SickKids®

Interim Guidance for the Management of Paediatric Patients with Confirmed COVID-19

Version 11

19th June 2021

Key changes from previously uploaded version 29th May 2021 – Version 10.0

1. **Update to summary paragraph for convalescent sera based on recent large RCT publication and minor amendment to the summary statement for convalescent sera – page 5, page 22**
2. **Update to Non-steroidal anti-inflammatory drugs (NSAIDs) summary paragraph based on recent publication of large cohort study – page 22**
3. **Update to summary paragraph for colchicine use in paediatric patients with COVID-19 to include data from two recent large RCTs – page 23**
4. **Minor amendment to remdesivir information in treatment table 3 to reflect availability of drug**

BACK TO CONTENTS

BACK TO CONTENTS

Summary Statements

Treatment recommendations:

General principles

- **Supportive care is the mainstay of therapy for paediatric patients with COVID-19.**
- **Use of experimental therapies for children with COVID-19 should ideally be offered in the context of clinical trials.**
- **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.**
- **Experimental therapies should not be offered to patients not requiring hospitalization.**
- **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.**
- **Experimental therapies should be offered only after informed consent has been obtained (and documented) as per Hospital policy.**

BACK TO CONTENTS

Table summary of treatment considerations

Severity	Summary of recommended treatment considerations
Mild (No risk Factors)	Supportive care only
Mild (Risk Factors for severe disease)	On a case-by-case basis: • **Consider use of remdesivir*** in patients considered at high risk for severe infections if there are no contra-indications for use
Moderate	On a case-by-case basis: • **Consider use of remdesivir*** in patients considered at high risk for severe infections if there are no contra-indications for use • **Dexamethasone* use should be considered** in patients requiring low flow oxygen, particularly if risk factors for severe disease or evidence of disease progression • For considerations relating to **tocilizumab** use in paediatric patients please see below • Consider antibiotic therapy if concern for secondary bacterial pneumonia**
Severe	On a case-by-case basis: • **Consider use of remdesivir*** if early in the disease course (symptom duration ≤10 days) and no contra-indications for use • **Dexamethasone* use should be considered** • For considerations relating to **tocilizumab** use in paediatric patients please see below • Consider antibiotic therapy if concern for secondary bacterial pneumonia**
Critical	• **Consider use of remdesivir*** on a case-by-case basis if early in the disease course (symptom duration ≤10 days) (Note remdesivir is unlikely to be beneficial in mechanically ventilated patients, but where early in the disease course may be considered on a case-by-case basis) • **Use of dexamethasone* is recommended** • For considerations relating to **tocilizumab** use in paediatric patients please see below • Consider antibiotic therapy if concern for secondary bacterial pneumonia**

*For dosing of remdesivir and dexamethasone refer to table 3 in full guidance
** For details of antibiotic guidance refer to Antibiotic therapy section in full guidance. Antibiotic therapy should follow SickKids empiric guidelines for community-acquired or hospital-acquired bacterial pneumonia, as appropriate.

BACK TO CONTENTS

BACK TO CONTENTS

Additional therapy considerations: (see full guidance for detailed discussion)

- The current data do not support a firm course of action regarding the use of non-steroid immunomodulatory agents or timing for their implementation in children with COVID-19. Therefore, presently **we do not routinely recommend the use of immunomodulatory therapy other than steroids in children with COVID-19 pending further data.**
- **Tocilizumab in paediatric patients with COVID-19:** please see comment below under Management considerations for Cytokine Release Syndrome (CRS)/secondary HLH and related inflammatory clinical entities secondary to COVID-19
- In relation to SARS-CoV-2 specific monoclonal antibodies**, the use of bamlanivimab is not routinely recommended in paediatric patients with COVID-19**.
- **There is Insufficient data to recommend either for or against the use of ivermectin for the treatment of paediatric patients with COVID-19.**
- **IVIG has not been demonstrated to be of benefit and should not be used routinely in paediatric patients with COVID-19.**
- **The use of convalescent plasma is not recommended outside of approved clinical trial settings in paediatric patients with COVID-19.**
- **The use of hydroxychloroquine for the treatment of hospitalised paediatric patients with COVID-19 is not recommended outside of a clinical trial setting due to lack of efficacy and potential for harm.**
- **The use of lopinavir/ritonavir for the treatment of hospitalised paediatric patients with COVID-19 is not recommended outside of a clinical trial setting.**

Recommendations for COVID-19 case management specialist team involvement

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:**
  - 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.

Note: Even in patients not initially requiring critical care support, if there is **any** suspicion of MAS/CRS as demonstrated by clinical instability/abnormal lab trends (refer to **appendix 1**) early involvement of the rheumatology team is strongly advised.

BACK TO CONTENTS

BACK TO CONTENTS

- **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

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

- Risk factors for severe COVID-19 in children are not yet clearly defined.
- 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
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 CRS/secondary HLH and related inflammatory clinical entities secondary to COVID-19

- The routine use of immunomodulatory agents other than corticosteroids in children with COVID-19 outside of clinical trials is not recommended
- On a case-by-case basis where there is evidence of worsening disease such as, increasing oxygen or ventilator requirement and/or evidence of systemic inflammation (e.g. elevated CRP), immunomodulatory agents such as tocilizumab and anakinra may be considered under expert guidance from specialist teams as detailed above**.**

- **In particular, for older children, aged 12 to 18 years, who have confirmed COVID-19 with moderate to severe disease managed in a ward level setting and have risk factors for disease progression, such as elevated BMI, tocilizumab* may be considered on a case-by-case basis in patients who have evidence of systemic inflammation (CRP 75 mg/L or higher) AND evidence of disease progression (increasing oxygen or ventilatory requirements) despite 24-48 hours of optimal dexamethasone therapy.**

- **For older children, aged 12 to 18 years, who have confirmed COVID-19 with severe or critical disease requiring intensive care setting management and are receiving optimal dexamethasone therapy, tocilizumab* may be considered on a case-by-case basis**

***Evidence for tocilizumab use based on treatment given within 14 days of hospital admission**

BACK TO CONTENTS

Table of Contents

BACK TO CONTENTS

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.

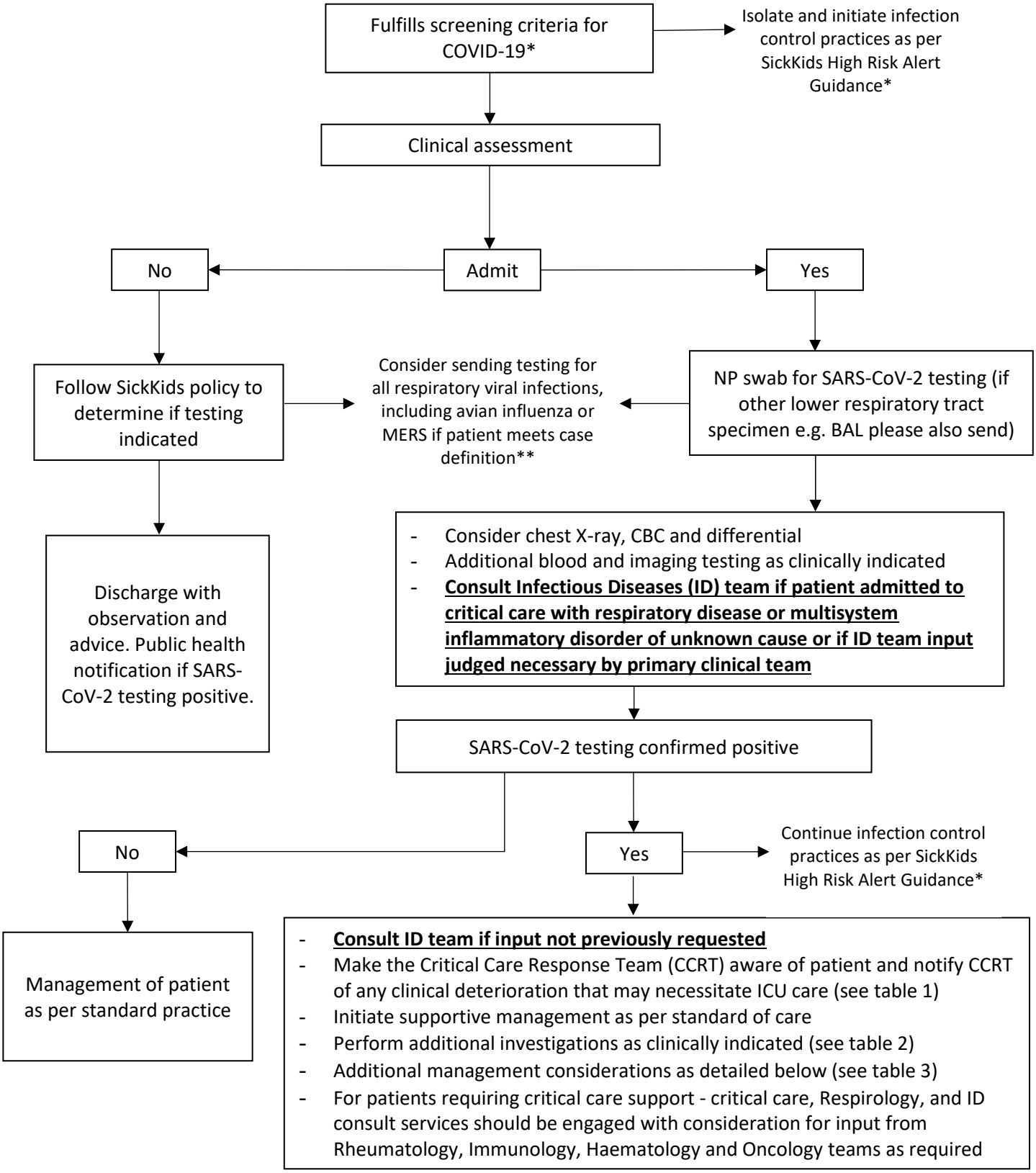
In developing this guideline, a scoping review of available literature on off-label and experimental therapies for use in treating patients with COVID-19 was conducted. A summary of this review is included as a separate document entitled "Summary of Scoping Review for Experimental Therapies and COVID-19." 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



*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

BACK TO CONTENTS

Table 1. Classification of Disease Severity in Children*

Disease severity	Mild disease	Moderate disease	Severe disease	Critical disease
Criteria	▪ Symptoms of acute upper respiratory tract infection and/or mild lower respiratory tract infection; may also include fatigue, myalgia, and gastrointestinal symptoms. ▪ Mild or no work of breathing ▪ No O_2 requirement	▪ Clinical and/or radiological signs of pneumonia present ▪ Increased respiratory rate ▪ Signs of increased work of breathing. ▪ O_2 saturation >92% on room air or low flow oxygen	▪ Moderate or severe work of breathing or significant hypoxia: warranting ICU admission for non-invasive ventilation	▪ Paediatric Acute respiratory Distress Syndrome (pARDS) necessitating invasive mechanical ventilation** ▪ May also be characterized by: - Shock/requirement of vasopressors to maintain blood pressure - Multi-Organ failure - Evidence of myocardial injury or heart failure - Acute kidney injury - Coagulation dysfunction

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

** **pARDS Classification**[6]

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	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]			
Chronic Lung Disease	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.[3]			
Left Ventricular dysfunction	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.			

BACK TO CONTENTS

Table 2. Suggested investigations in children with COVID-19 *

Mild disease	Moderate disease	Severe disease	Critical disease

▪ No routine investigations
▪ If admitting to hospital due to presence of risk factors or underlying conditions, consider performing investigations as for moderate disease.
	▪ Consider continuous Pulse Oximetry and ECG monitoring
	▪ CBC with Differential, Serum Creatinine, and ALT at baseline and repeat as clinically indicated.
	▪ Consider Chest X-ray at baseline
	▪ Blood cultures prior to initiation of antibiotics, and as clinically indicated
	▪ In consultation with Infectious Diseases, Immunology and Rheumatology consider additional testing to help identify early signs of disease progression, including:
	  ▪ Urea
	  ▪ Electrolytes,
	  ▪ Liver panel: AST, Bilirubin, GGT, Albumin
	  ▪ Lactate,
	  ▪ Ferritin,
	  ▪ CRP, ESR,
	  ▪ Fasting triglycerides,
	  ▪ LDH,
	  ▪ Coagulation panel** (including fibrinogen, PT/INR, PTT and D-
	  ▪ Chemokine/cytokine panel, including: IL-1b, IL-10, IL-6, IFN-g, CD163, and Soluble IL-2 Receptor Level (CD25), CXCL-9
	Selected investigations should be performed at baseline and repeated as clinically indicated.
		▪ **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:
		▪ 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.
		▪ Consider Cardiac enzymes including Troponin I and CK
		▪ If patient requires intubation and bronchoalveolar lavage as part of clinical care consider sending samples for SARS-CoV-2 PCR. (Notify microbiologist on call)
		▪ In addition to chemokine/cytokine panel testing, lymphocyte subsets testing should be considered following discussion with infectious diseases and rheumatology teams
		▪ **Note: due to the significant infection control risk with intra-hospital transport for CT chest scanning, this should only be performed in exceptional circumstances where results will significantly impact patient management**
		▪ **Note: Avoid bronchoscopy in proven cases of COVID-19: no clear diagnostic benefit and significant added risk of the procedure for healthcare workers**
			▪ **Investigations as for severe disease plus:**
			▪ Consider echocardiography if signs of myocardial dysfunction

* 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 21

BACK TO CONTENTS

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. 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, 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.

Note: Even in patients not initially requiring critical care support, if there is **any** suspicion of MAS/CRS as demonstrated by clinical instability/abnormal lab trends (refer to **appendix 1**) early involvement of the rheumatology team is strongly advised

- 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.

BACK TO CONTENTS

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.

Disease Severity	First-line therapy to consider	Other therapies/treatment considerations	Additional comments and precautions
Mild disease ▪ **No risk factors for severe disease present***	▪ Supportive care only		Acetaminophen should be used as first-line for fever or temperature management, unless contraindicated.
Mild disease ▪ **Risk factors for severe disease present***	In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team (see above) on a case-by-case basis: Consider use of **remdesivir** in patients considered at high risk for severe infections if there are no contra-indications for use		Remdesivir Please consult pharmacy prior to prescribing remdesivir. Contraindications for remdesivir: ALT/AST >5 x ULN, eGFR <30ml/min Remdesivir dosing < 40 kg: 5 mg/kg IV q24h x1, then 2.5 mg/kg IV q24h for 9 days ≥40kg: 200 mg IV q24h x1, then 100 mg IV q24h Total treatment duration up to 10 days -It is likely that benefit from remdesivir (if any) will occur from receiving this treatment earlier in the disease course -Note that information on the adverse effects of remdesivir in the pediatric population are still
Moderate disease	In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team (see above) on a case-by-case basis: ▪ Consider use of **remdesivir** in patients considered at high risk for severe infections if there are no contra-indications for use ▪ **Dexamethasone** use should be considered in patients requiring low flow oxygen, particularly if risk factors for severe disease or evidence of disease progression	In discussion with Infectious Diseases on a case-by-case basis: ▪ For patients who are not candidates for remdesivir, other agents with antiviral activity may be selectively considered in exceptional cases. ** ▪ Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases For considerations relating to **tocilizumab** use in paediatric patients please see below	

BACK TO CONTENTS

Severe disease	In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team (see above) on a case-by-case basis: ▪ Consider use of **remdesivir** if early in the disease course (symptom duration ≤10 days)† and no contra-indications for use ▪ **Dexamethasone** use should be considered	In discussion with Infectious Diseases on a case-by-case basis: ▪ For patients who are not candidates for remdesivir, other agents with antiviral activity may be selectively considered in exceptional cases. ** ▪ Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases For patients with evidence of ARDS or cytokine release syndrome/ related inflammatory clinical entities see sections below detailing further management considerations **including the use of other immunomodulatory agents such as tocilizumab**	limited and risk-benefit of using this should be assessed on an individual basis with close monitoring of toxicity 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 or until discharge from hospital if clinically recovered. 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
Critical disease	In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team (see above): ▪ Consider use of **remdesivir** on a case-by-case basis if early in the disease course (symptom duration ≤10 days)† and no contra-indications for use (Note: remdesivir is unlikely to be beneficial in mechanically ventilated patients, but where early in the disease course may be considered on a case-by-case basis) ▪ Use of **Dexamethasone** is recommended	In discussion with Infectious Diseases on a case-by-case basis: ▪ For patients who are not candidates for remdesivir, other agents with antiviral activity may be selectively considered in exceptional cases. ** ▪ Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases For patients with evidence of ARDS or cytokine release syndrome/related inflammatory clinical entities see sections below detailing further management considerations **including the use of other immunomodulatory agents such as tocilizumab**	

*** 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

† Based on ACTT -1 Study results:[7] analysis of Time to Recovery According to Subgroup demonstrated a recovery rate ratio favouring Remdesivir use in the subgroup of patients with symptoms duration ≤10 days.

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.[8] 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.[9] 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.[10] 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.[11]

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 use of antiviral therapies, such as remdesivir.

BACK TO CONTENTS

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.

Use of anti-COVID-19 specific monoclonal antibodies in children with COVID-19

A number of monocloncal antibody therapies have been developed for use in patients with COVID-19. Health Canada has approved the use of bamlanivimab in treatment of patients 12 years of age or older with mild to moderate coronavirus disease 2019 (COVID-19), who weigh at least 40 kg and who are at high risk of progressing to severe COVID-19 illness and/or hospitalization. At this time, the combinations of bamlanivimab plus etesevimab or casirivimab and imdevimab (REGN-COV2) have not been approved for use by Health Canada.

A phase 1-3 clinical trial of Casirivimab and imdevimab combination (REGN-COV2) in patients aged 18 years and older showed decreased viral load at day 7 and a non-significant trend towards decreased COVID-19-related medically attended visits by day 29 in the combination therapy group versus placebo.[12] Final phase three trial results are not yet available either in preprint format or in peer-reviewed publications. Available clinical evidence for bamlanivimab comprises published interim and final results from the BLAZE-1 trial, a randomized, double-blind, placebo-controlled phase II study conducted at 41 US centers.[13,14] The primary outcome was change in log viral load from baseline to day 11 after the positive SARS CoV-2 test. From the interim results, of the three doses tested, 700mg, 2800mg and 7000mg, compared with placebo, only the 2800-mg dose group showed a statistically significant difference in the primary outcome of change in log viral load from baseline to day 11 post positive SARS-CoV-2 test (-0.53; 95%CI -0.98 to -0.08; p=0.02). The secondary outcome of COVID-19 related hospitalization or emergency department visit occurred in only 14 participants at a rate of 1.6% (5 of 309) among treated subjects versus 6.3% (9 of 143) among placebo recipients. On publication of the final BLAZE-1 trial results, there was no longer any detectable significant difference for any bamlanivimab monotherapy group dosing for the primary outcome of viral load decrease.[14] This study did report a significant decrease in viral load on use of bamlanivimab therapy in combination with etesevimab with a significant decrease in ED visits of hospitalizations at day 29 in the combination therapy group versus control. Phase three trial results for this combination therapy, including use in children over 12 years, are not yet available either in preprint or peer-reviewed format. We note the phase two trial results were not powered to specifically investigate the outcome of ED visit or hospitalization attendance. Furthermore, Health Canada has released a safety alert for bamlanivimab monotherapy use due to reduced activity against SARS-CoV-2 variants with the E484K and L452R mutations.[15] Therefore, **the use of bamlanivimab is not routinely recommended in paediatric patients with COVID-19 pending further data.**

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.[1] 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.[16] 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.[17] 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) and related inflammatory clinical entities secondary to 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.[18] In particular, elevated levels of IL-6 have been shown to correlate with mortality in adult patients with COVID-19.[3] A number of recent publications have shown benefit in the use of tocilizumab in the management of adult patients with COVID-19 as highlighted in **appendix 6.** However, data on the use of non-steroid immunomodulatory agents in paediatric patients with COVID-19 is limited. Therefore, at present the routine use of immunomodulatory agents other than corticosteroids in children with COVID-19 outside of clinical trials is not recommended. On a case-by-case basis where there is evidence of worsening disease such as, increasing oxygen or ventilator requirement and/or evidence of systemic inflammation (e.g. elevated CRP), immunomodulatory agents such as tocilizumab and anakinra may be considered under expert guidance from specialist teams as detailed above.

In particular, for older children, aged 12 to 18 years, who have confirmed COVID-19 with moderate to severe disease managed in a ward level setting and have risk factors for disease progression, such as elevated BMI, tocilizumab may be considered on a case-by-case basis in patients who have evidence of systemic inflammation (CRP 75 mg/L or higher) AND evidence of disease progression (increasing oxygen or ventilatory requirements) despite 24-48 hours of optimal dexamethasone therapy. For older children, aged 12 to 18 years, who have confirmed COVID-19 with severe or critical disease requiring intensive care setting management and are receiving optimal dexamethasone therapy, tocilizumab may be considered on a case-by-case basis. Of note, for tocilizumab use in the RECOVERY Trial (see **appendix 6**) treatment was given within 14 days of hospital admission.

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

As the pandemic evolved, reports from different centers have shown 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 consideration to dose escalation according to clinical severity. In children, the overall absolute thrombotic risk is much lower than in adults. In the context of COVID-19, the risk of thrombotic events in children is much less clear. A recent publication with national data from the US confirmed a lower thrombotic complication rate in this population in comparison to adults. Furthermore, MIS-C/PIMS-TS patients seem to be at higher risk for developing thrombotic events than pediatric patients hospitalized with acute COVID-19.[19] On both instances, children aged 12 year and over seem to be more commonly affected. 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 to monitor for worsening of the coagulopathy. 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

Convalescent sera

- A number of observational and randomized clinical trials have been published regarding the use of convalescent plasma therapy in patients with COVID-19 with variable outcomes. To date, no serious adverse reactions or safety events have been recorded following COVID-19 convalescent transfusion. The RECOVERY trial group (UK) published the results of a very large open-label randomised controlled platform trial on the use of convalescent sera.[20] This study of adult patients aged over 18 years hospitalised with COVID-19 found that treatment with high-titre convalescent plasma did not improve survival or other pre-specified clinical outcomes. Presently, as per Health Canada recommendations, convalescent plasma is not available for use outside of approved clinical trial settings. Based on this information, at present **the use of convalescent plasma is not recommended outside of approved clinical trial settings in paediatric patients with COVID-19.**

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)

Previously it was suggested ibuprofen should be avoided in patients with COVID-19 due to concern for increased risk of complications.[21,22] For COVID-19, there are no firm data to suggest NSAIDs worsen the course of COVID-19. A large multicentre observational cohort study in England in over 4,000 NSAID versus non-NSAID users with COVID-19 found that NSAID use is not associated with higher mortality or increased severity of COVID-19.[23] However, there is potential for NSAIDs to interact with treatment of patients with multi-systemic inflammatory disease who may require aspirin therapy. Furthermore, in patients with severe COVID-19, especially those requiring ECMO therapy the risk of bleeding events is increased. Accordingly, as a pragmatic approach, 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.[24] 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.[25] 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).

Baracitinib

The ACTT-2 double-blind, randomized, placebo-controlled trial evaluated baricitinib (an oral Janus kinase inhibitor) plus remdesivir in hospitalized adults with COVID-19.[26] For the primary outcome of time to recovery,

patients receiving baricitinib had a median time to recovery of 7 days versus 8 days for control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03). No significant difference in 28-day mortality was observed. Given the modest efficacy, lack of data in pediatric patients and the fact that patients receiving corticosteroids were excluded from this trial, **the use of baracitinib is not routinely recommended in paediatric patients with COVID-19 pending further data.**

Colchicine

Two large trials have examined the role of colchicine in adult patients with COVID-19. The COLCORONA trial[27] studied the use of colchicine in an ambulatory setting for adults with risk factors for severe COVID-19 disease. This trial did not find a statistically significant decrease in composite of death or hospitalization in the group receiving colchicine compared to placebo for all enrolled patients, but did find a statistically significant decrease in primary outcome for the colchicine group in the subgroup of patients with confirmed SARS-CoV-2 positive PCR test. The RECOVERY Trial (preprint data) studied the effect of colchicine versus standard care in hospitalized patients with COVID-19 and did not show any significant impact on 28-day mortality. Neither of these studies included paediatric patients and given the fact that children in an ambulatory setting generally have very good outcomes from COVID-19, the role of colchicine in this setting is unclear. **Therefore, the use of colchicine is not recommended outside of a clinical trial setting in paediatric patients with COVID-19.**

Ivermectin

There are a number of small peer-reviewed and pre-print, non-peer-reviewed clinical trials examining the use of ivermectin in adult hospitalised patients with COVID-19. The sample size of most of the trials is small, with various doses and schedules of ivermectin used, differences in trial design, various comparator drugs and differences in use of concomitant medications, as well as poorly described outcome measures and participant inclusion criteria for some studies. Moreover, none of the studies included paediatric patients. Accordingly, at present **there is insufficient evidence to recommend either for or against the use of ivermectin for the treatment of children with COVID-19 and its use is not recommended outside of a clinical trial setting.**

Fluvoxamine

One randomised controlled trial[28] and a small cohort study[29] have been published relating to use of fluvoxamine in non-hospitalized adult patients with COVID-19. These preliminary studies have demonstrated significant decreases in clinical deterioration and hospitalization rates with the use of fluvoxamine. However, these studies did not include children and in view of the fact that children in an ambulatory setting generally have very good outcomes from COVID-19, **the role of fluvoxamine in this setting is unclear and its use is not recommended outside of a clinical trial setting in paediatric patients with COVID-19 pending further data**.

Inhaled budesonide

Data is available from two trials on the use of inhaled budesonide for adult patients with acute COVID-19 in the community. The STOIC Trial,[30] a small open label randomised controlled trial of 143 adults within 7 days of onset of mild COVID-19 symptoms, showed a significant risk reduction for the primary outcome of COVID-19 related urgent care visit in participants who received budesonide versus standard care (15% vs 3%). The PRINCIPLE Trial is a multicenter, open-label, randomized controlled trial in patients aged ≥65 years, or ≥50 years with comorbidities, and unwell ≤14 days with suspected COVID-19 in the community.[31] This trial found time to first self-reported recovery was shortened in the budesonide group versus usual care (HR 1.208, 95% CI 1.076-1.356) with interim analysis showing reduced COVID-19 related hospitalizations/deaths in the budesonide group (8.5% vs 10.3%). Further analysis of final results is pending for the PRINCIPLE trial and current published results are not

peer-reviewed. **No paediatric cases were included in these studies and therefore no recommendation can be given on the use of inhaled budesonide in the management of early COVID-19 in paediatric patients.**

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.[2] 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.[1] 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.[32]

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.[33] 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.[34,35]

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:[36]

- "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 our 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

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 SickKids ED and inpatient pathways on COVID-associated hyperinflammation / Kawasaki Disease.

Neonates and COVID-19

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

6. Appendix 1. Considerations for treatment of CRS/secondary HLH in children with COVID-19*

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)

Grade 1	Grade 2	Grade 3	Grade 4
Mild: ▪ supportive care only required	Moderate: ▪ requiring intravenous fluid (IV) support (not hypotension) ▪ Fevers ▪ Neutropenia ▪ Mild organ dysfunction (mild creatinine elevation and liver enzyme dysfunction)	Severe: ▪ Significant liver enzyme dysfunction and creatinine elevation not attributable to other condition ▪ Hypotension requiring IV fluid support (multiple fluid boluses) or low dose vasopressors ▪ Coagulopathy requiring fresh frozen plasma, fibrinogen concentrate or cryoprecipitate ▪ Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, CPAP, BiPAP)	Life threatening: ▪ Hypotension requiring high dose vasopressors ▪ Hypoxia requiring mechanical ventilation
▪ 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 Fi02 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 a case-by-case basis, the COVID-19 case management specialist team may consider initiation of immunomodulatory therapy such as tocilizumab and anakinra. 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.

BACK TO CONTENTS

- 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 Guergerian; 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 15th March to include mention of the consideration of use of tocilizumab due to new evidence 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 6 and appendix 7

BACK TO CONTENTS

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
- Drug-interactions: check http://www.covid19-druginteractions.org (Liverpool) for potential interactions.
- Myasthenia gravis
- Porphyria
- Retinal pathology
- Known G6PD deficiency (HCQ is considered generally safe in patients with G6PD deficiency,[37] 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/m^2/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.**

BACK TO CONTENTS

8. Appendix 3. Previous Changes to Document Versions

Key changes from previously uploaded version 29th May 2021 – Version 10.0

1. Update to dexamethasone wording for moderately ill patients and for duration to state up to 10 days or until discharge (summary table and treatment table, page 16/17).
2. Update to remdesivir dosing duration to state up to 10 days to allow option for shorter course (treatment table page 16).
3. Additional wording clarification added to tocilizumab section to highlight considerations for older children with adult-like phenotype (summary statements page 6 and section on related inflammatory clinical entities secondary to COVID-19 - page 20).
4. Additional evidence added to summary paragraph for anti-COVID-19 monoclonal antibodies (page 19).
5. Update to wording on prothrombotic events in children with COVID-19 to include recent evidence in the literature (Page 21).

Key changes from previously uploaded version 21st April 2021

1. Update in summary, CRS/HLH section (page 20) for wording on consideration of tocilizumab use in patients with COVID-19
2. Update to wording on use of remdesivir in patients with COVID-19
3. Brief statement on evidence for inhaled budesonide use in patients with COVID-19 in an ambulatory setting (page 22)

Key changes from previously uploaded version 15th March 2021

1. Update in summary, CRS/HLH section (page 20) and appendix 1 (page 26) regarding consideration of tocilizumab
2. Update to evidence summary appendix 6 for tocilizumab use in patients with COVID-19
3. Brief statement on evidence for fluvoxamine use in patients with COVID-19 in an ambulatory setting (page 22)

Key changes from previously uploaded version – Version 7.1, 15th February 2021

1. Minor update to summary section page 1 to include ivermectin statement
2. Update to remdesivir access use in table 3 – page 16
3. Statement on role of ivermectin and colchicine use in paediatric patients with COVID-19 – page 22
4. Update to evidence summary appendix 6 for tocilizumab use in patients with COVID-19

Key changes from previously uploaded version - Version 7.0, 4th January 2021

1. Updated summary section page 1
2. Additional clarification regarding specialty team involvement in patients with suspected MAS/CRS – page 15
3. Clarification of the word “early” in reference to remdesivir use in table 3 – page 16

4. New section on the role of monoclonal antibody therapies with particular reference to bamlanivumab – page 19
5. Statement on role of baricitinib use in paediatric patients with COVID-19 – page 22
6. Update to evidence summary appendix 6 for tocilizumab use in patients with COVID-19

Key changes from previously uploaded version – Version 6.0, 30th October 2020

1. Update to wording for use of remdesisvir 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

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 12 – table 3 – update to wording for antiviral choices in context of COVID-19. Hydroxychloroquine and lopinavir/ritonavir dosing considerations now removed from treatment table. Dexamethasone added to treatment table.
- 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 – up date to risk factor section with newly published paediatric data
- Page 16 and 22 – up dated 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 2020

- 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

Remdesivir

Only randomised clinical trials included in evidence summary

Study 1

Reference	Wang *et al.* Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020. DOI:https://doi.org/10.1016/S0140-6736(20)31022-9 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext
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 200md 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

Reference	Beigel *et al.* Remdesivir for the Treatment of Covid-19 — Preliminary Report. *NEJM* 2020. DOI: 10.1056/NEJMoa2007764 https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

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 (p0.001) 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

Reference	Goldman *et al.* Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *NEJM* 2020. DOI: 10.1056/NEJMoa2015301 https://www.nejm.org/doi/full/10.1056/NEJMoa2015301
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).

Study 4

Reference	Spinner *et al.* Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19. A Randomized Clinical Trial. *JAMA* 2020. 324(11): 1048-1057 https://jamanetwork.com/journals/jama/fullarticle/2769871
Study Design	Randomised controlled open-label trial
Population	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 Sa02>94% on ambient air. 584 patients enrolled – 193 in 10 day course group, 191 in 5 day course group and 200 standard care group. Medan 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.
Intervention	5 day course of Remdesivir vs 10 day course vs standard care
Primary Outcome	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
Secondary Outcomes	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.
Results	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.

Study 5

Reference	Beigel *et al.* Remdesivir for the Treatment of Covid-19 — Final report. *NEJM* 2020; 383:1813-1826 https://www.nejm.org/doi/full/10.1056/NEJMoa2007764
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. 1062 patients randomized (541 remdesivir, 521 placebo). 13% not requiring O2, 41% requiring O2, 26.8% ECMO or mechanical ventilation.
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 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
Secondary Outcome	Mortality at day 15 and 29
Results	<u>Primary outcome</u> Remdesivir group had a shorter median recovery time of 10 days vs placebo group of 15 days (p<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) <u>Secondary outcomes</u> 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)

	Odds of improvement higher in remdesivir group (p=0.001).

Study 6

Reference	WHO Solidarity trial consortium. Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results. N Engl J Med 2021; 384:497-511 DOI: 10.1056/NEJMoa2023184 https://www.nejm.org/doi/10.1056/NEJMoa2023184
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 ACTT 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

BACK TO CONTENTS

	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:
    - 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
    - Only included studies looking at treatment effect – studies looking solely at adverse effects or pharmacodynamics were excluded
    - Retracted publications not included (Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet*. 2020 May 22:S0140-6736(20)31180-6. doi: 10.1016/S0140-6736(20)31180-6.)
    - Note: Chloroquine studies not included
    - 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://www.bmj.com/content/369/bmj.m1849.long
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 conversation 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

Reference	Chen J, Liu D, Lui L *at al.* A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *J ZheJiang Univ (Med Sci)* 2020;49 (2): 215/219. DOI: 10.3785/j.issn.1008-9292.2020.03.03 http://www.zjujournals.com/med/EN/10.3785/j.issn.1008-9292.2020.03.03
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

Reference	Chen Z, Hu J, Zhang Z et al : Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.

	https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3
Study Design	Randomized controlled unblended study
Population	Hospitalized adults with laboratory-confirmed COVID-19 included, follow-up to day 5 post intervention. Inclusion criteria : Age ≥ 18 years; 2. Laboratory (RT-PCR) positive of SARS-CoV-2; 3. Chest CT with pneumonia; 4. SaO2/SPO2 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.

Study 4

Reference	Boulware *et al.* A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19, *NEJM* 2020. 10.1056/NEJMoa2016638 https://www.nejm.org/doi/full/10.1056/NEJMoa2016638
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

Reference	Horby P *et al.* on behalf of the RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with COVID_19: Preliminary results from a multi-centre, randomized, controlled trial. *medRxiv* (preprint) 2020. https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1.full.pdf
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).

Observational studies – 6 clinical studies

(In order of publication date online)

Study 1

Reference	Gautret *et al.* Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomized Clinical Trial. *Int J Antimicrob Agents* 2020 Mar 20;105949 https://www.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub
Study Design	Prospective non randomised trial – unmatched controls
Population	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.
Intervention/ Exposure	In HCQ group - oral hydroxychloroquine sulfate 200 mg, three times per day during ten days vs standard care
Primary Outcome	Nasophargyngeal virological clearance at day 6 post-inclusion
Secondary Outcome	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.
Safety/ adverse events	Not clearly reported
Results	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. *Swiss Med Wkly* 2020; 150: w20262 https://smw.ch/article/doi/smw.2020.20262

Study 2

Reference	Gautret *et al.* Clinical and Microbiological Effect of a Combination of Hydroxychloroquine and Azithromycin in 80 COVID-19 Patients With at Least a Six-Day Follow Up: A Pilot Observational Study. *Travel Med Infect Dis* 2020; 43: 101663 https://www.sciencedirect.com/science/article/pii/S1477893920301319?via%3Dihub
Study Design	Observational, prospective. Treatment group only, no control group.
Population	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.
Intervention/ Exposure	HCQ 200mg three times daily for ten days plus azithromycin (500 mg on day 1 followed by 250mg per day for four more days.
Primary Outcome	1. Aggressive clinical course requiring O2 therapy or transfer to ICU after at least three days of treatment

	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 https://www.sciencedirect.com/science/article/pii/S0399077X20300858?via%3Dihub
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	Geleris *et al.* Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *NEJM* 2020; DOI 10.1056/NEJMoa2012410 https://www.nejm.org/doi/full/10.1056/NEJMoa2012410
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	Roenberg *et al.* Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA* 2020. doi:10.1001/jama.2020.8630 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 receiving 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

Reference	Mahévas *et al.* Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ* 2020; 369:m1844. https://www.bmj.com/content/369/bmj.m1844
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

Available evidence	5 treatment RCTs, 1 post-exposure RCT and 6 observational studies
Working group discussion regarding evidence	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.

Lopinavir/ritonavir (LPV/r)

Study 1

Reference	Cao *et al.* R. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *NEJM* 2020. DOI: 10.1056/NEJMoa2001282 https://www.nejm.org/doi/full/10.1056/NEJMoa2001282
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.

Intervention	Lopinavir–ritonavir (400 mg and 100 mg, orally twice daily), plus standard care, or standard care alone, for 14 days.
Primary Outcome	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.
Secondary Outcomes	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.
Safety/ adverse events	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.
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

Reference	Fan-Ngai Hung *et al.* Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* 2020. DOI:https://doi.org/10.1016/S0140-6736(20)31042-4 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31042-4/fulltext
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 evenets 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, p0.0001). 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 (14.5days), p0.016. 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.

10. Appendix 5. Evidence summary for key studies on corticosteroid use in patients with COVID-19 as of 17th September 2020

Summary of key publications

17th July 2020

Reference	The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with COVID-10 – Preliminary Report. *NEJM* 2020. DOI: 10.1056/NEJMoa2021436 https://www.nejm.org/doi/full/10.1056/NEJMoa2021436
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

Reference	Jeronimo *et al.* Methylprednisolone as Adjunctive Therapy for Patients Hospitalized with COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial. *Clinical Infectious Diseases* 2020. https://doi.org/10.1093/cid/ciaa1177
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

Reference	Bruno M *et al.* Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19. The CoDEX Randomized Clinical trial. *JAMA* 2020. https://jamanetwork.com/journals/jama/fullarticle/2770277
Study Design	Multicenter randomized controlled trial
Population	Adults aged over 18 years admitted to 41 intensive Care Units in Brazil wth 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

Reference	Dequin *et al.* Effect of Hydrocortisone on 21-day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19. A Randomized Clinical Trial. *JAMA* 2020. https://jamanetwork.com/journals/jama/fullarticle/2770276
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	The Writing Committee for the REMAP-CAP investigators. Effect of Hydrocortisone on Mortality and Organ Support in Patients With severe COVID-19. The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. *JAMA* 2020. https://jamanetwork.com/journals/jama/fullarticle/2770278
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 of 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

2nd September 2020

Reference	The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and mortality Among Critically Ill Patients With COVID-19. A Meta-Analysis. *JAMA* 2020. https://jamanetwork.com/journals/jama/fullarticle/2770279

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

Reviewed evidence	5 RCTs and one meta-analysis reviewed
Working group discussion regarding evidence	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.

BACK TO CONTENTS

11. Appendix 6. Evidence summary for key studies on tocilizumab use in patients with COVID-19 – updated 8th February 2020

Tocilizumab

The following preprint and peer-reviewed literature randomized controlled trials were identified as of 8h March 2020 for inclusion in the evidence discussion regarding tocilizumab use in patients with acute COVID-19:

- Wang D, Fu B, Peng Z, *et al.* Tocilizumab Ameliorates the Hypoxia in COVID-19 Moderate Patients with Bilateral Pulmonary Lesions: A Randomized, Controlled, Open-Label Multicenter Trial. Available at SSRN: https://ssrn.com/abstract=3667681 or http://dx.doi.org/10.2139/ssrn.3667681
- Rosas I, Brau N, Waters M, *et al.* Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. *medRxiv*. 2020
- Salama C, Han J, Yau L, *et al.* Salama C et al. Tocilizumab in Patients hospitalized with Covid-19 pneumonia. NEJM. 2021
- Salvarani C, Dolci G, Massari M, *et al.* Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized with COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med* 2020.
- Stone JH, Frigault MJ, Serling-Boyd NJ, *et al.* Efficacy of Tocilizumab in Patients Hospitalized with COVID-19. *NEJM* 2020.
- Hemione O, Marlette X, Tharaux PL, *et al.* Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *Jama Intern Med* 2020.
- Gordon AC, Mouncey PR, Al-Beidh F, et al. (REMAP-CAP Investigators). Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. medRxiv (preprint) 2021.
- Horby et al. RECOVERY collaborative group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021. 3397: 1637-1645.https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00676-0/fulltext

A summary of key observations from these studies is detailed below (note some of these remain non-peer-reviewed as indicated).

1. Wang *et al.* (not yet peer-reviewed)

Reference	Wang D *et al.* Tocilizumab Ameliorates the Hypoxia in COVID-19 Moderate Patients with Bilateral Pulmonary Lesions: A Randomized, Controlled, Open-Label Multicenter Trial. Available at SSRN: https://ssrn.com/abstract=3667681 or http://dx.doi.org/10.2139/ssrn.3667681
Study Design	Open-label, multicenter RCT
Population	Adult hospitalised patients aged 18 -85 years old with moderate to severe disease (all requiring oxygen) and measured to have elevated IL-6 levels. Age inter-quartile range 55-71 years. Duration of symptoms to randomisation median 23 days (IQR 12-30)
Intervention	Tocilizumab plus standard care vs standard care alone
Primary Outcome	"cute rate" – fever attenuated for 7 days, twice COVID-19 PCR negative, CT chest – 50% improvement
Results	No significant difference in primary outcome. Cure rate for moderate: 19/20 (95%) in tocilizumab group vs 15/17 (88%) in control (p = 0.5843) Cure rate for severe: 13/14 (92.9%) in tocilizumab group vs 12/14 (85.7%) in control (p = 1.000)

2. COVACTA Trial (Not yet peer-reviewed)

Reference	Rosas I *et al.* Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. medRxiv. 2020 https://www.medrxiv.org/content/10.1101/2020.08.27.20183442v2
Study Design	Multicenter RCT involving 9 countries
Population	Hospitalised patients with severe COVID-19 aged over 18 years. 438 patients received the study treatment (294 received tocilizumab versus 144 placebo recipients). Median age of participants was 60.9 years. Median duration of 3 days on mechanical ventilation at the time of randomization. Note a lower proportion of patients in the tocilizumab arm received steroids compared to the placebo group (36.1% vs 54.9%).
Intervention	Tocilizumab versus placebo
Primary Outcome	Clinical status on 7-category ordinal scale at day 28
Results	The primary outcome was not met: Difference in clinical status based on 7-category ordinal scale at day 28 (median) for tocilizumab versus placebo was -1.0 (95% CI -2.5 to 0), p value = 0.36

3. EMPACTA Trial

Reference	Salama C, Han J, Yau L, *et al.* Salama C et al. Tocilizumab in Patients hospitalized with Covid-19 pneumonia. NEJM. 2021 https://www.nejm.org/doi/full/10.1056/NEJMoa2030340
Study Design	Placebo controlled randomised controlled trial
Population	Hospitalised adult patients aged 18 years and over with COVID-19 who were not yet receiving mechanical ventilation. Also included minority and high-risk groups. In total 377 patients received the study treatment (249 received tocilizumab and 128 received placebo).
Intervention	Tocilizumab (1 or 2 infusions) versus placebo
Primary Outcome	Combined outcome of mechanical ventilation, need for ECMO or death by day 28
Secondary Outcome	Median time to hospital discharge or readiness for discharge; Median time to improvement in clinical status; Median time to clinical failure; death
Results	PRIMARY OUTCOME 12 (95% CI 8.5 – 16.9) out of 249 in tocilizumab group versus 19.3 (95% CI 13.3 – 27.4) in placebo group progressed to the primary outcome: hazard ration 0.56, p 0.04. SECONDAR OUTCOMES Median time to hospital discharge or readiness for discharge: 6.0 in tocilizumab group vs 7.5 in placebo group, hazard ration 1.16 (95% CI 0.91 – 1.48) Median time to improvement in clinical status: 6.0 in tocilizumab group vs 7.0 in placebo group, hazard ration 1.15 (95% CI 0.90 – 1.48) Death: 26 in tocilizumab group vs 11 in placebo group, hazard ration 2.0 (95% CI -5.2 to 7.8)

4. RCT-TCZ-COVID-19 Study

Reference	Salvarani C, Dolci G, Massari M et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized with COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med 2020 https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772186

Study Design	Prospective, open-label, randomized clinical trial
Population	Patients hospitalized between March 31 and June 11, 2020, with COVID-19 pneumonia in 24 hospitals in Italy. Eligibility criteria included COVID-19 pneumonia documented by radiologic imaging, partial pressure of arterial oxygen to fraction of inspired oxygen (Pao2/Fio2) ratio between 200 and 300 mm Hg, and an inflammatory phenotype defined by fever and elevated C-reactive protein. 126 patients were randomized (60 to the tocilizumab group; 66 to the control group). The median (interquartile range) age was 60.0 (53.0-72.0) years, and the majority of patients were male (77 of 126, 61.1%).
Intervention	Tocilizumab use versus standard care (not placebo controlled)
Primary Outcome	Composite outcome of entry into the intensive care unit with invasive mechanical ventilation, death from all causes, or clinical aggravation documented by the finding of a Pao2/Fio2 ratio less than 150 mm Hg, whichever came first.
Secondary Outcome	Overall rate of patients admitted to the ICU with invasive mechanical ventilation at 14 and 30 days
Adverse events	Serious adverse events occurred in 3 patients: 2 severe infections (standard care) and 1 upper gastrointestinal tract bleeding (experimental) that prevented the treatment. There were 21 (17.1%) adverse events, 14 (23.3%) in the tocilizumab group and 7 (11.1%) in the standard care group. The most common adverse events were increased alanine aminotransferase level and decreased neutrophil count.
Results	17 patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86). Two patients in the experimental group and 1 in the control group died before 30 days from randomization, and 6 and 5 patients were intubated in the 2 groups, respectively. The trial was prematurely interrupted after an interim analysis for futility.

5. BACC Bay Tocilizumab Trial - October 21st 2020

Reference	Stone *et al.* Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *NEJM* 2020; DOI: 10.1056/NEJMoa2028836 https://www.nejm.org/doi/full/10.1056/NEJMoa2028836
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 enroled, 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 Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19: HR 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 HR 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.

6. CORIMUNO-TOCI-1 Trial

Reference	Hemione O, Marlette X, Tharaux PL et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. Jama Intern Med 2020. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772187
Study Design	Cohort-embedded, investigator-initiated, multicenter, open-label, bayesian randomized clinical trial
Population	Patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min of oxygen but without ventilation or admission to the intensive care unit. Conducted in 9 French hospitals. Of the 130 patients, 42 were women (32%), and median (interquartile range) age was 64 (57.1-74.3) years.
Intervention	Tocilizumab (64 patients) versus usual care alone (67 patients). (Not placebo controlled).
Primary Outcomes	2 primary outcomes were (1) the proportion of patients dead or needing non-invasive or mechanical ventilation on day 4 (>5 on the WHO-CPS); and (2) survival with no need for non-invasive or mechanical ventilation at day 14.
Secondary Outcomes	Clinical status assessed with the WHO-CPS at day 7 and day 14, overall survival, time to discharge, and time to oxygen supply independency.
Adverse Effects	Serious adverse events occurred in 20 (32%) patients in the tocilizumab group and 29 (43%) in the usual care group (P = 0.21)
Results	Primary Outcomes At day 4: In the tocilizumab group, 12 patients had a WHO-CPS score greater than 5 vs 19 in the usual care group (median posterior absolute risk difference [ARD] −9.0%; 90% credible interval [CrI], −21.0 to 3.1) At day 14, 12% (95% CI −28% to 4%) fewer patients needed noninvasive ventilation (NIV) or mechanical ventilation (MV) or died in the tocilizumab group than in the usual care group (24% vs 36%, median posterior hazard ratio [HR] 0.58; 90% CrI, 0.33-1.00) Secondary Outcomes The HR for mechanical ventilation or death was 0.58 (90% CrI, 0.30 to 1.09). At day 28, 7 patients had died in the tocilizumab group and 8 in the usual care group (adjusted HR, 0.92; 95% CI 0.33-2.53).

7. REMAP-CAP Trial

Reference	Gordon AC, Mouncey PR, Al-Beidh F, et al. (REMAP-CAP Investigators). Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. medRxiv (preprint) 2021. https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v1
Study Design	International, multicentre RCT using a multifactorial, adaptive platform
Population	Hospitalised adult patient aged over 18 years with COVID-19 (proven or suspected) within 24 hours of commencing respiratory or cardiovascular organ support in intensive care. Included patients receiving high flow nasal oxygen (28.8%), non-invasive (41.5%) and invasive (29.4%) mechanical ventilation. Tocilizumab could be repeated at 12-24h post-first dose. Of note, 717/865

	(82.9% subjects) reviewed corticosteroids at enrolment or with 48 hours. For all participants the median CRP was 136 (79-208) and ferritin 929 (472-1643). At the time of full analysis 353 patients had been assigned to tocilizumab, 48 to sarilumab and 402 to control.
Intervention	Tocilizumab or sarilumab versus standard care
Primary Outcome	Respiratory and cardiovascular organ support-free days up to day 21 (based on ordinal outcome scale)
Results	Tocilizumab and sarilumab both met the pre-defined triggers for efficacy: Median organ support-free days were 10 (interquartile range [IQR] -1, 16), 11 (IQR 0, 16) and 0 (IQR -1, 15) for tocilizumab, sarilumab and control, respectively. Relative to control, median adjusted odds ratios were 1.64 (95% credible intervals [CrI] 1.25, 2.14) for tocilizumab and 1.76 (95%CrI 1.17, 2.91) for sarilumab, yielding >99.9% and 99.5% posterior probabilities of superiority compared with control. Hospital mortality was 28.0% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control.

8. Horby *et al.* RECOVERY collaborative group

Reference	Horby *et al*. RECOVERY collaborative group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021. 3397: 1637-1645.https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00676-0/fulltext
Study Design	Open-label randomised controlled trial
Population	Patients aged 18 years or over, hospitalized with acute COVID-19. Included 131 NHS hospital sites in the UK. Those trial participants with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein [CRP] ≥75 mg/L) were eligible for randomisation. 2022 patients received tocilizumab plus usual standard of care and 2022 patients received usual standard of care alone. 4116 adults were included in the assessment of tocilizumab, including 562 (14%) patients receiving invasive mechanical ventilation, 1686 (41%) receiving non-invasive respiratory support, and 1868 (45%) receiving no respiratory support other than oxygen. Median CRP was 143 [IQR 107-204] mg/L and 3385 (82%) patients were receiving systemic corticosteroids at randomisation.
Intervention	Tocilizumab (1 or 2 doses) versus usual care (not placebo controlled)
Outcomes	PRIMARY All cause mortality at 28 days SECONDARY Time to discharge alive, composite progression to invasive mechanical ventilation, ECMO or death
Results	PRIMARY Patients allocated to tocilizumab were more likely to be discharged from hospital alive within 28 days (54% vs. 47%; rate ratio 1·22; 95% CI 1·12-1·34; p<0·0001). SECONDARY Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (33% vs. 38%; risk ratio 0·85; 95% CI 0·78-0·93; p=0·0005).

The following is a summary of key observational publications:

20th October 2020 - STOP-COVID Trial

Reference	Gupta A, Wang W, Hayek S *et al.* Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. *JAMA Intern Med* 2020. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2772185
Study Design	Multicenter cohort study
Population	4485 adults with COVID-19 admitted to participating intensive care units (ICUs) at 68 hospitals across the US from March 4 to May 10, 2020. Among the 3924 patients included in the analysis (2464 male [62.8%]; median age, 62 [interquartile range {IQR}, 52-71] years), 433 (11.0%) received tocilizumab in the first 2 days of ICU admission. Patients treated with tocilizumab were younger (median age, 58 [IQR, 48-65] vs 63 [IQR, 52-72] years) and had a higher prevalence of hypoxemia on ICU admission (205 of 433 [47.3%] vs 1322 of 3491 [37.9%] with mechanical ventilation and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of <200 mm Hg) than patients not treated with tocilizumab. Tocilizumab-treated patients were more likely to receive corticosteroids versus non-tocilizumab-treated patients (81 [18.7%] vs 440 [12.6%]).
Intervention	Treatment with tocilizumab in the first 2 days of ICU admission.
Primary Outcome	In-hospital death (censored at hospital discharge or last follow-up)
Adverse Events	Tocilizumab-treated and non-tocilizumab–treated patients experienced the following adverse events: secondary infection (140 [32.3%] vs 1085 [31.1%]); AST or ALT level elevation of more than 250 U/L (72 [16.6%] vs 452 [12.9%]); AST or ALT elevation of more than 500 U/L (37 [8.5%] vs 196 [5.6%]); arrhythmias (63 [14.5%] vs 602 [17.2%]); and thrombotic complications (46 [10.6%] vs 342 [9.8%]).
Results	125 (28.9%) patients treated with tocilizumab versus 1419 (40.6%) not treated with tocilizumab died (HR, 0.71; 95% CI, 0.56-0.92). The estimated 30-day mortality was 27.5% (95% CI, 21.2%-33.8%) in the tocilizumab-treated patients and 37.1% (95% CI, 35.5%-38.7%) in the non-tocilizumab–treated patients (risk difference, 9.6%; 95% CI, 3.1%-16.0%).

11th July 2020

Reference	Somers *et al.* Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *Clinical Infectious Diseases*, 2020 ciaa954. https://doi.org/10.1093/cid/ciaa954
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

Reference	Rossotti *et al* on behalf of the Niguarda COVID-19 Working Group. Safety and Efficacy of Anti-IL6-Receptor Tocilizumab use in Severe and Critical Patients Affected by Coronavirus Disease 2019: A Comparative Analysis. *Journal of Infection* 2020. https://doi.org/10.1016/j.jinf.2020.07.008
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

Reference	Guaraldi G *et al.* Tocilizumab in patients with severe COIVD-19: a retrospective cohort study. *The Lancet Rheumatology* 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
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

Reference	Price *et al.* Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized COVID-19 Patients. *Chest* 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.

BACK TO CONTENTS

Evidence Summary

Working group discussion regarding evidence	Based on the current evidence, the working group agreed that the data is currently inconclusive regarding whether tocilizumab is of benefit or not in the management of paediatric patients hospitalized with COVID-19. The working group were in agreement that use of tocilizumab is not routinely recommended outside of a clinical trial setting in paediatric patients hospitalized with COVID-19. However, members of the group suggested that on a case-by-case basis where there is evidence of worsening disease and rising inflammatory markers tocilizumab may be considered under expert guidance from specialist teams.

12. Appendix 7. Evidence summary for key studies on anakinra use in patients with COVID-19

Anakinra

Summary of recent key publications

Reference	Cavalli G *et al.* Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *The Lancet Rheumatology* 7th May 2020. https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext
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% patinets discontinued high-dose anakinra for adverse events – 14% bacteraemia, 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).

Reference	Huet T *et al.* Anakinra for severe forms of COVID-19:a cohort study. *The Lancet Rheumatology* May 29, 2020. https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30164-8/fulltext
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

BACK TO CONTENTS

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, p0.0063 and 0.22, p=0.0015 respectively). CRP decrease significantly greater in the anakinra group versus control (p<0.0001)

13.References

1. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. *Pediatrics*. 2020. doi:10.1542/peds.2020-0702
2. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med*. 2020;(NEJMc2005073). doi:10.1056/NEJMc1210001
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan , China : a retrospective cohort study. *Lancet*. 2020;6736(20):1-9. doi:10.1016/S0140-6736(20)30566-3
4. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - J Am Med Assoc*. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
5. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *Jama*. 2020;4720:2019-2021. doi:10.1001/jama.2020.4326
6. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428-439. doi:doi:10.1097/PCC.0000000000000350
7. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med*. 2020;383(19):1813-1826. doi:10.1056/nejmoa2007764
8. Bialek S, Gierke R, Hughes M, McNamara L, Pilishvili T, Skoff T. Morbidity and Mortality Weekly Report. Coronavirus Disease 2019 in Children United States, February 12-April 2, 2020. 2020.
9. Garazzino S, Montagnani C, Donà D, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents , preliminary data as at 10 April 2020. *eurosurveillance*. 2020;(0031296):1-4.
10. Shekerdemian LS, Mahmood NR, Wolfe K, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr*. 2020. doi:10.1001/jamapediatrics.2020.1948
11. Ogimi C, Englund JA, Bradford MC, Qin X, Boeckh M, Waghmare A. Characteristics and outcomes of coronavirus infection in children: The role of viral factors and an immunocompromised state. *J Pediatric Infect Dis Soc*. 2019;8(1):21-28. doi:10.1093/jpids/pix093
12. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med*. 2021;384(3):238-251. doi:10.1056/nejmoa2035002
13. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *N Engl J Med*. 2020:1-9. doi:10.1056/nejmoa2029849
14. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. *JAMA - J Am Med Assoc*. 2021;325(7):632-644. doi:10.1001/jama.2021.0202
15. Government of Canada. Bamlanivimab - Potential Risk of Treatment Failure Due to Circulation of Resistant SARS-CoV-2 Variants. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/75503a-eng.php. Published 2021.
16. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign : Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med*. 2020.

17. Cheifetz IM. Pediatric ARDS. *Respir Care*. 2017;62(6):718-731. doi:10.4187/respcare.05591

18. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

19. Whitworth HB, Sartain SE, Kumar R, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. *Blood*. 2021. doi:10.1182/blood.2020010218

20. Abani O, Abbas A, Abbas F, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet*. 2021;19:2049-2059. doi:10.1016/s0140-6736(21)00897-7

21. Day M. Covid-19 : ibuprofen should not be used for managing symptoms , say doctors and scientists. *Br Med J*. 2020;1086(March):2020. doi:10.1136/bmj.m1086

22. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir*. 2020;2600(20):30116. doi:10.1016/S2213-2600(20)30116-8

23. Drake TM, Fairfield CJ, Pius R, et al. Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study. *Lancet Rheumatol*. 2021;9913(21):1-9. doi:10.1016/s2665-9913(21)00104-1

24. Tian X, Li C, Huang A, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect*. 2020;9(1):382-385. doi:10.1080/22221751.2020.1729069

25. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med*. 2020:1-8. doi:10.1056/NEJMoa2008975

26. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*. 2020:1-13. doi:10.1056/NEJMoa2031994

27. Tardif J-C, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021;19(21):1-9. doi:10.1016/s2213-2600(21)00222-8

28. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(22):2292-2300. doi:10.1001/jama.2020.22760

29. Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of COVID-19. *Open Forum Infect Dis*. 2021:1-3. doi:10.1093/ofid/ofab050

30. Ramakrishnan S, Nicolau D V, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;19(21):1-10. doi:10.1016/s2213-2600(21)00160-0

31. PRINCIPLE Collaborative Group. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. *medRxiv (preprint)*. 2021.

32. Livingstone E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *JAMA - J Am Med Assoc*. 2020;(March 17). doi:10.1001/jama.2020.4344

33. Cai J, Xu J, Lin D. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis*. 2020. doi:https://doi.org/10.1093/cid/ciaa198

34. American Academy of Ophthalmology. Alert: Important coronavirus updates for ophthalmologists. https://www.aao.org/headline/alert-important-coronavirus-context. Published 2020. Accessed March 27, 2020.

35. ENTUK. Loss of smell as marker of COVID-19 infection. https://www.entuk.org/sites/default/files/files/Loss of sense of smell as marker of COVID.pdf. Accessed March 27, 2020.

36. COVID-19 Patient Updates. Canadian Dermatology Association. https://dermatology.ca/public-patients/covid-19-patient-updates/. Published 2020. Accessed May 11, 2020.

37. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020. doi:10.1016/j.ijantimicag.2020.105932

14.Important Information and Disclaimers About this Document

This Guidance Document is intended solely for healthcare providers at The Hospital for Sick Children ("SickKids"). Any use of this Guidance Document must be subject to the judgment of a patient's attending physician, taking into consideration all available information related to the condition of the patient and after review of the benefits and risks of the proposed course of action with the patient (if of an appropriate age) and/or the patient's parents or guardians.

The Guidance Document is NOT intended for use by patients or their families and is not designed or intended to constitute medical advice or to be used for diagnosis. The Guidance Document is NOT a substitute for the personalized judgment and care of a trained medical professional. SickKids does not recommend or endorse any information, procedure, or product that may be mentioned in this Guidance Document.

Every reasonable effort has been made to ensure that the information provided in the Guidance Document is accurate and in accordance with the standards accepted at the time it was created, however new and emerging research and experience may result in changes to these standards. You are responsible for ensuring that the materials are current and comply with all applicable laws.

The Guidance Document is provided "as is" with no representations or warranties of any kind, express, statutory or implied, as to the content or information produced by the Guidance Document. By viewing and using any information derived from the Guidance Document, you hereby waive any claims, causes of action and demands, whether in tort or contract, against SickKids (including its employees, physicians, directors and agents) in any way related to use of the Guidance Document or the information derived from it.