## Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19

The listed agents represent potential treatments for inpatient cases of COVID-19 largely based on limited evidence, none proven effective to date. Careful clinical consideration should be applied when deciding to use the agents listed in this select evidence review. This document should not be used as empiric or definitive treatment guidelines. Evidence is continuing to evolve, as such this document will be updated accordingly.

### AGENTS

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<th>Remdesivir (GS-5734)</th>
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<th>CONTRAINDICATIONS/ADVERSE EVENTS</th>
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<tr>
<td><strong>Antiviral with activity against Ebola, MERS, SARS</strong></td>
<td>Dose: 200mg IV x1 on day 1 then 100mg IV daily for the duration of the hospital course up to 10 days total</td>
<td>Emergency Use Authorization (EUA) is currently not available throughout NM system as of 5/6/20</td>
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</table>
| **Prodrug nucleotide analog of adenosine triphosphate; incorporates into nascent viral RNA chains and results in premature termination.** | Expanded Access via Gilead: Critically ill patients with severe COVID-19, requiring mechanical ventilation, not on vasopressors at time of initiation | Investigational – enrollment in clinical trial (NMH only): Contact ID, Dr. Babafemi Taiwo or Dr. Kari Krueger for enrollment in NIH clinical trial | FDA EUA Fact Sheet for Providers
Expanded Access Criteria - Gilead
- Hospitalized pts ≥18 y/o or ages ≥12 weighing ≥40kg with confirmed SARS-CoV-2 or known contact with COVID-19 pt and PCR pending
- Requiring invasive mechanical ventilation
- eGFR ≥30 ml/min
- ALT ≤ 5x ULN
- Written informed consent

**Exclusion criteria:** multi-organ failure, requirement of >1 vasopressor, eGFR< 30 or HD/CVVH | AE: Abnormal LFTs, hepatotoxicity, abnormal INR, PT & PTT, reversible kidney injury, nausea, vomiting, diarrhea, headache, rash

**Contraindications/Precautions:** Monitor for hepatotoxicity, monitor for nephrotoxicity as IV formulation contains cyclodextrin |

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### Evidence

- Preliminary results, from lay-press report, of NIAID ACT which compared remdesivir to placebo, with a 31% faster recovery time associated with remdesivir use (med time 11d v 15d, p<0.001). Results also suggest survival benefit with remdesivir, demonstrated via a mortality rate of 8.0% v 11.6% compared to placebo (p=0.059). (NIH Press Release)
- Preliminary results, from pharma-press report of SIMPLE study comparing 5d v 10d duration of remdesivir in hospitalized patients worldwide. Among 397 pts, no major differences in clinical outcomes comparing each duration. (Gilead)
- RCT of 237 hospitalized patients in Hubei, China with severe COVID-19 randomized 2:1 to remdesivir v placebo for up to 10 days. Study was underpowered but found no stat sig difference in time to clinical improvement with remdesivir (21d) v placebo (23d) nor difference in duration of oxygen support, length of hospitalization, rate of discharge, nor death. No major difference in adverse reactions among groups. (Wang)
- Non-controlled, open-label report of 53 included pts in US, Canada, Europe, and Japan designed to receive remdesivir (200mg D1, then 100mg D2-9) via compassionate use with confirmed SARS-CoV-2 and SaO2 <94% or those receiving oxygen support. 36 pts (68%) had improvement in oxygenation including extubation in 17/30 pts (57%) on mechanical ventilation and discontinuation of ECMO in 3/4 pts. 25 pts (47%) were discharged alive and 7 pts (13%) died, with an overall 28d clinical improvement of 84%. The median duration of symptoms prior to initiation of remdesivir was 12 days, 75% of pts received 10-day treatment course; 6% of pts received <5 days of therapy. 12 pts (23%) experienced serious adverse events: multi-organ dysfunction syndrome, septic shock, acute kidney injury and hypotension – all on invasive ventilation at baseline. (Grein)
- Case report of 1st COVID-19 pt in US: 35 YOM admitted to hospital on day 5 of illness after traveling from Wuhan, China. Patient with intermittent fevers on hosp days 1-5, but otherwise stable. On evening of hospital day 5-6 (illness day 9-10), patient’s SaO2 dropped to 90% on RA with bilateral rales and CXR w/ atypical pneumonia. Pt started on oxygen and abx and then IV remdesivir (compassionate use) started on hosp day 7. On hospital day 8 (illness day 12), the patient’s clinical condition improved (SaO2 94 to 96% on RA and defervesce) and bilateral lower lobe rales were no longer present. He was asymptomatic except for dry cough and rhinorrhea. (Holshue)

### Clinical Trials

- **Expanded Access: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection (US). NCT04323761**
- **Study to Evaluate the Safety and Antiviral Activity of Remdesivir in Participants With Severe Coronavirus Disease (COVID-19) (US). NCT04292899**
- **Adaptive COVID-19 Treatment Trial (US - NMH). NCT04280705**
- **Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment (US). NCT04292730**
- **The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients. NCT04321616**
- **Expanded Access Remdesivir (RDV; GS-5734™). NCT04302766**
- **Trial of Treatments for COVID-19 in Hospitalized Adults. NCT04315948**
- **Wang Y et al. Lancet. 29 April 2020.**
- **Grein NJ et al. N. Engl. J. Med. 10 April 2020.**
- **Holshue ML et al. N. Engl. J. Med March 2020.**

NMH is enrolled as study site for remdesivir use in Adaptive COVID-19 clinical trial with pt enrollment pending start of ACTT-2, please see IDS protocol for guidance.
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| **Sarilumab (Kevzara®)** | **Trial Regimens:**  
- Sarilumab 400 mg IV once  
- Placebo IV once | Investigational – enrollment in clinical trial (NMH only) | Consider checking inflammatory markers (D-dimer, CRP, ESR, ferritin, fibrinogen) prior to administration | **AE:** increased serum ALT and AST, antibody development, local injection site reaction, neutropenia |
| IL-6 receptor antagonist; Humanized monoclonal antibody | **Binds to soluble membrane-bound IL-6 receptors to inhibit IL-6 mediated pro-inflammatory response** | Contact Pulmonary Research, Dr. Richard Wunderink for enrollment in clinical trial | Consider checking for history or evidence of tuberculosis prior to initiation | **Contraindications/Precautions:** GI perforation, neutropenia, thrombocytopenia, hepatotoxicity, hyperlipidemia, infusion reactions, infection, tuberculosis |

**Evidence**
- Preliminary analysis of phase II trial comparing sarilumab 200mg v 400mg v placebo in COVID-19 patients with baseline categorization of severe (dyspnea, hypoxia, or >50% lung involvement on imaging), critical (respiratory failure, shock, or multi-organ failure), or multi-system organ dysfunction. Among 358 patients included in the trial, administration of sarilumab was associated with drastic reduction in CRP levels from highest baseline (−79% with 400mg dose, −77% with 200mg, −21% with placebo). In an exploratory analysis, sarilumab had no notable benefit when combining severe and critical subgroups, due to negative trends seen within the severe group. In the critical subgroup all exploratory outcomes were positive, with notable benefit in the 400mg dose compared to placebo (endpoints: died or on a ventilator 32% v 55%, 2-point clinical improvement on 7-point ordinal scale 59% v 41%, off oxygenation 58% v 41%, discharged 53% v 41%). As a result, the phase III trial will explore use of sarilumab 400mg dose v placebo in the critical study population.

**Clinical Trials**
- Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19. NCT04315298 (NMH)
- Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial - CORIMUNO-19 - VIRO. NCT04341870
- Sarilumab COVID-19. NCT04327388
- Anti-IL6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure. NCT04322773
- Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707

**References:**
- Kevzara [Package Insert]
### AGENTS

**Tocilizumab (Actemra®)**

- **IL-6 receptor antagonist; Humanized monoclonal antibody**
  - Binds to soluble membrane-bound IL-6 receptors to inhibit IL-6 mediated pro-inflammatory response

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<tr>
<td>Tocilizumab (Actemra®)</td>
<td>Various dosing regimens have been reported 400mg IV once <strong>OR 8mg/kg</strong> IV once, up to 800mg</td>
<td>Hospitalized patients with severe COVID-19</td>
<td>Consider checking inflammatory markers (D-dimer, CRP, ESR, ferritin, fibrinogen) prior to administration</td>
<td>AE: Increased ALT/AST, neutropenia, thrombocytopenia, injection site reaction, Upper respiratory tract infections, nasopharyngitis, headache, hypertension</td>
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### Evidence

- Retrospective observational study of 21 patients in China with ICU admission, shock, combined organ failure, or severe oxygenation impairment (RR ≥ 30 breaths/min, SpO2 ≤ 93% on room air, PaO2/FiO2 ≤ 300mmHg, or need for mechanical ventilation), use of tocilizumab (400mg IV x 1) plus SOC resulted in reduced oxygen requirements (16/21 pts), resolution of fever (21/21 pts) with evidence of lung lesion opacity absorbed on CT scan (19/21 pts). Improvements in CRP and lymphocytes were also noted. Majority of patients were discharged (19/21 pts) with a mean hospitalization period of 13.5 +/- 3.1 days after start of tocilizumab in early February 2020. No subsequent pulmonary infection, worsening of illness, death, or adverse drug reactions had been reported at the time of publication. SOC included: lopinavir, methylprednisolone, other symptom relievers and oxygen therapy. (Xu)

- Pre-print information: Retrospective, propensity-matched report of off-label compassionate-use of tocilizumab for those who did not receive IL-6 inhibitors (controls) for severe COVID-19 pneumonia. Pts included if they met the following criteria:氧 O2 rate>6L/hr, <80 y/o, rapidly deteriorating status (O2 rate by ≥3L/hr within prev 12hrs), elevated CRP lvs, and reported presence of disease >5d. At follow-up day 8, pts treated with tocilizumab (n=30; 23% in ICU, 77% non-ICU) compared to matched controls (n=29; 45% in ICU, 55% non-ICU) had reduced requirement for mechanical ventilation (OR 0.42). Among non-ICU patients, tocilizumab significantly reduced risk of subsequent ICU admission (OR 0.17). Among tocilizumab-treated pts 10% died, 57% were discharged from ICU, and 20% were discharged from the hospital. AE included mild hepatic cytolysis (n=3) and VAP (n=1). Two pts received concurrent hydroxychloroquine + azithromycin therapy x10d. (Roumier)

- Other centers in Italy utilized protocols with dosing recommendations similar to cytokine release syndrome consisting of 8mg/kg up to 800mg max dose q8-12hr for 3 total doses. Subsequent doses may be considered for those with partial or incomplete response. IL-6 and/or D-dimer should be checked 24hr after last administration. No published outcomes-related evidence to support. (Italy)

### Clinical Trials

- Favipiravir combined with tocilizumab in the treatment of COVID-19. NCT04310228
- Tocilizumab vs CRRT in management of cytokine release syndrome (CRS) in COVID-19 (TACOS). NCT04306705
- Tocilizumab to Prevent Clinical Decompensation in hospitalized, non-critically ill patients with COVID-19 pneumonia (COVIDOSE). NCT04331795
- A study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACTA) NCT04320615

### References

**Antiarrhythmic**

Increases pH of acidic intracellular vesicles that may lead to inhibition of endosome-mediated fusion, viral entry and pH dependent steps in viral replication. Anti-inflammatory and immunomodulatory properties that may inhibit release of inflammatory cytokines INFγ; IL-6, IL-1, TNF-α

Hydroxychloroquine (HCQ): Hydroxyl analog of chloroquine. Similar activity and properties to chloroquine w/ ▼ tox

### Hydroxychloroquine (HCQ)

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<tr>
<td>Hydroxychloroquine (HCQ)</td>
<td>400mg PO BID on day 1 then 200mg PO BID x 4 days OR 600mg PO BID on day 1 then 200mg TID x 4 days</td>
<td>Various dosing strategies have been reported: <strong>Do not crush tablet</strong> <strong>Do not order as oral suspension for patients without PO access, can be given via tube. Mixing instructions for oral suspension available</strong></td>
<td>No definitive evidence differentiating outcomes benefit with HCQ compared to supportive care outside of pre-print information, coupled with limited supply suggest cautious use of HCQ</td>
<td><strong>AE:</strong> QT prolongation, nausea, vomiting, cardiomyopathy, pancytopenia, hepatotoxicity, irreversible retinopathy, extrapyramidal reaction, pruritis</td>
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<td><strong>Antimalarial</strong></td>
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<td>Not recommended outside of clinical trials unless other indications justify its use, due to concerns about safety and efficacy</td>
<td>Avoid use with concurrent azithromycin (esp in pts with acute renal failure) due to QTc prolongation and risk of cardiac arrhythmias (Chorin, NIH Guidelines)</td>
</tr>
<tr>
<td><strong>HCQ:</strong> Hydroxyl analog of chloroquine. Similar activity and properties to chloroquine w/ ▼ tox</td>
<td></td>
<td></td>
<td><strong>FDA cautions against use for COVID-19 outside of hospital setting or clinical trial</strong></td>
<td>For patients with underlying CV disease or on concurrent QT prolonging medications, obtain baseline EKG and monitor QTc. Avoid use if baseline QTc &gt; 500ms or in pts with known congenital QT prolongation. Maintain electrolytes (K=4mEq/L, Mg=2mg/dl) while on therapy (Roden)</td>
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<td></td>
<td>Monitor for drug-drug interactions, WBC Food can increase bioavailability (CQ)</td>
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### Evidence

- Randomized, parallel-group trial to evaluate the efficacy of HCQ (400mg/day; 200mg BID x 5 days) v standard treatment (supportive care=control) in 31/62 patients with mild COVID-19 illness (excluded severe/critically ill) in Wuhan. Time to clinical recovery (TCTR) in days, clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment. Fever recovery time (3.2d vs. 2.2d, p=0.0008) and duration of cough (3.3d vs. 2.6d, p=0.0016) significantly shortened in HCQ versus control group, respectively; per chest CT, pneumonia improved 25/31 (80.6%) in HCQ vs. 17/31 (54.8%) in controls. Mild adverse reactions (HCQ): rash, headache. (Chen Z)
- Pre-print information: Non-randomized propensity-matched comparative study of pts receiving HCQ 600mg daily within 48hrs of hospitalization (n=84) v those who did not (control, n=97) combined with standard of care. Among 181 pts, all of whom had bilateral PNA and required supplemental oxygen, no difference was found in the composite outcome of transfer to ICU within 7 days or all-cause mortality (HCQ 20.2% v control 22.1%). ARDS developed within 7 days in 27.7% of those treated with HCQ 24.1% in controls. 9.5% of pts in HCQ group experienced EKG changes requiring discontinuation of therapy, with a median ±0.05 time of 4 days. Authors stated findings do not support use of HCQ in COVID PNA. (Mahévas)
- Pre-print information: Multicenter, open-label RCT of 150 pts hospitalized with COVID-19 who received HCQ 1,200mg daily x 3 days followed by 800mg daily + SOC (n=75) v SOC alone (control, n=75). 28-day negative conversion rates of SARS-CoV-2 was not different between HCQ + SOC v controls (85.4% v 81.3%, median time to negative conversion 8 v 7 days) nor were differences in negative conversion rates at days 4, 7, 10, 14, 21, including in a sub-analysis of pts who received HCQ within 7 days of symptom onset v those with initiation beyond 7 days. No difference in 28-day symptom alleviation (59.9% v 66.6%), however in a post-hoc analysis in which confounding use of other antiviral agents were removed, HCQ was associated with an improved rate of symptom alleviation, more rapid normalization of CRP, and a trend towards more rapid recovery of lymphopenia. Adverse event rate of 30% in HCQ (10% diarrhea) v 8.8% in controls. (Tang)
- Pre-print information: Retrospective review of 84 adult pts with COVID-19 in US treated with hydroxychloroquine and azithromycin combination therapy, which found a significant association with QTc prolongation (30% of pts with increase >40ms, 11% of pts with increase >500ms), placing these pts at higher risk for arrhythmias, although no cases of torsades were reported. Maximal QTc increase was noted on treatment days 3-4. Acute renal failure was noted to be a significant predictor of severe QTc prolongation, but baseline QTc and QTc +460ms did not predict QTc prolongation. Concurrent amiodarone use associated w/ risk. Authors recommend repeated monitoring of QTc for pts treated with HCQ/Azithro combination. (Chorin)
- Pre-print information: Retrospective review of 368 adult pts with COVID-19 at VAMC treated with HCQ alone (n=97), HCQ+Azithro (n=113), or controls receiving no HCQ (n=158). Higher mortality reported with HCQ alone (27.8%) compared to HCQ+Azithro (22.1%) & controls (11.4%) w/ similar rates of risk of mech ventilation (adjusted HR 1.43 HCQ alone v HR 0.43 HCQ+Azithro compared to controls). Emphasize need for results from ongoing RCT prior to recommended use of HCQ. (Magagnoli)
- Pre-print abstract only: Open-label study of 30 pts in Shanghai to evaluate the efficacy of HCQ for the treatment of COVID-19. Patients were randomized 1:1 to HCQ 400mg/day x 5 vs conventional therapy. Primary outcome was negative COVID test via pharyngeal swab on day 7 after randomization. On day 7, PCR was negative in 13 (86.7%) patients in the HCQ group and 14 cases (93.3%) in the control group. No sig difference in secondary outcomes such as median duration from hospitalization to negative test, median time for body temp normalization, radiological progression, and improvement in follow-up examination. Transient diarrhea and abnormal liver function experienced in 4 (HCQ) and 3 (control) pts. (Chen J)
- Prospective study to evaluate the PK of HCQ in 13 ICU patients with COVID-19 (med age 68 yo; 85% male; med wt 82.7kg [46% obese]; 12/13 pts ventilated) at Saint Etienne University Hospital in France. All patients received 200 mg TID of HCQ. Target trough: 1-2 mg/L. Monte Carlo simulations were also performed generating 200 patients with different dosing regimens to assess HCQ PK and effects of dosing regimen. Mean time to therapeutic levels (200mg TID): 2.7 days (only 61% reached target levels). Four patients required dose de-escalation (200mg BID) and two patients discontinued HCQ due to QT prolongation (381 to 510 ms and 432 to 550 ms) on day 2 and 3; HCQ blood levels of 0.03 mg/L and 1.74 mg/L, respectively. Authors concluded 200mg TID daily dosing is inappropriate and propose a loading dose of 800 mg on day 1, followed by 200 mg BID for 7 days based on their simulation study. (Perinel)

### References

- Roden DM et al. Consideration for Drug Interactions on QTc in Exploratory COVID-19 Treatment. Circulation. 2020 Apr 8 DOI: 10.1161/CIRCULATIONAHA.120.047521

NM ASP Evidence Review for Inpatient Treatment Options for COVID-19

Created 3.19.20 | Last Updated 5.6.20
Evidence

Outcomes of two kidney transplant recipients with COVID-19 pneumonia hospitalized in Parma, Italy 3/2-3/12/20. Both cases were SARS-CoV-2 positive per PCR, on Tacrolimus, MMF, & steroids with chest CT indicative for COVID19 pneumonia. Tac & MMF were discontinued on admission and both patients were started on HCQ (200mg BID) plus Lopinavir/r or Darunavir w/ cobicistat. Neither were on an ACEI or ARB. Both received non-invasive ventilation and were not transferred to ICU. Case 1: 75 y/o male, 120 months post-transplant. Symptoms (fever, cough, myalgia) started 3 days prior to admission. Graft function stable. Experienced worsening of respiratory condition over 24-38 hours and expired 5 days after admission before intubation. Case 2: 52 y/o female, 8 months post-transplant, symptoms started 1 day prior to admission. Developed AKI. Day 6, started to experience systemic inflammation (plasma IL-6: 108.2 pg/mL, normal: 0-10 pg/mL). Before intubation, Case 2 received colchicine 1mg, then 0.5 mg/day (day 8) given tocilizumab was unavailable. Antivirals were stopped. One day after start of colchicine, plasma IL-6 decreased to 36 pg/mL with stable respiratory status. Day 14, Case 2 was stable and alert on non-invasive ventilation. Renal and hepatic function normalized. (Gandolfini)

Clinical Trials:

- Colchicine Coronavirus SARS-CoV-2 Trial (COLCORONA) NCT04322682 (Montreal Heart Institute Quebec, Canada; recruiting) UofC and NY Univ School of Med first in US to participate.
- The Effects of Standard Protocol With or Without Colchicine in Covid-19 Infection NCT04360980 (Iran, recruiting)
- The ECLA PHRI COLCOVID Trial NCT04328480 (Latin America; recruiting)
- Randomized Open-blind Controlled Trial to Study the Benefit of Colchicine in Patients With COVID-19 NCT04350320 (Spain; recruiting)
- Colchicine in COVID-19: a Pilot Study NCT04375202 (Italy; recruiting)
- Colchicine in Moderate Severity Hospitalized Patients Before ARDS to Treat COVID-19 (COMBATCOVID19) NCT04363437 (New York; recruiting)
- The Greek Study in the Effects of Colchicine in Covid-19 complications Prevention (GRECCO-19) NCT04326790 (Greece; Not yet recruiting)
- Colchicine to Reduce Myocardial Injury in COVID-19 (COLHEART-19) NCT04355143 (Not yet recruiting)
- Colchicine Counteracting Inflammation in COVID-19 Pneumonia NCT04322565 (Not yet recruiting)
- Colchicine Twice Daily During 10 Days as an Option for the Treatment of Symptoms Induced by Inflammation in Patients With Mild and Severe Coronavirus Disease NCT04367168 (Not yet recruiting)

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<tr>
<td>Colchicine (Colcrys®)</td>
<td>Investigational dosing per NMH study protocol (pending): 1.2 mg once, followed by 0.6 mg every 12 hours for a total of 20 doses over 10 days or until the patient is exsanguinated from mechanical ventilation and able to reliably deny pain</td>
<td>Investigational in setting of COVID-19</td>
<td>Available as 0.6 mg tablets or 0.6 mg/5ml oral solution</td>
<td>AE: Dose-dependent GI adverse events with approved doses: diarrhea, nausea, vomiting, and abdominal pain</td>
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<td>Anti-inflammatory</td>
<td>Close monitoring in patients and dose adjustment required with severe hepatic or renal impairment</td>
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<td>Antimitotic effects prevent microtubule assembly and decreases leukocyte chemotaxis and migration and phagocytosis to inflamed areas</td>
<td>Caution and close monitoring of drug-drug interactions (DDI) with concomitant CYP3A4 and P-gp inhibitors, statins or fibrates due to increased colchicine concentrations and risk of adverse events</td>
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<td></td>
<td>Contraindications/Precautions: Pregnancy and nursing mothers: limited data; Category C</td>
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<td>May counteract the assembly of the NLRP3 inflammasome, reducing the release of IL-1b and other interleukins, including IL-6, to potentially prevent acute respiratory distress in severe cases of COVID-19 infections</td>
<td>Recommendations per NMH study protocol (pending): With concomitant use of moderate 3A4 inhibitor, decrease colchicine dose to 0.6mg every 24hrs</td>
<td></td>
<td></td>
<td>Risk of overdose with renal dysfunction, severe hepatic impairment or significant DDIs. Features may include: axonal neuropathy, CPK elevations, muscle pain/weakness, rhabdomyolysis, myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, aplastic anemia, elevated AST and ALT</td>
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<td>If CrCl &lt;30ml/min decrease colchicine dose to 0.6mg every 24hrs</td>
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<td></td>
<td>Acute overdose shown as GI symptoms in first 24 hours, then organ dysfunction (renal failure, circulatory collapse, marrow failure, muscle weakness, rhabdo, resp failure) in 7 days</td>
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<td>Colchicine Drug Interactions - Pharmacist's Letter</td>
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