Colchicine

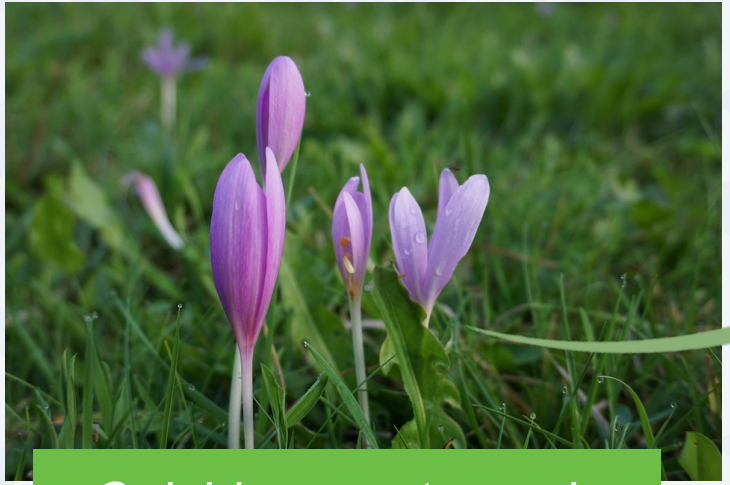
A Review of Pertinent Drug Information for SARS-CoV-2

Bradley J. Langford, BScPhm, ACPR, PharmD, BCIDP
Antimicrobial Stewardship Pharmacist
Hotel Dieu Shaver Health and Rehabilitation Centre
Bradley.Langford@oahpp.ca
@BRxAD

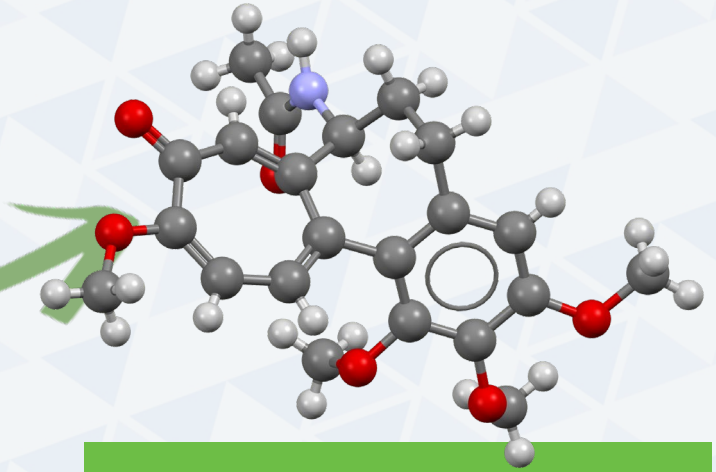
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Data Current as of February 10, 2021

Colchicine



Colchicum autumnale



Colchicine molecule

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Indications[1]

- Gout (FDA-Approved)
- Familial Mediterranean fever (FDA-Approved)
- Pericarditis (Off-label)
- Coronary Artery Disease (Off-label)[2]
- Acute Myocardial Infarction (Off-label)[3]
- COVID-19 (Off-label)

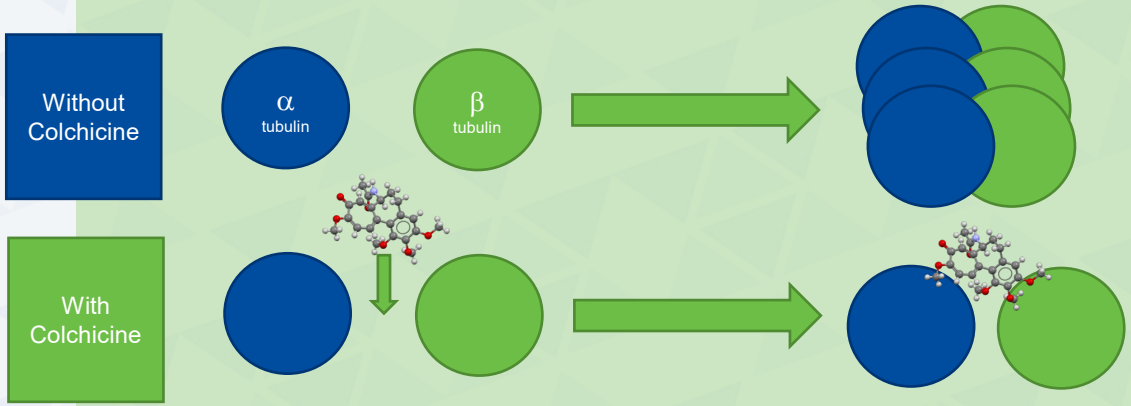
SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1.Reyes AZ, et al. Ann Rheum Dis 2020;61:42-45. https://doi.org/10.1136/annrheumdis-2020-219174
2.Nidorf SM, et al. N Engl J Med 2020;383:1838-1847. http://dx.doi.org/10.1056/NEJMoa2021372
3.Tardif J-C, et al. N Engl J Med 2019; 381:2497-2505. http://dx.doi.org/10.1056/NEJMoa1912388

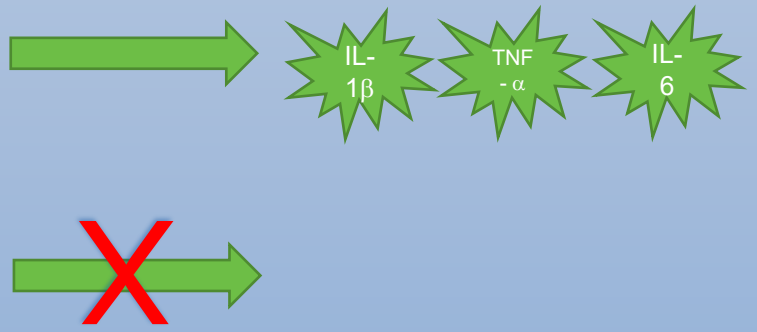
Mechanism of Action

Anti-inflammatory

Prevents microtubule formation



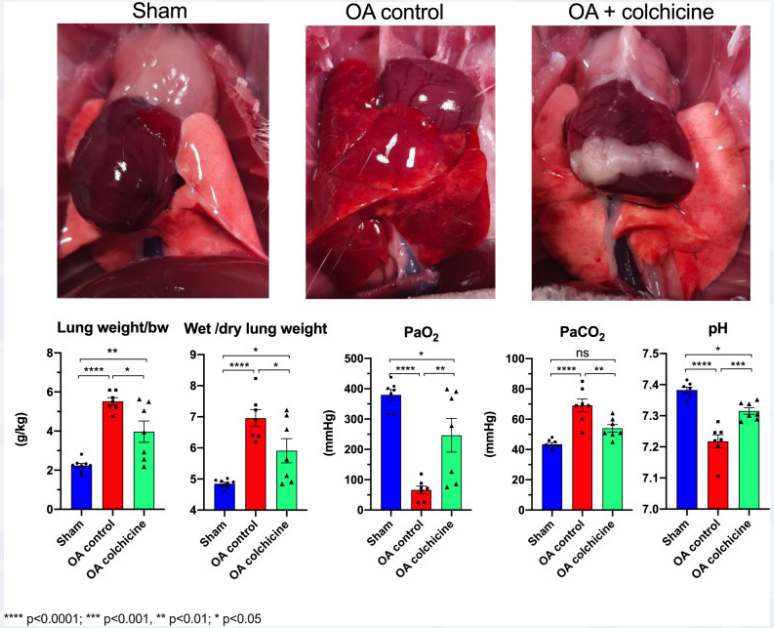
Inhibits inflammatory activity and subsequent cytokine production



SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Deftereos SG, et al. Hellenic J Cardiol. 2020;61:42-45. https://doi.org/10.1016/j.hjc.2020.03.002
Schlesinger N, et al. Curr Pharmacol Rep. 2020. https://doi.org/10.1007/s40495-020-00225-6

Colchicine and Lung Injury



- Rat model study where oleic acid (OA) was used to induce acute respiratory distress syndrome
- Colchicine pre-treatment x 3 days at 1 mg/kg was associated with reduced lung injury, lung edema, and improved oxygenation
- Lung neutrophil recruitment and activation was reduced by colchicine

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Dupuis J, et al. PLoS One. 2020;15 https://doi.org/10.1371/journal.pone.0242318

Mechanism of Action

Anti-viral

- Viral cell entry, virion assembly, and exit are partially mediated by microtubules
- Microtubules are involved in cell entry of coronaviruses
  1. via cytoplasmic end of spike protein
  2. transport and assembly of spike proteins into virions
- *In vitro* and modeling studies show colchicine may reduce viral activity in:
  - Flaviviruses, such as Zika and Dengue, in a molecular modeling study[1]
  - Respiratory syncytial virus (RSV) in rat model[2]
  - Human immunodeficiency virus (HIV) as a viral entry inhibitor in computational modeling[3]

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

1. Richter M, et al. ChemMedChem. 2019;14:469-483. https://doi.org/10.1002/cmdc.201800641
2. Lu N, et al. Biotech 2019;8:392. https://doi.org/10.1007/s13205-019-1617-z
3. Worachartcheewan A, et al. Med Chem 2019;15:328-340. https://doi.org/10.2174/1573406414666180924163756

Pharmacokinetics




Absorption

- Rapid absorption in jejunum and ileum, bioavailability 25-50%
- Tmax = 2 hours

Distribution

- Concentrates in neutrophils
- Accumulates in tissues
- Protein binding 50%
- Crosses into placenta and breast milk

Metabolism

- Enterohepatic cycling, mainly metabolized in liver

Elimination

- Largely excreted in feces, 10-20% via kidney
- Half-life 10-20 hours, intracellular 35-40 hours,
- Half life extended by renal failure

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Schlesinger N, et al. Curr Pharmacol Rep. 2020. https://doi.org/10.1007/s40495-020-00225-3
Product Monograph. Colchicine. Odan Laboratories. 2016. https://pdf.hres.ca/dpd_pm/00034804.PDF

Safety

Contraindications

- Severe hepatic impairment
- Concomitant use with P-glycoprotein (PGP) or CYP3A4 inhibitors in patients with renal or hepatic impairment

Precautions

- Beers Criteria: use with caution in older adults with CrCl < 30 mL/min
- Use of PGP or CYP3A4 inhibitors
- Mild to moderate renal or hepatic impairment

Pregnancy
Risk Class C. Manufacturer recommends avoiding in pregnancy

Lactation
No apparent impact on infant. Manufacturer recommends not using if breastfeeding

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Drugs and Lactation Database (LactMed). https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
Product Monograph. Colchicine. Odan Laboratories. 2016. https://pdf.hres.ca/dpd_pm/00034804.PDF

Adverse Drug Reactions

Gastrointestinal

- Diarrhea 20-50%, Na+/K+ ATPase inhibition, reducing Na and water absorption
- Nausea 4%
- Abdominal pain

Musculoskeletal

- <5%
- Myalgia, rhabdomyolysis is rare

Hematologic

- <1%
- Myelosuppression more common at higher doses/toxic levels
- Leukopenia, granulocytopenia, thrombocytopenia

Colchicine has a narrow therapeutic window. Toxicity can occur at typical COVID-19 doses and depends on hepatic function, renal function and presence of interacting medications

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Steward S, et al. Arthritis Res Ther 2020:22. https://doi.org/10.1186/s13075-020-2[illegible]20-7
Finkelstein Y, et al. Clin Toxicol 2010;48:407-15 https://doi.org/10.3109/15563650.2010.495345
Product Monograph. Colchicine. Odan Laboratories. 2016. https://pdf.hres.ca/dpd_pm/00034804.PDF

Drug-Drug Interactions

Cytochrome P450 3A4 Inhibitors
(for example)
Clarithromycin/Erythromycin
Cyclosporin
Diltiazem
Ketoconazole
Ritonavir
Verapamil

P-glycoprotein (PGP) Inhibitors
(for example)
Amiodarone
Atorvastatin, Lovastatin, Simvastatin
Clarithromycin/Erythromycin
Cyclosporin
Digoxin
Diltiazem
Quinidine
Ritonavir
Verapamil

Several cases reported of fatal outcomes with clarithromycin and colchicine

Colchicine Levels

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Reyes AZ, et al. Ann Rheum Dis 2020;61:42-45. https://doi.org/10.1136/annrheumdis-2020-219174
Villa Zapata L, et al. Drug Saf 2020;43:661-668. https://dx.doi.org/10.1007%2Fs40264-020-00930-7

Dosing

Optimal dosing of colchicine for treatment of COVID-19 is not established

*Colchicine is available in 0.3 mg and 0.6 mg tablets in US and 0.6 mg in Canada

	GRECCO-19 Trial	COLCORONA Trial	RECOVERY Trial (underway)
Loading Dose *starting at the time of COVID-19 positivity*	1.5 mg orally, then 0.5 mg after 60 minutes	0.5 mg orally twice daily x 3 days	1 mg orally once, then 0.5 mg in 12 hours
Maintenance Dose	0.5 mg orally twice daily for up to 3 weeks	0.5 mg orally once daily for total of 30 days	0.5 mg orally twice daily for total of 10 days or hospital discharge, whichever is sooner
Dose Adjustments	Patients excluded if GFR < 20 mL/min/1.73 m^2	Patients excluded if GFR < 30 mL/min/1.73 m^2	Maintenance dose 0.5 mg daily if receiving CYP3A4 inhibitor, renal impairment <30 mL/min/1.73 m^2, or weight <70kg

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Tardif JC, et al. medRxiv. 2021; https://doi.org/10.1101/2021.01.26.21250494
Deftereos SG, et al. JAMA Netw Open. 2020; https://doi.org/10.1001/jamanetworkopen.2020.13136
Randomized Evaluation of COVID-19 Therapy. Recovery Trial. https://www.recoverytrial.net/files/recovery-intervention-sheet-colchicine-v1-0-2020-11-26.pdf

Patient Counseling and Monitoring

- Counsel patients on potential drug-drug interactions
- Advise patients to immediately report neuromuscular toxicity
- If missed dose, do not double the next dose
- Check CBC at least once weekly

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Colchicine. In Dynamed [database online]. EBSCO Information Services. Accessed February 6, 2021

Relevant Studies

Study	Patients	Design	Intervention	Outcome	NNT
Della-Torre E	Outpatients COVID-19, n=9	Case Series	Colchicine 1 mg q12h on day one, then 1 mg daily until afebrile x 3 days	All patients defervesced within 3 days. One patient was hospitalized	N/A
Sandhu T	Hospitalized COVID-19, n=197	Cohort	Colchicine 0.6 mg q12h x 3 days, then 0.6 mg once daily for 9 days vs. non-colchicine control unit	Mortality: 49% vs.73% Intubation: 54% vs. 74%	5 6
Scarsi M	Hospitalized COVID-19, n=262	Cohort	Colchicine 1 mg/day (March 19-April 5, 2020) vs. standard of care (March 5-19, 2020)	Mortality $HR_{adjusted}$ 0.15 (95% CI 0.06 to 0.37)	5
Lopes M	Hospitalized COVID-19, n=72	Randomized Controlled	Colchicine 0.5 mg q8h x 5 days (1 mg if weight ≥ 80 kg), then 0.5 mg q12h x 5 days vs. placebo	Need for supplemental O_2 At day 2: 67% vs. 86%, day 7: 9% vs. 42%	3 to 6
GRECCO-19	Hospitalized COVID-19, n=105	Randomized Controlled (open-label)	Colchicine 1.5 mg followed by 0.5 mg after 60 min and maintenance doses of 0.5 mg twice daily vs. standard of care	2-step increase on WHO ordinal scale OR 0.11 (95%CI 0.01 to 0.96)	8
ColCORONA (pre-print)	Outpatients COVID-19, n=4488	Randomized Controlled	Colchicine 0.5 mg q12h x 3 days, then 0.5 mg once daily for 27 days	Composite of death or hospitalization OR 0.79 (95.1%CI 0.61 to 1.03)	91

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Della-Torre E, et al. Clin Immunol 2020. https://dx.doi.org/10.1016%2Fj.clim.2020.108490
Sandhu T, et al. Can J Infect Dis Med Microbiol 2020. https://doi.org/10.1155/2020/8865954
Scarsi M, et al. Ann Rheum Dis 2020;79:1286-1289. https://doi.org/10.1136/annrheumdis-2020-217712
Lopes M, et al. RMD Open. 2021. https://doi.org/10.1136/rmdopen-2020-001455
Deftereos SG, et al. JAMA Netw Open 2020;3:e2013136. https://doi.org/10.1001/jamanetworkopen.2020.13136
Tardif J-C, et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.06.21250494

ColCORONA Trial

Design

Randomized, double-blind, placebo-controlled, multi-center

Patients

Outpatients ≥ 40 years, COVID-19 diagnosis within 24 hours with at least one high risk factor:

- Age ≥ 70, obesity, diabetes, hypertension, respiratory disease, heart failure, coronary artery disease, fever ≥ 38.4C within 48h, dyspnea, cytopenia, or high neutrophil count along with low lymphocyte count

Intervention

Colchicine (0.5 mg twice daily for 3 days and once daily thereafter) or placebo for total of 30 days

Comparator

Matching placebo

Outcome

Primary: composite of death or hospitalization due to COVID-19 within 30 days

Secondary: need for mechanical ventilation within 30 days

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Tardif J-C, et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.26.21250494

ColCORONA Trial

- Stopped early (75% of target) due to resourcing, variable recruitment rate, desire to communicate results early
- Patients enrolled: 4488
  - PCR-confirmed SARS-CoV-2: 4159 (shortage of testing reagents early in pandemic)
  - Mean of 5.3 days after symptom onset
  - Mean treatment duration 26.2 days
- Baseline characteristics
  - Well-balanced, except more females in colchicine group (55.4% vs 52.5%)

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Tardif J-C, et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.26.21250494
ColCorona Frequenly Asked Questions. 2021. https://www.colcorona.net/faq

ColCORONA Trial

Intention-to-Treat

Clinical Outcome	Colchicine N=2235	Placebo N=2253	Odds Ratio (95%CI)
Primary Endpoint	104 (4.7%)	131 (5.8%)	0.79 (0.61 to 1.03)
Death	5 (0.2%)	9 (0.4%)	0.56 (0.19 to 1.67)
Hospitalization	101 (4.5%)	128 (5.7%)	0.79 (0.60 to 1.03)
Mech. Ventilation	11 (0.5%)	21 (0.9%)	0.53 (0.25 to 1.09)

NNT= 84 to prevent one hospitalization

PCR-proven COVID-19

Clinical Outcome	Colchicine N=2075	Placebo N=2084	Odds Ratio (95%CI)
Primary Endpoint	96 (4.6%)	126 (6.0%)	0.75 (0.57 to 0.99)
Death	5 (0.2%)	9 (0.4%)	0.56 (0.19 to 1.66)
Hospitalization	93 (4.5%)	128 (5.9%)	0.75 (0.57 to 0.99)
Mech. Ventilation	11 (0.5%)	21 (1.0%)	0.50 (0.23 to 1.07)

NNT= 72 to prevent one hospitalization

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Tardif J-C, et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.26.21250494

ColCORONA Trial

Hospitalization or Death - Stratified Results

Subgroup	Colchicine	Placebo	Odds Ratio (95%CI)
Diabetes			
Yes	27/444 (6.1%)	43/450 (9.6%)	0.61 (0.37 to 1.01)
No	77/1791 (4.3%)	88/1803 (4.9%)	0.88 (0.64 to 1.20)
Hypertension			
Yes	48/781 (6.1%)	64/848 (7.5%)	0.80 (0.54 to 1.18)
No	56/1454 (3.9%)	67/1405 (4.8%)	0.80 (0.56 to 1.15)
Smoking			
Non-smoker	59/1279 (4.6%)	71/1270 (5.6%)	0.82 (0.57 to 1.16)
Previous smoker	38/738 (5.1%)	56/770 (7.3%)	0.69 (0.45 to 1.06)
Active smoker	7/217 (3.2%)	4/212 (1.9%)	1.73 (0.50 to 6.01)
Sex			
Male	**58/997 (5.8%)**	**90/1070 (8.4%)**	**0.67 (0.48 to 0.95)**
Female	**46/1238 (3.7%)**	**41/1183 (3.5%)**	**1.07 (0.70 to 1.65)**
Body Mass Index			
≥ 30 kg/m^2	53/1012 (5.2%)	70/1040 (7.5%)	0.77 (0.53 to 1.11)
< 30 kg/m^2	50/1216 (4.1%)	61/1205 (5.1%)	0.80 (0.55 to 1.18)
Respiratory Disease			
Yes	35/583 (6.0%)	48/605 (7.9%)	0.74 (0.47 to 1.16)
No	69/1652 (4.2%)	83/1647 (5.0%)	0.82 (0.59 to 1.14)
Cardiovascular Disease			
Yes	6/119 (5.0%)	11/122 (9.0%)	0.54 (0.19 to 1.50)
No	98/2116 (4.6%)	120/2131 (5.6%)	0.81 (0.62 to 1.07)

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Tardif J-C, et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.26.21250494

ColCORONA Trial

Adverse Events

Adverse Event (AE)	Colchicine (N=2195)	Placebo (N=2217)	P Value
Any Serious AE	108 (4.9%)	139 (6.3%)	0.05
Pneumonia SAE	63 (2.9%)	92 (4.1%)	0.02
Pulmonary Embolism	**11 (0.5%)**	**2 (0.1%)**	**0.01**
Any Adverse Event	532 (24.2%)	344 (15.5%)	<0.0001
Gastrointestinal AE	**524 (23.9%)**	**328 (14.8%)**	**<0.0001**
Diarrhea	**300 (13.7%)**	**161 (7.3%)**	**<0.0001**
Nausea	43 (2.0%)	47 (2.1%)	0.71
Rash	4 (0.2%)	13 (0.6%)	0.03

NNH for pulmonary embolism = 250

NNH for GI Side effect = 11

NNH for diarrhea = 16

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Tardif J-C, et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.26.21250494

ColCORONA Trial

Limitations/Caveats

- Study institute holds patent on colchicine 0.5 mg for COVID-19
- Study was completed early, compromising statistical power
- Pre-print – not yet peer reviewed
- Lack of survival curve to better understand impact of treatment
- Length of treatment (30 days) extends risk but perhaps not benefit

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Tardif J-C, et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.26.21250494

Trials in Progress

26 Interventional trials currently listed on ClinicalTrials.gov

- 17 are currently recruiting
- 3 trials are completed

Largest remaining colchicine study is RECOVERY trial

- Estimated >5000 hospitalized patients in the UK will be randomized
- Colchicine 1 mg, 0.5 mg 12 hrs later, then 0.5 mg q12h for total 10 days
- Primary outcome: 28 day mortality
- Secondary outcomes: duration of hospital stay, composite of death, mechanical ventilation or ECMO

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Randomized Evaluation of COVID-19 Therapy (RECOVERY). 2020. https://www.recoverytrial.net/news/colchicine-to-be-investigated-as-a-possible-treatment-for-covid-19-in-the-recovery-trial

ClinicalTrials.gov [Internet]. Identifier NCT04381936 https://clinicaltrials.gov/ct2/show/study/NCT04381936

Summary

- Colchicine is an inexpensive widely available agent with anti-inflammatory and possible antiviral activity
- The degree of benefit and optimal populations for using colchicine in COVID-19 are uncertain
- Colchicine has a narrow therapeutic index and the risk of side effects and drug interactions is considerable
- Additional studies are underway to better understand the benefits vs. risks of colchicine in COVID-19

SIDP | SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Colchicine

A Review of Pertinent Drug Information for SARS-CoV-2

Bradley J. Langford, BScPhm, ACPR, PharmD, BCIDP
Antimicrobial Stewardship Pharmacist
Hotel Dieu Shaver Health and Rehabilitation Centre
Bradley.Langford@oahpp.ca
@BRxAD

SIDP SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

Data Current as of February 10, 2021