South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: COLCHICINE FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 20 October 2020 *(first update of original 6 August 2020 rapid review report)*

Key findings

- We conducted a rapid review of available clinical evidence regarding the efficacy and safety of colchicine treatment in COVID-19 patients requiring hospitalisation.
- A comprehensive search on 7 October 2020 identified six published reports (relating to 3 randomised controlled trials), as well as 19 planned or ongoing studies.
- Three randomised controlled trials included 248 participants in total. Two trials did not reach their planned sample size; it is unclear whether the third reached its sample size.
- A meta-analysis of the studies found no significant difference in mortality at day 14 to day 28 (RR 0.24, 95% CI 0.03 to 2.09) or progression to a WHO score of 7 or above between day 14 and 28 (RR 0.16, 95% CI 0.02 to 1.29) (very low certainty evidence).Colchicine's effect on the duration of hospitalization for COVID-19 is uncertain, and inconsistent across trials: 2 studies showed a modest reduction, while the largest trial reported no significant difference.
- Adverse events, particularly diarrhoea, were more frequent in those treated with colchicine.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
	X				

Recommendation: We recommend against the use of colchicine for the treatment of COVID-19 in hospitalised patients, unless in the context of an approved clinical trial.

Rationale: The evidence of efficacy and safety is very uncertain at this point, with insufficient evidence of clinically-relevant benefits and an uncertain risk of serious adverse effects.

Level of Evidence: RCTs of very low quality (not altered by additional evidence)

Review indicator: Evidence of safety and/or efficacy that is sufficient to change the recommendation.

(Refer to appendix 5 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish *(Chair)*, Helen Rees, Gary Reubenson *(Vice-Chair)*.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

Colchicine, an oral anti-inflammatory drug used to treat gout, has been proposed as a potential treatment for COVID-19. Its mechanisms of action include inhibition of neutrophil and monocyte recruitment, and inhibition of pro-inflammatory cytokines, both of which are thought to be important mediators of COVID-19 disease severity.[1,2]

RESEARCH QUESTION: Should colchicine be used for managing COVID-19 patients requiring hospital admission, with or without other medicines?

METHODS

We conducted a rapid review of the evidence relating to colchicine through the systematic searching of three electronic databases (Epistemonikos, the Cochrane COVID Register and www.covid-nma.com) on 17 July 2020, and updated the search on 7 October 2020. The search strategy is shown in Appendix 1. Screening of records was done independently and in duplicate (MM and AB for the update), with arbitration by the third reviewer where necessary, using Covidence systematic review software.

For living systematic reviews of RCTs on www.covid-nma.com, the quality of randomised controlled trials was assessed[3] using the Risk of Bias 2.0 tool.[4] Evidence profiles were also generated[3] for www.covid-nma.com using GRADEPro software[5], with all ordinal scale outcomes transformed to the WHO 10-point ordinal scale[6] for the purposes of standardisation (Appendix 3). A score of 6 corresponded with requiring oxygen by non-invasive ventilation (NIV) or high flow nasal cannulae (HFNO); 7 with intubation and mechanical ventilation; 8 with mechanical ventilation or vasopressors; 9 with mechanical ventilation and vasopressors, dialysis, or extracorporeal membrane oxygenation (ECMO); and 10 with death. MAGICapp[7], using GRADE methodology, was also consulted as a living ecosystem of evidence from the Australian guidelines for the clinical care of people with COVID-19. Relevant study data were extracted in a narrative table of results (MM for the update), with results reviewed, checked and reported by another reviewer (AB). RdW and AG reviewed the overall report.

Eligibility criteria for review

Population: Patients with confirmed COVID-19, no restriction to age or co-morbidity, but requiring admission to hospital.

Intervention: Colchicine, either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality; duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV-2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; progression to requiring oxygen; duration of ICU stay; adverse reactions and adverse events; clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement.

Study designs: Systematic reviews of trials, and if not available comparative study designs will be sought. Where not found, other study designs such as case series, non-randomised cohorts will be reported. Single case reports excluded.

RESULTS

Results of search

After the removal of 102 duplicates, two reviewers screened 63 records and identified three randomised controlled trials[8-10].See Figure 1 for the PRISMA flow diagram.

A total of 19 ongoing trials were identified among the 28 eligible full-text records. Table 1 shows the main characteristics and outcomes of the included trials, Table 2 describes the excluded studies and Table 3 summarises the ongoing trials.

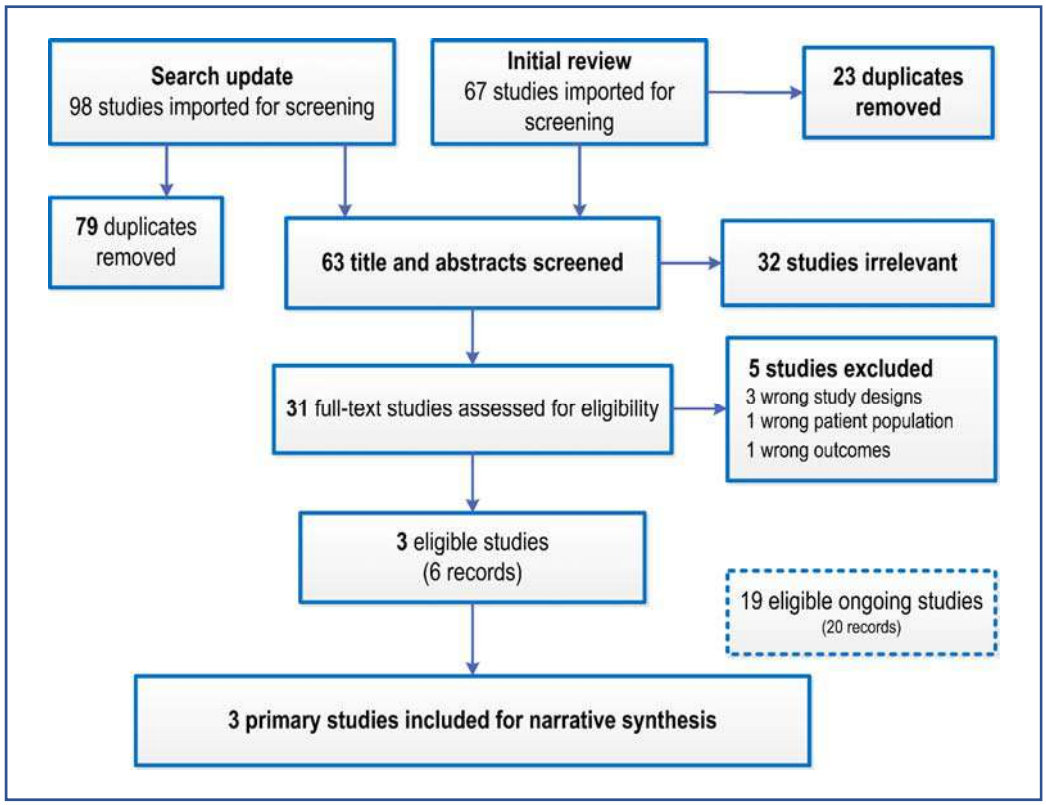

Figure 1. PRISMA flow diagram for review

Description of included studies

We found three randomised controlled trials, conducted in Greece, Brazil and Iran, which cumulatively included 248 patients with confirmed COVID-19 (with moderate to critical severity). The RCT by Deftereos et al. 2020[8], initially aimed to recruit 180 patients (which would provide 90% power to detect a 50% reduction in the primary clinical end point: time to a 2-point deterioration on a 7-point modified ordinal scale, at α=0.05), but only included 110 patients due to slow enrolment, as the incidence of COVID-19 declined in Greece. The 7-point modified ordinal scale used by the authors of the trial is shown in Appendix 2. The authors report that the trial was not powered to detect differences in rare adverse events. Of note, the vast majority of the included patients received concomitant treatment thought at the time to have an effect on SARS-CoV-2, mostly chloroquine or hydroxychloroquine (98%) and azithromycin (92%). Lopes et al. 2020[9] reported an interim analysis of a study that did not achieve the target sample size. Primary endpoints were clinical parameters, such as the time of need for supplemental oxygen; time of hospitalisation; need for admission and length of stay in ICU; and death rate and causes of mortality. Salehzadeh et al. 2020[10], included 100 patients and the planned outcomes included duration of hospitalisation; cessation of fever; mortality; transfer to ICU and discharge. However, the authors only reported duration of hospitalisation and inflammatory biomarkers.

Effects of the intervention

The currently available evidence on the safety and effectiveness of colchicine for the treatment of people with COVID-19 requiring hospitalisation is of very low certainty. The evidence profiles for the results are found in Table 4.1 and 4.2 and the quality appraisal of the included RCTs, taken from www.covid-nma.com, can be found in Table 5.1 -5.3.

All-cause mortality at day 14 to day 28

The included RCTs were not powered to detect a difference in mortality. A meta-analysis of the studies found no significant difference in mortality at day 14 to day 28 (RR 0.24, 95% CI 0.03 to 2.09; very low certainty evidence)[3]. We are very uncertain whether colchicine has an effect on all-cause mortality.

Duration of hospitalisation

Deftereos[8] reported the median (IQR) duration of hospitalisation was 12 days (9 to 22) in the colchicine group and 13 days (9 to 18) in the control group, with no significant difference between the two groups (p=0.91). Lopes[9] reported a significant reduction from a median (IQR) 8.5 days (5.5 to 11) in the control group to 6 days (4 to 8.5) in the colchicine group (p=0.03), similar to that reported by Salehzadeh[10], i.e. 8.12 (placebo) vs 6.28 (colchicine) days (very low certainty evidence, see Table 4.2).

Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab

None of the included studies reported on this outcome.

Time to negative SARS-CoV-2 PCR on nasopharyngeal swab

None of the included studies reported on this outcome.

Progression to ICU admission

Lopes[9] reported no difference in progression to ICU admission (RR 1.05, 95% CI 0.07-15, very low certainty of evidence).

Progression to mechanical ventilation (incidence of WHO 10-point scale progression score ≥ 7)

In the RCT by Deftereos[8], a total of 1/56 patients in the colchicine group and 6/54 in the control group progressed to a 10-point WHO score of 7 or above (where 7 is mechanical ventilation; 8 is mechanical ventilation or vasopressors; 9 is mechanical ventilation and vasopressors, dialysis, or ECMO; and 10 is death) at day 14 to day 28 (RR 0.16, 95% CI 0.02 to 1.29; very low certainty evidence) (Table 4.1). We are very uncertain whether colchicine has an effect on the incidence of progression to mechanical ventilation.

Progression to requiring oxygen by NIV or HFNO (incidence of WHO 10-point scale progression score ≥ 6)

Lopes[9] reported a significant reduction in time of supplemental oxygen, from 7 days to 3 days, favouring the colchicine group (p=0.02).

Duration of ICU stay

Lopes[9] reported no meaningful difference in duration of ICU stay, 11 (control, n=1) vs 12 (intervention, n=1) days.

Adverse reactions and adverse events

No serious adverse events were recorded, and we are very uncertain about the effect of colchicine on serious adverse events (very low certainty evidence, no estimable effect size due to zero event rate). In the RCT by Deftereos[8], a total of 43/55 (78%) patients in the intervention and 15/50 (30%) in the control group experienced adverse events (RR 2.61, 95% CI 1,67-4,07, very low certainty of evidence), as shown in Table 4.2. The most frequently reported adverse events in both groups was diarrhoea (significantly higher in intervention group: 45.5% vs 18%; p=0.003), with vomiting, nausea, and headache also reported in both groups. The aforementioned are all expected adverse effects associated with colchicine, when used at therapeutic doses for acute gout. Other adverse events in the control group were acute renal failure, pancytopenia, and thrombophlebitis; the intervention group reported one event thought to have been caused by colchicine (elevated liver enzymes, reversed following cessation) and five with uncertain relation to colchicine (elevated liver enzymes, rhinorrhagia, allergic reaction, cutaneous rash and chest discomfort).

Additionally, in the intervention group, two patients had to stop study drugs due to diarrhoea, five had abdominal pain and one developed muscle spasms. One patient per group (1.8% in intervention and 2.0% in control) developed an adverse event judged by field investigators as serious (one case each of thrombocytopenia and diarrhoea), but neither met the RCT's protocol definition of serious according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (i.e. noninvasive intervention indicated). These adverse events were consequently rated as moderate severity.

Other reported outcomes (not pre-specified for this review)

The primary endpoints reported by Deftereos[8] were surrogates based on laboratory values (maximum high-sensitivity cardiac troponin level and the time for C-reactive protein to reach more than 3 times the upper reference limit) and the time to deterioration by 2 points on the 7-grade WHO clinical status scale.

The median (IQR) peak high-sensitivity cardiac troponin values were 0.0112 (0.0043 to 0.0093) ng/mL in the control group and 0.008 (0.004 to 0.0135) ng/mL in the colchicine group (p = 0.34). Median (IQR) maximum C-reactive protein levels were 4.5 (1.4 to 8.9) mg/dL vs 3.1 (0.8 to 9.8) mg/dL (p = 0.73), respectively.

The mean (SD) duration to clinical deterioration of 2 points on a 7-grade[i] clinical status scale (based on the World Health Organization R&D Blueprint Ordinal Clinical Scale) was 20.7 (0.31) days in the intervention group and 18.6 (0.83) days in the control group.

The cumulative event-free (2-point clinical deterioration) 10-day survival was significantly higher for the intervention: 97% in the colchicine group and 83% in the control group (Gehan statistic, 4.9; P=0.03).

CONCLUSION

The current evidence is insufficient to support the inclusion of colchicine in treatment guidelines for COVID-19 patients requiring hospitalisation in South Africa. Additional trials may inform this evidence base further.

Reviewers: Updated review: Michael McCaul, Amanda Brand, Renee de Waal, Andy Gray.

Declaration of interests: MM (Centre for Evidence-based Health Care, Stellenbosch University and SA GRADE Network), AB (Centre for Evidence-based Health Care, Stellenbosch University and SA GRADE Network), RdW (School of Public Health and Family Medicine, University of Cape Town) and AG (Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal) have no relevant conflicts of interest to declare.

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[i] Note that the study reported on the 7-grade ordinal scale (Appendix 3), but the GRADE assessment by Bollig et al. converted these scores to a 10-grade ordinal scale (Appendix 4) to enable comparison with other publications.

Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings
Deftereos, SG et al. JAMA 2020[8] Journal publication	Prospective, open-label, randomised clinical trial Multicenter (n=16 tertiary care hospitals) Trial was terminated early due to slow enrolment in Greece in late April 2020.	Setting: Greece (in hospital) n = 54 (Standard treatment) n = 56 (Colchicine, in addition to standard treatment) Severity: Mild: n=0 / Moderate: n=102/ Severe: n=3 Critical: n=0 Age, median (IQR): 65 (54-80) intervention; 63 (55-70) control Gender Male, n (%): 30 (60.0) intervention; 31 (56.4) control Eligibility: 1. Subjects ≥18 years old with laboratory confirmed SARS-CoV-2 PCR, who presented with clinical symptoms including body temperature >37.5°C. AND 2. At least two of the following criteria: persistent cough, persistent throat pain, anosmia, ageusia, asthenia, arterial blood partial pressure of oxygen (PaO_2) <95 mmHg.	**Treatment** Colchicine (loading dose 1.5 mg; followed by 0.5 mg 60 minutes later if no adverse gastrointestinal effects; then 0.5 mg twice daily (reduced to once daily if body weight <60 kg) until hospital discharge or a maximum of 21 days.) Co-Intervention: Standard care Duration: 21 days **Control** Standard care: optimal medical treatment according to local protocols, as established by the National Public Health Organization and following the guidance of the European Centre for Disease Prevention and Control Concomitant treatment: Most patients received chloroquine or hydroxychloroquine (103; 98.1%) and azithromycin (97; 92.4%). No patients were reported to have received corticosteroids.	**In the report** The primary end points were the difference in maximal high-sensitivity cardiac troponin (hs cTn) levels, the time for C-reactive protein to reach levels > 3 times the upper reference limit, and the time from baseline to clinical deterioration, defined as a 2-grade increase on an ordinal clinical scale, based on the World Health Organization R&D Blueprint Ordinal Clinical Scale within a time frame of 3 weeks after randomisation or until hospital discharge (whichever occurred first). **All-cause mortality** Control: 4/54 (7.4%) vs intervention: 1/56 (1.8%). **Duration of hospitalisation** Median (IQR) hospitalisation was 12 (9-22) days in the intervention and 13 (9-18) days in the control group (p=0.91). **The percentage of participants requiring mechanical ventilation, in those who deteriorated by at least 2 points on the ordinal scale (as defined by Deftereos et al.):** Control: 6/7 (85.7%), Intervention= 1/1 (100.0%). **Number, type, severity, and seriousness of adverse events.** Adverse events were similar for the two groups, with no significant differences by event. The exception was diarrhoea, which was more frequent in the colchicine group; 25/55 (45.5%) patients in the intervention and 9/50 (18.0%) patients in the control group (P=0.003) experienced this event.

Citation	Study design	Population (n)	Treatment	Main findings
				Time to deterioration by 2 points on the 7-grade WHO clinical status scale Control: Mean (SD) 18.6 (0.83) days vs Intervention: 20.7 (0.31) days. **Cumulative event-free 10-day survival** Control: 83% vs Intervention: 97%. **Maximum high-sensitivity cardiac troponin level** Control: Median (IQR) 0.0112 (0.0043-0.0093) vs Intervention: 0.008 (0.004-0.0135) ng/mL. **Maximum C-reactive protein level** Control: Median (IQR) 4.5 (1.4-8.9) mg/dL vs Intervention 3.1 (0.8-9.8) mg/dL.
Lopes, MIF et al. medRxiv 2020[9] Pre-print	RCT, double blind, placebo controlled Single centre Interim analysis 11 April to 6 July 2020	Setting: Brazil n=19 (Colchicine) n=19 (Placebo) Age (years, median (IQR)): 48.0 (41.5 to 64.0) in intervention; 53.5 (35.5 to 65.5) in control 14 males (9 in intervention and 5 in control) Severity : Mild: n=0 / Moderate: n=12/ Severe: n=23 Critical: n=3 Comorbidities (% intervention; % control): Current or former smoking (12; 28), respiratory diseases (18; 11), cardiovascular diseases (47; 33), diabetes mellitus (29; 33), dyslipidemia (18; 33) Inclusion criteria:	**Treatment** Colchicine (0.5mg thrice daily for 5 days, then 0.5mg twice daily for 5 days) with loading dose of 1.0 mg if body weight was ≥ 80 kg Co-Intervention: Standard care as described for control Duration : 10 days **Control** Placebo Duration : 10 days All participants received the institutional treatment for COVID-19 with azithromycin	**All-cause mortality** Control: 0/18 vs Intervention: 0/17 **Discharge from hospital** Control: 13/18 (72%) vs Intervention: 16/17 (94%). RR 1.3 (95% CI 0.96 to 1.87). **Duration of hospitalisation** Duration: 23 (Colchicine) vs 26 (Placebo) days Time of hospitalisation, median (IQR) : Intervention: 6 (4-8.5) Control: 8.5 (5.5-11) p-value: 0.03 **Time of supplemental oxygen, median (IQR)** Intervention: 3 (1.5-6.5) Control: 7 (3-8.5) p-value: 0.02

Citation	Study design	Population (n)	Treatment	Main findings
		Individuals hospitalised with moderate or severe forms of COVID-19 diagnosed by RT-PCR in nasopharyngeal swab specimens and lung computed tomography scan involvement compatible with COVID-19 pneumonia; older than 18 years; body weight > 50 kg; normal levels of serum Ca2+ and K+; QT interval < 450 ms at 12 derivations electrocardiogram (according to the Bazett formula) and negative serum or urinary β-HCG if women under 50. Exclusion criteria: Mild form of COVID-19 or in need for ICU admission; diarrhea resulting in dehydration; known allergy to colchicine; diagnosis of porphyria, myasthenia gravis or uncontrolled arrhythmia at enrollment; pregnancy or lactation; metastatic cancer or immunosuppressive chemotherapy; regular use of digoxin, amiodarone, verapamil or protease inhibitors; chronic liver disease with hepatic failure; inability to understand consent form.	500 mg once daily for up to 7 days, hydroxychloroquine 400 mg twice daily for 2 days, then 400 mg once daily for up to 8 days and unfractionated heparin 5000 UI thrice daily until the end of hospitalization. Methylprednisolone 0.5 mg/kg/day for 5 days could be added if the need for supplemental oxygen was 6 L/min or more.	**Need for supplemental oxygen** Day 2, 53% vs 83% (Colchicine vs Placebo) Day 6, 24% vs 56% (Colchicine vs Placebo) Log-rank, p=0,01 **C-reactive protein, median (IQR)** Day 7, Placebo 2.2 (0.9-2.4) vs Intervention (0.4 (0.3-0.4) (p=0.0001) **Adverse events** The majority of adverse events were mild and did not lead to patient withdrawal. Diarrhoea was more frequent in the Colchicine group (p = 0.17). Cardiac adverse events were absent **Progression to ICU** Control: 1/18 vs Intervention: 1/17 **Length of ICU stay** 11 (Control, n=1) vs 12 (Intervention, n=1) days No variation
Salehzadeh, F et al. Research Square 2020[10] Pre-print	RCT, single centre 21 May to 20 June 2020.	Setting: Iran n= 50 (Hydroxycholorquine and Colchicine) n= 50 (Hydroxycholorquine and placebo) Median age 56, control 55.56 vs intervention 56.56 years Female 69%, control 56% vs intervention 62% Comorbidities (% intervention; % control): diabetes mellitus (10; 12), ischemic heart disease (12; 18), hypertension (6; 16), cancer/neoplastic disorder (2;	Treatment Colchicine (1 mg) Co-Intervention: Standard care Duration : 6 days Control Placebo tablet with no therapeutic effects in addition to standard care (hydroxychloroquine) Duration : 6 days	**Length of hospitalisation (mean)** 6.28 days (Colchicine) vs 8.12 days (Placebo), p<0.001

Citation	Study design	Population (n)	Treatment	Main findings
		2), COPD (0; 8), renal failure (8; 2), hypothyroidism (2; 2) Inclusion criteria: Pulmonary involvement seen in CT-Scan compatible with COVID-19 and Positive PCR of COVID-19 Exclusion: Sensitivity to any medications of regimens, renal failure, heart failure, pregnancy, participating in another clinical study and refusal to participate in the study before or during the follow-up period		

Table 2. Characteristics of excluded studies

Citation	Type of record	Reason for exclusion
Corral P, Corral G, Diaz R. *Colchicine and COVID-19*. The Journal of Clinical Pharmacology 2020;60(8):978.	Journal article (letter)	Wrong study design
Kobak S. *COVID-19 infection in a patient with FMF: does colchicine have a protective effect?* Annals of the Rheumatic Diseases 2020; 0(0):1-2.	Correspondence in journal	Wrong outcomes
Montreal Heart Institute. NCT04322682, first registered 26 March 2020. *Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA) (COVID-19).*	Trial registry	Wrong patient population
Brunetti L, Diawara O, Tsai A, et al. Colchicine to weather the cytokine storm in hospitalized patients with COVID-19. *Journal of Clinical Medicine* 2020;9(9):2961.	Journal article	Wrong study design (cohort)
Scarsi M, Piantoni S, Colombo 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. *Annals of the Rheumatic Diseases* 2020;79:1286-9.	Journal article	Wrong study design (cohort)

Table 3. Characteristics of planned and ongoing studies

Citation	Study design	Population (n)	Treatment
Azienda Ospedaliero - Universitaria di Parma. EUCTR2020-001258-23-IT, first registered 20 April 2020	Randomised controlled trial with parallel assignment	An estimated 310 patients will be recruited	Patients will be randomised to standard of care or **colchicine in tablet form**
Dhaka Medical College. NCT04527562, first registered 26 August 2020	Randomised controlled trial with parallel assignment	An estimated 300 participants will be recruited	Participants will be randomised to standard treatment per the national guidelines of Bangladesh plus placebo or **colchicine at a starting dose of 1.2 mg (single or 12 hourly divided dose), and 0.6 mg daily thereafter for 13 days. In the case of gastrointestinal compliants, omeprazole and antiemetic will be prescribed**
Dalili N, Kashefizadeh A, Nafar M, et al. *Adding colchicine to the antiretroviral medication - lopinavir/ritonavir (Kaletra) in hospitalized patients with non-severe Covid-19 pneumonia: a structured summary of a study protocol for a randomized controlled trial.* Trials 2020;21:489 AND Shahid Beheshti University of Medical Sciences. NCT04360980, first registered 24 April 2020	Randomised controlled trial with parallel assignment	An estimated 80 participants will be recruited	Participants will be randomised to standard treatment (3 g vitamin C, 400 mg tiamine, selenium, 500 mg omega-3, vitamins A and D, azithromycin, ceftriaxone and Kaletra 400 twice a day for 10 days) or **standard treatment plus 1.5 mg colchicine (loading dose) followed by 0.5 mg colchicine orally twice daily**
Estudios Clínicos Latino América. NCT04328480, first registered 31 March 2020	Randomised controlled trial with parallel assignment	An estimated 2500 participants will be recruited	Participants will be randomised to local standard of care or **local standard of care plus colchicine, preferentially administered orally (otherwise via nasogastric route, in the case of ventilation or contraindications to oral**

Citation	Study design	Population (n)	Treatment
			route) at dosage schedules dependent on concomitant lopinavir/ritonavir treatment
FFIS. EUCTR2020-001511-25-ES, first registered 15 April 2020	Randomised controlled trial with parallel assignment	An estimated 102 patients will be recruited	Patients will be randomised to unspecified control or **0.5 mg colchicine**
Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia. NCT04350320, first registered 17 April 2020	Randomised controlled trial with parallel assignment	An estimated 102 participants will be recruited	Participants will be randomised to standard therapy or **standard therapy plus colchicine at a loading dose of 1.5 mg (1 mg and 0.5 mg two hours later), with 0.5 mg every 12 hours thereafter for seven days and 0.5 mg every 24 hours until the completion of 28 days. Dosage will be adjusted in participants receiving lopinavir/ritonavir**
Fundación Universitaria de Ciencias de la Salud. NCT04539873, first registered 7 September 2020	Randomised controlled trial with parallel assignment	An estimated 128 participants will be recruited	Participants will be randomised to standard treatment per the Colombian guidelines or **colchicine 1.5 mg on the first day, followed by 0.5 mg every 12 hours on days 2 to 7 and 0.5 mg per day until completion on day 14 ± 1 days**
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran. NCT04367168, first registered 29 April 2020	Randomised controlled trial with parallel assignment	An estimated 174 participants will be recruited	Participants will be randomised to placebo tablets taken orally, 1.5 tablets on day 1 and half a tablet twice daily for 10 days thereafter, or **colchicine 1 mg at the same dosing frequency**
Kermanshah University of Medical Sciences. NCT04392141, first registered 18 May 2020	Randomised controlled trial with parallel assignment	An estimated 200 participants will be recruited	Participants will be randomised to standard treatment based on national recommendations or **standard treatment plus colchicine and a herbal extraction containing phenolic monoterpene fractions**
Lomonosov Moscow State University Medical Research and Educational Center. NCT04403243, first registered 27 May 2020	Randomised controlled trial with parallel assignment	An estimated 70 participants will be recruited	Participants will be randomised to ruxolitinib 5 mg taken orally twice daily for 10 days, or **colchicine 0.5 mg taken orally twice daily during the first three days and then 0.5 mg taken orally once daily if weight is < 86 kg, or twice daily if weight is > 86 kg, for seven days**
Maimonides Medical Center. NCT04363437, first registered 27 April 2020	Randomised controlled trial with parallel assignment	An estimated 70 participants will be recruited	Participants will be randomised to usual care or **1.2 mg colchicine (loading dose) followed by 0.6 mg two hours later, in the absence of severe gastrointestinal symptoms, on the first day; followed by 0.6 mg twice daily for 14 days or until discharge**
Maria Joyera Rodríguez. NCT04492358, first registered 30 July 2020	Randomised controlled trial with parallel assignment	An estimated 144 participants will be recruited	Participants will be randomised to standard of care or **colchicine 0.3 mg/kg/day (with adjustments for age, weight and kidney function) plus prednisone 60 mg/day for three days, followed by 0.5 mg/day colchicine for a further 14 days**
Mashhad University of Medical Sciences. IRCT20200408046990N2, first registered 25 April 2020	Randomised controlled trial with parallel assignment	An estimated 40 patients will be recruited	Patients will be randomised to placebo tablets once daily for two weeks or **1 mg colchicine tablets once daily for two weeks**

Citation	Study design	Population (n)	Treatment
Miami Cardiac and Vascular Institute. NCT04510038, first registered 12 August 2020	Randomised controlled trial with parallel assignment	An estimated 75 participants with cardiac injury will be recruited	Participants will be randomised to standard of care or **standard of care plus colchicine 0.6 mg twice daily for 30 days, with decreased dose of 0.3 to 0.6 mg daily in the case of gastrointestinal intolerance, CYP3A4 or protease inhibitor, chronic kidney disease at stage 4 or above, end stage renal disease, or dialysis**
Saghafi, F. IRCT20190810044500N5, first registered 18 May 2020	Randomised controlled trial with parallel assignment	An estimated 200 patients will be recruited	Patients will be randomised, in addition to standard treatment of 200 mg hydroxychloroquine daily, to two tablets of placebo for the first to the third day and one daily dose for 12 days thereafter; or **0.5 mg colchicine for the first to the third day and 1 mg daily for 12 days thereafter in addition to 200 mg hydroxychloroquine daily**
Sociedad Española de Cardiología. EUCTR2020-001841-38-ES, first registered 26 May 2020	Clinical trial with single group assignment	An estimated 240 patients will be recruited	Patients will receive 0.5 to 1 mg colchicine
University of California. NCT04355143, first registered 21 April 2020	Randomised controlled trial with parallel assignment	An estimated 150 participants will be recruited	Patients will be randomised to current care as determined by treating physician or **current care plus 0.6 mg colchicine tablets taken orally every 12 hours for 30 days**
University of Perugia. NCT04375202, first registered 5 May 2020	Randomised controlled trial with parallel assignment	An estimated 308 participants will be recruited	Participants will be randomised to current care or **current care plus 1 mg colchicine twice daily (0.5 taken orally every 8 hours) for 30 days, with dosage halved for those weighing < 100 kg**
Yale University. NCT04472611, first registered 15 July 2020	Randomised controlled trial with parallel assignment	An estimated 824 participants will be recruited	Participants will be randomised to standard of care or **standard of care plus rosuvastatin 40 mg daily and colchicine 0.6 mg twice daily for three days, and 0.6 mg once daily thereafter for the duration of hospitalisation**

Table 4.1: Summary of findings[3] (Deftereos et al. 2020[7], Lopes et al. 2020[8])

Author(s): C. Bollig, C. Schmucker, J.J. Meerpohl
Question: Colchicine compared to Standard Care for Moderate/Severe COVID-19
Setting: Worldwide
Bibliography: https://covid-nma.com

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Colchicine	Standard Care	Relative (95% CI)	Absolute (95% CI)		
Incidence viral negative conversion D7 - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Clinical improvement - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Incidence of WHO progression score (level 6 or above D14-D28) *												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	1/56 (1.8%)	7/54 (13.0%)	**RR 0.14** (0.02 to 1.08)	**111 fewer per 1.000** (from 127 fewer to 10 more)	⨁◯◯◯ VERY LOW	
Incidence of WHO progression score (level 7 or above D14-D28) *												
1	randomised trials	not serious	not serious	serious [b]	very serious [c]	none	1/56 (1.8%)	6/54 (11.1%)	**RR 0.16** (0.02 to 1.29)	**93 fewer per 1.000** (from 109 fewer to 32 more)	⨁◯◯◯ VERY LOW	
All-cause mortality D14-D28												
	randomised trials	not serious	not serious	serious [b]	very serious [c]	none	1/56 (1.8%)	4/54 (7.4%)	**RR 0.24** (0.03 to 2.09)	**56 fewer per 1.000** (from 72 fewer to 81 more)	⨁◯◯◯ VERY LOW	
Adverse events - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Serious adverse events D14-D28												
1	randomised trials	serious [a]	not serious	not serious [d]	very serious [e]	none	0/55 (0.0%)	0/50 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Risk of bias downgraded by 1 level: some concerns regarding deviation from inteded intervention and outcome measurement
b. Indirectness downgraded by 1 level: single study from a single country, therefore results in this population might not be generalizable to other settings
c. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants
d. We presume that the adverse event rates, and the corresponding relative risks, is similar across diverse settings; therefore not downgraded for indirectness
e. Imprecision downgraded by 2 levels: no events in both groups

* Progression scores from Deftereos et al were transformed to the WHO 10-point scale.

Table 4.2: Summary of findings from the [Australian guidelines for COVID-19](#) (Deftereos et al. 2020[8], Lopes et al. 2020[9])

Adverse events Within 21 days after commencing treatment 6 Important	Relative risk 2.61 (CI 95% 1.67 - 4.07) Based on data from 105 patients in 1 study	300 per 1000 783 per 1000 Difference: **483 more per 1000** (CI 95% 201 more - 921 more)	**Very Low** Due to serious risk of bias and very serious imprecision	We are uncertain whether colchicine increases or decreases adverse events (58 events). Uncertainty
Discharge from hospital 10 days after commencing treatment 6 Important	Relative risk 1.30 (CI 95% 0.96 - 1.78) Based on data from 35 patients in 1 study	722 per 1000 939 per 1000 Difference: **217 more per 1000** (CI 95% 29 fewer - 563 more)	**Low** Due to very serious imprecision	We are uncertain whether colchicine increases or decreases discharge from hospital (29 events). Uncertainty
Duration of hospital stay Days 6 Important	- Lower better Based on data from 100 patients in 1 study	8.12 (Mean) 6.28 (Mean) Difference: **1.84 lower**	**Very Low** Due to very serious risk of bias and very serious imprecision	We are uncertain whether colchicine increases or decreases duration of hospital stay. Uncertainty

Table 5.1: Quality appraisal: overall risk of bias for the primary outcome (2-grade increase on an ordinal scale for clinical deterioration) from Bollig et al.[3] (Deftereos et al. 2020[8])

Bias	Author's judgment	Support for judgment
Randomisation	Low	Quote: "Eligible patients were randomly assigned (1:1) to either the control group or the colchicine group. The randomization sequence was prepared by a statistician not involved in the trial using R software version 3.6.2 (R Project for Statistical Computing), and the corresponding assignment was provided to site coordinators electronically on each patient enrollment." Comment: There are minor imbalances in baseline data between the two groups (see Table 1). These imbalances do not systematically favor one group over the other, and we do not consider that they could impact the results of the trial.
Deviations from intervention	Some concerns	Comment: Unblinded study. No indication of participant crossover. Outcome data were analyzed by using intention-to-treat analysis.
Missing outcome data	Low	Comment: 110 randomized/105 analyzed. Risk assessed to be low for the outcomes: Mortality. Score 6 and above. Score 7 and above. Serious adverse events
Measurement of the outcome	Some concerns	Comment: Mortality is an observer-reported outcome not involving judgement. Score 6 and above and Score 7 and above are outcomes that reflect decisions made by the intervention provider. We consider that the assessment of Mortality and Score 7 and above cannot possibly be influenced by knowledge of the intervention assignment. Risk assessed to be low for outcomes: Mortality. Score 7 and above. For Score 6 and above, although the assessment could possibly be influence by knowledge of the intervention assignment, we did not consider this likely to have happened in the context of a pandemic. Serious adverse events may contain both clinically- and laboratory-detected outcomes, therefore it can be influenced by knowledge of the intervention assignment, but is not likely to. Risk assessed to be some concerns for outcomes: Score 6 and above. Serious adverse events.
Selection of the reported results	Low	Comment: the protocol and statistical analysis plan were available. Risk assessed to be low for the outcomes: Mortality. Score 6 and above. Score 7 and above. Serious adverse events.
Overall risk of bias	**Some concerns**	

Table 5.2: Quality appraisal: overall risk of bias for the primary outcome (Time of need for supplemental oxygen; time of hospitalization; need for admission and length of stay in ICU; and death rate and causes of mortality) from covid-nma.com (Lopes et al. 2020[9])

Bias	Author's judgment	Support for judgment
Randomisation	Low	Quote: "The randomization was performed 1:1 for placebo or colchicine by using the online tool at https://www.randomizer.org/." Comment: Allocation sequence random. Allocation sequence was concealed.
Deviations from intervention	Low	Comment: Double-blinded study. Data were analyzed using intention-to-treat analysis.
Missing outcome data	Some concerns	Comment: 38 randomized, 35 analyzed. Following contact with authors, 2 patients who discontinued due to ICU admission were discharged after 23 and 26 days (outcome known). Safety event unknown in these 2 patients. Risk assessed to be low for outcomes: Mortality. Incidence of clinical improvement. Incidence of WHO score 6 and above. Incidence of WHO score 7 and above. Risk assessed to be some concerns for outcomes: Adverse events. Serious adverse events.
Measurement of the outcome	Some concerns	Comment: This is a double-blinded study (participants and clinicians/carers). Mortality is an observer-reported outcome not involving judgement. is For the outcome incidence of WHO score 7 and above, we consider that the assessment cannot possibly be influenced by knowledge of the intervention assignment. Pneumonia (assessed via imaging) was the only serious adverse event reported and therefore not influenced by judgement. Risk assessed to be low for outcomes: Mortality. Incidence of WHO score 7 and above. Serious adverse events. Clinical improvement (defined as discharge from hospital) and incidence of WHO score 6 and above reflects decisions made by the intervention provider. Furthermore, adverse events reported contain both clinically- and laboratory-detected events. Assessment of these outcomes could possibly be influenced by knowledge of the intervention assignment but we did not consider this likely to have happened in the context of a pandemic. Risk assessed to be some concerns for the outcomes: Incidence of WHO score 6 and above. Adverse events.
Selection of the reported results	Some concerns	Comment: No protocol and statistical analysis plan were available. Risk assessed to be some concerns for the outcome: Mortality. Incidence of clinical improvement. Incidence of WHO score 6 and above. Incidence of WHO score 7 and above. Adverse events. Serious adverse events
Overall risk of bias	**Some concerns**	

Table 5.3: Quality appraisal: overall risk of bias for the primary outcome (Length of hospitalization; symptoms and Co-existed disease from covid-nma.com (Salehzadeh et al. 2020[10])

Bias	Author's judgment	Support for judgment
Randomisation	Some concerns	Quote: "Patients were randomized in 1:1 allocation in two groups (group-A and group-B) which contains 50 patients" Comment: No information on allocation sequence. No information on allocation concealment. Allocation sequence probably random.
Deviations from intervention	Some concerns	Quote: "prospective, open-label, randomized and double blind clinical trial"; "The participants of the placebo group were received a similar tablet without therapeutic effects" Comment: Blinding unclear as no description provided and contradictory descriptions used in study. No information on cross-over (no flow chart) No information on administration of co-intervention of interest: antivirals, anticoagulants. biologics, corticosteroids. Data analyzed appropriately; participants analyzed according to their intervention assignment.
Missing outcome data	Low	Comment: 100 patients randomized; 100 patients analyzed. Risk assessed to be low for the outcome: Mortality.
Measurement of the outcome	Low	Comment: Unclear blinding Mortality is observer-reported and not involving judgement. Risk assessed to be low for the outcome: Mortality.
Selection of the reported results	Some concerns	Comment: Neither the protocol nor the statistical analysis plan was available. The prospective registry was available. The mortality outcome was not listed. Risk assessed to be some concerns for the outcome: Mortality.
Overall risk of bias	**Some concerns**	

Appendix 1: Search strategy

Epistemonikos (title:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*) OR abstract:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*)) AND (title:(colchicine) OR abstract:(colchicine)) **Records retrieved: 36 in initial review; 53 in update (14 relevant to PICO question)**
Cochrane COVID Study Register Searched the register for the term "colchicine" **Records retrieved: 31 in initial review; 45 in update (12 relevant to PICO question)**
www.covid-nma.com Searched the website for the term "colchicine" **Records retrieved: 3**

Appendix 2: 7-point modified ordinal scale used by Deftereos et al. 2020[8]

DESCRIPTOR	LEVEL
Ambulatory, normal activities	1
Ambulatory, but unable to resume normal activities	2
Hospitalised, not requiring supplemental oxygen	3
Hospitalised, requiring supplemental oxygen	4
Hospitalised, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both	5
Hospitalised, requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both	6
Death	7

Appendix 4: standard 10-point WHO ordinal scale[6] used in evidence profiles by Bollig et al. 2020[3]

PATIENT STATE	DESCRIPTOR	LEVEL
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised moderate disease	Hospitalised; no oxygen therapy	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2≥200	7
	Mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2<200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis or ECMO	9
Dead	Dead	10

Appendix 5: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Very low certainty of evidence, from three RCTs, two of which failed to meet planned recruitment.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	No estimate of the size of a clinically-relevant beneficial effect can be stated with confidence.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Ongoing studies may provide more evidence in future.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	No estimate of the size of clinically-relevant harmful effects can be stated with confidence. The reported adverse effects are consistent with what is expected with colchicine use at the doses prescribed.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒	The balance of benefits and harms is uncertain.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	Colchicine is registered in South Africa and procured in the public sector, but available volumes are limited.
RESOURCE USE	**How large are the resource requirements?** More intensive ☒ Less intensive ☐ Uncertain ☐	Price of medicines/ treatment course – *"1.5 mg; followed by 0.5 mg 60 minutes later if no adverse gastrointestinal effects; then 0.5 mg twice daily (reduced to once daily if body weight <60 kg) until hospital discharge or a maximum of 21 days"7*

Medicine	Tender price (ZAR)*	SEP (ZAR)**
For ≥ 60 kg: Colchicine 0.5mg, 44 tablets	81.33	190.01
For < 60 kg: Colchicine 0.5mg, 24 tablets	44.36	103.64

* Contract circular RT289-2019 (1 August 2020) - 0.5mg (12 tabs) = R22.18
**SEP database, accessed 5 August 2020 https://mpr.code4sa.org/ - 0.5mg (12 tabs) = R51.82

Additional resources: Management of common gastrointestinal adverse effects.

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☐ Major ☐ Uncertain ☐ **Is the option acceptable to key stakeholders?** Yes ☐ No ☐ Uncertain ☐	
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☐ Uncertain ☐	Costs are minimal, but effect is uncertain, so impact on health inequity is irrelevant at this point.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	6 August 2020	OA, AB, AH, RdW, AG	Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. There is currently insufficient evidence of clinically-relevant benefits and an uncertain risk of adverse effects.
Second	20 October 2020	MM, AB, RdW, AG	Treatment of COVID-19 in hospitalised patients with colchicine is not currently recommended. There is currently insufficient evidence of clinically-relevant benefits and an uncertain risk of adverse effects.