Anti-inflammatory therapy for COVID-19 infection: the case for colchicine

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ABSTRACT
The search for effective COVID-19 management strategies continues to evolve. Current understanding of SARS-CoV-2 mechanisms suggests a central role for exaggerated activation of the innate immune system as an important contributor to COVID-19 adverse outcomes. The actions of colchicine, one of the oldest anti-inflammatory therapeutics, target multiple mechanisms associated with COVID-19 excessive inflammation. While many COVID-19 trials have sought to manipulate SARS-CoV-2 or dampen the inflammatory response once patients are hospitalised, few examine therapeutics to prevent the need for hospitalisation. Colchicine is easily administered, generally well tolerated and inexpensive, and holds particular promise to reduce the risk of hospitalisation and mortality due to COVID-19 in the outpatient setting. Successful outpatient treatment of COVID-19 could greatly reduce morbidity, mortality and the demand for rare or expensive care resources (front-line healthcare workers, hospital beds, ventilators, biological therapies), to the benefit of both resource-replete and resource-poor regions.

INTRODUCTION
As of 27 October 2020, almost 1 year after the first reported cases, the SARS-CoV-2 had resulted in over 43 million people infected and over 1.1 million deaths from COVID-19 worldwide. Clinical experience and data underline the role of excessive inflammation in the pathophysiology of the disease and suggest a potential role for colchicine, a drug with pleiotropic effects.

Biology of COVID-19: the role of inflammation
COVID-19 progression can be divided into three distinct phases (figure 1) including: (1) early infection phase, wherein the virus infiltrates host cells in the lung parenchyma; (2) pulmonary phase, in which viral propagation causes lung tissue injury as the host immune response is activated and (3) the inflammatory cascade, which is triggered by pathogen-associated molecular patterns (ie, viral RNA) and damage-associated molecular patterns (DAMPs, ie, cellular debris released during pyroptosis) exposed during active viral replication and release. This third phase of the inflammatory cascade may occur even as viral titers are falling and is comprised of components targeted by colchicine (activation of the inflammasome that drives the cytokine storm, activation of neutrophils and the neutrophil/thrombosis interface) (figure 2).

Activation of the inflammasome
Signals driven by SARS-CoV-2 act on macrophages and other myeloid cells to drive assembly of a proinflammatory protein complex, the nod-like receptor protein 3 (NLRP3) inflammasome, composed of NLRP3, apoptosis-associated speck-like protein adaptor and cysteine-dependent aspartate-directed protease-1 (caspase-1). Activated caspase-1 activity then converts the precursors pro-interleukin (IL)-1β and pro-IL-18 to their active forms.

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thrombosis. Neutrophils release the serine protease neutrophil elastase, which inhibits tissue factor pathway inhibitor and leads to generation of thrombin, the most potent activator of platelets. Neutrophil extracellular traps provide a platform to activate coagulation via active neutrophil elastase adherent to extracellular neutrophil DNA. Activated neutrophils and other leukocytes also aggregate with platelets directly to further exacerbate inflammothrombosis. In the setting of extreme inflammatory states, activated neutrophils adhere directly to each other (leukoaggregation), producing effective but usually transient vascular occlusions. Finally, neutrophils contribute to thrombosis via cytokine-induced release of α-defensin from neutrophil granules. Murine studies suggest that α-defensin, at concentrations similar to those observed in inflammatory conditions, results in accelerated, larger and denser thrombus formation. Human data suggest that patients with COVID-19...
infection have elevated levels of serum α-defensin proportional to COVID-19 disease severity.\textsuperscript{30}

**Clinical implications**

The connections between inflammation, thrombosis and poor COVID-19 outcomes are well established. On admission, patients from our own institution who were admitted to regular floors but subsequently transferred to the intensive care unit (ICU) had higher CRP concentrations (159±86 mg/L) than patients admitted to the regular floors overall (114±81 mg/L). On transfer to the ICU, CRP concentrations (184 mg/L±104) were higher still (unpublished, figure 3). Manifestations of profound inflammation in severe COVID-19 include acute respiratory distress syndrome and distributive shock.\textsuperscript{14 15 17} Myocardial injury due to acute coronary syndrome (type 1) and/or supply-demand mismatch in the setting of profound inflammatory response and haemodynamic changes (type 2) is also significantly greater in those with severe COVID-19.\textsuperscript{31} Vascular inflammation is associated with a large burden of both venous (deep venous thrombosis, pulmonary embolism) and arterial (myocardial infarction, stroke) thrombus.

Severe COVID-19 has also been characterised by extrapulmonary and extravascular manifestations. Acute kidney injury may be a result of direct inflammatory injury, given evidence of acute tubular necrosis with lymphocyte and macrophage infiltration of the tubulointerstitium on histopathology.\textsuperscript{32} The mechanism(s) of COVID-related hepatic injury remains unclear but preliminary studies suggest that the ACE2 receptor is preferentially expressed in cholangiocytes, suggesting that liver involvement may require direct SARS-CoV-2 infection and injury of cholangiocytes.\textsuperscript{33 34} Cytokine storm itself can drive multisystem organ injury overall. Together, these observations suggest that an anti-inflammatory agent with limited immunosuppressive potential could prove useful in preventing severe inflammatory injury and promoting improved patient outcomes.

**COLCHICINE**

**Historical perspective**

Although colchicine first received approval from the US Food and Drug Administration in 2009, its modern use dates back two centuries. Indeed, papyri dating from 1500 BC describe the use of colchicine’s source plant—*Colchicum autumnale*—for pain and inflammation, making colchicine one of the world’s oldest anti-inflammatory therapeutics.\textsuperscript{35} Currently, colchicine is approved for treating and preventing acute gout and familial Mediterranean fever, and is used off label in Behçet’s disease, pericarditis and other inflammatory conditions.\textsuperscript{36}

**Colchicine and microtubules: inhibition of neutrophil activity**

Microtubules are dynamic proteins that form via polymerisation of α-/β-tubulin dimers. Colchicine irreversibly intercalates into free α/β dimers that incorporate into and block microtubule extension.\textsuperscript{37} During inflammation, microtubules facilitate the movement of adhesion molecules onto cell surfaces. Colchicine concentrations are much higher in neutrophils than other leukocytes due to diminished activity of the P-glycoprotein membrane efflux pump that serves as an energy-dependent colchicine efflux
transporter. Thus, neutrophils appear to be more sensitive than other cells to lower serum concentrations of colchicine. Cronstein et al demonstrated that colchicine causes a quantitative decrease in leucocyte (L)-selectin expression and diminishes qualitative expression of endothelial (E)-selectin, two proteins involved in rolling and adhesion of neutrophils on endothelium. Disruption of microtubules also inhibits neutrophil rheologic capacity, inhibiting their transmigration out of blood vessels.

Additional studies show that colchicine directly inhibits intracellular neutrophil signalling and lysosomal enzyme release during phagocytosis. Colchicine-mediated inhibition of chemokine production by inhibiting activation of the NLRP3 inflammasome (figure 5). The mechanism(s) of colchicine’s action on the inflammasome remain an area of ongoing investigation. Colchicine’s interruption of inflammasome activation reduces IL-1β production, which in turn prevents the induction of IL-6 and TNF and the recruitment of additional neutrophils and macrophages. Whereas the effect of specific anti-IL-6 inhibition for COVID-19 treatment is somewhat controversial (online supplemental text 1), the ability of colchicine to affect multiple cytokines may offer unique advantages.

Colchicine and the Inflammation/thrombosis interface
Murine models show that colchicine inhibits neutrophil release of α-defensins, thereby potentially preventing large thrombus burdens. At supratherapeutic concentrations, colchicine, through its microtubule effects, converts normal discoid platelets to rounded, irregular structures and inhibits platelet activation by decreasing calcium entry. These mechanisms diminish in vitro platelet-to-platelet aggregation. In contrast, we demonstrated that standard clinical doses of colchicine do not decrease platelet-to-platelet aggregation but do diminish neutrophil-to-platelet aggregation, suggesting that colchicine at physiological doses may provide an inhibitory role at the inflammation/thrombosis interface without comprising homeostatic platelet-to-platelet function. Indeed, in vivo colchicine has not been shown to inhibit non-inflammatory-related thrombosis.

Adverse effects of colchicine
Colchicine metabolism occurs primarily inside hepatocytes via the cytochrome P450 3A4 (CYP3A4). Medications that strongly inhibit CYP3A4 may decrease colchicine’s pharmacological activity. As for other hepatic CYP3A4 inhibitors, the concomitant use of colchicine and cyclosporin may increase colchicine’s plasma levels.

Figure 4  Neutrophil metabolism in the presence of colchicine. Neutrophils were purified from healthy volunteer whole blood using the MACSxpress whole blood neutrophil isolation kit (Miltenyi Biotec, Bergisch Gladbach, Germany) and separated into four aliquots. Neutrophils were coincubated with and without lipopolysaccharide (LPS) and with and without colchicine. In vitro quantification of neutrophil metabolism, measured as extracellular acidification rate (ECAR) (mpH/min), was evaluated using a glycolysis stress test using a Seahorse XFe24 analyzer (Agilent Technologies, Santa Clara, California, USA). Using a modified assay, cells were first incubated with activators (LPS 10 ng/ml with or without colchicine 15 nM) for 10 min.

Figure 5  Colchicine inhibits inflammasome action and reduces supernatant levels of IL-1β. THP1 cells (macrophage cell line) were stimulated with monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals in the presence or absence of colchicine. Supernatants were analysed for IL-1β by Western blot. For the purposes of this figure, the original published blot was quantified using Image J. Adapted from Martinon et al.
inhibit CYP3A4 metabolism (eg, ritonavir, ketocazole, clarithromycin, cyclosporine, diltiazem, verapamil) pose a risk of drug-drug interactions. A small number of publications report cases of death after coadministration of clarithromycin and colchicine in patients with severe chronic renal disease.\textsuperscript{50} \textsuperscript{51} Similar cases have been rarely reported in patients receiving atorvastatin, a statin that is also processed by CYP-3A4, but not with statins that are not metabolised through CYP3A4. In a recent placebo-controlled randomised trial of 4745 patients with a recent myocardial infarction, patients receiving daily colchicine experienced no adverse effects related to the coadministration of statins, including atorvastatin.\textsuperscript{52} In another recent placebo-controlled randomised trial of 5522 patients with stable coronary artery disease, daily colchicine resulted in numerically higher rates of myalgia (HR 1.15, 95\% CI 1.01 to 1.31) and one case of rhabdomyolysis (the patient made a full recovery).\textsuperscript{53} However, a non-significant trend towards increased non-cardiovascular death was observed that requires further investigation. Overall, reports of severe colchicine toxicity tend to occur in the setting of errors in colchicine prescribing.

Approximately 10\%–20\% of colchicine is excreted renally.\textsuperscript{56} However, dose reductions may only be necessary in patients with severe renal impairment.\textsuperscript{54} As a lipophilic molecule, colchicine is usually protein-bound in plasma, with \( \text{PG glycoprotein} \) in the intestinal lining serving as the primary protein for gut excretion of colchicine. Cyclosporine and ranolazine compete for the ligand site on \( \text{PG glycoprotein} \) and can therefore lead to delayed elimination. At higher concentrations for longer durations, particularly in the setting of kidney disease, colchicine has been reported to occasionally induce a reversible neuromyopathy. Acute overdose may cause multiorgan system failure and death. Furthermore, increased adverse events may be noted in the simultaneous presence of moderate renal insufficiency with use of multiple CYP3A4 inhibitors.

A meta-analysis of 35 randomised trials of colchicine versus placebo found that the most common and significant adverse effect was diarrhoea.\textsuperscript{55} \textsuperscript{56} The only other adverse effect that occurred at a greater frequency than placebo was a set of pooled gastrointestinal symptoms including nausea, vomiting, diarrhoea, abdominal pain, loss of appetite, and bloating. A striking finding in this meta-analysis was the absence of increased infection rates in the colchicine compared with the placebo arm. However, in contrast to most available data, one retrospective and one prospective study did report increased pneumonia risk with colchicine (online supplemental table 1).

\textbf{COLCHICINE AND COVID-19: THE CLINICAL CASE}

Several of the biological therapies that have been studied and/or used in the setting of severe SARS-CoV-2 infection target some of the same pathways as colchicine, including IL-1\( \beta \) (ie, anakinra) and IL-6 (ie, tocilizumab and sarilumab).\textsuperscript{45} Colchicine differs from these agents in having pleotropic mechanisms of action, being less potent on any single target, and being an oral agent. In contrast to the biological agents used in the midost of cytokine storm, colchicine is not immunosuppressive, is not known to increase risk of infection, and is inexpensive. A review of the mechanisms of SARS-CoV-2 and colchicine in parallel reveals a potential intervention point that may prevent the progression from inflammatory activation (phase 2) to a hyperinflammatory state (phase 3). Taken together with the clinical data described herein, the potential benefits of colchicine are suggested to be maximised when used early in the disease process (ideally prior to phase 2, but certainly prior to phase 3), such as in non-hospitalised patients within a few days of diagnosis regardless of symptoms and/or within a few days of hospitalisation if not already critically ill. However, the optimal timing continues to require further investigation.

\textbf{Colchicine in non-rheumatological inflammatory conditions}

Multiple randomised studies have evaluated the use of colchicine in non-rheumatological inflammatory conditions. Two randomised trials in acute pericarditis demonstrated lower recurrence rate with colchicine versus conventional or placebo therapy.\textsuperscript{58} Colchicine reduced symptom persistence 72 hours after treatment initiation, and colchicine was beneficial even in the setting of recurrent pericarditis.\textsuperscript{59} Used after cardiac surgery, colchicine appears to prevent the inflammatory postpericardiotomy syndrome.\textsuperscript{60}

Colchicine may reduce risk of acute myocardial infarction (AMI). We demonstrated an association between daily colchicine use and decreased prevalence of AMI in patients with gout, a non-traditional cardiovascular risk factor.\textsuperscript{61} \textsuperscript{62} These findings were subsequently reproduced in an independent gout population.\textsuperscript{63} Two open-label prospective studies of daily colchicine use versus no colchicine use in patients with stable coronary artery disease already on aspirin and high-intensity statin therapy demonstrated a decrease in CRP levels with low-dose colchicine, and a significant reduction in cardiovascular events with daily colchicine vs no colchicine.\textsuperscript{64} \textsuperscript{65} The reduction in the primary clinical outcome was driven primarily by a reduction in AMI.\textsuperscript{66} The multicentre, double-blind COLchicine Cardiovascular Outcomes Trial (COLCOT) randomised 4745 patients within 30 days of AMI to colchicine or placebo and demonstrated a reduction in the primary composite endpoint of cardiovascular death, resuscitated cardiac arrest, AMI, stroke or urgent revascularisation with colchicine.\textsuperscript{32} The multicentre, double-blind Low Dose Colchicine 2 (LoDoCo 2) trial randomised 5522 patients with stable coronary artery disease and also demonstrated a reduction in the primary composite endpoint of cardiovascular death, AMI, stroke or urgent revascularisation.\textsuperscript{67} Finally, in cases where the thrombus burden remains refractory to standard antileptate and anticoagulant therapies, colchicine has been shown to be associated with thrombus resolution.\textsuperscript{68}

Our 400-patient randomised Colchicine in Percutaneous Coronary Intervention (Colchicine-PCI) trial demonstrated that when given as a standard loading dose prior to tissue injury (coronary stent placement), colchicine significantly dampened the upregulation of IL-6 and CRP.\textsuperscript{69} These effects were observed 22–24 hours after the acute event, providing a rationale to administer colchicine earlier in the disease process to prevent clinical manifestations of cytokine-induced injury. Consistent with a possible preventive role, colchicine is effective to prevent cytokine-based disease flares in gout and familial Mediterranean fever.\textsuperscript{70} Finally, colchicine has also been shown to dampen the inflammatory response and reduce CRP levels among subjects with metabolic syndrome.\textsuperscript{68} These data support the general anti-inflammatory effect of colchicine, independent of a specific disease state.

\textbf{Colchicine trials in COVID-19}

The recent open-label, multicentre Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial in the UK demonstrated a reduction in 28-day mortality with dexamethasone (n=2104) vs usual care (n=4321) in patients hospitalised with severe COVID-19.\textsuperscript{71}\textsuperscript{72} These data support the principle that an anti-inflammatory strategy in COVID-19 may be helpful. However,
glucocorticoids such as dexamethasone have intrinsic immunosuppressive drawbacks that colchicine does not share.

Several early studies have evaluated the benefit of colchicine in COVID-19 patients. A retrospective single-centre study of 87 ICU patients with COVID-19 demonstrated a lower risk of death in patients on colchicine (adjusted HR 0.41, 95% CI 0.17 to 0.98).\cite{10.1136/annrheumdis-2020-219174} The Greek Effects of Colchicine in COVID-19 (GRECO-19) trial was the first prospective open-label randomised trial evaluating colchicine versus usual care in early hospitalised patients. This study of 105 patients found a significant reduction in the primary clinical outcome of a two-point deterioration on WHO disease severity scale.\cite{10.1136/annrheumdis-2020-219174} The authors additionally noted suppression of D-dimer levels in the colchicine vs control group.\cite{10.1136/annrheumdis-2020-219174} An Italian study compared 122 hospitalised patients who received colchicine plus standard-of-care (lopinavir/ritonavir, dexamethasone or hydroxychloroquine) with 140 hospitalised patients receiving standard-of-care alone. Colchicine had a significant mortality benefit (84% vs 64% survival) vs controls.\cite{10.1136/annrheumdis-2020-219174} A third prospective study randomised 38 hospitalised COVID-19 patients to colchicine or placebo in a double-blinded manner.\cite{10.1136/annrheumdis-2020-219174} Patients receiving colchicine had less need for supplemental oxygen at day 7 (6% vs 39%) and were more likely to be discharged at day 10 (94% vs 83%). Colchicine subjects also had greater reduction of CRP and no increase in serious adverse events.\cite{10.1136/annrheumdis-2020-219174} Additional inpatient studies are ongoing (online supplemental table 2). Although the permitted use of other treatments could have biased the impact of colchicine in these studies, in the GRECO-19 trial no glucocorticoids were administered and other medications did not differ between the two groups; in the Italian study, there was no difference in outcomes among patients given colchicine who did or did not also receive dexamethasone.

Given its ease of use, tolerability and low cost, an argument for studying colchicine in the outpatient setting, to reduce hospitalisation and adverse outcomes, may be even more compelling. Unfortunately, data on the use of colchicine in the setting of outpatient COVID-19 cases are sparse. In a very small case series from Italy, nine outpatient patients with COVID-19 were administered colchicine, of whom only one subject was ultimately hospitalised. The hospitalised patient received 4 days of oxygen therapy and was discharged.\cite{10.1136/annrheumdis-2020-219174} Moreover, all patients experienced defer- vescence within 72 hours of colchicine initiation, suggesting an antipyretic effect. While these reports are insufficient to recommend colchicine for COVID-19 in clinical practice, they provide support for further study of colchicine in COVID-19, including in the outpatient setting. The ongoing ColCorona Trial (www.colcorona.net) is a large placebo-controlled trial of colchicine use within 2 days of COVID-19 diagnosis, regardless of symptoms, in patients with comorbidities that place patients at a higher risk of developing complications related to COVID-19 that may provide additional information.

CONCLUSIONS

Given the large body of data demonstrating colchicine’s inhibitory effects on neutrophil activity, cytokine generation and the inflammation/thrombosis interface, together with an overall lack of evidence for systemic immunosuppression, there is a rationale to study colchicine as a potential treatment for COVID-19. Given that colchicine is generally well tolerated, simple to take and inexpensive, demonstration of colchicine as a useful agent in COVID-19 would potentially spare patients morbidity and mortality, help to conserve valuable clinical resources (hospital floor and ICU beds, ventilators, etc), and dramatically reduce the cost of COVID-19 care. Colchicine might be of particular use in resource-poor rural and developing world settings, both of which have been increasingly affected by COVID-19. However, unless and until evidence is obtained from adequately designed and randomised placebo-controlled trials, this hypothesis must remain speculative.

The optimal dose of colchicine for daily use, even in well-established conditions such as gout, is unknown. Many but not all patients tolerate up to 1.2 mg daily in divided doses; whether lower doses such as 0.5 mg or less daily can be equally effective is unknown. The largest colchicine study for COVID-19 (ColCorona) is testing a dose of 0.5 mg daily based on prior cardiology trials. The duration of colchicine therapy for SARS-COV2 infection would also need to be determined. Most studies to date test a treatment duration of 2-4 weeks, concordant with the acute course of the infection; whether a shorter or longer treatment would be optimal is unknown. Finally, the timing of colchicine initiation is uncertain, with some studies beginning treatment in the outpatient setting, and others in the early inpatient setting. Given the recent track record of failure of treatment of severe COVID-19 treatment with anti-IL-6 biologics such as tocilizumab (a much more potent but also more specific immunosuppressive agent), it is likely that the severe inpatient setting is not the optimal condition under which to assess colchicine efficacy.
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REFERENCES


Supplemental Text 1: IL-6 in COVID-19 Infection

The review by Leisman et al (2020) demonstrated IL-6 concentrations in other conditions associated with markedly elevated cytokine levels (i.e., sepsis, CAR-T-associated cytokine release syndrome, and non-COVID-19 ARDS) were anywhere from 12 to 100 times higher than the IL-6 concentrations associated with severe or critical COVID-19 infection. The authors suggest that cytokine storm may not play as pivotal a role in COVID-19-induced end-organ dysfunction as previously thought. However, it is important to consider that these other hyperinflammatory conditions analyzed in the aforementioned have differing pathophysiology and biology compared to COVID-19, and as such a head-to-head comparison of IL-6 levels may not be entirely appropriate in evaluating the role of the cytokine response in COVID-19. In fact, studies have shown that elevated IL-6 levels in COVID-19 are associated with higher SARS-CoV-2 viral load and poorer prognosis, thus supporting the central role of a heightened inflammatory response in COVID-19 (1,2). This observation does not preclude the possibility that other cytokines associated with the release syndrome (e.g., IL-1β, which is more directly regulated by colchicine than IL-6)) may be equally or more important than IL-6 in COVID-19 responses.

Since the start of the COVID-19 pandemic, significant resources have been allocated to investigate the therapeutic efficacy of anti-IL-6 therapies with respect to severe COVID-19 infection. Thus far, the results of these studies have been equivocal at best. In a meta-analysis by Lan et al, although patients treated with tocilizumab were found to have lower all-cause mortality compared to the placebo group, the results did not achieve statistical significance, with risk of ICU admission and the need for mechanical ventilation similar between the two groups (3). None of the included studies were randomized controlled trials, however, and in many of them baseline characteristics/illness severity of patients were not matched. Larger-scale randomized trials have shown similar results, with trials of both tocilizumab and sarilumab failing to meet their primary endpoint (4,5). Furthermore, some studies have demonstrated that the immunosuppressive effects of anti-IL-6 therapies may actually contribute to adverse effects in COVID-19 patients due to secondary bacterial or, less commonly, fungal infections (3,6). Despite these overall
disappointing results, ongoing studies continue to investigate anti-IL-6 agents with respect to combination therapies, and alternative dosing regimens that may hold promise for COVID-19 infection.

Although colchicine has been shown to inhibit IL-6 secretion, it has multiple additional mechanisms of action that may potentially temper the COVID-19-induced hyperinflammatory response. Additionally, colchicine is not immunosuppressive compared to its anti-IL-6 counterparts, and thus may be a more suitable COVID-19 treatment. Finally, most studies of colchicine have aimed to dampen inflammation at an early stage, whereas most studies of anti-IL-6 therapeutics have been directed at treating the COVID-19 inflammatory response at a very advance stage of the infection, when targeting a single cytokine may simply be too little, too late.

References


**Supplemental Table 1. Studies Reporting the Risk of Pneumonia with Colchicine**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nidorf et al, NEJM 2020</td>
<td>Prospective double-blind trial, colchicine vs placebo</td>
<td>No increase in pneumonia in colchicine group</td>
</tr>
<tr>
<td>Tardif et al, NEJM 2020</td>
<td>Prospective double-blind trial, colchicine vs placebo</td>
<td>Increased pneumonia in colchicine group</td>
</tr>
<tr>
<td>Besisow et al, European Journal of Cardio-Thoracic Surgery 2018</td>
<td>Prospective randomized study, colchicine vs placebo</td>
<td>One patient with pneumonitis in colchicine group vs none in placebo group</td>
</tr>
<tr>
<td>Tsai et al, Frontiers in Pharmacology 2019</td>
<td>Retrospective cohort study, colchicine vs no colchicine</td>
<td>Higher cumulative incidence of pneumonia in colchicine group; higher with longer exposure</td>
</tr>
<tr>
<td>Spaetgens et al, Scientific Reports 2017</td>
<td>Retrospective cohort study, colchicine vs no colchicine</td>
<td>Increased pneumonia among past but not current colchicine users</td>
</tr>
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### Supplemental Table 2. Published and Ongoing Studies of Colchicine in COVID-19

<table>
<thead>
<tr>
<th>Study (Date)</th>
<th>Clinical Setting</th>
<th>Design (n)</th>
<th>Exclusion Criteria*</th>
<th>Intervention</th>
<th>Primary Outcome(s)</th>
<th>Secondary Outcome(s)</th>
<th>Significant Results</th>
<th>Inflammatory Measures</th>
<th>Reference</th>
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<tbody>
<tr>
<td>GRECCO-19</td>
<td>Early Inpatient</td>
<td>Randomized, open-label vs usual care (105)</td>
<td>Hepatic failure, eGFR &lt;20 mL/min/1.73 m², QTc ≥ 450 ms, early mechanical ventilation</td>
<td>Colchicine 1.5 mg loading dose + 0.5 mg after 60 minutes, then 0.5 mg BID</td>
<td>1) maximum high-sensitivity cardiac troponin level, 2) time for CRP to reach &gt;3x ULN, 3) Clinical deterioration by WHO scale</td>
<td>1) % requiring mechanical ventilation, 2) all-cause mortality, 3) adverse events</td>
<td>Clinical primary end point lower (p=0.02), Maximum D-dimer lower (p=0.04), Higher diarrhea incidence (p=0.003)</td>
<td>CPK, CRP, d-dimer, ferritin, LDH, procalcitonin, troponin</td>
<td>Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA Netw Open. 2020;3(6):e2013136.</td>
</tr>
<tr>
<td>Scarsi et al.</td>
<td>Early Inpatient</td>
<td>Randomized, open-label vs usual care (262)</td>
<td>Renal failure</td>
<td>Colchicine 1 mg per day (reduced to 0.5 mg if severe diarrhea)</td>
<td>Survival rates</td>
<td>Higher survival (84% vs 64%, p&lt;0.001)</td>
<td>CRP, Ferritin</td>
<td>CRP, Ferritin</td>
<td>Scarsi M, Piantoni S, Colombi E, et al. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. Ann Rheum Dis. 2020.</td>
</tr>
<tr>
<td>Lopes et al.</td>
<td>Inpatient, moderate to severe disease</td>
<td>Randomized, double-blind, placebo-controlled (38)</td>
<td>Weight ≤ 50 kg, abnormal calcium or potassium levels, QTc ≥ 450 ms, diarrhea causing dehydration, porphyria, myasthenia gravis, uncontrolled arthrythmia, metastastic cancer, immunosuppressive chemotherapy, CYP3A4 inhibitor use, hepatic failure</td>
<td>Colchicine 0.5 mg TID for 5 days, then 0.5 mg BID for 5 days</td>
<td>1) Supplemental oxygen, 2) LOS, 3) ICU admission, 4) ICU LOS, 5) all-cause mortality</td>
<td>Less need for supplemental oxygen (p=0.01), Shorter LOS (p=0.01), Reduction in CRP (p=0.001)</td>
<td>CRP, LDH</td>
<td>CRP, LDH</td>
<td>Lopes MIF, Bonomo LP, Giannetti MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. medRxiv. [Preprint]. Date Accessed: August 25, 2020. <a href="https://doi.org/10.1101/2020.08.06.20169173">https://doi.org/10.1101/2020.08.06.20169173</a>.</td>
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**eGFR** – estimated glomerular filtration rate, **QTc** – corrected QT interval, **CRP** – c-reactive protein, **LDH** – lactate dehydrogenase, **IL-6** – interleukin-6, **SARS** – severe acute respiratory syndrome, **CK** – creatinine kinase, **CrCL** – creatinine clearance, **TNF-alpha** – tumor necrosis factor-alpha, **GDF-15** – growth differentiation factor-15, **BNP** – B-type natriuretic peptide, **IBD** – inflammatory bowel disease,

* Patients with hypersensitivity to colchicine, <18, and pregnant were not included in most studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Intervention</th>
<th>Primary Outcomes</th>
<th>Secondary Outcomes</th>
<th>Status</th>
<th>CRP, LDH</th>
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<tr>
<td>Dalili et al. (March 20, 2020 to present)</td>
<td>Inpatient</td>
<td>Randomized, double-blind, placebo-controlled (80, anticipated)</td>
<td>Hypoxia, hepatic failure, eGFR &lt; 20 mL/min/1.73 m²</td>
<td>1) CRP change, 2) Clinical deterioration by WHO scale, 3) PCR viral load change, 4) CT severity</td>
<td>Ongoing</td>
<td>CRP, LDH</td>
</tr>
<tr>
<td>Mostafaie et al. (April 1, 2020 to present)</td>
<td>Inpatient</td>
<td>Randomized, double-blind, placebo-controlled (200, anticipated)</td>
<td>Severe kidney dysfunction</td>
<td>Colchicine plus Phenolic Monoterpene Fractions</td>
<td>All-cause mortality</td>
<td>1) Change in clinical manigestation, 2) LOS, 3) Lab parameters (CRP, Lymphocytes, LDH, IL-6, ESR)</td>
</tr>
<tr>
<td>COLCOVID (April 17, 2020 to present)</td>
<td>Early or Late Inpatient</td>
<td>Randomized, open-label vs usual care (2500, anticipated)</td>
<td>No evidence of SARS</td>
<td>Colchicine 1.5mg loading dose, then 0.5mg BID for 14 days or until discharge</td>
<td>All-cause mortality</td>
<td>Composite outcome: mechanical ventilation or death</td>
</tr>
<tr>
<td>COLVID-19 (April 18, 2020 to present)</td>
<td>Early Inpatient</td>
<td>Randomized, open-label vs usual care (308, anticipated)</td>
<td>Severe diarrhea, CrCL &lt; 30 mL/min, liver damage, CYP3A4 inhibitor use, tocilizumab use, neutrophilia, thrombocytopenia, diverticulitis or bowel perforation, ICU admission</td>
<td>Colchicine 0.5mg TID for 30 days</td>
<td>Rate of entering critical stage</td>
<td>1) WBC trend, 2) SOFA change, 3) Lab recovery (CK, ALT, ferritin), Disease remission, 4) Adverse events</td>
</tr>
<tr>
<td>CoCoVID-19 (April 20, 2020 to present)</td>
<td>Inpatient</td>
<td>Randomized, open-label vs usual care (310, anticipated)</td>
<td>Hypoxia, unstable hepatitis failure, antiviral use</td>
<td>Colchicine 1mg daily</td>
<td>1) Clinical improvement by WHO, 2) Discharge</td>
<td>1) Death, 2) Clinical change by WHO, 3) Mechanical ventilation, 4) LOS, 5) Time to mortality, 6) Time to PCR negative, 7) Fever remission time</td>
</tr>
</tbody>
</table>
| ACTCOVID19  
(April 21, 2020 to present)  Early Outpatient and Early Inpatient | Randomized, open-label vs usual care 4000, anticipated | Advanced kidney disease, advanced liver disease, CYP3A4 inhibitor use, therapeutic antiagulation or antiplatelet use | Outpatient: Colchicine 0.6mg BID for 3 days, then 0.6mg daily for 25 days. Inpatient: 1.2mg loading dose, then 0.6mg 2 hours later, then 0.6mg BID for 28 days | Outpatient: Composite hospitalization or death; Inpatient: Composite: mechanical ventilation or death | 1) Clinical deterioration by WHO, 2) Composite: MACE | Ongoing | None |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| COMBATCOVID19  
(April 26 to June 14, 2020)  Inpatient | Randomized, open-label vs usual care 70, anticipated | Hypoxia using >8L supplemental oxygen, unstable, cirrhosis, liver injury, CrCl < 30 mL/min, early mechanical ventilation, CYP3A4 inhibitor use, chemotherapy use | Colchicine 1.2mg loading dose, then 0.6mg 2 hours later, then 0.6mg BID for 14 days or until discharge | % requiring supplemental oxygen >8L NC | 1) Mechanical ventilation, 2) LOS, 3) Mortality, 4) Maximum CRP, 5) Maximum troponin | Pending Publication | CRP, troponin |
| COL-COVID  
(April 30, 2020 to present)  Early Inpatient | Randomized, open-label vs usual care 102, anticipated | Early mechanical ventilation, IBD, previous neuromuscular disease, < 1 year prognosis due to other disease, eGFR <30 mL/min, carhosis, liver injury, immunosuppressive or immunomodulatory use within 6 months | Colchicine 1mg, then 0.5mg 2 hours later, then 0.5mg BID for 7 days, then 0.5mg daily for 28 days total | 1) Clinical deterioration by WHO, 2) IL-6 changes | 1) Clinical improvement by WHO scale, 2) SOFA change, 3) NEWS change, 4) Mechanical ventilation time, 5) Supplemental oxygen, 6) Lab changes (CRP, TNF, GDF-15, IL-1β, D-dimer, Leukocytes, Lymphocytes, Platelets, LDH, Ferritin, Troponin, BNP, PCR status), 7) LOS, 8) ICU days, 9) Mortality | Ongoing | BNP, CRP, d-dimer, GDF-15, IL-1β, IL-6, LDH, TNF-alpha, troponin |
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Design</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Status</th>
<th>Identifier</th>
<th>ClinicalTrials.gov URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLHEART-19</td>
<td>Inpatient</td>
<td>Randomized, open-label vs usual care</td>
<td>No cardiac injury, CYP3A4 inhibitor use, severe hematologic disorder, severe neuromuscular disorder, severe renal impairment with hepatic impairment</td>
<td>Colchicine 0.6mg BID for 30 days</td>
<td>Composite of all-cause mortality, mechanical ventilation, or mechanical circulatory support</td>
<td>1) Lab changes (Troponin, BNP, CRP, D-dimer), 2) LVEF change, 3) Time to primary endpoint, 4) Number of mechanical ventilation and circulatory support, 5) Rehospitalization, 6) All-cause mortality</td>
<td>Ongoing</td>
<td>NCT04355143</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT04355143">ClinicalTrials.gov</a></td>
</tr>
<tr>
<td>COLORIT</td>
<td>Unspecified</td>
<td>Randomized, open-label</td>
<td>No hypoxia, normal CRP, liver failure, GFR &lt; 20 mL/min, QTc &gt; 450 ms, steroid or immunosuppressive use, active cancer, early mechanical ventilation</td>
<td>Colchicine 0.5mg BID for 3 days, then 0.5mg daily/BID based on weight for 7 days</td>
<td>Change from baseline in CAS COVID 19</td>
<td>1) Combination time to death or mechanical ventilation, 2) Lab changes (CRP, D-dimer), 3) EQ-5D change, 4) Lung CT exposure area change</td>
<td>Pending Publication</td>
<td>NCT04403243</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT04403243">ClinicalTrials.gov</a></td>
</tr>
<tr>
<td>ColchiVID</td>
<td>Inpatient</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>&gt; 70 years old, CrCl &lt; 30 mL/min, liver failure, CYP3A4 inhibitor use</td>
<td>Colchicine 1.5mg loading dose, then 0.5mg BID for 10 days</td>
<td>1) Number of patients with improvement in body temperature, myalgia, arthralgia, total lymphocyte count, D-dimer, fibrinogen, and ferritin, 2) Progression to severe disease</td>
<td>None</td>
<td>Ongoing</td>
<td>NCT04367168</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT04367168">ClinicalTrials.gov</a></td>
</tr>
<tr>
<td>COLCOVIDBD</td>
<td>Early Inpatient</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Hepatic failure, eGFR &lt;30 mL/min, decompensated heart failure, QTc &gt; 450 ms, IBD, chemotherapy use</td>
<td>Colchicine 1.2mg BID for 1 day, then 0.6mg daily for 13 days</td>
<td>Time to deterioration by 2 points on 7-grade clinical status scale.</td>
<td>1) LOS, 2) Supplemental oxygen, 3) Mechanical ventilation, 4) Mortality</td>
<td>Ongoing</td>
<td>NCT04527562</td>
<td><a href="https://clinicaltrials.gov/ct2/show/NCT04527562">ClinicalTrials.gov</a></td>
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<tr>
<th>Study</th>
<th>Type</th>
<th>Design</th>
<th>Criteria</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Sponsor</th>
</tr>
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<tbody>
<tr>
<td>Della-Torre et al. (Published May 31, 2020)</td>
<td>Outpatient</td>
<td>Non-randomized, open label case series (9)</td>
<td>None</td>
<td>Colchicine 1mg BID for 1 day, then 1mg daily until afebrile for 3 days</td>
<td>One patient hospitalized for 4 days</td>
<td>None</td>
</tr>
<tr>
<td>COLCORONA (March 23, 2020 to present)</td>
<td>Early Outpatient</td>
<td>Randomized, double-blind, placebo-controlled (6000, anticipated)</td>
<td>≤ 40 years old, no high-risk criteria, unstable, BID, neuromuscular disease, eGFR &lt;30 mL/min, cirrhosis, liver injury, chemotherapy use</td>
<td>Colchicine 0.5mg BID for 3 days, then 0.5mg daily for 27 days</td>
<td>Composite: Hospitalization or Death</td>
<td>Ongoing</td>
</tr>
<tr>
<td>ACTCOVID19 (April 21, 2020 to present)</td>
<td>Early Outpatient and Early Inpatient</td>
<td>Randomized, open-label colchicine vs IFN-beta vs ASA vs rivaroxaban vs usual care (4000, anticipated)</td>
<td>No high-risk criteria, advanced kidney disease, advanced liver disease, CYP3A4 inhibitor use, therapeutic anticoagulation or antiplatelets</td>
<td>Outpatient: Colchicine 0.6mg BID for 3 days, then 0.6mg daily for 25 days. Inpatient: 1.2mg loading dose, then 0.6mg 2 hours later, then 0.6mg BID for 28 days</td>
<td>Outpatient: Composite hospitalization or death; Inpatient: Composite: mechanical ventilation or death</td>
<td>Ongoing</td>
</tr>
<tr>
<td>COLCHI-COVID (May 25, 2020 to present)</td>
<td>Early Outpatient</td>
<td>Randomized, open-label vs usual care (1028, anticipated)</td>
<td>≥ 70 years old, no high-risk criteria, severe gastrointestinal disease, neuromuscular disease, eGFR &lt;30 mL/min, cirrhosis, liver injury, chemotherapy use, CYP3A4 inhibitor use,</td>
<td>Colchicine 0.5mg BID for 3 days, then 0.5mg daily for 18 days</td>
<td>1) Mortality, 2) Hospitalization</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>