Key changes from previously uploaded version

1. Update to wording for use of remdesivir in treatment table 3, page 12 and updates of evidence in appendix evidence summaries
2. Update to the wording for the role of thromboprophylaxis and COVID-19 page 9 and page 16
3. Update to wording of consultation of additional services in patients with COVID-19 on page 11
4. Removal of recommendation for tocilizumab use in HLH/CRS and updates to appendix evidence summary

Summary Statements for Management of Children with Confirmed COVID-19

Treatment recommendations:

1. Supportive care is the mainstay of therapy for patients with COVID-19.
2. Use of experimental therapies for children with COVID-19 should ideally be offered in the context of clinical trials.
3. Use of experimental therapies should only be considered on a case-by-case basis with caution and should only be given under expert guidance from Infectious Diseases if it is judged that the potential for unproven benefit is likely to outweigh the known and unknown risks.
4. Experimental therapies should not be offered to patients not requiring hospitalization.
5. Considerations for treatment should include severity of illness, patient and family preference, availability of antiviral therapy, risk of side effects, drug interactions, and concomitant diseases.
6. Experimental therapies should be offered only after informed consent has been obtained (and documented) as per Hospital policy.

Recommendations for COVID-19 case management specialist team involvement

7. Patient not initially requiring critical care support:
   • In patients with positive SARS-CoV-2 testing and symptoms that are compatible with COVID-19, involvement of additional services is recommended:
     o This includes notification of the Infectious Diseases (ID) consult service and Infection control team for all SARS-CoV-2 positive patients.
     o It is strongly recommended that there is an initial multidisciplinary team meeting involving services that will likely be engaged for the patient.
     o The thrombosis service should be notified of all patients with positive SARS-CoV-2 testing and symptoms compatible with COVID-19 if it is likely they will be admitted for more than 24 hours.
• Notification of other services is also prudent as appropriate. These include Respiratory Medicine, Rheumatology, Immunology, Haematology/Oncology, and Clinical Pharmacology.

• In patients with positive SARS-CoV-2 testing and acute respiratory, cardiac or neurological symptoms of concern:
  o The Critical Care Response Team (CCRT) should be made aware of patients upon admission and subsequently if there is evidence of clinical deterioration that might necessitate ICU care.

• In patients with positive SARS-CoV-2 testing where clinical symptoms might be reasonably explained by a clear alternate diagnosis:
  o Infectious diseases service consultation is at the discretion of the primary care team.

8. Patients requiring critical care support:
Critical Care team, Respiratory Medicine, ID, thrombosis team and Infection Control services should be engaged. An initial multidisciplinary team meeting it is strongly recommended involving services likely be engaged if the patient further deteriorates: including Rheumatology, Immunology, Haematology/Oncology, and Clinical Pharmacology.

Risk factors for severe illness in children with COVID-19
10. Populations that may be at higher risk for severe infection include infants <1 year of age, and children with comorbid conditions including: lung disease, immune compromise, obesity, congenital heart disease, sickle cell disease, genetic abnormalities, neurological disease, or diabetes mellitus.

Acute respiratory distress syndrome (ARDS) and children with COVID-19
11. In general, the principles of management of paediatric ARDS secondary to COVID-19 are likely to be aligned with those of the adult population. Specific management of ARDS in children with COVID-19 should be assessed on a case-by-case basis under the direction of critical care and respiratory teams.

Management considerations for Cytokine Release Syndrome (CRS)/secondary Hemophagocytic lymphohistiocytosis (HLH) in children with COVID-19
12. The routine use of immunomodulatory agents in children with COVID-19 outside of clinical trials is not recommended.
13. In exceptional circumstances, on a case-by-case basis where monitored cytokine levels or serum markers indicate clear evidence of cytokine storm, immunomodulatory agents may be considered under expert guidance from specialist teams as detailed above.

Antibiotic therapy
14. Antibiotic therapy should follow SickKids empiric guidelines for community-acquired or hospital-acquired bacterial pneumonia, as appropriate.
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<td>Immunoglobulin therapy (IVIG)</td>
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<td>10. Appendix 5. Evidence summary for key studies on corticosteroid use in patients with COVID-19 as of 17th September 2020</td>
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<td>11. Appendix 6. Evidence summary for key studies on tocilizumab and anakinra use in patients with COVID-19 as of 15th July 2020</td>
</tr>
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1. Introduction

For the majority of children, Coronavirus disease 2019 (COVID-19) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a mild illness. Current evidence from case series of affected children indicate that fewer than 10% have severe or critical disease and that death is a rare event.\(^1,2\) However, at this time, there are limited data on the full spectrum of COVID-19 in children and information on this topic is rapidly evolving.

Risk factors for severe disease in adults include older age (particularly above 70 years), male sex, and the presence of comorbidities, in particular hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, chronic kidney disease and immunosuppression.\(^3\)\(^-\)\(^5\) While there have been reports of critically ill children with comorbidities such as congenital heart disease, and hydronephrosis, and one death in a child presenting with intussusception, data are still quite limited, and therefore, the potential impact of underlying medical conditions on COVID-19 severity in children is presently unknown.\(^2\) However, given the adult data on comorbidities and based on what is known about the influenza virus, there is potential for immunocompromised children, or children with underlying chronic medical conditions (i.e. chronic lung disease or asthma) to be at increased risk of complications from COVID-19. Interestingly, a recent review of 2000 children with SARS-CoV2 infection in China indicated that infants and children less than 5 years old were more likely to have severe disease compared to older children.\(^1\)

2. Background to Guidance Development

The purpose of this guideline is to provide interim guidance to support clinicians within The Hospital for Sick Children (SickKids), Toronto who will be managing paediatric patients with COVID-19. For important information and disclaimers about this document, please see last page.

This guideline has been developed by members of the Division of Infectious Diseases, SickKids, Toronto, with input from a COVID-19 working group including representation from the following groups: (in alphabetical order)

- Critical Care – Dr Anne-Marie Guerguerian, Dr Gail Annich, Dr Steven Schwartz, Dr Andrew Helmers
- Emergency Medicine – Dr Kathy Boutis, Dr Suzanne Schuh
- Haematology/Oncology – Dr Jim Whitlock, Dr Ahmed Naqvi
- Immunology and Allergy – Dr Eyal Grunebaum, Dr Vy Kim, Dr Julia Upton
- Infectious Diseases – Dr Upton Allen, Dr Stanley Read, Dr Ari Bitnun, Dr Anu Wadhwa, Dr Michelle Science, Dr Shaun Morris, Dr Valerie Waters, Fellows: Dr Helen Groves, Dr Pierre-Philippe Piche-Renaud, Dr Taito Kitano
- Pharmacy – Kathryn Timberlake
- Paediatrics – Dr Jeremy Friedman, Dr Michael Weinstein, Dr Zia Bismilla, Dr Carolyn Beck
- Respiratory Medicine – Dr Felix Ratjen
- Rheumatology – Dr Rayfel Schneider, Dr Ronald Laxer
- Additional input on thrombosis management from Dr Leonardo Brandao

(input from additional divisions/stakeholders is pending)
This guideline is intended to cover initial case management, laboratory and radiological work-up and potential off-label and experimental use of medications in the management of paediatric patients with COVID-19. It does not provide recommendations for infection control and personal protective equipment use or guidance on testing of patients with possible COVID-19 as these are addressed in separate documents.

In developing this guideline, a scoping review of available literature on off-label and experimental therapies for use in treating patients with COVID-19 was conducted. A summary of this review is included as a separate document entitled “Summary of Scoping Review for Experimental Therapies and COVID-19.” This document details the grading system used as the basis for the current recommendations.

Please note that where mentioned, SARS-CoV-2 refers to the coronavirus species and the resultant disease/illness it causes is referred to as COVID-19.

Please note that information regarding off label use of licensed medications or experimental therapies (e.g. remdesivir) in paediatric patients with COVID-19 is intended only for children who require hospital care. For paediatric patients with COVID-19 who do not require hospital care, such therapies should NOT be prescribed.

This guideline is based on the best available evidence at the time of writing, taking into consideration drug availability in Canada. However, in view of the speed at which new relevant scientific data are being produced, this guideline is intended to be a “living” guideline that will be regularly updated as new evidence emerges. SickKids anticipates that the latest version will be available via the same link (Accessible via a SickKids login) or via external link here. We invite readers to send additional comments, relevant publications and other contributions to the Infectious Diseases Division at covid19working.group@sickkids.ca for the purpose of maintaining this “living guideline”.

3. Algorithm for management of patients with suspected COVID-19

Fulfills screening criteria for COVID-19* → Isolate and initiate infection control practices as per SickKids High Risk Alert Guidance*

Clinical assessment

- No
  - Follow SickKids policy to determine if testing indicated
  - Discharge with observation and advice. Public health notification if SARS-CoV-2 testing positive.

- Yes
  - Admit
    - Consider sending testing for all respiratory viral infections, including avian influenza or MERS if patient meets case definition**
    - NP swab for SARS-CoV-2 testing (if other lower respiratory tract specimen e.g. BAL please also send)

SARS-CoV-2 testing confirmed positive

- No
  - Management of patient as per standard practice

- Yes
  - Consult ID team if input not previously requested
    - Make the Critical Care Response Team (CCRT) aware of patient and notify CCRT of any clinical deterioration that may necessitate ICU care (see table 1)
    - Initiate supportive management as per standard of care
    - Perform additional investigations as clinically indicated (see table 2)
    - Additional management considerations as detailed below (see table 3)
    - For patients requiring critical care support - critical care, Respiratory, and ID consult services should be engaged with consideration for input from Rheumatology, Immunology, Haematology and Oncology teams as required

*Please see High risk alert: Novel Coronavirus (COVID-19) available from COVID-19 screening page on SickKids COVID-19 sharepoint resources

**Please see High Risk Alert: Avian influenza (H7N9) and Middle Eastern Respiratory Syndrome Coronavirus accessed via SickKids sharepoint resources
Table 1. Classification of Disease Severity in Children*

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Mild disease</th>
<th>Moderate disease</th>
<th>Severe disease</th>
<th>Critical disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>▪ Symptoms of acute upper respiratory tract infection and/or mild lower respiratory tract infection; may also include fatigue, myalgia, and gastrointestinal symptoms. &lt;br&gt; ▪ Mild or no work of breathing &lt;br&gt; ▪ No O₂ requirement</td>
<td>▪ Clinical and/or radiological signs of pneumonia present &lt;br&gt; ▪ Increased respiratory rate &lt;br&gt; ▪ Signs of increased work of breathing. &lt;br&gt; ▪ O₂ saturation &gt;92% on room air or low flow oxygen</td>
<td>▪ Moderate or severe work of breathing or significant hypoxia: warranting ICU admission for non-invasive ventilation</td>
<td>▪ Paediatric Acute respiratory Distress Syndrome (pARDS) necessitating invasive mechanical ventilation**&lt;br&gt; ▪ May also be characterized by:&lt;br&gt; - Shock/requirement of vasopressors to maintain blood pressure&lt;br&gt; - Multi-Organ failure&lt;br&gt; - Evidence of myocardial injury or heart failure&lt;br&gt; - Acute kidney injury&lt;br&gt; - Coagulation dysfunction</td>
</tr>
</tbody>
</table>

* No clear consensus is yet available to define criteria for severe disease in paediatric patients with COVID-19.
** pARDS Classification

<table>
<thead>
<tr>
<th>Age</th>
<th>Exclude patients with peri-natal related lung disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Within 7 days of known clinical insult</td>
</tr>
<tr>
<td>Origin of Edema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload</td>
</tr>
<tr>
<td>Chest Imaging</td>
<td>Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oxygenation</th>
<th>Non Invasive mechanical ventilation</th>
<th>Invasive mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PARDS (No severity stratification)</td>
<td>Mild</td>
</tr>
<tr>
<td>Full face-mask bi-level ventilation or CPAP ≥5 cm H₂O²</td>
<td>4 ≤ OI &lt; 8</td>
<td>8 ≤ OI &lt; 16</td>
</tr>
<tr>
<td>PF ratio ≤ 300</td>
<td>5 ≤ OSI &lt; 7.5²</td>
<td>7.5 ≤ OSI &lt; 12.3²</td>
</tr>
<tr>
<td>SF ratio ≤ 264²</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Special Populations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanotic Heart</td>
<td>Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease.³</td>
</tr>
<tr>
<td>Chronic Lung</td>
<td>Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.²</td>
</tr>
<tr>
<td>Left Ventricular</td>
<td>Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.²</td>
</tr>
</tbody>
</table>
Table 2. Suggested investigations in children with COVID-19 *

<table>
<thead>
<tr>
<th>Mild disease</th>
<th>Moderate disease</th>
<th>Severe disease</th>
<th>Critical disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No routine investigations</td>
<td>• Consider continuous Pulse Oximetry and ECG monitoring</td>
<td>• All investigations considered for moderate disease should be performed at baseline for patients with severe disease. These tests should be repeated as clinically indicated based on regular clinical assessment. The following additional investigations should be considered:</td>
<td>• Investigations as for severe disease plus:</td>
</tr>
<tr>
<td>• If admitting to hospital due to presence of risk factors or underlying conditions, consider performing investigations as for moderate disease.</td>
<td>• CBC with Differential, Serum Creatinine, and ALT at baseline and repeat as clinically indicated.</td>
<td>• Consider baseline 15 lead ECG to assess for evidence of myocarditis and to monitor QTc if using QTc-prolonging medications. ECG should be performed at baseline and more frequently if clinically indicated.</td>
<td>• Consider echocardiography if signs of myocardial dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Consider Chest X-ray at baseline</td>
<td>• Blood cultures prior to initiation of antibiotics, and as clinically indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• In consultation with Infectious Diseases, Immunology and Rheumatology consider additional testing to help identify early signs of disease progression, including:</td>
<td>• In consultation with Infectious Diseases, Immunology and Rheumatology consider additional testing to help identify early signs of disease progression, including:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Urea</td>
<td>▪ Urea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Electrolytes</td>
<td>▪ Urea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Liver panel: AST, Bilirubin, GGT, Albumin</td>
<td>▪ Electrolytes,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Lactate,</td>
<td>▪ Liver panel: AST, Bilirubin, GGT, Albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Ferritin,</td>
<td>▪ Lactate,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ CRP, ESR,</td>
<td>▪ Ferritin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Fasting triglycerides,</td>
<td>▪ CRP, ESR,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ LDH,</td>
<td>▪ Fasting triglycerides,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Coagulation panel** (including fibrinogen, PT/INR, PTT and D-</td>
<td>▪ LDH,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chemokine/cytokine panel, including: IL-1b, IL-10, IL-6, IFN-g, CD163, and Soluble IL-2 Receptor Level (CD25), CXCL-9</td>
<td>▪ Coagulation panel** (including fibrinogen, PT/INR, PTT and D-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selected investigations should be performed at baseline and repeated as clinically indicated.</td>
<td>• Chemokine/cytokine panel, including: IL-1b, IL-10, IL-6, IFN-g, CD163, and Soluble IL-2 Receptor Level (CD25), CXCL-9</td>
<td></td>
</tr>
</tbody>
</table>

* For some experimental therapies being considered, additional testing may be advised as directed in table 3 below

** Coagulation testing should be performed in consultation with the thrombosis team who will guide the need for initial and repeat coagulation laboratory testing based on clinical assessment. Please refer to Prothrombotic Events and COVID-19 section on page 17
4. Management of hospitalised patients with confirmed COVID-19

Supportive care

For patients with COVID-19, supportive care and treatment of complications should be provided as per standard clinical practice. **At present, supportive care is the mainstay of therapy for patients with COVID-19.**

General principles of using off-label/experimental therapies

- The use of experimental treatments for patients with COVID-19 should ideally occur within the context of controlled clinical trials.

- In patients not enrolled in clinical trials, use of experimental therapies, for example through compassionate use, should be considered on a case-by-case basis with caution and such treatments should only be given under expert guidance from Infectious Diseases if it is judged that the potential for benefit is likely to outweigh the risk.

Consideration for discussions should include evaluation of severity of illness, availability of experimental anti-viral therapy for off-label or compassionate use, side effect profile of anti-viral therapy and interactions with other treatments as well as family preferences.

When using licensed medications for off-label indications or experimental therapies, their use should be in line with SickKids policy and procedure. The patient and/or parent(s)/legally authorized substitute decision maker(s) should be informed of the potential anticipated benefits and potential adverse effects of the proposed therapy and the health practitioner should ensure a thorough consent discussion in accordance with SickKids consent to treatment policy. The process of discussion and verbal consent should be clearly documented in the patient's record. (policies.sickkids.ca/published/Published/clinh34/main%20document.pdf)

*Note: as stated above, for paediatric patients with COVID-19 who do not require hospital care, antiviral therapy should NOT be prescribed.*

- Experience with other viral infections suggests that for antiviral therapy to be maximally effective, it should be administered as early as possible in the illness course.
COVID-19 case management specialist team involvement

Patient not initially requiring critical care support:

Patients will be admitted under the care of the paediatric medical team or other primary care team who will direct subsequent consultation with additional services.

- In patients with positive SARS-CoV-2 testing and symptoms that are compatible with COVID-19, involvement of additional services is recommended:
  - This includes notification of the Infectious Diseases (ID) consult service and Infection control team for all SARS-CoV-2 positive patients.
  - It is strongly recommended that there is an initial multidisciplinary team meeting involving services that will likely be engaged for the patient.
  - The thrombosis service should be notified of all patients with positive SARS-CoV-2 testing and symptoms compatible with COVID-19 if it is likely they will be admitted for more than 24 hours.
  - Notification of other services is also prudent as appropriate. These include Respiratory Medicine, Rheumatology, Immunology, Haematology/Oncology, and Clinical Pharmacology.

- In patients with positive SARS-CoV-2 testing and acute respiratory, cardiac or neurological symptoms of concern:
  - The Critical Care Response Team (CCRT) should be made aware of patients upon admission and subsequently if there is evidence of clinical deterioration that might necessitate ICU care.

- In patients with positive SARS-CoV-2 testing where clinical symptoms might be reasonably explained by a clear alternate diagnosis:
  - Infectious diseases service consultation is at the discretion of the primary care team

Patient requiring critical care support:

- The Critical Care team, Respiratory Medicine, ID consult and Infection Control services would have been engaged.
- The thrombosis service should be notified of all patients with positive SARS-CoV-2 testing and symptoms compatible with COVID-19 if it is likely they will be admitted for more than 24 hours.
- It is strongly recommended that there is an initial multidisciplinary team meeting involving services that will likely be engaged if the patient further deteriorates:
  - These services include Rheumatology, Immunology, Haematology/Oncology, Thrombosis team and Clinical Pharmacology.
### Table 3. Experimental Treatment Considerations for Hospitalised Paediatric Patients (4 weeks-18 years) with Confirmed COVID-19 According to Clinical Severity

PLEASE NOTE EXPERIMENTAL ANTI-VIRAL THERAPIES SHOULD NOT BE ROUTINELY RECOMMENDED FOR PAEDIATRIC PATIENTS WITH COVID-19. THIS TABLE IS INTENDED SOLELY FOR THE USE OF INFECTIOUS DISEASES AND SPECIALIST CONSULTING TEAMS AT THE HOSPITAL FOR SICK CHILDREN, TORONTO, TO PROVIDE STRUCTURED GUIDANCE IN DECISION-MAKING FOR THE MANAGEMENT OF EXCEPTIONAL CASES OF PAEDIATRIC COVID-19.

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>First-line therapy to consider</th>
<th>Other therapies/treatment considerations</th>
<th>Additional comments and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild disease</td>
<td>▪ Supportive care only</td>
<td></td>
<td>Acetaminophen should be used as first-line for fever or temperature management, unless contraindicated. NSAIDS can be considered with caution pending further data (see section below for more detailed discussion)</td>
</tr>
<tr>
<td></td>
<td>▪ No risk factors for severe disease present*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild disease</td>
<td>▪ Routine use of experimental therapies not recommended</td>
<td></td>
<td>Remdesivir&lt;br&gt;Details on inclusion criteria for remdesivir compassionate use and application process can be accessed at: <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a>&lt;br&gt;Contraindications for remdesivir: ALT/AST &gt;5 x ULN, eGFR &lt;30ml/min&lt;br&gt;Consult Pharmacist prior to submission of remdesivir application.&lt;br&gt;<strong>Remdesivir dosing</strong>&lt;br&gt;&lt; 40 kg: 5 mg/kg IV q24h x1, then 2.5 mg/kg IV q24h for 9 days&lt;br&gt;&gt;40kg: 200 mg IV q24h x1, then 100 mg IV q24h for 9 days&lt;br&gt;-It is likely that benefit from remdesivir (if any) will occur from receiving this treatment earlier in the disease course&lt;br&gt;-Note that information on the adverse effects of remdesivir are still limited and risk-benefit of using this should be assessed on an individual basis with close monitoring of toxicity</td>
</tr>
<tr>
<td></td>
<td>▪ Risk factors for severe disease present*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate disease</td>
<td>▪ Routine use of experimental therapies not recommended</td>
<td>In discussion with Infectious Diseases on a case-by-case basis:&lt;br&gt;- For patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting the availability of the drug, other agents with antiviral activity may be selectively considered in exceptional cases. **&lt;br&gt;- Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td>Severe disease</td>
<td>Routine use of experimental therapies not recommended</td>
<td>In discussion with Infectious Diseases on a case-by-case basis:</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team (see above) on a case-by-case basis:</td>
<td>▪ For patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting the availability of the drug, other agents with antiviral activity may be selectively considered in exceptional cases. **</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ Consider use of remdesivir if early in the disease course and no contra-indications for use</td>
<td>▪ Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▪ <strong>Dexamethasone use should be considered</strong></td>
<td>For patients with evidence of ARDS or cytokine release syndrome see sections below detailing further management considerations</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Critical disease</th>
<th>In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team (see above):</th>
<th>In discussion with Infectious Diseases on a case-by-case basis:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>▪ Consider use of remdesivir if early in the disease course and no contra-indications for use</td>
<td>▪ For patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting the availability of the drug, other agents with antiviral activity may be selectively considered in exceptional cases. **</td>
</tr>
<tr>
<td></td>
<td>(note remdesivir is unlikely to be helpful in critical disease but under special circumstances e.g. immunocompromised status, may be considered on a case-by-case basis)</td>
<td>▪ Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases</td>
</tr>
<tr>
<td></td>
<td>▪ <strong>Use of Dexamethasone is recommended</strong></td>
<td>For patients with evidence of ARDS or cytokine release syndrome see sections below detailing further management considerations</td>
</tr>
</tbody>
</table>

* Please see risk factor discussion in section below.  
** See appendix 4 for current evidence summary regarding experimental agents with antiviral activity including hydroxychloroquine and lopinavir/ritonavir  
Note: Previously included information on dosing considerations for hydroxychloroquine and lopinavir/ritonavir is now moved to appendix 2

---

Dexamethasone  
**Dosing:**  
For management of patients with COVID-19 requiring oxygen support and mechanical ventilation the recommended dose of dexamethasone is 0.15 mg per kg PO or IV (max 6mg) once daily for a duration of up to 10 days  
Note that dexamethasone dosing for other indications e.g. asthma, CRS/HLH, croup etc. will differ and specific hospital guidance for these indications should be followed as appropriate  

For drug interactions in the setting of COVID-19 experimental therapies check at http://www.covid19-druginteractions.org
Risk factors for severe illness in children with COVID-19

There are some reports of moderate and severe infection in children requiring hospitalization. However, severe disease in children is uncommon and risk factors for severe disease in the paediatric population are yet to be clearly defined. One large study recently published in *Paediatrics* by Dong *et al.* noted that over 60% of severe and critical cases of COVID-19 in children occurred in those aged five years or less.¹ A further report from the United States CDC noted that among children with COVID-19, 147 were hospitalized (estimated range 5.7-20%) with 15 (0.58%-2%) admitted to ICU.⁷ Data on underlying medical conditions and risk factors in hospitalized patients was limited. Children aged less than 1 year accounted for the highest percentage of hospitalization and all patients admitted to ICU for which there was available information, had one or more underlying medical condition, however the nature of these conditions has not yet been specified. More recently data from a multicentre Italian study of children and adolescents also showed increased hospitalisation rates in children under 1 year old.⁸ Notably, the hospitalisation rate was similar between children with comorbidities and those without and mechanical ventilation was only required in 2 out of 168 children studied, one of whom was preterm and the other had congenital heart disease. In a cross-sectional study of 46 North American PICUs with 48 children admitted secondary to COVID-19, 83% were noted to have significant pre-existing comorbidities.⁹ Of these, comorbidities included; medically complex patients (long-term dependence on technological support, developmental delay, genetic abnormalities), immune suppression, obesity, diabetes, seizures, congenital heart disease, chronic lung disease, sickle cell disease.

Extrapolating from these and adult data, as well as from risk factors for severe disease in children with other human coronavirus infections, it might be reasonable to consider that immunocompromised children or children with comorbidities, such as obesity, congenital heart disease, lung disease, sickle cell disease, genetic abnormalities, neurological disease or diabetes mellitus, may be at increased risk of severe infection.¹⁰

Corticosteroids use in patients with COVID-19

A number of randomised controlled trials of the use of corticosteroids in patients with COVID-19 have been published including a prospective meta-analysis using pooled data from 7 trials. Details of these trials are summarized in appendix 5. Based on currently available evidence and understanding the limitations of extrapolating adult findings to children, we suggest the following:

1) **CRITICALLY ILL CATEGORY:** For children hospitalized with COVID-19 who require mechanical ventilation, the use of dexamethasone 0.15 mg per kg PO or IV (max 6mg) once daily for a duration of up to 10 days is recommended.

2) **SEVERE CATEGORY:** For children hospitalized with COVID-19 who require oxygen but do not require mechanical ventilation, dexamethasone (in the above suggested regimen) should be considered. Factors to take into consideration include the level of respiratory support required, the expected trajectory of the child’s respiratory status, risk factors for severe disease, co-morbidities, and the child’s state of immune compromise.

3) **MODERATE CATEGORY:** For children hospitalized with COVID-19 but who do not require any respiratory support, dexamethasone is not recommended.

4) **MILD CATEGORY:** For children with COVID-19 who have mild disease and are outpatients, dexamethasone is not recommended.

When the clinical decision has been made that dexamethasone should be used based on the indications above, initiation does not need to be delayed pending availability of antiviral therapies, such as remdesivir.
In children with COVID-19 who do not require oxygen therapy or mechanical ventilation but who require steroids for other reasons, such as patients presenting with symptoms of severe asthma in the context of COVID-19, cautious use of systemic steroids may be considered on a case-by-case basis where benefits of therapy are felt to outweigh the risks.

Use of corticosteroids in the setting of CRS/HLH management is discussed in appendix 1 and should only be considered on a case-by-case basis under the directions of specialists with expertise in managing these conditions.

Of note, the dosing for dexamethasone outlined above for the treatment of respiratory compromise in a child with acute COVID-19 is a lower dose than that which is normally used for other conditions such as asthma and CRS/HLH. For steroid dosing for these other conditions, please adhere to specific hospital guidance for these indications.

Acute respiratory distress syndrome (ARDS) and children with COVID-19

ARDS in paediatric cases of COVID-19 is likely to be an uncommon event. In their review of over 2000 paediatric patients with COVID-19, Dong et al. reported that only 0.6% progressed to ARDS or multi-organ failure. Information on the specific management of ARDS in paediatric cases of COVID-19 is limited at present. Extensive guidelines from the Surviving Sepsis Campaign on the management of critically ill adults with COVID-19 include recommendations for the management of ARDS in this population. In brief, these guidelines recommend appropriate ventilation strategies such as use of low tidal volumes, conservative fluid strategies over liberal fluids, use of prone ventilation, appropriate neuromuscular blockade and sedation, with move to elective ECMO as needed if refractory hypoxemia despite these measures. These guidelines also recommend that in mechanically ventilated adults with COVID-19 and ARDS, use of systemic steroids may be considered.

In general, the principles of management of paediatric ARDS secondary to COVID-19 are likely to be aligned with those of the adult population. However, there are key differences between paediatric and adult physiology as well as differences in the management of ARDS to consider with respect to the paediatric population. Accordingly, specific management of ARDS in children with COVID-19 will be assessed on a case-by-case basis under the direction of critical care and respiratory teams when appropriate.

Severe respiratory failure with COVID-19 may occur in children with underlying conditions such as asthma. In patients with COVID-19 presenting with asthma, please follow the Critical Care Response Team and Emergency Department recommendations.

Management considerations for Cytokine Release Syndrome (CRS)/secondary Hemophagocytic lymphohistiocytosis (HLH) in children with COVID-19

Cytokine release syndrome (CRS) has been highlighted as an important component of the critical illness associated with COVID-19 in adults. Severe COVID-19 has also been associated with a cytokine profile resembling secondary HLH. In particular, elevations in levels of IL-6 has been shown to correlate with mortality in adult patients with COVID-19. In light of these findings a number of immunomodulatory agents have been proposed as theoretical therapeutic options for patients experiencing CRS with COVID-19. The current data do not support a firm course of action regarding the use of immunomodulatory agents or timing for their implementation. Therefore, presently we do not recommend the use of immunomodulatory therapy other than steroids in children with COVID-19 pending further data.
circumstances, on a case-by-case basis where monitored cytokine levels or serum markers indicate clear evidence of cytokine storm, immunomodulatory agents may be considered under expert guidance from the respective clinical teams. Please refer to appendix 1 for further details on treatment considerations for patients with CRS/HLH secondary to COVID-19.

**Antibiotic therapy**

- **General considerations:**
  
  Other potential causes of pneumonia, such as non-SARS-COV-2 respiratory viruses, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and other bacterial pathogens should be considered in all children admitted with suspected COVID-19.

  Early data suggests that rates of secondary bacterial pneumonia in children with COVID-19 are low and thus far, adult centres are not reporting high rates of bacterial superinfection.

  Common organisms implicated in secondary bacterial pneumonia for influenza include; *Streptococcus pneumoniae*, *Staphylococcus aureus*, and non-typable *Haemophilus influenzae*.

- **Antibiotic therapy should follow SickKids antibiotic guidance for community-acquired bacterial pneumonia with additional consideration for *S. aureus* coverage.**
  
  - Ceftriaxone or cefuroxime should be considered as first line antibiotic treatment for suspected secondary bacterial pneumonia in children at least 1 month of age with COVID-19.
  
  - Ceftriaxone plus vancomycin is recommended in severe cases requiring critical care management
  
  - For severely Beta-lactam allergic patients, macrolides or fluoroquinolones (such as levofloxacin) with or without the addition of an anti-staphylococcal agent such as vancomycin or clindamycin are appropriate options
  
  - **Combination azithromycin therapy with hydroxychloroquine is not recommended as its use is not supported by available evidence and introduces the risk of additive toxicity, in particular related to prolongation of the QTc and reported increased rates of cardiac arrest.**

**Prothrombotic Events in patients with COVID-19**

Reports are emerging of a high prevalence of DVT/PE in adults hospitalized with COVID-19, particularly in critically ill patients. Anticoagulation prophylaxis is being offered to all adult patients with COVID-19 with dose escalation consideration according to D-dimer titres. In children, overall absolute thrombotic risk is much lower than adults and the risk of thrombotic events in the context of COVID-19 in children is much less clear. A coagulation panel (PT/INR, PTT, fibrinogen, platelet count, and D-dimer) should be considered at baseline in children with COVID-19 with projected stay > 24 hours and repeated as clinically indicated. Patients with limb swelling/redness/pain should undergo Doppler USS to exclude DVT and a relative low threshold for ordering CTPA should be considered, particularly in patients whose respiratory parameters/ chest pain worsens out of keeping with other markers of COVID19 disease severity.
Use of other therapies/areas of controversy

Convalescent sera

A small number of observational and randomized clinical trials have been published regarding the use of convalescent plasma therapy in patients with COVID-19. Thus far outcomes are variable and the evidence basis remains limited. A number of trials of convalescent plasma use in patients with COVID-19 are ongoing worldwide. To date, no serious adverse reactions or safety events have been recorded following COVID-19 convalescent transfusion. Presently, as per Health Canada recommendations, convalescent plasma is not available for use outside of approved clinical trial settings.

Immunoglobulin therapy (IVIG)

**IVIG has not been demonstrated to be of benefit and should not be used routinely in patients with COVID-19.** Some guidelines are recommending to consider the use of IVIG therapy at standard dosing in special patient populations such as those with IgG < 4g/L.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Recent commentaries have been published suggesting ibuprofen should be avoided in patients with COVID-19.\(^{14,15}\) There are limited data on the use of NSAIDs in the context of COVID-19 and much of the evidence is derived from work in sepsis and other respiratory diseases where complications were more common in patients taking ibuprofen.\(^{14}\) For COVID-19, there are no firm data to suggest NSAIDs worsen the course of COVID-19 and further data are needed to draw clear conclusions on this. Based on currently available information, the World Health Organization does not recommend against the use of ibuprofen.

As a pragmatic approach pending further data on this controversial issue, we suggest patients should be advised that acetaminophen is the preferred first line option for treatment of fever in COVID-19 provided there are no contra-indications to its use.

- For patients who are already on NSAID therapy for other medical conditions, pending further data we do not currently advise discontinuing these. If such patients develop COVID-19, they should be advised to consult with their care providers regarding continued NSAID use.

Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin Receptor Blockers (ARBs)

SARS-CoV-2 uses ACE2 as its cellular entry receptor.\(^{16}\) Controversy exists as to whether ACE inhibitors and ARBs could be beneficial in reducing COVID-19 severity or conversely exacerbate disease. One recent large study of adults with COVID-19 did not find any evidence of increased risk of severe COVID-19 and use of ACE inhibitors or ARBs.\(^{17}\) Therefore, patients on these medications should be advised to continue them as per standard practice for their care. For patients with COVID-19 who are on ACE inhibitors or ARBs, case-by-case decisions can be made regarding ongoing use based on clinical presentation and opinion from the primary medical team in consultation with Infectious Diseases or the multidisciplinary COVID-19 case management team (see above). Clinical trials on the use of ARBs e.g. losartan as therapy in COVID-19 are ongoing.
5. Additional clinical information on COVID-19 in paediatric patients

Clinical features of paediatric patients with COVID-19

One large case series has reported on the clinical characteristics of children with confirmed COVID-19. Of 1391 children assessed and tested from January 28th through February 26th 2020, a total of 171 had confirmed SARS-CoV-2 infection. The median age was 6.7 years with a male predominance and even spread amongst age groups. Of these 171, 48.5% had cough, 46.2% pharyngeal erythema, 41.5% fever (median duration 3 days), 8.8% had diarrhoea, 7.6% had fatigue, 7.6% had rhinorrhea, 6.4% had vomiting and 5.3% had nasal congestion.

Another larger case series of 2143 paediatric patients with confirmed COVID-19 was reported by the Chinese Center for Disease Control and Prevention. The median age was 7 years (Interquartile age 2-13 years). Over 90% were asymptomatic, mild or moderate cases and no deaths were reported. Of the paediatric cases who had severe or critical disease (5.8%) approximately 60% were aged five years or less.

Provisional data from Italy on 17th March 2020 highlighted that of 22,512 cases of COVID-19, only 1.2% were in patients aged less than 18 years old and that there were no deaths in patients aged under 20 years.

In a retrospective case series of 10 hospitalized paediatric cases from China, the mean age at hospitalization was 6 years, 80% had fever, 60% cough, 40% sore throat, 30% stuffy nose and 20% sneezing and rhinorrhea. In this series none of the children had diarrhoea or vomiting. The assumed incubation period was between 2 and 10 days and symptoms typically resolved within 1 week.

Symptoms of COVID-19 in children are typically milder than that of adult cases, and asymptomatic cases have also been reported. However, while severe disease is uncommon in children, there are increasing reports of children requiring intensive care support and deaths in children due to COVID-19 have also been reported.

There have been reports of atypical symptoms in adult cases of COVID-19 such as anosmia and acute conjunctivitis, with alerts being issued to otolaryngology and ophthalmology teams regarding these symptoms.

Reports of vascular and dermatological phenomena in association with COVID-19 have been described in both children and adults. The Canadian Dermatological Association notes the following skin changes with COVID-19:

- “Covid toes” (or covid hands) – similar to the type of cold related changes we have seen in the feet of people for many years, but often occurring in places where the conditions are not cold and damp. These seem to happen more commonly in younger patients.
- Rash with or without small blisters
- Widespread hives (urticaria)
- Small bruises and broken blood vessels (petechiae)

Paediatric multisystem inflammatory syndrome in the setting of the COVID-19 outbreak

There are increasing reports of children with significant systemic inflammatory response syndromes in countries experiencing COVID-19 outbreaks. Regions reporting this have noted a spike in cases that occurs approximately one month following the overall peak of COVID-19 cases.
This syndrome shares many features common to other paediatric inflammatory conditions and cases may present with features of Kawasaki disease (KD), shock and toxic-shock-like syndrome.

For further information on identification and management of this condition please refer to the document “Practice alert: Rise in cases of paediatric multisystem inflammatory syndrome in the setting of the COVID-19 outbreak” available on the SickKids Sharepoint, COVID-19 information for clinicians.

**Neonates and COVID-19**

Please refer to the SickKids Neonatal COVID-19 Management document available on the SickKids sharepoint, COVID-19, information for clinicians.
General principles

- Careful monitoring of patient clinical status and serum markers is crucial in determining need for therapeutic intervention in exceptional cases
- **First line management of CRS/secondary HLH is supportive**, i.e. oxygen and ventilator support, fluid management, vasopressor/inotropic support and treatment of complications.
- Symptom progression should be monitored using a modified Penn Grading Scale for CRS (see table 4 below)

### Table 4. CRS status grading for children with COVID-19 (adapted from Penn CRS criteria)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild:</td>
<td>Moderate:</td>
<td>Severe:</td>
<td>Life threatening:</td>
</tr>
<tr>
<td>▪ supportive care only required</td>
<td>▪ requiring intravenous fluid (IV) support (not hypotension)</td>
<td>▪ Significant liver enzyme dysfunction and creatinine elevation not attributable to other condition</td>
<td>▪ Hypotension requiring high dose vasopressors</td>
</tr>
<tr>
<td>▪ Fevers</td>
<td>▪ Hypotension requiring IV fluid support (multiple fluid boluses) or low dose vasopressors</td>
<td>▪ Hypotension requiring IV fluid support (multiple fluid boluses) or low dose vasopressors</td>
<td>▪ Hypoxia requiring mechanical ventilation</td>
</tr>
<tr>
<td>▪ Neutropenia</td>
<td>▪ Coagulopathy requiring fresh frozen plasma, fibrinogen concentrate or cryoprecipitate</td>
<td>▪ Coagulopathy requiring fresh frozen plasma, fibrinogen concentrate or cryoprecipitate</td>
<td></td>
</tr>
<tr>
<td>▪ Mild organ dysfunction (mild creatinine elevation and liver enzyme dysfunction)</td>
<td>▪ Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, CPAP, BiPAP)</td>
<td>▪ Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, CPAP, BiPAP)</td>
<td></td>
</tr>
</tbody>
</table>

- Symptoms may include high fever, rigors, myalgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnoea, tachypnoea and hypoxia
- Signs may include marked elevation in IL-6, interferon gamma and TNF-α

- Patients with grade 2 or higher symptoms should have serum and cytokine markers sent as per **investigation guidance** detailed in section 3 above
- The following progression in clinical status despite supportive care should trigger notification of the COVID-19 case management specialist team as detailed on page 6:
  - Haemodynamic instability despite intravenous fluids and vasopressor support
  - Worsening respiratory distress, including pulmonary infiltrates, increasing FiO2 requirement and/or need for mechanical ventilation
  - Rapid clinical deterioration
  - Presence of hyper-inflammation:
    - Lymphocyte counts <1000 cells/mL
    - Ferritin >500 ng/mL
    - LDH >300 U/L
    - D-Dimer >1000 ng/mL
    - Marked elevation in IL-6 and other measured cytokines (as detailed in table 2, page 5)
- On an exceptional case-by-case basis, the COVID-19 case management specialist team may consider initiation of immunomodulatory therapy. Anakinra has previously been proposed as a potential first line choice in light of its shorter half-life. However, there is a lack of available consensus for immunomodulatory therapy use in children with COVID-19.
For patients who are highly likely to receive biological agents for immunomodulatory therapy, a serum sample for QuantiFERON testing should be sent at baseline prior to commencing therapy in order to investigate for possible latent tuberculosis. A careful history of exposure risk should also be performed. Awaiting this result should not delay commencement of the immunomodulatory therapy.

If no clinical improvement with immunomodulatory treatment occurs within 12-18 hours, consideration may be given to further/increased doses of immunomodulatory therapy and/or corticosteroid therapy.
  - Optimal dosing of corticosteroids for use in patients with COVID-19 remains controversial. Dosing for management of CRS following CAR-T Cell therapy is suggested as 1-2 mg/Kg methylprednisolone as an initial dose, then 1-2 mg/Kg per day followed by a rapid taper after haemodynamic normalization.
  - If no response within 24-48 hours, consider alternative immunomodulatory therapy options for treatment of CRS.

*Appendix 1 was developed following the meeting of a specific COVID-19 working group on 15th April 2020 to address the management approach to patients with cytokine release syndrome in the setting of COVID-19. Key contributors to this CRS working group included: Critical care: Dr Anne-Marie Guergarian; Infectious Diseases: Dr Upton Allen, Dr Stanley Read, Dr Anupma Wadhwa, Dr Valerie Waters, Dr Shaun Morris, Dr Michelle Science; Oncology: Dr Ahmed Naqvi; Rheumatology: Dr Rayfel Schneider, Dr Ronald Laxer. The guidance presented above is a modified version of the SickKids guidance for management of CAR-T Cell therapy induced CRS (BMT4870/01 - CAR-T Cell Therapy - Administration and Management of Toxicities) on 22nd April 2020.

**Appendix 1 was further updated on 30th October to remove mention of the consideration of use of tocilizumab due to evidence for a lack of efficacy in adults with COVID-19.

A summary of key studies for use of tocilizumab and anakinra in patients with COVID-19 is provided in appendix 5
7. Appendix 2. Hydroxychloroquine and Lopinavir/ritonavir dosing

Hydroxychloroquine:

**Paediatric dosing:**
6.5 mg/kg/dose (max 400 mg/dose) PO BID x 1 day, followed by 3.25 mg/kg/dose (max 200 mg/dose) PO BID x 4 days

Note: Do not crush tablets. Extemporaneous suspension can be compounded if unable to take tablets.

Contraindications and Warnings for hydroxychloroquine
- QTc>500 msec
- Myasthenia gravis
- Porphyria
- Retinal pathology
- Known G6PD deficiency (HCQ is considered generally safe in patients with G6PD deficiency, G6PD testing is not currently considered necessary prior to use)

Perform ECG prior to commencing therapy and assess frequency of repeat on a case-by-case basis (especially if initial QTc is 450-500 msec).
- If adding additional QTc prolonging drugs e.g. azithromycin with hydroxychloroquine, daily ECG monitoring is required due to possible drug interactions causing QTc prolongation

Lopinavir/ritonavir (LPV/r)

**Paediatric dosing:**
- < 6 months:
  - 300 mg/m²/dose PO BID (dose limit: 800 mg/day) x 10-14 days
- 6 months to 12 yrs and <35kg:
  - 230mg - 300 mg/m²/dose PO BID (dose limit: 800 mg/day) x 10-14 days/day)
- > 12 yrs or ≥ 35 kg:
  - 400 mg PO BID x 10-14 days

Additional Testing Requirements for LPV/r:
- Amylase, and lipase and liver enzymes at baseline and thereafter as clinically indicated. under Infectious Diseases guidance.

Contra-indications to LPV/r include previous hypersensitivity. Care should be taken if history of cardiac disease and/or presence of drug interactions.**
8. Appendix 3. Previous Changes to Document Versions

Key changes from previously uploaded version – Version 5.2, 28th September 2020

- Page 13/14  Update to dexamethasone recommendations for severe and critical disease
- Page 17    Update on convalescent sera section
- Page 24    Appendix 4: Update to remdesivir evidence section
- Page 39    Addition of Appendix 5: Evidence summary for key studies on corticosteroid use in patients with COVID-19 as of 17th September 2020

Key changes from previously uploaded version – Version 5.1, 15th July 2020

- Page 10/11 – Additional statement regarding initial multidisciplinary MDT for COVID-19 case management specialist team involvement in all cases of children admitted with COVID-19
- Page 20 – appendix 1 - Considerations for possible treatment of CRS/secondary HLH in children with COVID-19 – statement regarding QuantiFERON testing prior to anakinra use.
- Page 25 – appendix 4 – new summary of evidence for the use of remdesivir, hydroxychloroquine and lopinavir/ritonavir in treatment of patients with COVID-19
- Page 39 - appendix 5 – new evidence summary for key studies on tocilizumab and anakinra use in patients with COVID-19 as of 15th July 2020

Key changes from previously uploaded version – Version 4.0, 15th May 2020

- Page 2 - Addition of summary statements at beginning of guidance document
- Page 4 - Addition of contents page and hyperlinks for document navigation
- Page 9 - Reformatting of table 2 (investigations) to be consistent with EPIC order wording and to increase ease of readability
- Page 9 – paragraph on prothrombotic issues and COVID-19 moved to section on page 17
- Page 12 – removal of azithromycin from treatment table due to lack of efficacy data and associations with cardiac arrest in combination with hydroxychloroquine in recent publications: statement added recommending against its use with hydroxychloroquine in antibiotic section. In cases where antiviral therapy is considered, remdesivir is now suggested as first line consideration with dosing updates
based on increasing evidence for its efficacy and conflicting evidence for hydroxychloroquine efficacy in recently data from published observations and clinical trials

- Page 15 – update to risk factor section with newly published paediatric data
- Page 16 and 22 – updated information regarding CRS/HLH and immunomodulatory therapy with newly published data
- Page 18 – addition of new study information on ACE inhibitors/ARBs and COVID-19
- Page 19 – additional information on clinical features of COVID-19 including paediatric multisystem inflammatory syndrome temporally associated with COVID-19
- Page 22 – updated anakinra and tocilizumab dosing

Key changes from previously uploaded version – Version 3.1, 24th April 2020

- Page 5: Update of investigation section (table 2) to include suggested cytokine testing IL-1, IL-10, IL-6, and IFN-gamma, sIL2r (CD25) and CD163
- Page 5: New statement regarding thrombosis risk in children with COVID-19 and appropriate investigations (table 2)
- Page 6/7: Statements regarding COVID-19 case management specialist team involvement
- Page 13: Comment on the use of convalescent plasma in the management of patients with COVID-19
- Page 12, 16, 17: Additional suggested considerations in the management of cytokine release syndrome in patients with COVID-19

Key changes from previously uploaded version – Version 2.3, 7th April

- New comment in background section highlighting that for paediatric patients with COVID-19 who do not require hospital care, antiviral therapy should NOT be prescribed.
- New comment regarding the process of informed verbal consent for parents relating to the option of experimental therapies in COVID-19 added under the section: “General principles of using off-label/experimental therapies”
- Guidance in table 3 now includes only paediatric hydroxychloroquine dosing based on weight with maximum doses included. Frequency of repeat ECGs in patients receiving hydroxychloroquine to be assessed on a case-by-case basis.
- Update on preliminary paediatric data from US CDC data added in risk factor section
9. Appendix 4. Evidence summary for agents with antiviral activity as of 11\textsuperscript{th} June 2020

**Remdesivir**

Only randomised clinical trials included in evidence summary – 3 studies

**Study 1**

| Study Design | Randomised controlled double-blind trial |
| Population | Adults aged over 18 years admitted to hospital with laboratory confirmed SARS-COV-2 infection. Symptom onset 12 days or less, SaO2 94% or less on room air, PaO2:FiO2 of 300 mmHg or less and radiologically confirmed pneumonia. 237 patients were enrolled (158 remdesivir, 79 placebo). Median age 65 years, median time to symptom onset 10 days. More patients with hypertension, diabetes, coronary artery disease in remdesivir group. More patients in control versus remdesivir group had been symptomatic for <10 days at the time of starting remdesivir or placebo. Study stopped early due to lack of patients – reducing statistical power to 58%. |
| Intervention | Remdesivir 200mg day 1, 100mg daily on days 1-10 versus placebo. LPV-r (18% patients), interferon (32 % patients), corticosteroids (66% patients) co-administration in both groups. |
| Primary Outcome | Primary endpoint was time to clinical improvement up to day 28 |
| Secondary Outcome | Secondary outcomes were the proportions of patients in each category of the six-point scale at day 7, 14, and 28 after randomisation; all-cause mortality at day 28; frequency of invasive mechanical ventilation; duration of oxygen therapy; duration of hospital admission; and proportion of patients with nosocomial infection. |
| Safety/ adverse events | Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early. |
| Results | Primary Outcome Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]) Secondary outcomes Patients receiving remdesivir had a numerically faster time to clinical improvement (non significant) than those receiving placebo with symptom duration of <10 days (hazard ratio 1.52 [0.95–2.43]) 28 day mortality was similar between groups (14% vs 13%) Clinical improvement rates at days 14 and 28, duration of mechanical ventilation, length of hospital stay, length of oxygen use were not significantly different between groups and viral load decreased similarly. |

**Study 2**

Study Design | Multi-centre (multiple countries) Randomised placebo-controlled double-blind trial
---|---
Population | Hospitalized adults with COVID-19 with evidence of lower respiratory tract involvement. 1063 patients randomized. Early unblinding of study results showed preliminary results on 1059 patients (538 remdesivir, 521 placebo) and these were released. Mean age 58.9 years, 64.3% male. Most patients had one (27%) or two (52.1%) coexisting conditions. Median time from symptom onset to randomization was 9 days. 88.9% had severe disease at baseline enrolment.
Intervention | Remdesivir (200mg loading dose on day 1, 100 mg daily for 9 further days) or placebo for 10 days.
Primary Outcome | Time to recovery
Secondary Outcome | Odds of improvement, mortality
Safety/ adverse events | 49 patients stopped remdesivir and 53 patients stopped placebo due to adverse event or death. Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).
Results | **Primary outcome**
Remdesivir group had a shorter median recovery time of 11 days vs placebo group of 15 days (p<0.001)
**Secondary outcomes**
Mortality by 14 days was 7.1% in remdesivir group versus 11.9% in the placebo group. Odds of improvement higher in remdesivir group (p=0.001).

**Study 3**

---|---
Study Design | Randomised controlled open-label trial
Population | Hospitalized patients (12 years and over) with confirmed SARS-CoV-2 infection, O2 saturation 94% or less on ambient air and radiologic evidence of pneumonia. 397 patients randomized (200 for 5 days, 197 for 10 days). Note at baseline patients in 10 day group had significantly worse clinical status that 5-day group (p=0.02).
Intervention | Remdesivir for either 5 days or 10 days
Primary Outcome | Clinical status on day 14
Secondary Outcome | Proportion of patients with adverse events that occurred on or after the first dose of remdesivir for up to 30 days after the last dose.
Safety/ adverse events | The most common adverse events were nausea (9% of patients), worsening respiratory failure (8%), elevated alanine aminotransferase level (7%), and constipation (7%). Percentage of patients with adverse events were similar between groups. (70% in 5-day and 74% in 10-day group).
Results | By day 14, a clinical improvement occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. Adjusted analysis showed no significant difference between 5-day and 10-day group (P=0.14).
<table>
<thead>
<tr>
<th>Study 4</th>
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<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>Randomised controlled open-label trial</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Hospitalized patients with SARS-CoV-2 infection within 4 days of randomization. Initially included adults over 18 years and then later amended to include adolescents over 12 years. Included moderate COVID-19 pneumonia patients (defined as any radiographic evidence of pulmonary infiltrates and SaO2&gt;94% on ambient air. 584 patients enrolled – 193 in 10 day course group, 191 in 5 day course group and 200 standard care group. Median duration of symptoms prior to intervention was 8-9 days. Note significantly higher proportions of standard care group received experimental therapy including hydroxychloroquine and lopinavir-ritonavir therapy.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>5 day course of Remdesivir vs 10 day course vs standard care</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Proportion of patients discharged by day 14 of the study – subsequently amended during the study to clinical status on a 7-point ordinal scale by day 11</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td>Time to 2-point or greater improvement in clinical status; time to 1-point or greater improvement in clinical status; time to recovery; time to discontinuation of oxygen support; duration of oxygen therapy; duration of hospitalisation.</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>5-day remdesivir group had significantly higher odds of a better clinical status by day 11 on the 7-point ordinal scale vs standard care (p 0.02). No significant differences between 5-day and 10-day group and standard care for any secondary end-points.</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Study 5</th>
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<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>Multi-centre (multiple countries) Randomised placebo-controlled double-blind trial</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Hospitalized adults with COVID-19 with evidence of lower respiratory tract involvement. 1062 patients randomized (541 remdesivir, 521 placebo). 13% not requiring O2, 41% requiring O2, 26.8% ECMO or mechanical ventilation.</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Remdesivir (200mg loading dose on day 1, 100 mg daily for 9 further days) or placebo for 10 days.</td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>Time to recovery using an 8-category ordinal scale to measure clinical improvement Of note primary outcome changed – originally planned to be comparison of clinical status at day 15</td>
</tr>
<tr>
<td><strong>Secondary Outcome</strong></td>
<td>Mortality at day 15 and 29</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><strong>Primary outcome</strong> Remdesivir group had a shorter median recovery time of 10 days vs placebo group of 15 days (p&lt;0.001) For severe patients remdesivir group had a shorter median recovery time of 11 days vs placebo group of 18 days (rate ratio for recovery, 1.31; 95% CI, 1.12 to 1.52) For critical patients (mechanical ventilation or ECMO) Rate ratio for recovery was 0.98 (95% CI, 0.70 to 1.36) <strong>Secondary outcomes</strong> Mortality by 15 days was 6.7% in remdesivir group versus 11.9% in the placebo group (hazard ratio, 0.55; 95% CI, 0.36 to 0.83)</td>
</tr>
</tbody>
</table>
Odds of improvement higher in remdesivir group (p=0.001).

Study 6

Reference

Study Design
Multicentre, multinational trial, hospitalized patients aged over 18 years with COVID-19

Population
Hospitalized adults with COVID-19. 11,330 patients from 405 hospitals in 30 countries: 2750 Remdesivir, 954 hydroxychloroquine, 1411 Lopinavir-ritonavir, 2063 interferon, 4088 no study drug. 35% <50 years; 45% 50-69 years; 19% >70 years. 63% on O2 (8% ventilated) at entry, 28% not on O2 at entry.

Intervention
Randomized equally to remdesivir, hydroxychloroquine, Lopinavir-ritonavir and interferon groups or to control

Primary Outcome
In hospital mortality

Secondary Outcome
Initiation of ventilation and hospitalization duration

Results
Death rate ratios for Remdesivir showed an RR of 0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control).
Overall conclusion: No study drug had any definite effect on mortality, either overall or in any subgroup defined by age or ventilation at entry

Evidence Summary

Available evidence
5 studies (two publications for the ACT study)

Working group discussion regarding evidence
There were significant limitations with the Wang et al. trial which was underpowered due to limitations in patient recruitment which may have impacted on the trial results. The Beigel et al. study, of which most patients had severe disease, did show shortened recovery time with remdesivir treatment compared to standard care. However this difference was not seen for critically ill patients and was most notable when the treatment was commenced early in the illness course. Spinner et al. looked at the use of remdesivir in moderate disease and found higher odds of better clinical status on a 7-point ordinal scale with 5 days of remdesivir versus standard care. However there were a number of limitations to this study and the clinical importance/relevance of the findings remains uncertain. The WHO solidarity trial failed to find any effect of remdesivir use on mortality in patients hospitalized with COVID-19.

In regards to adverse effects, these trials suggest that remdesivir as a 10-day treatment has an acceptable safety profile in adults. The third trial comparing a 5-day and 10-day course of remdesivir suggests there may be no difference in outcome between treatment durations. Based on this evidence, a shorter duration of treatment for patients not requiring mechanical ventilation or ECMO may be considered with duration extended up to a total of 10 days if no clinical improvement or ongoing clinical concern.

The working group recognise that no specific clinical trial data exists for the use of remdesivir to treat COVID-19 in the paediatric population. The working group were in agreement with the current guidance suggesting there may be benefit for the use of remdesivir in mild and moderate disease. However the group felt that the evidence for severe and critical diseases warranted a
wording change for these patient categories to highlight that remdesivir is unlikely to be of benefit in later disease or in critical disease but may be considered on a case-by-case basis.

Hydroxychloroquine (HCQ)

Summary of selection criteria for evidence included in evidence review:

- Only clinical trials of hydroxychloroquine in the use of patients with COVID-19 included
- All published randomised controlled trials: both peer-reviewed and non-peer-reviewed publications, including treatment and prophylaxis studies were included
- Observational studies inclusion criteria:
  o Only published observational studies in humans included:
    ▪ search of Pubmed.gov for “hydroxychloroquine” AND “COVID-19” revealed 351 results of which 6 observational studies met criteria
  o Only included studies looking at treatment effect – studies looking solely at adverse effects or pharmacodynamics were excluded
  o Note: Chloroquine studies not included
  o Note: In vitro studies not included

Randomized Controlled Trials – 5 studies

Study 1

| Reference | Tang W, Cao Z, Han M et al : Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020; 369. doi: [https://doi.org/10.1136/bmj.m1849](https://doi.org/10.1136/bmj.m1849) |  |
| Study Design | Multicentre, open label, randomised controlled trial |  |
| Population | Patients aged 18 years or older, admitted to hospital with laboratory confirmed COVID-19. Recruited from 16 government designated COVID-19 treatment centres in China. 150 participants (75 assigned to HCQ plus standard care and 75 to standard care). 148 patients had mild to moderate disease, 2 severe cases. Mean duration of symptom onset to randomisation 16.6 days (range 3-41 days). The rapid decline in eligible new cases of COVID-19 in China precluded achievement of target recruitment and early trial termination was endorsed. |  |
| Intervention | HCQ (loading dose 1200mg daily for three days followed by maintenance 800mg daily for remaining days up to two weeks in mild to moderate and three weeks in severe) plus standard care versus control group who received standard care. |  |
| Primary Outcome | Primary outcomes for this trial were whether patients had negative conversion of SARS-CoV-2 by 28 days and whether patients with severe covid-19 had clinical improvement by 28 days. |  |
Secondary Outcome | The listed secondary outcome in the trial registration was adverse events. Other pre-specified secondary outcomes not listed in the trial registration but included in the protocol were the probabilities of alleviation of clinical symptoms; improvement of C reactive protein, erythrocyte sedimentation rate, tumour necrosis factor α, interleukin 6, and absolute blood lymphocyte count; improvement of lung lesions on chest radiology; all cause death; and disease progression in patients with mild to moderate disease. The time frame for these secondary outcomes was from randomisation to 28 days. However due to early trial termination the results of these were not presented other than alleviation of clinical symptoms within 28 days.

Safety/ adverse events | Adverse events were reported in 7/80 (9%) HCQ non-recipient and in 21/70 (30%) of HCQ recipients. Most common adverse event in HCQ recipients was diarrhea and two HCQ recipients reported serious adverse events (disease progression and upper respiratory infection progression). No serious adverse events were reported in the control group.

Results | 109 (73%) patients (56 control, 53 HCQ group) had negative conversion well before 28 days. Remaining 41 (27%) patients were censored as they did not reach negative conversion. Probability of negative conversion by 28 days in HCQ group was 85.4% and 81.3% in the control group. Median time to negative conversion was similar in HCQ (8 days) compared to control group (7 days). The probability of alleviation of symptoms by 28 days was similar in both groups (59.9% in HCQ group versus 66.6% in control group) and median time to clinical symptom alleviation was similar (19 days in HCQ group versus 21 days in control group, P=0.97)

Study 2


Study Design | Unblended RCT

Population | Hospitalized patients with confirmed COVID-19 infection. 30 patients randomised (1:1).

Intervention | HCQ (400 mg/day x 5days) versus standard care. Standard care included included inhaled alpha-interferon, arbidol, with or without lopinavir/ritonavir.

Primary Outcome | Negative conversion rate of SARS-CoV-2 nucleic acid in respiratory pharyngeal swab on day 7 post randomisation.

Secondary Outcome | Median time to normothermia, radiographic progression as assessed by CT chest

Safety/ adverse events | Adverse events including diarrhoea and deranged LFTs were monitored: 4 cases in HCQ group (26.7%) and 3 cases in control group (20%) experienced adverse events (P>0.05)

Results | At day 7 post inclusion, virological clearance was reported in 86.7% in the HCQ group (median 4 days) and 93.3% of the control group (median 2 days), (P>0.05). Median time to normothermia was 1 day after hospitalisation for both groups. Radiographic progression occurred in 5 cases who received HCQ (33.3%) and 7 controls (46.7%).

Study 3

**Study Design**
Randomized controlled unblended study

**Population**
Hospitalized adults with laboratory-confirmed COVID-19 included, follow-up to day 5 post intervention. Inclusion criteria: 1. Age ≥ 18 years; 2. Laboratory (RT-PCR) positive of SARS-CoV-2; 3. Chest CT with pneumonia; 4. SaO2/O2 ratio > 93% or PaO2/FIO2 ratio > 300 mmHg under the condition in the hospital room (mild illness). Note severe and critical illness patients excluded. 62 patients enrolled (31 per group), 29 (46.8%) male, mean age 44.7 years.

**Intervention**
Patients randomly assigned to HCQ (200mg twice daily for 5 days) or control group who received standard care. All participants received the standard treatment (oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids). Details on proportions of patients receiving these treatments, particularly steroids, for each group is unclear.

**Primary Outcome**
Primary outcome is not clearly specified. Changes in time to clinical recovery defined as return of body temperature and cough relief, and radiological characteristics were identified as endpoints.

**Secondary Outcome**
No clear primary or secondary endpoint distinction

**Safety/ adverse events**
Two patients with mild adverse reactions in HCQ group (one patient with a rash and one patient with a headache).
No adverse events were reported in the control group.

**Results**
Return of normal temperature time was 2.2 days (SD 0.4) in HCQ group compared to 3.2 days (SD 1.3) in the control group (p 0.0008).
Cough relief occurred by day 2.0 (SD 0.2) in the HCQ group compared to 3.1 (SD 1.5) in the control group (p 0.0016).
No patients in the HCQ group progressed to severe illness compared to 4 (12.9%) in the control group.
On review of chest CT by day 5, improvement in pneumonia findings was noted in 25/31 of the HCQ group (80.6%) compared to 17/31 (54.8%) of the control group, p 0.048.

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**Study 4**

**Reference**

**Study Design**
Randomized, double-blind, placebo-controlled trial.

**Population**
Adults aged over 18 years with known expose to a person with laboratory-confirmed COVID-19, whether as household contact, a health care worker or a person with other occupational exposures. 821 participants recruited (414 HCQ, 407 placebo). Median age 40 years, 51.6% female participants, 27.4% reported chronic health conditions (hypertension, asthma most common), 66.4% healthcare workers (of whom 76.7% of exposures were from patients). Overall 87.6% (719 of 821) had high risk exposures without eye shields and surgical masks or respirators.

**Intervention**
Randomly assigned in 1:1 ratio to receive HCQ (800mg loading dose, 600mg 6-8 hours later, 600mg daily for 4 more days) or placebo as prophylaxis.

**Primary Outcome**
Symptomatic illness confirmed by positive molecular assay or if testing was unavailable, COVID-19 symptoms during 14 day follow-up

**Secondary Outcome**
Incidence of hospitalization for COVID-19 or death, incidence of PCR-confirmed SARS-CoV-2 infection, the incidence of Covid-19 symptoms, the incidence of discontinuation of the trial intervention owing to any cause, and the severity of symptoms (if any) at days 5 and 14.

**Safety/ adverse events**
Side effects were more frequent with HCQ than with placebo.
Among the participants who took any HCQ: 40.1% (140 of 349) reported a side effect by day 5, as compared with 16.8% (59 of 351) receiving placebo (P<0.001). Nausea, loose stools, and...
abdominal discomfort were the most common side effects. There were no serious intervention-related adverse reactions or cardiac arrhythmias.

Results Overall new COVID-19 developed in 107 participants (13%). Incidence of new COVID-19 did not differ significantly between those receiving HCQ (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]) (P=0.35).

Two hospitalizations were reported (one per group). No arrhythmias or deaths occurred. Of 113 persons in whom symptomatic illness developed, 16 had PCR-confirmed disease, 74 had illness that was compatible with probable Covid-19 per the U.S. case definition, 13 had possible Covid-19 with compatible symptoms and epidemiologic linkage, and 10 were adjudicated as not having Covid-19. (Four additional participants had positive PCR tests and were asymptomatic during the 14-day trial period; symptoms eventually developed in 3 of these participants.)

Study 5


Study Design Multicentre randomized, placebo-controlled trial.

Population 1561 adult patients in treatment arm, 3155 in control group. All adult patients. Mean age of study participants was 65.3 (SD 15.3) years (Table 1) and 38% patients were female. A history of diabetes was present in 27% of patients, heart disease in 26%, and chronic lung disease in 22%, with 57% having at least one major comorbidity recorded. At randomization, 17% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither.

Intervention Randomised to HCQ versus standard care only

Primary Outcome 28-day mortality

Secondary Outcome Duration of hospital stay and composite endpoint of invasive mechanical ventilation or death for those not on invasive mechanical ventilation at baseline enrolment.

Safety/ adverse events No excess of new major cardiac arrhythmia in patients treated with hydroxychloroquine

Results Primary Outcome

There was no significant difference in the proportion of patients who met the primary outcome of 28-day mortality between the two randomized arms (rate ratio, 1.09; 95% confidence interval [CI], 0.96 to 1.23; P=0.18)

Secondary Outcomes

Patients allocated to hydroxychloroquine were less likely to be discharged from hospital alive within 28 days (60.3% vs. 62.8%; rate ratio 0.92; 95% CI 0.85-0.99) and those not on invasive mechanical ventilation at baseline were more likely to reach the composite endpoint of invasive mechanical ventilation or death (29.8% vs. 26.5%; risk ratio 1.12; 95% CI 1.01-1.25).
### Study 1

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Study Design</td>
<td>Prospective non randomised trial – unmatched controls</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Hospitalized patients with COVID-19, aged over 12 years. 42 patient enrolled (26 HCQ, 16 supportive care) – note 6 patients enrolled in HCQ arm did not complete therapy – this included 3 ICU transfers, one death on day 3 post inclusion, one patient left the hospital, one patient stopped due to nausea. No intention to treat analysis performed. Mean age 51.2 years in treated group (n=20) and 37.3 in control group (n=16). Mean time to symptom onset 4.1 days in HCQ group and 3.9 days in control group. 16.7 % were asymptomatic, 61.1% had upper respiratory tract symptoms and 22.2 % had lower respiratory tract symptoms. Six patient also received azithromycin. Study conducted in France.</td>
<td></td>
</tr>
<tr>
<td>Intervention/Exposure</td>
<td>In HCQ group - oral hydroxychloroquine sulfate 200 mg, three times per day during ten days vs standard care</td>
<td></td>
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<tr>
<td>Primary Outcome</td>
<td>Nasopharyngeal virological clearance at day 6 post-inclusion</td>
<td></td>
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<tr>
<td>Secondary Outcome</td>
<td>Virological clearance overtime during the study period, clinical follow-up (body temperature, respiratory rate, long of stay at hospital and mortality), and occurrence of side-effects.</td>
<td></td>
</tr>
<tr>
<td>Safety/ adverse events</td>
<td>Not clearly reported</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>Primary: at day 6, 70% HCQ group had virological clearance versus 12.5% control group (p=0.001) At day 6 100% of patients treated with HCQ plus azithromycin were virologically cured. No clinical outcomes were reported and comparisons were not adjusted for baseline characteristics – for adjusted re-analysis please refer to Katherson et al. An independent appraisal and re-analysis of hydroxychloroquine treatment trial for COVID-19. <em>Swiss Med Wkly</em> 2020; 150: w20262 <a href="https://smw.ch/article/doi/smw.2020.20262">Link</a></td>
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### Study 2

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<tbody>
<tr>
<td>Study Design</td>
<td>Observational, prospective. Treatment group only, no control group.</td>
<td></td>
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<tr>
<td>Population</td>
<td>Hospitalised adult patients with COVID-19. 80 patients included. No control group for comparison. Median age 52 years, male 50%, 57.5% of patients had at least one chronic condition – hypertension, diabetes, chronic respiratory disease most common. Time from onset of symptoms to treatment mean 4.9 days. 53.8% presented with LRTI and 41.2% with URTI symptoms. Four patients asymptomatic.</td>
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<tr>
<td>Intervention/Exposure</td>
<td>HCQ 200mg three times daily for ten days plus azithromycin (500 mg on day 1 followed by 250mg per day for four more days.</td>
<td></td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>1. Aggressive clinical course requiring O2 therapy or transfer to ICU after at least three days of treatment</td>
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</tbody>
</table>
2. Contagiousness as assessed by PCR and culture
3. Length of stay in the ID ward

Secondary Outcome

None specified

Safety/adverse events

Adverse events stated to have been rare and minor

Results

65/80 (81.3%) had favourable outcome, 15% required O2 therapy. Three patients transferred to ICU. Note 15 patients still in hospital at time of writing, one patient still in ICU at time of writing and one patient died.
83% negative NP viral load at day 7 and 93% at day 8.
Of 65 discharged patients – mean time from treatment initiation to discharge was 4.1 days.

Study 3

Reference

Molina et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020; 50(4): 384

Study Design

Observational, retrospective. Treatment group only, no control group.

Population

11 consecutive patients hospitalised with COVID-19. 7 men, 4 women, mean age 58.7 years (range 20-77), 8 with significant comorbidities (obesity:2, solid cancer: 3, haematological cancer:2, HIV:1). Duration of symptoms prior to treatment initiation not specified.

Intervention/Exposure

Combination HCQ (600mg/day for 10 days) plus azithromycin (500 mg day one and 250 mg days 2-5)

Primary Outcome

Virologic and clinical outcomes – no further detail specified

Secondary Outcome

None specified

Safety/adverse events

In one patient combination therapy discontinued due to QT interval prolongation

Results

Within 5 days, one patient died, two were transferred to ICU.
NP viral PCR for SARS-COV-2 still positive in 8 out of 10 patients at days 5 -6 post treatment.

Study 4

Reference


Study Design

Observational, retrospective. No randomization to treatment.

Population

Hospitalized adult patients with a positive test result for SARS-COV-2 from NP or oropharyngeal swab specimen. 1446 consecutive patients admitted, 70 excluded as already intubated or died – 1376 included in the study. 811 (58.9%) received HCQ, of these 45.8% within 24 hours of presentation) Conducted at New York-Presbyterian Hospital – Columbia University Irving Medical Center.

Intervention/exposure

HCQ: loading dose of 600 mg twice on day 1, followed by 400 mg daily for 4 additional days with or without azithromycin at a dose of 500 mg on day 1 and then 250 mg daily for 4 more days in combination with HCQ was an additional suggested therapeutic option.
Control group did not receive HCQ or azithromycin.

### Primary Outcome
Time from study baseline to intubation or death

### Secondary Outcome
Secondary analysis used propensity-score matching and another that included the propensity score as an additional covariate. In the propensity-score matching analysis, the nearest-neighbour method was applied to create a matched control sample.

### Safety/ adverse events
Not specified

### Results
HCQ-treated patients had a lower PaO2:FiO2 at baseline than patients who did not receive HCQ (median, 233 vs. 360 mm Hg). Note 27 patients received remdesivir (22 HCQ group, 5 in no treatment group) and 30 patients were enrolled in an RCT of sarilumab use. 346 patients (25.2%) had a primary endpoint event (166 died, 180 intubated). In unadjusted analysis patients who received HCQ were more likely to be intubated or die than patients who did not (hazard ratio 2.37; 95% CI, 1.84 to 3.02). In adjusted analysis using inverse probability weighting according to propensity score matching there was no significant association between HCQ use and the composite primary end point of death or intubation (hazard ratio, 1.04; 95% CI, 0.82 to 1.32).

There was also no significant association between treatment with azithromycin and the composite endpoint (hazard ratio, 1.03; 95% CI, 0.81 to 1.31).

---

### Study 5

**Reference**
[https://jamanetwork.com/journals/jama/fullarticle/2766117](https://jamanetwork.com/journals/jama/fullarticle/2766117)

**Study Design**
Observational, retrospective.

**Population**
Random sample of inpatients with laboratory-confirmed COVID-19 admitted to hospitals in the New York City (NYC) metropolitan region between March 15 and 28, 2020. From a sample of 7914 hospitalised patients with COVID-19, 2362 records were randomly selected and 1438 were included in the analyses. Of these 735 patients (51.1%) received HCQ + azithromycin, 271 (18.8%) received HCQ alone, 211 (14.7%) received azithromycin alone and 221 (15.4%) received neither drug. HCQ was initiated at a median of 1 day post admission and azithromycin at a median of 0 days. Patients receiving either drug were more likely to be male. Median age in all groups was similar (HCQ + azithromycin, 61.4 years; HCQ alone, 65.5 years; azithromycin alone, 62.5 years; and neither drug, 64.0 years). Patients in the treatment groups, particularly HCQ + azithromycin, presented as having more clinically severe disease than the neither drug group. Patients receiving HCQ + azithromycin and HCQ alone had higher levels of ICU admission and mechanical ventilation than those receiving azithromycin alone and neither drug.

**Intervention/ Exposure**
1) HCQ with azithromycin, (2) HCQ without azithromycin (HCQ alone), (3) azithromycin alone, and (4) neither drug, defined as no receipt of either HCQ or azithromycin

**Primary Outcome**
In-hospital mortality

**Secondary Outcome**
Cardiac arrest and abnormal electrocardiographic (ECG) findings. Diarrhoea and hypoglycaemia adverse events were also examined.
Safety/adverse events | Most commonly reported adverse event was abnormal ECG findings (see secondary outcomes below)

Results | Primary outcome:
In unadjusted analyses: significant differences in in-hospital death were observed across the HCQ + azithromycin (n = 189, 25.7%), HCQ alone (n = 54, 19.9%), azithromycin alone (n = 21, 10.0%), and neither-drug (n = 28, 12.7%) groups (P < .001).
In adjusted analyses: no significant differences in mortality were found between patients receiving HCQ azithromycin (adjusted HR, 1.35), HCQ alone (adjusted HR, 1.08), or azithromycin alone (adjusted HR, 0.56), compared with neither drug

Secondary outcomes (only adjusted results listed below):
In logistic regression models of abnormal ECG findings, there were no significant differences between the groups receiving neither drug and each of the HCQ + azithromycin and HCQ alone groups.
In adjusted models with those receiving neither drug as comparison, cardiac arrest was more likely in patients receiving HCQ + azithromycin (adjusted OR, 2.13 [95% CI, 1.12-4.05]), but not HCQ alone (adjusted OR, 1.91 [95% CI, 0.96-3.81]) and azithromycin alone (adjusted OR, 0.64 [95% CI, 0.27-1.56]). Cardiac arrest was also more likely in patients taking HCQ alone vs azithromycin alone (adjusted OR, 2.97 [95% CI, 1.56-5.64]).
In models that stratified on receipt of mechanical ventilation, cardiac arrest was more likely in patients taking HCQ alone vs azithromycin alone among patients who did not receive mechanical ventilation (adjusted OR, 3.01 [95% CI, 1.07-8.51])

Study 6


Study Design | Comparative observational study using data collected from routine care.

Population | Four French tertiary care centres providing care to patients with covid-19 pneumonia between 12 March and 31 March 2020. 181 patients aged 18-80 years, with documented SARS-CoV-2 pneumonia who required oxygen but not intensive care. 84 patients received HCQ within 48 hours of admission and 89 patients in control group did not receive HCQ. 8 Patients received HCQ greater than 48 hours after admission.

Intervention/Exposure | HCQ at a dose of 600 mg/day within 48 hours of admission to hospital (treatment group) versus standard care without HCQ (control group).

Primary Outcome | Survival without transfer to the intensive care unit (ICU) at day 21.

Secondary Outcome | Overall survival, survival without acute respiratory distress syndrome (ARDS), weaning from oxygen, and discharge from hospital to home or rehabilitation (all at day 21).

Safety/adverse events | In HCQ group: of 84 patients receiving HCQ within 48 hours, 8 (10%) experience ECG changes requiring discontinuation of HCQ (median 4 days).

Results | Primary outcome:
Weighted analysis: survival without transfer to ICU at day 21 was 76% in HCQ group and 75% in control group (weighted hazard ratio 0.9, [95% CI: 0.4-2.1]).
Secondary outcomes at day 21: (only in verse probability of treatment weight analyses summarised)
Overall survival was 89% in HCQ group and 91% in control group (weighted hazard ratio 1.2, [95% CI: 0.4-3.3]). Survival without ARDS was 69% in the HCQ group compared with 74% in the control group (weighted hazard ratio 1.3, [95% CI: 0.7 - 2.6]). Weaning from oxygen occurred in 82% of patients in the HCQ group compared with 76% in the control group (weighted risk ratio 1.1, [95% CI: 0.9 - 1.3]). Discharge to home or rehabilitation occurred in 76% of the HCQ group compared with 82% of the control group (weighted related risk 0.9, [95% CI: 0.8 - 1.2]).

**Evidence Summary**

<table>
<thead>
<tr>
<th>Available evidence</th>
<th>5 treatment RCTs, 1 post-exposure RCT and 6 observational studies</th>
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<tbody>
<tr>
<td>Working group discussion regarding evidence</td>
<td>The working group recognises that evidence in paediatric patients is very limited. There is increasing evidence pointing towards a lack of benefit for the use of hydroxychloroquine in the treatment of patients with COVID-19. There are well-known harms with the use of this medication, with the potential for significant adverse events. The largest randomized clinical trial to date found hydroxychloroquine use did not reduce 28-day mortality in hospitalised patients with COVID-19 and hydroxychloroquine use was associated with an increased length of hospital stay and increased risk of progression to invasive mechanical ventilation or death compared to standard care. Other smaller studies have shown serious risk of bias and significant heterogeneity among trials with respect to study design, patient severity at baseline, dosing and timing of hydroxychloroquine administration. There was also inconsistency in the results across these smaller trials with the majority failing to show any clinical benefit. For hospitalised paediatric patients with COVID-19 there was consensus from the working group that use of hydroxychloroquine for the treatment of COVID-19 would not be generally recommended outside of a clinical trial setting due to lack of efficacy and potential for harm.</td>
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**Lopinavir/ritonavir (LPV/r)**

**Study 1**

<p>| Study Design | Randomised controlled open-label trial |
| Population | 199 hospitalized adults over the age of 18 years with positive SARS-COV-2 PCR testing, pneumonia confirmed by chest imaging and O2 saturation of 94% or less on inspired ambient air or PaO2:FiO2 at or below 300 mmHg. 99 LPV/r (5 did not receive any doses), 100 standard care only. Median age 58 years, 60.3% male. Median time between symptom onset and randomization 13 days. Systemic steroids given to 33% of LPV/r group and 35.7% of standard care group. At day 1 of admission, 0.5% required mechanical ventilation and/or ECMO and 15.6% required high-flow nasal cannulae oxygen or non-invasive oxygen, 14.1% required no supplemental oxygen. |</p>
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Lopinavir–ritonavir (400 mg and 100 mg, orally twice daily), plus standard care, or standard care alone, for 14 days.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>Time to clinical improvement, defined as the time from randomization to an improvement of two points (from the status at randomization) on a seven-category ordinal scale or live discharge from the hospital, whichever came first.</td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td>Clinical status as assessed with the seven-category ordinal scale on days 7 and 14, mortality at day 28, the duration of mechanical ventilation, the duration of hospitalization in survivors, and the time (in days) from treatment initiation to death. Virologic measures included the proportions with viral RNA detection over time and viral RNA titer area-under-the-curve (AUC) measurements.</td>
</tr>
<tr>
<td>Safety/ adverse events</td>
<td>46 patients (48.4%) in the LPV/r group and 49 (49.5%) in the standard-care group reported adverse events. LPV/r therapy was stopped early in 13 patients due to adverse effects.</td>
</tr>
</tbody>
</table>
| Results | **Primary outcome:**
| | LPV/r treatment was not associated with a difference in time to clinical improvement versus standard care (median, 16 days vs. 16 days; hazard ratio for clinical improvement, 1.31; 95% [CI], 0.95 to 1.80; P=0.09).
| | Secondary outcomes:
| | On modified intention-to-treat analysis, 28-day mortality was numerically lower in LPV/r group than in standard care, but was non-significant. (16.7% vs. 25.0%; difference, −8.3 percentage points; 95% CI, −19.6 to 3.0).
| | LPV/r group had a shorter ICU stay than standard-care group (median, 6 days vs. 11 days; difference, −5 days; 95% CI, −9 to 0).
| | Duration from randomization to hospital discharge was numerically shorter in LPV/r group versus standard (median, 12 days vs. 14 days; difference, 1 day; 95% CI, 0 to 3)
| | % of patients with clinical improvement at day 14 was higher in LPV/r group vs standard-care (45.5% vs. 30.0%; difference, 15.5; 95% CI, 2.2 to 28.8)
| | Viral RNA loads over time did not differ between LPV/r and standard groups. |

### Study 2

| Study Design | Multicentre, prospective, open-label, randomised, phase 2 trial |
| Population | Hospitalized adults with confirmed COVID-19. 127 patients recruited, 86 in combination group and 41 in control group. Median time from symptom onset to treatment was 5 days for combination and 4 for control group. Note only patients recruited less than 7 days from symptom onset received subcutaneous interferon beta 1b (only all three doses if commenced at day 1-2 of symptom onset). Therefore in combination group only 52 patients out of 86 received interferon therapy and the median number of doses of interferon beta-1b was two. 17 (13%) of 127 patients required oxygen treatment, 6 (5%) were admitted to intensive care, 5 required non-invasive support, 1 required mechanical ventilation. |
| Intervention | 14-day combination of LPV/r (400/100 mg every 12 h), ribavirin (400 mg every 12 h), and interferon beta-1b (three doses of 8 million international units on alternate days) (combination group) or to 14 days of LPV/r (400/100 mg every 12 h) (control group) |
| Primary Outcome | Time to SARS-COV-2 negative PCR testing on NP swab |
### Secondary Outcomes

Time to resolution of symptoms defined as a NEWS2 of 0 maintained for 24 h; daily NEWS2 and sequential organ failure assessment (SOFA) score; length of hospital stay; and 30-day mortality.

### Safety/Adverse Events

48% of the combination group reported adverse events versus 49% of the control group. Most common events were diarrhoea, fever, nausea, ALT elevation. One combination group patient had a serious event of impaired hepatic enzymes.

### Results

**Primary endpoint**

Combination group had a significantly shorter time to negative NP swab versus control (7 days vs 12 days, \( p < 0.0001 \)).

**Secondary endpoints**

- Time to symptom alleviation (NEWS2 of 0) was 4 days in combination group vs 8 days in control group (\( p < 0.0001 \)).
- Time to SOFA score of 0 was 3 days in combination group versus 8 days in control group (\( p < 0.041 \)).
- Median hospital stay was shorter in the combination group (9 days) versus control (14.5 days), \( p = 0.016 \).

Combination treatment was associated with significantly shorter time to negative viral load in all specimens when assessed individually (nasopharyngeal swab, posterior oropharyngeal saliva, throat swab, and stool samples) and in all specimens combined.

### Evidence Summary

**Available evidence**

2 RCTs - only one comparing LPV/r with standard care

**Working group discussion regarding evidence**

Cao et al. in their randomised controlled trial did not show a difference for the primary outcome of time to clinical improvement in the LPV/r group versus standard care. Concerns with this trial include the small size, the fact that therapy was started late in the disease course and that only 16% of patients required oxygen by HFNC, mechanical ventilation or ECMO.

Based on the available evidence, there remains a lack of evidence for efficacy of lopinavir/ritonavir for hospitalised paediatric patients with COVID-19. Accordingly, there was consensus from the working group that while some clinicians may consider the use of lopinavir/ritonavir for the treatment of COVID-19, in general its use would not be recommended outside of a clinical trial setting.
Summary of recent key publications

17th July 2020

| Study Design | Multicenter randomized controlled trial |
| Population | 176 UK National Health Organizations included. Adult patients with COVID-19. A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. At the time of enrolment, 16% were receiving invasive mechanical ventilation or ECMO, 60% were receiving oxygen, 24% were not receiving any oxygen support. |
| Intervention | Randomized 2:1 to usual care alone or usual care plus oral or IV dexamethasone (6mg) for up to 10 days or until discharge |
| Primary Outcome | 28 day mortality |
| Secondary Outcomes | Time until discharge and subsequent invasive mechanical ventilation, ECMO or death |
| Results | PRIMARY Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55). SECONDARY Shorter hospitalization in dexamethasone versus standard care (12 vs 13 days). Lower numbers of patients progressing to invasive mechanical ventilation in dexamethasone group versus usual care (RR 0.92). |

12th August 2020

| Study Design | Parallel, double-blind, placebo-controlled, randomized, phase IIb clinical trial |
| Population | Included hospitalized patients aged ≥ 18 years with clinical, epidemiological and/or radiological suspected COVID-19, at a tertiary care facility in Manaus, Brazil. In total 416 patients were randomized and the median number of doses administered per patient was 10. |
| Intervention | IV methylprednisolone (0.5 mg/kg), BID x 5 d vs placebo |
| Primary Outcome | 28 day mortality |
Secondary Outcomes | Early mortality (days 7 and 14); need for intubation by day 7; proportion of patients with oxygenation index (PaO2/FiO2) <100 by day 7.
---|---
Results | PRIMARY
28 day mortality was 72 out of 194 (37.1%) in the methylprednisolone group versus 76 out of 199 (38.2%) in the placebo group (P = 0.629).
A subgroup analysis showed that patients over 60 years in the MP group had a lower mortality rate at day 28.
SECONDARY
No significant differences were noted in any secondary outcomes

2nd September 2020


Study Design | Multicenter randomized controlled trial

Population | Adults aged over 18 years admitted to 41 intensive Care Units in Brazil with COVID-19 confirmed or suspected and moderate to severe ARDS. In total 299 patients were randomized: 151 in the dexamethasone groups and 148 in the control group.

Intervention | Dexamethasone 20mg dosing plus standard care for 5 days versus dexamethasone 10 mg dosing for 5 days plus standard care versus standard care alone

Primary Outcome | Ventilator free days during the first 28 days of the study

Secondary Outcome | Secondary outcomes were all-cause mortality at 28 days, clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death), ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, and Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) at 48 hours, 72 hours, and 7 days.

Adverse effects | Thirty-three patients (21.9%) in the dexamethasone group vs 43 (29.1%) in the standard care group experienced secondary infections, 47 (31.1%) vs 42 (28.3%) needed insulin for glucose control, and 5 (3.3%) vs 9 (6.1%) experienced other serious adverse events.

Results | PRIMARY
Significantly higher mean number of days free from mechanical ventilation in the dexamethasone treatment group versus standard care alone (6.6 vs 4.0, CI of diff 0.2-4.38).
SECONDARY
At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, −1.16; 95% CI, −1.94 to −0.38; P = .004). There was no significant difference in the pre-specified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days.

2nd September 2020


Study Design | Multicenter randomized double-blind sequential trial
**Population**
French study of adult patients admitted to intensive care units for COVID-19-related acute respiratory failure. Enrolled 76 patients in hydrocortisone group and 73 in placebo group. Median duration of symptoms prior to randomization 9-10 days.

**Intervention**
Low dose hydrocortisone for 14 days versus placebo

**Primary Outcome**
Death or persistent dependency on mechanical ventilation or high-flow oxygen therapy by day 21

**Secondary Outcomes**
Need for tracheal intubation (among patients not intubated at baseline); cumulative incidences (until day 21) of prone position sessions, extracorporeal membrane oxygenation, and inhaled nitric oxide; Pao2:Fio2 ratio measured daily from day 1 to day 7, then on days 14 and 21; and the proportion of patients with secondary infections during their ICU stay

**Results**
Study was intended to enroll 290 patients however was terminated early following recommendations of the data and safety review board upon publication of the UK RECOVERY trial data.

**PRIMARY:**
treatment failure on day 21, occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, −8.6% [95.48% CI, −24.9% to 7.7%]; P = .29).

**SECONDARY:**
Of the 4 prespecified secondary outcomes, none showed a significant difference. For post hoc outcome analysis showed death by day 21 occurred in 14.7% of hydrocortisone group and 20% of placebo group (p=0.057)

---

2nd September 2020

**Reference**

**Study Design**
REMAP-CAP is an ongoing, international, multicenter, open-label trial involving 121 clinical sites in Australia, Canada, France, Ireland, the Netherlands, New Zealand, UK and the US

**Population**
Adult patients with severe COVID-19 admitted to intensive care requiring invasive or non-invasive mechanical ventilation or high-flow nasal cannula oxygen at a flow rate 30L/min or greater and FiO2 0.4 or greater. In total 403 patients enrolled: 143 fixed-dose hydrocortisone, 152 shock-dependent hydrocortisone and 108 no hydrocortisone. Mean age of 59.5-60.4 years and mechanical ventilation at randomization in 50-63.5%.

**Intervention**
Hydrocortisone 50mg Q6H x 7days versus hydrocortisone 50mg Q6H with signs of shock for up to 28 days versus no hydrocortisone.

**Primary Outcome**
Organ support–free days up to day 21

**Results**
Trial stopped early following RECOVERY trial press release precluding definitive conclusions. For the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively, the median organ support–free days were 0 (IQR, −1 to 15), 0 (IQR, −1 to 13), and 0 (−1 to 11) days (composed of 30%, 26%, and 33% mortality rates and 11.5, 9.5, and 6 median organ support–free days among survivors). Trial did not meet the pre-specified statistical trigger for a trial conclusion of superiority

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2nd September 2020

**Reference**
### Study Design
Prospective meta-analysis that pooled data from 7 RCTs undertaken in Australia, Brazil, Canada, China, Denmark, France, Ireland, the Netherlands, New Zealand, Spain, the UK, and the US

### Population/Interventions
Exposures - Dexamethasone or Hydrocortisone or Methylprednisolone vs usual care/placebo. Included studies and level of severity/patient population:
1. The Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19 (DEXA-COVID 19) trial - mechanical ventilation
2. COVID-19 Dexamethasone (CoDEX) trial - mechanical ventilation
3. RECOVERY trial - only patients on mechanical ventilation at randomization included
4. REMAP-CAP trial - ICU admitted patients
5. Steroids-SARI trial - ICU admitted patients
6. CAPE COVID trial - ICU admitted patients or receiving at least 6 L/min of supplemental O2
7. Hydrocortisone for COVID-19 and Severe Hypoxia (COVID STEROID) - patients on 10 L/min of supplemental O2 or more

In total included 1703 patients (678 corticosteroid intervention and 1025 randomized to usual care or placebo). Median age 60 years of included subjects.

### Primary Outcome
All cause mortality at 28 days

### Secondary Outcome
Serious adverse events

### Results

**PRIMARY**
There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95% CI, 0.53-0.82]; P < .001 based on a fixed-effect meta-analysis).

**SECONDARY**
Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo.

### Evidence Summary

<table>
<thead>
<tr>
<th>Reviewed evidence</th>
<th>5 RCTs and one meta-analysis reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working group discussion regarding evidence</td>
<td>Available evidence suggests corticosteroid use is associated with reduced mortality for critically ill adult patients with COVID-19. Evidence from both the WHO meta-analysis and RECOVERY trial data also suggests favourable mortality outcomes with corticosteroid use for adult patients with COVID-19 who require oxygen support without invasive mechanical ventilation. There is no clear evidence for optimal dose or duration of corticosteroid therapy and no data available yet from use in the paediatric population. There is also no evidence to indicate that a higher dose of corticosteroids is associated with greater benefit on mortality outcomes than lower dose corticosteroids. The working group were in agreement that corticosteroid use is recommended in paediatric patients who are critically ill with COVID-19 and should be considered in paediatric patients with severe COVID-19. In the absence of further data, the working group suggest low dose dexamethasone as the type of corticosteroid. The duration will be determined by the clinical team on a case-by-case basis and is suggested to continue for a duration of up to 10 days or until clinical recovery in line with the RECOVERY trial treatment protocol.</td>
</tr>
</tbody>
</table>
Summary of recent key publications

11th July 2020

---|---
Study Design | Single Center (Michigan Medicine) observational, controlled study (retrospective chart review)
Population | 154 hospitalized patients with severe COVID-19 requiring mechanical ventilation over 16 years of age. Patients included were those excluded from sarilumab trial and choice for tocilizumab use based at clinician discretion (most patients were transfers from outside facilities). Included 78 tocilizumab recipients, 76 non-recipients. Median follow-up 47 days. Tocilizumab patients were younger (55 vs 60yrs), less likely to have chronic pulmonary disease (10% vs. 28%), and had lower D-dimer values at intubation (median 2.4 vs. 6.5 mg/dL).
Intervention | Tocilizumab (8mg/Kg to max of 800mg x1) versus tocilizumab un-treated controls
Primary Outcome | Survival probability post-intubation
Secondary Outcome | Day 28 status using ordinal illness severity scale integrating superinfections
Safety/ adverse events | Tocilizumab was associated with an increased proportion of patients with superinfections (54% vs. 26%; p<0.001), (no difference in 28-day case fatality rate among tocilizumab-treated patients with versus without superinfection [22% vs. 15%; p=0.42]).
Results | Survival probability was significantly higher among tocilizumab-treated compared to untreated patients (p=0.0189). Inverse probability of treatment weights-adjusted models, tocilizumab use was associated with a 45% reduction in hazard of death [hazard ratio 0.55 (95% CI 0.33, 0.90)] and improved status on the ordinal outcome scale [odds ratio per 1-level increase: 0.58 (0.36, 0.94)].

8th July 2020

---|---
Study Design | Single Center (ASST Grande Ospedale Metropolitano Niguarda, Milan) observational controlled study (retrospective)
Population | Hospitalised patients aged over 18 years with severe or critical COVID-19. Included 74 patients treated with tocilizumab and 148 matched controls. Median age 59 years, 81.5% male. Note study is not clear on why controls did not receive tocilizumab.
Intervention | Tocilizumab therapy (8mg/Kg up to max 800mg) versus matched controls who received standard care (including hydroxychloroquine, lopinavir/ritonavir or remdesivir)
Primary Outcome | Overall survival
Secondary Outcome | Duration of hospital stay, biochemistry trends
---|---
Safety/ adverse events | Note subjects who received tocilizumab outside of ICU showed a sudden need for intubation after administration. 27 infectious complications in 24 patients who received tocilizumab (32.4%) including 11 (14.9%) severe events and one death from septic shock.
Results | Primary outcome  
Tocilizumab use was associated with a better overall survival (HR 0.499 [95% CI 0.262-0.952], p=0.035) compared to control group. Note use did not seem to have benefit in severe disease but did show benefit in critical patients.  
Secondary Outcome  
Tocilizumab recipients demonstrated longer hospital stay versus controls HR of 1.658 (95% CI 1.088-2.524, p=0.019).

24th June 2020

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30173-9/fulltext
Study Design | Multicentre (three tertiary care centres in Bologna, Modena and Reggio Italy) Observational retrospective cohort study
Population | Adult patients hospitalised with severe COVID-19. 544 patients with severe pneumonia (179 non-randomly assigned to tocilizumab treatment, 365 standard care), 66% male, median age 67. Co-morbidities were more common in tocilizumab treated group. Of note 30% of patients treated with tocilizumab recived glucocorticoids versus 17% of patients in standard care group.
Intervention | Tocilizumab (8mg/Kg up to maximum of 800mg administered twice) plus standard care versus standard care
Primary Outcome | Composite of death or invasive mechanical ventilation
Secondary Outcome |  
Safety/ adverse events | In the tocilizumab group, one (<1%) patient had an episode of injection site reaction, with spontaneous resolution in a few hours. One (<1%) episode of severe neutropenia required granulocyte-colony stimulating factor administration. Regarding infections, overall 24 (13%) of 179 patients treated with tocilizumab were diagnosed with new infections, versus 14 (4%) of 365 patients treated with standard of care alone (p<0-0001).
Results | Primary Outcome  
Tocilizumab was associated with reduced risk of mechanical ventilation and death (adjusted hazard ratio 0-61, 95% CI 0-40–0-92; p=0-020). Of note this adjusted hazard ratio controlled for key confounders (including use of glucocorticoids). 20% of patients died in standard care group versus 7% in tocilizumab group (p=0.0007)

15th June 2020

https://journal.chestnet.org/article/S0012-3692(20)31670-6/fulltext
Study Design | Observational study – Single Center, retrospective chart review
Population | 239 hospitalized patients with COVID-19 (New Haven hospital). All over 18 years, median age 64 years; 36% black, 19% Hispanic. Included severe disease, defined as; receiving > 3 L supplemental O2 to maintain SpO2 >93%, critical disease, requiring mechanical ventilation (22%) and non-severe patients with evolving CRS defined as; increasing CRP and O2 requirements

Intervention | Tocilizumab 8mg/Kg (max 800mg) with second dose if markedly elevated BMI. Comparisons of severe versus non-severe disease patients. No comparisons were made between patients treated and not treated with tocilizumab due to the non-randomized study design.

Primary Outcome | 14-day survival

Secondary Outcome | Mechanical ventilation days and post-tocilizumab CRS response

Safety/ adverse events | Following tocilizumab treatment, few adverse events occurred: Six patients had posttreatment neutropenia, patients’ transaminase levels generally increased in grade after tocilizumab treatment, but no patient experienced grade 4 hepatotoxicity. No tocilizumab infusion reactions were observed.

Results | Primary outcome
Tocilizumab-treated patients with severe disease had higher admission levels of high-sensitivity C-reactive protein (120 vs 71 mg/L; P <.001) and received tocilizumab sooner (2 vs 3 days; P < .001), but their survival was similar to that of patients with non-severe disease (83% vs 91%; P = .11).

Secondary Outcome
Following tocilizumab administration. Oxygenation improved over 14 days but less so over the first 3 to 4 days. Temperature decreased immediately, but CRP levels decreased toward normal over 14 days.


Study Design | Randomized, double-blind, placebo-controlled trial

Population | Patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. 243 patients enrolled, median age was 59.8 years.

Intervention | Patients were randomly assigned in a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo.

Primary Outcome | Intubation or death

Secondary Outcome | Clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline

Results | Primary Outcome
The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P=0.64)

Secondary Outcomes
The hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; P=0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had worsening of disease.
The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8 to 7.8) in the placebo group (P=0.69).
At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen.

Evidence Summary

| Working group discussion regarding evidence | Based on the current evidence, in particular the lack of efficacy seen in the Stone et al. RCT, the working group were in agreement that use of tocilizumab is not indicated outside of a clinical trial setting in children admitted with COVID-19. |

Anakinra

Summary of recent key publications

| Study Design | Single center retrospective cohort study |
| Population | Hospitalised adult patients with COVID-19, moderate-to-severe ARDS and hyper-inflammation managed with non-invasive ventilation outside of ICU. Also received hydroxychloroquine and lopinavir/ritonavir therapy. 29 patients in anakinra recipient group and 16 non-anakinra recipient historical controls group (prior to hospital commencing use of anakinra). Median age 62 years, 83% male, 86% severe ARDS. |
| Intervention | Treatment with anakinra versus standard treatment. |
| Primary Outcome | 21 day outcomes for death, mechanical ventilation, respiratory function, biochemical markers e.g. CRP |
| Secondary Outcome | AS above (no specified primary and secondary outcomes) |
| Safety/ adverse events | 24% patients discontinued high-dose anakinra for adverse events – 14% bacteremia, 10% serum liver enzyme increase. |
| Results | At 21 days: anakinra group - 72% improved respiratory function, 17% progressed to mechanical ventilation, 10% died. Standard treatment group – 50% improved respiratory function, 6% progressed to mechanical ventilation, 44% died. Overall, compared with standard treatment, high-dose anakinra was associated with a higher survival rate at 21 days: cumulative survival of 90% in the anakinra group versus 56% in the standard treatment group (p=0.009). |

| Study Design | Prospective cohort study with historical control cohort, single center study. |
### Population
Hospitalised patients aged older than 18 years with severe COVID-19-related bilateral pneumonia. 52 patients in anakinra group, 44 historical control patients. Of note in anakinra group BMI was lower, duration of symptoms longer and more patients treated with hydroxychloroquine and azithromycin compared to historical group.

### Intervention
Anakinra (subcutaneous) recipients versus historical comparison group who received standard care only (including hydroxychloroquine, oral azithromycin and antibiotics)

### Primary Outcome
Need for admission to ICU with invasive ventilation or death

### Secondary Outcome
Death, need for invasive ventilation, difference in the mean oxygen therapy requirements between day 0 and 7, changes in CRP.

### Safety/ adverse events
No bacterial infections documented in anakinra group. 13% patients in the anakinra group and 9% patients in the historical group had an increase in liver aminotransferase. 19% patients in the anakinra group and 11% in the historical group developed a thromboembolic event.

### Results

**Primary outcome**
Need for invasive mechanical ventilation or death occurred in 25% of anakinra group and 73% of historical group (HR 0.22, CI: 0.11-0.41, p<0.0001)

**Secondary Outcomes**
Death alone and invasive mechanical ventilation alone less likely in anakinra group (HR 0.3, p=0.0063 and 0.22, p=0.0015 respectively).
CRP decrease significantly greater in the anakinra group versus control (p<0.0001)
12. References


13. Important Information and Disclaimers About this Document

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