Colchicine in Dermatology

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• Conflicts of interest: none.

• Disclosures:
  • No personal disclosures.
  • This presentation includes discussions of off-label uses of colchicine.
  • Discussion of drug-drug interactions is not comprehensive. Please review potential interactions between colchicine and your patients’ medications prior to prescribing.

• Please do not take photographs of any slides containing clinical images.
Colchicine

- *Colchicum autumnale*
- Gout and familial Mediterranean fever (FMF) and associated amyloidosis

(Wolverton SE, 2013, Lexicomp)
Uses in Dermatology (off-label)

• Neutrophilic inflammatory disease
  • Chronic urticaria **
  • Cutaneous vasculitis *
  • Pyoderma gangrenosum
  • Sweet syndrome **
  • Relapsing polychondritis

• Neutrophilic infiltrative disease
  • Palmoplantar pustulosis *
  • Psoriasis **

• Neutrophilic bullous disease
  • Dermatitis herpetiformis **
  • Linear IgA Dermatosis
  • Epidermolysis bullosa acquisita **
  • Mucous membrane pemphigoid **
  • Subcorneal pustular dermatosis (Sneddon-Wilkinson disease)

• Pustular appendageal disease
  • Hidradenitis suppurativa **
  • Acne vulgaris **

• Other
  • Actinic keratosis *
  • Recurrent aphthous stomatitis (including Behçet disease) *
  • Morphea/localized scleroderma and reticulate hyperpigmented scleroderma
  • Dermatomyositis
  • Primary anetoderma
  • Pachydermoperiostosis
  • Type II lepra reaction
  • Condyloma

*prospective controlled trial(s)
**retrospective trial or case series

More recent:


**SAPHO syndrome with acne fulminans and severe polyosteoitis involving axial skeleton.**

Divya BL¹, Rao PN¹.

**Cutis.** 2017 Dec;100(6):E23-E26.

**Disfiguring ulcerative neutrophilic dermatosis secondary to doxycycline and isotretinoin in an adolescent boy with acne conglobata.**

Sotoodian B¹, Kuzel P¹, Brassard A¹, Fiorillo L².


**Colchicine may assist in reducing granulation tissue in junctional epidermolysis bullosa.**

Kim M¹,², Jain S¹,², Harris AG¹,², Murrell DF¹,².


**Ulcerative necrobiosis lipoidica responsive to colchicine.**

Schofield C¹, Sladden MJ.


**Colchicine may be of therapeutic benefit in prurigo pigmentosa.**

An I¹, Ucmak D¹, İbítogoğlu İ², Demir V³, Akdeniz Ş⁴.


**Generalized annular granuloma associated with crowned dens syndrome, which resolved with colchicine treatment.**

Cozzani E¹, Basso D¹, Cimmino MA², Larosa M³, Burlando M¹, Rongioletti F¹, Drago F¹, Parodi A¹.

**J Dermatolog Treat.** 2018 May 18;1-5. doi: 10.1080/09546634.2018.1473553. [Epub ahead of print]

**Therapeutic strategies for pigmented purpuric dermatoses: a systematic literature review.**

Plachouris KM¹, Florou V², Georgiou S¹.


**Schamberg's disease: case report with therapeutic success by using colchicine.**

Cavalcante ML³, Masuda PY¹, Brito FE¹, Pinto ACV², Ilumira G¹, Nunes AJF¹.
Pharmacokinetics

- $F$: ~45%; jejunum and ileum
- $V_D$: 5-8 L/kg
  - Distribution: leukocytes (up to 10 days), kidney, spleen, liver
- $t_{1/2}$: 27-31 h (2x in renal failure, 10x in cirrhosis + renal failure)
- $t_{\text{max}}$: 30-120 min (2\textsuperscript{nd} peak 6 h)
- Protein binding: ~39%
- Metabolism: Hepatic (CYP3A4)
- Elimination: bile in feces; 10-20% unchanged in urine

(Wolverton SE, 2013 and Bhat et al., Ann NY Acad Sci. 2009)
**Mechanism of Action**

- Inhibits β-tubulin polymerization into microtubules → mitotic arrest (metaphase), decreased cell motility/chemotaxis; prevents activation, degranulation, migration of neutrophils

- May interfere with NALp3 (cryopyrin) inflammasome activation and intracellular assembly of neutrophil and monocyte inflammasome complex (decreased activation of interleukin-1β)

- Inhibits synthesis of tumor necrosis factor-α, leukotriene B₄, prostaglandin E₂, thromboxane A₂; activity of cyclooxygenase-2; release of insulin, histamine, parathyroid hormone

- Inhibits delayed hypersensitivity reactions

- Inhibits melanosome movement in melanophores

Contraindications

• P-glycoprotein or strong CYP3A4 inhibitor plus renal or hepatic impairment
• Leukopenia, thrombocytopenia, blood dyscrasias
• Known allergy/hypersensitivity (Canadian labeling)
• Serious gastrointestinal, renal, hepatic, cardiac disease (Canadian labeling)

(Wolverton SE, 2013, Lexicomp)
Pregnancy Category

• Crosses human placenta; FDA Category C
• Present in sera and breast milk; administer “with caution”; amount ingested by nursing baby is <10% of the weight-adjusted maternal dose

(Bhat et al. Ann NY Acad Sci. 2009 and Lexicomp)
Adverse effects

- GI: diarrhea (up to 77%), vomiting (17%), nausea (4-17%)
- CNS: fatigue (up to 4%), headache (2%)
- Endocrine/metabolic: gout (4%)
- Pulmonary: pharyngolaryngeal pain (3%)

- Rare: alopecia, aplastic anemia, azoospermia/oligospermia, bone marrow suppression, dermatitis, depression, DIC, granulocytopenia, hepatotoxicity, hypersensitivity reaction, increased CPK, ALT, AST, lactose intolerance, leukopenia, myalgias, myasthenia, myopathy, myotonia, neuropathy, peripheral neuritis, purpura, rhabdomyolysis, thrombocytopenia, toxic epidermal necrolysis, toxic neuromuscular disease

(Bhat et al. Ann NY Acad Sci. 2009 and Lexicomp)
Overdose/toxicity

- Estimated at 0.5-0.9 mg/kg
- Can be fatal; stop immediately when GI symptoms occur; NOT dialyzable or hemoperfusible [colchicine specific antigen-binding immunoglobulin (Fab) may be used]
- 24 hours: gastrointestinal symptoms +/- leukocytosis, dehydration; hypokalemia, hyponatremia, metabolic acidosis
- 24-72 hours: bone marrow toxicity, hepatotoxicity, renal failure, DIC, cardiac arrhythmia, acute respiratory distress syndrome, neuromuscular disturbances
- 3rd phase (recovery): rebound leukocytosis, resolution of organ system derangement, alopecia

Formulations

• Oral
  • Capsules and tablets

• Intravenous formulation (no longer available)
  • Shorter half-life
  • Removed from market due to toxicity
    • FDA 2/6/2008; 23 deaths (pancytopenia, acute renal failure, disseminated intravascular coagulation)

(Bhat et al. Ann NY Acad Sci. 2009 and Lexicomp)
Dosing

• Usual dose*: 0.6 mg PO BID-TID, taper as disease activity allows

*Variability in dosing published in trials, series, and case reports (see handout 2 for details)
Interactions

• Risk X (do not combine): antihepaciviral combination products, conivaptan, fusidic acid, grapefruit juice, idelalisib (phosphoinositide 3-kinase inhibitor)

• Risk D (consider modification of therapy): P-glycoprotein/ABCB1 inhibitors (protease inhibitors, macrolide antibiotics, calcineurin inhibitors, carvedilol, reserpine, sodium channel blockers, calcium channel blockers, most azole antifungals, proton pump inhibitors, quinine, SSRIs, spironolactone, tamoxifen, ulipristal, some tyrosine kinase inhibitors, dexamethasone, mifepristone); HMG-CoA reductase inhibitors, stiripentol

• Risk C (monitor therapy): P-glycoprotein/ABCB1 inducers; kinase inhibitors (tropomyosin, tyrosine and CDK), digoxin, fibric acid derivatives, fosaprepitant, luliconazole, lumacaftor, choline C 11, cyanocobalamin, multivitamins,
Monitoring Parameters

• CBC, urinalysis, renal and hepatic function (baseline, monthly for first few months, then at least every 3 months)

• Consider CPK/CK (especially if concurrent statin or fibric acid derivative therapy)

• Extra vigilance in renal patients

(Wolverton SE, 2013, Lexicomp)
Managing adverse effects

• Tolerance may be enhanced by starting low, going slow
• Gastrointestinal symptoms: dose reduction; diarrhea can be controlled with aluminum-containing antacids or antidiarrheal medications
• Myelosuppression and aplastic anemia: drug discontinuation
• Myotoxicity/rhabdomyolysis (especially renal dysfunction, elderly, concomitant cyclosporine, diltiazem, verapamil, fibrates, statins): discontinuation

(Wolverton SE, 2013, Lexicomp)
Key Points

• Colchicine primarily works by inhibiting β-tubulin polymerization, inhibiting microtubule-dependent cellular functions

• Particular efficacy in treating diseases characterized by polymorphonuclear leukocyte infiltration/inflammation

• Dosing should be titrated based on tolerability and comorbidities

• Potential interactions with other P450 3A4 substrates, inhibitors, and inducers should be considered prior to and during therapy

(Morgan AS and Yang DT. Blood. 2013.)
References
