Running head: Colchicine-induced myelosuppression in cases

Full manuscript title: Examining the Characteristics of Colchicine-Induced Myelosuppression in Clinical Cases: A Systematic Review

Author names and ORCID: Bernice L Sim [1], Beatrice Z Sim[2], Matthew Tunbridge[3], David F L Liew[4], Philip C Robinson[5]
[1] 0000-0002-0536-8715
[2] 0000-0003-1845-4476
[3] 0000-0001-8814-1008
[4] 0000-0001-8451-8883
[5] 0000-0002-3156-3418

PR reports personal fees from Abbvie, Atom Biosciences, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Kukdong, Novartis, UCB, Roche, Pfizer; meeting attendance support from BMS, Pfizer and UCB and grant funding from Janssen, Novartis, Pfizer and UCB Pharma.

Bernice L Sim BSc, MPH[a], Beatrice Z Sim BSc/MBBS, FRACP[b], Matthew Tunbridge BSc/ MBBS [b], David F L Liew MBBS, FRACP[c,d], Philip C Robinson MBChB, PhD, FRACP[b,e]

[a] St. George's Hospital Medical School, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom
[b]Faculty of Medicine, The University of Queensland, Herston, QLD, Australia.
[c]Department of Rheumatology and Department of Clinical Pharmacology and Therapeutics, Austin Health, 145 Studley Rd, Heidelberg VIC 3084, Australia
[d]Department of Medicine, University of Melbourne, Parkville, VIC, Australia
[e]Department of Rheumatology, Royal Brisbane & Women's Hospital, Metro North Hospital and Health Service, Herston, Queensland, Australia

BLS, BZS, MT, DFLL, PCR report no conflicts of interest

Statement of ethics and consent: This manuscript does not require ethics approval

Corresponding Author:
Associate Professor Philip Robinson
University of Queensland School of Clinical Medicine
Royal Brisbane & Women's Hospital
Herston
Queensland 4006
Australia

Phone +61 7 3646 7893

Fax +61 7 3646 1474

Email philip.robinson@uq.edu.au

Key Indexing Terms: ("colchicine") AND ("myelosuppression", "bone*", "marrow", "suppression", "aplasia", "leukopenia/leucopenia", "lymphopenia", "neutropenia")

Abstract

Objectives

The use of colchicine has been associated with varying degrees of myelosuppression. Despite expanded use in cardiovascular and inflammatory conditions, there remains clinician concern due to potential myelosuppressive side effects. A systematic review was conducted to explore the reported adverse myelosuppressive events of colchicine.

Methods

A systematic review was conducted using the MeSH subheading ("colchicine") AND ("myelosuppression", "bone*", "marrow", "suppression", "aplasia", "leukopenia/leucopenia", "lymphopenia", "neutropenia") on 1 September 2020 and was updated on 30th November 2021 for PubMed, Science Direct, Scopus, EMBASE and Cochrane. The search included references from 1978 to 2020, and was limited to English language observational studies (case reports, case series, case control and cohort studies) or trial data.

Results

Three thousand, two hundred and thirty-three articles were screened, with 30 studies of 47 patients with myelosuppression from colchicine identified. Most patients with myelosuppression had comorbidities, including renal impairment (21/47,44.7%). 15/47 (31.9%) and 13/47 (27.7%) patients were reported to be concurrently taking Cytochrome P450 inhibitors (CYP3A4) and P-glycoprotein efflux transporter inhibitors (P-gp) respectively. Patients with renal impairment accounted for the majority of overall patients taking these CYP3A4 and P-gp inhibitors (8/15 [53.3%] and 8/13 [61.5%] respectively). Thirteen out of twenty-one patients with renal impairment had worsening cytopenias during colchicine use. The presentations ranged from moderate anaemia (Grade 2) to severe thrombocytopenia, neutropenia, and leukopenia (Grade 4).

Conclusion

Colchicine has few reports of myelosuppression. The majority had pre-existing renal impairment or concomitant CYP3A4 or P-gp inhibitor use. Caution should be taken in this subset of patients with increased monitoring.

1.0 Introduction

Colchicine, originally derived from the ancient plant *Colchicum autumnale,* has been used for thousands of years as a prophylaxis and treatment for gout flares and in more recent times, in inflammasome-mediated conditions such as Familial Mediterranean Fever (FMF)[1]. In the last decade, it has also increasingly been recognised to have a role in managing cardiovascular disease and more recently, reduce mortality in myocardial infarction and ischaemic stroke [2-4].

This has led to increased scrutiny of colchicine's safety, and therefore its pharmacology. Colchicine is a substrate for cytochrome P450 (CYP3A4 isoenzyme) and P-glycoprotein efflux transporter (P-gp) [5]. It has a long terminal half-life and a bioavailability of 24-88% [6]. It is 10-20% renally metabolised with the remainder due to hepatic metabolism [7,8]. Peak plasma concentrations can be found 1 hour after administration and anti-inflammatory effects typically occur between 24 and 48 hours after ingestion [7]. The main mechanism of action of colchicine is the inhibition of microtubule activation in rapidly dividing inflammatory cells. It plays a vital role in the treatment of crystal arthropathies through inhibition of the release of glycopeptide crystal-derived chemotactic factor from neutrophil lysosomes after phagocytosis of monosodium urate crystals [9]. However, colchicine has shown to have relatively high concentrations in leukocytes, interacting with adhesion, mobilisation, and degranulation of lysosomes [10]. Colchicine's inhibition of leukocyte chemotaxis has further been shown in concentrations as low as 1 x 10^{-8}/L. Recent studies have further shown an inhibition of adhesion molecules on neutrophil membranes, thereby reducing neutrophil transmigration [8].

Cases of myelosuppression have been reported in studies, particularly with cases of colchicine toxicity from overdose and drug interactions. Other known side effects of colchicine observed are gastrointestinal with nausea, vomiting, diarrhoea, neuropathy, and myopathy [11,12]. Increased rates of infection is not a feature of colchicine use[13].

This systematic review explores reported cases of myelosuppression with colchicine administration in rheumatic conditions, and the circumstances in which they occur. We aim to characterise the demographic and clinical factors associated with the development of myelosuppression, particularly focusing on the pre-existing comorbidities and medications that may increase its risk. As the use of colchicine has expanded to include cardiovascular and dermatological conditions, this systematic review hopes to address uncertainties around its use and potential concern over adverse myelosuppressive events. This review aims to clarify the published data to assist physicians when treating and monitoring patients with colchicine.

2.0 Methods

2.1 Search strategy

This systematic review was completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMA) as shown in Figure 1. The review was registered prospectively with PROSPERO (CRD42020205707).

A systematic review was conducted using the MeSH subheading ("colchicine") AND ("myelosuppression", "bone*", "marrow", "suppression", "aplasia", "leukopenia/leucopenia", "lymphopenia", "neutropenia") on 1 September 2020 and was updated on 30th November 2021 PubMed, Science Direct, Scopus, EMBASE and Cochrane. This included references from 1978 to 2020. The search was limited to English language observational studies (case reports, case series, case control and cohort studies) or trial data. Demographic details and clinical findings were extracted.

2.2 Eligibility criteria

The search was limited to English language observational studies (case reports, case series, case control and cohort studies) or trial data. Studies were assessed using prospective inclusion/exclusion criteria (Supplementary file 1).

Intentional therapeutic overdoses due to the treatment of disease flares that were given above the maximum recommended daily colchicine dose were included. Two reviewers completed an initial screen of 2,705 titles and abstracts to remove exclusions and duplications, with a third moderating any conflicts. A second screen assessed 95 full-text articles for final inclusion. Two reviewers assessed these full text articles, with a third moderating any conflicts.

2.3 Data Extraction

Thirty articles for final inclusion were analysed and relevant information was extracted using a prospective data extraction form. Two reviewers were involved in the data extraction with a third moderating any discrepancies. Results are presented as number (% total), mean±SD or median+IQR.

Myelosuppression was defined as any one of the following: leukopenia (<3000/mm^3), neutropenia (<1500/mm^3), thrombocytopenia (<75,000/mm^3), and anaemia (<10g/dl for females, <13.5g/dl for males) [14].

Grading for myelosuppression was based on previously published scales [14]

The probability of adverse drug reactions was based on the Naranjo Adverse Drug Reaction Probability scale, where each study was scaled and results were reported as: “Certain”, “Probable”, “Possible”, or “Unlikely”[15].

Details from the included articles were extracted: these included demographics, comorbidities, renal function, other medications, method of diagnosis, treatment course, and outcome. Haematological outcomes measured were haemoglobin (Hb), white cell count (WCC), platelet (Plt), and neutrophil counts. These have been represented in Table 1 and 2.

3.0 Results

The initial search results yielded 2705 references. Two thousand, six hundred and ten articles were excluded and 95 included after the first review of title and abstract. After full text review, 54 references were excluded, leaving 41 articles. A further 11 articles were excluded due to qualitative data being unable to be reported adequately or studies that involved intravenous colchicine use. Thirty articles comprising of 47 patients who had myelosuppression from colchicine were included [16-45].

3.1 Clinical characteristics

Out of the patients reported, 25 (53.2%) were female, 22 (46.8%) were male. These patients had a mean age of 48 ± 27 years old.

Of the 47 patients that had an indication for colchicine listed, 17 used colchicine for gout (36.2%), 16 for Familial Mediterranean Fever (FMF) (34.0%), 4 for arthralgias (8.5%), 2 for Behçet's Disease (4.3%). The remainder of indications for colchicine can be seen on Table 1.

The mean average Charlson Comorbidity Index (CCI) score was 3.2±2.4 across all reported cases and 4.3±2.2 in those with renal impairment. Across the data, the most commonly reported comorbidities included haematological disease, cardiovascular disease, and renal disease.

Twenty one patients were reported to have chronic renal impairment or acute kidney injury from colchicine drug interactions. Thirteen out of twenty one patients (62.0%) were reported to have worsening of their chronic renal impairment during colchicine use.

Other recorded side effects noted were diarrhoea (42.6%), abdominal pain (19.1%), vomiting (12.8%), fever (17.0%), pneumonia (4.3%), erythematous skin eruptions (4.3%), and mental

confusion (4.3%) (Table 2). Within the renal patients, other side effects noted were diarrhoea (57.1%), abdominal pain (23.8%), vomiting (23.8%), fever (23.8%), pneumonia (9.5%), erythematous skin eruption (4.8%), and mental confusion (9.5%).

3.2 Concurrent medications

In patients regularly prescribed colchicine, 15/47 (31.9%) and 13/47 (27.7%) patients were reported to be concurrently taking CYP3A4 inhibitors and P-gp inhibitors respectively. Eight out of twenty one people who had renal impairment took both CYP3A4 and P-gp inhibitors. These renal patients accounted for the majority of overall patients taking these CYP3A4 and P-gp inhibitors (53.3% and 61.5% respectively).

3.3 Myelosuppression

The median average time to myelosuppression from initiating colchicine dosage in an addition to a different drug or a due to a cumulative dose was 7 days (IQR: 4.8-10.5) (Table 2).

3.4 Treatment and Outcomes

Presentations ranged in severity. In mild cases, discontinuation of colchicine was sufficient for recovery of cell counts (17/47, 36.2%).

In 10/47 cases (21.3%), administration of granulocyte-colony stimulating factor (G-CSF) was required for profound neutropenia. Of those 10 cases treated with G-CSF, 5 recovered (50.0%) and 5 died (50.0%).

Indications for colchicine treatment and management outcomes are indicated at Table 1 and Table 2 respectively.

Twenty four patients recovered, while 18 were deceased across 47 patients, however, within the renal impaired group, 12/21 (57.1%) patients were deceased while 6/21 (28.6%)

recovered. Recovery rates in patients with pre-existing renal impairment were lower than those without pre-existing renal impairment (Table 2).

3.5 Treatment outcomes for renal impaired patients

Renal impairment was classified as those with stated pre-existing renal impairment (defined as: kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR or GFR <60 mL/min/1.73m2 for ≥3 months[46]) or acute kidney injury (AKI) within each study (n=21).

Across the studies, many reports of colchicine doses taken prior to myelosuppression due to acute flares were nearly three times greater than their normal daily colchicine dose. The median cumulative colchicine dose taken prior to myelosuppression was 3.0±2.9mg while the renally impaired group took a cumulative mean average of 2.5±2.4mg. However, mean daily colchicine dose across all participants and renally impaired group was 0.8±0.8mg and 0.8±0.8mg respectively.

3.6 Haematological cell counts

Across the patients, the mean nadir haemoglobin count was 10.1±2.8 (Grade 1), indicating mild anaemia. Thrombocytopenia was unremarkable across the studies as a whole, however, patients who had worsening of their pre-existing renal conditions or developed acute kidney due to colchicine toxicity had severe thrombocytopenia of 69.0±38.0 $x10^9$/L (Grade 4). Nadir white cell counts were 2.0±1.8 $x10^9$/L (Grade 2 Leukopenia), only in those with renal failure. Across the studies included, nadir neutrophil counts were at 1.2±1.6 $x10^9$/L (Grade 2 neutropenia), while the renal impairment group had worse neutropenia (0.7±0.6 x 10^9/L (Grade 3)). Overall, median duration of myelosuppression was 7 days (4.0-10.8) days.

None of the 30 reported studies had severe myelosuppression across all cell lines (defined as: Hb<6.5g/dL, platelets<25$x10^9$/L, neutrophils <0.5$x10^9$/L, leucocytes <1$x10^9$/L) [14].

A large portion of myelosuppression cases (15/47, 31.9%) were in patients who concomitantly took CYP3A4 inhibitors, such as clarithromycin and cyclosporin (Table 3). A significant number of these patients (13/47, 27.7%) also took P-gp inhibitors, such as erythromycin and amiodarone (Table 3).

3.7 Naranjo Drug Reaction Scale

Naranjo adverse drug reaction probability scales across the studies attributed colchicine causality to “possible” or “probable”. There remains uncertainty if colchicine is the main causative agent to myelosuppression (Figure 2).

An overall representation of dose of colchicine taken with or without CYP3A4 inhibitors by patients is represented in Figure 2.

4.0 Discussion

To our knowledge, this is the first systematic review to examine published cases of myelosuppression in colchicine use in the context of rheumatic conditions. We identified 30 reports of 47 patients with myelosuppression. Across the studies, there were 15/47 patients on CYP3A4 inhibitors, while 13/47 patients were on P-gp inhibitors, suggesting drug interactions contributed to myelosuppression. Within the renally impaired groups, there were 8/21 people taking CYP3A4 inhibitors while 8/21 people took P-gp inhibitors. Amongst the 30 reports, the Charlson Comorbidity Index reported a mean of 3.2±2.4 (Table 2). Notably, four patients had febrile neutropenia, although two of these cases had chronic renal impairment, while one case developed septic neutropenia as a result of co-administration with anakinra.

While excluded from the study, a study by Sag et al. [47] contained paediatric cases that presented a contrast with adult cases, where a decrease in colchicine doses resolved leukopenia. Although information on concurrent medications of these patients was not

reported, this provides a comparison to adult cases, where myelosuppression was dependent on comorbidities and other medication use.

Across the studies, none of the cases reported severe myelosuppression across all haematological cell lines. Further, cases with the most severe myelosuppression were observed to have taken a higher than recommended colchicine daily dose due to acute flares and had pre-existing renal impairment or were taking CYP3A4 inhibitors/P-gp inhibitors concomitantly with their dosage of colchicine during the time of myelosuppression (Figure 2). Colchicine has a widely acceptable safety profile within the rest of the patient population. However, there is a need for further monitoring in multi-morbid patients and those with renal impairment. Many cases represented in peer-reviewed literature based on the Naranjo adverse drug reaction scale indicated an uncertainty as to whether colchicine was the main causal agent of myelosuppression.

Due to the increasing use of colchicine in recent years, it is important to clarify as much as possible the safety of this drug. Colchicine is increasingly being used in cardiovascular conditions and in patients with other co-morbidities and who take other medications that may cause drug interactions. Numerous studies involving the use of colchicine in cardiovascular conditions have described its safety and efficacy. As discussed in a study by Andreis et al., haematological adverse events were not increased by use of colchicine, and its use was concluded to be safe [48].

In this study, despite worsening of some cell lines across the studies, these cases of myelosuppression were particularly concentrated in those with pre-existing renal conditions or in those on other medications due to co-morbidities, specifically CYP3A4 inhibitor interaction with colchicine use such as clarithromycin and cyclosporine[49]. CYP3A4 metabolism and P-gp inhibitor transportation have known interactions with colchicine's oral bioavailability, metabolism, and excretion[49 50,51]. The use of colchicine with strong CYP3A4 inhibitors such as

clarithromycin and P-gp inhibitors such as cyclosporine should be closely monitored, particularly when patients have co-morbidities such as renal or hepatic impairment (Table 3). However, within the general population, only minimal effects of cell counts can be attributed to the use of colchicine alone.

Due to quantitative limitations in this study, the frequency of myelosuppression caused by colchicine use could not be examined. However, the Cardiovascular Outcomes Trial (COLCOT) from Tardiff et al. examining the safety of low dose colchicine in myocardial infarction showed no serious adverse events of anaemia, leukopenia, or thrombocytopenia in the colchicine group compared to the placebo group [3]. Further, in the Low Dose Colchicine (LoDoCo) trial, Nidorf et al. reported neutropenia and other disturbances to the haematological lines were uncommon in the colchicine group [52]. The frequency of myelosuppressive events in these two studies were not significantly increased in colchicine use compared to the placebo groups, further suggesting that myelosuppressive events is uncommon and potentially due to complicating factors such as co-administration of interacting medications.

Over the past decade, there has been increasing awareness of safety concerns around the use of some anti-inflammatory medication to treat gout flares. This includes glucocorticoid toxicity and non-steroidal anti-inflammatory use (NSAID) side effects such as exacerbation of hypertension and increased cardiovascular events [53]. As a result, there has been an increased appreciation of the effectiveness of colchicine in the prophylaxis of gout flares preceding the initiation of urate-lowering therapy[54]. As the value of colchicine in acute gout flares is increasingly recognised, there have also been exciting developments of its therapeutic use being explored in cardiovascular and dermatological conditions. With these new developments, there may be concerns amongst unfamiliar prescribers over myelosuppressive side effects of colchicine. Results from this review provide reassurance around the lack of myelosuppressive adverse events seen in this case series and other recently large randomised controlled trials.

There are limitations to this work. The main limitation is the lack of quantitative data in studies. This made quantitative data analysis challenging and as a result, a large portion of these studies were excluded for this reason. In addition, most studies included were case reports and therefore the rate of myelosuppression with colchicine use was unable to be examined.

Collating and assessing the collective experience of adverse event reports is generally considered an effective method for signal detection of rare events. However, broader pharmacoepidemiological studies using data linkage to match full blood count results with prescribing and clinical context may reveal more about the durability of such a signal, particularly as colchicine becomes more widely used in non-rheumatological indications

5.0 Conclusions

Traditionally, colchicine continues to be used as the mainstay prophylactic treatment in gout and familial Mediterranean fever, amongst other rheumatic conditions. In recent times, therapeutic uses of colchicine have expanded significantly in non-rheumatological conditions [55]. However, there remains some concern in some clinicians' minds about myelosuppression with colchicine use. Our systematic review found that bone marrow suppression generally only occurred in those with pre-existing renal conditions, in patients with comorbidities where CYP3A4 and P-gp inhibitor medications were used in addition to colchicine, and in one case of anakinra interaction with colchicine. The doses taken immediately prior to myelosuppression were also higher than the usual prescribed daily doses. We were able to conclude that adverse drug reactions are likely multi-factorial.

Colchicine's expanding use and indications both in rheumatology and non-rheumatological conditions makes it a unique and important drug for the present and future. This review hopes to overcome any uncertainties over the use of colchicine and enable clinicians to use it with confidence.

6.0 Declarations of Competing Interest

BLS, BZS, MT, DFL, and PCR declare no conflicts of interest.

PCR reports personal fees from Abbvie, Atom Biosciences, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Kukdong, Novartis, UCB, Roche, Pfizer; meeting attendance support from BMS, Pfizer and UCB and grant funding from Janssen, Novartis, Pfizer and UCB Pharma.

7.0 References

1. Demidowich AP, Davis AI, Dedhia N, Yanovski JA. Colchicine to decrease NLRP3-activated inflammation and improve obesity-related metabolic dysregulation. Med Hypotheses 2016;92:67-73.
2. Robinson PC, Terkeltaub R, Pillinger MH, et al. Consensus Statement Regarding the Efficacy and Safety of Long-Term Low-Dose Colchicine in Gout and Cardiovascular Disease. Am J Med 2021.
3. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. N Engl J Med 2019;381:2497-505.
4. Imazio M, Nidorf M. Colchicine and the heart. European Heart Journal 2021;42:2745-60.
5. Ozen S, Kone-Paut I, Gül A. Colchicine resistance and intolerance in familial mediterranean fever: Definition, causes, and alternative treatments. Semin Arthritis Rheum 2017;47:115-20.
6. Chappey O, Scherrmann JM. [Colchicine: recent data on pharmacokinetics and clinical pharmacology]. Rev Med Interne 1995;16:782-9.
7. Slobodnick A, Shah B, Krasnokutsky S, Pillinger MH. Update on colchicine, 2017. Rheumatology (Oxford) 2018;57:i4-i11.
8. Leung YY, Yao Hui LL, Kraus VB. Colchicine--Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum 2015;45:341-50.
9. Marzo-Mas A, Barbier P, Breuzard G, et al. Interactions of long-chain homologues of colchicine with tubulin. Eur J Med Chem 2017;126:526-35.
10. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of Action of Colchicine in the Treatment of Gout. Clinical Therapeutics 2014;36:1465-79.
11. Stewart S, Yang KCK, Atkins K, Dalbeth N, Robinson PC. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. Arthritis Research & Therapy 2020;22:28.
12. Kuncl RW, Duncan G, Watson D, Alderson K, Rogawski MA, Peper M. Colchicine myopathy and neuropathy. N Engl J Med 1987;316:1562-8.
13. McEwan T, Robinson PC. A systematic review of the infectious complications of colchicine and the use of colchicine to treat infections. Semin Arthritis Rheum 2021;51:101-12.
14. Mori S, Hidaka M, Kawakita T, et al. Factors Associated with Myelosuppression Related to Low-Dose Methotrexate Therapy for Inflammatory Rheumatic Diseases. PLoS One 2016;11:e0154744-e.

15. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
16. Lee K-Y, Kim DY, Chang JY, Bang D. Two cases of acute leukopenia induced by colchicine with concurrent immunosuppressants use in Behçet's disease. Yonsei medical journal 2008;49:171-3.
17. Dogukan A, Oymak FS, Taskapan H, Güven M, Tokgoz B, Utas C. Acute fatal colchicine intoxication in a patient on continuous ambulatory peritoneal dialysis (CAPD). Possible role of clarithromycin administration. Clin Nephrol 2001;55:181-2.
18. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poisoning: the dark side of an ancient drug. Clinical Toxicology 2010;48:407-14.
19. Millaire A, de Groote P, Decoulx E, Goullard L, Ducloux G. Treatment of recurrent pericarditis with colchicine. Eur Heart J 1994;15:120-4.
20. Mullins M, Cannarozzi AA, Bailey TC, Ranganathan P. Unrecognized fatalities related to colchicine in hospitalized patients. Clin Toxicol (Phila) 2011;49:648-52.
21. Sussman JS, Brozena SC, Skop N, Korecka M, Shaw LM. Accidental intravenous colchicine poisoning. Ther Drug Monit 2004;26:688-92.
22. Yonkof J, Young D, Maheshwari B, Crespo M. COLCHICINE TOXICITY IN A PATIENT WITH CHRONIC URTICARIA MASQUERADING WITH FEATURES OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS. Annals of allergy, asthma, & immunology 2018;121:S127-S8.
23. Ben-Chetrit E, Navon P. Colchicine-induced leukopenia in a patient with familial Mediterranean fever: the cause and a possible approach. Clin Exp Rheumatol 2003;21:S38-40.
24. Haj Yahia S, Ben Zvi I, Livneh A. Colchicine intoxication in familial Mediterranean fever patients using clarithromycin for the treatment of Helicobacter pylori: a series of six patients. Rheumatol Int 2018;38:141-7.
25. Langenberg-Ververgaert KPS, Laxer RM, Punnett AS, Dupuis LL, Finkelstein Y, Abla O. Chemotherapy-Colchicine Interaction in a Child with Familial Mediterranean Fever and Hodgkin Lymphoma. Mediterr J Hematol Infect Dis 2018;10:e2018019.
26. Talerico R, Cardillo C, De Vito F, et al. Mesothelioma in Familial Mediterranean Fever With Colchicine Intolerance: A Case Report and Literature Review. Front Immunol 2020;11:889.
27. Yakut HA, G.; Şahin,S.; Yazıcı, MU.; Gündüz, RC.; Kalkan, G. RETROSPECTIVE EVALUATION OF CASES OF COLCHICINE TOXICITY IN A PEDIATRIC INTENSIVE CARE UNIT
. Nobel Medicus 2015;11:24-8.
28. Montseny JJ, Meyrier A, Gherardi RK. Colchicine toxicity in patients with chronic renal failure. Nephrology, dialysis, transplantation 1996;11:2055-8.
29. Wong OF, Koo CK, Tang KS, Chow KC, Lau CL. Bronchiolitis Obliterans Organising Pneumonia in a Case of Colchicine Overdose. Hong Kong journal of emergency medicine 2011;18:249-53.
30. Abodunde OA, LevakaVeera RR, Desai R, Nweke N, Berrou M. Colchicine toxicity precipitated by interaction with sunitinib. J Clin Pharm Ther 2013;38:243-5.
31. Beggs AE, Reeves DJ, Noel NS. Leukopenia associated with long-term colchicine administration. Am J Health Syst Pharm 2012;69:2147-8.
32. Chen SC, Huang MC, Fan CC. Potentially fatal interaction between colchicine and disulfiram. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:1281.
33. Cheng VC, Ho PL, Yuen KY. Two probable cases of serious drug interaction between clarithromycin and colchicine. South Med J 2005;98:811-3.

34. Dickinson M, Juneja S. Haematological toxicity of colchicine. Br J Haematol 2009;146:465.
35. Dixon AJ, Wall GC. Probable colchicine-induced neutropenia not related to intentional overdose. Ann Pharmacother 2001;35:192-5.
36. Eleftheriou G, Bacis G, Fiocchi R, Sebastiano R. Colchicine-induced toxicity in a heart transplant patient with chronic renal failure. Clin Toxicol (Phila) 2008;46:827-30.
37. Garrouste C, Philipponnet C, Kaysi S, Enache I, Tiple A, Heng AE. Severe colchicine intoxication in a renal transplant recipient on cyclosporine. Transplant Proc 2012;44:2851-2.
38. Huang WH, Hsu CW, Yu CC. Colchicine overdose-induced acute renal failure and electrolyte imbalance. Ren Fail 2007;29:367-70.
39. Kubler PA. Fatal colchicine toxicity. Med J Aust 2000;172:498-9.
40. Liu YK, Hymowitz R, Carroll MG. Marrow aplasia induced by colchicine. A case report. Arthritis Rheum 1978;21:731-5.
41. Miller MA, Hung YM, Haller C, Galbo M, Levsky ME. Colchicine-related death presenting as an unknown case of multiple organ failure. J Emerg Med 2005;28:445-8.
42. Neuss MN, McCallum RM, Brenckman WD, Silberman HR. Long-term colchicine administration leading to colchicine toxicity and death. Arthritis Rheum 1986;29:448-9.
43. Roberts WN, Liang MH, Stern SH. Colchicine in acute gout. Reassessment of risks and benefits. Jama 1987;257:1920-2.
44. Tahrani AA, Sharma S, Macleod A, Moulik P. A case of multi-organ failure. Int J Clin Pract 2007;61:514-6.
45. Tran B-C, Dixon R. 1864: GOUT AND GASTRITIS: A DEADLY COMBINATION. Critical care medicine 2016;44:541-.
46. Guidelines K. Kidney Disease Improving Global Outcomes. [Internet. Accessed Available from: https://kdigo.org/guidelines/.
47. Sag E, Bayindir Y, Adiguzel A, et al. Colchicine and Leukopenia: Clinical Implications. The Journal of pediatrics 2020;224:166-70.e1.
48. Andreis A, Imazio M, Casula M, Avondo S, De Ferrari GM. Colchicine efficacy and safety for the treatment of cardiovascular diseases. Internal and Emergency Medicine 2021;16:1691-700.
49. Hung IFN, Wu AKL, Cheng VCC, et al. Fatal Interaction between Clarithromycin and Colchicine in Patients with Renal Insufficiency: A Retrospective Study. Clinical Infectious Diseases 2005;41:291-300.
50. Imai S, Momo K, Kashiwagi H, Miyai T, Sugawara M, Takekuma Y. Prescription of Colchicine with Other Dangerous Concomitant Medications: A Nation-Wide Survey Using the Japanese Claims Database. Biological and Pharmaceutical Bulletin 2020;43:1519-25.
51. Terkeltaub RA, Furst DE, Digiacinto JL, Kook KA, Davis MW. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. Arthritis Rheum 2011;63:2226-37.
52. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med 2020;383:1838-47.
53. Pillinger MH, Mandell BF. Therapeutic approaches in the treatment of gout. Semin Arthritis Rheum 2020;50:S24-S30.

54. Wortmann RL, MacDonald PA, Hunt B, Jackson RL. Effect of Prophylaxis on Gout Flares After the Initiation of Urate-Lowering Therapy: Analysis of Data From Three Phase III Trials. Clinical Therapeutics 2010;32:2386-97.
55. Dasgeb B, Kornreich D, McGuinn K, Okon L, Brownell I, Sackett DL. Colchicine: an ancient drug with novel applications. Br J Dermatol 2018;178:350-6.

8.0 Table titles and Figure Legends

Table 1: Patient demographics from 30 studies of patients with myelosuppression from colchicine.

Table 2: Patient clinical presentation, and investigation results from 30 studies of patients with myelosuppression from colchicine.

Table 3: CYP3A4 and P-gp Inhibitor interacting medications with colchicine in examined cases

FIGURE 1: Prisma flow diagram of studies assessed for colchicine use and myelosuppression. 2610 articles were excluded based on title and abstract as studies did not include cases of myelosuppression after colchicine use. 54 full-text articles were excluded in the second screen as patients were put on intravenous colchicine or patients had intentionally overdosed on colchicine. an additional 11 full-text articles were excluded as data was in qualitative form and could not be extracted for quantitative analysis.

FIGURE 2: cases taken/not taken dose exceeding recommended colchicine dose, with concurrent renal impairment and use of CYP3A4 inhibitor/P-gp Inhibitor and corresponding Naranjo Adverse Drug Reaction

*patient was on concurrent azathioprine

Supplementary File 1: Inclusion and exclusion criteria of search

Table 1: Patient demographics from 30 studies of patients with myelosuppression from colchicine.

Characteristics (n=47)	Patient results
Age (years old)	48 ± 27
Sex	25 (53.2%) females, 22 (46.8%) males
Ethnicity	8 (17.0%) Caucasian 1 (2.0%) Jewish Moroccan/Syrian 1 (2.0%) Turkish 2 (4.0%) Korean 1 (2.0%) African American 1 (2.0%) Italian 33 (70.0%) Not reported
Indication for colchicine	17 (36.2%) Gout 16 (34.0%) Familial Mediterranean Fever 4 (8.5%) Arthralgias 2 (4.3%) Behcet's Disease 1 (2.1%) Renal amyloidosis 1 (2.1%) Primary biliary cirrhosis 1 (2.1%) Post-pericardiotomy 1 (2.1%) Pericarditis 1 (2.1%) Active hepatitis 1 (2.1%) Pseudogout 2 (4.3%) Chronic pain

Table 2: Patient clinical presentation, and investigation results from 30 studies of patients with myelosuppression from colchicine.

	All patients n = 47	Patients w renal impairment[1] n=21
Naranjo Adverse Drug Reaction Probability Scale[2]	"Possible" or "Probable"	"Possible" or "Probable"
Charlson Comorbidity Index (CCI) (mean±SD)	3.2±2.4 (n=47)	4.3±2.2
Investigations (mean±SD)		
Nadir Hb (g/dL)	10.1±2.8 (Grade 1)	9.7±3.2 (Grade 2)
Nadir Plt (x10^9/L)	153.1±137.8 (None)	69.0±38.0 (Grade 4)
Nadir neutrophil count (x10^9/L)	1.2±1.6 (Grade 2)	0.7±0.6 (Grade 3)
Nadir WCC (x10^9/L)	8.7±31.2 (None)	2.0±1.8 (Grade 2)
Concurrent medications CYP3A4 inhibitors P-gp Substrate	CYP3A4 Yes 15 No 32 P-gp Inhibitor Yes 13 No 34	CYP3A4 Yes 8 No 13 P-gp Inhibitor Yes 8 No 13

[1] **Impaired renal function defined as: patients recorded impaired renal function based on individual study*

[2] *Likelihood of causality, by the Naranjo Adverse Drug Reaction Probability Scale: Probable or definite (≥5), Possible (1-4), Unlikely (≤0) 45. Diseases BMNIoDaDaK. Adverse Drug Reaction Probability Scale (Naranjo) in Drug Induced Liver Injury 2019 [cited 2022 27 February]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548069/.*

Lead time to myelosuppression (days)	Median: 7.0 IQR: 4.8-10.5	Median 7.0 IQR: 4.0-10.0
Regular daily colchicine dose (mg)[3]	0.8±0.8	0.8±0.8
Colchicine dose taken prior to myelosuppression (mg)[4] (cumulative dose)	3.0±2.9	2.5±2.4
Duration of myelosuppression (days) (median±IQR)	Median: 7.0 IQR: 4.0-10.8	Median: 7.0 IQR: 4.0-9.0
Hypocellularity on bone marrow aspirate	14/47 (29.8%)	10/47 (21.3%)
Additional side effects	Diarrhoea 20/47 (42.6%) Abdominal pain 9/47 (19.1%) Vomiting 6/47 (12.8%) Fever 8/47 (17.0%) Pneumonia 2/47(4.3%) Erythematous skin eruptions 2/47(4.3%) Mental confusion 2/47(4.3%)	Diarrhoea 12/21 (57.1%) Abdominal pain 5/21 (23.8%) Vomiting 5/21 (23.8%) Fever 5/21 (23.8%) Pneumonia 2/21(9.5%) Erythematous skin eruption 1/21(4.8%) Mental confusion 2/21(9.5%)
Treatment		
Supportive care	5	3
Ceasing colchicine	17	8
G-CSF	10	6
Gastric Lavage and Activated Charcoal	8	0
Not reported	7	4
End Outcomes		
Recovery	24 (51.0%)	6 (28.6%)

[3] *Maximum dose of colchicine is <3mg/day in adults (5)*

[4] *Acute colchicine dose taken during a flare immediately before myelosuppression. Some doses were above the daily recommended colchicine dosage.*

Death	18 (38.0%)	12 (57.1%)
Not reported	5 (11.0%)	3 (14.3%)

Table 3: CYP3A4 and P-gp Inhibitor interacting medications with colchicine in examined cases

CYP3A4 Inhibitors used with colchicine	**P-gp Inhibitors used with Colchicine**
Strong	Clarithromycin Cyclosporin Erythromycin Amiodarone
Clarithromycin	
Moderate	
Diltiazem Erythromycin	
Unspecified potency	
Cyclosporin Levothyroxine Amiodarone Metformin Omeprazole	

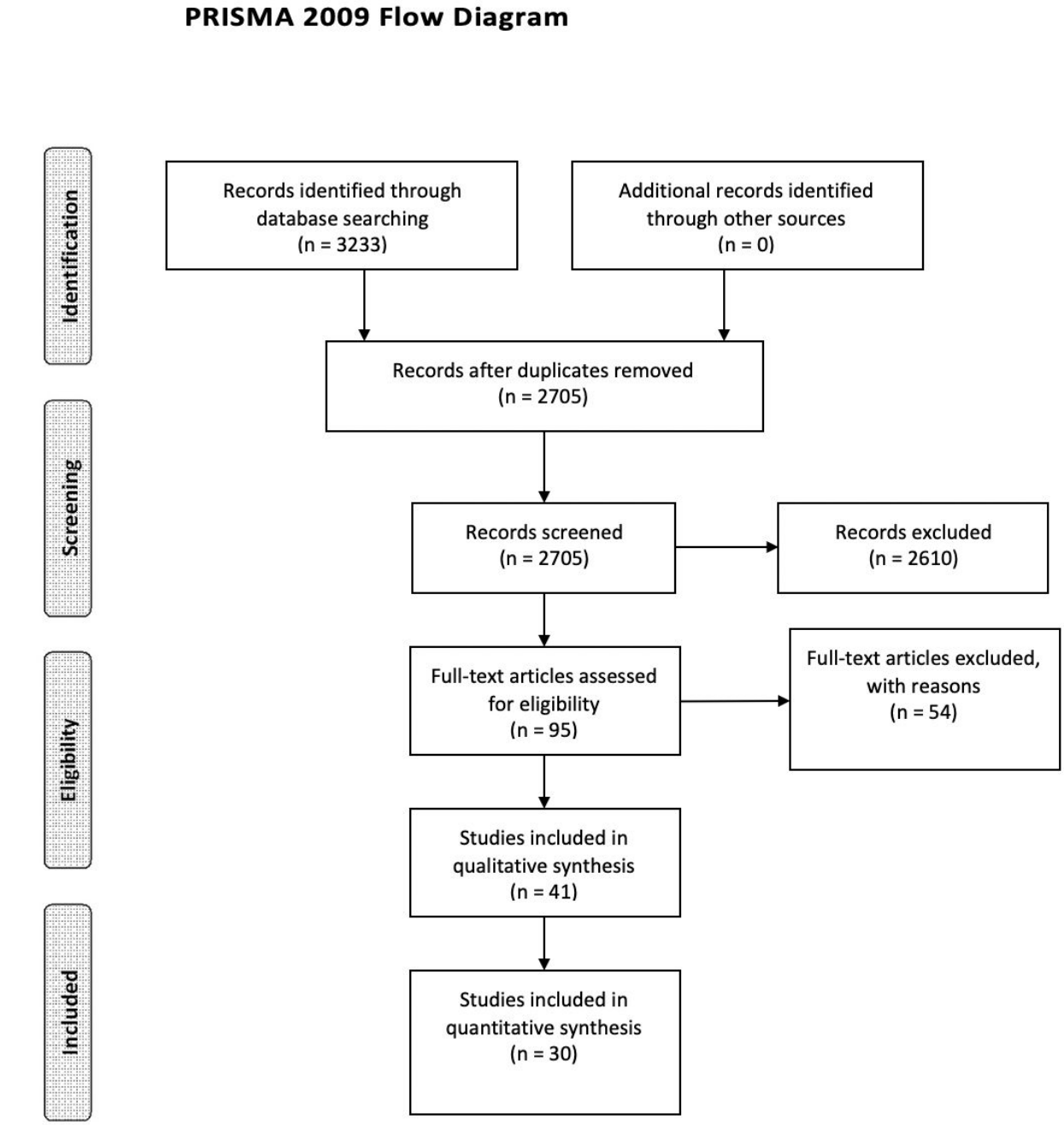
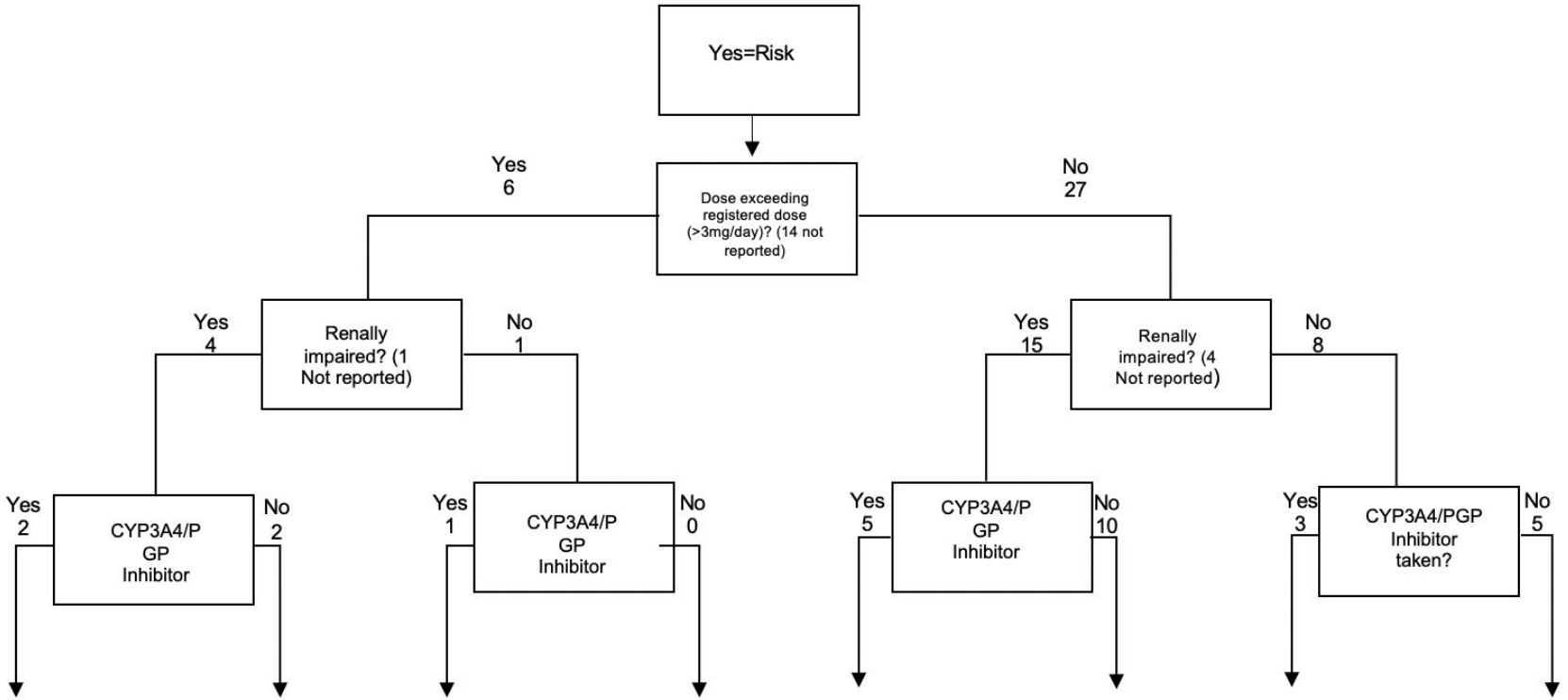


FIGURE 1



Severity of Haematological cell lines								
Thrombocytopenia	Grade 4 (2)	Grade 2 (1), NR (1)	NR (1)	-	Grade 1 (2), NR (3)	Grade 4 (1), Grade 3 (3), Grade 1 (2). None (2), NR (2)	Grade 1 (1), NR (2)	Grade 3 (1), Grade 4 (2), None (1), NR (1)
Neutropenia	Grade 3 (1), NR (1)	Grade 4 (1), NR (1)	Grade 4 (1)	-	Grade 1 (1), NR (4)	Grade 4 (1), Grade 3 (1), NR (8)	NR (3)	Grade 4 (1), NR (4)
Leukopenia	Grade 1 (1), Grade 2 (1)	Grade 4 (1), None (1)	Grade 4 (1)	-	Grade 4 (1), Grade 3 (1), Grade 2 (1), Grade 1 (1), NR (1)	Grade 4 (4), Grade 3 (3), None (2), NR (1)	Grade 2 (2), None (1)	Grade 4 (1), Grade 3 (1), Grade 2 (1), None (2)
Anaemia	Grade 2 (1), NR (1)	Grade 4 (1), NR (1)	Grade 2 (1)	-	Grade 3 (1), Grade 2 (2), None (1), NR (1)	Grade 2 (1), Grade 1 (1), None (1), NR (6)	None (1), NR (2)	None (1), Grade 1 (2), NR (2)
Naranjo Adverse Drug Reaction				-				
Definite/probable	2	1	1	-	3	8	1	3*
Possible	0	1	0	-	2	2	2	2
Doubtful	0	0	0	-	0	0	0	0

FIGURE 2