Summary of Review for Experimental Therapies and COVID-19

Introduction and Scope of this document

This document is intended to serve as an interim overview of currently available evidence and expert consensus regarding experimental therapeutics for COVID-19. Due to the urgency for interim guidance, a full systematic review to assessing evidence has not been performed and the table presented represents a targeted scoping review. Some of the subjective judgements are solely the consensus opinion of the authors and consulted experts. The focus of the treatments included is to present antiviral treatments and therapies currently under investigation or that have been suggested by clinicians and researchers as possible strategies. Supportive care and treatment of complications, including ARDS and secondary bacterial pneumonia are not addressed in this table and clinical guidance is available elsewhere.

There is no current evidence from randomized controlled trials to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19. **Accordingly, the use of treatments detailed below should occur within the context of controlled clinical trials**. Use of these experimental medications outside of this context, for example for compassionate use, should be considered with caution and only given under expert guidance if it is judged that the potential for benefit is likely to outweigh the risk.

Where experimental use of therapy is performed it should be in line with local policies and procedures for compassionate use of medications, with informed patient or caregiver consent, carefully monitored, and accompanied by appropriate systematic data collection for the benefit of informing guidance in the future.

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

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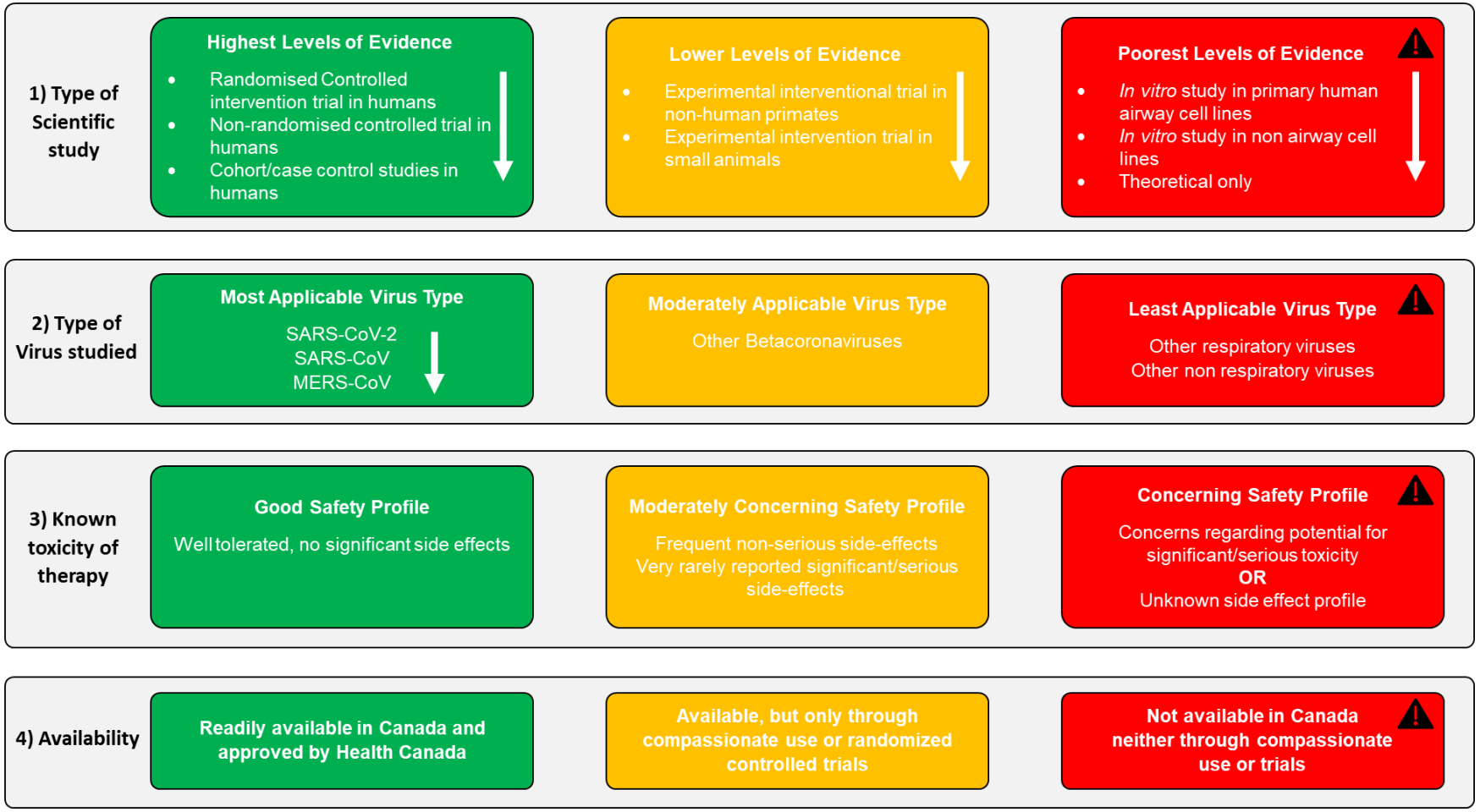
Developed by Helen Groves, Pierre-Philippe Piché-Renaud, Taito Kitano and the Division of Infectious Diseases at the Hospital for Sick Children
Revised by K. Timberlake, E. Leung, Pharmacists

Evidence Summary

Evidence collected on the treatment of COVID-19 was graded according to four main categories, including type of study, study of virus being studied, known toxicity/adverse effects of the medication and availabilityof the medication. The level of evidence for each category was assessed according to the following matrix:



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Using this matrix evidence for each experimental therapy was graded as follows: (please note as more evidence becomes available graded within this table will change)

Table Grading Key:

- Evidence exists to suggest benefit of treatment might exceed risk, may be considered in some situations for compassionate use under expert guidance.
- Less evidence exists or concerns regarding toxicity or availability; further data is needed to indicate whether benefit of treatment exceeds risk but has been used by some experts worldwide for compassionate use. Suggest to await further data.
- No/poor evidence for effectiveness or significant concerns regarding potential toxicity therefore currently no evidence that benefit of treatment exceeds risk. Not recommended outside of clinical trials at this time.

Table 1: Experimental treatments and COVID-19

Antiviral therapy						
Agent	**Presumed mechanism of action**	**Documented adverse effects**	**Dosing: Pediatric and Adult***	**Availa-bility in Canada**	**Evidence with COVID-19**	**Evidence with other viruses/ARDS**
Nucleoside analogues						
Remdesivir	Intracellular incorporation of the pharmacologically active nucleoside triphosphate form into nascent RNA chains by the viral RNA-dependent RNA-polymerase, causing premature RNA chain termination.[1]	Trial for evaluation of safety in 94 adults yet to be published; communication from Gilead mentioned that the only significant adverse effect were transient grade 1 or grade 2 increases in AST and ALT. From Ebola RCT: 1/175 adults had an episode of hypotension during loading dose.[2]	Extrapolated from evidence in treatment for Ebola: < 40Kg: 5mg/kg Loading dose; Then 2.5mg/kg IV q24h for 10-14 days ≥40kg: 200mg IV x1 then 100mg IV q24h for days 2 to 20	Not approved by Health Canada. Clinical trials ongoing. May be available on compassion-nate use basis. Online application https://rdvcu.gilead.com/	Use reported in one patient in the US. Clinical trials ongoing in China including a phase 3 placebo-controlled, double-blinded RCT. One in-vitro study published for COVID-19: inhibition of SARS-CoV-2 viral growth (qRTPCR detection) in Vero cells without significant cytotoxicity.[3] Mentioned as options in several guidelines worldwide including Italian, Belgium, US guidelines on the management of COVID-19.	Ebola: Evaluated through RCT, no difference in outcome compared to placebo. In-vitro experiments have shown remdesivir inhibits bat coronaviruses, endemic human coronavirus (OC43, 229E), and the human pathogenic coronaviruses, MERS-CoV and SARS-CoV.[4,5] Mice models have shown Remdesivir significantly reduces lung SARS and MERS viral load and improves clinical signs of disease as well as respiratory function.[4,5] In a Rhesus Macaque model of MERS CoV

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						infection, prophylactic or early treatment improves clinical respiratory function and radiological signs, and reduces lung viral load and histopathological changes.[6]
Galidesivir (BCX4430 – Immucilin-A) ⊗	Inhibition of viral RNA polymerase activity. Incorporation into nascent viral RNA strands would cause premature termination of transcription and replication of viral RNA. SARS-CoV-2-RdRp is a possible binding target.	Study to Evaluate the Single Dose Safety, Tolerability and Pharmacokinetics of IV BCX4430 if ongoing (NCT03800173).		Not available in Canada	Molecular docking study showed that it might bind to SARS-CoV-2 RdRp, with binding energies comparable to those of native nucleotides.[7] No in-vitro or in-vivo study with COVID-19 available yet. No clinical trial ongoing.	BCX4430 exhibits broad-spectrum antiviral activity against numerous viruses, including bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses (Including SARS and MERS) and flaviviruses in vitro using HeLa cells.[8]
Ribavirin ⊗	Ribavirin is a guanosine analog nucleoside inhibitor which stops viral RNA synthesis and viral mRNA capping	Significant side effect (severe anemia), liver dysfunction with elevation of ALT in 29% of patients.[9]		Available in Canada	No difference in survival when used for ARDS. [10] In *in vitro* studies Ribavirin did reduce SAR-CoV-2 levels but required high levels to achieve this.[3]	**SARS** consensus: inconclusive data and potential harm.[9] No RCT with placebo comparison. **MERS:** Studies showed no difference in 28-days mortality, 90-days mortality and MERS RNA clearance with Ribavirin & IFN.[11] May have synergy with Kaletra
Protease inhibitors						
Agent	**Presumed mechanism of action**	**Documented adverse effects**	**Dosing: Pediatric and Adult***	**Availa-bility in Canada**	**Evidence with COVID-19**	**Evidence with other viruses/ARDS**
Lopinavir/Ritonavir: Kaletra (LPV/r) ⚠	Inhibit 3-chymotrypsin-like protease of coronavirus: Docking and molecular dynamic experiments were applied to examine the effect of inhibitors on	Generally well established toxicity profile. Most commonly reported side effects are gastrointestinal i.e. diarrhoea, nausea, vomiting. Also	<6 months: 300 mg/m2/dose PO bid (Dose limit: 800 mg /day) 6 months to 12 yrs: 230-300 mg /m2/dose PO bid (Dose limit: 800 mg/day)	Available in Canada	Results of open label clinical trial on lopinavir–ritonavir versus standard care in adult patients with COVID-19 failed to show difference in primary outcome of time to clinical improvement. Severe	**SARS:** When LPV/r was added as an initial treatment to ribavirin and corticosteroid therapy, the death rate was lower than among those who received ribavirin and corticosteroids (1/44 [2.3%] versus 99/634

	coronavirus proteinase - of the HIV1 proteinase inhibitor tested the highest affinity for blocking the coronavirus protease was lopinavir.[12]	known to cause anaemia, liver dysfunction, pancreatitis, arrhythmias, prolongation of the QT and rarely severe drug reaction. Risk of multiple drug interactions. Use with caution in hepatic impairment, no dose adjustment in renal impairment	- >12 yrs or ≥35 kg: 400 mg PO bid Adult: 400/100 PO BID (up to 10-14 days, per WHO)		adverse events eg. ARDS were more common in standard care group compared to lopinavir-ritonavir.[13] Currently used in China– consensus guideline, weak recommendation.[14] Used in Korea and reported in case reports.[15] Also used clinically in Italy and Japan as part of consensus guideline. One observational study in COVID-19 patients did not find reduced duration of viral RNA detection in those receiving lopinavir-ritonavir. In a Singapore cohort 2 of 5 treated patients deteriorated to respiratory failure. Unclear if this was related to lower treatment dosing.[16]	[15.6: %]; p , 0.05).[9] Interpretation of this study if difficult due to uncontrolled interventions. **MERS:** In MERS experimentally infected Marmosets lopinavir/ritonavir-treated and interferon-β1b-treated Marmosets had better outcome than control animals, with improved clinical, Radiological, pathological findings, and lower mean viral loads in necropsied lung.[17] Combination LPV/r and ribavirin appeared beneficial in a small study of post-exposure prophylaxis against MERS in healthcare workers.[18]
Darunavir/ Cobicistat ⊗	Similar to lopinavir: Inhibit 3-chymotrypsin-like protease of coronavirus. Docking and molecular dynamic experiments were applied to examine the effect of inhibitors on coronavirus proteinase – of the HIV1 proteinase inhibitor tested the best was lopinavir and Darunavir's binding site	Diarrhea, nausea, rash.		Available in Canada	Clinical trial is ongoing. Mentioned as option for treatment in Italian and Thai guidelines on the clinical management of COVID-19.	Established anti-HIV medication. No clear data on spectrum of activity against coronaviruses or other respiratory viruses. No in vitro or clinical data to support the use of darunavir as a treatment for COVID-19.

	affinity was half that of lopinavir.[12]					
Interferon therapy						
Agent	**Presumed mechanism of action**	**Documented adverse effects**	**Dosing: Pediatric and Adult***	**Availa-bility in Canada**	**Evidence with COVID-19**	**Evidence with other viruses/ARDS**
Interferon-β1 (IFN-β1) ⊗	Stimulate innate antiviral immunity.	Clinical experience based on use in MS: Possible side effects of IFNβ include various autoimmune reactions, capillary leak syndrome, anaphylactic shock, thrombotic-thrombocytopenic purpura, insomnia, headache, alopecia, and depression.[19]		Available in Canada	Note new trial of inhaled beta interferon (SNG001) via a nebuliser device started in UK – results pending. Use recommended in critically ill patients in Spanish interim advice guidelines and one US guideline.	**SARS:** Type I IFNs have shown activity in limited animal and observational clinical studies. In mice given intraperitoneal IFN-B/D 4 hours post SARS-CoV exposure, dose-related reductions in lung viral titers were noted.[20] One small observational study of IFNaflacon-1 combined with corticosteroids reported improved clinical outcomes in SARS **MERS:** RCT ongoing with LPV/r and INF- β1b.[21] No preliminary results yet available. In vitro, MERS-CoV appears to be more sensitive to type I IFNs than SARS-CoV, especially IFN-β. In rhesus Macaques model of MERS-CoV infection noted some benefit of early treatment with IFN-β1b.[22]
Aerosolized α-Interferon ⊗	Stimulate innate antiviral immunity.	Multiple side effects reported for systematic administration in formulary. Rare severe side effects include anaphylaxis, pericarditis and		Available in Canada	Currently used in China – consensus guideline, weak recommendation.[14]	Reported use in small case studies and case reports in MERS. Difficult to assess clinical benefit based on these observation studies as no controls and often used in combination with several antiviral agents.[23]

		important CNS side effects				
Recombinant interferon ⛔	Stimulate innate antiviral immunity.	Side effects as reported for IFN- α/ β1		Available in Canada	No data	No difference in 90-days mortality and MERS RNA clearance with Ribavirin & rIFN.[11]
Other antivirals						
Agent	**Presumed mechanism of action**	**Documented adverse effects**	**Dosing: Pediatric and Adult***	**Availa-bility in Canada**	**Evidence with COVID-19**	**Evidence with other viruses/ARDS**
Favipiravir ⚠	Viral RNA polymerase inhibitor	Hyperuricemia (4.79%) diarrhea(4.79%) Neutropenia(1.80%) Increased AST(1.80%) or ALT(1.60%) Psychiatric symptom reactions also reported. No data on renal or hepatic dosing, but metabolites are primarily renally cleared.	Adult; Loading dose: 1600mg PO BID. Then, 600mg PO BID Day 2-5. Contraindicated in pregnant women. No pediatric dose information.	Not marketed in Canada – unavailable through SAP at the current time but studies enrolling in other countries, such as Thailand and China.	In-vitro study published for COVID-19: some inhibition of SARS-CoV-2 viral growth (qRTPCR detection) in Vero cells (less potent than Chloroquine and Remdesivir in the same study).[3] Currently used in China and Japan as part of treatment guidelines. Results from a trial in China (ChiCTR200030254): Prospective, multicenter, open-labelled, randomized superiority trial in 240 patients comparing FPV to Arbidol (also used CQ, Ribavirin, IFN in both groups). While patients in the FPV group showed increased recovery rate at 7 days, they had increased adverse effects.[25]	Some evidence in mortality reduction for severe Influenza, Lassa virus and SFTS virus.
Oseltamivir ⛔	For influenza: competitive inhibition of neuraminidase enzyme. No reported mechanism of action for coronaviruses.	Frequent adverse reactions include headaches, pain, nausea, vomiting. Rare but documented hypersensitivity		Available in Canada	No difference in survival when used for ARDS[10]. Noevidence of benefit for use in COVID-19	SARS: No effect in *in vitro* studies.[26] Used initially anecdotally in SARS and MERS but no evidence on its clinical effects.

		reactions and neuropsychiatric events. Other rare side effects include hepatitis, seizure and severe GI symptoms. Renal adjustment required.				
Baloxivir marboxil (Xofluza) ⊗	Orally administered Viral endonuclease inhibitor	Gastrointestinal side effects (nausea, diarrhea), bronchitis, headache May chelate with polyvalent cations Converted to active metabolite by UGT1A3 and CYP3A4 (minor). Has not been studied in severe hepatic impairment (Class C), and current trial excludes these patients.	Influenza Adult dose: 40 - <80kg: 40mg single dose ≥80 kg: 80mg single dose Influenza Pediatric dose: same as adult weight based dosing, but only for ≥12 yrs COVID19 trial Adult dose (China): 80mg x 3 doses (day 1, day 4, day 7). No more than 3 administrations in total.	Approved in Canada but not marketed – unclear if SAP is available. Not available to order from the company yet (3/10/2020)	COVID19 trial ongoing with different dosing proposed from influenza, and WHO identifies it as a potential candidate.	Influenza: licensed in USA for acute uncomplicated influenza, and in Japan for all influenza.
Umifenovir (Arbidol) ⊗	Inhibition of virus-mediated fusion with target membrane and a resulting block of virus entry into target cells.[27]	With the exception of possible allergic reactions, main adverse effects include nausea, diarrhoea, dizziness and elevated serum transaminase. The rate of adverse drug reactions is about 6.2%.		Unclear if available in Canada	No difference in survival when used for ARDS.[10] Recommended as treatment option in Chinese guidelines. Results from a trial in China (ChiCTR200030254): Prospective, multicenter, open-labelled, randomized superiority trial in 240 patients comparing Famiravir to Arbidol.	SARS: Russian study showed some in-vitro activity – original article is in Russian therefore cannot appraise this study effectively.[28]

					Patients in the FPV group showed increased recovery rate at 7 days, versus arbidol.[25]	
Immunological therapies						
Agent	**Presumed mechanism of action**	**Documented adverse effects**	**Dosing: Pediatric and Adult***	**Availa-bility in Canada**	**Evidence with COVID-19**	**Evidence with other viruses/ARDS**
Tocilizumab	IL-6 receptor antibody. Elevated levels of IL-6 has been associated with disease severity in COVID-19. Blockage of this is presumed to decrease the cytokine release induced by COVID-19 and reduce lung damage.	Common – headache, nasopharyngitis and diarrhoea, increased ALT noted. *Health Canada warning for serious DILI reports Rare/serious – hypersensitivity reactions including fatal anaphylaxis and SJS reported, risk of infections: disseminated fungal, disseminated TB, bacterial and viral pathogens *FDA blackbox warning for serious infection risk. Administration is not recommended for people with active infections such as tuberculosis. Need IGRA/Quantiferon	<30 kg: 10 mg/kg/dose IV every 4 weeks in JIA – dosing in treated cases in China unclear and no reported paediatric treatments given. Adult dosing for RA: 4mg/kg IV x1 q4week (max 800mg), can increase to 8mg/kg IV q4week based on clinical response Adult dosing for cytokine release syndrome: <30kg: 12mg/kg (max 800 mg) ≥30kg: 8 mg/kg (max 800mg) May repeat up to 3 doses (at least 8h apart) if no clinical improvement after first dose Dosing for COVID-19 in Chinese guidelines:[30] Initial dose is 4-8mg/kg with the recommended dose of 400mg diluted	Available in Canada – used to treat rheumatoid arthritis in children: licenced above 2 years.	Multi-center, randomized clinical trials ongoing. Preliminary results released by the National Health Commission showed that in 20 patients with severe COVID-19 temperature dropped within one day in all 20 and 19 patients were discharged from hospital within two weeks. However of these 20 patients only 2 patients were ventilated and one on non-invasive support and the study had no controls. Therefore difficult to draw firm conclusions regarding benefit. Currently included in Chinese guidelines: For use in patients with extensive lung lesions and severe cases who also show an increased level of IL-6 in laboratory testing.	No data or previous trials with MERS or SARS. Link between interleukin-6 as a marker of severity in ARDS.[31] Murine model showed that IL-6 suppression is a critical feature of the protective mechanism in pneumovirus-related ARDS.[32]

		and hepatitis B testing prior to use. Of note, Tocilizumab has an extensive half-life that approximates human IgG (241.8 +/- 71.4h).[29]	with 0.9% normal saline to 100ml. The infusion time should be more than 1 hour. One extra administration can be given after 12 hours (same dose as before). No more than two administrations should be given with the maximum single dose no more than 800mg. SQ dosing differs from IV Hepatic dose adjustment recommended; discontinue if ALT/AST > 5x ULN			
Systemic cortico-steroids ⚠	Supress host immune response	Multiple known side effects including induced diabetes, avascular osteonecrosis, immune-suppression, psychosis, hyperglycaemia, etc.	Chinese guidelines suggest a cautious use of stress dose of corticosteroids may be appropriate e.g. for refractory shock may be used for a short duration: the recommended dose of methylprednisolone should not exceed 1-2mg/Kg /day in BID dose for 3-5 days.	Available in Canada	WHO[33] and CDC[34] do NOT recommend. Generally used for patients with ARDS in China. Descriptive study showed no difference in survival when used for ARDS.[10]	SARS: No clear benefit and possible harm with delayed viral clearance, avascular osteonecrosis, induced diabetes.[9] No difference in survival when used for ARDS.[10] MERS: In vitro data suggesting cortisone, prednisolone and dexamethasone did not suppress viral growth.[35]
Inhaled cortico-steroids ⛔	Supress host immune response	Usually well tolerated. Reported side effects include dizziness, fatigue, headache, urticaria, oral candidiasis, arthralgia, hoarseness, nasal	As per asthma treatment dosing: Low-dose therapy: 80 to 160 mcg/day divided BID Medium-dose therapy: >160 to 320 mcg/day divided BID	Available in Canada	*In vitro* data suggests Ciclesonide on SARS-CoV-2 infected VeroE6/TMPRSS2 Cells inhibits viral replication.[35] Inhaled steroids for COVID-19 are being used as standard in severe cases of	MERS: *In vitro* data suggests Ciclesonide and mometasone on MERS-CoV infected VeroE6/TMPRSS2 Cells inhibits viral replication. Fluticasone did not suppress viral growth.[35]

		congestion, nasopharyngitis, paradoxical bronchospasm, pneumonia.	High-dose therapy: >320 mcg/day divided BID		COVID-19 in Japan – no evidence yet published on the efficacy of this.	
Anakinra ⊗	IL-1 receptor blocker. Has been reported to be effective in the management of macrophage activation syndrome (MAS). Presumed to decrease cytokine storm which is known to occur in COVID-19.	Most common serious side effects are infection and neutropenia. Need to exclude tuberculosis, hepatitis B and C prior to use. Most common non-serious side effect is localised injection side reaction and GI effects. Thrombocytopenia, headache, arthralgia, liver enzyme dysfunction have been reported. Can cause systemic reactions.		Available in Canada.	No data yet available. Swedish Orphan Biovitrum (SOBI) starting clinical trial on Anakinra and Emapalumab in severe COVID-19.	Re-analysis of data from a phase 3 RCT of Anakinra in sepsis, showed significant survival benefit in patients with hyperinflammation, without increased adverse events.[36]
Sarilumab ⊗	IL-6 receptor antibody. Elevated levels of IL-6 has been associated with disease severity in COVID-19. Blockage of this is presumed to decrease the cytokine release induced by COVID-19 and reduce lung damage.	Associated with transaminase elevations, should not be initiated in patients with ALT or AST > 1.5 x ULN. Associated with hypersensitivity reactions and hyperlipidemia. GI perforation has also been reported. Risk of infections: disseminated		Not clear if readily available in Canada	Rationale for use extrapolated from Tocilizumab, but currently no specific evidence available. Phase 2/3 clinical trials ongoing in France and in the US to evaluate the clinical efficacy of Sarilumab compared with placebo for adults hospitalized with severe COVID-19.	No evidence with other viruses.

		fungal, TB, bacterial and viral pathogens. *FDA blackbox warning for serious infection risk. Administration is not recommended for people with active infections such as tuberculosis. Need IGRA/Quantiferon and hepatitis B testing prior to use.				
Eculizumab ⊗	Blocks C5 and Neutrophil Extracellular Trap production in the lungs which are key components in ARDS pathogenesis.[37]	Disseminated and severe *Neisseria* infections. Theoretical risk of severe infections from other capsulated organisms. Isolated reports of *Aspergillus, Pseudomonas and* HSV severe infections.[38] Other S/Es include nausea, GI upset, rash, anaemia, neutropenia.		Available in Canada; Extremely costly	Trials ongoing – no specific in vitro evidence with eculizimub however In mice deficient in C3 (C3–/–), Relative to control mice, SARS-CoV-infected C3–/– mice exhibited significantly less weight loss and less respiratory dysfunction despite equivalent viral loads in the lung.	No direct evidence for other viral infections *In vivo* or *in vitro*
Convalescent serum ⊗	Antibody from patients recovered from COVID-19 neutralizes the virus.	Chills, fever (not enough data). Risk of transmission of bloodborne viral or other infection.		None yet available	Clinical trials currently ongoing. Case series of 5 patients with severe COVID-19 who recovered following administration of convalescent serum.[39] Limitations include study size, no control group, patients all on various other	Combined review of convalescent sera for influenza and SARS showed reduced mortality however included studies were commonly of low or very low quality, lacked control groups, and at moderate or high risk of bias.[40]

					therapies and administered three weeks after hospital admission.	
Intravenous Ig ⊗	Inactivate auto-reactive immune cells	Headache, aseptic meningitis, anaphylaxis, renal dysfunction, etc..	Up to 2g/Kg Regimen recommended in China: 0.2g/kg/day for 3-5 days.	Available in Canada	No evidence for use in COVID-19. However some guidelines are advocating its use in special populations eg. If IgG <400	No difference in survival when used for ARDS.[10]
Monoclonal antibodies ⊗	Selected and used on the basis of their virus-neutralizing activity and/or cell-killing activity to blunt viral propagation via direct mechanisms.	None currently available, other monoclonal antibodies associated with rashes, allergic reactions, flu-like symptoms. Serum-sickness and anaphylaxis reported.		None available at this time	In vitro evidence: SARS CoV monoclonal antibody antibody CR3022 completely neutralized wild-type SARS-CoV and CR3022, could bind potently with 2019-nCoV receptor binding domain.[41] No in vivo studies reported.	In vitro evidence of neutralising antibodies against MERS-CoV.[42] None of these have been used in clinical trials or in vivo studies. Previous trials with SARS – efficacy unclear. For non-respiratory viruses used for a large number of viruses as therapy including: Ebola virus, H5N1 influenza virus, human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV), hepatitis C virus (HCV), Marburg virus, dengue virus, rabies virus, Hendra virus, Nipah virus, yellow fever virus, and West Nile virus.[43]
Plasma-pheresis ⊗	Clearance of virus from blood or clearance of chemokines/cytokines in ARDS	Hypotension, fevers and chills, nausea and fatigue		Available in Canada	No known trials	Two case reports of use in ARDS in adults, one with pancreatitis[44] and one with Myasthenia Gravis.[45] One *in vitro* study of extracorporal MERS-CoV pseudovirus and glycoprotein elimination showed this can be successfully achieved by lectin affinity

						plasmapheresis. No *in vivo* trials.[46]
Other treatment modalities						
Agent	**Presumed mechanism of action**	**Known adverse effects**	**Dosing: Pediatric and Adult**	**Availa-bility**	**Evidence with COVID-19**	**Evidence with other viruses**
Chloroquine	Chloroquine is known to block virus infection by increasing endosomal pH required for virus/ cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[3]	Cardiovascular – rare cases of cardiomyopathy, QT prolongation and arrhythmias Extrapyramidal effects – usually resolve on stopping Hematologic – rare reversible agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia Hypoglycaemia Retinal toxicity Clinical consideration for renal dose adjustment with CrCL<10ml/min	Pediatric dosing: 20mg/kg/day divided BID Adult dosing recommended by Chinese studies: Chloroquine tab 500 mg BID x 10 days for patients with mild/mod/severe cases of novel coronavirus pneumonia, who don't have contra-indications Adult dosing recommended by Chinese studies: Chloroquine tab 500 mg BID x 10 days for patients with mild/mod/severe cases of novel coronavirus pneumonia, who don't have contra-indications Adult dosing recommended by WHO: 2.5g Chloroquine over 3 days	Chloroquine not currently available in Canada due to long-term backorder Stockpiles may be available	One in-vitro study published for COVID-19: inhibition of SARS-CoV-2 viral growth (qRTPCR detection) in Vero cells without significant cytotoxicity.[3] Letter by Gao *et al.* states 100 patients have demonstrated that Chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, and shortening disease – no results presenting to support this statement therefore hard to interpret.[47] Chloroquine or Hydroxychloroquine is recommended by many guidelines worldwide (see table below) on management of COVID-19 - use in mild cases at high risk or severe cases.	A detailed overview of all *in vitro* activity of Chloroquine against coronaviruses is summarised by Colson *et al.*[48] Biot *et al.* Studied inhibition of chloroquine derivatives against human SARS-CoV in Vero cells and found it showed inhibitory activity.[49] *In vivo:* lethal HCoV-OC43 infection in newborn C57BL/6 mice can be treated with Chloroquine acquired transplacentally or via maternal milk.[50] Chikungunya: Chloroquine effective in vitro, but failed to work in primate model, and actually increased viral levels (mechanism thought to be 2/2 complex immunomodulatory effect and delaying cellular and humoral response).[51]
Hydroxychloroquine sulfate	As for Chloroquine	Similar, but more tolerable safety profile compared to Chloroquine	Pediatric doses: 400mg PO twice daily x2 doses, then 200mg	Available in Canada	In a small study (n=26 treatment , n= 16 controls) of patients aged over 12 years with confirmed	Biot *et al.* Studied inhibition of ferroquine derivatives against human SARS-CoV in Vero cells and found all but

		Use with caution in renal or hepatic impairment (hepatic metabolism, up to 60% excretion in urine)	BID for an additional 4 days Considered generally safe in G6PD deficiency.[48] Adult Dose (rec from in vitro data): 400mg PO BID x1 day, followed by 200mg PO BID x4 days Adult Dose (per WHO in COVID19 trial): 400mg q24h x 5 days Note adult dosing in recent French trial used oral Hydroxychloroquine sulfate 200 mg three times per day for 10 days.[52] *do not crush (extemporaneous solution compounding if unable to take tablets)		COVID-19 (asymptomatic, URTI and LRTI patients) Hydroxychloroquine treatment was associated with faster viral load reduction compared to control.[52] However this is a small study and controls were patients with exclusion criteria or who refused treatment. Of note patients receiving both Hydroxychloroquine and azithromycin had more rapid viral clearance. RCT in China on 62 patients comparing HCQ to standard of care. Quicker clinical improvement in the HCQ group with less frequent progression to severe disease. Of note, no data reported on adjunctive treatments or other antivirals used in both groups.[53] Another RCT in China compared HCQ to standard of care in 30 patients. There was no difference noted in length of hospitalization, clinical recovery and radiological progression in both groups.[54] In vitro data in Vero Cells infected with SARS-CoV-2 suggests Hydroxychloroquine is	Hydroxychloroquine showed inhibitory activity.[49]

					effective at inhibiting SARS-CoV-2 infection COVID-19, inhibiting both entry and post-entry stages.[55,56] Proposed that the immunomodulatory effect of Hydroxychloroquine may be useful in controlling cytokine storm in late phase COVID-19. Chloroquine or Hydroxychloroquine is recommended by Italian guidelines on management of COVID-19 - use in mild cases at high risk or severe cases.	
Artesunate ⊗	Unknown. It is hypothesized that the cleavage of endoperoxide bridge in the pharmacophore of DHA generates reactive oxygen species (ROS), which increases oxidative stress and causes protein damage via alkylation.	Hypotension, Anxiety, ataxia, dizziness, headache, metallic taste, restlessness, slurred speech, skin rash, Hypoglycemia, Anorexia, diarrhea, nausea, vomiting, Anemia, hemolysis, neutropenia, reticulocytopenia, Increased serum ALT, Tremor, Increased blood urea nitrogen		Only available via SAP in Canada for Malaria	No evidence in COVID-19 yet. Ongoing clinical trial in China.	Some evidence in CMV, HSV 2 and Ebola[57]
Ivermectin ⊗	Believed to have antiviral activity through the inhibition of inhibition of the importin (IMP) α/β1 heterodimer responsible for	Dermatologic reactions, mild GI symptoms (Diarrhea, nausea), increase in hepatic enzymes in 2% of patients. Not recommended in		Available in Canada	Shown to have potent in-vitro inhibition of SARS-CoV-2 with reduction in viral RNA at 48h in Vero-hSLAM cells 2 hours post infection.[58]	Shown to have antiviral activity on other RNA viruses (Influenza, HIV, DENV) through the inhibition of importin α/β-mediated transport.[59,60]

	integrase protein nuclear import.	pregnant or breastfeeding women.				
Nitazoxanide ⊗	Inhibits replication of influenza viruses, RSV and canine coronavirus. Mechanism variable: blocks maturation of Influenza hemagglutinin at the post-translational stage, potentiates interferon responses.	Diarrhoea, nausea, headaches, dizziness, rash		Available in Canada as special access medication	One in-vitro study published for COVID-19: some inhibition of SARS-CoV-2 viral growth (qRTPCR detection) in Vero cells but less potent than Chloroquine and Remdesivir in the same study.[3]	Tizoxanide, the active circulating metabolite of nitazoxanide, inhibited replication of 16 strains of influenza A/H1N1, H3N2, H3N2v, H3N8, H5N9, H7N1, and one strain of influenza B as well as canine coronavirus *in vitro*.[61]

*** Note Dosing not provided where no dosing available, or where not currently recommended**

LPV/r: Lopinavir/ritonavir; HCQ: Hydroxychloroquine; CQ: Chloroquine; DRV/cobi: Darunavir/cobicistat; FPV: Favipiravir or famiravir; IFN: Interferon.

Disease category	Massachusetts General Hospital (US)	Belgium	Italy (Lombardia protocol)	France	Netherlands	Switzerland	Spain	Thailand	Japan
Mild-to-moderate disease No risk factors*	No antiviral treatment	No antiviral treatment. Paracetamol as first line, NSAIDS with caution.	No antiviral treatment	No antiviral treatment	No antiviral treatment	No antiviral treatment	No antiviral treatment	No antiviral treatment. Paracetamol as first line	No antiviral treatment (consider Ciclesonide)
Mild-to-moderate disease Risk group	For mild cases: supportive care with very close monitoring and consideration of application for clinical trial of Remdesivir. For moderate cases: obtain Remdesivir through clinical trial or compassionate use	Consider HCQ 400mg at diagnosis and 12 h later followed by 200 mg BID for up to 5 days if no contra-indication** If no HCQ available consider Chloroquine for up to 5 days.	LPV/r + Chloroquine or HCQ for 5-7 days	Consider LPV/r; duration depending on monitoring of viral excretion	Consider Chloroquine for 5 days	? (not mentioned)	Consider HCQ + LPV/r	Chloroquine + DRV/cobi	Consider LPV/r or Favipiravir +/- Ciclesonide
Severe disease	Obtain Remdesivir through clinical trial or compassionate use. Consider adding HCQ or Chloroquine for 5 days. Consider LPV/r for 10 days. If LPV/r is not available consider DRV/cobi.	Start HCQ if no contraindication** If no HCQ available, consider Chloroquine. Consider LPV/r as second choice if HCQ/Chloroquine contraindicated or in children <10 Kg	Remdesivir + Chloroquine or HCQ for 5-20 days (if no Remdesivir: maintain LPV/r with Chloroquine)	Remdesivir; duration depending on monitoring of viral excretion (No second choice)	Chloroquine D1 (600-300 mg; D2-D5 300 mg BID) LPV/r as second option (for 10-14 days)	LPV/r (atazanavir/ritonavir as second choice)	In patients with pneumonia or rapid progression: LPV/r + interferon beta-1-b	Chloroquine + DRV/cobi + Favipiravir	LPV/r or Favipiravir

Critical disease	As for severe disease + Consider interferon beta B1. Consider tocilizumab for patients with evidence of cytokine release syndrome (send IL-6 level prior to first dose).	Remdesivir (compassionate use) If Remdesivir unavailable consider HCQ: caution in cases of renal/liver/cardiac failure.	Remdesivir + Chloroquine or HCQ for 5-20 days (if no Remdesivir: maintain LPV/r with Chloroquine)	Remdesivir; duration depending on monitoring of viral excretion LPV/r as second choice (case by case)	Remdesivir (for 10 days) + Chloroquine (for 5 days)	Remdesivir as first choice (for 10 days) LPV/r (+ HCQ if < 65 years/no comorbidity) as second choice (if Remdesivir unavailable). Tocilizumab (in case of MOF and inotropic support)	HCQ + LPV/r + interferon beta 1b + use of Remdesivir. Consider use of Tocilizumab for critically ill patient in intensive care with elevated D-dimer and Il-6 levels		LPV/r or Favipiravir

Summary table of interim guidance for management of patients with suspected/confirmed COVID-19 by country – as of early March 2020 (Adapted from Belgium interim advice document)[62]

LPV/r: Lopinavir/ritonavir; HCQ: Hydroxychloroquine; DRV/cobi: Darunavir/cobicistat.

*****Risk factors: age >55-65 years, underlying end organ dysfunction (e.g. heart, lung, liver), diabetes, cardiovascular disease, chronic obstructive pulmonary disease, arterial hypertension, use of biologics, history or transplant or immunosuppression, all patients with HIV.

** contraindications for Hydroxychloroquine: QTc >500msec; drug interactions; myasthenia gravis; porphyria; retinal pathology; epilepsy. Pregnancy is not a contra-indication. Perform basic biochemistry daily and ECG daily if initial QTc > 45o msec. Avoid quinolones and macrolides if possible or monitor QTc closely if these are needed.

References

1. Warren, T. K. *et al.* Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* **531**, 381–385 (2016).

2. Wang, K., Zhou, F. & Dingyu, Z. Evaluation of the Efficacy and Safety of Intravenous Remdesivir in Adult Patients with Severe Pneumonia caused by COVID-19 virus Infection: study protocol for a Phase 3 Randomized, Double-blind, Placebo-controlled, Multicentre trial. *BMC trials* 1–30 (2020). doi:10.21203/RS.2.24058/V1

3. Wang, M. *et al.* Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2019–2021 (2020). doi:10.1038/s41422-020-0282-0

4. Sheahan, T. P. *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat. Commun.* **11**, (2020).

5. Sheahan, T. P. *et al.* Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci. Transl. Med.* **9**, (2017).

6. de Wit, E. *et al.* Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc. Natl. Acad. Sci.* 201922083 (2020). doi:10.1073/pnas.1922083117

7. Elfiky, A. A. Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): A molecular docking study. *Life Sci.* (2019). doi:10.1016/j.bbamem.2019.183135

8. Warren, T. K. *et al.* Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. *Nature* **508**, 402–405 (2014).

9. Stockman, L. J., Bellamy, R. & Garner, P. SARS: Systematic review of treatment effects. *PLoS Med.* **3**, 1525–1531 (2006).

10. Liu, Y., SUn, W., Li, J. & Chen, L. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. *PREPRINT* **681**, (2020).

11. Omrani, A. S. *et al.* Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: A retrospective cohort study. *Lancet Infect. Dis.* **14**, 1090–1095 (2014).

12. Dayer, M. R., Taleb-Gassabi, S. & Dayer, M. S. Lopinavir; a potent drug against coronavirus infection: Insight from molecular docking study. *Arch. Clin. Infect. Dis.* **12**, (2017).

13. Cao, B. *et al.* A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N. Engl. J. Med.* 1–13 (2020). doi:10.1056/NEJMoa2001282

14. Jin, Y. H. *et al.* A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil. Med. Res.* **7**, 1–23 (2020).

15. Lim, J. *et al.* Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. *J. Korean Med. Sci.* **35**, 1–6 (2020).

16. Young, B. E. *et al.* Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *Jama* 1–7 (2020). doi:10.1001/jama.2020.3204

17. Chan, J. F. W. *et al.* Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERSCoV infection in a nonhuman primate model of common marmoset. *J. Infect. Dis.* **212**, 1904–1913 (2015).

18. Park, S. Y. *et al.* Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. *J. Hosp. Infect.* **101**, 42–46 (2019).

19. Walther, E. & Hohlfeld, R. Multiple sclerosis. Side effect of interferon beta therapy and their management. *Neurology* **53**, (1999).

20. Barnard, D. L. *et al.* Evaluation of immunomodulators, interferons and known in vitro SARS-CoV inhibitors for inhibition of SARS-CoV replication in BALB/c mice. *Antivir. Chem. Chemother.* **17**, 275–284 (2006).

21. Arabi, Y. Treatment of Middle East respiratory syndrome with a combination of lopinavir-ritonavir and interferon-beta1b (MIRACLE trial): study protocol for a randomized controlled trial. *Trials* **81**, (2018).

22. Falzarano, D. *et al.* Interferon-α2b and ribavirin treatment improves outcome in MERS-CoV-infected rhesus macaques. *Nat. Med.* **19**, 1313–1317 (2014).

23. Kim, U. J., Won, E. J., Kee, S. J., Jung, S. I. & Jang, H. C. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-a for Middle East respiratory syndrome. *Antivir. Ther.* **21**, 455–459 (2016).

24. Cai, Q. *et al.* Experimental Treatment with Favipiravir for COVID-19 : An Open-Label Control. *Engineering* (2020). doi:10.1016/j.eng.2020.03.007

25. Chen, C. *et al.* Favipiravir versus Arbidol for COVID-19 : A Randomized Clinical Author affiliations : *Medrxiv Prepr.* (2020). doi:https://doi.org/10.1101/2020.03.17.20037432

26. Tan, E. L. C. *et al.* Inhibition of SARS Coronavirus Infection in Vitro with Clinically Approved Antiviral Drugs. *Emerg. Infect. Dis.* **10**, 581–586 (2004).

27. Boriskin, Y., Leneva, I., Pecheur, E. & SJ, P. Arbidol: A Broad-Spectrum Antiviral Compound that Blocks Viral Fusion. *Curr. Med. Chem.* **15**, (2008).

28. Khamitov, R. *et al.* Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures. *Vopr. Virusol.* **53**, 9–13 (2008).

29. Nishimoto, N. & Mima, T. Tocilizumab. in *Rheumatoid Arthritis* 367–371 (2009).

30. National Health Commission & State Administration of Traditional Chinese Medicine. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia. **Version 7**, (2020).

31. Swaroopa, D. *et al.* Association of serum interleukin-6, interleukin-8, and Acute Physiology and Chronic Health Evaluation II score with clinical outcome in patients with acute respiratory distress syndrome. *Indian J. Crit. Care Med.* **20**, 518–525 (2016).

32. Percopo, C. M. *et al.* Critical Adverse Impact of IL-6 in Acute Pneumovirus Infection. *J. Immunol.* **202**, 871–882 (2019).

33. World Health Organization. Novel Coronavirus (2019-nCoV) technical guidance: Patient management. https://www-who-int.myaccess.library.utoronto.ca/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management.

34. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) Infection, Updated February 12, 2020. https://www-cdc-gov.myaccess.library.utoronto.ca/coronavirus/2019-ncov.

35. Matsuyama, S. *et al.* The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15. *bioRxiv - Prepr. Artic.* 2020.03.11.987016 (2020). doi:10.1101/2020.03.11.987016

36. Shakoory, B. *et al.* Interleukin-1 Receptor Blockade Is Associated with Reduced Mortality in Sepsis Patients with Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial∗. *Crit. Care Med.* **44**, 275–281 (2016).

37. Klein, K. U. *et al.* Recent advances in understanding acute respiratory distress syndrome. *F1000Research* **7**, 1–11 (2018).

38. Benamu, E. & Montoya, J. G. Infections associated with the use of eculizumab: Recommendations for prevention and prophylaxis. *Curr. Opin. Infect. Dis.* **29**, 319–329 (2016).

39. Shen, Ch. *et al.* Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA - J. Am. Med. Assoc.* 1–8 (2020). doi:10.1001/jama.2020.4783

40. Mair-Jenkins, J. *et al.* The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: A systematic review and exploratory meta-analysis. *J. Infect. Dis.* **211**, 80–90 (2015).

41. Tian, X. *et al.* Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg. Microbes Infect.* **9**, 382–385 (2020).

42. Goo, J. *et al.* Characterization of novel monoclonal antibodies against MERS-coronavirus spike protein. *Virus Res.* **278**, (2020).

43. Pelegrin, M., Naranjo-Gomez, M. & Piechaczyk, M. Antiviral Monoclonal Antibodies: Can They Be More Than Simple Neutralizing Agents? *Trends Microbiol.* **23**, 653–665 (2015).

44. Kohli, R. S., Bleibel, W., Shetty, A. & Dhanjal, U. Plasmapheresis in the treatment of hypertriglyceridemic pancreatitis with ARDS. *Dig. Dis. Sci.* **51**, 2287–2291 (2006).

45. Yamakova, Y., Ilieva, V., Petkov, R. & Yankov, G. Nanomembrane-Based Therapeutic Plasmapheresis after Non-Invasive Ventilation Failure for Treatment of a Patient with Acute Respiratory Distress Syndrome and Myasthenia Gravis: A Case Report. *Blood Purif* **48**, 382384 (2019).

46. Koch, B. *et al.* Lectin affinity plasmapheresis for Middle East respiratory syndrome-coronavirus and marburg virus glycoprotein elimination. *Blood Purif.* **46**, 126–133 (2018).

47. Gao, J., Tian, Z. & Yang, X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci. Trends* 1–2 (2020). doi:10.5582/bst.2020.01047

48. 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* 105932 (2020). doi:10.1016/j.ijantimicag.2020.105932

49. Biot, C. *et al.* Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J. Med. Chem.* **49**, 2845–2849 (2006).

50. Keyaerts, E. *et al.* Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. *Antimicrob. Agents Chemother.* **53**, 3416–3421 (2009).

51. Roques, P. *et al.* Paradoxical effect of chloroquine treatment in enhancing chikungunya virus infection. *Viruses* **10**, 268 (2018).

52. Gautret, P. *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open- label non-randomized clinical trial. *Int. J. Antimicrob. Agents* **In press**, (2020).

53. Chen, Z. *et al.* Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *Medrxiv Prepr.* (2020). doi:https://doi.org/10.1101/2020.03.22.20040758 .

54. Chen, J. *et al.* A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). [Article in Chinese]. *J. Zhejiang Univ.* (2020). doi:DOI : 10.3785/j.issn.1008-9292.2020.03.03

55. Liu, J. *et al.* Hydroxychloroquine , a less toxic derivative of chloroquine , is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov.* 6–9 (2020). doi:10.1038/s41421-020-0156-0

56. Yao, X. *et al.* In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Main point : Hydroxychloroquine was found to be more potent than chloroquine at inhibiting SARS-CoV-2 in vit. *Clin. Infect. Dis.* (2020). doi:https://doi.org/10.1093/cid/ciaa237

57. Raffetin, A. *et al.* Use of artesunate in non-malarial indications. *Med Mal Infect* **48**, 238–249 (2018).

58. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A. & Wagstaff, K. M. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 104787 (2020). doi:10.1016/j.antiviral.2020.104787

59. Götz, V. *et al.* Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Sci. Rep.* **6**, 1–15 (2016).

60. Wagstaff, K. M., Sivakumaran, H., Heaton, S. M., Harrich, D. & Jans, D. A. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem. J.* **443**, 851–856 (2012).

61. Rossignol, J. F. Nitazoxanide: A first-in-class broad-spectrum antiviral agent. *Antiviral Res.* **110**, 94–103 (2014).

62. Ierssel, S. Van, Dauby, N. & Bottieau, E. Interim Clinical Guidance for Patients Suspected of/Confirmed with COVID-19 in Belgium. (2020). Available at: https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf. (Accessed: 20th March 2020)