Colchicine – an established medication with new purpose
(an old drug with new purpose)

Learning objectives
You will learn:

- Emerging research on new therapeutic uses of colchicine, beyond the treatment of gout
- The mechanism of action of colchicine, and current understanding of its anti-inflammatory and antiviral effects
- Updates to the American College of Rheumatology (ACR) guidelines on the management of gout
- The value of colchicine in cardiovascular disease, with a focus on pericarditis and lowering the risk of ischaemic cardiovascular events after myocardial infarction (MI)

Introduction
Colchicine is currently approved for the prevention and treatment of gout flares in adults. However, off-label uses for colchicine are many and include the treatment of acute calcium pyrophosphate arthritis (pseudogout), sarcoid and psoriatic arthritis, Behcet’s disease and pericarditis; recent studies have shown its efficacy in preventing major adverse cardiovascular events in patients who have suffered a recent MI. Consequently, new therapeutic uses of colchicine, beyond gout, are being explored. Currently, ten colchicine clinical trials are in progress for the treatment of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.1,2
Mechanism of action

Colchicine is an inhibitor of mitosis and microtubule assembly. It binds to soluble, non-polymerised tubulin heterodimers to form a tight tubulin-colchicine complex. Colchicine interferes with microtubule formation and elongation when used at lower doses; at higher doses, it promotes microtubule depolymerisation. Since microtubules are involved in a variety of cellular processes such as cell division, maintenance of cell shape, cell signalling, signal transduction, cell migration and cellular transport, colchicine can inhibit these functions. Furthermore, inhibition of amoeboid motility by colchicine prevents disruption of membrane-dependent functions, such as chemotaxis and phagocytosis.1

Colchicine interferes with several inflammatory pathways

Most of the anti-inflammatory effects of colchicine are probably due to the disruption of microtubule function; hence, cells with high proliferative rates are disproportionately affected by the drug. The anti-inflammatory effects are diverse (Figure 1) and include:1

- Inhibition of neutrophil chemotaxis, adhesion and mobilisation
- Disruption of superoxide production
- Inflammasome inhibition
- Reduction of tumour necrosis factor (TNF)-α and its receptors.

Colchicine has antiviral properties

Tubulin ligands have the potential to inhibit the replication of viruses that depend on the microtubule network for intracellular transport of viral particles in the host cell. Colchicine has been reported to cause a significant decrease in replication of flaviviruses and may influence HIV viral load. The colchicine-tubulin complex may block both viral entry and replication of coronaviruses, and animal studies indicate that colchicine reduces replication of respiratory syncytial virus.1

Figure 1. Anti-inflammatory mechanism of action – colchicine

The colchicine-tubulin complex may block both viral entry and replication of coronaviruses
Colchicine in the pharmacotherapy of gout

Gout is one of the commonest forms of inflammatory arthritis that affects adults and is associated with impaired quality of life. Gout is caused by the chronic accumulation of monosodium urate (MSU) crystals, which preferentially deposit within joints and periarticular structures. This occurs as a consequence of hyperuricaemia, an excess of uric acid (Table 1). It is important to note that the majority of individuals with hyperuricaemia do not develop gout.2

**Table 1. Causes of hyperuricaemia**

- Over-production of uric acid (±10% of sufferers)
  - Haematological malignancies, haemolysis, psoriasis
  - Rare genetic disorders (e.g. Lesch-Nyhan syndrome)
- Under-excretion of uric acid (±90% of attacks)
  - Diets high in purine-rich foods (seafood, offal, alcohol particularly beer), sweetened processed foods and drinks
  - Metabolic syndrome including hypertension, diabetes, obesity and dyslipidaemia
  - Genetic predisposition
  - Drugs: diuretics, low-dose aspirin, cyclosporine.

The gout flare represents an acute inflammatory response to deposited MSU crystals; the affected joint is swollen, red, hot and extremely sensitive to any touch. The first metatarsophalangeal (big toe) is the joint most often affected, accounting for 50% of all attacks. Gout flares usually self-resolve within 7-10 days and are interspersed with asymptomatic periods. Over time, prolonged hyperuricaemia may result in more frequent and severe flares that also affect the upper limbs and multiple joints (polyarticular flares).2

Tophi or subcutaneous deposits usually develop over time in the absence of urate-lowering therapy (ULT), approximately 10 years after the initial gout flare. The transition from normouricaemia to clinically evident gout occurs in a number of stages (Figure 2). Factors that contribute to the transition from hyperuricaemia to clinically evident gout are not well understood.2

Atypical manifestations of gout occur more frequently in women and elderly individuals. These may include the development of tophi without accompanying flares, occasionally observed in patients who are receiving corticosteroids for other conditions, and first presentation as a flare that involves several joints symmetrically distributed. Uncommonly, gout may involve proximal large joints other than the knee and the spine.2

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It is important to note that the majority of individuals with hyperuricaemia do not develop gout.

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**Figure 2. Disease progression in gout**

SNP: single-nucleotide polymorphism; BMI: body mass index; MSU: monosodium urate
Management of gout

Several randomised clinical trials were conducted in recent years and provide additional evidence on the management of gout; these findings led to the 2020 update of the ACR guidelines.3

What are the ACR recommendations for the management of gout flares?

Colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids are recommended as first-line therapy, depending on renal function. When colchicine is the chosen agent, low-dose colchicine over high-dose colchicine is strongly recommended given similar efficacy and a lower risk of adverse effects, particularly diarrhoea. Using an interleukin-1 (IL-1) inhibitor over no therapy (beyond supportive/analgesic treatment) is conditionally recommended for patients experiencing a gout flare in whom colchicine, NSAIDs and glucocorticoids are either ineffective, poorly tolerated or contraindicated. Adrenocorticotropic hormone is recommended for patients who are unable to take oral medications.3 Canakinumab is also an effective therapy for gout flares but its use is limited by cost; it is currently reserved for patients in whom other options are ineffective or contraindicated. The IL-1 receptor antagonist, anakinra, has been shown to be non-inferior to colchicine, NSAIDs and prednisone in the management of acute gout flares.2

What are the indications for initiation of ULT?

Sustained reduction in serum urate (SU) levels using ULT is vital in the long-term management of gout, which aims to reduce gout flares and resolve tophi. Indications for ULT are outlined in Table 2.3

There is a high certainty of evidence regarding the efficacy of ULT in reducing flare frequency, tophi and SU concentrations in patients with subcutaneous tophi, radiographic damage attributable to gout or frequent gout flares. For patients who have infrequent flares and no tophi, the potential clinical benefit of ULT is lower than for those with more burdensome gout.2,3

In patients with moderate-to-severe chronic kidney disease (CKD) stage ≥3, SU >9mg/dl or urolithiasis, who are experiencing their first gout flare, there may be benefit to initiating ULT as there is a higher likelihood of gout progression and the development of clinical tophi in these patients. Furthermore, there may be the added benefit of using ULT to prevent progression of renal disease.

The ACR recommends against initiation of ULT in patients experiencing their first flare of ‘uncomplicated’ gout, noting, however, that there may be specific patients who would prefer or benefit from ULT, underscoring the need for shared decision-making between practitioner and patient. Because the majority of patients with asymptomatic hyperuricaemia (including those with comorbid CKD, cardiovascular disease, urolithiasis or hypertension) are unlikely to progress to gout within five years, the ACR recommends against the initiation of ULT as the benefits would not outweigh potential treatment costs or risks for the large number of patients unlikely to progress to gout. This is also the case for patients with asymptomatic hyperuricaemia with MSU crystal deposition, as noted on imaging tests such as ultrasound or dual-energy computed tomography.

Table 2. Indications for pharmacological ULT – ACR guidelines

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<th>Strongly recommend initiating ULT over no ULT</th>
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<tr>
<td>• Frequent gout flares (≥2/year)</td>
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<td>• Subcutaneous tophi</td>
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<td>• Radiographic damage (any modality) attributable to gout.</td>
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<tr>
<th>Conditionally recommend initiating ULT over no ULT</th>
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<tr>
<td>• Previously experienced &gt;1 flare but have infrequent flares (&lt;2/year) and no tophi</td>
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<tr>
<td>• For patients experiencing their first flare and CKD stage ≥3, SU &gt;9mg/dl, or urolithiasis.</td>
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<tr>
<th>Conditionally recommend against initiating ULT over no ULT</th>
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<tr>
<td>• First flare of ‘uncomplicated’ gout</td>
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<tr>
<td>• For patients with asymptomatic hyperuricaemia (SU &gt;6.8mg/dl with no prior gout flares or subcutaneous tophi).</td>
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When it is decided that ULT is indicated while the patient is experiencing a gout flare, the ACR conditionally recommends starting low-dose ULT during the gout flare over starting ULT after the gout flare has resolved. Patients are likely to be motivated to take ULT due to the symptoms related to the current flare, and concerns about prolonging the flare by initiating ULT during one are unfounded. A lower starting dose of any ULT reduces the risk of flare associated with initiation, as well as specific safety issues such as allopurinol hypersensitivity syndrome.4

What are the ACR recommendations for choice of ULT?

An increasing number of urate-lowering drugs are available and can be grouped based on their mechanism of action. The xanthine oxidase inhibitors (XOIs), allopurinol and febuxostat, inhibit urate formation; uricosuric drugs (e.g. probenecid) inhibit renal urate transporters; and the recombinant uricase, pegloticase, inhibits enzymes that metabolise urate.2

Allopurinol is the preferred first-line agent for ULT based on its efficacy, tolerability, safety and lower cost. Febuxostat is useful for patients with allopurinol hypersensitivity syndrome. Probenecid is useful if XOIs are not tolerated, or in combination with allopurinol.

In the patient with CKD stage ≥3, either allopurinol or febuxostat can be used; initiate treatment at a low dose (allopurinol ≤100mg/day, febuxostat ≤40mg/day) with subsequent dose titration. If using probenecid, initiate at a low dose (500mg once to twice daily), with subsequent dose titration.

Anti-inflammatory prophylaxis therapy with ULT

Because ULT may precipitate gout flares, concomitant anti-inflammatory prophylaxis (e.g. daily or twice-daily colchicine, short courses of ‘handbag’ NSAIDs or corticosteroids) continued for 3-6 months after ULT initiation is strongly recommended.

Management of lifestyle factors in patients with gout

Conditional recommendations include limiting intake of alcohol, purine-rich foods and high-fructose corn syrup, regardless of disease activity, as is using a weight loss programme (avoiding crash diets, which may precipitate flares) for those who are overweight or obese. However, dietary modification is extremely difficult to maintain in the long term and has minimal effect on SU levels. Low-dose aspirin and diuretic use should be assessed and minimised where possible, but may be necessary to manage cardiovascular risk, hypertension and heart failure.2,3

What is the value of colchicine in cardiovascular disease?

Pericarditis

Acute pericarditis is usually a self-limiting process with negligible mortality but significant morbidity. A minority of cases develop recurrent or incessant symptoms, but only a few progress to chronic constriction. Recent evidence on therapeutic targets in pericarditis has demonstrated that NLRP3 inflammasome blockade is the cornerstone of the clinical benefits of colchicine, which extend from acute and recurrent pericarditis to transient constriction and post-pericardiectomy syndrome (PPS).5,6

Meta-analysis of 10 randomised trials assessing the efficacy and safety of colchicine in 1 981 patients with pericarditis or PPS confirms that colchicine is efficacious and safe for the prevention of recurrent pericarditis, with significant reductions in the risk of recurrence, the risk of rehospitalisation...
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The use of adjunctive colchicine in the management of inflammatory pericardial diseases is standard of care in current practice. Many cardiovascular drugs have the pharmacokinetic potential to increase the risk for colchicine adverse events, so careful medication reconciliation is advised before prescribing colchicine in the cardiac patient to avoid potentially harmful interactions.

With regard to colchicine dosing in the management of pericarditis, clinical guidelines recommend adjunctive low doses (0.6mg twice a day, or 0.6mg once a day if weight <70kg) for at least three months during an episode of acute pericarditis and at least six months for recurrent episodes.5,6

MI

Because acute coronary syndromes are associated with higher risks of recurrent events and exacerbated inflammation, anti-inflammatory treatment may reduce the risk of atherosclerotic events among patients with coronary artery disease. In the Low-Dose Colchicine (LoDoCo) trial,8 patients with stable coronary disease treated with colchicine (0.5mg once daily) had fewer cardiovascular events than those not receiving colchicine. However, that trial enrolled only 532 patients and was not placebo controlled.

The Colchicine Cardiovascular Outcomes Trial (COLCOT) evaluated the effects of colchicine on cardiovascular outcomes in 4,745 patients who were recruited within 30 days after a MI. Patients were randomly assigned to receive either low-dose colchicine (0.5mg once daily) or placebo, and followed for a median of 22.6 months. Treatment with colchicine led to a significantly lower risk of ischaemic cardiovascular events than placebo (Figure 3). This result was due predominantly to a lower incidence of strokes and urgent hospitalisations for angina leading to coronary revascularisation.9

![Figure 3. COLCOT – cumulative incidence of cardiovascular events (intention-to-treat population)9](image)

Shown are the Kaplan–Meier event curves for the primary efficacy composite endpoint of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalisation for angina leading to coronary revascularisation in the colchicine group and the placebo group in a time-to-event analysis. The inset shows the same data on an enlarged y-axis.
Colchicine and COVID-19

COVID-19 results in an intense inflammatory response, predominantly affecting the respiratory system. NLRP3 inflammasome activation has been implicated in acute lung injury or acute respiratory distress syndrome in certain patients infected with COVID-19. Within this pathophysiological framework, colchicine is a potential candidate for treatment of COVID-19 as it possesses potent anti-inflammatory action, an element of which is NLRP3 inflammasome inhibition, without the adverse effects of steroids and NSAIDs.¹⁰

The Greek Study in the Effects of Colchicine in COVID-19 Complications Prevention (GRECCO-19),¹⁰ a prospective, open-label trial, randomised 105 patients hospitalised with COVID-19 in a 1:1 allocation to either standard medical treatment or the addition of colchicine (1.5mg loading dose followed by 0.5mg after 60 minutes and maintenance doses of 0.5mg twice daily) with standard medical treatment, for as long as three weeks. Participants who received colchicine had a statistically significant time to clinical improvement. There were no significant differences in high-sensitivity cardiac troponin or C-reactive protein levels; of interest, however, there was an attenuated D-dimer increase in patients treated with colchicine compared with those in the control arm, which suggests an anti-inflammatory and antithrombogenic effect.

Using colchicine safely – drug interactions

As new therapeutic uses for colchicine are explored, safe use of the drug should remain of primary importance, particularly as many patients may be on therapies for comorbidities. It must be remembered that colchicine is metabolised in the liver and the intestine; colchicine is a CYP3A4 and P-glycoprotein (P-gp) substrate. As such, P-gp inhibitors (Table 3) have been reported to cause colchicine toxicity. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine given with P-gp and potent CYP3A4 inhibitors.¹

<table>
<thead>
<tr>
<th>Table 3. P-gp inhibitors causing colchicine toxicity</th>
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<td>• Antacids, such as cimetidine</td>
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<td>• Antibiotics, such as erythromycin and tetracycline</td>
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<td>• Calcium channel blockers, such as diltiazem and verapamil</td>
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<td>• Immunosuppressants, such as cyclosporine and tacrolimus</td>
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<td>• HIV protease inhibitors, such as lopinavir and ritonavir</td>
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<td>• Azole antifungals, such as itraconazole and ketoconazole</td>
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<tr>
<td>• Anti-arrhythmic drugs, such as amiodarone and quinidine</td>
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<tr>
<td>• Selective oestrogen receptor modulators, such as tamoxifen</td>
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Key learnings

- There are many off-label uses for colchicine
- Colchicine is an inhibitor of mitosis and microtubule assembly; it interferes with several inflammatory pathways and has antiviral properties
- Colchicine is used in the treatment of acute gout flares; the ACR also recommends its use in patients with chronic disease, as prophylaxis concomitant with ULT
- Colchicine is safe and efficacious for the treatment of recurrent pericarditis, and there is evidence of a significantly lower risk of ischaemic cardiovascular events when used in patients with recent MI
- Colchicine is a potential candidate for the treatment of COVID-19
- Colchicine is a CYP3A4 and P-gp substrate; caution is required when concurrently prescribing medicines that inhibit this pathway.
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