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

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

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.

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.

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

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.

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.
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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).

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

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

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

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

There is no funding for this systematic review.

References

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama. 2020. Epub 2020/02/08.

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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.

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.

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

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

Interpreting results and writing manuscript	March 18th to 21st

Funding

There is no funding for this systematic review.

References:

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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).

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.

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.

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

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