# Medications for Outpatients with COVID-19

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#### **SCIENCE TABLE**

COVID-19 ADVISORY FOR ONTARIO

June 15, 2021

### **Objectives**

- Provide evidence-based recommendations on the use of medications for managing COVID-19 in the outpatient setting.
- Address patient questions about the appropriate use of medications for acutely managing COVID-19.
- Describe tools and resources that can be used to help support prescribing for outpatients with COVID-19.

### Disclosures

- Dr. Miller has no conflicts of interest to declare
- Dr. Niel has no conflicts of interest to declare
- Mr. Raybardhan has no conflicts of interest to declare



### Case

- Telephone appointment: "We tested positive for COVID-19"
- Mr. A, Mrs. A and their teenage son Adem have all tested positive for COVID-19. So far, Mr. and Mrs. A have mild respiratory symptoms and Adem is asymptomatic. They are isolating at home. Mrs. A asks if you received the articles she emailed to you. She is wondering if you can prescribe some medication to prevent their infections from getting worse like her cousin who is now in hospital with Covid-19. You promise to review the articles and call her back.

### Long story short . .

## Nothing works

Health Coronavirus

#### Covid: Asthma drug 'speeds up recovery at home'

By Philippa Roxby Health reporter

() 13 April



A cheap drug, commonly used to treat asthma, can help people at home recover more quickly from Covid-19, a UK trial has found.



### Inhaled budesonide

#### STOIC trial<sup>1</sup>

- open label trial, 167 adults with mild COVID, budesonide 800 mcg BID up to 28 days or usual care, primary end point "urgent care visit"
- 11 (15%) in usual care and 2 (3%) in budesonide had a visit, NNT 8
- BUT stopped early (not enough COVID around during lockdown), no difference in hosp, progression of disease. Reasons for urgent care visits mostly non-covid, clinical recovery less than one day less
- PRINICPLE trial<sup>2</sup>
  - Open label trial, age over 65 or over 50 with risk factors, 751 received budesonide 800 mcg BID, 1028 usual care
  - No change in progression, hospitalization and death. Recovery 3 days faster in budesonide group
  - Also stopped early, also risk to bias
- Remember cost to patient, risk of pneumonia, risk of drug shortages

<sup>1.</sup> Ramakrishnan S, et al. The Lancet Respiratory Medicine. 2021. 10.1016/S2213-2600(21)00160-0

<sup>2.</sup> Yu LM, et al. medRxiv. 2021. 10.1101/2021.04.10.21254672

#### Coronavirus: Dexamethasone proves first life-saving drug

By Michelle Roberts Health editor, BBC News online

🕚 16 June 2020 | 📮 Comments



A cheap and widely available drug can help save the lives of patients seriously ill with coronavirus.



### Dexamethasone

- RECOVERY trial large platform RCT in the UK
  - I clear benefit on progression and death in both moderate and severe groups
  - Also looked at patients not receiving oxygen, 501 pts receiving dex, 1032 not receiving dex showed no benefit and potential harm (ie greater likelihood of progression of disease)
- Clear recommendation NOT to use dexamethasone in patients not requiring supplemental O2
- Patients being managed in the community on supplemental O2, consider dexamethasone in the same way you would in hospitalized patients, 6 mg orally daily x up to 10 days (d/c when supplemental O2 no longer needed)

RECOVERY Collaborative Group. New England Journal of Medicine. 2021;384(8):693-704. 10.1056/NEJMoa2021436



### Colchicine reduces the risk of COVID-19related complications

Positive results from COLCORONA trial show that colchicine is the only effective oral medication for treating non-hospitalized patients

January 22, 2021 22:58 ET | Source: Montreal Heart Institute

### Colchicine

- COLCORONA outpatients with mild disease
  - did not show a difference in their primary outcome (death)
  - Possible small reduction in hospitalization (not significant)
  - High rates of side effects (diarrhea mostly)
- RECOVERY hospitalized patients, including those not on 02
  - Colchicine arm stopped due to non-effect
  - No significant change in death, progression to invasive ventilation or on duration of hosp
- Harms narrow therapeutic window, diarrhea, renal impact, drug interactions
- Clear recommendation NOT to prescribe colchicine to those with mild disease

#### COVID-19: High vitamin D levels may protect Black people



Researchers reexamine the role of vitamin D in COVID-19. Igor Alecsander/Getty Images

- Previous research has linked vitamin D deficiency to a higher risk of getting COVID-19 and experiencing more severe disease, especially among Black and Hispanic individuals.
- A new observational study suggests that even "sufficient" vitamin D levels, as guidelines currently define them, are associated with a higher risk of COVID-19 for Black people.
- Current guidelines for assessing vitamin D status are based on maintaining bone health rather than immune function.



### Vitamin D

- RCTs studying Vitamin D in a range of severities and a range of doses, all hospitalized patients
  - SHADE study
  - Effect of Single High Dose of Vit D3 on Hospital Length of Stay in Patients with Moderate to Severe Covid19
- Limitations: All studies poor quality (underpowered, poor follow-up, incomplete data, inconsistent use of patient oriented outcomes)
- Currently no benefit shown on patient-important outcomes (mortality/ progression of disease/ need for mechanical ventilation, length of hospitalization)
- Minimal risk in low dose, continues to be indicated for bone health for many Canadians (Osteoporosis Canada Recommends 400IU per day for all adults aged 19-50 and 800 IU per day for adults over 50.)
- But WHY did the observational studies show a possible link between low Vit D levels and Covid-19 infection and mortality?
- Clear recommendation: Do not treat mild COVID-19 with Vitamin D

 Meltzer DO, et. al. Association of Vitamin D Levels, Race/Ethnicity, and Clinical Characteristics With COVID-19 Test Results. JAMA Netw Open. 2021;4(3):e214117.
 Murai IH, Fernandes AL, Sales LP, et al. Effect of a Single High Dose of Vitamin D<sub>3</sub> on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. JAMA. 2021;325(11):1053–1060. doi:10.1001/jama.2020.26848. December 08, 2020 3 min read



### 'This was a gift to us': Ivermectin effective for COVID-19 prophylaxis, treatment



Numerous studies have provided evidence supporting the use of ivermectin to prevent and treat COVID-19, according to the Frontline COVID-19 Critical Care Alliance.



### Ivermectin

#### • 7 RCTs

 total of 751 patients either mild disease, a mix of severities or unspecified severity, both studied for prevention and treatment

#### Limitations:

- Poor quality studies very few events, inconsistent outcomes, wide variation in usual care/comparator drugs, widely varying dosage
- Hard to generalize mostly LMIC, control arms that don't reflect current standard of care (use of hydroxychloroquine)
- No reduction in disease progression, hospitalization and death

#### Risks to consider:

- drug shortages, side effects, potential for toxicity due to self treatment with veterinary ivermectin
- Clear recommendation: Do not use ivermectin to treat or prevent mild covid

Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ*. 2020;370:m2980.

\$40M worth of COVID-19 antibody treatments are sitting on the shelf. These doctors don't understand why



FEDERAL POLITICS



OTTAWA— A potentially life-saving treatment that could keep COVID-19 patients out of hospitals is sitting unused in Canada despite being approved by this country's medical regulators.

#### President Trump Received Experimental Antibody Treatment

Mr. Trump received a single dose of an antibody cocktail made by the biotech company Regeneron. The company's C.E.O. has known the president for years.



A pharmacist in Chandler, Ariz. prepares an injection during a trial for Regeneron's antibody treatment in August. Adriana Zehbrauskas for The New York Times

### **Monoclonal antibodies**

- Bamlanivimab single monoclonal antibody, Canada bought a huge stockpile.
- ACTIV-3 study
  - No change of organ dysfunction, O2 use, stopped due to futility.
- BLAZE-1 study
  - outcomes: viral load and "hospitalization" (ER visit with or without hospital stay), poor quality study, no
    patient-important outcomes, homogenous subjects (mostly Caucasian males), issues with study design
- Consider:
  - Requires outpatient infusion capacity
  - FDA revoked EUA due to concerns about variants resistant to monotherapy
  - May interfere with vaccine response- ACIP recommends waiting 90 days for vaccination after using this drug.
- Clear recommendation: Do not treat mild covid with Bamlanivimab monotherapy
- Monoclonal antibody "cocktails" evidence still emerging, none currently available in Canada

### Hydroxychloroquine

 Multiple studies of hydroxychloroquine for prevention and treatment of all levels of COVID-19 disease

					Pharmacological treatments All-cause mortality D28 r2/N2		ts						
Study	Follow up days	Intervention 1	Intervention 2	r1/N1			Α	в	Risk o C	f Bias D	Е	Overall	Risk Ratio [95% CI]
Mild outpatients Amaravadi R, 2021 Mild outpatients	28	Hydroxychloroquine	Placebo	0/17	0/17		-	5				-	1
Omrani A, 2020	21	Hydroxychloroquine	Placebo	0/152	0/152			-			-		1
Skipper CP, 2020	30	Hydroxychloroguine	Placebo	1/244	1/247		- 📮		-	-	Ξ.	-	0.10% 1.01 [0.06, 16.09]
Mild outpatients Mitja O, 2020	28	Hydroxychloroquine	Standard care	0/169	0/184				-	Ξ.	Ξ.	a	1
1.01 [0.06, 16.09							1.01 [0.06, 16.09]						
Dubee V, 2021	28	Hydroxychloroquine	Placebo	6/125	11/125	<b>⊢</b> •→•	-		-				0.84% 0.55 [0.21, 1.43]
Chen CP, 2020	14	Hydroxychloroquine	Standard care	0/21	0/12				-				С
Cavalcanti AB, 2020	15	Hydroxychloroquine	Standard care	7/221	6/229	<u>ні</u> -	4 💻						0.67% 1.21 [0.41, 3.54]
Abd-Elsalam S, 2020	28	Hydroxychloroquine	Standard care	6/97	5/97	<u> </u>							0.58% 1.20 [0.38, 3.80]
Ulrich RJ, 2020	30	Hydroxychloroguine	Placebo	7/67	6/61	<del>г. – ́                                  </del>							0.73% 1.06 [0.38, 2.99]
Tang W, 2020	28	Hydroxychloroquine	Standard care	0/75	0/75		- =						1
Beltran-Gonzalez J, 2021		Hydroxychloroguine	Placebo	2/33	6/37	·							0.33% 0.37 [0.08, 1.73]
Ader F, 2021	28	Hydroxychloroguine	Standard care	11/151	12/152	ц <u>і</u>							1.25% 0.92 [0.42, 2.03]
Self W, 2020	28	Hydroxychloroguine	Placebo	25/242	25/237	н							2.82% 0.98 [0.58, 1.65]
Mild to critical Pan H, 2020	28	Hydroxychloroquine	Standard care	104/954	84/909	i							10.43% 1.18 [0.90, 1.55]
Horby P, 2020	28	Hydroxychloroquine	Standard care	421/1561	790/3155	i.							75.29% 1.08 [0.97, 1.19]
Severe/critical Hernandez-Cardenas C, 2	021 30	Hydroxychloroguine	Placebo	40/106	44/108	ц.					-		6.96% 0.93 [0.66, 1.29]
Mixed po	oulation	400 mg/day											1.06 [0.97, 1.16]
Heterogeneity: Q = 5.32, p = 0	.99; $I^2 = 0.0\%$ ; $\tau^2 = 0$	0.00; Test for subgroup diffe	rences: Q = 0.00; p	<b>630/4235</b> = 0.97	990/5797								
Piek of bies ratings:		( different loading dose)											1.06 [0.97, 1.16]
Low Risk of Bias	Bias A: Bias due to randomization		Intervention 1 bett		etter	Intervention 2 I	ervention 2 better		Data source: the COVID-NMA initiative (https://covid-nma.com/)				
Some Concerns	B: Bias due to de	eviation from intended interver	ntion		Г	1	7						
High Hisk of Blas	D: Bias due to m	utcome measurement	i.		0.04	5 1	5						
	E: Bias due to se	election of reported result			0.03	6 1	0						
						Risk Ratio							

### Hydroxychloroquine

- Minimal change in symptom severity
- Higher rates of adverse drug events (primarily GI)
- No change in post-hoc analysis in patients on concomitant supplements (zinc, vitamin C)

Does hydroxychloroquine reduce severity of COVID-19 in adult outpatients?



Skipper CP, Pastick KA, Engen NW, et al. Hydroxychioroquine in nonhospitalized adults with early COVID-19.A randomized trial.Ann Intern Med. 2020. [Epub ahead of print]. doi:10.7326/H20-4207 http://annals.org/aim/article/doi/10.7326/H20-4207

Annals

### Hydroxychloroquine

- Risk when taken in excess, cardiac effects
- Risk of drug shortage for those with a true indication
- Recommendation NOT to treat mild covid with hydroxychloroquine

### Antibiotics

- Interest in azithromycin (anti-inflammatory, anti-bacterial properties) has been suggested for treatment of COVID-19
- Azithromycin alone or in combination has not been shown to improve patientimportant outcomes including death
- Serious adverse events (including cardiac) have been reported
- Co-infection with a bacterial infection and COVID-19 is very rare
- Recommendation NOT to prescribe antibiotics for mild COVID infection

1. Patel H, et al. Comparison of Cardiac Events Associated With Azithromycin vs Amoxicillin. *JAMA Netw Open.* 2020;3(9):e2016864. doi:10.1001/jamanetworkopen.2020.16864 2. Rosenberg ES, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA.* 2020;323(24):2493–2502. doi:10.1001/jama.2020.8630

3. Langford BJ et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clin Microbiol Infect. 2020 Dec;26(12):1622-1629. doi: 10.1016/j.cmi.2020.07.016.

4. Langford BJ, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect. 2021 Apr;27(4):520-531. doi: 10.1016/j.cmi.2020.12.018

### **Antibiotics and "the Silent Pandemic"**

- Antibiotic resistance stands to increase due to COVID-19
- Primarily being driven by changes in practices, health care delivery, empiric antibiotic use
- Overall increase in utilization, community spillover, amplification -> net impact still unknown



 Abdullah A Mamun et al. Community Antibiotic Use at the Population Level During the SARS-CoV-2 Pandemic in British Columbia, Canada, *Open Forum Infectious Diseases*, 2021;, ofab185, https://doi.org/10.1093/ofid/ofab185
 Subramanya SH et al. The potential impact of the COVID-19 pandemic on antimicrobial resistance and antibiotic stewardship [published online ahead of print, 2021 May 25]. Virusdisease. 2021;1-8. doi:10.1007/s13337-021-00695-2

### Antibiotics

- Unknown COVID-19 status, diagnostic uncertainty, further exacerbated in virtual care settings
- RESIST THE URGE to prescribe antibiotics
- Choosing Wisely "the Cold Standard" has useful decision tools

### Antibiotics

#### MANAGING RTIS: VIRTUAL CARE AND COVID-19

	Patient presents via virtual visit/phone call Do assessment to determine: 1. If COVID-19 test needed 2. Visit type required		SUSPEC OR CON COVID-
Virtual visit	Refer for COVID-19 testing if compatible symptoms <sup>2</sup> Location will vary based on jurisdiction	In-person visit (Using appropriate precautions)	EAR PA (In child months
Viral prescription (Supportive management) See 'Points to Remember'' on the	Virtual re-assessment by primary care provider if required Refer to COVID-19	Viral prescription (supportive management) or antibiotic prescription (secondation of delayed)	SORET
next page	test results if applicable	(Inmediate or delayed) based on clinical assessment See 'Points to Remember' on the next page	SINUS
COVID-19 NEGATIVE	COVID-19 NEGATIVE &	COVID-19 POSITIVE	COPD
- Determine whet	- Offer reassurance	Ensure home solation and monitoring in place	SUSPE
continue to be managed virtual (see table)	- ly	Determine whether patient can continue to be managed virtually	
			COMMO

	INDICATIONS FOR VIRTUAL VISIT	INDICATIONS FOR
CTED IFIRMED 19	<ul> <li>Fever</li> <li>Respiratory symptoms</li> <li>No shortness of breath</li> </ul>	<ul> <li>Shortness of breath or hypoxia (if monitoring available)</li> <li>Concerns of dehydration</li> <li>Suspicion of secondary bacterial infection</li> <li>Any red flags**</li> </ul>
dren over 6 of age)	<ul> <li>Symptoms &lt;48 hours</li> <li>Fever &lt;39°C</li> <li>Pain controlled with oral pain medication</li> <li>Otherwise feels well</li> </ul>	<ul> <li>Symptoms &gt;48 hours despite adequate pain medications</li> <li>Fever ≥39°C</li> <li>Feels unwell</li> </ul>
HROAT	<ul> <li>Mild symptoms         &lt;48 hours         <ul> <li>Low suspicion for bacterial pharyngitis, e.g.:</li> <li>Over 15 years of age</li> <li>No fever</li> <li>Presence of cough or runny nose</li> </ul> </li> </ul>	<ul> <li>Persistent or worsening symptoms &gt;48 hours, or</li> <li>High suspicion of bacterial pharyngitis, e.g.:</li> <li>Severe pain</li> <li>No cough or runny nose</li> <li>Fever without alternate cause</li> </ul>
STION	<ul> <li>Mild symptoms &lt;7 days</li> <li>No red flags***</li> </ul>	<ul> <li>Presence of <u>red flags</u>***</li> </ul>
RBATION	<ul> <li>Patient able to do their activities of daily living</li> <li>Patient known to provider and reliable for virtual follow-up</li> </ul>	<ul> <li>Patient is too short of breath to do their activities of daily living</li> </ul>
ONIA	<ul> <li>Should be assessed in-person</li> </ul>	Assess clinically
INZA- LNESS, HITIS, DN COLD,	High fever controllable with antipyretic     Cough     Congestion     Body aches     Mild GI symptoms	<ul> <li>Concerns of dehydration</li> <li>Suspicion of secondary bacterial infection</li> <li>Any red flags**</li> </ul>



### **Other things**

- ASA
  - Rationale antiplatelet therapy to mitigate COVID-19 associated systemic inflammation and activation of coagulation pathway
  - Evidence RECOVERY trial
    - > 14000 hospitalized patients -> no benefit on mortality or risk of progression
    - Ongoing trials in ambulatory population (ACTIV-4b, ACT-COVID-19, LEAD-COVID-19)
- Convalescent plasma
  - Rationale passive immunity
  - Evidence no benefit in hospitalized patients (RECOVERY, CONCOR-1) and ambulatory patients (C3P0)
    - Only available through Canadian Blood Services currently not collecting

1. Horby PW et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. https://www.medrxiv.org/content/10.1101/2021.06.08.21258132v1 (Preprint)

2. Talasaz AH et al. Recent Randomized Trials of Antithrombotic Therapy for Patients With COVID-19: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021 Apr 20;77(15):1903-1921. doi: 10.1016/j.jacc.2021.02.035.

3. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet. 2021 May 29;397(10289):2049-2059. doi: 10.1016/S0140-6736(21)00897-7.

### **Outpatient therapies**

Outpatient Treatment of SARS-CoV-2 Infection to Prevent COVID-19 Progression 🚥 Myron S Cohen 🐱, David A Wohl, William A Fischer, II, David J Smith, Clinical Infectious Diseases, ciab494, https://doi.org/10.1093/cid/ciab494 Published: 28 May 2021 Pharma

#### With \$1.2B deal for molnupiravir, U.S. bets on **Merck's oral COVID-19 antiviral**

Viewpoint

November 11, 2020

A Critical Need

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FREE

Therapy for Early COVID-19

Peter S. Kim, MD<sup>1</sup>; Sarah W. Read, MD, MHS<sup>1</sup>; Anthony S. Fauci, MD<sup>2</sup>

JAMA. 2020;324(21):2149-2150. doi:10.1001/jama.2020.22813

by Kevin Dunleavy Jun 9, 2021 9:22am



### **Outpatient therapies**

- Need for therapies to prevent disease progression and long-term complications
- Challenges in testing and risk factors for progression
- Early pandemic therapies focused on "repurposed" agents with little emphasis on pre-clinical/clinical development
- Current outpatient therapies have high-barrier for adoption

### **Outpatient therapies**

Agent	Drug Class	Route of administration	Phase of study
Camostat mesylate	Protease inhibitor	Oral	Phase 2/3*
Interferon Beta	Immune modulator	Inhaled	Phase 2/3*
BMS-986414/BMS- 986413	Monoclonal antibody	Subcutaneous	Phase 2/3*
Molnupiravir	Broad-spectrum RNA antiviral	Oral	Phase 2/3

\*Acclerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) - 2 Trial (Outpatient Monoclonal Antibodies and other Therapies Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002) - NCT04575597

# Drugs and COVID-19

Clinical studies are trying to find out if there are drugs that are effective and safe to treat or prevent COVID-19. Here's what we know so far about whether these medications are effective for COVID-19.



Recommended (proven effective)

Currently not recommended (not enough information)



Recommended against (does not help and can cause harm)

Some patients need these medications for conditions other than COVID-19, so it is important to use these drugs wisely so that there is enough supply for everyone who needs them.

Talk to your doctor or pharmacist if you have questions.

SCIENCE TABLE

#### Hydroxychloroquine Dexamethasone Malaria, arthritis drug Corticosteroid Recommended in hospitalized patients requiring oxygen therapy Chloroquine Malaria drug Tocilizumab Immunosuppressant Lopinavir/Ritonavir Recommended in patients who are (Kaletra<sup>®</sup>) HIV drug critically ill or moderately ill with worsening symptoms Ivermectin Remdesivir Antiparasitic drug Antiviral Recommended in hospitalized patients requiring oxygen therapy Colchicine Gout medication Vitamins and Supplements Antibiotics Vitamin C, vitamin D, zinc Drugs that kill bacteria **Budesonide** . Antibody cocktails Inhaled corticosteroid Combination antibody therapies

### Conclusion

- There are currently no drugs or biologics recommended for evidence-based management of asymptomatic or mildly ill patients with COVID-19.
- Many treatments are supported by small, poor quality evidence with a high risk of bias and/or have the capacity to cause harm that far outweighs their benefits.
- Studies continue to evaluate the role of repurposed and new medications for management of COVID-19.
- Lack of strong evidence for pharmacotherapy in mildly ill patients with COVID-19 reinforces the importance of prevention with public health measures including vaccination.

### Resources

 Ontario Science Advisory Table – Executive summary, Science Briefs on many drugs discussed with more to come

https://covid19-sciencetable.ca/sciencebrief/#infectious-diseases-clinical-care/

BC Centre for Disease Control – executive summary and drug specific recommendations

http://www.bccdc.ca/health-professionals/clinical-resources/covid-19care/clinical-care/treatments



