Pharmacologic Management of COVID19 Infection: Review of the Evidence and Treatment Algorithms

MSERS March 4, 2021
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Faculty/Presenter Disclosure

- Dr. Benjamin Thomson, Associate Professor, Queen's University

- Relationships with commercial interests:
  Grants/Research Support:
  → Old: CIP, POEM (Western University), Innovation Research Grant, CTAQ (Queen's University), CIHR (CONNECT, ACHIEVE), PDOPPS trial funding

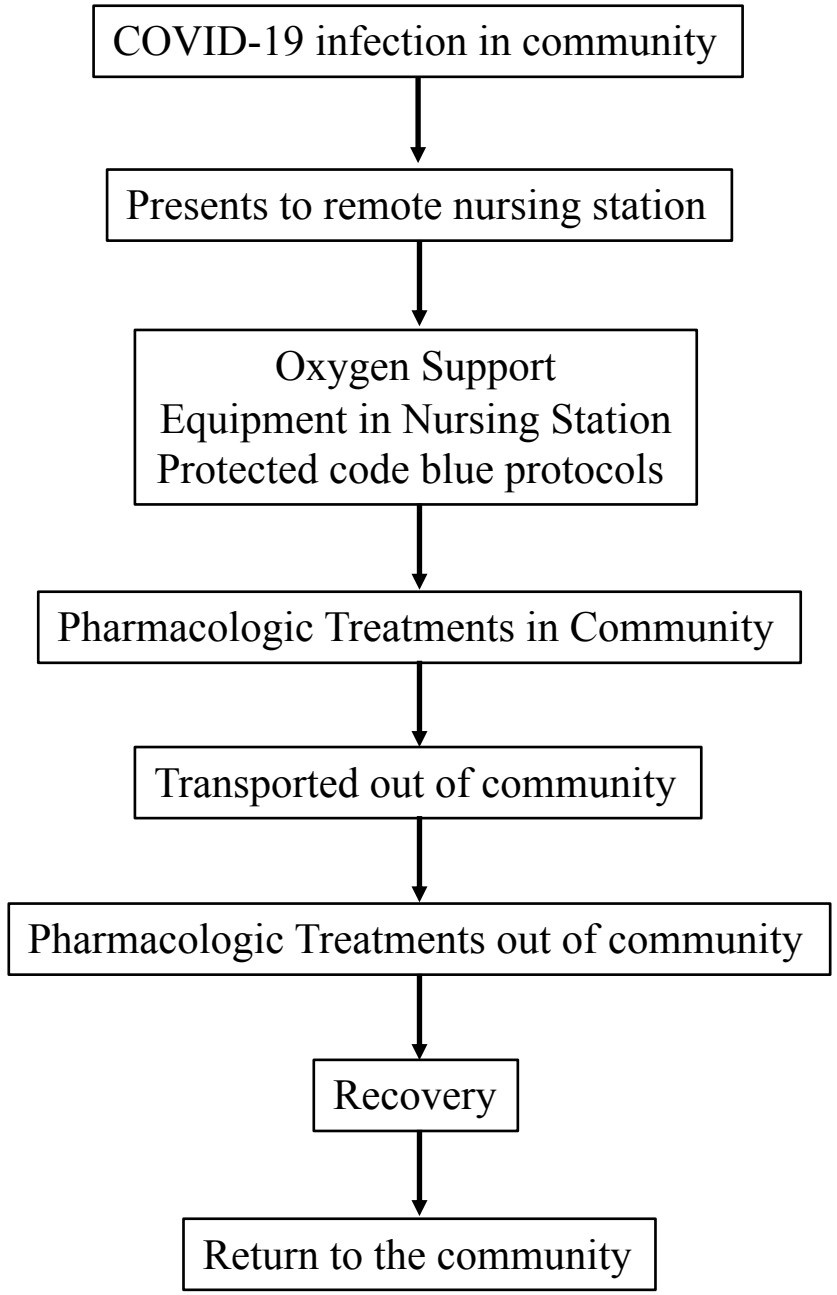
  → Current: None

  Speaking fees: Baxter Canada

Mitigating Potential Bias

- No mitigation has been required. Content in this talk does not relate to either research grant topics, funding guidelines or funding organization objectives.

The Path of the COVID19 patient



MSERS Sessions 1 and 2

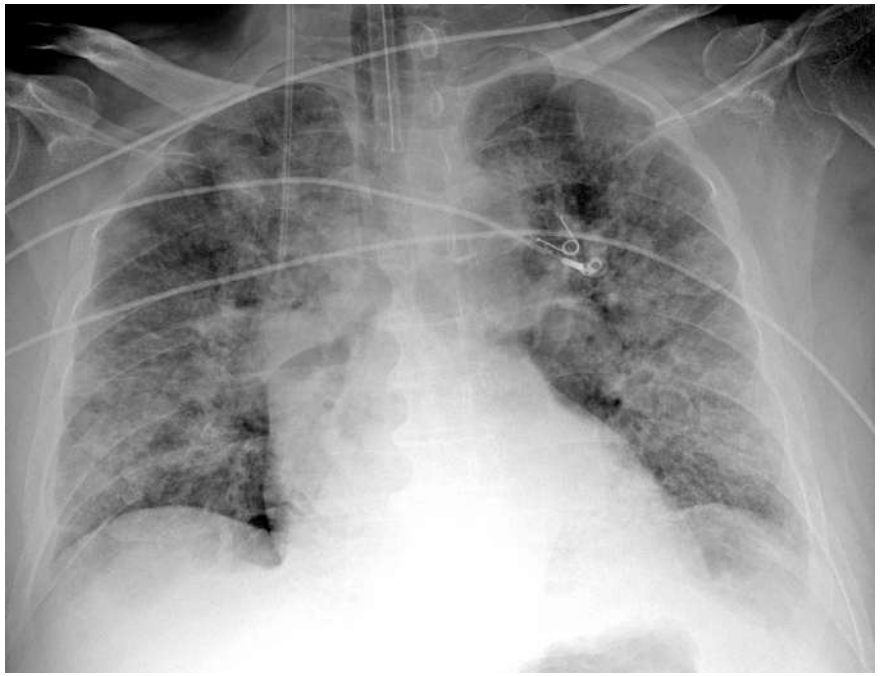
MSERS Session 3

MSERS Session 3

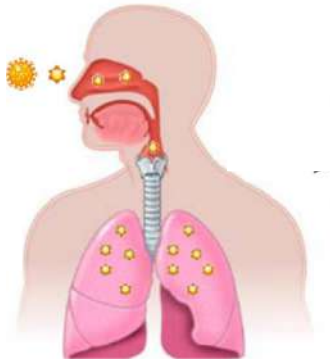
MSERS Session 3

Learning Objectives

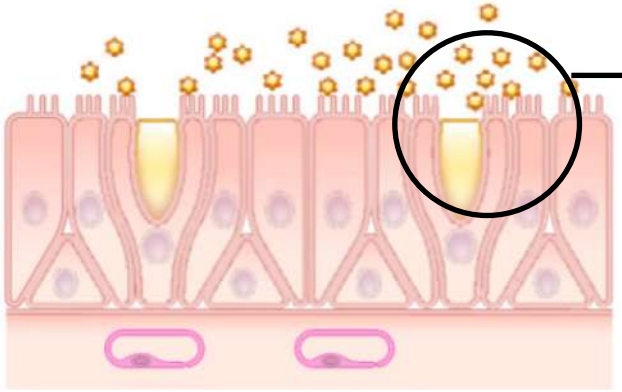
- Identify the treatment options for patients with COVID-19 pneumonia
- Identify candidates for COVID-19 pneumonia therapies who may present to a remote nursing station
- Identify considerations in patients returning to remote communities after receiving COVID-19 treatment elsewhere
- Identify implications of a patient's COVID-19 treatment on vaccination
- Identify long-term sequelae of COVID-19 infection which may impact patients returning to their community



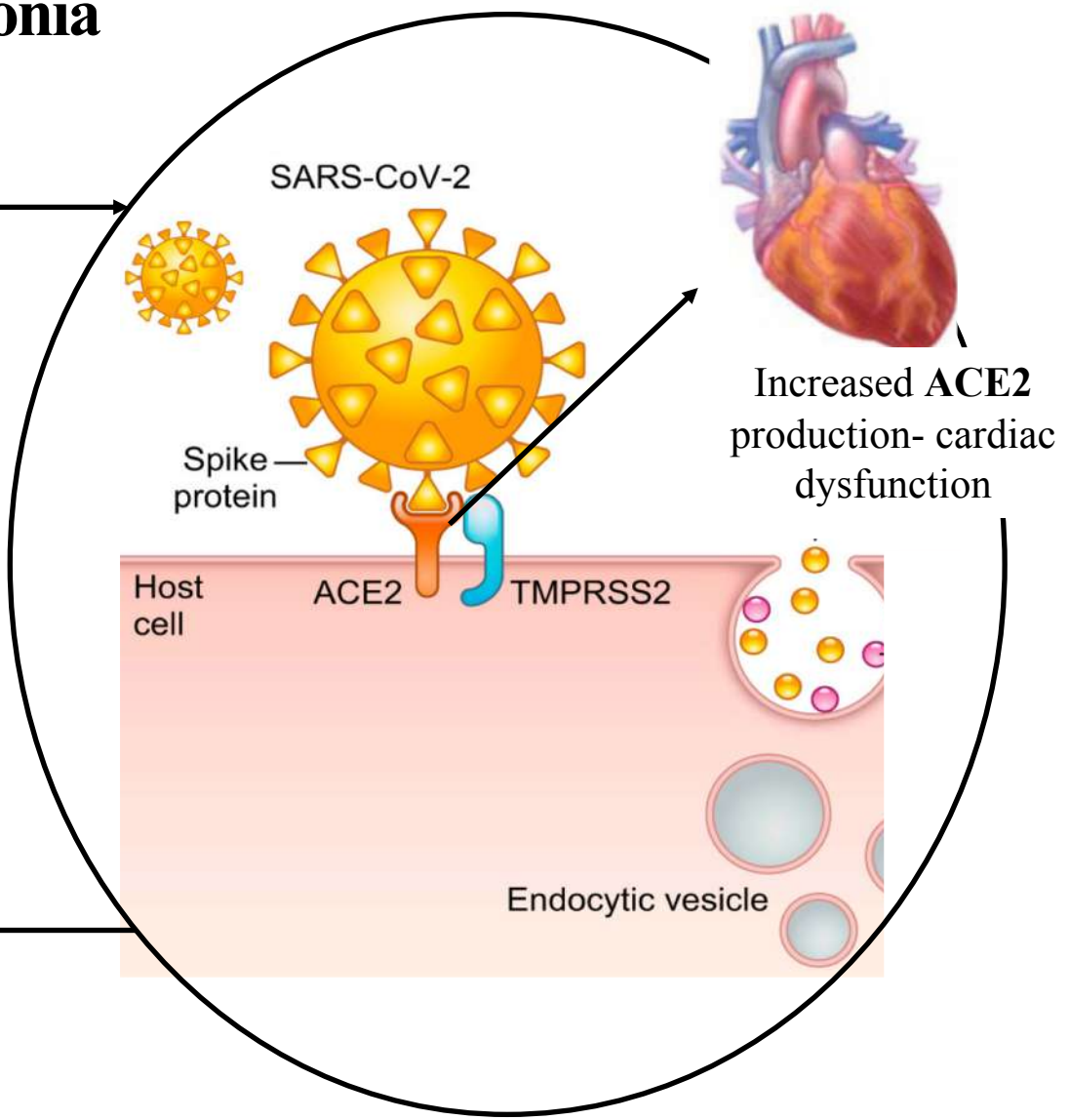
Physiology Summary: Pneumonia



Entry of SARS-COVID19 into respiratory tract

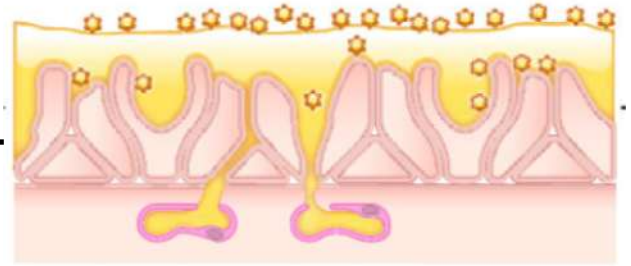


Infection of the Respiratory Epithelium

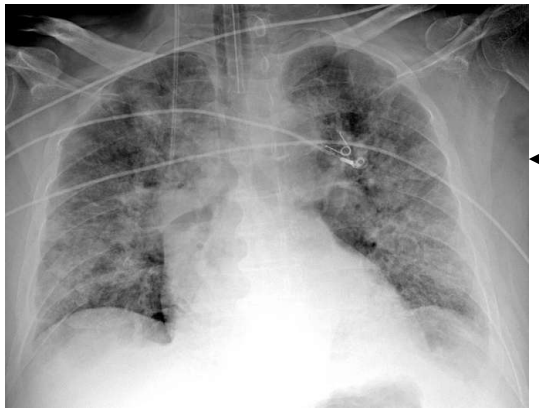


Increased **ACE2** production- cardiac dysfunction

Spike Protein on the SARS-COVID19 virus binds host cell surface **ACE2 receptor**, signaling entry into cell, where the **virus replicates**



Viral replication causes death/necrosis of Respiratory Epithelium, mucous production, leakage of dying cell contents



Pneumonia

Modified from Muniyappa and Gubbi, AJP 318 (2020): E736-E741

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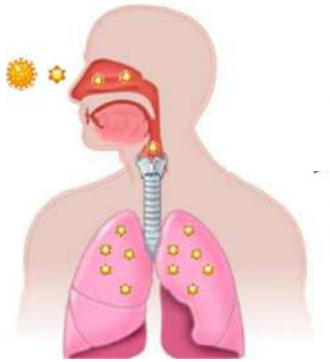
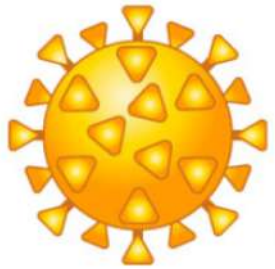
Physiology Summary: Continued



Entry of SARS-COVID19
into respiratory tract

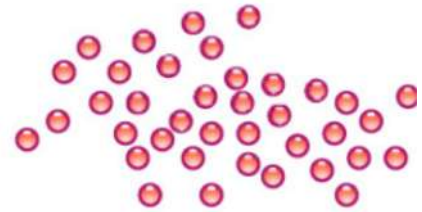


SARS-COVID19
has several other effects

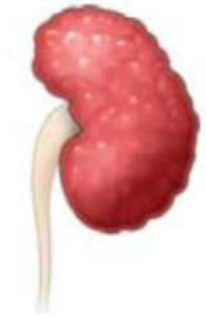
Suppress activity of two types of T cells (TH1 and TH17 cells)

These T cells usually inhibit excessive action of innate immune system (neutrophils, natural killer cells) and their cytokines

Relief of inhibition of these cells leads to massive increase in cytokine release "**Cytokine storm**" (eg. **IL6**, TNF)



Marked Systemic inflammation,
ARDS, Multiorgan Failure



Acute Kidney Injury

Modified from Muniyappa and Gubbi, AJP 318 (2020): E736-E741

Drug targets based on Physiology

- Antibodies to the SPIKE protein (***Bamlanivimab, Etesevimab***, or combined ***Casirivimab/Imdevimab***)
- Antibodies from people who have suffered from COVID19 (***Convalescent Plasma***)
- Inhibit viral replication (***Remdesevir:*** Inhibits viral RNA polymerase)(***Lopinavir/Ritonavir***: inhibits viral protease)
- Improve T cell function (***Hydroxychloroquine***)
- Improve host immune anti-viral response (***Ivermectin***)
- Decrease the inflammation generally associated with cytokine storm (***Corticosteroids***)
- Decrease the inflammation specifically associated with cytokine storm, like IL-6 (***Tocilizumab***)
- Other (***High dose Vitamin C, Zinc, Vitamin D***)

Do any of these (i) Improve outcomes and (ii) I can start them in remote community prior to transfer?

Drug Evidence

	Patient education	In Clinical use	Clinical use may increase in future	May impact return to community
Ineffective	👍🏼	No	No	No
Uncertain Effectiveness	👍🏼	👍🏼	👍🏼	👍🏼
Effective (at least sometimes)	👍🏼	👍🏼	👍🏼	👍🏼

Drug targets based on Physiology: What works?
Ineffective (1-13)

Enhance T cell function: Hydroxychloroquine

→ Ineffective for prophylaxis
→ Ineffective for treatment, with or without Azithromycin
→ Can cause malignant arrhythmias in susceptible patients

Improve host immune anti-viral response: Ivermectin (*in vitro* not *in vivo*)

→ Works *in vitro*
→ Clinical trials show improved/worse/same mortality

Inhibit viral replication: Lopinavir/Ritonavir

→ Two large randomized controlled trials- ineffective in COVID19

Do patients who take ACE inhibitors have higher (or lower) risk of death from COVID19 infection?

→ Appears no difference, although there may be a race difference (Black patients may have increased risk)
→ Current recommendation is not to modify decisions about ACEi treatment due to COVID19 infection

Drug targets based on Physiology: What works?
Uncertain Effectiveness (14-15)

Zinc: → Current recommendations: "recommends against using zinc supplementation above the recommended dietary allowance"

Zinc Supplements and COVID-19

A video with Dr. Joshua Ritchie, Dean of the Refuah Institute in Israel, recommending dietary supplementation with zinc to protect against COVID-19 is zooming around the Internet. The question, is to what extent science should apply the brakes?

High dose Vitamin C

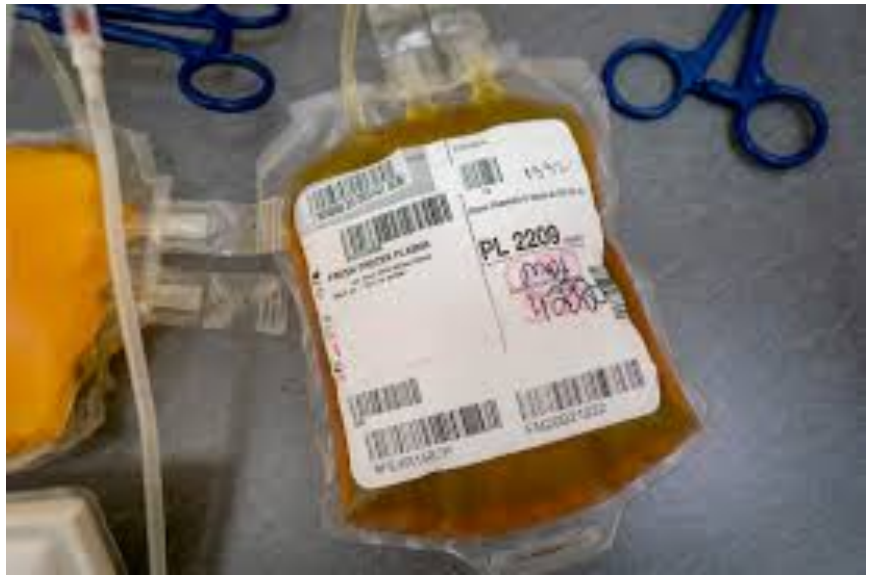
→ Doses used in some programs are 20-40 times higher than regular doses.
→ Hyperoxalosis and renal calculi reported (14)

High dose Vitamin D

→ Doses used (5000-10000 IU PO daily) are significantly higher than regular doses
→ Hypervitaminosis D with hypercalcemia reported (15)

Drug targets based on Physiology: What works?
Effective (at least sometimes):
Convalescent Plasma (16-22)

- "There are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for COVID19 treatment."



- Almost 100,000 hospitalized COVID19+ patients in USA have received this
- This strategy was ineffective in Influenza and RSV infections
- FDA (in USA) deemed "may be effective"
- High dose may be more effective than low dose for reduction in mortality
- May cause all known transfusion reactions
  (HIV/Hepatitis B and C infections, allergic/anaphylactic reactions, TRALI, etc)
- There is a theoretical risk of suppressed long-term immunity

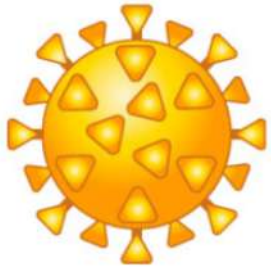
***** If patient has received convalescent plasma, Vaccination should be delayed for 90 days *****

Drug targets based on Physiology: What works?
Effective (at least sometimes):
Monoclonal Antibodies to the SPIKE protein (23-24)

- **BLAZE-1** and **BLAZE-4** trials: treatment of outpatients with mild COVID-19 at high risk for severe COVID-19

  → Single IV infusion of Bamlanivimab or Bamlanivumab + Etesevimab or placebo within 3 days of + SARS-COVID19
  → All patients "high risk for progressing to severe COVID-19 and/or hospitalization"
  (eg. BMI ≥ 35, DM, CKD, Age>65 or > 55 with HTN or COPD, , immunocompromised)
  → Combined therapy (compared to placebo) led to 5% absolute (70% relative) reduction in death/hospitalization
  → NOT authorized for inpatient therapy except in trial.

- Combined **Casirivimab** plus **Imdevimab** (compared to placebo) IV infusion, in high risk outpatients, led to reduction in 28 days ER visits or hospitalization (3 vs 9%)



Drug targets based on Physiology: What works?
Effective (at least sometimes):
Monoclonal Antibodies to the SPIKE protein (23-24)

Eli Lilly Canada Inc	Bamlanivimab (LY-CoV555)	Immune sera and immunoglobulins, for human use	2020-10-12	Authorized (with terms and conditions)
Eli Lilly Canada Inc	Bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016)	Immune sera and immunoglobulins, for human use	2021-02-16	Under review
Gilead Sciences Canada Inc	Remdesivir	Antivirals for systemic use, for human use	2020-06-19	Authorized (with conditions)
Hoffmann-La Roche Limited	Casirivimab and imdevimab	Immune sera and immunoglobulins, for human use	2021-02-24	Under review

Health Canada Approvals Site

- Bamlanivimab has been approved for use in Canada – etesevimab/casirivimab/imdevimab "under review"

- None are in widespread use in Ontario- if Etesevimab is approved…..Consider use in indigenous communities?
- Delay vaccine for 90 days

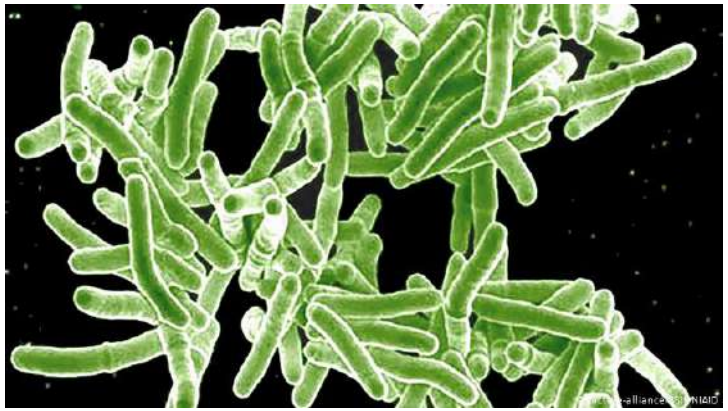
Drug targets based on Physiology: What works?
Effective (at least sometimes): Tocilizumab (29-31)

- Monoclonal antibody to IL-6 may reduce the severity of cytokine storm, enhancing mortality.

- EMPACTA: In patients with severe COVID19, reduced mortality+invasive ventilation (12.0 vs 19.3%, p=0.04)
- COVACTA: Shorter hospitalization in toculizumab arm (20 vs 28 days, p=0.04) shorter ICU stay (9.8 vs 15.5 days, p=0.05)
- REMAP-CAP: in patients in ICU who were admitted to ICU < 24 hours and required respiratory support, improved mortality (28 vs 36%) and number organ-support free days

- In Canada, typically reserved for rapidly deteriorating, or severely ill patients recently admitted to an ICU.
- Not an option for remote communities- anyone this sick should be in a tertiary center asap.

Longterm, increased risk of tuberculosis and other opportunistic infections (pneumonia) in these patients!



No vaccination delay required

Drug targets based on Physiology: What works?
Effective (at least sometimes): Dexamethasone (25-28)

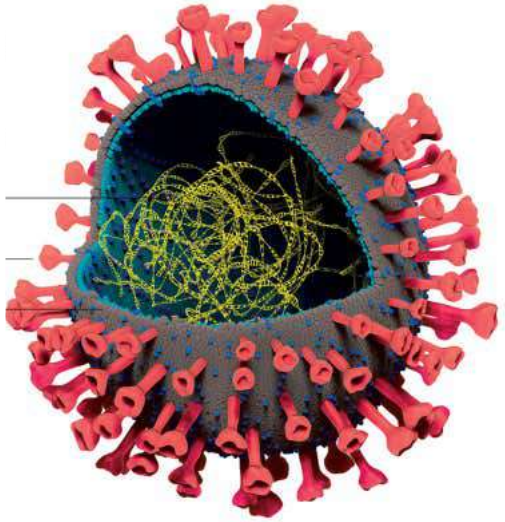
- Retrospective trials at the start of the COVID19 pandemic failed to show benefit

- RECOVERY randomized controlled trial: Dexamethasone (6 mg PO or IV daily for up to 10 days) reduced 28 day mortality:
  → Mechanical ventilation (29.3 vs 41.4%, $p < 0.05$)
  → Supplemental oxygen without mechanical ventilation (23.3 vs 26.2%, $p<0.05$)
  NO benefit if not receiving supplemental oxygen (17.8 vs 14.0%, no statistically significant difference)

- Three additional randomized controlled trials found similar results

- Who benefits?
  → Requiring supplemental oxygen
  → Probably high risk groups

Drug targets based on Physiology: What works?
Effective (at least sometimes):
Remdesevir

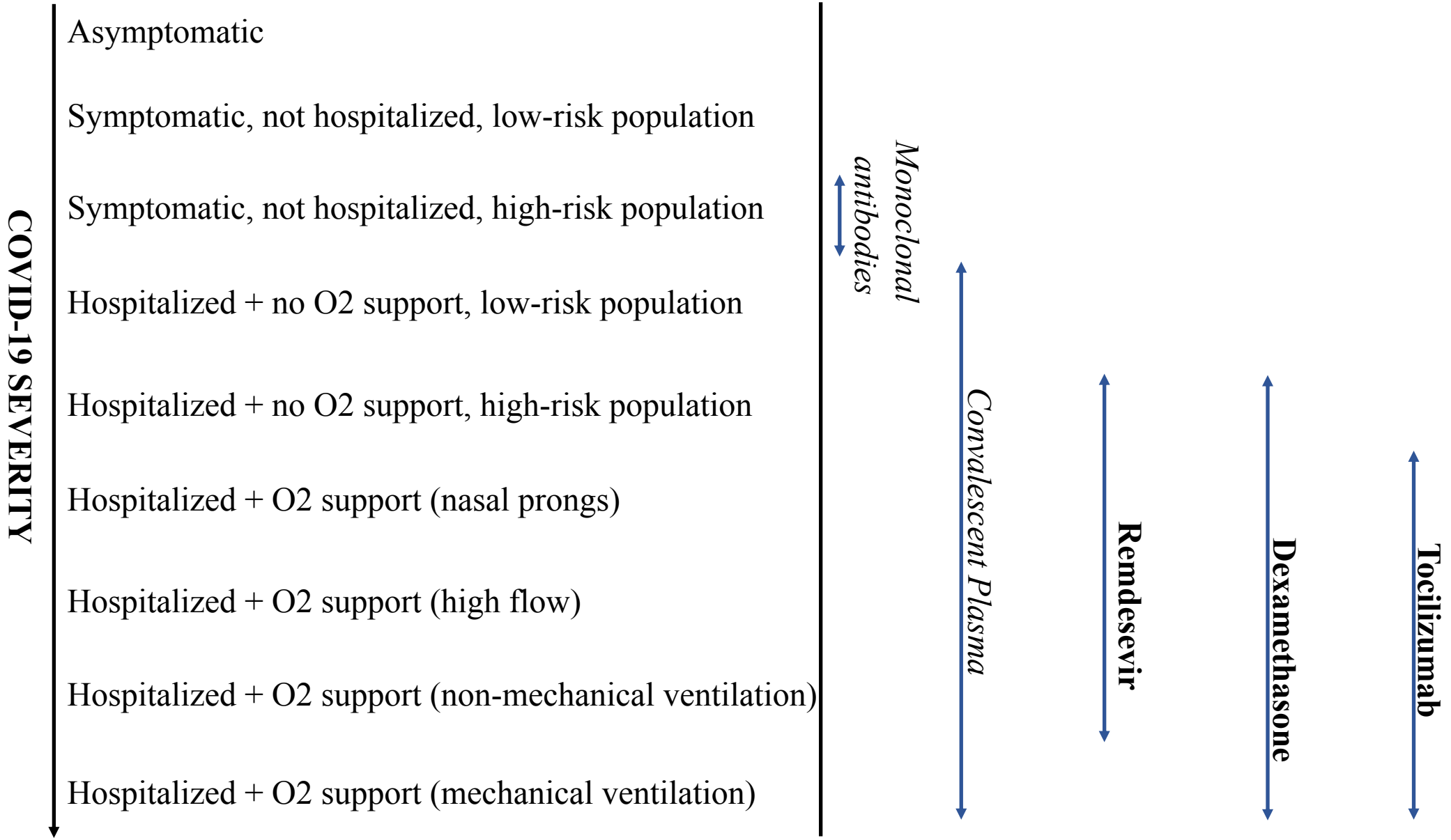


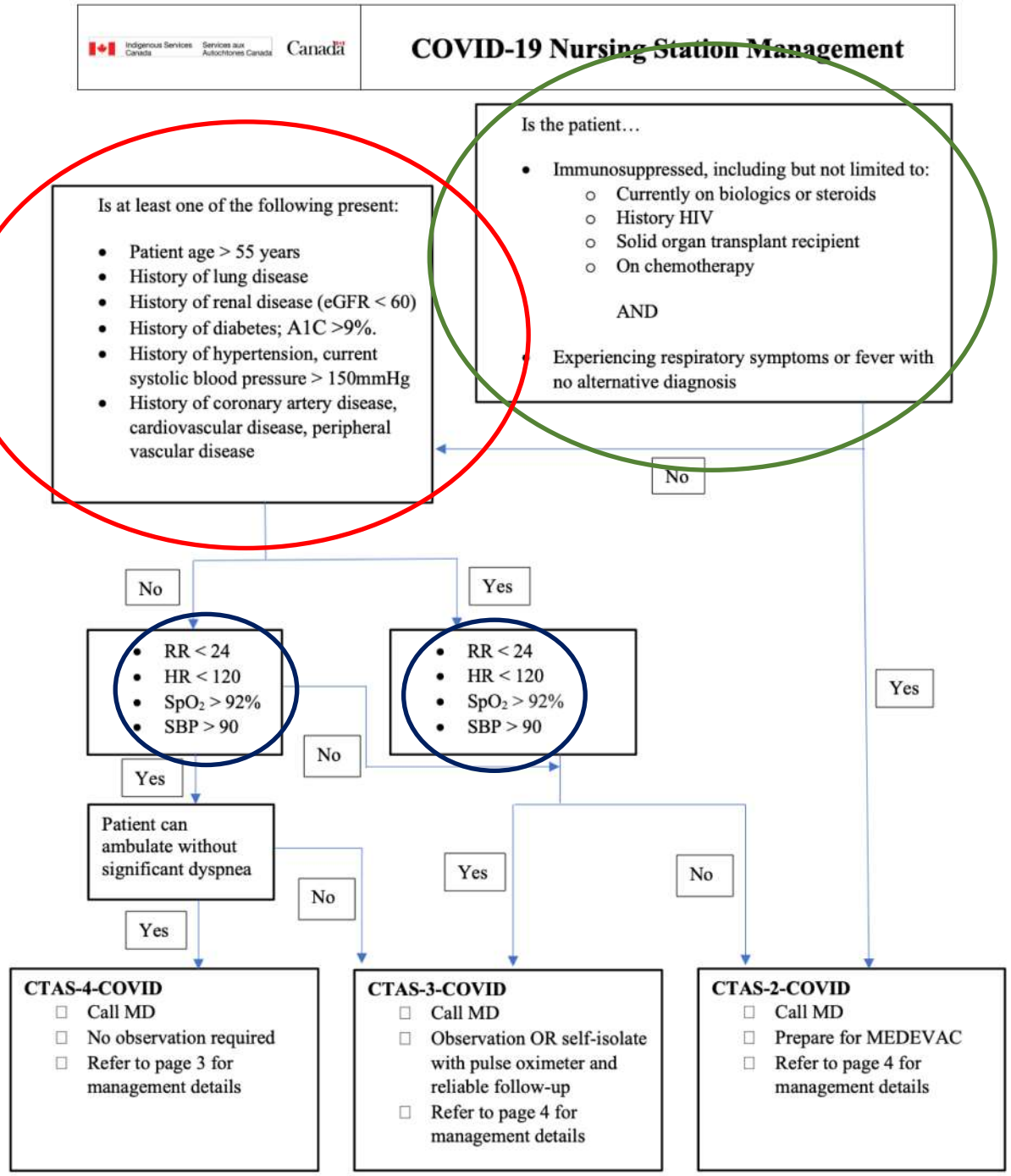
- Inhibit viral replication through inhibition of viral RNA polymerase
- Initial interest based on SARS (2003)
- ACTT-1 Trial: In hospitalized COVID-19 patients
  - → Remdesevir decreased median recovery time (10 vs 15 days, $p<0.001$)
  - → Remdesevir trend to improved mortality (11.4 vs 15.2% day 29, $p>0.05$)
- SOLIDARITY trial: No improvement in mortality
  - → Patients in SOLIDARITY were less sick than in ACTT-1 (effect on mortality?)
- Best evidence for hospitalized + requiring oxygen; Limited to no evidence if on mechanical ventilation

No effect on vaccination schedule

Long-term effects are relatively uncertain

Putting it all together





High Risk

+

Requiring oxygen

=

CTAS-2

Not High Risk

+

Requiring oxygen

=

CTAS-2

Immunocompromised

=

CTAS-2

CTAS-3: No COVID-19 Tx
CTAS-4: No COVID-19 Tx

CTAS-2 “May consider Dexamethasone if highly suspicious for COVID19”

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CTAS-2-COVID Order Sheet

Date of Assessment	
Consulting MD	
Medication Allergies	
Facility	
ORNGE PTAC	

Patient Sticker

Vitals on Assessment	HR:	RR:	BP:	SpO_2:	T:	Glucose:

Baseline Supplemental Oxygen Requirements			
Time	SpO_2	Delivery Method	Volume (L/min)
:			

Notify MD at each change in oxygen delivery method

Labs	
☐ CBC with differential	☐ INR/PTT
☐ Electrolytes	☐ Ca^{2+} **AND** Mg^{2+}
☐ Creatinine	☐ BUN
☐ Bilirubin	☐ ALT
☐ Troponin	☐ LDH
☐ CK	☐ Blood cultures x2

Investigations
☐ NP swab for COVID-19
☐ Chest X-ray
☐ Baseline ECG
i-STAT (if possible)
☐ Chem8
☐ Troponin
☐ VBG

IF fever over 38°C or purulent sputum
☐ Start IV ceftriaxone 1g q 24hrs. **OR** if severe penicillin allergy ☐ Levofloxacin 750 mg po once daily x 5 days (ensure renal dosing). **OR** if recent hospitalization ☐ Piperacillin-tazobactam 4.5g IV q6h (ensure renal dosing).
CONSIDER ☐ Dexamethasone 6 mg PO/IV if high index of suspicion for COVID-19 ☐ Vancomycin if MRSA history ☐ Oseltamivir if recent influenza outbreak in region

Additional Orders

RN Name: _____ RN Signature: _____

THIS IS NOT A MEDICAL DIRECTIVE; IT IS A GUIDANCE DOCUMENT FOR DOCTORS AND NURSES.

Indigenous and Northern Affairs Canada / Affaires autochtones et du Nord Canada

CTAS-3-COVID Order Sheet

Date of Assessment	
Consulting MD	
Medication Allergies	
Facility	
ORNGE PTAC	

Patient Sticker

Vitals on Assessment	HR:	RR:	BP:	SpO_2:	T:	Glucose:

Reassess vitals q6h. IF patient SpO_2 <92% OR respiratory rate >24 OR experiencing worsening dyspnea, transfer to CTAS-2-COVID and notify MD and ORNGE.

Labs	
☐ CBC with differential	☐ INR/PTT
☐ Electrolytes	☐ Ca^{2+} **AND** Mg^{2+}
☐ Creatinine	☐ BUN
☐ Bilirubin	☐ ALT
☐ Troponin	☐ LDH
☐ CK	☐ Blood cultures x2

Investigations
☐ NP swab for COVID-19
☐ Chest X-ray
☐ Baseline ECG
i-STAT (if possible)
☐ Chem8
☐ Troponin
☐ VBG

IF fever over 38°C or purulent sputum
☐ Amoxicillin 1g PO TID x5 days and doxycycline 200mg PO ONCE then 100mg PO BID x5 days **OR** if significant respiratory comorbidities **OR** if amoxicillin in last 3 months
☐ Amoxicillin-clavulin 875mg po BID x5 days (ensure renal dosing) and doxycycline 200mg PO ONCE then doxycycline100mg PO BID x5 days. **OR** if penicillin allergy
☐ Doxycycline 200mg PO ONCE then doxycycline100mg BID x5 days and cefuroxime 500mg PO BID x5 days.
CONSIDER
☐ Vancomycin if MRSA history
☐ Oseltamivir if recent influenza outbreak in region

Additional Orders
☐
☐
☐

This patient is high-risk and likely to require MEDEVAC if condition worsens.
Discuss with MD.
For patients with SpO_2 >94%, may return to self-isolation if possible and ONLY with portable pulse-oximeter AND a means of follow-up from nursing station BID. For patients with SpO_2 ≥ 92% or ≤94%, plan to remain in nursing station for MEDEVAC.

RN Name: _____ RN Signature: _____

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Indigenous Services Canada / Services aux Autochtones Canada — Canada

CTAS-4-COVID Order Sheet

Date of Assessment	
Consulting MD	
Medication Allergies	
Facility	
Method of Contact	

Patient Sticker

Vitals on Assessment	HR:	RR:	BP:	SpO_2:	T:	Glucose:

This patient must be re-assessed by phone <u>in 24h</u> for change in triage status. IF patient SpO_2 <92% OR develops a respiratory rate >24 OR experiences worsening dyspnea, transfer to CTAS-2-COVID and notify MD and ORNGE.

Labs	
☐ CBC with differential	☐ INR/PTT
☐ Electrolytes	☐ Ca^{2+} **AND** Mg^{2+}
☐ Creatinine	☐ BUN
☐ Bilirubin	☐ ALT
☐ Troponin	☐ LDH
☐ CK	☐ Blood cultures x2

Investigations
☐ NP swab for COVID-19
☐ Chest X-ray
☐ Baseline ECG
i-STAT (if possible)
☐ Chem8
☐ Troponin
☐ VBG

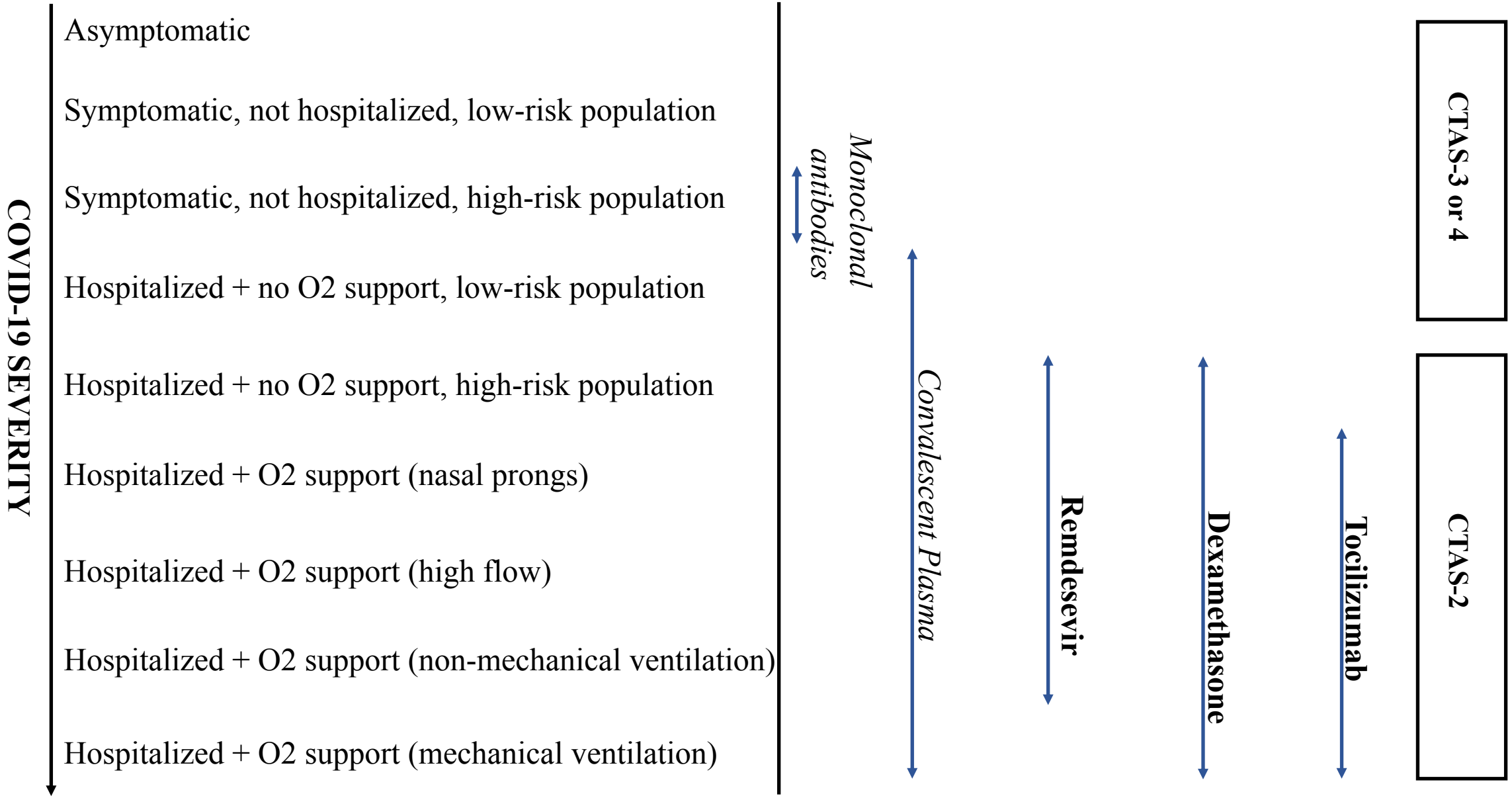
IF fever over 38°C or purulent sputum
☐ Amoxicillin 1g PO TID x 5 days and/or doxycycline 200mg PO ONCE then doxycycline 100mg PO BID x 5 days. **OR** if amoxicillin in last 3 months ☐ Amoxicillin-clavulin 875mg po BID x 5 days and/or doxycycline 200mg PO ONCE then doxycycline100mg PO BID x 5 days. **OR** if penicillin allergy ☐ Cefuroxime 500mg PO BID x 5 days and/or doxycycline 200mg PO ONCE then doxycycline 100mg PO BID x 5 days.
CONSIDER ☐ Oseltamivir if recent influenza outbreak in region

Additional Orders
☐
☐
☐

Discharge to self-isolation if reliably reachable by phone with 24hr follow-up from nursing station to re-assess status. Advise patient to contact nursing station if condition worsens.

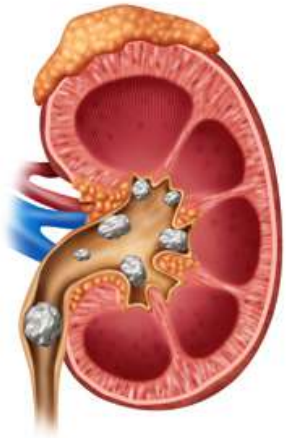
RN Name: _____ RN Signature: _____

Putting it all together



Implications of COVID-19 Treatment on Returning Community Members

- Monoclonal antibodies and convalescent plasma : Delay vaccine administration 90 days.
- Tocilizumab may increase risk of tuberculosis and opportunistic infections
- No long term effects of Remdesevir unknown
- In patients who received (and discharged on) high dose Vitamin C, consider hyperoxalosis and kidney stones risk
  Should have dose reduced
- In patients who received (and discharged on) high dose Vitamin D, consider hypervitaminosis D
  Should have dose reduced



Long-term Sequelae of COVID-19 Infection in Returning Community Members

- Most people with COVID19 fully recover within 3-4 weeks.
- Older patients, patients with comorbid conditions are more likely to have persistent symptoms
- Common lingering symptoms:
  - → Fatigue
  - → Dyspnea and cough
  - → Arthralgias
- Less common lingering symptoms:
  - → Headaches
  - → Loss of taste or smell
  - → Palpitations
  - → Difficulty sleeping
- Specific organ damage:
  - → Cardiac damage leads to fibrosis→ CHF, chronic dyspnea
  - → Pulmonary fibrosis → Chronic dyspnea
  - → CNS involvement → Seizures, Acceleration of Parkinson's or Alzeimer's disease
- Prevalence of the above remains uncertain

Thank you

References available on request

Multi-**S**ubspecialty **E**ducation for low-**R**esource **S**ettings **(MSERS)** Series

- Lectures available online
  https://apil.ca/multi-subspecialty-education-for-low-resource-settings-msers/

- Please complete evaluations to keep these sessions relevant and ongoing
  → Evaluation for THIS session please click on link in chat box:
  → For MSERS session1 (Dr. Laurie Mazurik): https://www.surveymonkey.com/r/MSERS0001
  → For MSERS session2 (Dr. Cory MacFarlane and Dr. Azad Mashari): https://www.surveymonkey.com/r/MSERS0002
  → For today MSERS session3 (Dr. Ben Thomson): https://www.surveymonkey.com/r/MSERS0003

- For Certificate of Attendance, complete the Evaluation of the session and it will be emailed to you

- Special guest (Obstetrics/Gynecology) to cover the following requested topics next 4 sessions!
  → Reading the Pap smear, common Pap findings and when to worry (could be likely "an approach to a pap result")
  → Contraception: Risk factors of different types, and what kind of education should I be giving my patients?
  → Vaginal pruritus
  → Approach to vaginal discharge
  → Approach to vaginal or perineal pain

Thank you