
Vomiting	Not applicable, no events in control group Based on data from 194 severe patients in 1 RCT	0[4]	63 (14 to 112)	Moderate ⊕⊕⊕O (Serious risk of bias)[7]	Lopinavir/ritonavir probably increases vomiting.

[1]We chose the baseline risk from severe COVID-19 patients in the study from: Guan WJ. doi: 10.1056/NEJMoa2002032. The severe patients from this study were defined by the American Thoracic Society guidelines for community-acquired pneumonia but are consistent with WHO definition of severe.
[2]We rated down two levels: one for risk of bias (Open-label study), one for imprecision (Wide confidence interval includes no difference).
[3]We rated down three levels: one for risk of bias (Open-label study), two for imprecision (Very wide confidence interval includes important harm).
[4]We used the control group of the study itself to serve as baseline risk (Cao B. doi: 10.1056/NEJMoa2001282).

[5]We chose the baseline risk from severe COVID-19 patients in the study from: Cao B. doi: 10.1056/NEJMoa2001282. The severe patients from the referred study were defined by an oxygen saturation (SaO_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2: FiO_2) at or below 300 mg Hg, but are consistent with WHO definition of severe. The baseline risk was viral clearance at day 21 instead of day 23.
[6]Observational studies started at low certainty/quality of evidence. In addition, we rated down one level for risk of bias (Did not adjust for disease severity).
[7]We rated down one level for risk of bias (Open-label study).
[8]We rated down three levels: one for risk of bias (Open-label study), two for imprecision (Very wide confidence interval includes important benefit and important harm).

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Appendix 4 (as supplied by the authors): COVID-19 guideline panel members		
Name	**Title/Duty**	**Affiliation**
Guideline steering committee members		
Gordon Guyatt	Professor/Methodologist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada
Zhikang Ye	PhD student/Methodologist	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada
Bin Du	Professor/Critical care physician	Medical intensive care unit, Peking Union Medical College Hospital, Beijing, China
Suodi Zhai	Professor/Pharmacist	Department of Pharmacy, Peking University Third Hospital, Beijing, China
Bram Rochwerg	Assistant professor/Critical care physician	Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada
Other panel members		
Intensive Care Medicine		
Haibo Qiu	Professor	Department of Critical Care Medicine, Zhongda hospital, School of Medicine, Southeast University, Nanjing, China
Li Jiang	Professor	Department of Critical Care Medicine, Xuanwu Hospital, Capital Medical School, Beijing, China
Ling Sang	Associate Professor	Department of Critical Care Medicine, the First Affiliated Hospital of GuangZhou Medical University, GuangZhou Institute of Respiratory Health, Guangzhou, China
François Lamontag	Professor/Methodologist	Centre de recherche du CHUS de Sherbrooke, Sherbrooke, QC, Canada
Robert A Fowler	Professor/Methodologist	Department of Medicine, Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada
Neill K Adhikari	Associate scientist/ Methodologist	Department of Medicine, Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada
Srinivas Murthy	Associate	Department of Paediatrics, University of British Columbia,

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	professor/Methodologist	Vancouver, BC, Canada
Yaseen M Arabi	Professor	Intensive Care Department, King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia
Luis Enrique Colunga Lozano	Physician	Department of Clinical Medicine, Health Science Center, Universidad de Guadalajara, Guadalajara, Mexico
Pharmacy		
Dong Liu	Professor	Department of Pharmacy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
Li Wei	Professor	Department of Pharmacy, the First Affiliated Hospital of Guangzhou University of Medical
Aizong Shen	Professor	Department of Pharmacy, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, China
Fang Liu	Chief pharmacist	Department of Pharmacy, Peking University Third Hospital, Beijing, China
Respiratory and Critical Care Medicine		
Ning Shen	Professor	Department of Respiratory and Critical Care Medicine, Peking University Third Hospital, Beijing, China
Jason Phua	Associate professor	Fast and Chronic Programmes, Alexandra Hospital, National University Health System, Singapore (J Phua MRCP)
Younsuck Koh	Professor	Department of Pulmonary and Critical Care Medicine, Asan Medical Center, Seoul, South Korea
Infectious disease		
Mark Loeb	Professor	Department of Pathology and Molecular Medicine and Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada
Nurse		
Tianyi Huo	Nurse	General Surgery Department, Peking University Third Hospital,

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		Beijing, China
Ying Wang	Methodologist	Department of Pharmacy, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China
Patient partners		
Minhua Huang	Patient representative	Guangdong kuaiwen information technology co. LTD, Guanzhong, China
Zaonan Jiang	Patient representative	Kunshan Guanghui precise matal co.ltd, Kunshan, China

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Appendix 5 (as supplied by the authors): Declaration of interests

You have been accepted an invitation to participate in the development of a guideline addressing the management of patients with COVID-19.

Policy on declaration of interests

We are committed to ensuring the integrity of our guideline. We will strive to be transparent about our potential conflicts of interest.

We ask that you declare any relevant interests that might conflict with the decisions you will make for this guideline. We are interested in any possible conflicts as a result of your activities in the preceding 36 months and the next 12 months. A conflict of interest arises when a person has a personal or organizational interest that may influence or appear to influence the work on the guideline. This may be a financial or non-financial interest.

This declaration will cover a number of different areas - we recommend having any information on the following to hand before you start completing this form:

- ✓ Board Membership
- ✓ Employment
- ✓ Grants/Pending Grants
- ✓ Stock and Ownership
- ✓ Intellectual Interests

You may have a conflict for one or more of the interventions we will be discussion. **The interventions are: steroids, antiviral drugs, convalescent plasma.**

Below you will be asked questions about possible conflicts. If you answer yes to any question we would like you to specify for what intervention you are conflicted.

Board Membership

(e.g. advisory board, management board)

- ▫ For the preceding 36 months and the next 12 months from today, have you been a member of a board? *
  YES ☐ NO ☐

  If Yes, tell us for which interventions you are conflicted: _____

  If Yes, please provide the details of all your board membership, including (1) the name of the organization, eg. company or academic society; (2) the type of the board, eg.

Advisory board, management board, academic board; (3) your role/title in the organization; (4) whether there is any interest related to the article topic, eg. YES or NO; (5) whether you receive payment from the board, eg. YES or NO. If you have more than one board membership, please state them all in separate lines.
Eg. XX company, advisory board, member, NO, YES.

Employment

- For the preceding 36 months and the next 12 months from today, do you have other employment besides your primary institute and the organization you have mentioned in this statement? *
  YES ☐ NO ☐

  If Yes, tell us for which interventions you are conflicted: _____

  If Yes, please provide the details of the organization, including (1) the name of the organization, eg. company; (2) your role/title in the organization; (3) whether there is any interest related to the article topic, eg. YES or NO; (4) whether you receive payment from the board, eg. YES or NO. If you have more than one secondary employment, please state them all in separate lines.
  Eg. XX company, chief medical officer (CMO), NO, YES.

Grants/Grants Pending

- Have you received, or are expecting to receive Grants over the preceding 36 months and the next 12 months? *
  YES ☐ NO ☐

  If Yes, tell us for which interventions you are conflicted: _____

  If Yes, please provide the details of the grants, including (1) the name of the organization who offers the grant, eg. company, National Natural Science Foundation of China; (2) your role in the grant; (3) the role of the organization in the grant or study, eg. whether the organization had any role in: study design; data collection, access, analysis, or interpretation; writing of the report; or the decision to publish; (4) whether there is any interest related to the article topic, eg. YES or NO. If you have more than one grant, please state them all in separate lines.
  Eg. National Natural Science Foundation of China, principle investigator, the organization takes no role in the study, NO.

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Stock, Stock Options, Other Forms of Ownership

- Have you received, or are planning to receive stock or payments from stock over the preceding 36 months and the next 12 months? *
  YES ☐ NO ☐

  If Yes, tell us for which interventions you are conflicted: _____

  If Yes, Please provide the details of the grants, including (1) stock received from which organization, eg. company; (2) whether there is any interest related to the article topic, eg. YES or NO. If you hold more than one stock, please state them all in separate lines.
  Eg. XX Company, NO.

Intellectual Interests

The questions that follow will elicit information about personal beliefs, career advancement and other interests that are not mainly financial.

Personal Beliefs *

- Do you have strongly held beliefs related to the article topic?
  YES ☐ NO ☐
  If Yes, for which interventions you have strongly held beliefs: _____

  If Yes, please state details: _____

Previously Published Opinions *

- Have you ever authored, coauthored, or publicly provided an opinion related to the article topic, e.g., a clinical practice guideline, textbook, review article, meeting poster or presentation, public lectures or letter to the editor?
  YES ☐ NO ☐
  If Yes, for what interventions you have published opinions: _____

  If Yes, please state details: _____

Treatments

- Do you prescribe or otherwise recommend treatments or strategies that may be addressed by this article?
  YES ☐ NO ☐
  If Yes, what interventions that we will be considering in the guideline do you prescribe or recommend for patients with COVID-19? _____
  If Yes, please state details: _____

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Confirmation Statement

I confirm that the information I have provided in this declaration is accurate.

Email Address: _____*

Signature: _____*

Print Name: _____*

Date: _____*

Chapter 5: Conclusion to the Thesis

This concluding chapter summarizes the manner in which the methodological issues impacted on the recommendations, the key findings and recommendations, the contribution of the recommendations to practice, and the potential future research.

Methodological issues and the guidelines

Indirect evidence

This COVID-19 guideline and corticosteroids systematic review rating down for indirectness played an important role in the final rating of quality of evidence as low or very low quality. For the corticosteroids recommendation in patients with severe COVID-19 and ARDS, indirect evidence from ARDS provided low quality evidence that corticosteroids may reduce mortality and duration of mechanical ventilation, and low or moderate quality evidence for safety outcomes. The evidence came from randomized trials at low risk of bias, with consistent results, precise estimates, and no concerns regarding publication bias (Table 2 of chapter 3). Thus, for mortality and duration of mechanical ventilation, the review rated down twice for indirectness but not for other factors, so the evidence quality proved low rather than very low. The indirect evidence from ARDS proved higher than the direct evidence from patients with severe COVID-19 with ARDS, because the direct evidence came from a single observational study with serious imprecision (Table 1 of chapter 3).

For recommendation in patients with severe COVID-19 who do not have ARDS, despite our decision to only rate down one for indirectness, indirect evidence from SARS and MERS provided very low quality evidence regarding corticosteroids and mortality.

(Table 4 and Table 5 of chapter 3). Indirect evidence from influenza provided very low quality evidence that corticosteroids may increase mortality, superinfection and the need for mechanical ventilation (Table 6 of chapter 3). The reason is that the indirect evidence from SARS, MERS and influenza came from a limited number of observational studies with serious imprecision.

Because we rated down twice for indirectness and once for imprecision or inconsistency, indirect evidence from randomized trials in community acquired pneumonia provided very low quality evidence for mortality and length of intensive care unit stay (Table 7 of chapter 3). However, it did provide low quality evidence for need for mechanical ventilation (rating down two for indirectness but not at all for other concerns) and safety outcomes (rating down only one for indirectness).

This thesis highlights the importance of indirect evidence when direct evidence is sparse, evidence that is often neglected in the systematic review and guideline process. The thesis further highlights the issues that systematic review and guideline authors will confront when deciding how many levels to rate down for indirectness, and suggests a focus on the underlying biology when making the decision. One key principle implemented in making the decision here was the difference in inferences regarding benefit and harm: uncertainty regarding the application of a body of evidence from one population to another will in general be greater for benefit outcomes than for harm outcomes.

Baseline risk calculation

Previously published guidelines addressing gastrointestinal bleeding prophylaxis did not define the risk groups (1, 2). A big challenge in making quantitative estimates for risk is how to both identify the baseline risk of people with no risk factors and the risk ratios of each risk factor. Fortunately, with respect to estimates of relative risk, the authors of a high credibility systematic review shared their evidence (3), prior to publication, with us. On this basis the guideline regarding gastrointestinal bleeding prophylaxis in critically ill patients classified clinically important gastrointestinal bleeding into low (1-2%), moderate (2-4%), high (4-8%) and highest risk (8-10%). If patients had two or more moderate risk factors, we elevated it to the high risk category. The estimate of baseline risk required more imagination. As described in chapter 1 of the thesis and the appendix 1 of chapter 2, we used data from the largest and lowest risk randomized controlled trial (4) that enrolled patients with at least 1 risk factor and worked backwards to estimate what would have happened in a population without any risk factors. This demonstrates the necessity for unconventional approaches that result from the regrettable habit of authors of observational studies of prognosis to report only relative effects and leave researchers with little idea of absolute risk.

The panel decided that these estimates were sufficiently credible to make different recommendations for varying risk groups. They suggested using acid suppression prophylaxis for people with 4% or higher risk of gastrointestinal bleeding.

Guideline developers may realize the value of need for stratifying risk groups on the basis of the best available evidence for prognosis and use approaches such as the one

we implemented here. Other BMJ rapid recommendations have also provided risk stratified recommendations, in several cases going through their own struggles to define both baseline risk and relative effects (5).

Values and preferences

Failure to explicitly identify values and preferences underlying guideline recommendations remains a major limitation (6). One of the big challenges panels face is – with the exception of a few areas such as thrombosis and bleeding (7) - the paucity of literature addressing values and preferences. This situation requires the panel making inferences on the basis of very limited evidence – often largely their own experience. To do so, the panel must ensure that they try to put themselves in the minds of the people or patients for whom the guideline is directed. Formal surveys of the panel, currently seldom undertaken, may help to achieve this goal and make the process of arriving at values for the guideline more transparent.

The COVID-19 guideline panel team formulated the recommendations based on inferred values and preferences. The values and preferences statements must be, as much as possible, tailored to the situation at hand, requiring to the panel to clearly define the critical tradeoffs. For the COVID-19 recommendations, the key tradeoff was between uncertain or very uncertain benefits, with more certainty regarding burdens and harms. The panel postulated that when the quality of evidence for benefit was low, patients facing this choice would be inclined to choose the intervention, but when very low would tend to decline. That panel was aware, however, that there was very little

evidence to support this inference, and that values and preferences were very likely to differ between individuals. Both these considerations dictated that all recommendations would be weak rather than strong.

The panel implemented this approach in making their recommendations. For the corticosteroids recommendations, the evidence summary indicated that corticosteroids may result in a substantial reduction in mortality in patients with severe COVID-19 and ARDS (low quality evidence), and the harm of short-term use of corticosteroids is limited. Thus, this guideline weakly recommended use of corticosteroids in patients with severe COVID-19 and ARDS.

In patients with severe COVID-19 who do not have ARDS, the indirect evidence regarding the benefit in mortality and other outcomes was judged of very low quality and proved inconsistent between indirect evidence coming from community acquired pneumonia, SARS, MERS and influenza. Low quality evidence suggests that short use of corticosteroids have modest harm. In this context, the benefit in critical outcome is very uncertain and there are likely modest harms. Thus, this guideline weakly recommended against use of corticosteroids in patients with severe COVID-19 who do not have ARDS.

The gastrointestinal bleeding prophylaxis guideline panel inferred that, since prophylaxis may increase pneumonia, most patients would require a reduction in clinically important gastrointestinal bleeding by at least about 2% in order to choose acid suppression. The panel noted however, that they were not confident in this

inference, and that values and preferences are likely to differ across patients. The evidence shows that prophylaxis likely reduces clinical important bleeding more than 2% in patients with high or highest risk; this guideline weakly recommends use of prophylaxis in patients with high or highest risk. Both guidelines provide a model for explicit statements regarding values and preferences.

Key findings and implications

In chapter 2, this BMJ rapid recommendations provides two recommendations regarding indications and agents for gastrointestinal bleeding prophylaxis in critically ill patients. This is the first guideline to categorize the bleeding risk and explicitly formulate recommendations for different populations with different bleeding risks. This therefore provides the most specific guidance yet available for use of gastrointestinal bleeding prophylaxis in critically ill patients.

Any guideline is at risk of becoming quickly outdated with publication of new evidence. An important trial using an innovative cluster-crossover design comparing PPIs to H2RAs was published soon after the publication of our guideline (8). We therefore updated the NMA that had informed our guideline to address the new evidence (9). The results suggested that PPIs and H2RAs are most likely to have a similar effect on mortality and compared to no prophylaxis and achieve important reductions in clinically important gastrointestinal bleeding for higher bleeding risk patients. Thus, we infer that this evidence would not change the recommendations.

In chapter 3, this systematic review and meta-analysis provides the direct and indirect

evidence regarding corticosteroids in COVID-19. This systematic review provides evidence for chapter 4 to formulate the corticosteroids recommendations.

In chapter 4, the COVID-19 guideline formulated recommendations in three therapeutic areas: corticosteroids, convalescent plasma and antiviral drugs, all of which were critically important for the decision making at that time when we lacked convincing direct evidence and clinicians had high uncertainty regarding treatment of their COVID-19 patients. The message from the guidelines was essentially to, with the exception of steroids in the critically ill, hold off using drugs until there was more evidence of benefit. These recommendations were variably observed, but some clinicians did indeed exercise restraint in using drugs for which there was high uncertainty of benefit.

The advice we provided clinicians has proved to be wise. Our only positive recommendation was for corticosteroids in ARDS. Subsequent living network meta-analysis of randomized trials has shown a mortality benefit in this population – and in severe but not critically ill COVID-19 patients and demonstrated hydroxychloroquine and lopinavir-ritonanvir provide no benefit and steroid remain the only drug with a clear mortality benefit in COVID-19 patients (10).

Future research and direction

Our COVID-19 guideline was developed in the context of clinicians' urgent need for guidance in managing their patients. From the start of the process to publication of the guideline proved about three months. We demonstrated the possibility of rigorously developing and publishing urgently needed guidance: this model for producing

trustworthy rapid recommendations or guidelines addressing practice changing evidence and urgent public diseases merits more widespread application. In the context of BMJ Rapid Recommendations (11), we will commit ourselves to future rapid recommendations in response to changing practice evidence. In doing so, we will be mindful of the insights we have learned from this work including the importance of indirect evidence, the need for stratifying risk groups on the basis of the best available evidence for prognosis, and the necessity for an optimally rigorous, explicit and transparent process for inferring and applying value and preference judgements in trading off desirable and undesirable consequences of applying candidate interventions. Ultimately, the BMJ Rapid Recommendations will provide a model for living guidelines that forward-looking organizations will adopt.

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