CORTICOSTEROIDS FOR COVID-19
Learning objectives

At the end of this module, you will be able to:

• Recognize the role for corticosteroid therapy in the management of patients with COVID-19.

• Identify possible corticosteroid dosing regimens for patients with severe and critical COVID-19.

• Identify key considerations in safe administration of corticosteroids.
Special note

Drugs and doses stated here are for illustrative purposes only.

Decisions regarding the use of any medication must be made by a licensed provider and take into account each patient's specific clinical history and other circumstances, and be in accordance with relevant local management and prescribing guidelines.
Corticosteroids in COVID-19: summary of recommendations

In September 2020, the following recommendations regarding systemic corticosteroids for patients with COVID-19 were released by WHO:

– **Strong recommendation**: We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19.

– **Conditional recommendation**: We suggest not to use corticosteroids in the treatment of patients with non-severe COVID-19.
Corticosteroids in COVID-19: recommendation

Population
This recommendation applies only to people with these characteristics:

- Patients with confirmed COVID-19

Disease severity
- Non-severe
  - Absence of signs of severe or critical disease

- Severe
  - Oxygen saturation <90% on room air
  - Signs of pneumonia
  - Signs of severe respiratory distress

- Critical
  - Requires life sustaining treatment
  - Acute respiratory distress syndrome
  - Sepsis
  - Septic shock

Corticosteroids
- Recommendation against (weak)
- Recommendation in favour (strong)

Overview of drug: corticosteroids

- Systemic corticosteroids are powerful immunomodulators.

- Severe and critical COVID-19 are associated with a severe immune response leading to acute lung injury and acute respiratory distress syndrome (ARDS).

- Corticosteroids are generally low-cost, easy to administer and accessible. Dexamethasone has been listed as a WHO essential medication since 1977, and prednisolone since 1979.\(^1\,^2\)
Reviewing the evidence and recommendations regarding corticosteroids
In July 2020, WHO partnered with principal investigators of 7 corticosteroid trials and formed the Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group to conduct a prospective meta-analysis (PMA) of randomized trials for corticosteroid therapy for COVID-19.⁴
• The WHO Therapeutics and COVID-19 Guideline Development Group (GDG), a group of international content experts, patients, clinicians and methodologists with no conflicts of interest and balanced in terms of gender, geography, expertise, and patient representation, met in July 2020.4

• The GDG produced recommendations following standards for trustworthy guideline development using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation), in full compliance with the WHO Handbook for guideline development, 2nd edition.5

• The GDG took an individual patient perspective to values and preferences. A high value also was placed on resource allocation, given the burden of the pandemic for health care systems globally. Values considered include:
  - Applicability
  - Balance of benefits and harms
  - Resource implications, feasibility, equity and human rights
  - Acceptability
Understanding the strength of recommendations

<table>
<thead>
<tr>
<th>Strong</th>
<th>Conditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>For patients:</strong> most individuals in this situation would want the recommended course of action and only a small proportion would not.</td>
<td>• <strong>For patients:</strong> The majority of individuals would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td>• <strong>For clinicians:</strong> Most individuals should receive this course of action.</td>
<td>• <strong>For clinicians:</strong> Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient circumstances.</td>
</tr>
<tr>
<td>• <strong>For policymakers:</strong> The recommendation can be adapted as a policy in most situations including for the use as performance indicators.</td>
<td>• <strong>For policymakers:</strong> Policy making will require substantial debates and involvement of many stakeholders. Policies are also likely to vary between regions.</td>
</tr>
</tbody>
</table>
Evidence: Corticosteroids vs standard of care in severe-critical COVID-19

The GDG made a strong recommendation for systemic corticosteroids in severe and critical COVID-19 based on moderate certainty of evidence which showed reduction in mortality of 3.4% in patients with COVID-19 who are critically or severely ill.
Conditional recommendation against systemic corticosteroids in non-severe COVID-19

- The GDG made a conditional recommendation against corticosteroid therapy for patients with non-severe COVID-19, based on the following:
  
  - **Low certainty evidence** which suggested an increased 28-day mortality in patients with non-severe COVID-19.
  
  - Systemic corticosteroid use has potential harms (e.g. hyperglycaemia, neuromuscular weakness, superinfection).
  
  - Indiscriminate use of the therapy for COVID-19 may potentially rapidly deplete global resources, and deprive patients who may benefit from it most.
Corticosteroids in COVID-19: categories of illness severity (1/2)

- There are different definitions for severe disease, critical disease and use of respiratory support in COVID-19.
- In the RECOVERY trial, patient populations were divided into those who received oxygen alone and those who received invasive mechanical ventilation.
- The GDG decided against defining patient populations on the basis of access to health interventions and attributed the effect of intervention in the RECOVERY trial to illness severity.
- Thus, for the purposes of these recommendations, disease severity categorization was based on the WHO Clinical management of COVID-19 interim guidance with the following adjustments:

Criteria for oxygen saturation threshold for Severe COVID-19 was adjusted from 94% to 90%

- The panels noted that this was arbitrary and should be interpreted cautiously in determining which patients should be offered systemic corticosteroids.
- Clinicians must use their judgement to determine whether a low oxygen saturation is a sign of severity or is normal (e.g. in a patient with chronic lung disease).
- Similarly, a saturation > 90-94% on room air may be abnormal if the clinician suspects that this number is downward trending.
## WHO COVID-19 disease severity categorization

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical COVID-19</td>
<td>Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.</td>
</tr>
<tr>
<td>Severe COVID-19</td>
<td>Defined by any of:</td>
</tr>
<tr>
<td></td>
<td>- oxygen saturation &lt; 90% on room air.</td>
</tr>
<tr>
<td></td>
<td>- respiratory rate &gt; 30 breaths per minute in adults and children &gt; 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old.</td>
</tr>
<tr>
<td></td>
<td>- signs of severe respiratory distress (i.e. accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).</td>
</tr>
<tr>
<td>Non-severe COVID-19</td>
<td>Defined as absence of any signs of severe or critical COVID-19.</td>
</tr>
</tbody>
</table>
Deep dive into the evidence
The RECOVERY trial

- The RECOVERY trial\(^6\) demonstrated a lower 28-day mortality in patients who received corticosteroids and were either receiving oxygen alone or receiving invasive mechanical ventilation, compared to usual care.
  - Largest of the 7 trials: enrolled 6425 hospitalized patients
  - At time of randomization: 60% receiving oxygen only (with or without non-invasive ventilation), 16% receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 24% receiving neither
  - Approximately \(\frac{1}{3}\) randomized to dexamethasone and \(\frac{2}{3}\) randomized to usual care
    - Dexamethasone 6mg was given daily for up to ten days
Dexamethasone in hospitalized patients with COVID-19

Prospective meta-analysis (PMA) by the WHO REACT Working Group

- Pooled data on **1703 patients with critical COVID-19** from **seven randomized clinical trials** that evaluated efficacy of corticosteroids across **12 countries on 5 continents**.⁸⁻¹¹
  - Definition of “critical” varied across studies.
    - RECOVERY trial recruited both critically ill and non–critically ill hospitalized patients. Because it was not possible to distinguish whether patients had been critically ill but not receiving invasive mechanical ventilation at the time of randomization, only data on patients who received invasive mechanical ventilation in RECOVERY were included.
  - Corticosteroid preparations and dosing varied across studies.

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**Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19**

A Meta-analysis

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The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group
As of September 2020, available data across 7 studies suggests corticosteroids offer:

- Reduced 28-day all-cause mortality in patients with critical COVID-19
- Reduced 28-day all-cause mortality in patients with severe COVID-19
- Increased risk of 28-day mortality in patients with non-severe COVID-19
- Reduced risk of need for invasive mechanical ventilation at 28-days from hospitalization
- Reduced duration of hospitalization
- Low likelihood of serious adverse events in patients with critical COVID-19


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**Table:** Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19.

<table>
<thead>
<tr>
<th>Drug and Trial</th>
<th>Initial dose</th>
<th>Steroids n/N</th>
<th>No Steroids n/N</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>High: 20 mg IV daily</td>
<td>20/7</td>
<td>12/27</td>
<td>2.00 (0.21, 18.69)</td>
<td>0.87</td>
</tr>
<tr>
<td>CoDEK (NCT04327401)</td>
<td>High: 20 mg IV daily</td>
<td>89/128</td>
<td>78/128</td>
<td>0.80 (0.49, 1.31)</td>
<td>17.69</td>
</tr>
<tr>
<td>RECOVERY (NCT04381836)</td>
<td>Low: 8 mg PO/IV daily</td>
<td>105/264</td>
<td>283/663</td>
<td>0.50 (0.44, 0.78)</td>
<td>53.95</td>
</tr>
<tr>
<td>Overall (Dexamethasone, fixed-effect)</td>
<td></td>
<td>186/459</td>
<td>361/823</td>
<td>0.04 (0.50, 0.82)</td>
<td>72.50</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPE-COV (NCT01951749)</td>
<td>Low: 200 mg IV daily</td>
<td>11/75</td>
<td>20/77</td>
<td>0.46 (0.20, 1.04)</td>
<td>6.44</td>
</tr>
<tr>
<td>COVID STEROID (NCT04348305)</td>
<td>Low: 200 mg IV daily</td>
<td>6/15</td>
<td>2/14</td>
<td>4.00 (0.65, 24.66)</td>
<td>1.31</td>
</tr>
<tr>
<td>REMAP-CAP (NCT02735707)</td>
<td>Low: 50 mg IV q8h</td>
<td>29/105</td>
<td>29/92</td>
<td>0.71 (0.38, 1.33)</td>
<td>11.12</td>
</tr>
<tr>
<td>Overall (Hydrocortisone, fixed-effect)</td>
<td></td>
<td>43/195</td>
<td>51/179</td>
<td>0.69 (0.43, 1.12)</td>
<td>18.87</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids-SARI (NCT04244591)</td>
<td>High: 40 mg IV q12h</td>
<td>13/24</td>
<td>13/23</td>
<td>0.91 (0.29, 2.87)</td>
<td>3.27</td>
</tr>
<tr>
<td>METCOVID (NCT04345729)</td>
<td>High: 0.5 mg/kg q12h</td>
<td>58/77</td>
<td>50/70</td>
<td>0.74 (0.30, 1.83)</td>
<td>5.35</td>
</tr>
<tr>
<td>Overall (Methylprednisolone, fixed-effect)</td>
<td></td>
<td>71/95</td>
<td>83/93</td>
<td>0.80 (0.39, 1.63)</td>
<td>8.63</td>
</tr>
</tbody>
</table>

**Diagram:** The diamonds shown with solid lines are from fixed-effect meta-analyses (primary analysis). The diamond shown with dashed lines is from a random-effects meta-analysis.

* The RECOVERY and METCOVID trial results are for patients who were receiving invasive mechanical ventilation at randomization.
Clinical considerations when administering corticosteroids
Corticosteroids in COVID-19: clinical use

<table>
<thead>
<tr>
<th>Route</th>
<th>Systemic corticosteroids may be administered orally or intravenously.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Daily regimen of dexamethasone 6 mg once daily is equivalent to:</td>
</tr>
<tr>
<td></td>
<td>- 150 mg of hydrocortisone daily (e.g. 50 mg every 8 hours) or</td>
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<td></td>
<td>- 40 mg of prednisone daily or</td>
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<tr>
<td></td>
<td>- 32 mg of methylprednisolone daily (e.g. 8 mg every 6 hours or 16 mg every 12 hours).</td>
</tr>
<tr>
<td>Duration</td>
<td>Up to 7–10 days.</td>
</tr>
<tr>
<td>General monitoring</td>
<td>Monitor glucose levels (even if no diabetes diagnosed previously).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special populations to monitor closely for complications</th>
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</thead>
<tbody>
<tr>
<td>- Patients receiving other immunosuppressants/immunomodulators.</td>
</tr>
<tr>
<td>- Patients with these conditions:</td>
</tr>
<tr>
<td>- diabetes (specially with diabetic ketoacidosis)</td>
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<tr>
<td>- severe immunodeficiency disorders</td>
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<tr>
<td>- haematological and other malignances</td>
</tr>
<tr>
<td>- low number of white blood cells</td>
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<td>- organ transplantations</td>
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<tr>
<td>- iron overload states</td>
</tr>
<tr>
<td>- severe burns</td>
</tr>
<tr>
<td>- injection drug use</td>
</tr>
<tr>
<td>- malnutrition</td>
</tr>
<tr>
<td>- open wound following trauma.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples of possible complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hyperglycaemia or decompensated diabetes</td>
</tr>
<tr>
<td>- Immunosuppression</td>
</tr>
<tr>
<td>- Superinfections: bacterial, fungal, viral, parasites</td>
</tr>
<tr>
<td>- Poor wound healing.</td>
</tr>
</tbody>
</table>

The drugs and doses stated here are for illustrative purposes only. Decisions regarding the use of any medication must be made by a licensed provider and take into account each patient’s specific clinical history and other circumstances, and be in accordance with relevant local management and prescribing guidelines.
Corticosteroids in COVID-19: contraindications

- Relatively few absolute contraindications to corticosteroids exist, and clinician judgment and shared decision making should be utilized when considering systemic corticosteroids.

- Patients excluded from randomization in the trials often were those for whom corticosteroids could not be stopped (e.g. patients on chronic steroids prior to entering the trial, who would require a continuing or tapering dose).

- Risks of systemic corticosteroids include:
  - Hyperglycaemia (especially in diabetics)
  - Hypernatremia
  - Gastrointestinal bleeding
  - Neuropsychiatric effects
  - Neuromuscular weakness
  - Superinfection/immunocompromise
  - Stroke or myocardial infarction
Corticosteroids in COVID-19: serious adverse events

- Clinicians should be aware of risks of systemic corticosteroids any time that they are prescribed, and consider the individual risk to each patient.

- From the COVID-19 prospective meta-analysis, serious adverse events noted to be statistically significant were hyperglycaemia (elevated blood sugar) and hypernatremia (elevated blood sodium).

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Corticosteroids in COVID-19: uncertainties

Many things remain unknown about the use of corticosteroids in COVID-19, including:

- Generalizability in resource-limited settings (i.e. low and middle income countries)
- Generalizability among patient populations (e.g. children, immunocompromised, patients with tuberculosis)
- Optimal steroid preparation, dosing and timing of drug initiation
- Long-term effect of systemic corticosteroids on mortality and functional outcomes in those recovering from COVID-19
- Impact of systemic corticosteroids on immunity and the risk of subsequent infection
- Impact on mortality beyond 28 days
- Effect on viral replication
Antenatal corticosteroid therapy

- WHO recommends antenatal corticosteroid therapy for women at risk of preterm birth from 24 to 34 weeks of gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available.

- For women with mild or moderate COVID-19, the benefits of antenatal corticosteroid might outweigh the risks of potential harm to the mother.
  - The balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman and may vary depending on the woman’s clinical condition, her wishes and that of her family, and available health care resources.
Summary
Summary

• Give systemic corticosteroids for severe and critical COVID-19.

• Be aware and monitor for potential adverse events due to corticosteroid administration.

• Use shared decision-making in discussing corticosteroids for patients in whom the risks and benefits remain unclear (e.g. immunocompromised, tuberculosis, paediatric, non-severe disease)
Visual summary

A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. https://doi.org/10.1136/bmj.m3379
Resources


   https://app.magicapp.org/#/guideline/4717

   https://doi.org/10.1136/bmj.m3379

References

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4. WHO GDG Clinical practice guideline on corticosteroids for COVID-19, Bios. 7 July 2020
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