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Potential/Off Label Investigational Treatments for Covid-19

Drug	Caution	Dose Considerations	Adverse Effects and Monitoring	Drug Interactions
Remdesivir Proposed mechanisms: Nucleotide prodrug that inhibits RNA-dependent RNA polymerase activity	Exclusion criteria from clinical trials: • Evidence of multi-organ failure • Need of inotropic agents • Creatinine clearance < 30 ml/min, dialysis, or hemofiltration • Transaminases > 5X ULN • Concomitant use of lopinavir/ritonavir **Note that these criteria will likely exclude a great many patients in critical care.**	If the estimated creatinine clearance decreases by more than ≥ 50% from baseline, remdesivir should be held and resumed only when the estimated creatinine clearance returns to baseline. If ALT and/or AST increase to > 3 times ULN remdesivir should be held. Dosing may be resumed when the ALT and/or AST returns to baseline. Remdesivir should be stopped and not restarted if: • ALT ≥3 × ULN and bilirubin ≥2 × ULN • ALT and/or AST increases to > 5 times ULN	Transaminase elevations +/- mild, reversible PT prolongation (usually no clinically important change in INR) and infusion related hypotension.	In clinical trials, participants must abstain from acetaminophen for 14 days after they begin remdesivir.
Chloroquine Proposed mechanisms: Inhibition of viral entry, inhibition of viral release into the host cell, reduction of viral infectivity and immune modulation	• QT >500 msec (Bazett) • Myasthenia gravis • Porphyria Retinal pathology Epilepsy • Hypersensitivity to 4-aminoquinolone compounds	70% of excretion renal, but no dose adjustments in product monograph. No dose adjustments for hepatic impairment in product monograph.	Dizziness, headache, nausea, vomiting, diarrhea, dysrhythmias, sudden cardiac death. Perform baseline ECG and regularly monitor if initial QT interval 450-500 msec. Consider daily monitoring, especially when used with azithromycin.	Possible additive QT and/or PR interval prolongation with other medications exhibiting these effects. Possible additive effects with drugs causing hypoglycemia. Increased exposure of amiodarone, bepridil, flecainide and mexiletine and digoxin. CYP3A4 and CYP2C8 inhibitors may increase exposure to chloroquine. These include: Trimethoprim, macrolide antibiotics (clarithromycin and erythromycin only), azole antifungals, HIV protease inhibitors, diltiazem, verapamil, amiodarone

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Hydroxychloroquine Proposed mechanism: Assumed to be similar to that of chloroquine.	• QT > 500 msec • Myasthenia gravis • Porphyria • Retinal pathology • Epilepsy • Hypersensitivity to 4-aminoquinolone compounds	Product monograph suggests use with caution in patients with hepatic or renal impairment, and that dose reductions may be needed. However, no guidance offered.	Dizziness, headache, nausea, vomiting, diarrhea, dysrhythmias, sudden cardiac death. Perform baseline ECG and regularly monitor if initial QT interval 450-500 msec. Consider daily monitoring, especially when used with azithromycin.	Possible additive QT and/or PR interval prolongation with other medications exhibiting these effects. Possible additive effects with drugs causing hypoglycemia. Possible additive risk of seizure. May increase levels of CYP2D6-metabolized medications. E.g. metoprolol, trazodone (active anxiogenic metabolite) May increase levels of P-glycoprotein substrates. These include: Digoxin, Cyclosporine, Verapamil, Dabigatran (and to a lesser extent apixaban, rivaroxaban), Loperamide Increased exposure of amiodarone, bepridil, flecainide and mexiletine and digoxin; CYP3A4 and CYP2C8 inhibitors may increase exposure to hydroxychloroquine. These include: Trimethoprim, macrolide antibiotics (clarithromycin and erythromycin only), azole antifungals, HIV protease inhibitors, diltiazem, verapamil, amiodarone
Lopinavir/ Ritonavir Proposed mechanism: SARS-CoV-2 protease inhibition is proposed mechanism.	Contraindicated in patients taking drugs that are heavily dependent on CYP3A4 for clearance. These include: • Alfuzosin • Dronedarone • Fusidic acid • Colchicine • Rifampin • Lurasidone	2 tablets (supplied as 200/50 mg tablets) BID for 14 days. Also available as an oral solution containing 400 mg lopinavir/100 mg ritonavir per 5 mL. No dose adjustments are likely to be needed for renal impairment. No dose adjustments for hepatic impairment, but lopinavir exposure	Diarrhea, nausea/vomiting, elevated transaminases. Pancreatitis rare.	Many interactions. Potent CYP3A4 inhibitor. • Psychotropics warranting caution and close monitoring, if necessary: Quetiapine, clonazepam, trazodone Medications require review prior to prescribing.

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	• Pimozide • Ergot derivatives • elbasvir/grazoprevir • lovastatin, simvastatin • salmeterol • Sildenafil when used for treatment of PAH • Vardenafil when used for PAH or ED • Midazolam, triazolam	increased 30% in patients with mild/moderate hepatic impairment. Use with caution in this population.		
Azithromycin (COVID studies have used with hydroxychloroquine)	History of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin and in those with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibacterial agent	No adjustment for hepatic impairment or mild to moderate renal impairment (GFR GFR 10-80 mL/min). Exposure increases 35% in patients with GFR <10 mL/min compared to patients with normal renal function. Product labelling does not recommend dose adjustment, but exercising caution when azithromycin is administered to subjects with severe renal impairment.	Nausea, vomiting, diarrhea, adominal pain, rashes and Increase in transaminase and/or alkaline phosphatase levels in patients receiving intravenous azithromycin When used with hydroxychloroquine, baseline ECG. Consider daily monitoring, when used with chloroquine or hydroxychloroquine.	Few clinically important interactions. May increase levels of P-glycoprotein substrates. These include: Digoxin, Cyclosporine, Verapamil, Dabigatran (and to a lesser extent apixaban, rivaroxaban), Loperamide While azithromycin's real-world risk of QT interval prolongation is unclear, monitor patients with risk factors for QT interval prolongation. Loop diuretics which can cause low K, Ca and Mg levels, Amiodarone, haloperidol, quetiapine, olanzapine, risperidone, fluoroquinolones, citalopram/escitalopram. Nonpharmacologic risk factors for QT interval prolongation and Torsade de Pointe include: Low K, Mg, Ca levels, Age ≥65 years, cardiac history, female, baseline QT interval prolongation)
Tocilizumab	Serious drug-induced liver injury, in some cases resulting in acute liver failure requiring a transplant, has been reported in patients treated with tocilizumab. The drug is generally not recommended in	Critically ill patients: Recommended for patients who are receiving recommended doses of dexamethasone and who are within 14 days of hospital admission (or within 14 days of a new COVID-19	Increased risk of serious infection including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have	Inhibition of IL-6 may induce the expression of cytochrome P-450 enzymes, increasing the metabolism of CYP substrates. When starting or stopping therapy with tocilizumab, patients taking medications that are metabolised by CYP3A4, 1A2, 2C9 or 2C19 may have to have doses increased to maintain therapeutic effect). Given half-life of 13

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Drug	Caution	Dose Considerations	Adverse Effects and Monitoring	Drug Interactions
	patients with active liver disease and transaminase levels greater than 3-times the upper limit of normal. However, because most patients with cytokine release syndrome will have elevated transaminases, decision to treat should consider potential benefit versus risk.	diagnosis if the infection was acquired in a health care setting). Moderately ill: Recommended for patients with serum CRP of ≥ 75 mg/L and evidence of disease progression (i.e., increasing oxygen or ventilatory requirements) despite 24 to 48 hours of recommended doses of dexamethasone therapy (or a dose-equivalent corticosteroid) AND should also be within 14 days of hospital admission (or within 14 days of a new COVID-19 diagnosis if the infection was nosocomially acquired). Not currently recommended for patients with mild illness. Meta-analyses of 9 randomized controlled trials found that tocilizumab reduces mortality when compared to control or usual care (pooled RR 0.90; 95% CI 0.83 to 0.97). In patients not on invasive mechanical ventilation or ECMO, tocilizumab decreases the progression to mechanical ventilation (RR 0.78 (95% CI 0.68 to 0.90). Tocilizumab also decreases the progression to death or invasive mechanical ventilation (RR 0.83; 95% CI 0.77 to 0.90).	occurred in patients receiving tocilizumab for approved indications. Gastrointestinal perforations rare (caution diverticulitis and other symptomatic lower GI conditions). Monitorfor hepatotoxicity, thrombocytopenia, neutropenia, and late-presenting secondary infections.	days, the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy. In patients with rheumatoid arthritis, tocilizumab decreased simvastatin exposure 57%.

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		8 mg/kg as one dose infused over 60 minutes; can be repeated 8 to 12 hours later if continued clinical deterioration or inadequate response to first dose. The total dose should not exceed 800 mg, and the drug should not be administered more than twice. There are no studies to help guide dosing in patients with renal or hepatic insufficiency. However, Health Canada advised withholding in patients with transaminase levels > 3 times the upper limit of normal to minimize the risk of drug-induced liver injury.		
Colchicine	Use with care in geriatrics or debilitated patients and those with cardiac, renal (contraindicated CrCl <30cc/min), or gastrointestinal disease or on concomitant medications which inhibit CYP3A4 and/or P-glycoprotein (e.g. amiodarone, macrolides, fluconazole). Dosage reduction may be necessary in these cases and is indicated if weakness, anorexia, nausea, vomiting, or diarrhea appears.	The ColCORONA phase 3, multicentre, randomized double-blind, placebo-controlled trial stopped early and undergoing peer-review. Randomized 4488 adult participants, age >40 years (adults), dx SARS-CoV2 within preceding 24 hours (PCR from nasopharyngeal swab OR household member with a POSITIVE nasopharyngeal swab with COVID19 symptoms, OR clinical algorithm in symptomatic patient without obvious alternative cause), outpatients (not hospitalized nor considering hospitalization), PLUS one of: age >=70 years, obesity (BMI >=30), diabetes,	Gastrointestinal (diarrhea, vomiting, nausea); Hematological (leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia, bone marrow depression, disseminated intravascular coagulation) ColCORONA Trial medication-related adverse events 24.2% colchicine vs 15.5% placebo, ARR 8.7% NNH 11.5; at least 1 treatment emergent GI adverse event in 23.9%	When used for approved indications, dosage reductions needed when used with CYP3A4 and p-glycoprotein inhibitors. Guidance around dosage adjustments in setting of COVID are unclear.

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		uncontrolled HTN (SBP >=150 mmHg), known respiratory disease, known heart failure, known CAD, fever >38.4C within the last 48 hrs, dyspnea at the time of presentation, bicytopenia, pancytopenia or neutrophilia AND lymphopenia Exclusions: women of childbearing age NOT practicing adequate contraception, IBD, chronic diarrhea or malabsorption, concomitant progressive neuromuscular disease, GFR<30cc/min/1.73 m2, severe liver disease, current tx with colchicine, chemo for cancer, sensitivity to colchicine. Intervention: colchicine 0.5 mg BID for 3 days and then daily for 27 days. VS Placebo. Trial medications delivered to patient's house within 4 hours with telephone clinical evaluation at 15 and 30 days. ?confirmation of treatment adherence ?outcome capture Primary endpoint (composite of death or hospitalization for COVID-19) in 4.7% of patients in colchicine vs 5.8% placebo. P=0.08. ARR 1.1% Among patients with PCR confirmed COVID, primary	colchicine group, as compared with 14.8% placebo	

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		endpoint 4.6% colchicine and 6% placebo p= 0.04 ARR 1.4% NNT 72 patients. SAE 4.9% colchicine vs 6.3% placebo p=0.05 "NNT" 52 patients PE 0.5% colchicine vs 0.1% placebo p = 0.01 Prespec subgroup analysis: age>=70 years. 18/190 (9.5%) colchicine and 27/213 (12.7%) OR 0.72 (95% CI 0.38 to 1.36)		
Dexamethasone	Neuropsychiatric effects are diverse and include insomnia, irritability, depression, mania, psychosis, delirium. Induces CYP3A4 metabolism.	RECOVERY RCT (UK) found decreased 28 day mortality for inpatients receiving respiratory support (35% decrease in ventilated patients and 20% decrease in patients on oxygen supplementation) among those SARS-CoV2 patients aged <70 years requiring supplemental O2 particularly those requiring greater respiratory support, randomized to dexamethasone 6 mg once daily for up to 10 days compared to placebo (Group, 2020). Subgroup analysis: **Older age:** **aged <70 years** receiving dexamethasone, 129/1141 died by day 28 (11.3%) compared to 428/2504 patients receiving standard of care (16.5%; [RR 0.64; 95%CI 0.53-0.78]). ARR 5.2%	Mood, sleep, cognition, hemoglobin, occult blood loss, blood pressure, serum potassium, glucose, BMD, IOP if systemic use >6 weeks, HPA axis suppression (if chronic)	CYP3A4 inducers may decreased the concentration of dexamethasone. Avoid this combination in life threatening conditions. CYP3A4 inhibitors may increase the serum concentration of dexamethasone. Concurrent use of dexamethasone with warfarin can increase risk of bleeding. With NSAIDs, it can increase the risk of GI ulceration or bleeding. (1-2)

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		NNT 20 **aged ≥70 <80**, mortality rate at day 28 was 155/469 (33.0%) for those randomized to dexamethasone, compared to 271/859 for those receiving standard of care alone (31.5%). RR 1.03 (95% CI 0.84−1.25) **aged ≥80**, mortality rate at day 28 was 198/494 (40.1%) for those receiving dexamethasone compared to 411/958 (42.9%) receiving standard of care alone. RR 0.89 (95% CI 0.75 – 1.05) **Days since symptom onset:** Consistent with increased clinical benefit observed for those patients requiring additional oxygen support, **dexamethasone treatment had a greater impact at reducing mortality for patients with >7 days since symptom onset at time of trial randomization.** 28-day mortality for patients with >7 days since symptom onset: 212/1184 (17.9%; dexamethasone) vs. 604/2507 (24.1%; standard of care) (RR 0.69 [95%CI 0.59-0.80]). 28-day mortality for patients with ≤7 days since symptom onset: 269/916 (29.4%; dexamethasone), vs. 500/1801 (27.8%; standard of care) (RR 1.01 [95% CI 0.87-1.17]).		

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		Supplemental O2: No reduction in mortality if not receiving supplemental O2. In patients not receiving oxygen, mortality of 17.8% among those received dexamethasone, compared with 14.0% for those who received usual care (rate ratio 1.19, 95% CI 0.91 to 1.55).		
Baricitinib Janus kinase inhibitor; may mitigate response of proinflammatory cytokines to virus.	Not yet approved in Canada. FDA emergency use authorization for treatment of hospitalized patients needing supplemental oxygen, mechanical ventilation or ECMO.	Randomized trial: 1033 hospitalized patients with confirmed SARS-CoV-2 infection and either radiographic infiltrates, $SpO_2 \leq 94\%$ on room air, or need for supplemental oxygen or mechanical ventilation, randomized to either baricitinib 4 mg or placebo once daily (both with remdesivir) for 14 days or until hospital discharge, in addition to IV remdesivir for up to 10 days. Primary endpoint: Median time to recovery within 29 days after randomization: 7 days for baricitinib vs. 8 days for placebo (hazard ratio: 1.16; 95% CI 1.01 to 1.32) Secondary endpoint: Improvement in clinical status at day 15: Higher odds in baricitinib vs. placebo (OR 1.26; 95% CI 1.01 to 1.57) Secondary endpoint: Composite of death, progression to noninvasive	Risk of infections, thromboembolic events, hypersensitivity reactions and hepatic enzyme elevations.	Strong OAT3 inhibitors (e.g., probenecid) can increase baricitinib exposure. Dose reduction recommended.

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		or invasive mechanical ventilation or worsening clinical status: Less likely with baricitinib (23%) vs. placebo (28%) (OR 0.77; 95% CI 0.60 to 0.98). Secondary endpoint: Death by day 29; No difference between groups (5.1% baricitinib vs. 7.8% placebo). Adult dose: 4 mg once per day for 14 days or until hospital discharge, whichever is first; adjustments needed for renal and hepatic impairment. Must be used with remdesivir		
Fluvoxamine Selective Serotonin Reuptake Inhibitor Proposed mechanism for COVID-19: Sigma-1 receptor agonist regulating production of inflammatory cytokines (Sukhatme, 2021) Administer within 7 days of symptom onset in patients who are not on supplemental oxygen.	Contraindications: • Hypersensitivity to fluvoxamine • Concurrent use with MAOI (including linezolid or IV methylene blue) or use within 14 days of discontinuing MAOI • Concurrent use with alosetron, astemizole, cisapride, mesoridazine, pimozide, ramelteon, terfenadine, thioridazine, or tizanidine Caution in older adults due to increased risk of falls and orthostatic hypotension.	Regimen recommended if drug is less well tolerated (Ontario COVID-19 Science Advisory Table recommendations): Start at 50 mg at bedtime on day 1, 50 mg BID on day 2, then 100 mg BID on day 3 for total of 10-15 days. Clearance is decreased with hepatic impairment.	Nausea, diarrhea, xerostomia, anorexia, headache, insomnia, drowsiness, dizziness. falls, QTc prolongation: avoid in patients with risk for prolonged QT (e.g., other QT prolonging medication, etc.). Hyponatremia: monitor sodium at baseline and in a week's time after initiation, particularly in patients at higher risk of hyponatremia	Substrate of CYP2D6 (primarily) and CYP1A2. Potent inhibitor of CYP1A2 and CYP2C19 and a mild to moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4. Potential interactions with CYP1A2 substrates (e.g., theophylline, clozapine), CYP3A4 substrates (e.g., carbamazepine, methadone, cyclosporine, sildenafil), CYP2C9 and CYP2C19 substrates (e.g., phenytoin, warfarin) with a narrow therapeutic index. Monitor and adjust dose if necessary. Fluvoxamine is not recommended for concurrent use with prodrugs metabolized by CYP1A2 and CYP2C19. There is a clinically significant reduction in drug levels (e.g. clopidogrel).

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	Pharmacokinetic considerations: • Exposure can be 3-fold higher and maximum concentrations 2-fold higher in older adults compared to younger individuals (Orlando, 2010). • Non-linear kinetics: exposure can be greater than expected proportional increases with changes in dose (Hartter, 1998, Spigset, 1998). Significant interindividual variability in serum concentrations (4-6 fold) irrespective of age and comorbidities (Hartter, 1998).		(e.g., older age, concomitant diuretics).	Increased risk of serotonin syndrome with other serotonergic agents. Potential, increased risk of bleeding with anticoagulants and antiplatelets.

*List of substrates, inhibitors and inducers are representative only, and not exhaustive.

Pharmacokinetic studies among older adults have not been done with the exception of azithromycin which found that older women experienced 30-50% increased AUC. This pharmacokinetic difference was not felt to be clinical relevant.

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