

COVID-19 Scientific Advisory Group

Rapid Evidence Report

Colchicine for the treatment of COVID-19

February 23, 2021

Since completion of this report, an additional potentially relevant paper has come to attention, to be reviewed for inclusion in any possible future update of this literature synthesis:

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. doi:10.1001/jamanetworkopen.2020.13136



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Lay Summary

BACKGROUND

- Colchicine is a medication used to treat gout and some other inflammatory diseases. It has been available in Canada for a long time, and is effective at treating gout, where it is used for a short course. Its use can be limited by side effects like fatigue, nausea, vomiting, and diarrhea. There is a potential to overdose on colchicine (with potentially fatal results) by taking more than the recommended dose. A press release from the Montreal Heart Institute reported that a new study (Tardif et al.) showed that if taken soon after COVID-19 diagnosis, colchicine could reduce the risk of progression of COVID in patients over 40 years old who were at risk of developing more severe disease.
- This review summarizes the scientific research on colchicine to provide guidance to public health officials and clinicians.

KEY FINDINGS

- Of eight studies on colchicine, seven were low quality and one was moderate-high quality (the study by Tardif et al., noted above). The preprint of this study (meaning it has not yet undergone full review) does not clearly show that there is a benefit with colchicine treatment, and if there is, it is very small. There are key weaknesses of this study that limit how certain we can be of the results.
- When all the studies are considered together it is not clear that there is benefit to colchicine treatment. However, there are 26 ongoing clinical trials of colchicine, and as the result of these trials become available, it should be clearer if there is a benefit of colchicine in patients with COVID-19.
- Colchicine treatment has side effects that may be serious in patients with COVID-19. The Tardif study showed that nearly 25% of people receiving colchicine had some sort of gastrointestinal side effect (eg. diarrhea, stomachache, or vomiting) and this is a well-known side effect that was also documented in other studies. In patients who might already be dehydrated due to their COVID-19 diagnosis, this could make it worse. A small number of people receiving colchicine developed blood clots in their lungs (more than those receiving the placebo), a serious complication that may lead to death.
- Right now, it isn't clear that colchicine provides a meaningful benefit in patients with COVID-19, but there are concerning harms.

RECOMMENDATIONS

- At this time, colchicine should not be prescribed or taken to treat COVID-19.
- Clinicians and researchers in Alberta should support high quality clinical trials in Alberta or in the context of a well designed multicentre study to help find out if colchicine has a benefit in treating COVID-19.

Authorship and Committee Members

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Topic: Colchicine in the treatment of COVID-19

1. **What is the evidence for colchicine as a treatment for COVID-19?**
2. **What risks or harms are associated with the use of colchicine for the treatment of COVID-19?**

Context

- Colchicine is an anti-inflammatory medication commonly used for treating gout (CPhA, 2020). It is thought that colchicine's anti-inflammatory activity may mitigate the progression to "cytokine storm" characteristic of severe COVID-19 and may reduce the severity of disease (Hossen et al., 2020).
- Colchicine has been marketed in Canada for at least 40 years. Currently, there are five active licenses for 0.6 mg tablets in Canada, held by: Odan Laboratories Ltd., Euro-Pharm International Canada Ltd., JAMP Pharma Corporation, Pharmascience Inc., and Sandoz Canada Inc. It has a well-established safety profile, interactions profile, and contraindications.
- A [press release](#) issued by the Montreal Heart Institute on a preprint from Tardif et al. has fueled interest in colchicine (in a novel 0.5 mg dose, conventional dosing is 0.6 mg) as a potential treatment for COVID-19.
- The 0.5 mg dose of colchicine used in the Tardif (preprint) study, developed by Pharmascience Inc., is not yet approved for market by Health Canada.

Key Messages from the Evidence Summary

- The body of primary evidence regarding colchicine as a treatment for COVID-19 can be dichotomized: two low quality randomized controlled trials (RCTs) and observational data (five studies); and one large moderate-high quality RCT (Tardif).
- As with the evidence for other potential treatments, most of the included primary studies are at high risk of bias due to small sample sizes, limited blinding, non-standardized interventions and controls, and confounding factors. Tardif et al. (preprint) is the exception – although the trial was stopped early by the steering committee (and is underpowered as a result) - the study is large, well-controlled, and generally at lower risk of bias due to performance or confounding.
- Guidelines from Australia and Quebec published after review of Tardif (preprint) do not recommend colchicine for COVID-19 treatment outside of a clinical trial. Of updated guidelines, those from British Columbia (BC) are the most permissive, suggesting that colchicine should not be used routinely but may be offered (with informed consent) to those over 40 years, who also meet at least one high-risk criterion (as per the study population).
- One moderate-high quality meta-analysis of RCTs was identified. Juul et al. (preprint) (includes three small low-quality RCTs, assessed with the Cochrane risk of bias tool) suggested that colchicine has no significant effect on the risk of mortality in COVID-19 patients (RR 1.03; 95% CI 0.07 to 16.01).
- A large multi-centre study (n=4488) in non-hospitalized subjects with ≥ 1 risk factor for severe disease by Tardif et al. (preprint) is the most influential study considered in this review. It reported no difference in the intention to treat primary

outcome (composite of death or hospitalization) between the colchicine and placebo groups (104/2235 (4.7%) vs. 131/2253 (5.8%) respectively; OR 0.79; 95% CI 0.61 to 1.03; p=0.08). Individual outcomes of COVID-19 related hospitalization, death, and need for mechanical ventilation were also not significant. A secondary sub-group analysis in subjects that were PCR positive (n=4159) was statistically significant for the composite outcome (OR 0.75; 95% CI 0.57 to 0.99; p=0.04) and for COVID-19 related hospitalization (OR 0.75; 95% CI 0.57 to 0.99). Mortality and need for mechanical ventilation were not significantly different in this subgroup. A significant increased risk of PE was also observed (see below).

- Tardif (preprint) has several key weaknesses. First, the study was stopped for “logistical issues” (Tardif, preprint, p. 9), stated by the authors related to maintaining the study call centre and the need to provide results to decision-makers in a timely fashion – presumably made without knowledge of the results. Second, the study does not provide data on all-cause hospitalization, only COVID-related hospitalization, which is relevant given the relatively high rate of side effects. Finally, it is unclear if the outcome assessors were blinded to the group assignment of the participant (though this may be clarified through peer review).
- Two small RCTs of low quality suggest that colchicine may reduce the odds of clinical progression in COVID-19.
- Evidence from observational studies is mixed, and of low quality. Three observational studies suggested that colchicine reduced COVID-19 mortality, while two did not. Vrachatis et al.(2020) a low-quality systematic review with four observational studies and two RCTs, reported that patients who were administered colchicine +/- standard care had 65% lower odds of mortality compared to patients who received standard care alone (OR 0.35; 95% CI 0.24-0.52). The high risk of bias limits the certainty of the findings from the observational studies and from the Vrachatis (2020) systematic review.
- Colchicine has a narrow therapeutic index, whereby small differences in blood concentrations can progress from therapeutic to serious adverse events, Side effects of colchicine are well known and commonly include abdominal pain, nausea, vomiting, diarrhea, fatigue, and pharyngolaryngeal pain, which may occur in >20% of patients (Slobodnick et al., 2018).
- In the low-quality literature, diarrhea was reported in four small studies as significantly more likely to occur in participants treated with colchicine compared to the control.
- In the Tardif trial, overall adverse event rates in the colchicine group were 24.2% versus 15.5% in the placebo group, driven by gastrointestinal events (23.9% vs. 14.8%, respectively). Overall, however, serious adverse events (including pneumonia) were higher in the placebo group than the intervention group (6.3% compared to 4.9%, respectively, p=0.05).
- Of concern is the finding of statistically significantly increased risk of pulmonary embolism in the colchicine group compared to the placebo group (0.5% vs. 0.1% respectively; p=0.01) reported by Tardif (preprint). Although pulmonary embolism

is not known as a side effect of colchicine, the signal raises concern and more evidence is needed to establish the risk to patients.

Committee Discussion

The committee reached consensus on the recommendations as presented. Discussion was largely focused on the quality and credibility of Tardif et al. (preprint) and the results and adverse events reported in that study.

The Montreal Heart Institute press release framed the results of Tardif as positive; however, examination of the study suggests that the primary results are negative, and that the small benefits in secondary analysis are uncertain. There was lack of detail in the manuscript regarding why the study was stopped early, resulting in the study being underpowered to detect if true benefits exist.

The committee also raised concern over the adverse events reported in the evidence. Colchicine is not a benign drug. With the side effect profile reported in the literature and the potential for serious harm, it is presently inappropriate to recommend colchicine without clear evidence of benefit. However, given the number of ongoing clinical trials, evidence of benefit may be established in the future.

Recommendations

1. At this time, colchicine is not recommended for treatment of patients with COVID-19 to prevent progression to severe disease.

Rationale: At present there is insufficient evidence to recommend the use of colchicine in community-based patients to prevent COVID-19 progression. The existing evidence does not clearly establish benefit, and colchicine has a significant side effect profile that may result in harm to patients.

2. Where possible, investigators should support well-designed clinical trials in Alberta or within the context of a well-designed multicenter Canadian study of colchicine as a treatment for COVID-19.

Research Gaps

- More evidence is needed to determine if colchicine therapy for COVID-19 leads to clinically important improvements in patient outcomes. It is noted that there are at least 26 ongoing clinical trials of colchicine; this review should be updated when more results are available.
- More evidence is needed to clarify the risk of harm to patients from colchicine treatment and if that risk is outweighed by the potential benefits of treatment.
- If benefit is established in subsequent trials, it will be important to clarify the optimal timing of colchicine treatment for COVID-19 and which populations (eg. mild, moderate, or severe COVID-19) might derive the most benefit from colchicine.

Strength of Evidence

The body of evidence for this review can be dichotomized into low quality studies (small RCTs and observational), and the moderate quality Tardif study. Tardif et al. (preprint) is a multi-centre RCT conducted in 5 countries enrolling 4488 non-hospitalized subjects

over age 40 with at least one risk factor for severe disease. The study was underpowered (target enrollment 6000) as it was stopped early (stated due to logistical issues) and Caucasians were heavily overrepresented in both trial groups. The primary outcome of this moderate to high quality study (composite of death and hospitalization due to COVID-19) was null as were individual outcomes (including need for mechanical ventilation). A secondary pre-specified analysis (stated by authors, not reported on clinicaltrials.gov) among only PCR positive patients (n=4159) reported a reduction in the composite outcome and risk of hospitalization. Downs & Black critical appraisal (Downs & Black, 1998) of Tardif (preprint) resulted in a score of 22, usually interpreted as “good quality”.

Two additional RCTs were identified and estimated to be low quality as they were small, with inadequate blinding and risk of performance bias and confounding. Five observational studies of colchicine for COVID-19 were identified, and tended to be low quality, with high risk of bias from confounding factors, inadequate controls, and small sample sizes.

There were several systematic reviews retrieved in the database search that discussed the effectiveness of colchicine as a treatment for COVID-19; however, they all identified and included the same studies (notably, Deftereos (2020) and Lopes (2021)). To minimize duplication, two studies with a meta-analysis were selected for inclusion: Juul et al. (preprint) and Vrachatis (2021). Juul (preprint) is the second edition of a living systematic review that includes only RCTs (two included in database results, one that was not identified; does not include Tardif) but is of reasonable quality. Vrachatis (2021) includes all the relevant studies that were identified in the present database search (both RCTs and observational studies) but is overall of low quality as it does not address risk of bias in the primary literature and thus has low certainty findings.

There is heterogeneity in study designs and comparators, and high risk of bias in the primary studies, which generally show reduced clinical progression (represented by hospitalization, ICU admission, or mortality outcomes) in patients offered colchicine compared to placebo or standard care comparator groups, although the effect size and statistical strength varies.

The studies have been done in varied geographic regions, with the RCTs arising from Greece, Brazil and Quebec (this study includes centres in ten American jurisdictions, Brazil, Quebec, South Africa, and Spain); the observational studies are from the United States, Israel, Colombia, and Italy. Although these regions all have different population health statistics and epidemic dynamics, there is no reason to suspect that the effect of colchicine in COVID-19 would be different in the study populations and Albertans.

Limitations of this review

This review is subject to some limitations. As with studies of other treatments for COVID-19, the body of evidence is limited and changes quickly. Since this is a rapid review, the literature search was thorough but not systematic and it is possible that relevant studies were not identified. In addition, the language limitations placed on the search results may have excluded relevant studies in languages other than English. Preprint articles were not as prevalent as expected (three of thirteen included articles);

however, the public discourse on colchicine is not yet at full volume so the proportions of preprint to peer-reviewed literature may change as the ongoing clinical trials release their results.

Summary of Evidence

A literature search was conducted for articles published in English in 2020-21. The librarian designed the search strategy around the concepts of “colchicine” and “COVID-” and searched in Ovid Medline, LitCOVID, PubMed, Trip Pro, World Health Organization Global Coronavirus database, MedRxiv, BioRxiv, Google/Google Scholar, and Clinicaltrials.gov.

143 articles were identified in the database search; following screening by title/abstract and full-text exclusion based on predetermined inclusion/exclusion criteria, 15 articles met the criteria for inclusion. Four additional articles were identified *ad hoc*, resulting in 19 articles that have been narratively synthesized below. The breakdown of study designs of the 19 included articles are as follows in Table 1 below.

Table 1. Study designs of the 19 articles included in this review.

	Peer-reviewed	Preprint
Systematic Review / Meta-analysis (5)	Vrachatis et al., 2020 Di Lorenzo et al., 2020 Louchet et al., 2020 Martinez-Lopez et al., 2020	Juul et al., preprint
RCT Designs (3)	Deftereos et al., 2020 Lopes et al., 2021	Tardif et al., preprint
Observational Designs (5)	Brunetti et al., 2020 Gendelman et al., 2020 Sandhu et al., 2020 Scarsi et al., 2020	Pinzón et al., preprint
Guidelines (5)	National COVID-19 Clinical Evidence Taskforce, 2021a National COVID-19 Clinical Evidence Taskforce, 2021b National COVID-19 Clinical Evidence Taskforce, 2021c South African National Department of Health, 2020 BCCDC, 2021 INESSS, 2021	

Note: The systematic reviews by Di Lorenzo (2020), Louchet (2020) and Martinez-Lopez (2020) are included as they discuss drug interactions and adverse effects of colchicine. They do not include a discussion of the effectiveness of colchicine as a treatment for COVID-19.

What is the evidence for colchicine as a treatment for COVID-19?

Evidence from secondary and grey literature

Guidelines from Australia (National COVID-19 Clinical Evidence Taskforce, 2021a-c), South Africa (South African National Department of Health, 2020), and Quebec (National Institute for Excellence in Health and Social Services (INESSS), 2021) all recommend against using colchicine as a treatment for COVID-19 outside of a clinical trial, citing insufficient evidence of effectiveness. It must be noted that the South African

guidelines have not been updated since October 2020; however, the Australian guidelines are dated 29 January 2021 (post-COLCORONA) and the INESSS guidance was published on 4 February 2021 (post-COLCORONA). Conversely, the BC Centre for Disease Control (BCCDC) does not recommend colchicine for routine use, however, recognizes that it may be offered (with informed consent) to those over 40 years, with at least one high-risk criteria (based on findings from the Tardif COLCORONA study (preprint)) (BCCDC, 2021).

As described above, several systematic reviews and meta-analyses on colchicine for COVID-19 treatment were identified in the database search (neither included Tardif). To minimize duplication, only two were selected for inclusion – Juul et al. (preprint) and Vrachatis et al. (2020). Juul et al. (preprint) is the second edition of a living systematic review includes three RCTs (two that were included in the database search results). Juul et al. (preprint) is estimated to be of moderate quality. Vrachatis (2020), estimated to be of low quality due to a lack of risk of bias assessment, pools the findings of six primary studies that were all identified either in the database search or *ad hoc*. These are four observational studies (Scarsi (2020), Brunetti (2020), Sandhu (2020), and Pinzón (preprint)) and two RCTs (Deftereos (2020) and Lopes (2020)).

These two systematic reviews reached opposite conclusions: the pooled findings of Juul et al. (preprint) (3 RCTs) suggest that colchicine has no significant effect on the risk of mortality in COVID-19 patients (RR 1.03; 95% CI 0.07 to 16.01; $p = 0.98$; $I^2 = 0\%$; two trials). Conversely, Vrachatis (2020) (4 observational studies, 2 RCTs) found that the patients who were administered colchicine +/- standard care had 65% lower odds of mortality compared to patients who received standard care alone (OR 0.35; 95% CI 0.24-0.52; $I^2 = 0\%$). When the analysis was limited to peer-reviewed studies (thus eliminating Pinzón (preprint)), the odds of mortality were further reduced by 7% (OR 0.28; 95%CI 0.18-0.44; $I^2 = 0\%$).

Evidence from the primary literature

Although most of the primary literature that was identified in the database search was pooled in the systematic review by Vrachatis et al. (2020), the absence of a risk of bias assessment limits the utility of that review. The characteristics and findings of the studies are thus presented here for independent assessment. The eight pieces of primary literature relating to colchicine as a COVID-19 treatment (three preprints) are presented in Tables 2 and 3 below.

The most notable study, Tardif et al. (preprint), is described in more detail here. Participants were recruited from 22 sites across multiple jurisdictions: Quebec, Brazil, South Africa, Spain, and the United States (Arizona, Arkansas, California, Florida, Minnesota, Mississippi, New York, North Carolina, South Carolina and Texas). Patients were eligible for the trial if they were over 40 years old, were newly diagnosed with COVID-19 by polymerase chain reaction (PCR) testing or epidemiological link within 24 hours of enrollment, not hospitalized, and had at least one risk factor for severe disease (including but not limited to >70 years old, BMI ≥ 30 , diabetic, uncontrolled hypertension, heart disease, etc.). The primary outcome of interest was a composite of death or hospitalization due to COVID-19 infection in the 30 days following

randomization, the secondary outcomes of interest were mortality, hospitalization, or need for mechanical ventilation.

The primary intention to treat analysis was conducted on the whole study population, while secondary analysis was conducted only on those with PCR-confirmed SARS-CoV-2 infection (author stated this was a pre-specified analysis, but this is not listed in the study register). According to the study register on clinicaltrials.gov, the study was triple-blind (participants, care providers, and investigator), although the manuscript does not provide details on who assessed participants and how they were blinded to participant allocation. Data on pneumonias, other serious adverse events, and non-serious adverse events were also collected. The dosing regimen used was a novel dose formulation (colchicine 0.5 mg for which a patent application has been filed, rather than 0.6 mg, which is the usual dosing for gout) and was for an extended period of 4 weeks compared to dosing for conventional anti-inflammatory indications such as gout and pericarditis.

The steering committee intended to enroll 6000 participants to detect a significant ($p < 0.05$) 25% relative risk reduction with colchicine with a power of 80% given a primary endpoint event rate of 7% in the placebo group. However, the study was ended at 75% enrollment (4506 participants) due to “logistical issues related to maintaining the central study call center active 24 hours per day for a prolonged period of time, as well as the need to provide healthcare systems with study results in a timely fashion given the state of the COVID-19 pandemic” (Tardif et al., preprint, p. 9), and is thus underpowered. Participants in the two study groups are not significantly different from each other but skew heavily Caucasian (~93% in each group).

In the primary analysis (all enrolled participants), colchicine had no significant effect on mortality, COVID related hospitalization, mechanical ventilation, or the composite. In the secondary analysis (PCR-confirmed COVID-19), colchicine had no effect on mortality (5/2235 (0.2%) and 9/2253 (0.4%) respectively; OR 0.56; 95% CI 0.19 to 1.66) or need for mechanical ventilation compared to placebo, but showed significantly reduced odds of reaching the composite endpoint (96/2235 (4.6%) vs. 126/2253 (6.0%) respectively; OR 0.75; 95% CI 0.57 to 0.99; $p = 0.04$) as well as reduction in COVID related hospitalization. Overall hospitalization results are not presented in the preprint manuscript.

Within subgroups, colchicine treatment was significant for the primary outcome for men but not women (with no statistical analysis conducted to compare the two groups); no other subgroups showed a difference in effectiveness.

The most common adverse events resulting from colchicine treatment were gastrointestinal - diarrhea was reported by 13.7% and 7.3% of patients in the colchicine and placebo groups, respectively. A numerically small but statistically significant number of participants in the colchicine group (11/2195) reported pulmonary embolism compared to 2 participants (out of 2217) in the control group ($p = 0.01$).

Table 2. Randomized controlled trials studying the effectiveness of colchicine as a treatment for COVID-19. Three RCTs are included in the narrative synthesis.

Reference	Study Design	Population	Intervention	Comparator	Outcome	Notes
Deftereos et al., 2020 Greece (GRECCO trial)	RCT (open label)	Hospitalized patients with lab-confirmed COVID-19 (n= 105)	Colchicine administration (1.5-mg loading dose followed by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily) with standard medical treatment for as long as 3 weeks. (n= 50)	Standard care (not described) (n=55)	<ul style="list-style-type: none"> - The clinical primary end point occurred in 7 patients (14.0%) in the control group and in 1 patient (1.8%) in the colchicine group (P = .02), (OR 0.11 (95% CI, 0.01-0.96; P = .046)) - Cumulative event-free 10-day survival was 83% vs 97% in the control and colchicine groups, respectively (Gehan statistic, 4.9; P = .03) 	<ul style="list-style-type: none"> - low- moderate quality study - The primary end point of the clinical phase was the time from baseline to clinical deterioration, defined as a 2-grade increase on an ordinal clinical scale within a time frame of 3 weeks after randomization or until hospital discharge - small sample size
Lopes et al. (2021) Brazil	RCT (double-blind)	Adults hospitalized for moderate-severe COVID-19 (n=75)	<p>Colchicine: 0.5 mg thrice daily for 5 days, then 0.5 mg twice daily for 5 days; if body weight \geq 80 kg, the first dose was 1.0 mg. Dosage reduced in patients with chronic kidney disease</p> <p>Standard care: azithromycin 500 mg once daily for up to 7 days, HCQ 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.</p>	Placebo + Standard care	<ul style="list-style-type: none"> - 2 patients of the placebo group died (two male; death rate of 6%) and 0 of the colchicine group (no statistics) - Colchicine group had reduced time on supplemental oxygen - At day 2, 67% versus 86% of patients maintained the need for supplemental oxygen, while at day 7, these values were 9% versus 42%, in the colchicine and placebo groups, respectively (log rank test, 10.6; p=0.001) 	<ul style="list-style-type: none"> - Low quality study - High risk of bias from confounding - High risk of performance bias & non-standardized controls - small sample size - Over-representation of women in placebo group compared to intervention group *Length of stay described but is not an outcome of interest here

Reference	Study Design	Population	Intervention	Comparator	Outcome	Notes
			(Note: All patients received the institutional protocol treatment with HCQ, azithromycin and heparin. Seven patients in each group received methylprednisolone.)			
Tardif et al., preprint (COLCORONA) Canada (Quebec)	RCT (triple-blind; unclear description of who)	Adults with lab-confirmed or clinically suspected COVID-19, non-hospitalized, and had at least one high-risk criteria (n=4488) Mean enrollment at 5.3 days post symptom-onset	Colchicine: (0.5 mg twice daily for the first 3 days and then once daily for 27 days thereafter	Placebo	<p>In all patients:</p> <ul style="list-style-type: none"> - Odds of death in colchicine group (5/2235 vs 9/2253; OR, 0.56, 95% CI, 0.19 to 1.67) - hospitalization due to COVID-19 in colchicine group (101/2235 vs 128/2253; OR, 0.79, 95% CI, 0.60 to 1.03) - need for mechanical ventilation in colchicine group (11/2235 vs 21/2253; OR 0.53, 95% CI, 0.25 to 1.09) <p>In PCR confirmed COVID-19 patients:</p> <ul style="list-style-type: none"> - Odds of death in colchicine group (2/2075 vs 9/2084; OR 0.56, 95% CI, 0.19 to 1.66) - Odds of hospitalization in colchicine group (93/2075 vs 123/2084; OR 0.75, 95% CI, 0.57 to 0.99) - Composite endpoint (hospitalization OR death): 96/2075 vs 126/2084, OR 0.75; 95% CI, 0.57 to 0.99; P=0.04 	<ul style="list-style-type: none"> - Moderate - high quality study - Appropriate management of confounding risk factors - Appropriately blinded - Appears to be well-controlled (low risk of performance bias) - Potential for selection bias, but does not appear to be a high risk - Large study, but slightly underpowered (enrollment stopped at 75% of recruitment) - 107 lost to follow-up (43 in intervention, 64 in control group) included in intention to treat analysis

Table 3. Observational studies describing the effectiveness of colchicine as a treatment for COVID-19. Five studies are included in the narrative synthesis.

Reference	Study Design	Population	Intervention	Comparator	Outcome	Notes
Brunetti et al., 2020 United States (New Jersey)	Matched cohort study	Consecutive lab-confirmed severe COVID-19 patients admitted to hospital Regression n= 303 (Score matched n= 66)	Colchicine + standard care (n=33) 72.7% (n = 24) of the patients received a loading dose of 1.2 mg. The maintenance dose was 0.6 mg twice daily	Standard care	- Three deaths (9.1%) in the colchicine group versus 11 deaths (33.3%) in the standard of care group (OR 0.2; 95% CI 0.05-0.80) after 28 days - Significance is lost in unmatched analysis (unadjusted OR, 0.38; 95% confidence interval, 0.13–1.11; p = 0.077) - Colchicine was associated with a significant reduction in mortality after adjustment for age, comorbidity index, and c-reactive protein (odds ratio, 0.21; 95% confidence interval, 0.06–0.71; p = 0.012)	- low quality - Risk of bias from confounding - Reasonable attempt at blinding
			Other medications administered as needed: hydroxychloroquine (HCQ), azithromycin, remdesivir, tocilizumab. (Note: HCQ and azithromycin removed from institutional guidelines before the end of the study)			
Gendelman et al. (2020) Israel	Retrospective observational study	Samples screened for SARS-CoV-2 in administrative database (n= 14520; COVID+ n= 1317)	Hydroxychloroquine administration or Colchicine administration (no dosages given)	No HCQ or colchicine	HCQ (n.s.) COVID +ve: 3/1317 (0.23%) COVID -ve: 33/13203 (0.25%) Colchicine (n.s.) COVID +ve: 7/1317 (0.53%) COVID -ve: 64/13203 (0.48%) No significant protective effect of colchicine against SARS-CoV-2 infection	- Small number of patients with a <i>priori</i> colchicine administration - Moderate quality study
Pinzón et al. (preprint) Colombia	Cross-sectional study	Adults hospitalized with lab-confirmed COVID-19	Colchicine (0.5 mg every 12 hours for 7 to 14 days) +	Corticosteroid treatment was mostly with dexamethasone,	- Colchicine was administered in 145 (48.2%) patients and of them 14 (9.7%) died vs 23 (14.7%) of	- low quality, opportunistic study - high risk of bias from confounding

Reference	Study Design	Population	Intervention	Comparator	Outcome	Notes
		pneumonia (n=301)	corticosteroid standard care	some with prednisolone or methylprednisolone	those who did not receive it (n.s.; p = 0.179) - Mortality not significantly different (OR = 0.618; 95% CI: 0.305–1.253)	- no assessor blinding - timing of colchicine administration not reported
Sandhu et al. (2020) United States (New York)	Case Control study - Two floors of hospital designated for COVID care; one floor assigned to colchicine intervention, the other as a control	Adults hospitalized with moderate-severe lab-confirmed COVID-19. (n=197) Not randomized	Colchicine 0.6 mg twice a day for three days and then 0.6 mg once a day for a total of 12 days (n=53) Other medications at physician discretion: (hydroxychloroquine, steroids, insulin, enoxaparin, apixaban, rivaroxaban, warfarin, heparin, or oseltamivir Patients excluded if taking: lamivudine, dolutegravir, tocilizumab, convalescent plasma	No colchicine treatment (n=144)	- Patients who received colchicine had a lower rate of intubation (47.1% versus 87.2%, P < 0.0001) and lower mortality (47.1% versus 80.8%, P = 0.0003) compared to control group in comprehensive group analysis with inflammatory markers for at least two timepoints	- Low quality study - Assessors not blinded; potential performance bias - risk of confounding from additional medications - small sample size - Higher prevalence of hypertension and diabetes mellitus in control group - No significant difference between groups for other administered medications
Scarsi et al., 2020 Italy	Case control study	Adults hospitalized with lab-confirmed COVID-19 (n=272)	Colchicine (1 mg/day (reduced to 0.5 mg/day, if severe diarrhoea) + standard care (n=122) Standard of Care at physician discretion: HCQ was given orally 200 mg two times per day. Intravenous dexamethasone was administered at 20 mg/day for 5 days, followed by 10 mg/day for 5 days. Patients received antibiotics and supportive care when required.	Standard care (SoC) (n=140)	- 20 patients treated with colchicine (16.3%) and 52 patients in the SoC group (37.1%) died for complications related to COVID-19 (p<0.001) - a lower risk of death was independently associated with colchicine treatment (HR=0.151 (95% CI 0.062 to 0.368), p<0.0001) (Cox proportional hazards survival analysis)	- low quality - Potential risk of bias from confounding, no assessor blinding

Two RCTs (Deftereos (2020), Lopes (2020)) identified in the primary literature suggested that colchicine has some effect on COVID-19 progression. Deftereos (2020) suggests that colchicine can reduce the odds of clinical progression by 91% (OR 0.11; 95% CI, 0.01-0.96; P = .046). Both Deftereos (2020) and Lopes (2020) show that colchicine can limit clinical progression in hospitalized patients, however, this finding is not certain due to the high risk of bias from confounding and the relatively small sample sizes. In addition, both studies are estimated to be of relatively low quality.

The conflicting findings of the RCTs are mirrored by the findings of the observational studies. Brunetti (2020), Sandhu (2020), and Scarsi (2020) all show that colchicine had a significant effect on mortality from COVID-19, while Pinzón (preprint) and Gendelman (2020) show that colchicine does not affect COVID-19 disease progression. Notably, these studies are all estimated to be of low-moderate quality due to the small sample sizes and high risk of bias from confounding factors.

Synthesis of the Information Relating to Question 1

The evidence on colchicine as a treatment for COVID-19 is too variable to be conclusive. As an anti-inflammatory agent, it is possible that it may have some effect on COVID-19 disease progression; however, the true benefit and the effect size is unclear.

The highest quality RCT (Tardif et al., preprint) does not demonstrate an effect in the primary analysis, although in a secondary analysis of PCR positive patients appears to reduce COVID-related hospitalization in male patients; a beneficial effect on mortality or need for mechanical ventilation has not been demonstrated (and is underpowered to detect an effect). The highest-quality systematic review shows no significant effect of colchicine on mortality (Juul et al., preprint), although this SR includes only small RCTs (and not Tardif). High risk of bias in the second systematic review, the other RCTs and the observational studies limits the certainty of the other positive findings. The guidelines identified in the grey literature are appropriately cautious and do not recommend routine use of colchicine. Taken together, the body of evidence does not support the use of colchicine outside of a clinical trial or without appropriate informed consent procedures.

What risks or harms are associated with the use of colchicine for treating COVID-19?

Evidence from secondary and grey literature

As colchicine has been available for several years, it has a well-documented safety profile. The product monograph from the Canadian Pharmacists Association (CPhA) lists the following common side effects: abdominal pain, nausea, vomiting, diarrhea, fatigue, and pharyngolaryngeal pain (CPhA, 2020). Less common side effects include (but are not limited to) body rash, rhabdomyolysis, hematologic side effects, hepatotoxicity, muscle pain & weakness, and neuropathy (CPhA, 2020). These side effects are confirmed in a systematic review of drugs currently under investigation for treatment of COVID-19 (Martinez-Lopez et al., 2020); however, Juul et al. (preprint) suggests that in COVID-19 treatment specifically, there is no significant difference in non-serious adverse events between colchicine & control; high heterogeneity (RR 0.88; 95% CI 0.18 to 4.39; p = 0.87; I² = 79.1%; three trials). However, the overall adverse

event rate was 24% versus 15% in the Tardif trial driven by GI events, although this did not appear to be treatment limiting.

Colchicine is contraindicated in people taking other Cytochrome P450 inhibitors or P-glycoprotein inhibitors, especially in people with hepatic or renal dysfunction, and interacts with these medications to result in poor colchicine metabolism and potential toxicity (CPhA, 2020). Colchicine has been shown to interact with antineoplastic medications in the cytochrome P450 or P-glycoprotein inhibitor families (Di Lorenzo et al., 2020), thus presenting a potential contra-indication in cancer patients.

Colchicine should be avoided during pregnancy if possible (CPhA, 2020). Colchicine has not been associated with congenital abnormalities; however, it has been associated with increased risk for preterm deliveries at ≤ 36 weeks' gestation (15% [n=32/214] vs 5.9% [n=51/867]; $P < .01$) and a lower median birthweight in singleton full-term children (3090 g vs 3315 g; $P < .01$) (Louchet et al., 2020).

In the event of overdose, colchicine is severely toxic and can be fatal. On average, the lethal dose of colchicine is estimated to be 65 mg, although deaths have been reported with 7 mg (CPhA, 2020).

Evidence from the primary literature

In the primary literature for colchicine as a COVID-19 treatment, diarrhea and/or gastrointestinal events were listed in four studies as significantly more likely to occur in the colchicine-treated group compared to the control group (Deftereos et al., 2020; Lopes et al., 2020; Scarsi et al., 2020; Tardif et al., preprint). Deftereos (2020) notes that the diarrhea was generally self-limiting, but could lead to lower dosing (Deftereos et al., 2020; Scarsi et al., 2020).

Tardif (preprint) noted an increased risk of gastrointestinal adverse events (23.9% vs. 14.8%; $p < 0.0001$) and diarrhea (13.7% vs. 7.3%; $p < 0.0001$). This may be a concern in non-hospitalized patients who may be at risk of volume contraction. Further, Tardif (preprint) reported a statistically significant increased risk of pulmonary embolism (0.5% vs. 0.1%; $p = 0.01$); the cause of this is unclear but given that PE is a serious and potentially fatal complication, this raises a safety concern. This finding was not clearly explained in the text.

Synthesis of the Information Relating to Question 2

The evidence from the COVID-19 trials suggests that colchicine has known side effects at the recommended dosing regimens; the number of side effects and potential for toxicity listed in the product monograph suggest that it should be used with care. In outpatients with SARS-CoV-2, volume contraction may occur and could be exacerbated by the presence of gastrointestinal adverse events and diarrhea. Finally, the signal of an increased risk of the serious and potentially fatal event of pulmonary embolism is of concern.

Evolving Evidence

Research on SARS-CoV-2 is continually evolving and as such the evidence will continue to be assessed as new information is provided. As colchicine is a novel

potential treatment for COVID-19, there are 28 ongoing clinical trials that will be publishing results in the coming months. These are listed in table 4 below.

Table 4. Ongoing clinical trials of colchicine as a treatment for COVID-19, registered on Clinicaltrials.gov, as of 8 February 2021.

	NCT Number and jurisdiction	Study Name	Intended enrollment	Design	Status
1	NCT04724629 Brazil	Survival TRial Using CytoKines in COVID-19 (STRUCK)	60	Open-label RCT	Recruiting
2	NCT04328480 Argentina	The ECLA PHRI COLCOVID Trial. Effects of Colchicine on Moderate/High-risk Hospitalized COVID-19 Patients. (COLCOVID)	1200	Open-label RCT	Recruiting
3	NCT04510038 United States	Colchicine vs Current Standard of Care in Hospitalized Patients With COVID-19 and Cardiac Injury (COLHEART-19)	75	Open-label RCT	Not yet recruiting
4	NCT04363437 United States	COLchicine in Moderate-severe Hospitalized Patients Before ARDS to Treat COVID-19 (COMBATCOVID19)	70	Open-label RCT	Recruiting
5	NCT04527562 Bangladesh	Colchicine in Moderate Symptomatic COVID-19 Patients (COLCOVIDBD)	299	Triple-blind RCT	Complete
6	NCT04359095 Colombia	Effectiveness and Safety of Medical Treatment for SARS-CoV-2 (COVID-19) in Colombia	1200	Open-label RCT	Recruiting
7	NCT04557780 Pakistan	Study to Investigate the Treatment Effect of Colchicine in Patients With COVID-19	102	Open-label RCT	Recruiting
8	NCT04322682 Canada	Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA) (COVID-19)	4506	Triple-blind RCT	Complete
9	NCT04324463 Canada	Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019	4000	Open-label RCT	Recruiting

		(COVID-19) Trial (ACTCOVID19)			
10	NCT04603690 Pakistan	Study to Investigate the Benefits of Colchicine in Patients With COVID-19	n/a	Open-label RCT	Withdrawn
11	NCT04350320 Spain	Trial to Study the Benefit of Colchicine in Patients With COVID-19 (COL-COVID)	102	Open-label RCT	Complete
12	NCT04326790 Greece	The GRreek Study in the Effects of Colchicine in Covid-19 cOmplications Prevention (GRECCO-19)	180	Open-label RCT	Recruiting
13	NCT04381936 UK	Randomised Evaluation of COVID-19 Therapy (RECOVERY)	40000	Open-label RCT	Recruiting
14	NCT04322565 Italy	Colchicine Counteracting Inflammation in COVID-19 Pneumonia (ColCOVID-19)	310	Open-label RCT	Recruiting
15	NCT04375202 Italy	Colchicine in COVID-19: a Pilot Study (COLVID-19)	308	Open-label RCT	Recruiting
16	NCT04654416 Colombia	Clinical Outcome of Patients With COVID-19 Pneumonia Treated With Corticosteroids and Colchicine	301	Cross-sectional study	Complete
17	NCT04403242 Russia	COLchicine Versus Ruxolitinib and Secukinumab In Open Prospective Randomized Trial (COLORIT)	70	Open-label RCT	Recruiting
18	NCT04492358 Spain	Treatment for Moderate/Severe COVID-19 in a Fragile and Vulnerable Population, Admitted to a Geriatric Hospital Unit or in a Transicional Care Center	144	Open-label RCT	Recruiting
19	NCT04539873 Colombia	Impact of Colchicine in Hospitalized Colombian Patients With COVID-19 (COLCOVID19)	128	Open-label RCT	Recruiting
20	NCT04392141 Iran	Colchicine Plus Phenolic Monoterpenes to Treat COVID-19	200	Double-blind RCT	Recruiting
21	NCT04360980 Iran	The Effects of Standard Protocol With or Without	80	Double-blind RCT	Recruiting

		Colchicine in Covid-19 Infection			
22	NCT04516941 Switzerland	CorONa Virus edoxabaN ColchicinE (CONVINCE) COVID-19 (CONVINCE)	420	Open-label RCT	Not yet recruiting
23	NCT04355143 United States	Colchicine to Reduce Cardiac Injury in COVID-19 (COLHEART-19) (COLHEART-19)	150	Open-label RCT	Recruiting
24	NCT04507867 Mexico	Effect of a Nss to Reduce Complications in Patients With Covid-19 and Comorbidities in Stage III	240	Single-blind RCT	Not yet recruiting
25	NCT04278404 United States	Pharmacokinetics, Pharmacodynamics, and Safety Profile of Understudied Drugs Administered to Children Per Standard of Care (POPS) (POPS or POP02)	5000	Prospective observational study	Recruiting
26	NCT04472611 United States	Colchicine/Statins for the Prevention of COVID-19 Complications (COLSTAT) Trial (COLSTAT)	466	Open-label RCT	Not yet recruiting
27	NCT04416334 Spain	Preemptive Therapy With Colchicine In Patients Older Than 60 Years With High Risk Of Severe Pneumoniae Due To Coronavirus (COLCHI-COVID)	954	Open-label RCT	Recruiting
28	NCT04367168 Mexico	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 (ColchiVID)	174	Double-blind RCT	Recruiting

Appendix

List of Abbreviations

AHS: Alberta Health Services

BC: British Columbia

BCCDC: BC Centre for Disease Control
CI: Confidence Interval
COVID-19: Coronavirus Disease 2019
CPhA: Canadian Pharmacists Association
HCQ: Hydroxychloroquine
OR: Odds Ratio
RCT: randomized controlled trial
RR: Risk Ratio
SoC: Standard of Care

Methods

Literature Search

A literature search was conducted by Rachel Zhao from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published in English from 2020-2021, and included: Ovid Medline, LitCOVID, PubMed, Trip Pro, World Health Organization Global Coronavirus database, MedRxiv, BioRxiv, Google/Google Scholar, and Clinicaltrials.gov. The full strategy is included at the end of the appendix. Briefly, the search strategy was based around two key concepts: “colchicine” and “COVID-19”.

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Table 5 below. 143 articles were identified by KRS with references and abstracts provided for further review; 28 ongoing clinical trials were identified in the search of Clinicaltrials.gov. 95 articles were excluded from the review in accordance with the inclusion/exclusion criteria stated below. Four articles were identified *ad hoc*, resulting in 19 included articles.

Table 5. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> - Any population - COVID-19 - Patients are treated with colchicine alone or as add-on treatment - Authors describe an objective, clinically relevant outcome (hospital admission, ICU admission, death) - Systematic review, meta-analysis, RCT, observational study, large case series (n ≥ 50) - Published 2020-2021 - Any jurisdiction - English 	<ul style="list-style-type: none"> - Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions - Non-coronavirus respiratory infection - Not treated with colchicine - Non-human study - Outcomes other than hospital admission, ICU admission or death - Editorial, commentary, narrative review, study protocol, case report or small case series (n < 50)

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 6 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (Urwin, Gavinder & Graziadio, 2020; Viswanathan et al, 2012; Wynants et al., 2020; Brouwers et al., 2010).

Table 6. Narrative overview of the literature included in this review.

	Description
Volume	5 systematic reviews were included (1 was pre-review), 3 RCTs were included (1 was pre-review), 5 observational studies were included (1 was pre-review), 0 case series were included, 5 guidelines from reputable sources were included.

<p>Quality</p>	<p>In general, the body of evidence regarding the use of colchicine in COVID-19 is of low-moderate quality, and dichotomizes into one large moderate to high quality RCT and lower quality evidence (small lower quality RCTs and observational studies). Observational studies of colchicine tended to be lower quality, with high risk of bias from confounding factors, inadequate controls, and small sample sizes. One of the three RCTs was estimated to be moderate quality (Tardif et al., preprint), while the other two were estimated to be low-moderate quality as they were small, with inadequate blinding and risk of performance bias and confounding.</p> <p>There were several systematic reviews identified on this topic; however, they all identified and included the same studies (Deftereos and Lopes). To minimize duplication, two studies with a meta-analysis were selected for inclusion: Vrachatis et al. (2021) and Juul et al. (preprint). Vrachatis (2021) includes all the relevant studies that were identified in the present database search (both RCTs and observational studies) but is overall of low quality as it does not address risk of bias in the primary literature. Juul (preprint) is the second edition of a living systematic review that includes only RCTs (two included in database results, one that was not identified) but is of reasonable quality.</p> <p>The included guidelines were all identified from reputable public health agencies, with appropriate evidence cited to make an informed decision and all erring on the side of caution.</p>
<p>Applicability</p>	<p>The studies do not arise from any specific geographic region. The RCTs arise from Greece, Brazil and Quebec (22 sites across the United States, Brazil, South Africa, Canada, and Spain); the observational studies are from the United States, Israel, Colombia, and Italy. Although these regions all have different population health statistics and epidemic dynamics, there is no reason to suspect that colchicine would not be effective when administered to Albertans.</p>
<p>Consistency</p>	<p>Notwithstanding the heterogeneity in study designs and comparators, the primary literature inconsistently shows reduced clinical progression (represented by hospitalization, ICU admission, or mortality outcomes) in patients offered colchicine compared to placebo or standard care comparator groups; the primary outcome of the highest quality evidence (Tardif RCT) was negative.</p>

Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to January 25, 2021

#	Searches	Results
1	exp Coronavirus/ or Coronavirus Infections/ or coronaviru*.mp. or corona viru*.mp. or ncov*.mp. or n-cov*.mp. or novel cov*.mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-CoV-2.mp. or SARSCoV-2.mp. or SARSCoV2.mp. or SARSCoV19.mp. or SARS-Cov-19.mp. or SARSCov-19.mp. or SARSCoV2019.mp. or SARS-Cov-2019.mp. or SARSCov-2019.mp. or severe acute respiratory syndrome coronaviru*.mp. or severe acute respiratory syndrome cov 2.mp. or 2019 ncov.mp. or 2019ncov.mp.	116890
2	exp Colchicine/	15163
3	(colchicine or colcemid* or demecolcine or colchamine or lumicolchicine*).mp.	22388
4	2 or 3	22388
5	1 and 4	94
6	remove duplicates from 5	90
7	limit 6 to (english language and yr="2020 -Current")	84

LitCOVID

Search string: colchicine

83 results were retrieved.

PubMed

```
(((wuhan[tw] AND (coronavirus[tw] OR corona virus[tw])) OR coronavirus*[ti] OR COVID*[tw] OR nCov[tw] OR 2019 ncov[tw] OR novel coronavirus[tw] OR novel corona virus[tw] OR covid-19[tw] OR SARS-COV-2[tw] OR Severe Acute Respiratory Syndrome Coronavirus 2[tw] OR coronavirus disease 2019[tw] OR corona virus disease 2019[tw] OR new coronavirus[tw] OR new corona virus[tw] OR new coronaviruses[all] OR novel coronaviruses[all] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[nm] OR 2019 ncov[tw] OR nCov 2019[tw] OR SARS Coronavirus 2[all]) AND (2019/12[dp]:2020[dp])) AND ("colchicine"[MeSH Terms]) OR (colchicine[Title/Abstract] OR colcemid*[Title/Abstract] OR demecolcine[Title/Abstract] OR colchamine[Title/Abstract] OR lumicolchicine*[Title/Abstract])) AND (english[Language])
```

80 results were retrieved.

TRIP PRO

```
(coronaviru* OR "corona virus" OR ncov* OR n cov* OR COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 OR SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019 OR "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*" OR "2019 ncov" OR 2019ncov OR Hcov*) AND (colchicine or colcemid* or demecolcine or colchamine or lumicolchicine*) from:2020
```

17 results were retrieved.

WHO Global research on coronavirus (database)

Title, abstract, subject: colchicine

Filter: English language

79 result were retrieved.

medRxiv and bioRxiv

Search string: covid colchicine

Posted between "01 Jan, 2020 and 26 Jan, 2021"

41 results were retrieved.

Google / Google Scholar

Search string: colchicine COVID-19 after:2020

200 results were screened. 5 were kept.

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