Recommendations for therapeutics in the management of critically ill COVID-19 patients
Disclosures

• No financial disclosures
• Methods chair for WHO therapeutics clinical practice guideline
• I routinely treat critically ill patients with COVID-19
Trustworthy Clinical Practice Guidelines

Formulate question
Select outcomes
Rate importance of outcomes
Systematic Review (outcomes across studies)
Evidence Profile (GRADEpro)

1. Pooled estimate of effect for each outcome
2. Quality of evidence for each outcome

Start
RCT observational
Rate down
1. risk of bias
2. inconsistency
3. indirectness
4. imprecision
5. publication bias

Rate up
1. large effect
2. dose-response
3. antagonistic bias

Formulate recommendations
- For or against an action
- Strong or weak (strength)

Strong or weak:
- Quality of evidence
- Balance benefits/drawbacks
- Values and preferences
- Resource use (cost)

Wording
- *We recommend...* | *Clinicians should...*
- *We suggest...* | *Clinicians might...*
- unambiguous
- clear implications for action
- transparent (values & preferences statement)
The Network Meta-analysis

Hydroxychloroquine, azithromycin

Interferon beta

Lopinavir-ritonavir

rhG-CSF

Remdesivir

JAKi

ACEi/ARB

IL-6i

Umifenovir

Vitamin C

Ivermectin

Doxycycline, ivermectin

Proxalutimide

Lopinavir-ritonavir, interferon beta-1a

Sulodexide

Vitamin D

Colchicine

Corticosteroids

Azithromycin

Anticoagulant

Favipiravir

Standard care/Placebo

Data sources

Published 121
Preprints 52
Unpublished 23
Upcoming 10

Analysed in review

Participants

56327
15263
5177
1805

To be included in next update

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Recommendations In Favour
Recommendations Against
Severe or Critical Disease

Population
This recommendation applies only to people with these characteristics:

- Patients with confirmed COVID-19
- Absence of signs of severe or critical disease
- SpO₂<90% on room air
- Respiratory rate >30 in adults
- Raised respiratory rate in children
- Signs of severe respiratory distress
- Requires life sustaining treatment
- Acute respiratory distress syndrome
- Sepsis
- Septic shock
Corticosteroids

**Recommendation 1**

Patients with severe and critical COVID-19

We recommend corticosteroids

**Evidence profile**

- **Mortality with critical illness**: 415 events per 1,000 people, favours usual supportive care
- **Mortality with severe illness**: 334 events per 1,000 people, favours usual supportive care
- **Gastrointestinal bleeding**: 49 events per 1,000 people, no important difference
- **Superinfections**: 186 events per 1,000 people, no important difference
- **Hypoglycemia**: 235 events per 1,000 people, favours usual supportive care
- **Neuromuscular weakness**: 69 events per 1,000 people, no important difference
- **Neuropsychiatric effects**: 35 events per 1,000 people, no important difference

Evidence quality: Moderate

**Recommendation 2**

Patients with non-severe COVID-19

We suggest no corticosteroids

**Evidence profile**

- **Mortality with non-severe illness**: 476 events per 1,000 people, favours usual supportive care
- **Gastrointestinal bleeding**: 151 events per 1,000 people, no important difference
- **Superinfections**: 186 events per 1,000 people, no important difference
- **Hypoglycemia**: 235 events per 1,000 people, no important difference
- **Neuromuscular weakness**: 69 events per 1,000 people, no important difference
- **Neuropsychiatric effects**: 35 events per 1,000 people, no important difference

Evidence quality: Low

- The panel judged that almost all fully informed patients with severe COVID-19 would choose to take corticosteroids.
Corticosteroids Reduce Mortality in ARDS

COVID ARDS
RR 0.89 (0.76 to 1.05)

Non-COVID ARDS
RR 0.71 (0.54 to 0.92)
• Effect consistent between tocilizumab and sarilumab

• Assumes all patients will also be getting corticosteroids

• Access/availability may require triage to highest risk

• Ontario Science Table – Toci 400mg IV x 1
JAK2 inhibitors

• Similar benefits to IL-6 inhibitors

• No studies evaluating combination therapy

• Benefit – oral administration compared to IL-6 but multiple dosing

• Evidence is for Baricitinib – not Ruxolitinib or Tofacitinib

• Adjustment in renal disease/liver disease

Suggested regimen

Baricitinib
4 mg Oral Daily

Ruxolitinib
5 mg Oral Twice daily

Tofacitinib
10 mg Oral Twice daily

For 14 days or until hospital discharge
### Using these drugs in severe or critical COVID-19

<table>
<thead>
<tr>
<th></th>
<th>Per 1000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>34 fewer (moderate)</td>
</tr>
<tr>
<td><strong>Invasive mechanical ventilation</strong></td>
<td>30 fewer (moderate)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>No important difference</td>
</tr>
<tr>
<td><strong>Hospital length of stay</strong></td>
<td>4.5d fewer (low)</td>
</tr>
</tbody>
</table>

- Most patients enrolled in IL-6 studies and JAK2 studies were also getting corticosteroids – no effect modification
- No (or extremely limited data) looking at co-admin of 3 agents
Applicability

1. Pregnant women and children were not enrolled into these trials. Although no rationale to suggest that these populations would respond differently.

2. Decision for use to be made between clinician and patient (or decision maker) discussing whether potential benefits outweighs the risks.

3. Risks: ongoing concern about secondary bacterial or fungal infections. Trials were mostly carried out in high income settings and with short length of followup.
Remdesivir

- Weak recommendation for in non-severe at high risk
- For hospitalized patients
- NEW TRIAL DATA SUGGESTS BENEFIT IN SEVERE BUT NOT CRITICAL DISEASE?
- RECOMMENDATION PENDING

Figure 6: Meta-analysis of the effects of remdesivir vs control on mortality in Solidarity and other trials, by respiratory support at study entry. High-flow and low-flow oxygen were not recorded separately at entry into Solidarity. Ventilation includes non-invasive ventilation. Full details of these meta-analyses are given in the appendix (p 33). Solidity data are from figure 2 and table 2, and other data are published (supplementary table 10). O-E = observed minus expected number of deaths. RR ratio. "IV is the variance of the log rank statistic O-E then RR is obtained by taking log, RR to be (O-E)/V with normal variance 1/V. Summation of (O-E) and of V yields the stratified total (providing the inverse-variance-weighted average of the separate log, RR values).

Lancet 2022; 399: 1941–53
Recommendations against
Mortality numbers look encouraging but data VERY LOW certainty

Recommend further trial enrolment
Bad MATH+? Covid treatment paper by Pierre Kory retracted for flawed results

A Wisconsin physician who has been publishing inaccurate treatments for Covid-19 has had a paper on a hospital protocol his group says radically reduced hospital deaths from the infection after one of the facilities cited in the study said the data were incorrect.

Pierre Kory, whose take have included medical director of the Trauma and...
Other things that don’t work regardless of disease severity

• Hydroxychloroquine
• Lopinavir-ritonavir
• Convalescent plasma
• Corticosteroids in non-severe disease
• Monoclonals (limited efficacy in omicron)
WHO Guideline Dissemination

• BMJ - https://www.bmj.com/content/370/bmj.m3379


• MAGICApp – https://app.magicapp.org/#/guideline/nBkO1E
Thank you

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