Clinical Update

COVID-19 Antiviral Therapy

Last updated: June 25, 2020

Recommended Medication Management Overview

	COVID-19 Disease Severity			
	Mild	Moderate	Severe	Critical
Definition	No evidence of pneumonia or hypoxia	Pneumonia but NOT requiring supplemental O_2, SpO_2 > 94% on RA	Pneumonia requiring supplemental O_2 or $SpO_2 \leq 94\%$ on RA	Pneumonia requiring mechanical ventilation or presence of septic shock or other organ failure requiring ICU level care
Antivirals for COVID-19	Not indicated. Emergency use remdesivir cannot be given for non-severe disease per current FDA authorization.		Remdesivir x 5 days recommended if supply available and no contraindications present.	Remdesivir x 5 days (or up to 10 days in mechanically ventilated Pts.) may be given if supply available and no contraindications present. A large multicenter RCT did not find benefit compared to placebo in patients who were mechanically ventilated at baseline.
Co-infection	Empiric antibiotics NOT routinely recommended.	Consider empiric antibiotics targeting common pathogens (e.g. ceftriaxone + azithromycin for CAP) if suspicion for superimposed bacterial pneumonia. Need for continuing antibiotics should be re-assessed daily. Discontinuation recommended if cultures do not indicate presence of bacterial co-infection. Treatment duration should NOT routinely exceed 5 days. Use of immunomodulators (e.g. tocilizumab) may predispose patients to more infections with opportunistic pathogens.		
Immuno-modulation	Corticosteroids/other immunomodulation NOT recommended unless separate indication exists.		Low-dose corticosteroids* for up to 10 days recommended. NOTE: current evidence indicates that patients early in the course of disease (≤ 7 days from symptom onset) may not benefit. In patients with evidence of cytokine storm, insufficient evidence to recommend for or against immunomodulation with an IL-6 antagonist (e.g. tocilizumab) or other agents. See full section for further details.	
Anti-thrombotic therapy	No indication in ambulatory patients	Standard VTE prophylaxis recommended as per standard of care for other hospitalized adults. Patients should be monitored for thromboembolism and therapeutic anticoagulation initiated if known thromboembolic event occurs or is highly suspected when imaging is not possible.		
Chronic medications	No indication to stop/modify/initiate ongoing therapy with statins, ACE inhibitors/ARBs, or NSAIDs due to COVID-19 alone.			

***Corticosteroid dosing** (all doses shown are approximate equivalent doses to dexamethasone 6mg once daily, which was used for 10 day duration in RECOVERY trial)**:** Dexamethasone: 6 mg IV/PO once daily; Prednisone: 40 mg PO once daily; Methylprednisolone: 30-40 mg IV/PO once daily; Hydrocortisone: 80 mg IV BID x 10 days

NOTE: Unless an appropriate concomitant indication exists (e.g. refractory shock, severe ARDS, etc.), **we do NOT recommend doses higher or durations longer than those described.** Due to potential negative effects of steroids on control of viral replication and other general adverse effects, we do not recommend exceeding doses or durations found to be safe and effective. In addition, a possible interaction exists by which dexamethasone may reduce exposure to remdesivir via dose-dependent induction of CYP3A4. This is not expected to be clinically meaningful if low doses of dexamethasone are used.

Changes from Last Release

- Medication management outline added to first page.
- Results of large multicenter RCT (RECOVERY trial) indicate mortality benefit with low-dose corticosteroids in COVID-19 patients requiring mechanical ventilation or supplementary oxygen.
- Evidence summaries reorganized into antivirals and immunomodulators. Section added on corticosteroids.
- Additional evidence published:
    - Remdesivir – RCT in moderate COVID-19 showed reduction in time to clinical improvement. No benefit of 10 day duration over 5 day duration.
    - HCQ – Large multicenter RCT did not indicate clinical benefit, HCQ increased adverse events compared to placebo. Separate RCT for post-exposure prophylaxis did not show efficacy in preventing disease. FDA has revoked previous emergency use authorization for HCQ to treat COVID-19.
    - Convalescent plasma – Pilot RCT published. Did not show benefit but was underpowered.
    - Colchicine – small study published, new section added to document. Insufficient evidence to support routine use.

Evidence Summary for Specific Investigational Treatments

The table below provides a general risk/benefit assessment for specific agents based on currently available evidence. Click on drug name to go to full section for that drug.

The following professional organizations have also published guidelines addressing use of these agents: NIH, IDSA, and WHO. This document will be updated on an ongoing basis and recommendations may change.

Benefit is likely to outweigh risk			
Remdesivir – Benefit likely to outweigh risk for hospitalized COVID-19 patients with $SpO_2 \leq 94\%$ or requiring supplemental oxygen if no exclusion criteria are met. Insufficient evidence to assess in hospitalized patients not needing supplemental oxygen or ambulatory patients.			
Low-dose corticosteroids – Benefit likely to outweigh risk for patients **requiring mechanical ventilation or supplemental oxygen**. Benefit unlikely to outweigh risk if oxygen supplementation is not required.			
Benefit may or may not outweigh risk			
Tocilizumab (or other IL-6 blockers) – Risk/benefit is unknown, no comparative evidence is available.			
Convalescent plasma – NOT AVAILABLE AT ADVENTIST HEALTH. Efficacy not yet demonstrated for treatment of any infectious disease including COVID-19. Risk/benefit is unknown.			
Colchicine – Insufficient evidence to recommend routine use.			
Benefit is unlikely to outweigh risk			
Hydroxychloroquine or chloroquine	HIV protease inhibitors (e.g. lopinavir/ritonavir)	Ivermectin	Tetracyclines
Azithromycin	Interferon + ribavirin	Nitazoxanide	Famotidine

For full sections on each agent in the remainder of the document, individual studies referenced have been assigned a quality of evidence grade based on both methodology (randomized vs. observational) and standardized risk of bias tools. Full description of methodology and scoring for each study is available on SPTC SharePoint page.

Antivirals / Drugs that Inhibit SARS-CoV-2 Replication

Remdesivir

Benefit is likely to outweigh risk
If available, remdesivir is recommended for patients meeting the criteria in the FDA Emergency Use Authorization. If supply is insufficient to treat all patients meeting these criteria, we recommend developing a fair process for allocating remdesivir guided by clinical data on subgroups of patients that are most likely to benefit (see below)**.** Overall assessment of evidence to date: • Remdesivir shortened time to clinical improvement in a large multicenter NIH trial (ACTT-1). A separate randomized trial in China did not replicate this finding, however it was underpowered. • No clear evidence to date that remdesivir significantly reduces mortality or duration of viral shedding. • In mechanically ventilated patients, remdesivir did not improve any outcomes compared to placebo. This may be considered when determining patient allocation of remdesivir if supply is insufficient to treat all patients. • Number of days since symptom onset did not affect likelihood of benefiting from remdesivir in ACTT-1. We do NOT recommend this to be used as a factor when determining patient allocation of remdesivir. • 5 day courses of remdesivir were equally efficacious to 10 day courses in hospitalized patients with severe disease in a multicenter randomized trial. Mechanically ventilated patients were excluded, leading the FDA EUA to recommend a 10 day course for these patients. Given ACTT-1 results indicate 10 days of remdesivir is not superior to placebo in mechanically ventilated patients, it is reasonable to use 5 day durations in all patients if supply is limited.

FDA Emergency Use Authorization (April 30, 2020) This is NOT equivalent to a full FDA approval and is based on preliminary evidence. See this link for FAQ on FDA EUA process.	
Availability/ Acquisition	Contact your state public health department for details. In state of California, contact county MHOAC. Gilead is no longer accepting applications for expanded use. Individual compassionate use requests may still be made for **pregnant or pediatric** patients: https://rdvcu.gilead.com/
Required Criteria for Use (ALL must be fulfilled)	• Hospitalized patient with suspected or confirmed COVID-19 • Severe disease: $SpO_2 \leq 94\%$ on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO • FDA-approved fact sheet must be given to patient prior to administration of remdesivir • Baseline SCr and LFTs available. ALT must be < 5x ULN to initiate remdesivir. LFTs must be monitored daily while on therapy. See adverse events section. • Prescribing provider or designee must report any medication errors or severe adverse events to the FDA within 7 days of the event: http://www.fda.gov/medwatch/report.htm
Dosing	• Adults: 200 mg IV once on day 1 followed by 100 mg IV daily on days 2-5 (5 days total) • Pediatrics < 40 kg: 5 mg/kg IV once on day 1 followed by 2.5 mg/kg IV daily on days 2-5 (5 days total)

Adverse Effects	• Infusion-related reactions including nausea, vomiting, diaphoresis, and/or shivering
	• Transaminase elevations
	  o Do not initiate if ALT ≥ 5x upper limit of normal (ULN). Discontinue if ALT ≥ 5x ULN during therapy. May be reinitiated once ALT below 5x ULN
	  o Discontinue if patient experiences ALT elevations of any degree with signs/symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR
	• Remdesivir is formulated with cyclodextrin which accumulates in patients with renal dysfunction. Use with caution in patients with CrCl < 30 mL/min. Experience with other drugs containing cyclodextrin suggests this theoretical concern may not be clinically significant.

Mechanism	Adenosine nucleotide analog prodrug – inhibits viral replication
Drug-Drug Interactions	University of Liverpool COVID-19 interaction checker is recommended to assess DDIs for all patients. Remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4 and inhibits CYP3A4 in vitro.

Remdesivir Evidence Review

COVID-19 Randomized Controlled Trials

Study	Risk of Bias	n	Disease Severity	Symptom Duration	Treatment
Wang Y. *Lancet* 2020	Low risk	237	Hospitalized, severe or critical ($SpO_2 \leq 94\%$ or requiring supplemental O_2)	12 days or less Median: 10 days IQR: 9-12 days	Remdesivir* x 10 days vs. Placebo
NIAID ACTT-1 *NEJM* 2020	Some concerns	1,059	Hospitalized, any severity (88.7% severe, 25.6% mechanically ventilated)	Median: 9 days IQR: 6-12 days	Remdesivir* x 10 days vs. Placebo
Goldman J. *NEJM* 2020	Low risk	397	Hospitalized, severe but not ventilated ($SpO_2 \leq 94\%$ or requiring supplemental O_2)	Information not available	Remdesivir* x 5 days vs. Remdesivir* x 10 days
SIMPLE-2 Trial	Cannot assess, full data not yet published	584	Hospitalized moderate COVID-19 (not requiring supplemental O_2)	Information not available	Remdesivir* x 5 days vs. Remdesivir* x 10 days vs. Standard of care

*Dosing of remdesivir for all studies was 200mg IV x 1 on day 1 followed by 100mg IV once daily starting day 2

Remdesivir vs. Placebo

	Remdesivir	Placebo	Difference (95% CI)	p-value
Time to clinical improvement*, days			Hazard Ratio for improvement	
Wang	21	23	1.23 (0.87 to 1.75)	0.24
ACTT-1	11	15	1.31 (1.12 to 1.54)	<0.001
Odds of clinical improvement*				
Wang (day 28)	65%	58%	Diff: 7.5% (-5.7 to 20.7)	not sig.
ACTT-1 (day 15)			OR: 1.5 (1.18 to 1.91)	0.001
Mortality				
Wang (day 28)	14%	13%	Diff: 1.1% (-8.1 to 10.3)	not sig.
ACTT-1 (day 14)	7.1%	11.9%	HR: 0.7 (0.47 to 1.04)	0.059
PCR negative conversion			Absolute difference	
Wang (day 7)	50%	49%	1.2% (-14% to 16%)	not sig.
Discontinuation due to adverse events				
Wang	12%	5%	Statistical analysis not performed	
ACTT-1	7.2%	7.1%	Statistical analysis not performed	

*Clinical improvement based on ordinal scale, 1=discharged or meeting criteria for discharge, 2=hospitalized without supplemental O_2, 3=hospitalized with supplemental O_2, 4=HFNC or NIV, 5=invasive mechanical ventilation, 6=dead
Wang: improvement defined as 2-point improvement on scale or discharged, whichever occurs first
ACTT-1: improvement defined as meeting category #1 regardless of baseline severity

Remdesivir 5 Days vs. 10 Days

Outcome	5 Days	10 Days	Standard of Care	Baseline Adjusted Difference (95% CI)
Median days to clinical improvement				
SIMPLE-1 (severe disease)	10	11	N/A	0.79 (0.61 to 1.01)
Odds of clinical improvement				
SIMPLE-1 (severe disease)	64%	54%	N/A	-6.5% (-15.7 to 2.8)
SIMPLE-2 (moderate disease)	70%	65%	61%	p=0.026 vs. SOC for 5d, not sig. for 10d
Death				
SIMPLE-1 (severe disease)	8%	11%	N/A	Not reported, p=0.14
SIMPLE-2 (moderate disease)	0%	1%	2%	Difference not sig. for either 5 or 10d
Discontinuation due to adverse events				
SIMPLE-1 (severe disease)	4%	10%	N/A	4.8% (-0.5 to 10.1)

Hydroxychloroquine (HCQ) / Chloroquine (CQ)

Benefit is unlikely to outweigh risk

The Subcommittee recommends AGAINST use of hydroxychloroquine or chloroquine, with or without azithromycin, for treatment of COVID-19 outside of a clinical trial setting.

Preliminary results from a large multicenter RCT in the U.K. comparing HCQ to usual care in the treatment of COVID-19 in hospitalized patients found no benefit. Multiple observational studies also suggest no benefit, and many indicate a substantial number of patients suffer adverse events from HCQ.

A multinational placebo-controlled RCT found HCQ was not effective in preventing COVID-19 after high- or medium-risk exposure.

Mechanism of Action: May potentially inhibit viral entry into cells through several proposed mechanisms, including interference with terminal glycosylation of ACE-2 receptors, increasing pH of endosomes, and binding to sialic acids and gangliosides on host cells. Also has immunomodulating effects.

Evidence Summary: COVID-19 Clinical Outcomes

Study	Evidence Quality	Patients	Comparison	Findings	
				Efficacy	Safety
RECOVERY Trial RCT, multicenter, U.K. (n=4,674)	Unable to assess, not yet published in full	Treatment: Hospitalized COVID-19 Pts.	HCQ x 10 days (800mg q6h x 2 doses, then 400mg q12h x 9 days) vs. Usual care	No significant difference in 28-day mortality (25.7% HCQ vs. 23.5% usual care, HR 1.11, 95% CI 0.98-1.26, p=0.1)	Data not available, not yet published in full
Boulware D RCT, multinational, US. and Canada (n=821)	Moderate Some concerns	**Post-exposure prophylaxis** after high or medium risk 10+ min exposure to confirmed case	HCQ x 5 days (1400mg day 1 + 600mg daily) vs. Placebo x 5 days Started within 4 days of exposure	No benefit of HCQ over placebo in preventing confirmed/probable COVID-19 (11.8% vs. 14.3%, p=0.35) or lab-confirmed COVID-19 (2.7% vs. 2.2%, p=0.82)	HCQ increased adverse events compared to placebo (40.1% vs. 16.8% p<0.001)
Tang W RCT, multicenter, China (n=150)	Moderate Some concerns	Treatment: Hospitalized COVID-19 Pts.	HCQ 1,200mg/day x 3 days followed by 800mg/day for total duration 2-3 weeks vs. Standard of care alone	No difference in duration of viral shedding or time to symptom resolution.	Significantly more HCQ Pts. than controls experienced adverse events, 30% vs. 8.8% (p=0.001).
Rosenberg E Observational, multicenter, U.S., 25 centers in NY state (n=1,438)	Low Moderate risk of bias	Treatment: Hospitalized COVID-19 Pts. (overall mortality 20%)	HCQ + AZ vs. HCQ alone vs. AZ alone vs. Neither drug	No difference in mortality between any group after adjusting for confounders.	HCQ +/- AZ associated with ~2-fold increase in cardiac arrest vs. AZ alone or neither drug.

HCQ/CQ Evidence Summary: COVID-19 Clinical Outcomes (continued)

Study	Evidence Quality	Patients	Comparison	Findings	
				Efficacy	Safety
Geleris J Observational, single center, U.S. (n=1,376)	Low Moderate risk of bias	Treatment: Hospitalized but not intubated COVID-19 Pts.	HCQ 600mg BID x 2 then 400mg daily (median 5 days) +/- AZ vs. No HCQ	No difference in composite of intubation or death (HR 1.04, 95% CI 0.82 – 1.32) after accounting for confounding variables.	Not assessed.
Sing S Observational, multicenter, U.S. (n=1,800) *Not peer reviewed	Low Moderate risk of bias	Treatment: Hospitalized COVID-19, any severity	HCQ vs. No HCQ (Pts. receiving any other anti-SARS-CoV-2 Tx excluded)	After propensity score matching, no benefit of HCQ on 30 day mortality (11.4% vs. 12%, p=0.72) or need for mechanical ventilation (5% vs. 6%, p=0.81)	No difference in incidence of VTach, VFib, or sudden cardiac death. Other markers like ECG findings not assessed.
Chen J RCT, single center, China (n=30)	Low High risk of bias	Treatment: Non-severe COVID-19	HCQ 400mg/day x 5 days vs. Standard of care alone	No difference in PCR negative conversion on day 7, duration of viral shedding, time to fever resolution, or long term radiological improvement.	No difference in reported adverse effects.
Borba M RCT, single center, Brazil (n=81)	Low High risk of bias	Treatment: Hospitalized severe COVID-19 Pts.	CQ 600mg BID x 10 days (high dose arm) vs. CQ 450mg BID x 2, then daily x 4 days (low dose arm)	N/A – no control group and study terminated early due to safety concerns, no efficacy analysis.	Increased mortality in high dose arm (39% vs. 15%, p=0.03). Increased incidence of QTc > 500 in high dose (18.9% vs. 11.1%)

The following studies were reviewed and excluded due to being anecdotal in nature: Gautret P, Molina J, Million M

The following studies were reviewed and excluded due to lack of peer review PLUS bias concerns: Huang M, Mallat J, Magagnoli J, Chen Z, Kim M, Mahevas M

Evidence Summary: In-Vitro/Animal Studies

Study	Findings	EC_{50}
Yao X et al. *Clin Infect Dis* 2020	Inhibition of SARS-CoV-2 replication by HCQ and CQ in Vero cells.	HCQ: 0.72 µM CQ: 5.47 µM
Wang M et al. *Cell Research* 2020	Inhibition of SARS-CoV-2 replication by CQ in Vero cells.	1.13 µM

Lopinavir/ritonavir and other HIV protease inhibitors

Benefit is unlikely to outweigh risk
The Subcommittee recommends **AGAINST** use. Randomized trial demonstrated no clinical benefit in severe COVID-19.
NIH guidelines: "the panel recommends **AGAINST** use outside of the context of a clinical trial (AI for lopinavir/ritonavir, AIII for other protease inhibitors)"
IDSA guidelines: "use recommended **ONLY** in the context of a formal clinical trial"

Mechanism of Action: Inhibits viral replication – HIV-1 protease inhibitor

Evidence Summary: COVID-19 Clinical Outcomes

Study	Evidence Quality	Patients	Comparison	Findings	
				Efficacy	Safety
LOTUS China Trial. *NEJM* 2020 RCT, single center, China (n=199)	Moderate Some concerns	Hospitalized severe COVID-19 Pts. w/ PNA on imaging	LPV/r 400/100mg PO BID x 14 days vs. Standard of care alone	No difference in time to symptom resolution, time to PCR negative conversion, or mortality	14% of LPV/r Pts. discontinued treatment due to adverse effects
Zhou F Case series, multicenter, China (n=191)	Anecdotal	Hospitalized COVID-19 Pts.	Factors associated with mortality assessed. Antiviral use (LPV/r) included in analysis.	LPV/r use not associated with mortality or duration of viral shedding.	Not designed to assess.
Young BE Case series, Singapore (n=18)	Anecdotal	Hospitalized COVID-19 Pts.	Pts. receiving LPV/r compared to Pts. who did not	No reduction in viral shedding seen with LPV/r	4/5 Pts. treated with LPV/r developed N/V/D, 3/5 developed abnormal LFTs

Evidence Summary: In-Vitro/Animal Studies

Study	Drug	Findings	EC_{50}
Choy K. *Antiviral Res* 2020	Lopinavir/ritonavir	Inhibition of SARS-CoV- in Vero cells at relatively high concentrations.	26.63 µM
Meyer S. Preprint	Darunavir/cobicistat	Failure to inhibit SARS-CoV-2 in Vero cells at clinically achievable concentrations.	>100 µM
Yamamoto M. Preprint	Nelfinavir	Inhibition of SARS-CoV- in Vero cells.	1.13 µM

Interferon + Ribavirin

Benefit is unlikely to outweigh risk
In a single small phase 2 trial, combination therapy was associated with decreased time to negative PCR conversion in patients with mild disease, however toxicity is substantial and risk-benefit tradeoff is therefore not favorable in mild disease. Interferons have pro-inflammatory effects which may be deleterious to patients with more severe or later stages of COVID-19. Interferon has not been studied in these patients and therefore cannot be recommended at this time. Monotherapy with either of these agents is not expected to be beneficial based on existing data.

Mechanism of Action: Ribavirin: inhibits viral replication – nucleoside analog.
IFN: immunomodulating cytokine with several general antiviral effects

Evidence Summary: COVID-19 Clinical Outcomes

Study	Evidence Quality	Patients	Comparison	Findings	
				Efficacy	Safety
Hung I RCT, single center, China (n=127)	Moderate Some concerns	Non-severe COVID-19 Pts.	Combination therapy* vs. LPV/r 400/100mg PO BID x 14 days *Combination therapy = LPV/r 400/100mg PO BID x 14 days + Ribavirin 400mg PO BID x 14 days + Interferon beta-1b 8 million international units every other day x 0-3 doses based on time from symptom onset (if ≥7 days only LPV/r and ribavirin given, no IFN)	0 deaths in either group. Combination therapy associated with shorter time to negative PCR (7 days vs. 12 days, p=0.001)	Significant difference in ADRs not noted although not systematically monitored and Pts. had very few comorbidities.

Evidence Summary: In-Vitro/Animal Studies

Study	Drug	Findings	EC_{50}
Choy K. *Antiviral Res* 2020	Ribavirin	Failed to inhibit SARS-CoV-2 in Vero cells at achievable concentrations.	>500 µM
Wang M. *Cell Research* 2020	Ribavirin	Inhibition of SARS-CoV-2 in Vero cells required toxic concentrations.	109.5 µM

Nitazoxanide

Benefit is unlikely to outweigh risk
No clinical data available to support use for COVID-19. In vitro activity against COVID-19 (this does not imply clinical benefit).

Mechanism of Action: mechanism of antiviral activity unclear but proposed to be via immunomodulatory effects

Evidence Summary: COVID-19 Clinical Outcomes

No data.

Evidence Summary: In-Vitro/Animal Studies

Study	Findings	EC_{50}
Wang M et al. *Cell Research* 2020	Inhibition of SARS-CoV-2 by nitazoxanide in Vero cells.	2.12 µM

Azithromycin

Benefit is unlikely to outweigh risk
The Subcommittee recommends AGAINST use for treatment of COVID-19. We also recommend AGAINST use for superimposed bacterial PNA in any patient receiving HCQ/CQ – doxycycline is recommended instead for atypical coverage if clinically indicated. No clinical or in vitro data available to support use for COVID-19 or any other coronavirus. Growing evidence of harm when added to HCQ/CQ due to additive cardiotoxicity. Both the NIH and IDSA recommend against use outside of clinical trial settings.

Mechanism of Action: No proven inhibitory mechanism for coronaviruses. Some immunomodulating effects.

Evidence Summary: COVID-19 Clinical Outcomes

Study	Evidence Quality	Patients	Comparison	Findings	
				Efficacy	Safety
Rosenberg E Observational, multicenter, U.S., 25 centers in NY state (n=1,438)	Low Moderate risk of bias	Hospitalized COVID-19 Pts. (overall mortality 20%)	Groups analyzed: HCQ + AZ HCQ alone AZ alone Neither drug	No difference in mortality after adjusting for confounders.	HCQ + AZ associated with ~2-fold increase in cardiac arrest vs. AZ alone or neither drug.

The following studies were reviewed and excluded due to being anecdotal in nature: Gautret P, Molina J, Chorin E, Ramireddy A, Mercuro N

The following studies were reviewed and excluded due to lack of peer review PLUS bias concerns: Lane J

Evidence Summary: In-Vitro/Animal Studies

No data suggesting inhibition of SARS-CoV-2 or any other coronavirus.

Tetracyclines

Benefit is unlikely to outweigh risk
No clinical or in vitro data available to support use for COVID-19. May be used for superimposed bacterial pneumonia.

Mechanism of Action: Theoretical mechanism of activity has been described involving zinc chelation inhibiting viral replication, however no in vitro or clinical data currently exist to support use to treat COVID-19.

Evidence Summary:

No data suggesting clinical benefit or in-vitro inhibition of SARS-CoV-2 or any other coronavirus.

Ivermectin

Benefit is unlikely to outweigh risk
No clinical data available to support use for COVID-19. In vitro data show inhibition of SARS-CoV-2 but at concentrations that are unlikely to be achievable in humans.

Mechanism of Action: Inhibition of nuclear transport of viral proteins via IMP α/β1

Evidence Summary: COVID-19 Clinical Outcomes

No data.

Evidence Summary: In-Vitro/Animal Studies

Study	Findings	IC_{50}
Caly L et al. *Antiviral Res* 2020	Inhibition of SARS-CoV-2 by ivermectin in Vero cells, however at concentrations ~15-23x higher than achievable peak concentrations in humans. Smit M et al. documented median peak concentration of ivermectin in humans of 105-119 ng/mL using high-dose 600mcg/kg/day regimen. This converts to 0.12 – 0.14 µM (molecular mass of ivermectin = 875.1 g/mol). IC_{50} of ivermectin vs. SARS-CoV-2 is 2.2 – 2.8 µM	2.2 – 2.8 µM

Famotidine

Benefit is unlikely to outweigh risk
No clinical or in vitro data available to support use for COVID-19. A study was prompted by unpublished anecdotal reports and is currently ongoing. No results are available.

Mechanism of Action: May bind to proteases based on digital molecular modeling however no actual antiviral mechanism has been confirmed to date.

Evidence Summary:

No data suggesting clinical benefit or in-vitro inhibition of SARS-CoV-2 or any other virus.

Immunomodulatory Agents

Corticosteroids

Benefit is likely to outweigh risk (situational)

Results from a large multicenter RCT (RECOVERY Trial) indicate a mortality benefit with dexamethasone 6mg IV/PO once daily x 10 days in COVID-19 patients **requiring supplemental oxygen or mechanical ventilation.**

No benefit and a possible trend towards harm was seen in patients not requiring supplemental oxygen at baseline.

Other notable information from the RECOVERY results:

- **Timing relative to disease onset:** No benefit was seen in patients ≤ 7 days from symptom onset. Steroids may negatively impact immune response if used early in course of disease during periods of rapid viral replication. Literature in other viral respiratory infections (e.g. influenza) indicate steroids prolong duration of viral shedding and may have other negative effects.
- **Steroid selection:** Dexamethasone was used in RECOVERY due to minimal mineralocorticoid effects and therefore theoretically less fluid balance disturbance, however any corticosteroid used at an equivalent anti-inflammatory dose is expected to have similar efficacy.
- **Steroid dosing** (approximate equivalent anti-inflammatory doses to dexamethasone 6mg once daily):
  NOTE: Unless an appropriate concomitant indication exists (e.g. refractory shock, severe ARDS, etc.), **we do NOT recommend doses higher than those described below** for management of severe COVID-19. Due to potential negative effects of steroids on control of viral replication and other general adverse effects, we do not recommend exceeding doses or durations found to be safe and effective. In addition, a possible interaction exists by which dexamethasone may reduce exposure to remdesivir via dose-dependent induction of CYP3A4. This is not expected to be clinically meaningful if low doses of dexamethasone are used.
  - Dexamethasone: 6 mg IV/PO once daily for up to 10 days
  - Prednisone: 40 mg PO once daily for up to 10 days
  - Methylprednisolone: 30-40 mg IV/PO once daily for up to 10 days (exact equivalent dose = 32 mg)
  - Hydrocortisone: 80 mg IV BID for up to 10 days
  - NOTE: this dosing is for management of severe COVID-19. Unless an If concomitant indications for corticosteroid use are present, dosing may be modified as appropriate.
- **Duration:** in RECOVERY, steroids were continued for up to 10 days or hospital discharge, whichever occurred first.

Evidence Summary: COVID-19 Clinical Outcomes

Study	Evidence Quality	Patients	Comparison	Findings
RECOVERY Trial RCT, multicenter, U.K. (n=6,425) *Not peer reviewed	Moderate Some concerns	Hospitalized COVID-19 patients	Dexamethasone 6 mg IV/PO once daily x 10 days vs. Usual care	Reduced mortality in dexamethasone arm in Pts. requiring mechanical ventilation or supplemental O_2. Ventilated: HR 0.65, 95% CI 0.48 to 0.88, p=0.0003 Supplemental O_2: HR 0.8, 95% CI 0.67 to 0.96, p=0.002 No benefit in Pts. not requiring supplemental O_2 (HR 1.22, 95% CI 0.86 to 1.75, p=0.14) Adverse events not reported.
Li H Systematic review + meta-analysis	Most studies graded high risk of bias	Patients with coronavirus infections (incl. SARS, MERS, COVID-19)	Corticosteroids vs. No corticosteroids	3 studies specific to COVID-19, all observational and with major limitations: 1 found significant increase in mortality, 2 found possible (nonsignificant) trend towards reduction in mortality.

IL-6 Antagonists (e.g. tocilizumab)

Adventist Health Requirements for Use:

- Facility must have signed memorandum of understanding in place with Glendale IRB.
- Glendale IRB informed consent document should be completed prior to ordering, accessible via this link. Completed consent documents should be submitted to JoyceTL@ah.org within 5 days after drug administration.
- Infectious diseases consultation required and patient must meet ALL of the following:
  - Hospitalized with positive SARS-CoV-2 PCR and radiological evidence of pneumonia
  - Oxygen saturation at rest on room air ≤ 93%, or requiring oxygen therapy or mechanical ventilation
  - Rapid worsening in respiratory or circulatory status within 24 hour period
  - Laboratory findings consistent with cytokine storm:
    - Major criteria (consider use if either criteria met):
      - CRP > 150 mg/L (15 mg/dL) *only lab threshold specifically linked to efficacy of tocilizumab in current literature*
      - IL-6 > 80 pg/mL
    - Minor criteria (may consider use if 1 or more met AND high clinical suspicion for cytokine storm):
      - Ferritin > 1,000 ng/mL (or > 300 ng/mL with doubling within 24 hr. period)
      - D-dimer > 1 mg/L
      - LDH > 300 units/L
- Exclusion criteria (do NOT give IL-6 inhibitor if ANY present): Hypersensitivity; Chronic immunosuppressant use or a known immunocompromising condition; Active co-infection with bacterial, fungal, non-COVID-19 viral pathogen; Known active or latent TB infection (administration while QuantiFERON pending is acceptable); ALT or AST >3x ULN; Absolute neutrophil count <1,000/mm^3; Platelets <100,000/mm^3; Bowel diverticulitis or perforation; Known demyelinating CNS disease.

Benefit may or may not outweigh risk

- NIH guideline recommendation: "insufficient evidence to recommend either for or against (AIII)"
- IDSA guideline recommendation: "recommended **ONLY** in the context of a formal clinical trial"
- Insufficient evidence to demonstrate efficacy in treating cytokine release syndrome in severe COVID-19. 3 non-peer-reviewed observational studies suggest possible mortality benefit in critically ill patients, however due to small sample sizes and high risk of bias present, no conclusions can be drawn.
- IL-6 inhibitors are immunosuppressants and have been associated with increased risk of infectious complications when used for other indications. The risk if used during an active infection is unclear due to lack of adequate evidence but may be substantial.
- Other risks include GI perforation, myelosuppression, hepatic injury, and dyslipidemias.
- Dosing:
  - Tocilizumab: 400 mg IV x 1 dose
  - Sarilumab: 200 mg subcutaneously x 1 dose

Mechanism of Action: IL-6 blocker. IL-6 is thought to play a key role in cytokine cascade in severe COVID-19 cases.

Evidence Summary: COVID-19 Clinical Outcomes

Study	Evidence Quality	Patients	Treatment	Findings
Martinez-Sanz J Observational, multicenter, Spain (n=1,229) *Not peer reviewed	Low Moderate risk of bias	Hospitalized COVID-19 Pts. alive and not transferred to OSH within 24 hrs. of ED admission	TOCI (median 600mg) vs. No TOCI	No difference in death or composite of death or ICU admission. In sensitivity analysis TOCI associated with lower incidence of death/ICU admission when CRP >150mg/L but not when CRP ≤150mg/L

Tocilizumab Evidence Summary: COVID-19 Clinical Outcomes (continued)

Study	Evidence Quality	Patients	Treatment	Findings
Rossi B Observational, single center, France (n=246) *Not peer reviewed	Very Low Serious risk of bias	Severe hospitalized COVID-19 Pts	TOCI 400mg IV x 1 vs. No TOCI	In propensity-matched cohort (n=168), TOCI associated with reduction in composite of all-cause mortality or mechanical ventilation (HR = 0.49, 95%CI 0.3 to 0.81). Mean CRP in TOCI Pts. = 168 mg/L
Campochiaro C Observational, single center, Italy (n=65)	Very Low Serious risk of bias	Severe COVID-19 + worsening of O2 requirement and LDH > 220 U/L plus either CRP ≥ 100mg/L or ferritin ≥900ng/L	TOCI vs. No TOCI All Pts. got HCQ, LPV/r, and CTX + AZ	Clinical improvement on ordinal scale by day 28 occurred in 69% of TOCI Pts. vs. 61% of standard treatment Pts. (p=0.61). Mortality = 15% in TOCI Pts. vs. 33% in standard treatment (p=0.15). Small sample size limits interpretation. Median CRP in TOCI Pts. = 156 mg/L
Ip A Observational cohort, multicenter, U.S. (n=547) *Not peer reviewed	Very Low Serious risk of bias	ICU COVID-19 Pts.	TOCI given in ICU (n=134) vs. No TOCI	Unadjusted analysis: TOCI Pts. had lower mortality than controls (46% vs. 56%) but were younger and had less comorbidities. Propensity score-adjusted analysis: Hazard Ratio for mortality with TOCI = 0.76, 95% CI 0.57-1, p=0.053

The following studies were reviewed and excluded from the table due to critical limitations / lack of peer review: Wadud N, Ramaswamy M, Colaneri M, Capra R

Other Small Molecule Targeted Immunomodulators

Benefit may or may not outweigh risk

IF a small molecule targeted immunomodulator is to be used to manage cytokine storm, the Subcommittee prefers use of IL-6 antagonists over other agents at this time due to comparatively greater available literature and experience. There is insufficient evidence to adequately assess risk/benefit for any of these agents, including IL-6 antagonists.

Other small molecule targeted immunomodulators have been proposed as potential options for managing patients with evidence of cytokine storm due to COVID-19. These include:

- IL-1 inhibitors: anakinra
- JAK inhibitors: baricitinib, ruxolitinib, fedratinib
- TNF-a inhibitors: etanercept
- Bruton tyrosine kinase (BTK) inhibitors: ibrutinib, acalabrutinib, zanubrutinib

Convalescent Plasma

Convalescent plasma is NOT currently available for use at Adventist Health.

Insufficient evidence to demonstrate efficacy or safety in COVID-19 patients or any other infectious disease. A randomized trial in COVID-19 patients in China did not show efficacy however it was underpowered due to lack of enrollment and a possible benefit of convalescent plasma therefore cannot be ruled out.

Observational studies in other viral infections are conflicting. Many suggest potential for improved outcomes, however are at high risk of bias. A randomized trial in severe influenza did not identify a benefit of convalescent plasma.

Major risks of therapy include allergic reactions, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), pro-coagulopathic effects, and viral antibody-dependent enhancement (ADE).

Mechanism of Action: Plasma of patients who have recovered from COVID-19 is collected and infused into a patient with active severe disease. This plasma contains antibodies against SARS-CoV-2 which may theoretically improve outcomes.

Evidence Summary: COVID-19

Study	Evidence Quality	Patients	Treatment	Findings	
				Efficacy	Safety
Li L RCT, multicenter, China (n=103)	Moderate Some concerns	Hospitalized severe COVID-19 Pts.	Convalescent plasma vs. Usual care	No significant difference in clinical improvement at day 28 (51.9% plasma vs. 43.1% usual care, HR 1.4, 95% CI 0.79-2.49, p=0.26) or mortality (15.7% plasma vs. 24% usual care, OR 0.65, 95% CI 0.29-1.46, p=0.3). Study terminated early, lack of power makes findings difficult to interpret.	2/52 Pts. (3.8%) receiving plasma had transfusion-associated adverse event
Liu S Observational, U.S. (n=195) *Not peer reviewed	Very Low Serious risk of bias	Hospitalized COVID-19 Pts.	Convalescent plasma (n=39) vs. Matched controls (n=156)	Proportion of Pts. with stable or improved oxygen status at days 1, 7, and 14 not significantly different. After adjusting for additional variables, improvement seen with convalescent plasma on day 14 but not days 1 or 7. Possible mortality benefit with convalescent plasma seen but serious risk of bias present.	
Joyner M Case series, U.S. (n=5,000) *Not peer reviewed	Anecdotal	Hospitalized severe or high-risk COVID-19. 66% ICU Pts.	Convalescent plasma 200-500 mL x 1. Plasma source/ titers not reported	< 1% of transfusions resulted in a serious adverse event (7 reports of TACO, 11 TRALI, 3 severe allergic reactions). NOTE: adverse events had to be proactively reported by the treating physician and thus may have been underreported. Overall day 7 mortality = 14.9%, no control group to compare to.	

The following small case series were reviewed and excluded due to anecdotal nature: Zeng Q, Shen C, Duan K, Zhang B

Evidence Summary: Other Viruses

SARS

- No randomized controlled trials.
- In an observational study, Soo et al. (n=40) found convalescent plasma was associated with a significant reduction in mortality compared to patients receiving methylprednisolone. This study was graded high risk of bias however and corticosteroids have been associated with worse outcomes in SARS which may confound the results.

Influenza

- Several observational studies demonstrated promising results, summarized in a 2014 systematic review. Meta-analysis suggested possible mortality benefit, however most studies were judged to be at high risk of bias.
- Beigel et al: Phase 3 RCT (n=138) comparing high-titer (≥1:80) plasma to control plasma (titer ≤ 1:10) in hospitalized severe influenza A patients with median 3 day symptom duration. No change in rate of clinical improvement on day 7 (OR 1.22 95% CI 0.65–2.29, p=0.54) or negative PCR conversion. Severe adverse events reported in 34% of patients, most commonly ARDS and allergic transfusion reactions.
- 2 RCTs also analyzed use of **hyperimmune IV immunoglobulin (hIVIG)** which is made by isolating/concentrating the pathogen-specific antibodies from convalescent plasma:
    - Hung et al: pilot RCT (n=35) comparing hIVIG to standard IVIG for severe H1N1 infection. hIVIG was associated with significantly lower viral load on days 5 and 7 post-infusion and reduced mortality in multivariate analysis. Small sample size limits conclusions.
    - Davey et al: multicenter, multinational RCT (n=313) comparing hIVIG to saline infusion (placebo) for severe influenza A or B infection. hIVIG was not associated with clinical improvement or mortality.

Ebola

- An observational cohort described 84 Pts. who received convalescent plasma compared to 418 controls treated at the same center who did not receive convalescent plasma. Convalescent plasma was not associated with decreased risk of death, however a follow-up report noted that most donor plasma had relatively low titers.

Colchicine

Benefit may or may not outweigh risk
Insufficient evidence to recommend routine use in COVID-19. A small study in Greece indicated colchicine may prevent clinical deterioration in COVID-19 patients, however important limitations, including small sample size and imbalances in baseline characteristics, impact reliability of the findings. Colchicine was also associated with a significant increase in GI-related adverse events in this study. Larger studies are ongoing and it is prudent to wait for results prior to routinely adopting use of colchicine.

Evidence Summary: COVID-19

Study	Evidence Quality	Patients	Treatment	Findings	
				Efficacy	Safety
Deftereos S RCT, Greece (n=105)	Low High risk of bias	Hospitalized severe COVID-19 Pts.	Colchicine 1.5mg load, then 0.5mg BID for up to 3 weeks vs. Usual care	No significant difference in changes in inflammatory markers. Colchicine patients had prolonged time to clinical deterioration on ordinal scale vs. usual care (20.7 days vs. 18.6 days, p=0.02). Small sample size and other concerns limit interpretation.	Diarrhea in 45.5% of colchicine Pts. vs. 18% of controls (p=0.003), numerically higher incidence of some other ADRs, not significant but small sample size limits interpretation.

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