



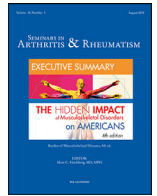
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A systematic review of the infectious complications of colchicine and the use of colchicine to treat infections

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ABSTRACT

Objective: Colchicine has been used historically as an anti-inflammatory agent for a wide range of diseases. Little is known regarding the relationship between colchicine use and infectious disease outcomes. The objective of this study was to systematically examine infectious adverse events associated with colchicine usage and the clinical use of colchicine for infectious diseases.

Methods: A systematic review was conducted in accordance with PRISMA methodology. PubMed, EMBASE, Scopus and Cochrane Library databases were searched (up to 12th October, 2020) for interventional and observational studies that included colchicine usage associated with infectious adverse events or infectious disease outcomes.

Results: A total of 9,237 studies were initially identified and after exclusions, 36 articles comprising 21 interventional studies and 15 observational studies were included in this systematic review. There were 19 studies that reported infectious adverse events and 17 studies that examined the efficacy of colchicine in treating infectious disease. Only two out of six studies reported a significant benefit using colchicine in the management of viral liver disease. There was some evidence colchicine is beneficial in managing COVID-19 by reducing time to deterioration, length of stay in hospital and mortality. Colchicine had some benefit in managing malaria, condyloma accuminata and verruca vulgaris, viral myocarditis and erythema nodosum leprosum based on case-series or small, pilot clinical studies.

Two of the clinical trials and five of the observational studies reported significant associations between infectious adverse events and colchicine usage. Risk of pneumonia was found in three studies and post-operative infections were reported in two studies. Risks of urinary tract infections, *H. pylori* and *C.difficile* were only reported by one study each.

Conclusion: There is a current lack of clinical evidence that colchicine has a role in treating or managing infectious diseases. Preliminary studies have demonstrated a possible role in the management of COVID-19 but results from more clinical trials are needed. There is inconclusive evidence that suggests colchicine is associated with increased risk of infections, particularly pneumonia.

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Introduction

Colchicine is a drug that has longstanding use to treat gout, Behcet's disease and Familial Mediterranean Fever. New applications in pericarditis, liver disease, vasculitis, cardiovascular disease and dermatology have helped increase interest in colchicine [1]. There are also several clinical trials currently underway exploring the role of colchicine in combating the SARS-CoV-2 pandemic [2]. Colchicine interrupts microtubule assembly which is required for cellular processes such as maintenance of cell shape, intracellular trafficking, cell signaling, migration and division [3]. Its anti-inflammatory effects are primarily due to

inhibiting neutrophil recruitment, chemotaxis, adhesion, mobilization, superoxide production and inflammasome activation [3]. Colchicine has also exhibited anti-viral properties *in vitro* through interruption of the tubular network required by some viruses for replication [4–6]. Despite the historic usage of colchicine little is known about the risks or benefits colchicine poses clinically in infectious disease. A meta-analysis limited to double-blinded randomized clinical trials reported that colchicine did not increase the risk of infectious adverse events [7]. However, most of these studies had small cohorts and were not powered to identify statistical differences in uncommon events such as infections. The efficacy of colchicine in managing infectious diseases has not been reviewed systematically to our knowledge. Since the therapeutic landscape for colchicine has been evolving rapidly it is worthwhile to review what is known clinically regarding

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the relationship between colchicine and infectious disease risk, severity and management.

Methods

This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [8].

Eligibility criteria: The PICOS framework was applied to identify studies relevant to this review.

- 1) *Participants*: Children or adults receiving colchicine for any clinical indication.
- 2) *Intervention*: Colchicine alone or in combination at therapeutic doses.
- 3) *Comparison*: Placebo, no treatment, standard treatment, alternate treatment.
- 4) *Outcomes*: Infection adverse events (number, type and severity) and/or infectious disease progression (survival, complications, microbiology and pathology).
- 5) *Study Design*: Clinical trials (randomized, non-randomised, controlled, quasi-experimental), prospective and retrospective cohort studies, case-control, cross-sectional and case series. The following studies were excluded: pre-clinical, animal studies, editorials, case reports, systematic reviews and meta-analysis.

Studies were only included if they reported either infectious adverse events and/or colchicine's effect on infectious disease progression. Infectious diseases were only relevant if there was clear infective etiology reported (e.g. idiopathic pericarditis was excluded but tuberculous pericarditis was included). Studies reporting colchicine overdose or drug-drug interactions were excluded.

Search Strategy: Electronic databases (PubMed, EMBASE, SCOPUS and Cochrane Library) were searched from inception to 12th October 2020. The initial search was performed in PubMed with the following search string: "(colchicine[MeSH Terms] OR colchicine[Text]) AND (infections[MeSH Terms] OR bacteria*[Text] OR Virus[Text] OR Viral [Text] OR tuberculosis[Text] OR mycobacterium[Text] OR fungal [Text] OR "adverse effect*" [Text] OR "side effect*" [Text] OR "drug-related side effects and adverse reactions"[MeSH Terms]) AND (English[filter])." The other databases were searched using analogous keywords and phrases. Only papers in English were included. Bibliographical references from included studies were manually searched and included if relevant. All titles and abstracts were screened by a single reviewer to identify articles fulfilling eligibility criteria. Full-text screening was performed by a single reviewer to identify articles that reported infectious adverse events associated with colchicine usage or the efficacy of colchicine in managing infectious disease. Data was extracted from full-text studies to include publication details (author, year of publication), disease state, study details (intervention, colchicine dosage, length of study, sample size), participant details (age, gender) and relevant outcomes (number and severity of infectious adverse events as well as efficacy of treatment against infectious diseases). A qualitative data synthesis was performed due to the heterogeneity in study design, disease states, interventions and outcomes. The studies were categorised based on whether colchicine was used to treat infectious disease or associated with infectious adverse events.

Results

Study characteristics

Searches of PubMed, EMBASE, Scopus and Cochrane Library were performed on 12th October 2020 and identified a total of 9,237 studies after duplicates were removed. After title and abstract searching 9,039 articles were removed leaving 198 papers. A further 162

articles were excluded after full-text screening. An overview of the study selection process and reasons for article exclusions are outlined in Figure 1. A total of 36 articles were included in this review. There were 21 interventional studies and 15 observational studies. A summary of the key characteristics and major findings of the intervention and observational studies are presented in Table 1 and Table 2, respectively. The majority of studies were randomized controlled trials (n=21), followed by retrospective cohort studies (n=6), case-series (n=5), case-control (n=2), cross-sectional (n=1) and a survey (n=1). A number of different disease states were studied including coronavirus disease 2019 (COVID-19) (n=7), viral liver disease (n=6), gout (n=4), Behcet's disease (n=2), osteoarthritis (n=2), condyloma acuminata and verrucae vulgaris (n=2), idiopathic pulmonary fibrosis (n=1), lung resection surgery (n=1), metabolic syndrome (n=1), joint arthroplasty (n=1), erythema nodosum leprosum (n=1), tuberculous pericarditis (n=1), alcoholic liver cirrhosis (n=1), falciparum malaria (n=1), myocardial infarction (n=2), post-myocardial revascularization (n=1), myocarditis (n=1) and mixed disease states (n=1). Clinical trials varied in duration (4 days to 6 years) and sample size (12 to 4745 enrolled patients). The doses of colchicine ranged from 0.5mg to 5.0mg a day with cumulative doses of 12 to 2,628mg. Observational studies ranged from 4 to 386,010 participants and the specific doses of colchicine were often not reported. The studies were categorized and analysed based on those where colchicine was used to treat infectious disease (n=17) and those that reported infectious adverse events (n=19).

Treating infectious disease

Viral liver disease

In the retrospective cohort study by Arrieta et al. [9] patients who received colchicine (1.0mg daily, 5 days a week) were significantly less likely to develop hepatocellular carcinoma at 3 years follow up compared to the non-colchicine group (9% vs 29%, respectively, $p < 0.05$). There was a significant increase in survival in the colchicine group (252±11 months vs. 218±21 months, $P < 0.05$). In managing hepatitis C patients, colchicine was compared to ribavirin and interferon- α [10,11]. Albillos et al. [10] found no significant change in disease related outcomes (hepatitis venous pressure gradients, hepatic vascular resistance, hemoglobin, ALTs or serum HCV-RNA) between ribavirin and colchicine (1.0mg daily, 6 months). Angelico et al. [11] reported that 23% of patients treated with interferon- α alone were HCV-RNA negative compared to only 10% of patients treated with adjunct colchicine (1.0mg daily, 6 days a week, 1.5 years) ($P < 0.05$). Due to the poor outcome the study was terminated prematurely. Hepatitis B infections were managed with colchicine in three studies [12–14]. The study by Floreani et al. [12] found a sustained antibody response in 4 out of 6 colchicine (1.0mg daily, 5 days a week, 6 months) patients compared to 2 of the 6 control patients. Lin et al. [13] reported the cumulative incidence of cirrhosis development in the colchicine (1.0mg daily, 5 days a week, 4 years) group was 32% at 4 years compared to 73.2% in the control group ($P = 0.057$). Episodes of acute exacerbation, defined as an acute rise in ALTs by > 300 U/L was significantly lower in the colchicine group compared to control (32% vs 63% per patient year, $P < 0.05$). Wang et al. [14] found the cumulative survival at 51 months was 75.9% in the colchicine (1.0mg daily, 26 months) group and 75.3% in placebo ($P > 0.05$). Wang et al. [14] reported no significant difference in hepatitis B complications between colchicine or placebo.

COVID-19

A total of 5 studies reporting the effectiveness of colchicine in managing COVID-19 were included. A randomized controlled trial by Deftereos et al. [15] evaluated the effectiveness of colchicine (1.0mg daily, 3 weeks) on cardiac and inflammatory biomarkers and clinical outcomes in hospitalised COVID-19 patients. A total of 105 patients

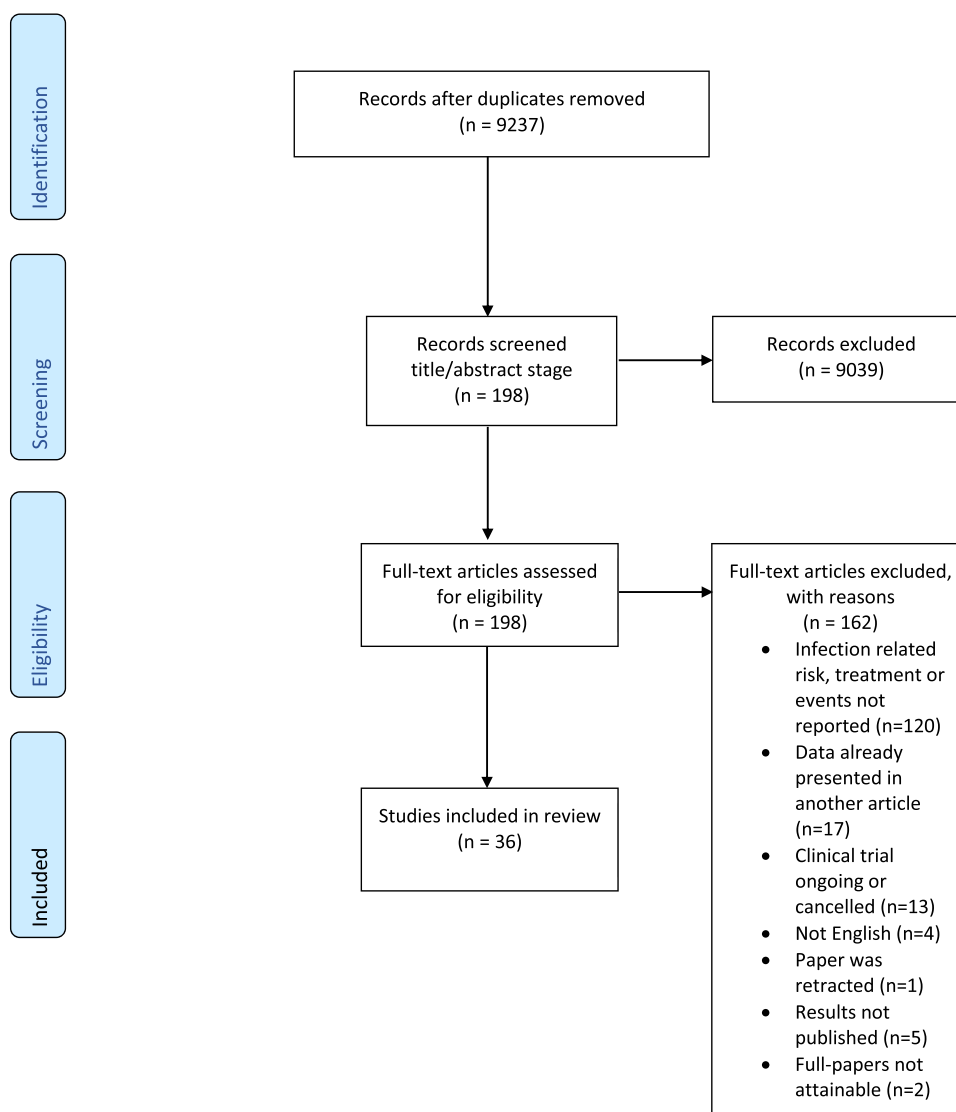


Fig. 1. PRISMA flow chart summarizing the study selection process.

were enrolled and randomized to colchicine (n=55) and control (n=50). The primary clinical endpoint (time to clinical deterioration) occurred in 14.0% of the control group and 1.8% in the colchicine group (OR 0.11, 95% CI, 0.01-0.96, $P < 0.05$). The primary biochemical endpoint (high-sensitivity cardiac troponins and C-reactive protein) was not statistically different between colchicine and control. Event free survival was 18.6 days in the control group and 20.7 days in the colchicine group ($P < 0.05$). A cohort study of hospitalized COVID-19 patients by Scarsi et al. [16] compared colchicine (n=122) to standard of care (n=140). At 21 days follow up there was a lower risk of death in patients treated with colchicine compared to standard of care (HR 0.15, 95% CI, 0.06-0.37, $P < 0.05$). A retrospective observational study by Brunetti et al. [17] compared COVID-19 patients given colchicine (1.2mg daily) to standard of care. The primary endpoint was in-hospital death within 28 days of follow up. Mortality at 28 days was 9.1% in the colchicine group compared to 33.3% in the control (OR 0.20, 95% CI, 0.05-0.80, $P < 0.05$). Patients were also more likely to be discharged by day 28 compared to standard therapy (OR 5.0, 95% CI, 1.25-20.1, $P < 0.05$). A case-series by Delle-Torre et al. [18] reported 9 patients with COVID-19 who were considered at high risk for progression to respiratory failure. Colchicine (1.0mg daily) was started after a median of 8 days from diagnosis and after 72 hrs of colchicine treatment all patients' fevers were abated. A case-series of 5 patients with

COVID-19 and iatrogenic allogeneic was reported by Montealegre-Gomez et al. [19]. All 5 cases received colchicine (0.5-1.0mg daily, 1-3 weeks) to manage the symptoms of iatrogenic allogeneic for up to 3 weeks prior to COVID-19 diagnosis. Despite all the cases having several co-morbidities and considered at high risk of deterioration, all 5 cases experienced only minor symptoms and did not require hospitalization.

Tuberculous pericarditis

A pilot study by Liebenberg et al. [20] aimed to determine the efficacy of colchicine in managing tuberculous pericarditis in South Africa. The study included 33 HIV-positive patients who all received standard TB treatment. The intervention group received colchicine (1.0mg daily, 6 weeks) as an adjunct therapy. There was no significant difference in the development of pericardial restriction between colchicine and control (RR: 1.07, CI 95%, 0.46-2.46, $P > 0.05$).

Malaria

Reba et al. [21] investigated the effectiveness of a colchicine-quinine combination compared to quinine monotherapy in treating *P. falciparum* in a group of American soldiers while in Vietnam. Colchicine-quinine combination achieved cures in 77% of patients compared to 27% in quinine alone after 45 days of follow up.

Table 1
Data extraction of clinical trials included in this review (n=21).

Reference	Disease State	Intervention	Comparator	Daily Dose of Colchicine (mg)	Cumulative Dose of Colchicine (mg)	Length of Intervention	Length of Follow-up	Total Sample Size	Participant Characteristics	Outcomes
Albillos et al. [10]	Hepatitis C	Ribavirin, 1-1.2mg daily	Colchicine, 0.5mg twice daily	1.0	183	6 months	6 months	42 (21 colchicine + 21 Ribavirin)	Not reported	No significant changes in hepatic venous gradient pressure, hepatic vascular resistance, hemoglobin, ALTs or serum HCV-RNA between groups.
Angelico et al. [11]	Hepatitis C	Colchicine, 1.0mg once daily 6 days a week + Interferon- α , 6mIU subcutaneous twice weekly for 6 months then 3mIU for 6 months	Interferon- α , 6 mIU subcutaneously twice weekly for 6 months, then 3mIU for 6 months	1.0	469	1.5 years	1.5 years	65 (31 colchicine/ Interferon- α + 34 Interferon- α)	Mean age 48, 58% males	Interferon- α + colchicine dual therapy resulted in 10% of patients being HCV-RNA negative compared to 23% in the Interferon- α monotherapy group (P<0.05).
Antoniou et al. [34]	Idiopathic pulmonary fibrosis	Colchicine, 1.0mg							daily + prednisolone 10.0mg daily	IFN- γ 1b, 200 μ g subcutaneous 3 times weekly + prednisolone 10mg daily
1.0	730	2 years	2 years	50 (18 colchicine + 32 IFN- γ 1b)	Mean age 67, 84% males	Pneumonia was responsible for 2 deaths in both the IFN- γ 1b and colchicine groups.				
Bessissow et al. [35]	Lung resection surgery	Colchicine, 0.6mg 4hrs before surgery, 0.6mg after surgery, 0.6mg twice daily for 9 days.	Placebo	1.2	12	10 days	30 days	100(49 colchicine + 51 placebo)	Mean age 69, 45% males	Post-operative infection rates at 30-days were 12% for the colchicine group and 6% for placebo (p>0.05).
Das et al. [32]	Knee osteoarthritis	Colchicine, 0.5mg twice daily + peroxicam, 20mg once daily	Placebo + peroxicam, 20mg once daily	1.0	150	5 months	5 months	39 (19 colchicine + 20 placebo)	Mean age 53, 33% males	Upper respiratory tract infections were reported in 5% of patient visits in the colchicine group compared to 1% in placebo p>0.05).
Davatchi et al. [31]	Behcet's disease	Colchicine, 1.0mg once daily	Placebo	1.0	122	4 months	4 months	169 (cross over study)	Mean age 32, 32% males	There was 1 case of UTI and 1 case of infectious diarrhea reported in colchicine group and none in placebo.
Deftereos et al.[15]	COVID-19	Colchicine, 1.5mg loading dose, 0.5mg 60mins later, 0.5mg twice daily maintenance dose for up to 3 weeks	Standard of care	1.0	14.0 (assuming 12-13 days in hospital)	12-13 days (median hospital duration)	12-13 days (median hospital duration)	105(55 colchicine + 50 control)	Median age 64, 58% males	Primary clinical end point rate was 14.0% in control group and 1.8% in colchicine group (OR 0.11, 95% CI, 0.01-0.96, P<0.05). Event free survival was 18.6 days in control group and 20.7 days in colchicine group (P<0.05). There was no statistically significant difference in parameters such as high-sensitivity cardiac troponin and C-reactive protein.
Demidowich et al. [37]	Metabolic syndrome	Colchicine, 0.6mg twice daily	Placebo	1.2	108	3 months	3 months	40 (21 colchicine + 19 placebo)	Mean age 46, 23% males	Upper respiratory tract infections were reported in 6.5% of patient visits in the colchicine group compared to 12.5% in the placebo (P>0.05).

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Table 1 (Continued)

Reference	Disease State	Intervention	Comparator	Daily Dose of Colchicine (mg)	Cumulative Dose of Colchicine (mg)	Length of Intervention	Length of Follow-up	Total Sample Size	Participant Characteristics	Outcomes
Floreani et al. [12]	Hepatitis B	Colchicine, 1.0mg once daily, 5 days a week	No treatment	1.0	130	6 months	18 months	12 (6 colchicine + 6 control)	Mean age 44, 92% males	Sustained antibody response was achieved in 4 out of 6 colchicine patients and in 2 of the 6 untreated patients.
Kar et al. [25]	Erythema nodosum leprosum	Colchicine, 0.5mg three times daily	Aspirin, 0.6g, three times daily	1.5	6	4 days	4 days	68 (34 colchicine + 34 aspirin)	Mean age not reported, 80% males	Colchicine and aspirin were equally effective in managing mild reactions. For moderate reactions, 64% showed response to colchicine compared to 29% in aspirin group. For severe reactions, neither drug was useful.
Leung et al. [33]	Knee osteoarthritis	Colchicine, 0.5mg twice daily	Placebo	1.0	112	16 weeks	16 weeks	109(54 colchicine + 55 placebo)	Mean age 31, 33% males	Upper respiratory tract infections were reported in 31.5% of the colchicine group and 18.2% in placebo (p>0.05). There was 1 reported urinary tract infection in the placebo group with none in the colchicine group.
Liebenberg et al. [20]	Tuberculous pericarditis	Colchicine, 1.0mg per day	Placebo	1.0	42	6 weeks	16 weeks	33 (19 colchicine + 14 placebo)	Mean 31, 34% males	Risk of developing pericardial constriction was not significantly different between colchicine and control (RR 1.07;95% CI, 0.46-2.46, p>0.05).
Lin et al. [13]	Hepatitis B	Colchicine, 1.0mg daily 5 days a week	No treatment	1.0	1043	4 years	4 years	65 (38 colchicine + 27 control)	Mean age 40, 88% males	Cumulative incidence of cirrhosis development in colchicine group was 32% at 4 years compared to 73.2% in the control group (P=0.057). The incidence of acute exacerbations was lower in the colchicine group (32% vs 63% per patient year, P<0.05).
Morgan et al. [38]	Alcoholic liver cirrhosis	Colchicine, 0.6mg twice daily	Placebo	1.2	876-2628	2-6 years	6 years	549 (274 colchicine + 275 placebo)	Mean age 55, 98% males	Spontaneous bacterial peritonitis was observed in 6.9% of colchicine users compared to 9.1% in the placebo group (P>0.05)
Nirdorf, et al.[40]	Chronic coronary disease	Colchicine, 0.5mg daily	Placebo	0.5	435 (median 29.0 months of treatment)	29.0 months median	28.6 months (mean)	5522 (2762 colchicine + 2760 placebo)	Mean age 66, 85% males	Hospitalisation for infections occurred in 5.0% of colchicine group and 5.2% in placebo (HR 0.95, 95% CI, 0.75-1.20). Hospitalisation for pneumonia occurred in 1.7% of colchicine group and 2.0% of placebo (HR 0.84, 95% CI, 0.75-1.20).
Reba et al. [21]	Falciparum malaria	Colchicine, 0.5mg 10 times 1 st day, 0.5mg twice on 2 nd day + Quinine sulfate, 650mg every 8hrs for 14 days	Quinine sulfate, 650mg every 8hrs for 14 days	5.0mg then 1.0mg	6	2 days	8 weeks	60 (22 (colchicine + 38 control)	Ages 18-31, 100% males	Colchicine-quinine therapy achieved cures in 77% of patients compared to 27% in quinine alone.
	Gout			0.5	56	16 weeks	24 weeks		Mean age 69, 63% males	

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Table 1 (Continued)

Reference	Disease State	Intervention	Comparator	Daily Dose of Colchicine (mg)	Cumulative Dose of Colchicine (mg)	Length of Intervention	Length of Follow-up	Total Sample Size	Participant Characteristics	Outcomes
Schlesinger et al. [29]		Colchicine, 0.5mg daily	Canakinumab doses: Single dose 25mg, 50mg, 100mg, 200mg or 300mg. Four doses at four-weekly intervals (50mg, 50mg, 25mg, 25mg)					432 (108 colchicine + 324 Canakinumab)		Infectious events were reported in 12.0% of colchicine users compared to 18.0% of total canakinumab users. No serious infectious events were reported in colchicine group compared to 6 serious infections (pneumonia, gangrene, sepsis, tonsillitis, ear infection and erysipelas) in canakinumab users.
Tardif et al. [41]	Myocardial infarction	Colchicine, 0.5mg once daily	Placebo	0.5	588	19.6 months (median)	23 months (median)	4745 (2366 colchicine + 2379 placebo)	Mean age 61, 82% males	Total Infectious events were reported in 2.2% of the colchicine group compared to 1.6% in the placebo (p>0.05). Pneumonia was significantly more likely to occur in the colchicine group being reported in 0.9% of patients compared to 0.4% in the placebo (P<0.05). Septic shock was reported in 0.1% of patients in both colchicine and placebo group.
Wang et al. [14]	Hepatitis B	Colchicine, 1.0mg once daily	Placebo	1.0	780	26 months (median)	15-51 months 26 months (median)	100(50 colchicine + 50 placebo)	Mean age 60, 94% males	Cumulative survival at 51 months was 75.9% in the colchicine group and 75.3% in placebo (p>0.05). There was no significant difference in hepatitis B complications between colchicine or placebo.
Yamanaka et al. [28]	Gout	Febuxostat, 10-40mg daily	Colchicine, 0.5mg once daily + Febuxostat, 40mg daily OR Febuxostat, 40mg daily	0.5	42	12 weeks	24 weeks	255 (101 febuxostat stepwise dose + 102 colchicine/Febuxostat+52 Febuxostat)	Mean age 47, 100% males	Infectious events were reported in 21.9% of patients in the stepwise febuxostat treatment group compared to 20.0% in febuxostat + colchicine and 22.0% in febuxostat 40mg. There was no significant difference between groups (p>0.05).
Zarpelon et al. [42]	Post-operative myocardial revascularisation	Colchicine, 1.0mg twice daily in pre-operative period (24 hrs before surgery), 0.5mg twice daily until discharge	Placebo	1.0	14.0 (assuming 14 days in hospital)	14 days (average length of hospital stay)	14 days (average length of hospital stay)	140 (71 colchicine, 69 placebo)	Mean age 61, 68% males	Patients in colchicine group were more likely to experience post-operative infections compared to control group (26.8% and 8.7%, respectively, P<0.05).

Table 2
Data extraction of observational studies included in this review (n=15)

Reference	Disease State	Study Design	Study Size and Characteristics	Study Duration	Colchicine Exposure	Comparator	Outcomes
Arrieta et al. [9]	Viral liver cirrhosis	Retrospective cohort	N= 186 (116 colchicine, 70 control) Mean age 52, 34% males	Study period 1980-2000 Mean follow up 84 months	Colchicine, 1mg daily, 5 days a week	No colchicine	At 3 years of follow up, development of HCC was significantly less in colchicine group compared to non-colchicine group (9% vs 29%, p <0.05).
Brunetti et al.[17]	COVID-19	Retrospective cohort	N=66 (33 colchicine, 33 control) Median age 63, 65% males	Study length 28 days	73% of patients in colchicine cohort received a loading dose of 1.2mg and maintenance dose of 0.6mg twice daily.	Standard of care	Patients were more likely to be discharged by day 28 compared to standard therapy (OR 5.0, 95% CI, 1.25-20.1, P<0.05). Mortality at 28 days was 9.1% in the colchicine group compared to 33.3% in the control (OR 0.20, 95% CI, 0.05-0.80, P<0.05).
Delle-Torre et al.[18]	COVID-19	Case-series	N=9	-	Colchicine, 1.0mg loading dose, followed by 1.0mg daily until 3 rd day of axillary temperature <37°C.	-	After 72 hrs of colchicine therapy fevers in all 9 patients resolved abated and all subsequently recovered from COVID-19.
Gendelman et al.[43]	COVID-19	Case-control	N=14520 (1317 positive COVID-19 and 13203 negative COVID-19). Mean age 37 years, 53% males	Study period February 23 rd to March 31 st 2020.	Colchicine, dose unspecified, prescribed from January 1 st 2020	No colchicine	The rate of colchicine usage was not statistically different between those who tested positive or negative for COVID-19 (0.53% vs 0.48%, p>0.05).
Gigax et al. [22]	Intraurethral condyloma acuminata	Case-series	N=4 Mean age 23, 100% males	-	Colchicine, 10mL 0.5% intraurethral injections, 3-7 times	-	Four cases of young men were treated successfully with colchicine.
Gultekin et al. [24]	Myocarditis	Case-series	N=5 Mean age 42, 100% males	2 years	Colchicine, 0.5mg twice daily	-	Initial ejection fractures were 21%, 18%, 25%, 20% and 21% before colchicine therapy. After 2 years ejection fractures were 59%, 45%, 40%, 25% and 41%.
Haslak et al.[44]	COVID-19 and childhood auto-inflammatory disease	Web survey	N=404 children with autoimmune diseases Median age 11.1 years, 46% males	Study period 11 th March to 15 th May 2020	Colchicine, unspecified dose	-	There were 376 patients on colchicine treatment with only 6 of these patients contracting COVID-19. All cases recovered completely.
Montealegre-Gomez et al.[19]	COVID-19 and Iatrogenic allogenesi	Case-series	N=5 (patients on colchicine for symptomatic management of iatrogenic allogenesi)	-	Colchicine, 0.5-1.0mg daily for 1-3 weeks prior to COVID-19	-	The 5 patients all had significant co-morbidities and experienced only mild symptoms of COVID-19 (headache, cough, arthralgias) without need for hospitalisation
Nelson.[23]	Verruca Vulgaris	Case-series	N=10	-	Colchicine, 0.1mL of 1.0mg/mL solution injected into each verruca once a week	-	6 warts out of 18 in the 10 patients disappeared and did not recur after 3 months. 10 warts partially regressed but recurred and 2 were unaffected.
Pata et al. [30]	Behcet's disease and H.pylori infection	Cross-sectional	N=80 (40 Behcet's disease, 40 control) Mean age 37, 45% males	Mean colchicine therapy 3.7 years	Colchicine, dose unspecified	No colchicine	The percentage of <i>H. pylori</i> positive patients by histological diagnosis was 94% in patients taking colchicine but only 44% in patients not on colchicine (P<0.05)
Salt et al. [36]	Total joint arthroplasty and post-operative infections	Retrospective case-control	N=2,212 (1,106 cases, 1,106 control) Mean age 60, 49% males	Study period 2007-2009 Median follow up 555 days	Colchicine, dose unspecified, at least once 1 month before or after operation	No colchicine	The study found that 11% of cases were prescribed colchicine compared to 9% of controls in the peri-operative period (Chi ² =7.5, p <0.05).
Scarsi et al.[16]	COVID-19	Retrospective Cohort	N=262 (122 colchicine, 140 control)	-	Colchicine, 1.0mg daily + Standard of Care	Standard of Care (hydroxychloroquine and/or IV dexamethasone and/or lopinavir/ritonavir)	There was a lower risk of death in patients treated with colchicine compared to standard care (HR 0.151, 95% CI, 0.062-0.368, P<0.05).

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Table 2 (Continued)

Reference	Disease State	Study Design	Study Size and Characteristics	Study Duration	Colchicine Exposure	Comparator	Outcomes
Spaetgens et al. [27]	Gout and pneumonia/UTIs	Retrospective cohort	N=384,328 (131,565 gout patients, 252,763 controls) Mean age 64, 74% males	Study period 1987-2014 Mean follow up 6.7 years	Colchicine, dose unspecified	No colchicine	No significant pneumonia risk in gout patients with current colchicine usage (adjusted HR, 0.88, 95% CI, 0.54-1.44). Recent exposure (31-91 days) and past exposure (>91 days) were associated with increased pneumonia risk (adjusted HR, 1.60, 95% CI, 1.13-2.27) and (adjusted HR, 1.49, 95% CI, 1.32-1.68), respectively. Increased UTI risk with current and recent colchicine usage (adjusted HR 1.05, 95% CI, 1.24-1.64) and (adjusted HR: 1.29, 95% CI, 1.12-1.49), respectively. No association with pneumonia related mortality in gout patients stratified by colchicine usage. Increased risk of UTI related mortality in gout patients who never used colchicine (adjusted HR: 1.25, 95% CI, 1.04-1.49).
Tsai et al. [26]	Gout and pneumonia	Retrospective cohort	N=24,410 (12,205 colchicine, 12,205 no colchicine) Mean age 55, 70% males	Study length 13 years	Colchicine, categorized into days of usage: < 8 days, 8-32 days. ≥ 33 days and cumulative dosage: low (9mg), median (9-24mg) and high (≥ 24 mg)	No colchicine	A higher incidence of pneumonia was found for colchicine users (adjusted HR, 1.42, 95% CI, 1.32-1.53). This increased risk was similar across age groups, genders and co-morbidities. Increased cumulative days of colchicine use (> 33 days) and high doses (>24mg) were associated with increased pneumonia risk suggesting a dose response relationship.
Young-Xu et al. [39]	Mixed autoimmune and Clostridium Difficile.	Retrospective cohort	N=386,010 (77,202 colchicine, 308,808 no colchicine) Mean age 65, 99% males	Study length 2 years	Colchicine, minimum 30 day prescription, categorized as low or high dosage (≥ 1.2 mg daily, ≥ 90 pills, > 60 days)	No colchicine	Colchicine users were more likely to experience CDI (adjusted RR 1.44, 95% CI, 1.15-1.97). There was a dose response relationship and colchicine use was associated with increased risk of CDI recurrence (adjusted RR 1.23, 95% CI, 1.03-1.49), ICU admission or death (adjusted RR 1.44, 95% CI, 1.02-2.01).

Condyloma accuminata and verruca vulgaris

The case-series by Gigax et al. [22] reported successful treatment of refractory intraurethral condyloma acuminata in 4 young males with weekly rounds (between 3–11) of intraurethral injections of 10 mL 0.5% colchicine. A case-series by Nelson. [23] explored the effectiveness of using colchicine injections to treat verruca vulgaris in ten patients. Patients received 0.1mL injections of a 1.0mg/mL colchicine solution into each wart once a week. Only 6 out of 18 warts across the patients completely disappeared without recurrence after 3 months.

Myocarditis

The case series by Gultekin et al. [24] investigated the effect of colchicine in managing five patients diagnosed with Epstein-Barr virus (EBV) and cytomegalovirus (CMV) myocarditis over a 2 year period. Adjuvant low-dose colchicine therapy (1.0mg daily, 2 years) was used in conjunction with traditional heart failure therapy. Initial ejection fractions were 21%, 18%, 25%, 20% and 21% before colchicine therapy. After 2 years ejection fractions were 59%, 45%, 40%, 25% and 41%.

Erythema nodosum leprosum

A study by Kar et al. [25] trialed treating lepromatous leprosy with colchicine (1.5mg daily, 4 days) compared to aspirin. For mild reactions both colchicine and aspirin were equally effective. For moderate reactions, 64% showed response to colchicine compared to 29% in aspirin group. For severe reactions, neither drug was useful. Colchicine was more effective in controlling neuritis and joint pain symptoms associated with erythema nodosum leprosum compared to control.

Infectious adverse events

There were four studies conducted that reported infectious adverse events in gout patients using colchicine [26–29]. A retrospective study by Tsai et al. [26] compared the incidence of pneumonia in gout patients based on colchicine usage. A higher incidence of pneumonia was found for colchicine users (adjusted HR: 1.42, 95% CI, 1.32–1.53). This increased risk was similar across age groups, genders and co-morbidities. Increased cumulative days of colchicine use (> 33 days) and high doses (>24mg) were associated with increased pneumonia risk suggesting a dose response relationship. The retrospective cohort study by Spaetgens et al. [27] found inconsistent infection risk associated with colchicine. There was no significant pneumonia risk in gout patients with current colchicine usage (adjusted HR, 0.88, 95% CI, 0.54–1.44). However, recent exposure (31–91 days) and past exposure (>91 days) were associated with pneumonia risk (adjusted HR, 1.60, 95% CI, 1.13–2.27 and adjusted HR, 1.49, 95% CI, 1.32–1.68, respectively). Risk of urinary tract infections (UTIs) was also associated with current and recent colchicine usage (adjusted HR 1.05, 95% CI, 1.24–1.64 and adjusted HR: 1.29, 95% CI, 1.12–1.49, respectively). There was no association with pneumonia related mortality in gout patients stratified by colchicine usage. There was increased risk of UTI related mortality in gout patients who never used colchicine (adjusted HR: 1.25, 95% CI, 1.04–1.49). A randomized control trial by Schlesinger et al. [29] comparing colchicine (0.5mg daily, 16 weeks) to canakinumab for gout prophylaxis reported infectious adverse events in 13 colchicine patients (12.0%) and 58 canakinumab patients (18.0%). No serious infections were reported in the colchicine group but there were 6 serious infections (pneumonia, gangrene, sepsis, tonsillitis, ear infection and erysipelas) in 4 patients on canakinumab. The authors only attributed erysipelas as being related to canakinumab. The authors did not provide analysis regarding whether these differences were of statistical significance. A randomized controlled trial by Yamanaka et al. [28] comparing varying febusostat doses with a febusostat/colchicine combination found no significant differences in infectious related adverse events.

There were two studies conducted that reported infectious adverse events in patients with Behcet's disease [30, 31]. The cross-sectional study by Pata et al. [30] reported that the prevalence of *H. pylori*, determined by histological diagnosis, was 94% in patients on colchicine but only 44% in patients not on colchicine ($P < 0.05$). The mean duration of colchicine exposure was 3.7 years but doses were not reported. A cross-over trial by Davatchi et al. [31] reported 1 UTI in the colchicine group (1.0mg daily, 4 months) and 1 case of infectious diarrhea in the control group. Statistical analysis was not performed comparing the incidence of infectious events.

There were two studies of patients with osteoarthritis who received colchicine [32, 33]. The study by Das et al. [32] found no significant difference in upper respiratory tract infections after 5 months between colchicine (1.0mg daily, 5 months) and control (5% vs 1% of patient visits, respectively, $P > 0.05$). Similarly, Leung et al. [33] reported no significant difference in upper respiratory infections colchicine (1.0mg daily, 16 weeks) and placebo (31.5% vs 18.2%, respectively, $P > 0.05$).

A randomized, open-label study by Antoniou et al. [34] reported 8 respiratory infections in patients with idiopathic pulmonary disease treated with IFN- γ compared to 2 in the colchicine group (1.0mg daily, 2 years). Pneumonia was responsible for 2 deaths in both the colchicine and INF- γ cohorts. Bessisow et al. [35] investigated whether colchicine reduced post-operative atrial fibrillation or atrial flutter after lung resection. Patients received either placebo or colchicine (1.2mg daily, 9 days). After 30 days post-operation, the rate of infections was 12% for colchicine group and 16% for control with no significant difference (adjusted HR, 1.36, 95% CI, 0.38–4.86, $P > 0.05$). One patient developed acute respiratory distress syndrome on day 3 due to suspected pneumonia but recovered on day 11.

A retrospective, case-control study by Salt et al. [36] examined the infection risk of immunosuppressive medications in patients undergoing large joint arthroplasty. The study found that 11% of cases were prescribed colchicine compared to 9% of controls in the peri-operative period ($\text{Chi}^2 = 7.5$, $p < 0.05$). The dose and duration of colchicine was not provided.

Demidowich et al. [37] evaluated the efficacy and safety of colchicine for improving metabolic outcomes in people with metabolic syndrome. There was no significant difference in upper respiratory tract infections in the colchicine (1.0mg daily, 4 months) group compared to control (6.5% vs 12.5% patient visits, $P > 0.05$).

Morgan et al. [38] investigated the efficacy and safety of colchicine in patients with alcoholic liver cirrhosis. Treatment with colchicine (1.2mg daily) lasted between 24 to 72 months. The primary outcome was all cause mortality but secondary outcomes included complications of liver disease. There was no significant difference in spontaneous bacterial peritonitis in the colchicine and placebo groups (6.9% vs 9.1%, respectively, $P > 0.05$).

A retrospective cohort study by Young-Xu et al. [39] explored the relationship between colchicine use and *Clostridium Difficile* Infection (CDI). Data was obtained from United States Veterans Affairs system regarding patients who filled a 30-day prescription of colchicine ($n = 77,202$). These were matched to colchicine non-users ($n = 308,808$). Colchicine users were more likely to experience CDI (adjusted RR 1.44, 95% CI, 1.15–1.97). However, patients prescribed < 1.2mg daily of colchicine exhibited a non-significant risk of CDI (adjusted RR 1.21, 95% CI, 0.76–1.94) as opposed to patients prescribed ≥ 1.2 mg daily (adjusted RR 1.37, 95% CI, 1.09–1.73). This dose response was further supported with significant risk of CDI associated with prescriptions of colchicine for ≥ 90 pills or > 60 days. Colchicine use was associated with increased risk of CDI recurrence (adjusted RR 1.23, 95% CI, 1.03–1.49), ICU admission or death (adjusted RR 1.44, 95% CI, 1.02–2.01).

A large randomized controlled trial by Nirdoff et al. [40] investigated the effect of colchicine in reducing the risk of cardiovascular events in patients with chronic coronary disease. A total of 5,522

patients were randomized to colchicine (n=2,762) and placebo (n=2,760). The median duration of colchicine treatment, 0.5mg daily, was 29 months. Hospitalisation rates for infections were 5.0% in the colchicine group and 5.2% in placebo (HR 0.95, 95% CI, 0.75-1.20, $P > 0.05$). Hospitalisation rates for pneumonia were 1.7% in the colchicine group and 2.0% in placebo (HR 0.84, 95% CI, 0.75-1.20, $P > 0.05$).

Tardif et al. [41] explored the effect of colchicine (0.5mg daily, 19.6 months) in reducing cardiovascular events after myocardial infarction. A total of 4,745 patients were enrolled and assigned to colchicine (n=2,366) or placebo (n=2,379). The median duration of treatment was 19.6 months in colchicine group and 19.5 months in placebo. Infectious adverse events were reported in 2.2% of the colchicine group compared to 1.6% in the placebo with no significant difference ($P > 0.05$). Pneumonia was significantly more likely to occur in the colchicine group compared to placebo (0.9% vs 0.4%, respectively, $P < 0.05$). Septic shock was reported in 0.1% of patients in both colchicine and placebo group.

A study by Zarpelon et al. [42] explored whether colchicine (2.0mg daily, 24hrs before surgery and 1.0mg daily after surgery until discharge) was effective in reducing atrial fibrillation in the post-operative period of myocardial revascularization. A total of 140 patients were enrolled and assigned to receive colchicine (n=71) or control (n=69). Patients in colchicine group were more likely to experience post-operative infections compared to control group (26.8% and 8.7%, respectively, $P < 0.05$). Details about the type of post-operative infections were not reported.

There were two studies reporting the association between colchicine usage and COVID-19 infection. A case-control study by Gendelman et al. [43] explored the association between COVID-19 and the use of hydroxychloroquine or colchicine. A sample of 14,520 patients was obtained from the Maccabi Health Services database with 1,317 positive cases of COVID-19. The rate of colchicine usage was not statistically different between those who tested positive or negative for COVID-19 (0.53% vs 0.48%, $P > 0.05$). A web survey was conducted by Haslak et al. [44] of 404 children with autoimmune diseases. There were 376 patients on colchicine treatment and only 6 of these patients contracted COVID-19. All cases recovered completely.

Discussion

This review was based on results from interventional and observational studies with significant heterogeneity in disease states, colchicine doses and lengths of intervention. In light of these limitations, conclusions can only tentatively be drawn from the results of this systematic review.

There was minimal evidence that colchicine has a role in combating any infectious disease or its complications. In viral liver disease colchicine was primarily used to prevent liver cirrhosis or complications due to its anti-fibrotic effects [3]. Only Albillos et al. [10] and Angelico et al. [11] monitored viral load in response to colchicine treatment and found no significant change and a deleterious effect, respectively. Some viruses require the microtubule network for their replication cycle including viral entry, intracellular transport, virion assembly and exit. Colchicine has been shown to interrupt hepatitis C, flaviviruses and varicella-zoster replication in vitro [4–6] and respiratory syncytial virus (RSV) replication in mice [45]. However, other viruses such as herpes simplex (HSV) do not depend on the cytoskeleton for replication and are potentially unaffected by colchicine [46]. The impact of colchicine on viral load in viral hepatitis remains unknown. Floreani et al. [12] reported an increased antibody response in patients treated with colchicine. However, this was a pilot study with a small sample size and no significant difference between treatment and control could be drawn. There was no conclusive evidence supporting the role of colchicine in preventing complications in viral hepatitis. Arrieta et al. [9] reported a significant protective effect with delayed development of hepatocellular

carcinoma. However, HBV and HCV are not believed to play a direct role in hepatocarcinogenesis and this effect was presumed to occur due to colchicine inhibiting the chronic inflammatory process and cellular proliferation exhibited in all liver disease, regardless of etiology. However, this hypothesis is not supported by a meta-analysis which found colchicine has no use in the management of alcoholic and non-alcoholic liver cirrhosis [47]. Although Lin et al. [13] reported a significant reduction in hepatitis B complications, this was defined as an acute change in ALT liver enzymes. There was no correlation to symptoms and the study found no significant difference in overall disease prognosis.

Colchicine has been shown previously to be effective as an adjunct to NSAIDs in managing acute idiopathic pericarditis and preventing recurrences [48]. These studies are based on idiopathic pericarditis with no confirmed infective origin and were subsequently excluded in this review. The study by Liebenberg et al. [20] with tuberculosis pericarditis patients found colchicine provided no significant benefit in reducing pericardial constriction. This study was a pilot study, limited to HIV positive patients and the power of the study was insufficient to detect any small differences in outcomes. The effect of colchicine in treating myocarditis is not understood. There is some evidence demonstrated by cardiac MRI that myocarditis, associated with idiopathic pericarditis is responsive to colchicine treatment [49]. The only clinical evidence in viral myocarditis was a small case series by Gultekin et al. [24] which suggested colchicine improved ventricular ejection fraction in EBV/CMV myocarditis. This study did not report on any changes in viral loads. Pre-clinical studies have suggested that colchicine treatment can in fact decrease macrophage infiltration and lead to increased viral load in both the heart and pancreas of coxsackievirus B3 infected mice leading to increased mortality [50].

The majority of evidence for the use of colchicine in managing COVID-19 was from observational studies. The case-series were generally published at the beginning of the pandemic and helped support the hypothesis that colchicine could dampen the systemic inflammatory response observed in patients with severe disease. The retrospective study by Brunetti et al. [17] was able to demonstrate significant differences in mortality and length of stay in hospital. The GRECCO-19 trial was the first published randomized-controlled trial and found colchicine reduced the time to clinical deterioration but there was no difference in high-sensitivity cardiac troponin or C-reactive protein levels. It is unclear whether the clinical benefit was due to colchicine disrupting viral replication or its anti-inflammatory action. Studies involving colchicine and COVID-19 are limited by the inconsistency in standard of care in the control groups. Patients were also enrolled at varying time points after diagnosis of COVID-19 and it is unclear at what stage in the disease progression colchicine treatment is most beneficial. More results from clinical trials are needed before any conclusions can be drawn regarding the effectiveness of colchicine in managing COVID-19.

Reba et al. [21] found benefit in a colchicine-quinine therapy in treating *P. falciparum* using a large initial dose (5.0mg on 1st day). Colchicine may potentiate the anti-malarial effects of quinine by inhibiting merozoite invasion into red blood cells [51]. Colchicine itself is not believed to be an ideal drug against malaria since its IC_{50} is approximately 1000 times more in *P. falciparum* than mammalian cell lines creating a high risk of toxicity [52]. There was some benefit in using colchicine to treat moderate erythema nodosum leprosum reactions in lepromatous leprosy. Colchicine was used to manage the immune reaction with no evidence of impacting the causative *Mycobacterium leprae* infection. There was little evidence for colchicine in treating condyloma acuminata and verruca vulgaris as both studies were small case-series.

The second objective of this systematic review was to identify if colchicine resulted in increased risk of infectious adverse events. Only two of the clinical trials reported statistically significant

associations of infections with colchicine usage [41, 42]. This result aligned with the meta-analysis by Stewart et al. [7] that found no significant infection risk from pooled double-blinded randomized controlled trials. Many of the colchicine infectious events tended to be relatively uncommon and the clinical trials with small cohorts were not powered to make statistical comparisons. In the observational studies colchicine was associated with increased risks of pneumonia, CDI, UTIs, post-operative infections and *H. pylori* [26, 27, 30, 36, 39]. The majority of these studies did not report specific colchicine doses, length of usage and infection etiology (ie. bacterial, viral etc.). However, there appeared to be a dose response to pneumonia risk in the study by Tsai et al. [26] suggesting a possible causal relationship. The two largest clinical trials by Tardif et al. [41] and Nirdoff et al. [40] reported conflicting results. The findings by Spaetgens et al. [27] were inconsistent and there was no logical explanation why recent and past exposure conferred pneumonia risk but current colchicine use did not elevate risk. The severity of pneumonia did not appear to be related to colchicine use with these studies finding no differences in septic shock, ICU admissions or death. There appeared to be no significant association between colchicine and risk of COVID-19 infection. There was some evidence suggesting a relationship between colchicine and *Clostridium difficile* infection. The results by Young-Xu et al. [39] supported a dose response relationship and also found ICU admissions and death were associated with colchicine usage. A significant limitation in this study is that gastrointestinal events are the most common adverse effects associated with colchicine usage. Positive laboratory tests were required for the diagnosis of CDI but the increased prevalence of gastrointestinal symptoms due to colchicine may have decreased testing thresholds in the colchicine group. The increased risk of CDI was only accounted for patients on large doses (> 1.2mg daily) of colchicine. This result may not be generalizable to the majority of patients who are on colchicine for gout prophylaxis that requires recommended doses of only 0.6mg–1.2mg daily. The association of *H. pylori* with colchicine usage [30] was specific to patients with Behcet's disease and therefore the results may not be generalizable to majority of colchicine users. A causative relationship between colchicine and *H. pylori* infection seems unlikely since the study by Pata et al. [30] included patients from Turkey where the vast majority of the population are infected with *H. pylori* in their childhood prior to any colchicine exposure. [53]

The possible susceptibility of patients to infections of presumed bacterial etiology (pneumonia, UTIs and *C.difficile*) could be due to multiple reasons. Colchicine selectively accumulates in neutrophils and disrupts neutrophil recruitment, adhesion and mobility. Neutrophils are the primary cells involved in the innate immune response to extracellular bacteria. Colchicine can also lead to bone marrow suppression (particularly neutropenia) from toxic oral doses [54, 55], IV administration [56] or by concurrent drug interactions. However, at clinical doses, neutropenia has also been reported in some case studies [57] and a case-control study by Todd et al. [58] found higher rates of blood dyscrasias with previous colchicine exposure. Colchicine also disrupts the NADPH oxidase complex system needed in the synthesis of superoxide anions used by neutrophils to kill bacterial pathogens. These combined effects may render the host susceptible to bacterial infections.

A significant strength of this study is the broad scope of study designs, disease states, colchicine doses and intervention lengths that were included. This provided a wide perspective of the clinical evidence regarding the associations between colchicine and infectious disease. A limitation to this study is that we only included studies that specifically reported infectious adverse events. Many randomized controlled trials have been performed using colchicine but did not report infectious events in either the colchicine or control groups. As a result, it is unclear whether this represented no infectious events or that the infectious adverse events were simply not documented.

Conclusions

This systematic review suggest there is limited scope for the use of colchicine in treating or managing infectious disease. Although colchicine has shown some anti-viral activity *in vitro* this has not been conclusive demonstrated clinically thus far. There is some inconclusive evidence suggesting colchicine may confer an increased risk of pneumonia and post-operative infections with studies showing conflicting results. There is promising evidence that colchicine may be a safe, effective treatment in managing COVID-19 but more results from clinical trials are needed.

Declaration of Competing Interest

TM and PR report no conflicts of interest related to this work. PR reports personal fees from Abbvie, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Roche and UCB. Research grant funding from Janssen, Novartis, Pfizer and UCB. Non-financial support from BMS. All unrelated to this work.

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