COVID-19 IN THE CRITICALLY ILL. WHAT WE KNOW, AND WHAT WE NEED TO KNOW

Presented by Dr. Srinivas Murthy and Dr. Rob Fowler

All attendees will enter the meeting with their mic muted and will be unable to turn on their video.
Moderator:

Sarah Forgie  MD, MEd, FRCPC  
President  
Association of Medical Microbiology and Infectious Disease (AMMI) Canada
Webinar Housekeeping Notes

If you have a question for our speaker or panelists, please use the Q&A feature. Questions will be answered live following the presentation. (please note we cannot guarantee that all questions will be answered)

If you are experiencing technical difficulties, please use the chat feature or email krystal@ammi.ca.
A recording of all the CUPA-tea webinars are available on the AMMI Canada Website (ammi.ca) under the Clinical Update tab.

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This activity is eligible for MOC section 1 credits as an unaccredited group learning activity. Please note that unaccredited group learning activities are only eligible for 0.5 credits for every hour of learning, with a maximum of 50 credits per cycle. If you have any questions about how to enter these credits into Mainport, please contact the Royal College Service Centre at cpd@royalcollege.ca
Co - Moderator:

Marianna Ofner PhD, RN
**Senior Advisor** COVID-19 Clinical Issues Task Group
Public Health Agency of Canada
**Adjunct Professor** University of Toronto
Dr. Srinivas Murthy’s research focuses upon improving the management of severe infections in adults and children. He has assisted with international health organizations on a number of outbreaks and is active with a number of clinical trials and research on COVID19.
Dr. Rob Fowler’s clinical and academic focus includes access and outcomes of care for critically ill patients and infection-related critical illness. He has assisted or worked with national and international health care organizations during SARS, pandemic and avian influenza, Middle East Respiratory Syndrome, Ebola and COVID-19.
Disclosures

– Dr. Rob Fowler
  • CIHR funding for the CATCO trial.

– Dr. Srinivas Murthy
  • CIHR funding for the CATCO trial.
  • Receive salary support as the Health Research Foundation and Innovative Medicines Canada Chair in Pandemic Preparedness Research
Objectives

• Provide an update on the epidemiology and characteristics of critically ill patients with COVID-19.

• Outline the latest evidence for clinical management of critically ill patients with COVID-19.

• Discuss major research gaps to reduce mortality and other outcomes for critically ill patients with COVID-19.
COVID-19 IN THE CRITICALLY ILL. WHAT WE KNOW, AND WHAT WE NEED TO KNOW

Rob Fowler, MDCM, MSc
Critical Care Medicine
University of Toronto

Srinivas Murthy, MDCM, MSc
Pediatric Infectious Diseases & Critical Care Medicine
University of British Columbia
Epidemiology

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200907-weekly-epi-update-4.pdf?sfvrsn=f5f607ee_2
Resurgence in Covid-19 deaths approaching mid-April peak

Daily deaths of patients diagnosed with coronavirus (7-day rolling average)

Latin America now accounts for 43 per cent of average global deaths.

Aug 26-Sep 1
Average daily deaths 5,406

Mar 9-15
Average daily deaths 421

Peak deaths Apr 10-16 6,784

The US share of average global daily deaths has risen again to 16 per cent

* Canada, Bermuda, Greenland and St Pierre and Miquelon
ICU data - UK

Figure 14  In-hospital survival to 90 days following admission to critical care
## ICU data - UK

### Table 12: Outcome by combinations of organ support *

<table>
<thead>
<tr>
<th>Organ support received *</th>
<th>Patients with COVID-19 and outcome reported (N=10704)</th>
<th>Patients with viral pneumonia (non-COVID-19), 2017-19 (N=5782)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discharged alive from critical care</td>
<td>Died in critical care</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Any respiratory support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic only</td>
<td>2199 (80.4)</td>
<td>537 (19.6)</td>
</tr>
<tr>
<td>Advanced</td>
<td>4018 (52.2)</td>
<td>3684 (47.8)</td>
</tr>
<tr>
<td>Any renal support</td>
<td>1233 (43.2)</td>
<td>1618 (56.8)</td>
</tr>
<tr>
<td>Combinations of advanced respiratory, advanced cardiovascular and renal support:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced respiratory support only</td>
<td>2124 (63.9)</td>
<td>1202 (36.1)</td>
</tr>
<tr>
<td>Advanced respiratory and advanced cardiovascular support only</td>
<td>763 (45.8)</td>
<td>904 (54.2)</td>
</tr>
<tr>
<td>Advanced respiratory and renal support only</td>
<td>576 (48.5)</td>
<td>612 (51.5)</td>
</tr>
<tr>
<td>Advanced respiratory, advanced cardiovascular and renal support</td>
<td>555 (36.5)</td>
<td>966 (63.5)</td>
</tr>
</tbody>
</table>
Hospital data - Canada
ICU Data - Canada

(n=328)
Total ICU mortality – 26%
Mechanical ventilation mortality – 31%
Clinical Manifestations & Syndromes
Associated with COVID-19

Symptom

- History of fever
- Shortness of breath
- Cough (no sputum)
- Fatigue / Malaise
- Diarrhoea
- Cough (with sputum)
- Vomiting / Nausea
- Muscle aches
- Altered consciousness / confusion
- Headache
- Chest pain
- Sore throat
- Abdominal pain
- Runny nose
- Wheezing
- Joint pain
- Cough (bloody sputum / haemoptysis)
- Conjunctivitis
- Skin rash
- Seizures
- Bleeding
- Disturbance or loss of smell*
- Skin ulcers
- Lymphadenopathy
- Ear pain
- Disturbance or loss of taste*

Proportion

N=811, submitted
Co-morbidities in hospitalized patients with COVID-19

N=811, submitted
Mechanisms of Injury

- Predominantly respiratory presentation
- Binding of virus to ACE2 receptor
- Replication and release of virus
- Infection of Type II pneumatocytes
- T lymphocyte, monocyte, neutrophil
- TNF-a, IL-1, 6 release
- Increased vascular permeability
- Thickened Alveolar Interstitium
- Hyaline membrane formation
- Activation of Coagulation
- Hypoxia, work of breathing

doi.org/10.1016/S2213-2600(20)30076-X
COVID-19 related pulmonary Inflammation

https://doi.org/10.1016/S0140-6736(20)30183-5
Pulmonary Pathophysiology: Interstitial mononuclear inflammatory infiltrates dominated by lymphocytes

doi.org/10.1016/S2213-2600(20)30076-X
An invader’s impact
In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body’s response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm.

1 Lungs
A cross section shows immune cells crowding an inflamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.

2 Heart and blood vessels
The virus (teal) enters cells, likely including those lining blood vessels, by binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.

3 Brain
Some COVID-19 patients have strokes, seizures, confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

4 Eyes
Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

5 Nose
Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose’s nerve endings and damage cells.

6 Liver
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

7 Kidneys
Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

8 Intestines
Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in ACE2 receptors. Some 20% or more of patients have diarrhea.

Science, 2020
Autopsy studies

Tissue-specific tolerance in fatal Covid-19

David A Dorward* Ph.D.1,2, Clark D Russell MBChB3,4, In Hwa Um Ph.D.4, Mustafa Elshani M.Sc.4, Stuart D Armstrong Ph.D.5, Rebekah Penrice-Randal M.Sc.5, Tracey Millar M.Sc.5, Chris EB Lerpiniere RGN6, Giulia Tagliavini M.Sc.1, Catherine S Hartley M.Sc.6, Nadine P Randle Ph.D.5, Naomi N Gachanja M.Sc.1, Philippe MD Potev M.Sc.1, Alison M Anderson MBE7, Victoria L Campbell Ph.D.5, Alasdair J Duguid MB BChir8, Wael Al Qsous MD9, Ralph BouHaidar MD2, J Kenneth Baillie Ph.D.2,10,11, Kevin Dhaliwal Ph.D.1,12, William A Wallace Ph.D.1, Christopher OC Bellamy Ph.D.1,13, Sandrine Prost Ph.D.1,14, Colin Smith MD2,6, Julian A Hiscox Ph.D.5,13,14, David J Harrison Ph.D.7,4, Christopher D Lucas* Ph.D.1,15 on behalf of the ICECAP consortium.

- Virus detected in a variety of organs
- Discrepancy in local viral burden and local inflammatory profile
- Lungs – lots of inflammation, little virus
- Gut, kidneys – lots of virus, little inflammation
There is broad consensus on the need for research to: focus on actions that can save lives now; facilitate actions so that those affected are promptly diagnosed and receive optimal care; and catalyse the full integration of all innovations within each research area.

Moreover, there is an imperative to support research priorities in a way that leads to the development of sustainable global research platforms pre-prepared for the next disease X epidemic. This will allow for accelerated research, innovative solutions and R&D of diagnostics, therapeutics and vaccines, as well as the timely and equitable access to these life-saving tools for those at highest risk.
Therapeutics
Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review

Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou*, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Song, Xiaoying Gu, Lulu Guan, Yuan Wei, Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao

Summary

Background Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed

<table>
<thead>
<tr>
<th>Treatments*</th>
<th>Total (n=191)</th>
<th>Non-survivor (n=54)</th>
<th>Survivor (n=137)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>181 (95%)</td>
<td>53 (98%)</td>
<td>128 (93%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Antiviral treatment</td>
<td>41 (21%)</td>
<td>12 (22%)</td>
<td>29 (21%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>57 (30%)</td>
<td>26 (48%)</td>
<td>31 (23%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>46 (24%)</td>
<td>36 (67%)</td>
<td>10 (7%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Hydroxychloroquine
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Philippe Gautret a, b, $, Jean-Christophe Lagier a, c, $, Philippe Parola a, b, Van Thuan Hoang a, b, d, Line Meddeb a, Morgane Mailhe a, Barbara Doudier a, Johan Courjon e, f, g, Valérie Giordanengo h, Vera Esteves Vieira a, Hervé Tissot Dupont a, c, Stéphane Honoré i, j, Philippe Colson a, c, Eric Chabrière a, c, Bernard La Scola a, c, Jean-Marc Rolain a, c, Philippe Brouqui a, c, Didier Raoult a, c

https://doi.org/10.1016/j.ijantimicag.2020.105949
Randomised Evaluation of COVID-19 Therapy (RECOVERY)
Last updated on 8 Apr 2020
RR 1.09 (0.96–1.23)
Log-rank p=0.18

Number at risk
Active       1561       1337       1227       1161       1125
Control     3155       2750       2525       2410       2346
<table>
<thead>
<tr>
<th>Age, years ($\chi^2 = 0.4; p=0.51$)</th>
<th>Hydroxychloroquine</th>
<th>Usual care</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>160/925 (17.3%)</td>
<td>314/1874 (16.8%)</td>
<td>1.04 (0.85–1.25)</td>
</tr>
<tr>
<td>≥70 &lt;80</td>
<td>126/342 (36.8%)</td>
<td>206/631 (32.6%)</td>
<td>1.16 (0.92–1.46)</td>
</tr>
<tr>
<td>≥80</td>
<td>132/294 (44.9%)</td>
<td>268/650 (41.2%)</td>
<td>1.13 (0.91–1.41)</td>
</tr>
<tr>
<td><strong>Sex ($\chi^2 = 1.0; p=0.31$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>274/961 (28.5%)</td>
<td>543/1974 (27.5%)</td>
<td>1.04 (0.90–1.21)</td>
</tr>
<tr>
<td>Women</td>
<td>144/600 (24.0%)</td>
<td>245/1181 (20.7%)</td>
<td>1.19 (0.96–1.47)</td>
</tr>
<tr>
<td><strong>Days since symptom onset ($\chi^2 = 0.0; p=0.97$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7</td>
<td>176/622 (28.3%)</td>
<td>338/1275 (26.5%)</td>
<td>1.09 (0.91–1.32)</td>
</tr>
<tr>
<td>&gt;7</td>
<td>240/930 (25.8%)</td>
<td>444/1871 (23.7%)</td>
<td>1.10 (0.94–1.29)</td>
</tr>
<tr>
<td><strong>Respiratory support at randomization ($\chi^2 = 0.6; p=0.45$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No oxygen received</td>
<td>57/362 (15.7%)</td>
<td>99/750 (13.2%)</td>
<td>1.22 (0.87–1.70)</td>
</tr>
<tr>
<td>Oxygen only</td>
<td>251/938 (26.8%)</td>
<td>473/1873 (25.3%)</td>
<td>1.08 (0.92–1.26)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>110/261 (42.1%)</td>
<td>216/532 (40.6%)</td>
<td>1.03 (0.81–1.30)</td>
</tr>
<tr>
<td><strong>Baseline risk ($\chi^2 = 0.3; p=0.57$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30%</td>
<td>145/994 (14.6%)</td>
<td>275/1993 (13.8%)</td>
<td>1.06 (0.87–1.30)</td>
</tr>
<tr>
<td>≥30% &lt;45%</td>
<td>135/317 (42.6%)</td>
<td>245/635 (38.6%)</td>
<td>1.13 (0.91–1.40)</td>
</tr>
<tr>
<td>≥45%</td>
<td>138/250 (55.2%)</td>
<td>268/527 (50.9%)</td>
<td>1.16 (0.93–1.43)</td>
</tr>
</tbody>
</table>

**All participants** | 418/1561 (26.8%) | 788/3155 (25.0%) | **1.09 (0.96–1.23)** |

p=0.18
<table>
<thead>
<tr>
<th>Trial</th>
<th>Deaths/Patients</th>
<th>HCQ death analyses</th>
<th>Risk ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated</td>
<td>Variance of O-E</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HCQ</td>
<td>SOC</td>
<td>O-E</td>
</tr>
<tr>
<td>SOLIDARITY*</td>
<td>75/794</td>
<td>56/785</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>(9.4%)</td>
<td>(7.1%)</td>
<td>30.1</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>396/1542</td>
<td>2(368/1566)**</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>(25.7%)</td>
<td>(23.5%)</td>
<td>189.7</td>
</tr>
<tr>
<td>Total</td>
<td>471/2336</td>
<td>424/2351**</td>
<td>31.7</td>
</tr>
<tr>
<td></td>
<td>(20.2%)</td>
<td>(18.0%)</td>
<td>219.7</td>
</tr>
</tbody>
</table>

[HCQ worse if RR>1]

Treatment effect 2p = 0.03, adverse
Lopinavir-Ritonavir
1596 patients randomised to lopinavir-ritonavir
3376 patients randomised to usual care

28-day mortality (22.1% l-r vs. 21.3% usual care)
Relative risk 1.04 [95% CI 0.91-1.18] p=0.58

No beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay

Results consistent in different subgroups of patients

Findings 86 were randomly assigned to the combination group and 41 were to the control. The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4·37 [95% CI 1·86–10·24], p=0·0010). No patients died during the study.

Interpretation Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19. Future clinical study of a double antiviral therapy with interferon beta-1b as a backbone is warranted.
Remdesivir
Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

Remdesivir - compassionate-use – was given to patients hospitalized with Covid-19.

Of the 61 patients who received remdesivir, 8 could not be analyzed.

Conclusions
In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)
Hazard ratio 1.23 (95% CI 0.87–1.75); log-rank p=0.24
Remdesivir for the Treatment of Covid-19 — Preliminary Report

Kaplan–Meier Estimates of Cumulative Recoveries.

A Overall

B Patients Not Receiving Oxygen

C Patients Receiving Oxygen

D Patients Receiving High-Flow Oxygen or Noninvasive Mechanical Ventilation

E Patients Receiving Mechanical Ventilation or ECMO

No. at Risk
Remdesivir Placebo

P<0.001

No. at Risk
Remdesivir Placebo

No. at Risk
Remdesivir Placebo

No. at Risk
Remdesivir Placebo
### Time to Recovery According to Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Recovery Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1059</td>
<td>1.32 (1.12–1.55)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>844</td>
<td>1.33 (1.11–1.59)</td>
</tr>
<tr>
<td>Europe</td>
<td>163</td>
<td>1.40 (0.90–2.16)</td>
</tr>
<tr>
<td>Asia</td>
<td>52</td>
<td>1.20 (0.65–2.22)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>563</td>
<td>1.39 (1.12–1.73)</td>
</tr>
<tr>
<td>Black</td>
<td>219</td>
<td>1.14 (0.81–1.61)</td>
</tr>
<tr>
<td>Asian</td>
<td>134</td>
<td>1.04 (0.68–1.57)</td>
</tr>
<tr>
<td>Other</td>
<td>143</td>
<td>1.89 (1.15–3.10)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>247</td>
<td>1.23 (0.88–1.72)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>748</td>
<td>1.33 (1.10–1.61)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt;40 yr</td>
<td>119</td>
<td>2.03 (1.31–3.15)</td>
</tr>
<tr>
<td>40 to &lt;65 yr</td>
<td>558</td>
<td>1.16 (0.94–1.44)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>382</td>
<td>1.37 (1.02–1.83)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>682</td>
<td>1.31 (1.07–1.59)</td>
</tr>
<tr>
<td>Female</td>
<td>377</td>
<td>1.38 (1.05–1.81)</td>
</tr>
<tr>
<td>Symptoms duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 days</td>
<td>664</td>
<td>1.28 (1.05–1.57)</td>
</tr>
<tr>
<td>&gt;10 days</td>
<td>380</td>
<td>1.38 (1.05–1.81)</td>
</tr>
<tr>
<td>Baseline ordinal score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (not receiving oxygen)</td>
<td>127</td>
<td>1.38 (0.94–2.03)</td>
</tr>
<tr>
<td>5 (receiving oxygen)</td>
<td>421</td>
<td>1.47 (1.17–1.84)</td>
</tr>
<tr>
<td>6 (receiving high-flow oxygen or noninvasive mechanical ventilation)</td>
<td>197</td>
<td>1.20 (0.79–1.81)</td>
</tr>
<tr>
<td>7 (receiving mechanical ventilation or ECMO)</td>
<td>272</td>
<td>0.95 (0.64–1.42)</td>
</tr>
</tbody>
</table>

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19 
A Randomized Clinical Trial

Christoph D. Spiller, MD; Robert L. Gottlieb, MD, PhD; Gerard J. Criner, MD; José Ramón Arribas López, MD; Anna Maria Cattelan, MD; Alex Soriano Villadomu, MD; Oyemba Obgugu, MD; Prshant Malhotra, MD; Kathleen M. Mullane, DO; Antonella Castagna, MD; Louis Y. Ann Chai, MD; Meta Reestenberg, MD; Dwen Tak Yin Tsang, MD; Enos Benamoun, MD; Paul Le Tellier, MD; Shan Chen Chang, MD; Devi Sen Gupta, MD; Robert H. Hyland, DPhil; Anu O. Osinusi, MD; Huyen Cao, MD; Christiana Blair, MS; Hongyan Wang, PhD; Anuj Gaggar, MD; PhD; Diana M. Brainard, MD; Mark J. McPhail, MD; Sanjay Bhagani, MD; Mi Young Ahn, MD; Arjun J. Sanyal, MD; Gregory Huhn, MD; Francisco M. Marty, MD, for the GS-US-540-5774 Investigators

Figure 2. Clinical Status on a 7-Point Ordinal Scale on Study Days 11, 14, and 28 by Treatment Group

Clinical status
- Discharged
- Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than per-protocol remdesivir administration)
- Hospitalized, not requiring supplemental oxygen; requiring ongoing medical care (COVID-19-related or otherwise)
- Hospitalized, requiring low-flow supplemental oxygen
- Hospitalized, requiring noninvasive ventilation or high-flow oxygen
- Hospitalized, requiring invasive mechanical ventilation or ECMO
- Death
Remdesivir Trial vs. SoC – still enrolling

“Solidarity” clinical trial for COVID-19 treatments
WHO’s COVID-19 SOLIDARITY Trial Lands in Canada & Led by Sunnybrook Health Sciences Centre: Treatments for COVID-19 (CATCO)

Apr 10, 2020 | Canada, Coronavirus, COVID-19, Sunnybrook Health Sciences Centre, University of British Columbia, World Health Organization | 0 comments

The World Health Organization’s (WHO) SOLIDARITY Trial has commenced in Canada as up to 20 participating hospitals gear up for first patient first visit. The study, supported by the Canadian Institutes of Health Research (CIHR), reflects an unprecedented level of global collaboration as this major trial assesses the safety and effectiveness of different drugs, and drug combinations in people who are hospitalized with COVID-19. The initiative is known in Canada as Canadian Treatments for COVID-19 or CATCO. NCT04330690
Corticosteroids
Glucocorticoids were commonly used to Treat COVID-19
International Severe Acute Respiratory & Emerging Infection Consortium

85973 patients
545 sites
42 countries

Proportion

Nasal / mask oxygen therapy
Antibiotic agent
Invasive ventilation
High flow oxygen therapy
Non–invasive ventilation
Inotropes / vasopressors
Prone ventilation
Corticosteroid agent
Antiviral agent
Tracheostomy
Other
Renal replacement therapy
Antifungal agent
Off–label / compassionate use medications
Extracorporeal
Inhaled nitric oxide
Interleukin inhibitors
Convalescent plasma
Early supportive therapy and monitoring

- **supplemental oxygen** to patients with SARI, respiratory distress, hypoxaemia, or shock
- **Use conservative fluid management** in patients with SARI when no evidence of shock
- **Give empiric antimicrobials** for all likely pathogens causing SARI
- Do not routinely give **systemic corticosteroids** for viral pneumonia outside **clinical trials**
- **Closely monitor** patients with SARI for signs of clinical deterioration
- **Understand co-morbid conditions** to tailor management
- **Communicate** early with patient and family
Clinical Trials Were Needed
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

ABSTRACT

Randomly assigned 2104 patients with COVID-19 to dexamethasone 6 mg daily for up to 10 days vs 4321 to usual care
# RECOVERY TRIAL

Table 2. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexamethasone (N=2104)</th>
<th>Usual Care (N=4321)</th>
<th>Rate or Risk Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality at 28 days</td>
<td>482/2104 (22.9)</td>
<td>1110/4321 (25.7)</td>
<td>0.83 (0.75–0.93)</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged from hospital within 28 days</td>
<td>1413/2104 (67.2)</td>
<td>2745/4321 (63.5)</td>
<td>1.10 (1.03–1.17)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation or death†</td>
<td>456/1780 (25.6)</td>
<td>994/3638 (27.3)</td>
<td>0.92 (0.84–1.01)</td>
</tr>
<tr>
<td>Death</td>
<td>387/1780 (21.7)</td>
<td>827/3638 (22.7)</td>
<td>0.93 (0.84–1.03)</td>
</tr>
</tbody>
</table>

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.
# RECOVERY TRIAL

## Respiratory Support at Randomization

<table>
<thead>
<tr>
<th>Support Type</th>
<th>Dexamethasone</th>
<th>Usual Care</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive mechanical ventilation</td>
<td>95/324 (29.3%)</td>
<td>283/683 (41.4%)</td>
<td>0.64 (0.51–0.81)</td>
</tr>
<tr>
<td>Oxygen only</td>
<td>298/1279 (23.3%)</td>
<td>682/2604 (26.2%)</td>
<td>0.82 (0.72–0.94)</td>
</tr>
<tr>
<td>No oxygen received</td>
<td>89/501 (17.8%)</td>
<td>145/1034 (14.0%)</td>
<td>1.19 (0.91–1.55)</td>
</tr>
<tr>
<td>All Patients</td>
<td>482/2104 (22.9%)</td>
<td>1110/4321 (25.7%)</td>
<td>0.83 (0.75–0.93)</td>
</tr>
</tbody>
</table>

Chi-square trend across three categories: 11.5

P < 0.001

# Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis

JAMA. Published online September 02, 2020. doi:10.1001/jama.2020.17023

<table>
<thead>
<tr>
<th>Drug and trial</th>
<th>ClinicalTrials.gov identifier</th>
<th>Initial dose and administration</th>
<th>No. of deaths/total No. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
<th>Favors no steroids</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>DEXA-COVID 19 NCT04325061</td>
<td>High: 20 mg/d intravenously</td>
<td>2/7 2/12</td>
<td>2.00 (0.21-18.69)</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>CoDEX NCT04327401</td>
<td>High: 20 mg/d intravenously</td>
<td>69/128 76/128</td>
<td>0.80 (0.49-1.31)</td>
<td></td>
<td></td>
<td>18.69</td>
</tr>
<tr>
<td></td>
<td>RECOVERY NCT04381936</td>
<td>Low: 6 mg/d orally or intravenously</td>
<td>95/324 283/683</td>
<td>0.59 (0.44-0.78)</td>
<td></td>
<td></td>
<td>57.00</td>
</tr>
<tr>
<td></td>
<td>Subgroup fixed effect</td>
<td></td>
<td>166/459 361/823</td>
<td>0.64 (0.50-0.82)</td>
<td></td>
<td></td>
<td>76.60</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>CAPE COVID NCT02517489</td>
<td>Low: 200 mg/d intravenously</td>
<td>11/75 20/73</td>
<td>0.46 (0.20-1.04)</td>
<td></td>
<td></td>
<td>6.80</td>
</tr>
<tr>
<td></td>
<td>COVID STERIOD NCT04348305</td>
<td>Low: 200 mg/d intravenously</td>
<td>6/15 2/14</td>
<td>4.00 (0.65-24.66)</td>
<td></td>
<td></td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>REMAP-CAP NCT02735707</td>
<td>Low: 50 mg every 6 h intravenously</td>
<td>26/105 29/92</td>
<td>0.71 (0.38-1.33)</td>
<td></td>
<td></td>
<td>11.75</td>
</tr>
<tr>
<td></td>
<td>Subgroup fixed effect</td>
<td></td>
<td>43/195 51/179</td>
<td>0.69 (0.43-1.12)</td>
<td></td>
<td></td>
<td>19.94</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>Steroids-SARI NCT04244591</td>
<td>High: 40 mg every 12 h intravenously</td>
<td>13/24 13/23</td>
<td>0.91 (0.29-2.87)</td>
<td></td>
<td></td>
<td>3.46</td>
</tr>
<tr>
<td></td>
<td>Overall (fixed effect)</td>
<td></td>
<td>222/678 425/1025</td>
<td>0.66 (0.53-0.82)</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>Overall (random effects)</td>
<td></td>
<td>222/678 425/1025</td>
<td>0.70 (0.48-1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[P = .31 \text{ for heterogeneity; } I^2 = 15.6\%\]
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<tr>
<th>Subgroup</th>
<th>No. of deaths/total No. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
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<th>Weight, %</th>
</tr>
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<tbody>
<tr>
<td><strong>Invasive mechanical ventilation (IMV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ($I^2 = 0%$)</td>
<td>14/70</td>
<td>0.41 (0.19-0.88)</td>
<td></td>
<td></td>
<td>2.7</td>
</tr>
<tr>
<td>Yes ($I^2 = 44.1%$)</td>
<td>208/608</td>
<td>0.69 (0.55-0.86)</td>
<td></td>
<td></td>
<td>31.7</td>
</tr>
<tr>
<td><strong>Oxygen treatment without IMV (RECOVERY)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>298/1279</td>
<td>0.86 (0.73-1.00)</td>
<td></td>
<td></td>
<td>65.6</td>
</tr>
<tr>
<td><strong>Taking vasoactive medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ($I^2 = 0%$)</td>
<td>51/184</td>
<td>0.55 (0.34-0.88)</td>
<td></td>
<td></td>
<td>50.2</td>
</tr>
<tr>
<td>Yes ($I^2 = 0%$)</td>
<td>76/169</td>
<td>1.05 (0.65-1.69)</td>
<td></td>
<td></td>
<td>49.8</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 ($I^2 = 0%$)</td>
<td>72/338</td>
<td>0.67 (0.48-0.94)</td>
<td></td>
<td></td>
<td>42.7</td>
</tr>
<tr>
<td>&gt;60 ($I^2 = 49.7%$)</td>
<td>150/339</td>
<td>0.69 (0.51-0.93)</td>
<td></td>
<td></td>
<td>57.3</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female ($I^2 = 0%$)</td>
<td>60/202</td>
<td>0.66 (0.43-0.99)</td>
<td></td>
<td></td>
<td>27.4</td>
</tr>
<tr>
<td>Male ($I^2 = 14.7%$)</td>
<td>162/476</td>
<td>0.66 (0.51-0.84)</td>
<td></td>
<td></td>
<td>72.6</td>
</tr>
<tr>
<td><strong>Symptomatic, d</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7 ($I^2 = 69.1%$)</td>
<td>51/130</td>
<td>0.63 (0.39-1.04)</td>
<td></td>
<td></td>
<td>22.4</td>
</tr>
<tr>
<td>&gt;7 ($I^2 = 0%$)</td>
<td>139/418</td>
<td>0.64 (0.49-0.83)</td>
<td></td>
<td></td>
<td>77.6</td>
</tr>
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<td>High: 20 mg/d intravenously</td>
<td>3/7 11/12</td>
<td>0.07 (0.01-0.86)</td>
</tr>
<tr>
<td>CoDEX</td>
<td>NCT04327401</td>
<td>High: 20 mg/d intravenously</td>
<td>7/128 15/128</td>
<td>0.44 (0.17-1.11)</td>
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<td>NCT02517489</td>
<td>Low: 200 mg/d intravenously</td>
<td>28/75 30/73</td>
<td>0.85 (0.44-1.65)</td>
</tr>
<tr>
<td>COVID STEROID</td>
<td>NCT04348305</td>
<td>Low: 200 mg/d intravenously</td>
<td>1/15 0/14</td>
<td>3.00 (0.11-79.91)</td>
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<td>NCT04244591</td>
<td>High: 40 mg every 12 h intravenously</td>
<td>23/24 23/23</td>
<td>0.33 (0.01-8.61)</td>
</tr>
</tbody>
</table>

Odds ratio (95% CI)
The Bottom Line

• Glucocorticoids appear to increase survival for patients with COVID-19
• Effects may be greatest among those who have high severity of illness
• The effect appears similar among many formulations
• Glucocorticoids are now standard of care for sick hospitalized patients with COVID-19
Anti-interleukins
## Inflammatory Markers in ICU Patients with COVID-19

Wang Y. AJRCCM 10.1164/rccm.202003-0736LE

Initial reports highlighted higher inflammatory marker levels in sicker patients with COVID-19.

<table>
<thead>
<tr>
<th>Inflammatory marker</th>
<th>Survivors (n = 211)</th>
<th>Non-survivors (n = 133)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP, mg/L</td>
<td>28 (6-67)</td>
<td>101 (61-153)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCT, ng/ml</td>
<td>0.04 (0.03-0.09)</td>
<td>0.21 (0.13-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-2R, U/ml</td>
<td>716 (458-954)</td>
<td>1098 (721-1512)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>10.8 (2.7-37.4)</td>
<td>61.1 (29.9-132.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-8, pg/ml</td>
<td>12.5 (6.9-20.8)</td>
<td>28.3 (14.7-59.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-10, pg/ml</td>
<td>2.5 (2.5-7.0)</td>
<td>10.5 (5.9-18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNF-α, pg/ml</td>
<td>8.2 (6.1-10.2)</td>
<td>10.7 (7.5-15.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Critically ill patients with COVID-19 & ARDS had lower circulating cytokine levels than patients with bacterial sepsis and similar to other critically ill patients.

...but, COVID-19 now appears not to be typically characterized by cytokine storm.
Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia

• COVACTA trial did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality

• Primary endpoint not met: 7-category ordinal scale at 4 weeks (p=0.36; odds ratio [95% CI] = 1.19 [0.81, 1.76])

• No difference in secondary endpoints

Sarilumab (Kevzara)

Sanofi provides update on Kevzara® (sarilumab) Phase 3 trial in severe and critically ill COVID-19 patients outside the U.S.

• PARIS – September 1, 2020 – Sanofi today announced that the global Phase 3 trial investigating intravenously administered Kevzara® (sarilumab) at a dose of 200 mg or 400 mg[a] in severely or critically ill[b] patients hospitalized with COVID-19 did not meet its primary endpoint and key secondary endpoint when Kevzara was compared to placebo added to usual hospital care. The 420-patient randomized trial was conducted outside the U.S. in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia and Spain (86 in placebo, 161 in 200 mg, and 173 in 400 mg arms).

Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients

- PARIS and TARRYTOWN, N.Y. - July 2, 2020 – Sanofi and Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced that the U.S. Phase 3 trial of Kevzara® (sarilumab) 400 mg in COVID-19 patients requiring mechanical ventilation did not meet its primary and key secondary endpoints when Kevzara was added to best supportive care compared to best supportive care alone (placebo).
Antibody Mediated Therapies
Convalescent Plasma
The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis  JID 2015:211.Mair-Jenkins et al

John Mair-Jenkins, Maria Saavedra-Campos, J. Kenneth Baillie, Paul Cleary, Fu-Meng Khaw, Wei Shen Lin, Sophia Makk, Kevin D. Rooney, Convalescent Plasma Study Group, Jonathan S. Nguyen-Van-Tam, and Charles R. Beck

32 studies of SARS coronavirus and severe influenza: reduction in mortality, especially when plasma administered early.

JAMA | Preliminary Communication

Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma

Chenguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; Yang Yang, MD; Jinxiu Li, MD; Jing Yuan, MD; Fuxiang Wang, MD; Delin Li, PhD; Minghui Yang, PhD; Li Xing, MM; Jinli Wei, MM; Haixia Xiao, PhD; Yan Yang, MM; Jixun Qu, MD; Ling Qing, MM; Li Chen, MD; Zhixiang Xu, MM; Ling Peng, MM; Yanjie Li, MM; Haixia Zheng, MM; Feng Chen, MM; Kun Huang, MM; Yujing Jiang, MM; Dongjing Liu, MD; Zheng Zhang, MD; Yingxia Liu, MD; Lei Liu, MD

CONCLUSIONS AND RELEVANCE In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.
A Randomized, Open-Label Trial of CONvalescent Plasma for Hospitalized Adults With Acute COVID-19 Respiratory Illness: CONCOR-1

Donald Arnold, Philippe Bégin, Jeannie Callum

Two Arms (2:1 Allocation)

Arm 1: COVID-19 CP 500ml
Arm 2: Standard of care

n=1200 patients

Primary Outcome: Intubation or hospital mortality 30 days.
Convalescent Plasma - CCCTG
Monoclonal Antibodies
One Lilly press release yesterday in outpatients...
Anticoagulation
Acute pulmonary embolism and COVID-19 pneumonia: a random association?

Gian Battista Danzi, Marco Loffi, Gianluca Galeazzi, Elisa Gherbesi

*European Heart Journal*, ehaa254, [https://doi.org/10.1093/eurheartj/ehaa254](https://doi.org/10.1093/eurheartj/ehaa254)
ATTACC: Antithrombotic Therapy to Ameliorate Complications of COVID-19

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
University of Manitoba

Collaborator:
University Health Network, Toronto

Information provided by (Responsible Party):
University of Manitoba

ClinicalTrials.gov Identifier: NCT04372589

Recruitment Status: Recruiting
First Posted: May 4, 2020
Last Update Posted: June 4, 2020

See Contacts and Locations
Research question: In patients treated in the ICU for sepsis with vasopressors, what is the effect of high-dose intravenous vitamin C (50 mg/kg/dose) q6h for 96h, vs. placebo, on the primary outcome of mortality or persistent organ dysfunction (mechanical ventilation, new dialysis, vasopressors) at 28 days?

Sample size: 800
Other Therapies and Trials to Mention?

• Interferon-beta-1a,
• interleukin-1 receptor antagonist (Anakinra)
• .....
Ventilation & Oxygenation Controversies
Ventilation & Oxygenation
more evidence needed

Recommendations for adult and pediatric patients with ARDS who are treated with non-invasive or high flow oxygen systems

⚠ High-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) should be considered. Patients treated with either HFNO or NIV should be closely monitored for clinical deterioration.

Recommendations for adult and paediatric patients with ARDS in whom a lung protective ventilation strategy fails

⚠ In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxemia despite lung protective ventilation.

Nosocomial Transmission

Figure 1. Exhaled Aerosol Dispersal Pattern during High-Flow Oxygen Administration with a Conventional, Noninvasive Face Mask.
Clinical management of patients with COVID-19: Second interim guidance

August 17, 2020

This guidance document has been endorsed by: Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI) Canada.

Clinical management of patients with COVID-19: Second interim guidance

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Caring for critically ill patients with COVID-19 is based on the usual management of viral pneumonia with respiratory failure with additional precautions to reduce risk of transmission.

**Usual critical care**

Many patients with severe COVID-19 develop acute respiratory distress syndrome (ARDS). Evidence-based guidelines for ARDS in the context of COVID-19 include treatments such as

- Conservative intravenous fluid strategies
- Empirical early antibiotics for possible bacterial pneumonia
- Lung-protective ventilation strategies
- Periodic prone positioning during mechanical ventilation
- Consideration of extracorporeal membrane oxygenation
Questions?
Please enter one thing you have learned from today's presentation into the chat box
We Appreciate Your Feedback

Please take a few moments following the webinar to complete the evaluation form.

The Survey has also been linked in the chat box prior to the end of the webinar.
An email will be sent to you tomorrow with a survey link.

Accreditation

This activity is eligible for MOC section 1 credits as an unaccredited group learning activity. Please note that unaccredited group learning activities are only eligible for 0.5 credits for every hour of learning, with a maximum of 50 credits per cycle. If you have any questions about how to enter these credits into Mainport, please contact the Royal College Service Centre at cpd@royalcollege.ca
Thank you for joining us!

A recording of all the CUPA-T.E.A webinars are available on the AMMI Canada Website (ammi.ca) under the Clinical Update tab.

Upcoming Events
Stay tuned for more CUPA-T.E.A (Clinical Updates from PHAC and AMMI Canada) in October!
Supplemental Slides
Clinical Management of Patients with COVID-19

- Section 5.0 Management of Mild COVID-19
- Section 6.0 Management of Moderate COVID-19
- Section 7.0 Management of Severe COVID-19
- Section 8.0 Management of critical COVID-19

Coding for interventions:

☑️ Do – the intervention is beneficial (strong recommendation) OR the intervention is a best practice statement

☒ Don’t – the intervention is known to be harmful.

⚠️ Consider – the intervention may be beneficial in selected patients (conditional recommendation) OR be careful when considering this intervention.
Section 5.0  Management of Mild COVID-19

- Patients with mild disease do not require hospitalization, unless there is concern for rapid deterioration or an inability to return promptly to hospital.

- Isolation is necessary to contain virus transmission. All patients cared for outside hospital should be instructed to follow public health protocols for self-isolation and return to hospital if symptoms worsen. Self-isolation protocols are available from PHAC and provincial/territorial and local public health departments.

- Provide patients with mild COVID-19 information on symptomatic treatment. antipyretics for fever and aches, hydration, monitoring their symptoms.

- Counsel patients with mild COVID-19 and their caregivers about the signs and symptoms of complications that should prompt urgent care. If they develop symptoms like difficulty breathing, pain or pressure in the chest, confusion, drowsiness, or weakness, they should seek follow-up care.

- Antibiotics should not be prescribed to patients with suspected or confirmed mild COVID-19 unless there is clinical suspicion of a bacterial infection.
Section 6.0  Management of Moderate COVID-19

Patients with moderate suspected or confirmed COVID-19 (i.e. with clinical signs of pneumonia but no signs of severe pneumonia, including SpO2 ≥ 90% on room air) who are not determined to be at high risk of deterioration may not require hospitalization, but they should be isolated.

The decision regarding the location of care should be made on a case-by-case basis and will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and conditions at home, including the presence of vulnerable persons in the household.

For patients at high risk for deterioration, admission to hospital should be considered. The median time to acute respiratory distress syndrome (ARDS) ranges from 8 to 12 days. Lymphopenia, neutrophilia, elevated serum alanine aminotransferase and aspartate aminotransferase levels, elevated lactate dehydrogenase, high CRP, and high ferritin levels may be associated with greater illness severity.

Antibiotics should not be prescribed to patients with suspected or confirmed moderate COVID-19 unless there is clinical suspicion of a bacterial infection.
Section 7.0  Management of Severe COVID-19

7.1 Oxygen Therapy and Monitoring

- Give supplemental oxygen therapy immediately to patients with COVID-19 who have severe acute respiratory infection and respiratory distress, hypoxaemia or shock, and target saturations of 90-96% SpO₂ during resuscitation.
- Closely monitor patients with COVID-19 for signs of clinical deterioration, such as rapidly progressive respiratory failure or shock and respond immediately with supportive care interventions.
- Understand the patient’s co-morbid conditions and tailor management accordingly.
- Use conservative fluid management in patients with severe acute respiratory infection when there is no evidence of shock.

7.2 Treatment of Co-infections

- Give empiric antimicrobials to treat all likely pathogens causing severe acute respiratory infection and sepsis as soon as possible, within 1 hour of initial patient assessment for patients with sepsis.
- Frequently re-evaluate and de-escalate empiric therapy where possible on the basis of microbiology results and clinical judgment.
8.1 Acute Respiratory Distress Syndrome (ARDS)

- Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy and prepare to provide advanced oxygen/ventilatory support.
- Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions.
- Among hospitalized adult patients who have COVID-19 and require supplemental oxygen or mechanical ventilation, clinicians should strongly consider dexamethasone 6 mg IV daily for 10 days (or until off oxygen or discharge if earlier) or equivalent glucocorticoid dose.

**Recommendations for mechanically ventilated adult and pediatric patients with ARDS:**

- Implement mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH₂O).
- In adult patients with severe ARDS, prone ventilation for 12-16 hours per day should be considered.
- Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.
- In patients with moderate or severe ARDS, higher PEEP instead of lower PEEP is suggested.
- In patients with moderate-severe ARDS (PaO₂/FiO₂ < 150), neuromuscular blockade by continuous infusion should not be routinely used.
- Avoid disconnecting the patient from the ventilator, which results in loss of PEEP and atelectasis.
- Use in-line catheters for airway suctioning and clamp the endotracheal tube when disconnection is required (e.g., transfer to a transport ventilator).

**Recommendations for adult and pediatric patients with ARDS who are treated with non-invasive or high flow oxygen systems:**

- High-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) should be considered. Patients treated with either HFNO or NIV should be closely monitored for clinical deterioration.

**Recommendations for adult and paediatric patients with ARDS in whom a lung protective ventilation strategy fails:**

- In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxemia despite lung protective ventilation.
Section 8.0  Management of Critical COVID-19

8.2 Septic Shock

- Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥ 60-65 mmHg AND lactate is ≥ 2 mmol/L, in absence of hypovolemia.

- Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] < 5th centile or 2 SD below normal for age) or two or more of the following: altered mental state; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnea; mottled or cool

**Recommendations for resuscitation strategies for adult and paediatric patients with septic shock.**

- In resuscitation for septic shock in adults, give 250-500 mL crystalloid fluid as a rapid bolus in the first 15-30 minutes and reassess for signs of fluid overload after each bolus.

- In resuscitation for septic shock in children, give 10-20 mL/kg crystalloid fluid as a rapid bolus in the first 30-60 minutes and reassess for signs of fluid overload after each bolus.