
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, 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 (SpO2) ≤ 93% on room air.

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 I² 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, and the baseline mortality risk of patients with severe COVID-19 from an observational study of patients with severe COVID-19. 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 tool6 to choose the most methodologically rigorous systematic review to be updated. We used a modified version of the Cochrane risk of bias tool10 to assess risk of bias in RCTs, and a revised version of the Newcastle–Ottawa Scale11,12 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 indirectness17 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 including 84 patients with COVID-19 and ARDS, 5 cohort studies including 679 patients with COVID-19 but without ARDS, 3 studies (2 cohort studies and 1 RCT) including 7087 patients with SARS, and 2 cohort studies 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. Our search for primary studies identified 1 new eligible RCT published in 2020. Including 6 RCTs identified from the previous review, we included 7 RCTs including 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. Our search for primary studies identified 1 new eligible study published in 2020. Including 30 studies identified from the previous review, we included 31 eligible studies of which 21 with 9536 patients were included in meta-analyses.

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


ARDS

Evidence for patients with COVID-19 and ARDS was available from a single observational study of 84 patients 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 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 (MD 0.1 days longer, 95% CI 0.02 to 7.2 days longer). Low-quality evidence shows that corticosteroids may reduce the duration of mechanical ventilation (MD –4.8 days, 95% CI –7.0 to –2.6), but increase serious hyperglycemia (risk increase 8.1%, 95% CI 0.7% to 16.2%), gastrointestinal bleeding and superinfection.

<table>
<thead>
<tr>
<th>Study or subgroup: year</th>
<th>Corticosteroid</th>
<th>Control</th>
<th>Risk ratio</th>
<th>M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu et al., 2012</td>
<td>2</td>
<td>12</td>
<td>0.33 (0.08 to 1.31)</td>
<td></td>
</tr>
<tr>
<td>Meduri et al., 2007</td>
<td>15</td>
<td>63</td>
<td>0.56 (0.30 to 1.03)</td>
<td></td>
</tr>
<tr>
<td>Rezk et al., 2013</td>
<td>0</td>
<td>18</td>
<td>0.08 (0.00 to 1.32)</td>
<td></td>
</tr>
<tr>
<td>Steinberg et al., 2006</td>
<td>28</td>
<td>89</td>
<td>0.99 (0.64 to 1.52)</td>
<td></td>
</tr>
<tr>
<td>Tongyo et al., 2016</td>
<td>34</td>
<td>98</td>
<td>0.86 (0.60 to 1.23)</td>
<td></td>
</tr>
<tr>
<td>Villar et al., 2020</td>
<td>29</td>
<td>139</td>
<td>0.58 (0.39 to 0.85)</td>
<td></td>
</tr>
<tr>
<td>Zhao et al., 2014</td>
<td>9</td>
<td>24</td>
<td>0.84 (0.43 to 1.61)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>117</td>
<td>443</td>
<td>0.72 (0.55 to 0.93)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>154</td>
<td>408</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
Study or subgroup; year  Log (odds ratio)  SE  Odds ratio  IV, random, 95% Cl  %  Favours corticosteroid  Favours no corticosteroid
Brun-Buisson et al., 2011$^{43}$  0.9517  0.3066  2.59 (1.42 to 4.72)  69.23  
Lu et al., 2020$^{23}$  2.78 (0.96 to 19.26)  30.77  
Overall ($I^2 = 0.0\%, p = 0.768$)  2.30 (1.00 to 5.29)  100.00  

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.

Study; year  HR (95% Cl)  %  Weight
Long et al., 2016$^{25}$  0.83 (0.41 to 1.66)  60.96  
Lau et al., 2009$^{24}$  1.29 (0.55 to 2.70)  39.04  
Overall ($I^2 = 60.5\%, p = 0.111$)  0.83 (0.41 to 1.66)  100.00  

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.

Study or subgroup; year  Log (odds ratio)  SE  Odds ratio  IV, random, 95% Cl  %  Favours corticosteroid  Favours no corticosteroid
Brun-Buisson et al., 2011$^{43}$  0.9517  0.3066  2.59 (1.42 to 4.72)  69.23  
Cao et al., 2016$^{44}$  0.5933  0.3679  1.81 (0.88 to 3.72)  30.77  
Delaney et al., 2016$^{47}$  0.6152  0.2561  1.85 (1.12 to 3.06)  100.00  
Kim et al., 2011$^{42}$  0.7885  0.3872  2.20 (1.03 to 4.70)  100.00  
Lee et al., 2015$^{45}$  0.5481  0.2128  1.73 (1.14 to 2.63)  100.00  
Li et al., 2017$^{47}$  -0.223  0.182  0.80 (0.56 to 1.14)  100.00  
Linko et al., 2011$^{52}$  1.4134  0.6543  4.11 (1.14 to 14.82)  100.00  
Lu et al., 2020$^{19}$  2.30 (1.00 to 5.29)  100.00  

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\textsuperscript{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\textsuperscript{26} reported an increase in the composite outcome of mortality or ICU admission with steroid use. Two cohort studies\textsuperscript{21,22} suggested that corticosteroids use was associated with prolonged viral shedding (very low-quality evidence).

<table>
<thead>
<tr>
<th>Study or subgroup; year</th>
<th>Corticosteroid</th>
<th>Usual care</th>
<th>Risk ratio</th>
<th>Heterogeneity: ( P = 0% )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confalonieri et al., 2005\textsuperscript{73}</td>
<td>0</td>
<td>23</td>
<td>8</td>
<td>Events events Total Total 0.06 (0.00 to 0.96)</td>
</tr>
<tr>
<td>El-Ghamrawy et al., 2006\textsuperscript{74}</td>
<td>3</td>
<td>17</td>
<td>6</td>
<td>17 Events events Total Total 0.50 (0.15 to 1.68)</td>
</tr>
<tr>
<td>Gang et al., 2016\textsuperscript{75}</td>
<td>3</td>
<td>29</td>
<td>3</td>
<td>29 Events events Total Total 1.00 (0.22 to 4.55)</td>
</tr>
<tr>
<td>Marik et al., 1993\textsuperscript{76}</td>
<td>1</td>
<td>14</td>
<td>16</td>
<td>Events events Total Total 0.38 (0.04 to 3.26)</td>
</tr>
<tr>
<td>Nafae et al., 2013\textsuperscript{77}</td>
<td>4</td>
<td>60</td>
<td>6</td>
<td>20 Events events Total Total 0.22 (0.07 to 0.71)</td>
</tr>
<tr>
<td>Sabry et al., 2011\textsuperscript{78}</td>
<td>2</td>
<td>40</td>
<td>6</td>
<td>40 Events events Total Total 0.33 (0.07 to 1.55)</td>
</tr>
<tr>
<td>Torres et al., 2015\textsuperscript{79}</td>
<td>6</td>
<td>61</td>
<td>9</td>
<td>59 Events events Total Total 0.64 (0.24 to 1.70)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>19</td>
<td>244</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

| **Less severe**        |               |            |            |                               |
| Blum et al., 2015\textsuperscript{80}     | 16            | 392        | 13         | 393 Events events Total Total 1.23 (0.60 to 2.53) |
| Fernández-Serrano et al., 2011\textsuperscript{81} | 1             | 23         | 1          | 22 Events events Total Total 0.96 (0.06 to 14.37) |
| McHardy et al., 1972\textsuperscript{82}  | 3             | 40         | 9          | 86 Events events Total Total 0.72 (0.20 to 2.51) |
| Meijvis et al., 2011\textsuperscript{83}  | 9             | 151        | 11         | 153 Events events Total Total 0.83 (0.35 to 1.94) |
| Snijders et al., 2010\textsuperscript{84} | 6             | 104        | 6          | 109 Events events Total Total 1.05 (0.35 to 3.15) |
| Wagner et al., 1956\textsuperscript{85}   | 1             | 52         | 1          | 61 Events events Total Total 1.17 (0.08 to 18.30) |
| **Subtotal (95% CI)** |               |            |            |                               |
| **Total events**       | 36            | 762        | 41         |                               |

| **Total (95% CI)**     | 1006          | 1028       | 0.70 (0.50 to 0.98) |
| **Heterogeneity: \( P = 0\% \)** |               |            |                               |

**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**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effects</th>
<th>Absolute effect estimates</th>
<th>Quality of evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td>HR 0.41 (95% CI 0.20 to 0.83)</td>
<td>Based on data from 84 patients with COVID-19 and ARDS in 1 observational study\textsuperscript{a}</td>
<td>Diff. (95% CI)%</td>
<td>Very low (serious imprecision\textsuperscript{†})</td>
</tr>
<tr>
<td></td>
<td>Baseline risk for control group, * %</td>
<td>-29.2 (−44.3 to −6.8)</td>
<td>Very low (serious imprecision\textsuperscript{†})</td>
<td>We are very uncertain of the effect of corticosteroids on mortality</td>
</tr>
</tbody>
</table>


* Mortality baseline risk from patients with COVID-19 and ARDS without corticosteroid treatment.

†Observeational 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 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 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 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>
<thead>
<tr>
<th>Outcomes</th>
<th>Absolute effect estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative effects</td>
</tr>
<tr>
<td>Mortality</td>
<td>RR 0.72 (95% CI 0.55 to 0.93) Based on data from 851 patients and ARDS in 7 RCTs</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>Based on data from 297 patients in 3 RCTs</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>Based on data from 324 patients in 3 RCTs</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>Based on data from 888 patients in 6 RCTs</td>
</tr>
<tr>
<td>Serious hyperglycemia</td>
<td>RR 1.12 (95% CI 1.01 to 1.24) Based on data from 565 patients in 3 RCTs</td>
</tr>
<tr>
<td>Neuromuscular weakness</td>
<td>RR 0.85 (95% CI 0.62 to 1.18) Based on data from 271 patients in 2 RCTs</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>RR 0.71 (95% CI 0.30 to 1.73) Based on data from 250 patients in 2 RCTs</td>
</tr>
<tr>
<td>Superinfection</td>
<td>RR 0.82 (95% CI 0.67 to 1.02) Based on data from 798 patients in 5 RCTs</td>
</tr>
</tbody>
</table>

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. †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.

†1We rated down 2 levels owing to indirectness; 1 for inconsistency (I² = 73%, heterogeneity p value 0.03) and 1 for imprecision because effect estimate is consistent with benefit or harm. §We rated down by 1 level 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; 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 suggest that corticosteroid use may be associated with a delay in Middle East respiratory syndrome coronavirus (MERS-CoV) RNA clearance (HR 0.35, 95% CI 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 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) and increase the number of patients requiring mechanical ventilation (OR 5.54, 95% CI 1.83 to 16.80) (Table 6).

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

Thirteen RCTs 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 (10.4%, 95% CI 4.3% to 13.8%), duration of mechanical ventilation (1.8 days shorter, 95% CI 0.6 to 3.0 days), length of stay (2.9 days shorter, 95% CI 1.5 to 4.3 days), and time for SARS-CoV RNA to become undetectable in plasma (8.0 days earlier, 95% CI 4.0 to 12.0 days; Table 4).
ICU stay;72–76,78,82 and length of hospital stay;71–76,78,81,82,84 (Table 7, Figure 5). Meta-analysis of 8 RCTs71,72,75,78,79,81,82,84 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 study73 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 superinfection71–74,78,81,82,84 and gastrointestinal bleeding71–75,79,80,82),

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effects</th>
<th>Absolute effect estimates</th>
<th>Quality of evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>OR 0.75 (95% CI 0.52 to 1.07) Based on data from 290 patients with MERS in 1 observational study23</td>
<td>10.4* (-4.7 to 0.6) Very low (serious indirectness and serious imprecision§)</td>
<td>We are very uncertain of the effect of corticosteroids on mortality</td>
<td></td>
</tr>
<tr>
<td>MERS-CoV RNA clearance</td>
<td>HR 0.35 (95% CI 0.17 to 0.72) Based on data from 189 patients with MERS in 1 observational study23</td>
<td>29.8† (-24.0 to –7.3) Very low (serious indirectness and serious imprecision¶)</td>
<td>We are very uncertain of the effect of corticosteroids on MERS-CoV RNA clearance</td>
<td></td>
</tr>
</tbody>
</table>

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 corticosteroids 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 because of the small sample size.
¶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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effects</th>
<th>Absolute effect estimates</th>
<th>Quality of evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>OR 1.70 (95% CI 1.31 to 2.21) Based on data from 8530 participants from 11 observational studies43–45,47,52,55,57–59,61,68</td>
<td>10.4* (2.8 to 10.0) Very low (serious indirectness¶)</td>
<td>We are very uncertain of the effect of corticosteroids on mortality</td>
<td></td>
</tr>
<tr>
<td>Superinfection</td>
<td>OR 2.74 (95% CI 1.51 to 4.95) Based on data from 6114 participants from 7 observational studies43,44,47,52,55,57,65</td>
<td>7.2† (3.3 to 20.5) Very low (serious risk of bias and indirectness§)</td>
<td>We are very uncertain of the effect of corticosteroids on superinfections</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>OR 5.54 (95% CI 1.83 to 16.80) Based on data from 4364 participants from 4 observational studies52,57,59,61</td>
<td>41.8§ (15.0 to 50.6) Very low (serious risk of bias and indirectness¶)</td>
<td>We are very uncertain of the effect of corticosteroids on need for mechanical ventilation</td>
<td></td>
</tr>
</tbody>
</table>

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.7
†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).
### Mortality

**RR 0.70 (95% CI 0.50 to 0.98)**  
Based on data from 2034 patients in 13 RCTs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effects</th>
<th>Baseline risk for control group*</th>
<th>Difference (95% CI)</th>
<th>Quality of evidence</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td>10.4%</td>
<td>−3.1% (−0.2% to −5.2%)</td>
<td>Very low</td>
<td>We are very uncertain of the effect of corticosteroids on mortality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Length of ICU stay</th>
<th>Based on data from 1376 patients in 8 RCTs</th>
<th>The median length of ICU stay was 8.3 days</th>
<th>MD −1.7 days (−3.4 to 0.1)</th>
<th>Very low</th>
<th>We are very uncertain of the effect of corticosteroids on length of ICU stay</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Length of hospital stay</th>
<th>Based on data from 1636 patients in 10 RCTs</th>
<th>The median length of hospital stay was 14.3 days</th>
<th>MD −1.8 days (−2.8 to −0.8)</th>
<th>Very low</th>
<th>We are very uncertain of the effect of corticosteroids on length of hospital stay</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Need for mechanical ventilation</th>
<th>Based on data from 1017 patients in 5 RCTs</th>
<th>18.0%</th>
<th>−10.4% (−13.8% to −4.3%)</th>
<th>Low</th>
<th>Corticosteroids may reduce need for mechanical ventilation</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Duration of mechanical ventilation</th>
<th>Based on data from 199 patients in 5 RCTs</th>
<th>The median duration of mechanical ventilation was 11.3 days</th>
<th>MD −3.5 days (−5.2 to −1.8)</th>
<th>Very low</th>
<th>We are very uncertain of the effect of corticosteroids on duration of mechanical ventilation</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Serious hyperglycemia</th>
<th>Based on data from 1476 patients in 8 RCTs</th>
<th>9.2%</th>
<th>5.7% (0.18% to 15.3%)</th>
<th>Low</th>
<th>Corticosteroids may increase serious hyperglycemia events</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal bleeding</th>
<th>Based on data from 1228 patients in 8 RCTs</th>
<th>3.0%</th>
<th>−0.03% (−1.7% to 3.7%)</th>
<th>Low</th>
<th>Corticosteroids may have little or no impact on gastrointestinal bleeding</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Neuropsychiatric events</th>
<th>Based on data from 1142 patients in 4 RCTs</th>
<th>1.6%</th>
<th>1.4% (−0.5% to 7%)</th>
<th>Low</th>
<th>Corticosteroids may result in a small increase in neuropsychiatric events</th>
</tr>
</thead>
</table>

| Superinfection | Based on data from 1500 patients in 8 RCTs | 3.7% | 1.1% (−1.1% to 5.5%) | Low | 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. † 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; the cause of pneumonia across the studies is inconsistent and might not represent the COVID-19 population.**

§We rated down 2 levels owing to indirectness; 1 for inconsistency (I² = 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 p = 0.04 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. Direct evidence from 1 observational study 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. 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. 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 that included the latest published studies. For CAP, the results on which we focus are similar to those of other recent reviews 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 that also found increased mortality associated with corticosteroid use. One review 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 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.

**References**

3. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment, are ongoing.

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Competing interests: Bram Rochwerg is an investigator in a trial, supported by a Canadian Institute of Health Research grant, evaluating the effect of corticosteroids in COVID-19 patients. No other competing interests were declared.

This article has been peer reviewed.

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