COVID-19 PRIMER

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University of British Columbia: Department of Internal Medicine

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I. Clinical Presentation

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Introduction

- Clinical presentation is non-specific and may range from asymptomatic to severe pneumonia and death
- Symptoms and signs typically develop 5-6 days after infection (mean incubation period 5-6 days, range 1-14 days)[1]
- 97.5% of patients develop symptoms within 11.5 days of infection
- Viral shedding persisted for a median of 20 days in survivors and persisted until death in non-survivors.[2]
- Majority have mild disease and recover
    - 80% of laboratory confirmed patients have mild to moderate disease
    - 13.8% have severe disease (dyspnea, respiratory rate $\geq$ 30/minute, O2 saturation $\leq$ 93%, PaO2/FiO2 ratio < 300 and/or lung infiltrates > 50% of lung field within 24-48 hours)
    - 6.1% are critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure)

Symptoms

Typically derived from inpatient cohorts:

- Dry cough (67.7%)
- Fatigue (23-38.1%)
- Sputum production (23-33.4%)
- Shortness of breath (18.6%)
- Sore throat (13.9%)
- Headache (13.6%)
- Myalgia or arthralgia (14.8-15%)
- Chills (11.4%)
- Nausea or vomiting (4-5%)
- Nasal congestion (4.8%)
- Diarrhea (3.7-5%)
- Hemoptysis (0.9%)
- Conjunctival congestion (0.8%)
- **Notes:**
    - Fever is the most common symptom, but only present in 48% on admission - will typically develop during admission in 88%
    - Patients can sometimes present with only GI symptoms

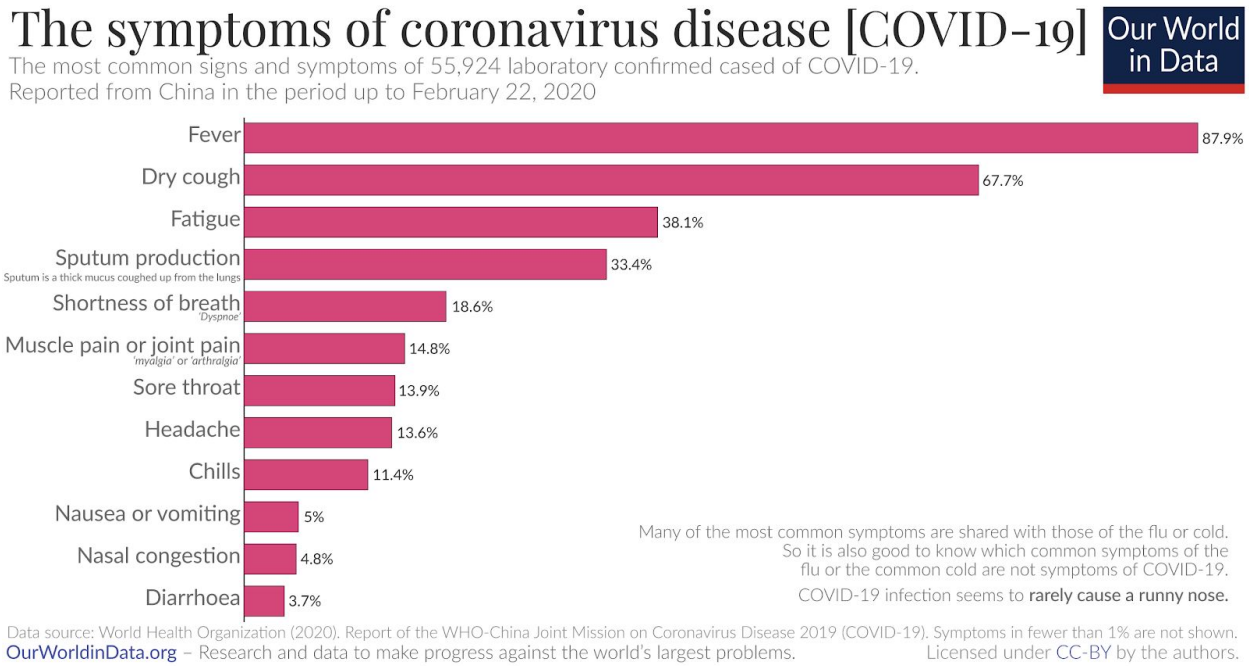
Asymptomatic patients [1,2,3]

- There is little literature on mass screenings and identifying patients with asymptomatic infections
- One study looked at the Princess cruise quarantined in Japan. Of the 3711 patients on the cruise, 3063 were tested (Mizumoto et al, EuroSurveillance March 2020)
    - Through mathematical analysis, they believe that about **18% were asymptomatic**

Symptoms near the time of presentation in various cohorts

	Guan et al. NEJM (largest cohort)	Shi et al Lancet	Yang et al. Lancet (critically ill pts)	Chen et al.	Huang et al.	Xu et al. BMJ
Constitutional						
Fever	473/1081 (43%)	18/21 (86%)	46/52 (88%)	82/99 (83%)	40/41 (98%)	48/62 (77%)
Myalgia	164/1081 (15%)		6/52 (12%)	11/99 (11%)		
Headache	150/1081 (14%)	2/21 (10%)	3/52 (6%)	8/99 (8%)	2/38 (8%)	21/62 (34%)
Upper respiratory						
Rhinorrhea	53/1081 (5%)	5/21 (24%)	3/52 (6%)	4/99 (4%)		
Sore throat	153/1081 (14%)			5/99 (5%)		
Lower respiratory						
Dyspnea	205/1081 (19%)	9/21 (43%)	33/52 (64%)	31/99 (31%)	22/40 (55%)	2/62 (3%)
Chest tightness		5/21 (24%)				
Cough	745/1081 (68%)	15/21 (71%)	40/52 (77%)	81/99 (82%)	31/41 (76%)	50/62 (81%)
Sputum	370/1081 (34%)	3/21 (14%)			11/39 (28%)	35/62 (56%)
Hemoptysis	10/1081 (1%)				2/39 (5%)	2/62 (3%)
Gastrointestinal						
Nausea/Vomiting	55/1081 (5%)	2/21 (10%)	2/52 (6%)	1/99 (1%)		
Diarrhea	42/1081 (4%)	1/21 (5%)		2/99 (2%)	1/38 (3%)	3/62 (8%)

-The Internet Book of Critical Care, by @PulmCrit



Signs

- Vitals
    - Fever (temperature ≥ 37.3 C) (87.9-94%)[1,2]
    - Moderate hypoxemia
    - Respiratory rate ≥ 24 breaths per minute (29%)[2]
    - Heart rate ≥ 125 beats per minute (1%)[2]
- Physical examination[4]
    - Throat congestion (1.7%)
    - Tonsil swelling (2.1%)
    - Enlargement of lymph nodes (0.2%)
    - Rash (0.2%)

Complications and Clinical Outcomes

- Wang D et al Wuhan, China (138 patients hospitalized with COVID-19 pneumonia) complications included:[5]
    - Shock (8.7%)
    - Acute cardiac injury (7.2%)
    - Arrhythmia (16.7%)
    - ARDS (19.6% of all patients and 61.1% of patients requiring ICU admission)
    - AKI (3.6%)
- Guan et al China (1099 patients COVID-19 confirmed +) outcomes:[4]
    - The median duration of hospitalization, if required, was 12 days.
    - Oxygen therapy was required in 41.3% of patients.
    - ICU admission in 5% of patients.
    - Non-invasive mechanical ventilation in 5.1% of patients.
    - Invasive Mechanical ventilation in 2.3% of patients.
    - Death in 1.4% of patients
- Cytokine storm syndromes[12]
    - A subset of patients with severe COVID-19 disease found to have a cytokine profile that resembles secondary haemophagocytic lymphohistiocytosis (sHLH)
    - Patients have increased interleukin (IL)-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α
    - Subset of patients with hyperinflammation may benefit from immunosuppression

Risk Factors for Disease Severity

- Higher D-dimer and more severe lymphopenia associated with mortality
- Higher neutrophil:lymphocyte ratio in more severe cases (>5)
- A high procalcitonin or significant change may indicate bacterial superinfection

Risk Factors Associated with In-Hospital Death

- Older age[2]
- Higher SOFA scores[2]
- D-Dimer >1μg/mL[2]
- Cardiovascular diseases[13]
- Secondary infection[13]
- Elevated inflammatory indicators (Ferritin and IL-6)[13]

Laboratory Findings

- CBC
    - Normal WBC 4-10 x 109/L (62%)[2]
    - Lymphopenia < 0.8 x 109/L (IQR 0.6-1.1) (40-70.3%)[2,5]
    - Leukopenia (33.7%)[4]
    - Anemia (15%)[2]
    - Mild thrombocytopenia < 100 (7%)[2]
- Prolonged PTT (30-58%)
    - 13.0 seconds (IQR 12.3-13.7)[5]
- LFTs
    - ALT > 40 U/L (31%)[2]
- Elevated LDH (39.9-67%)
    - 261 U/L (IQR 182-403)[2,5]
- ABG
    - Mild acidosis
    - Normal lactate
    - Severe base deficit
- CRP
    - Average 33 in non-severe, 58 in more severe[6]
- Serum ferritin
    - > 300 ug/L (80%)[2]
- CK
    - > 185 (13%)[2]
- IL-6
    - 7.4 pg/mL (5.3 - 10.8 pg/mL)[2]

Admission laboratory pattern in patients with COVID-19

	Guan et al NEJM (largest cohort)	Shi et al Lancet	Chen et al Lancet	Huang et al. Lancet	Xu et al. BMJ
WBC count	4.7 (3.5-6)	7.8 (2.5)	7.5 (4)	6.2 (4-10.5)	4.7 (3.5-5.8)
Platelet count	168 (132-207)	213 (100)	214 (79)	164 (132-263)	176 (136-215)
Lymphocyte count (normally >1)	1 (0.7-1.3)	1 (0.3)	0.9 (0.5)	0.8 (0.6-1.1)	1 (0.8-1.5)
Hemoglobin	13.4 (12-15)	12.7 (1.3)	13 (1.5)	12.6 (11.8-14)	13.7 (12.9-15.2)
ALT (U/L)		51 (25)	39 (22-53)	32 (21-50)	22 (14-34)
AST (U/L)		48 (21)	34 (26-48)	34 (26-48)	26 (20-32)
Bilirubin uM/L (normal range 5-22 uM/L)		14 (4)	15 (7)	12 (10-14)	
Creatinine (normal range up to ~80-100 uM)		68 (15)	76 (25)	74 (58-86)	72 (61-84)
Prothrombin time (normal range ~12.7-15.4)		10.5 (0.4)	11 (2)	11 (10-12.4)	
APTT (normal range ~21-37 seconds)		34 (7)	27 (10)		
Thrombin time (normal range ~15-18.5)		32 (8)			
Fibrinogen mg/dL		192 (350)			
D-dimer (mg/L) – (Nl range seems to vary?)		6.9 (1.1)	0.9 (0.5-2.8)	0.5 (0.3-1.3)	0.2 (0.2-0.5)
Creatinine kinase			85 (51-184)		
LDH (normal range up to 250 U/L)			336 (260-447)	286 (242-408)	205 (184-260)
C-Reactive Protein mg/L		61 (40)	51 (42)		
Procalcitonin	<0.5 in 95% patients		0.5 (1)	0.1 (0.1-0.1)	0.04 (0.03-0.06)
Erythrocyte sedimentation rate (ESR)			50 (23)		
Ferritin			808 (490)		

Laboratory findings are generally nonspecific. Substantial *deviation* from these values might argue *against* a diagnosis of COVID-19. However, in most cases, laboratory findings are unlikely to be tremendously helpful.

-The Internet Book of Critical Care, by @PulmCrit

Imaging Findings

- Chest x-ray
    - Features on chest x-ray
        - Bilateral patchy infiltrates
        - Gravitational distribution
        - Asymmetry if bacterial super-infection
    - **NOTE:**
        - *Almost 50% of non-severe patients and almost 25% of severe patients had normal x-rays*
        - No CT abnormalities were noted on initial presentation in 2.9% of the patients with severe disease and in 17.9% of those with nonsevere disease
- CT chest
    - Features on CT chest[7]
        - Ground-glass opacities (GGO) (86.1%)
        - Mixed GGO and consolidation (64.4%)
        - Vascular enlargement in the lesion (71.3%)
        - Traction bronchiectasis (52.5%)
        - Peripheral distribution (87.1%)
        - Bilateral involvement (82.2%)
        - Lower lung predominant (54.5%)
        - Multifocal (54.5%)
    - CT evidence of viral pneumonia may precede RT-PCR test results[8]
- COVID-19 Radiology Database

    - https://www.sirm.org/category/senza-categoria/covid-19/
- Lung ultrasound - **DO NOT USE PoCUS UNNECESSARILY - SEE PoCUS GUIDELINES**
    - Features on lung ultrasound[9]
        - Thickening of pleural line with pleural line irregularity
        - B lines (focal, multifocal and confluent)
        - Consolidations (multifocal small, non-translobar, translobar with occasional mobile air bronchograms)
        - Pleural effusions are uncommon
    - Clinical application
        - Focal B lines are main feature in early stage and mild infection
        - Alveolar interstitial syndrome is main feature in progressive stage and critically ill patients
        - A lines in convalescence
        - Pleural line thickening with uneven B lines in pulmonary fibrosis[9]
        - Pattern 1: diffuse b-line profile, responds well to PEEP
        - Pattern 2: basal PLAPs points showing consolidation/parapneumonic effusions/atelectasis where front areas ventilated, rear areas are atelectatic and responsive to pronation
        - Useful in evaluating effect of high PEEP and managing recruitment maneuvers[10]

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II. Testing

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Introduction

The provincial guidelines around testing have been changing. This section will provide some guidance on which patients should be tested and when and where healthcare providers should be tested. Currently, the BC Center for Disease Control has decided the following populations be tested[1]:

1. Hospitalized, or likely to be hospitalized
2. Health care workers
3. Residents of long term care facilities
4. Part of an investigation of a cluster of outbreak

Who to test

The BC COVID-19 Symptom Self Assessment Tool is available to guide patients and health care workers whether they should get tested.

- **Patients: Hospitalized, or likely to be hospitalized**

Any patient with an influenza-like illness (ILI) who you order an influenza swab on will automatically be tested for COVID-19 at all locations. The specific clinical presentations required for testing varies at the three sites but the presence of fever, cough and respiratory symptoms that cannot be managed at home warrant testing. The site specific criteria are as follows:

- SPH: Fever (temp > 37.5 or clinical judgment) or new difficulty breathing or cough https://drive.google.com/file/d/1edSrNBTq89K7pVcmcEnUgrQQjTPMDjvr/view?usp=sharing
- VGH: Fever, respiratory symptoms (new or worsening cough, sore throat or sneezing), or shortness of breath/difficulty breathing http://ipac.vch.ca/Documents/Emerging%20Infections%20and%20VHF/COVID-19%20VCH%20Identification%20and%20Assessment%20Algorithm.pdf
- RCH: Fever, respiratory symptoms and radiographic evidence of pneumonia. Testing can be considered for GI symptoms if there is no other clear cause or atypical presentations in the elderly such as delirium or acute functional decline[4]

- **Health care workers**

  If you are feeling unwell, please let your team and the CMR at your site know **immediately** and do not present to work.

  The following categories of health care workers require testing:

  - Symptomatic health care workers - the definition of symptomatic varies between the sites - please refer to the site specific documents for most updated criteria.
    - SPH: Fever +/- cough or 2 of the following: fever, cough, shortness of breath, diarrhea, fatigue, malaise, myalgia or rhinorrhea. Travel or known exposure is not required and asymptomatic patients are not screened. https://drive.google.com/file/d/1edSrNBTq89K7pVcmcEnUgrQQjTPMDjvr/view?usp=sharing
    - VGH: Contact with a confirmed or probable case of CoVID19 OR fever >/= 37.5 OR New cough OR Shortness of breath OR other concerning clinical symptoms based on clinical judgement https://drive.google.com/file/d/1LKAuC9huTfGhyXKdJ-BWLIhwITCVTiKQ/view?usp=sharing
    - RCH:
  - Health care workers with confirmed COVID-19 who require a negative test after symptom resolution to return to work.

Where can healthcare workers be tested?

The recommendations for site-specific testing are summarized here but please refer to the respective site-specific primers for more details. Regardless of where you get tested, please

identify yourself as a healthcare worker providing direct patient care delivery (coded as HCW1 with the BC CDC testing):

- SPH: Present to the SPH Emergency Department Triage and identify yourself as a healthcare worker. If you meet the screening criteria below, you will be triaged as a CTAS-2 and will receive a nasopharyngeal swab. You will be called in 24-72 hours with your result and you should self-isolate until you've received your result.
- VGH: Physicians and residents can present to the Blusson Spinal Cord Center at 818 W10th Ave between 8am-4pm.
- RCH: Please liaise with Emma Schon, CMR or Dr. Gerald Da Roza and they will advise regarding which location has the shortest turnaround time.
- Additional site for Vancouver Community with PHC: Gravel lot adjacent to Honoria Conway at St. VIncent's (entrance off 33rd ave), open Mon-Sun 9am-4pm.

At present, all HCW should be getting tested at VCH or PHC sites as the turnaround time is faster. Will update this as FHA gets access to testing on site.

You've been tested - now what?

The result times vary from less than a day to up to 72 hours. Once you have been tested, please self-isolate immediately and await for your results. If you are confirmed negative, please continue to self isolate and return to work when your symptoms have resolved or wear a mask to work. If you are confirmed positive, please follow the instructions given to you by Public Health and liaise with your site lead. Different sites have different protocols regarding negative testing prior to returning to work.

Who does not need to be tested?

The following populations do not require testing:

- Individuals with no symptoms or mild symptoms that can be managed at home
- Returning travellers and returning travellers with onset of mild illness within 14 days of return to Canada
- People living in the same household as a patient with respiratory symptoms.

These patients, with or without a history of travel, who have respiratory symptoms that can be managed at home, should self-isolate at home for at least 14 days after onset of respiratory symptoms.

How to test

Recommended sample types for testing COVID-19 are[2]:

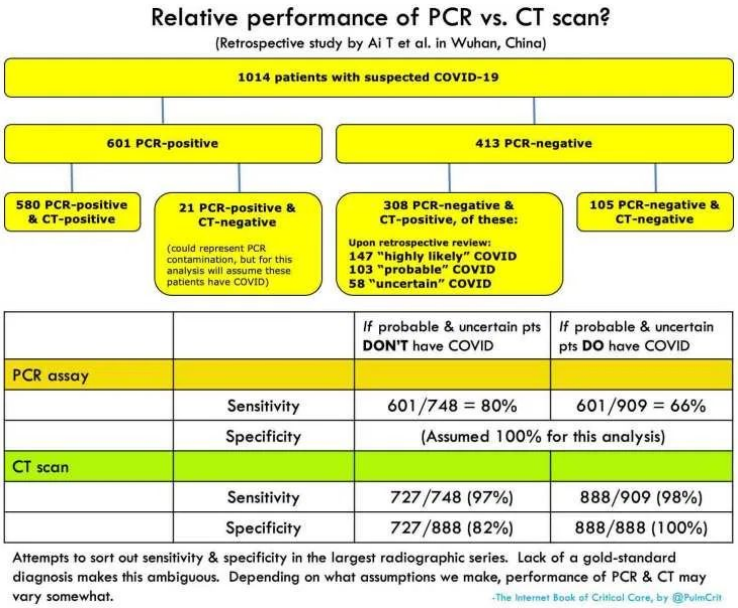
- Nasopharyngeal (NP) swab or bronchoalveolar lavage (BAL) for clinically stable patients or outpatients

- NP swab and a lower respiratory specimen (sputum/tracheal aspirate/BAL) for admitted critically ill patients.

Use contact and droplet precautions with a surgical mask and eye protection when collecting a nasopharyngeal or throat swab or sputum[1]

About the Test

- Uses real time (RT) PCR assay based on primers originally published by Chinese scientists and now globally accepted; these give a quantitative result and samples that meet a particular threshold are considered positive[3,4]
- "Kits" typically include a non-infectious positive control sample and are manufactured by biotechnology companies[4]
- Limitations
    - Assay relies upon capturing an adequately deep specimen (must reach nasopharynx), so inadequately obtained specimens may result in false negatives[4,5,6]
    - Other potential pre-analytical vulnerabilities: handling, transport and storage of swabs, interfering substances, contamination (with other specimens, patients on antiretrovirals)[6]
    - Since COVID-19 is a *spectrum* disease and not a binary disease, patients with a higher viral load (e.g. later vs earlier in disease course) are more likely to test positive[5,6]
    - Other potential analytical vulnerabilities: instrument malfunctioning, active viral recombination, insufficient harmonization of primers[6]
    - We do not currently have a clear "gold standard" for which to assess the RT-PCR test's performance[5]
        - There are studies comparing performance of CT based diagnosis vs RT-PCR[5,6,7,8]
        - Serological assays (i.e. IgG, IgM) are being developed[5]
- In general, **specificity** appears to be high[5]
- In general, **sensitivity** is likely not as great (i.e. not as good of a "rule-out")[5,6,7,8]
    - CT scans likely have higher sensitivity, particularly earlier in disease course[5,6,7,8]
    - Ai et al, 202: In patients with suspected COVID-19 who initially tested negative, repeat NP swab was positive in 23% (15/64) patients[8]
    - Bottom line: If suspected to have COVID-19, then treat, isolate and consider re-testing later in disease course



		If probable & uncertain pts **DON'T** have COVID	If probable & uncertain pts **DO** have COVID
PCR assay			
	Sensitivity	601/748 = 80%	601/909 = 66%
	Specificity	(Assumed 100% for this analysis)	
CT scan			
	Sensitivity	727/748 (97%)	888/909 (98%)
	Specificity	727/888 (82%)	888/888 (100%)

Attempts to sort out sensitivity & specificity in the largest radiographic series. Lack of a gold-standard diagnosis makes this ambiguous. Depending on what assumptions we make, performance of PCR & CT may vary somewhat.

-The Internet Book of Critical Care, by @PulmCrit

Test results

- **For tested patients**
  The various sites have different mechanisms on how test results are reported. The results are made available either on the respective EMRs or by notification from Public Health. As per the BCCDC, all test results will be reported to the ordering provider. In addition, all positive results will be reported to Public Health for follow-up with employees. Ordering providers can also call for results using the Laboratory Test Results Call Centre 1-877-747-2522. Please do not call the testing laboratory directly, as the staff is focused on providing timely testing. The following are summaries of the current procedures but please refer to the site-specific documents for further details. https://patienteduc.fraserhealth.ca/file/covid-19-home-isolation-while-waiting-for-novel-co-473387.pdf
    - SPH: All samples are being run at the SPH Microbiology Laboratory. For inpatients, POSITIVE results are called to the MRP, negative results will NOT be called, all available under the Microbiology tab on Cerner. The expected turnaround time is 4-6 hours, and they have a new machine running 24h.
    - VGH: All samples collected at VCH for influenza/RSV and/or COVID-19 will be forwarded directly to the VGH Microbiology Laboratory. NP swabs and bronchoalveolar lavages will be tested at VGH and all other specimen types will be forwarded to the BCCDC. VGH will be providing testing 3 times daily at 06:00, 12:00 and 16:00, 7 days/week (insert ref #3) The results will be available on PCIS under the Microbiology tab, under special virology testing. If the request is urgent, please call the lab as there have been delays in the posting of results of completed tests.

- RCH/BCCDC: At present, testing from Fraser Health Authority is going to the BCCDC lab with a turnaround time of 4-6 days. If there is a positive result on a patient admitted to the ward, Public Health should be notifying the ward though this is not always happening. The results will be uploaded to Meditech though there may be delays. Please add windows log in to the UCI Prov Lab Sign Up so results can be obtained through Meditech. If a test is confirmed positive on the ward, please notify Dr. Da Roza immediately to ensure appropriate contact tracing can be initiated.

Physicians should call the medical microbiologist if the test needs to be expedited or if they have not received test results after 72 hours. BCCDC will not be able to assist patients or physicians calling before the 72 hour timeframe.

- **For tested healthcare workers**
  If you do not receive a call within 24 hours, call 1-833-707-2792 to speak with a nurse to get your results. This line is available 7 days/week from 8:30am - 4:30pm.

  BC CDC:
  http://www.bccdc.ca/resource-gallery/Documents/Statistics%20and%20Research/Statistics%20and%20Reports/Epid/Influenza%20and%20Respiratory/ERV/BCCDC_PHL_Updated_nCoV_Lab_Guidance.pdf

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III. Personal Protective Equipment (PPE)

Robert Yao, Eric J. Zhao. Last updated Mar 19, 2020.

Summary

- Viral transmission of COVID-19 from asymptomatic individuals is occuring
- There is a global shortage of vital PPE HOWEVER masks must be changed after each exposure to patient with droplet precautions (suspected or confirmed case)
- For non-aerosol-generating procedures, the appropriate PPE for patient care is:
    - Gloves
    - Gown
    - Medical mask
    - Eye protection (face shield or goggles)
- For aerosol-generating procedures (see below for a list), the appropriate PPE for patient care is:
    - N95
    - Eye protection
    - Gloves
    - Gown
    - Aprons if gowns are not fluid resistant
- CTU members should wear the following at all times when in Emergency Departments
    - VGH: Surgical mask + eye protection
    - SPH: Surgical mask
    - RCH: Surgical mask + eye protection
    - All: change PPE if dirty, damaged, or used for COVID positive or suspected
- All HCWs in Fraser Health Authority are asked to wear surgical masks while at work

- Scrubs:
    - Scrubs are being made available for all personnel working in the cohort COVID19 wards and in the ED
    - Do NOT take them home - put in laundry hampers after use
    - Ideally this will become more widespread as resources increase

Minimizing the need for PPE

- Restrict healthcare worker access to rooms of patients if they are not involved in direct care.
    - If you witness misutilization, please speak to the offending individual and if necessary, to someone in leadership
- Bundle activities to minimize the number of times a room is entered (eg, check vitals during med administration, deliver food while performing other care).
- Hospitals are restricting the number and type of outside visitors

Rational use of PPE

Healthcare workers involved in direct care of COVID-19 patients should use the following PPE[1]:

- Gown
- Gloves
- Medical mask
- Eye protection (goggles or face shield)

For aerosol-generating procedures, use the following PPE:

- N95
- Eye protection
- Gloves
- Gown
- Aprons if gowns are not fluid resistant

N95s have been used for extended periods during prior outbreaks (i.e wearing the same respirator while caring for multiple patients who have the same diagnosis). Evidence indicates they maintain their effectiveness when used for extended periods HOWEVER the current policies do not recommend doing this at current time. This may change depending on our supplies.

How to don and doff PPE

- https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf
- https://media.phsa.ca/home/iframe?url=BCCA/bccahealth%5cRemovingPPE_20200312
- Note extra hand hygiene step before removing mask/N95
- Feel free to watch colleagues and offer pointers if mistakes are being made; we are in this together

code blue

Code Blue Protocol PPEs

Code blues should be considered as aerosol-generating and use the following PPEs:

Donning:

- Tie up hair, wash hands
- Booties extending to mid-calf (optional)
- Gown (disposable preferred; Aprons if gowns are not fluid resistant)
    - Tie with a single knot
- N95 mask with seal check
- Eye protection (face shield preferred)
- Head cover (optional) with a single tie around the neck (have partner double check for open areas)
- Double glove with surgical gloves over the gown
    - If using nitrile long gloves -> one over and one under the gown

Doffing:

- Step into ante-room or go to corner of the room farthest away from the patient
- Remove disposable gown from mid section and remove gloves in a single motion (make it into a ball) and discard
    - If nitrile gloves, use alcohol to wash outside of the gloves
- Wash hands
- Remove knot around the head cover and let it drop
- Wash hands
- Remove booties and wash hands
- Remove face shield using the straps behind the head
- Remove N95 one strap at a time, avoid touching outside of mask
- Wash hands

Future Directions for Code Blue protocol PPEs:

- Development of code blue PPE carts **i**n anticipation for potential aerosol-generating procedures (CPR, intubation) on the ward to allow for rapid response

Aerosol-generating procedures

This is not an exhaustive list of aerosol-generating procedures.

- Nasopharyngeal swab: because it can induce coughing.[2]
    - The BCCDC and ECDC differ on this point, with BCCDC saying NP swabs can be performed using contact and droplet precautions with procedural mask and eye protection, and do not require the use of an N95 respirator
- Nasopharyngeal aspirates, washes, scoping
- BiPAP and CPAP

- Nebulized therapy
- Opti-Flow
- Intubation,
- Bronchial suctioning
- Bronchoscopy
- Sputum induction
- CPR, especially with bag-mask ventilation
- Autopsies involving respiratory tissues

Priorities for the use of N95 respirators

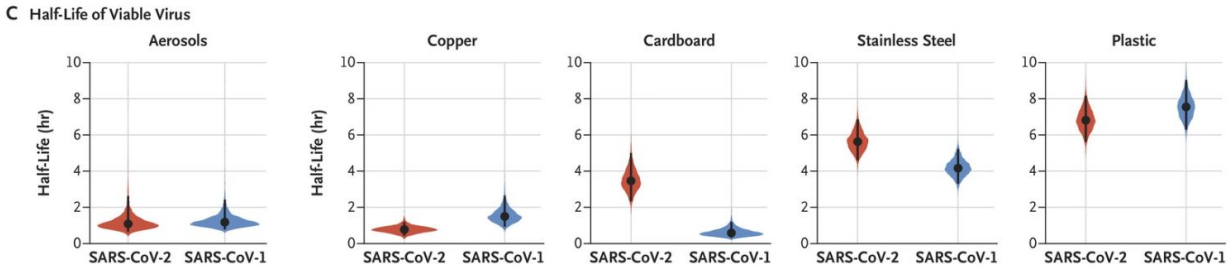
- Highest priority: healthcare workers performing aerosol-generating procedures.
- N95s can be used for up to 4 hours for multiple patients without removing them, unless it is damaged, soiled, or contaminated (eg, symptomatic suspected case coughing on you).

Priorities for the use of surgical masks

- Highest priority: symptomatic confirmed cases of COVID-19, followed by suspected cases
- Next highest priority: those caring for COVID-19 patients

Modes of transmission

- SARS-CoV-2 can spread from person-to-person through respiratory droplets in air or deposited on surfaces, and possibly by the fecal-oral route.
- SARS-CoV-2 remained viable in aerosols for at least 3 hours in one study.[4]
- SARS-CoV-2 is more stable on plastics and stainless steel than on copper and cardboard; viable virus was detected up to 72 hours after application to these surfaces.[4]
- Therefore aerosol and fomite transmission of SARS-CoV-2 is plausible.



Viral shedding

Over the course of the infection, the virus has been identified in respiratory tract specimens 1-2 days before the onset of symptoms and it can persist for 7-12 days in moderate cases and up to 2 weeks in severe cases.

It should be noted that viral RNA shedding does not directly equate with infectivity.[3]

Infection in asymptomatic individuals

The virus has been detected in asymptomatic persons. On the Diamond Princess cruise ship, where all passengers and staff were tested regardless of symptoms, 51% of laboratory confirmed cases were asymptomatic at the time of a positive test.[5] In Italy, 6.7% of the laboratory-confirmed cases have been asymptomatic.[6]

Transmission in pre-symptomatic stage of infection

Potential transmission from an asymptomatic person has been reported in a familial cluster of five COVID-19 patients hospitalised with fever and respiratory symptoms that had contact before their onset of symptoms with an asymptomatic family member, a young 20-year-old woman, upon her return from Wuhan. She remained asymptomatic for the entire 19 days of laboratory and clinical monitoring.[7]

Pre-symptomatic transmission has been inferred through modelling, with the proportion of pre-symptomatic transmission estimated at 48-62%.[8] The serial interval (time between successive cases in a chain of transmission, 4.0-4.6 days for COVID-19) is shorter than the main incubation period (5 days), suggesting many secondary transmissions would have already occurred by the time symptomatic cases are detected and isolated.[9]

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IV. Guidelines for ICU/HAU Consultation

Craig Cavanaugh, Rami Elzayat, Carmen Wong. Last Updated Mar 20, 2020.

While the majority of patients with COVID-19 improve after experiencing mild respiratory symptoms, there are patients who will develop critical illness requiring ICU-level care. These patients may experience complications due to respiratory failure, multiorgan failure, septic shock, or cardiac complications including cardiomyopathy, arrhythmias, and myocarditis[1].

Guidelines

- Call Critical Care Outreach Team (CCOT) if patient requires 4L NP to keep SpO2>92%
- Call ICU if patient requires 6L NP
- Early involvement of ICU/HAU is KEY
- Avoid aerosolizing measures, including high flow oxygen and BiPAP, if query or confirmed COVID
- Avoid nebulized medications, due to aerosolization, and use MDI only if necessary to maintain supply

Predictors of Poor Outcome

- Age
- Presence of underlying disease (i.e. cardiac comorbidities)[2,3]
- Presence of secondary infection
- Elevated inflammatory markers (elevated CRP, d-dimer) [2,3]

Code Blue Planning

Code Team and Responsibilities

- SPH: Anesthesiology will be called for all intubations of COVID confirmed or suspected cases - responsible for intubation. See SPH specific document for phone number
- Other sites: no specific guidelines in place, please call your code blue team as usual

COVID-19 POSITIVE AND PRESUMED POSITIVE CPR PROTOCOL

General Principles:

- All patients should have a clear designation of COVID-19 positive, COVID-19 suspected, COVID-19 not suspected, COVID-19 negative made clear on their chart.
- If CPR appropriate, **EARLY ICU consult for COVID-19 positive or presumed positive and clinical deterioration**
- ACLS with outlined modifications below
- Recognition that **intubation, bag mask ventilation and chest compressions** are aerosol generating and **require airborne PPE**
- If cardiac arrest **during intubation** secure airway prior to starting CPR; otherwise chest compressions and rapid identification of VT/VF take precedence

Assessment

Initial exam to confirm if a code blue should be activated	• **DON Airborne precautions prior to patient contact** • Visually inspect for absence of signs of life (respiratory effort/chest rise) • Do not auscultate for breath sounds or listen/feel for breath sounds by approaching patient's airway • Palpate femoral or brachial pulse to confirm cessation of cardiac activity • Do not bag mask ventilate patient • Cover airway with BVM plus high efficiency hydrophobic filter or clear plastic cover or facemask **THEN** initiate chest compressions • Communicate CODE status and COVID-19 status to code team

Code Team

Team Members/Role	• 1 RT, 2 Code RN, Physician team leader, Airway expert • Airway to be managed by best possible operator (Staff Anesthesia first choice, ICU staff/Fellow/Clinical Associate if Anesthesia unavailable) • Code team to wear airborne PPE prior to entering room • If available, one additional physician to be outside the room donned in PPE as backup if needed • Minimize code team personnel

ACLS Management

Considerations to protect against virus transmission	• Early defibrillation may prevent need for airway and ventilator support • Place BVM with high efficiency hydrophobic filter interposed between mask and Ambu bag on patient ASAP→ **do not ventilate patient** • Airway management by expert, video laryngoscopy preferred • **Pause** CPR for intubation • Consider **early application of LUCAS device** to limit staff exposure • Clamp ETT prior to circuit disconnect/connecting to ventilator

Transport/Return of Spontaneous Circulation (ROSC)

Post ROSC care	• Communication with ICU regarding disposition and timing of transfer • Avoid CXR/ECG until ICU • Team to DOFF, then DON new PPE prior to transfer of patient as assumed to be heavily contaminated following resuscitation • Ensure all contaminated equipment disposed of or cleaned • Ensure a clear path to ICU destination

Authors: Sonny Thiara, Ruth MacRedmond, George Isac, Mypinder Sekhon, Erik Vu, Craig Fava, Kali Romano, Adam Thomas

Vancouver Providence

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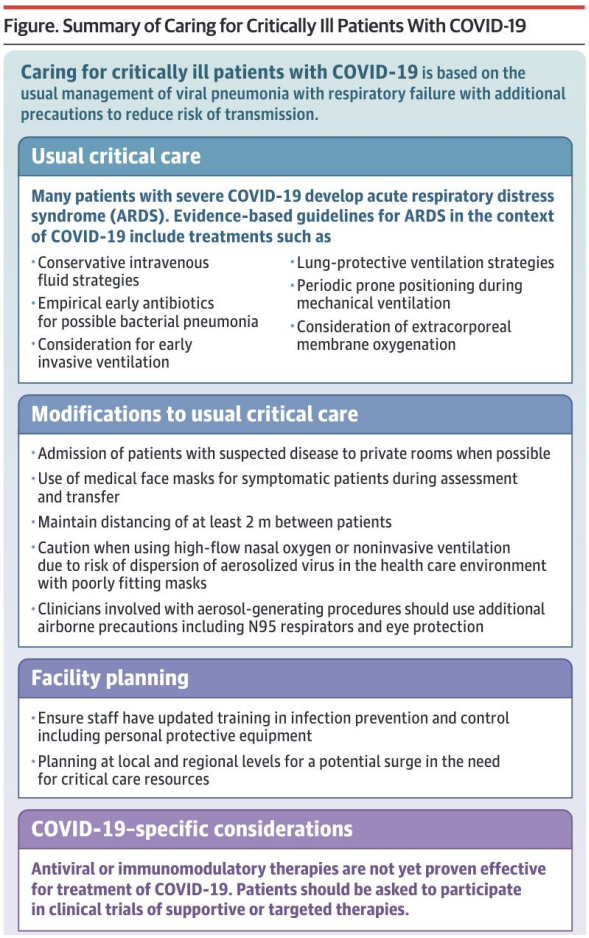
V. Supportive Measures

Elina Liu, Ben Schwartzentruber, Carmen Wong, Charles Yang. Last updated Mar 20, 2020.



Guiding Principle

The majority of the deaths from COVID-19 are from cardiovascular events secondary to ARDS / respiratory failure.

General

- Implement infection control measures immediately in those with symptoms (see Symptoms primer):
    - Droplet and contact precautions for all suspected cases with appropriate isolation
    - PPE for HCP (see PPE primer)
- Obtain nasopharyngeal swabs (see Testing primer)
- Negative pressure rooms generally are not required unless aerosolizing procedures are to be completed, including the following:
    - Non-invasive ventilation (including BiPAP and optiflow / high-flow nasal cannula)
    - Intubation, including manual (bag-mask) ventilation & open endotracheal suctioning
    - CPR
    - Sputum induction
    - Nebulized therapy
    - Airway suctioning
    - High frequency oscillatory ventilation
    - Tracheostomy care

- Bronchoscopy

Monitoring

- Ward: q4h vital signs and PRN
  - Early reports describe the possibility of clinical deterioration in the 2nd week of illness, with 25-30% of hospitalized patients requiring intensive support[1]
  - Monitor for:
    - Arrhythmia (23%), shock (1-10%), ARDS (3-27%)[2,3]
  - Median time between symptom onset and ARDS is 8 days (ACP online)
- ICU: continuous vital signs monitoring with telemetry
  - According to JAMA article by Wang et al, in ICU patients:
    - ARDS 61% hospitalized cases
    - Arrhythmia 44% hospitalized cases
    - Shock 31% hospitalized cases

Hypoxemic Respiratory Failure

See Treatment and HAU/ICU Consult primers

- DO: give supplemental O2 by nasal prongs or facemask to target SpO2 > 94% if in respiratory distress, then above 90% once stable[4]
- DO: if full code → early intubation[1] (critical care outreach at 4 L of oxygen, ICU consult at 6 L oxygen)
- AVOID: non-invasive ventilation and high-flow nasal cannula:
  - Aerosolizing procedures increase risk of disease transmission
  - Associated with high failure rate and need for emergent intubation
  - In cases where the patient has concurrent NIV-indicated conditions (e.g., heart failure, COPD) contact the attending physician +/- ICU before initiating
- Medications:
  - Empiric antibiotics for CAP & oseltamivir while results pending[4]
  - Bronchodilators via MDI with spacer - AVOID using nebulized medications[6]
  - No evidence demonstrating benefit of systemic corticosteroids in viral pneumonia; in fact, may be harmful[5]

Care for Patients Not Suitable For Critical Care

- Hold goals of care discussion early, understanding patient's values and preferences
- Continue medical management as above
- Ensure multidisciplinary approach to address multimorbidity
- Early review of home medications to identify any that may be harmful in context of severe illness and minimize drug-drug interaction
- Involve family members and caregivers in patient-centred decision-making
- If worsening respiratory failure, consult palliative care, initiate comfort measures

- Resources: See supplement at end of primer on BC Centre for Palliative Guidelines algorithm https://www.talkdyingtome.com/new-blog-1/2020/3/19/goals-of-care-discussions-in-the-age-of-covid-19?fbclid=IwAR3jC6OCw4xyjsSpGfz3PzKauF-TgvokI2Jxa0T6EjFNaQKc0stD7D-JjPQ

Fevers and pain

- Acetaminophen, max 4 g per day unless signs of liver synthesis dysfunction (then 2 g per day)
- Controversy regarding NSAID use in this population
    - AVOID: use for pain fever, as there are other options until evidence more clear
    - For people already on NSAIDs for a good indication, monitor carefully
- No specific guidelines on opioids for pain; prescribe using usual caution in respiratory failure (unless as palliative measure for dyspnea)

Hypotension / Shock

- Fluid resuscitation - conservative IV fluids to minimize risk of worsening hypoxemia
- Reserve IV fluids for hard indications such as hypotension, shock, AKI
    - Hypotonic fluids, starches and albumin should generally be avoided[4,7]

Hypertension, Heart Failure

- ACE inhibitors/ ARBs: currently, there does not exist any experimental or clinical data to demonstrate beneficial or adverse outcomes with background use of ACE inhibitors.[8]
    - Continuation is highly recommended, unless there are other reasons to do so (hypotension, etc) per the HFSA/ACC/AHA.[8]

Intubation & Ventilation Strategies[4,6,7]

- Intubation - **airborne precautions**
    - To be done by the COVID Airway Team as per your local institution
        - refer to relevant SPH, VGH, RCH COVID documents
    - Preoxygenation will be key as these patients often have low oxygen reserve and high demand
- Viral pneumonia without ARDS (⅓ of ventilated cases per JAMA Murthy)
- ARDS (⅔ of ventilated cases per JAMA Murthy): acute onset of hypoxemic respiratory failure with bilateral infiltrates
    - Empiric antibiotics for bacterial co-infection until diagnosis is excluded
    - Conservative fluid strategies
    - Lung protective ventilation:
        - Limit tidal volumes starting at 6 mL/kg of ideal body weight

        - Limit plateau pressures <= 30 cm H2O (unless there is extrapulmonary restrictive physiology such as obesity, pleural effusions, or abdominal compartment syndrome)
        - Permissive hypercapnia
        - Optimal titration of PEEP / FiO2 to target PaO2 55-80 mmHg, SpO2 88-95%
    - Periodic prone positioning
- If refractory hypoxemia evolves (e.g. Pa02/Fi02 ratio < 150 after attempting all of the above
  strategies), consider the following additional strategies:
    - Non-conventional modes of ventilation such as APRV
    - Inhaled epoprostenol: Dosing 10 – 50 ng/kg/min. An active humidification system is required to use this therapy.
        - Patients who do not demonstrate a physiological response (increase in PaO2 of 20% from baseline) after 30 minutes should be discontinued from inhaled epoprostenol therapy.
        - A daily assessment should be performed in an attempt to discontinue inhaled epoprostenol therapy.
    - Consider ECMO

Arrhythmia, Cardiac Injury

- Arrhythmia relatively common in the critically ill
- If symptoms of chest pain, palpitations, or dyspnea, OR findings of irregular heart beat:
    - STAT ECG, troponin
- Manage as per ACLS
- Cardiomyopathy with low EF may develop several days after peak of respiratory symptoms

Hepatitis

- Mild elevations in transaminases are commonly seen with COVID-19, but fulminant liver failure is not commonly reported
- Severity of ALT and AST elevation correlates with disease severity
- Workup and manage as per usual risk factors

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VI. PoCUS Guidelines

From the Canadian Internal Medicine Ultrasound Society.

Main message

Minimize the use of POCUS in patients with proven or suspected CoVID infection. Only consider POCUS if it has the possibility to significantly alter care.

Indications for POCUS

- Procedural guidance (particularly thoracentesis)
- To evaluate a possible alternative diagnosis (ie heart failure)
- To avoid the contamination risks associated with a dedicated radiology study

Contraindications for POCUS during COVID pandemic

- Repeat lung POCUS in a known/highly suspected COVID patient to assess progressive hypoxia
- As a diagnostic modality in patients who have already received a definitive test (PCR)
    - Note that there are NO pathognomonic POCUS findings for CoVID
- Educational scans

POCUS providers

- Novice users should NOT be performing POCUS on potential CoVID patients
- If possible, perform POCUS under the supervision of one of the POCUS faculty

- Be sure to save all clips (4-6 seconds) for future review with POCUS faculty and for clinical comparison over time
- If there are any questions about the role for POCUS in a CoVID patient, please contact Dr Katie Wiskar (VGH) or Dr Barry Chan (SPH) from 0800-1700.

POCUS machines

- Scans should only be done using dedicated CoVID machines
- At SPH, this is the CoVID ward machine
- At VGH, this is the Butterfly (new). Please contact Dr Katie Wiskar (0800-1700) to obtain access to this machine.
- Machine cleaning and infection control
    - Do not bring any extra equipment (towels, gel bottles) into the room
    - Use only single-use gel packets
    - Do not use POCUS in rooms during aerosol-generating procedures
    - For users of the Butterfly: place both the probe and the device (smartphone) in individual sterile probe covers
    - Clean visibly soiled areas before disinfecting
    - Disinfect all surfaces of the machine using Caviwipes. Allow to dry completely before the next use.
    - If no anteroom is available, the device should be disinfected prior to leaving the patient room

VII. Treatment

Ashley Yip, Ilyse Darwish, Rahel Zewude. Last updated Mar 20, 2020.

Standard Treatment

- Please see Spectrum App COVID-19 guidelines (*Fraser Health Authority*)
- No specific treatments are recommended, many under investigation *(see below)*
- Supportive care: ensure adequate caloric intake, correct electrolyte imbalances, supplemental oxygen as needed, conservative fluid management if no shock (*see above Supportive Measures section*)
- Empiric antimicrobial therapy for patients with sepsis or suspected CAP/HAP until bacterial infection ruled out
- Systemic corticosteroids are *not* recommended and may be harmful
- Use Tylenol preferentially over NSAIDs
- Oseltamivir until influenza is ruled out while seasonal influenza circulates

Therapeutic Agents Under Investigation

THIS IS FOR INTEREST ONLY AT THIS POINT. NO TREATMENT BEYOND SUPPORTIVE MEASURES ABOVE ARE APPROVED FOR USE IN BRITISH COLUMBIA.

1. Favipiravir

- Developed for Ebola but has broad-spectrum activity against influenza, arenavirus, bunyavirus and filovirus[1]
- **Mechanism of action:** nucleotide analogue that inhibits RNA-dependent RNA polymerase
- Approved in Japan for influenza
- **On-going clinical trials**
    - China
    - Phase 2 trial in Thailand

2. Hydroxychloroquine and Chloroquine

Chloroquine is a medication widely used for the past 70 years as an antimalarial as well as anti-inflammatory agent. Hydroxychloroquine is an analogue of chloroquine with lesser drug-drug interaction effects and is widely used for autoimmune diseases such as lupus and rheumatoid arthritis.

- **Mechanism of Action of chloroquine and hydroxychloroquine[2]**
    - Increases endosomal pH required for virus/cell fusion
    - Interferes with glycosylation of cellular receptors of SARS-CoV
    - Acts on both entry and post-entry stages i.e. antiviral activity observed in vitro, before and after cells were infected with SARS-CoV[3,4]
    - Long known anti-inflammatory property that may synergistically enhance the antiviral property, described above[3]
- **Indications[6]**
    - Mild COVID - symptoms are mild and no radiographic findings of pneumonia
    - Moderate COVID - symptoms such as cough, fever, and radiographic findings of pneumonia
    - Severe COVID
        - Respiratory Rate>=30 breath/min
        - O2 saturation =< 93% at rest state
        - Arterial partial pressure of O2 (PaO2)/oxygen concentration (FiO2) =<300mmHg
        - Patients with 24-48 hour progression of radiographic findings
- **Doses**
    - Chloroquine 500mg PO BID for first two days then 500mg daily for 5 more days. Handbook for Covid Treatment from Zhejiang University recommends the above[6] dose and advises chloroquine treatment course should not exceed 7 days
    - However, expert consensus from Gunadong Province, published on February 20th, recommends chloroquine 500mg PO BID for 10 days[7]

    - Hydroxychloroquine 400mg PO BID on day 1 followed by 200mg PO BID for 4 more days used in China[4,5]
    - Hydroxychloroquine 200mg PO daily for 10 days used in Italy (Lombardy)[10]
    - Consider adding azithromycin for 5 days to increase virological clearance (Gautret et al., *Journal of Antimicrobial Agents,* March 17 2020)
- **Evidence:**
    - 15 trials have been conducted in 10 Chinese hospitals on efficacy of chloroquine and hydroxychloroquine, ongoing 23 clinical trials in China, no full access to clinical trial data yet, however [2,10]
    - China reported results of >100 patients in these trials have demonstrated that chloroquine is superior to the control treatment in inhibiting the exacerbation of COVID pneumonia, improving radiographic findings, promoting a seronegative conversion, and shortening disease course [2]
    - No severe adverse events were noted in these patients[2]
    - In vitro studies in vero cells derived from kidney cells of African green monkey Showed anti-viral activity of both chloroquine and hydroxychloroquine to decrease viral replication in a concentration dependent manner with hydroxychloroquine having more potent antiviral activity over chloroquine[5]
- **Guideline Recommendations:**
    - China - the national guideline recommends using chloroquine at 500mg PO BID for mild, moderate, severe cases of COVID for no more than 10 days [8]
    - Netherlands -the Centre of Disease Control (CDC) recommended to offer chloroquine as an option for severe infections that require admission to hospital and oxygen therapy or ICU admission. The recommended dose is 600mg PO X 1 on day 1 followed by 300mg PO at 12h then 300mg PO BID for a total of 2-5 days. The Dutch CDC,however, still recommends supportive management as a reasonable treatment option as well[10]
    - Italy - Italian Society of Infectious and Tropical disease (Lombardy section) also recommends use of chloroquine and hydroxychloroquine in COVID patients with mild respiratory symptoms and comorbidities and COVID patients with severe respiratory failure. They recommend the use of chloroquine 500mg PO BID or hydroxychloroquine 200 mg daily for 10 days, with duration variation of 5 to 20 days based on clinical severity[10]
- **Side Effects:**
    - Photosensitivity (reduce by taking at bedtime)
    - Nausea, vomiting
    - Retinal toxicity (long term use)
    - Cardiomyopathy
    - Pancytopenia
    - Hepatotoxicity
    - Extrapyramidal reaction
- **Cautionary measures for chloroquine:**
    - Monitor for anemia, thrombocytopenia or leukopenia

- Monitory for electrolyte abnormalities
- Monitor for hepatic and renal dysfunction
- Recommended routine ECG to rule out QT prolongation or bradycardia
- Avoid concurrent administration with other QT prolonging medications

- **On-going trials**
  - Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV). Trial Link
  - Raoult et al. in France. 24 patients with coronavirus. 75% had repeat negative RT-PCR after hydroxychloroquine 600 mg po daily for 6 days compared to 10% in the control group

3. Tocilizumab

- Actemra (Roche) or Kevzara (Sanofi, Regeneron)
- Approved by FDA for rheumatoid arthritis
- **Mechanism of action**
  - Humanized monoclonal antibody
  - Specifically binds soluble and membrane bound IL-6 receptor to inhibit signal transduction and resultant inflammation
  - Cytokine storm may occur with COVID-19 infection, resulting in the release of cytokines, including IL-6,, IL-12 and tumour necrosis factor alpha
  - Interfering with IL-6 may be a therapeutic target in severe, critical COVID-19
- **Indications**
  - Severe COVID-19[12]
    - Respiratory rate $\geq$ 30 breaths/minute
    - SpO2 $\leq$ 93% while breathing room air
    - PaO2/FiO2 $\leq$ 300 mmHg
  - Critical COVID-19[12]
    - Respiratory failure requiring mechanical ventilation
    - Shock
    - Combined with other organ failure requiring ICU admission
  - Initial phase with high viral load (afebrile for > 72 hours and/or after at least 7 days after onset of symptoms)[13]
  - Elevated IL-6 > 40 pg/mL *or* elevated d-dimer and/or /ferritin and/or fibrinogen[13]
- **Contraindications**[13]
  - Age < 18
  - AST/ALT 5 times upper limit of normal
  - Neutrophils < 500 cells/mmc
  - Platelets less than 50,000 cells/mmc
  - Documents sepsis from pathogens other than COVD-19
  - Presence of related comorbidities, according to clinical judgement, to a poor outcome
  - Complicated diverticulitis or intestinal perforation

    - Cutaneous infection
    - Anti-rejection immunosuppressive therapy
    - Caution in pregnancy. There is placental transfer starting at 16 weeks gestation, with higher levels accumulating towards the end of pregnancy
- **Dose**
    - Chinese pilot study[12]
        - 400 mg intravenously as a single dose. Consider repeating once 8-12 hours after if no clinical response
    - Italian guidelines[13]
        - If < 30 kg, 8 mg/kg (maximum dose 800 mg) over 60 minutes
        - If > 30 kg, 12 mg/kg over 60 minutes
        - Second infusion 8-12 hours after initial infusion
        - If partial or incomplete clinical response, consider third infusion 16-24 hours after initial infusion
        - After 24 hours from last infusion, repeat IL-6 and/or d-dimer
        - Recommended dose rounding:
            - 50-60 kg: 400 mg
            - 61-85 kg: 600 mg
            - Over 86 kg: 800 mg
    - Dosing adjustments required for hepatic impairment
- **Adverse effects**
    - Increased ALT/AST
    - Neutropenia
    - Thrombocytopenia
    - Injection site reaction
    - Upper respiratory tract infections
    - Nasopharyngitis
    - Headache
    - Hypertension
- **Evidence**
    - A retrospective Chinese pilot study of 21 patients with severe or critical COVID-19[12]
        - Patients were treated with tocilizumab 400 mg iv once and standard care (lopinavir, methylprednisolone, oxygen therapy)
        - The use of tocilizumab was associated with normalization of fever, improvement in oxygen saturation, improvement in chest CT, normalization of lymphopenia, decreased CRP
- **On-going clinical trials**
    - A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19). Trial Link
    - Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019-A Multicenter, Randomized and Controlled Clinical Trial Study Trial Link

- Phase 2 and 3 trial in USA

4. Remdesivir

- Developed in 2016 to treat Ebola virus[14]
- In 2017, remdesivir was found to have activity against coronavirus family of viruses[15]
- Available for compassionate use from the manufacturer, Gilead (compassionateaccess@gilead.com)
- **Mechanism of action**
  - Pro-drug of an adenosine triphosphate analog that inhibits RNA polymerase
  - By incorporating into RNA, additional nucleotides cannot be added and results in termination of RNA transcription
  - Has activity against RNA virus families including Filoviridae, Paramyxoviridae, Pneumoviridae and Orthocoronavirinae
  - Viruses with mutations in RNA polymerase may develop partial resistance
- **Dose**
  - 200 mg loading dose on day 1 then 100 mg po daily for 9 days
    - This is the dose used in trials for Ebola, and the dose being used in clinical trials[16]
- **Evidence**
  - In-vitro study showed remdesivir to be active against clinical isolate of SARS-CoV-2 in human cell line[18]
  - Case report of patient in the United States with confirmed COVID-19 improving after one day with remdesivir[19]
  - Reduces severity of disease, virus replication and damage to lungs in rhesus monkeys infected with MERS-CoV[20]
- **On-going clinical trials**
  - A list of US clinical trials on remdisivir efficacy and safety in COVID treatment
  - A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults Trial Link
  - A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment Trial Link
  - A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe COVID-19 Trial Link
  - A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe 2019-nCoV Respiratory Disease. Trial Link
  - A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Mild and Moderate 2019-nCoV Respiratory Disease. Trial Link

- A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults Trial Link

5. Lopinivir/ritonivir

- Kaletra (AbbVie)
- **Evidence**
  - A randomized controlled trial found no benefit of lopinir-ritonivir compared to standard care in patients with severe COVID[21]

Other treatment-related information

1. NSAID use

- **Recommendation:** NSAIDS may be used with caution in patients without contraindications. Use acetaminophen preferentially over NSAIDs.
- **Background**
  - Coronaviruses bind to their target cells through ACE2 and ACE2 can be increased by ibuprofen. A letter in *Lancet Respiratory Medicine* by Fang *et al.* proposed that NSAIDs may worsen COVID[22]
  - There is currently no scientific evidence establishing a link between ibuprofen and worsening of COVID-19
  - The WHO does not recommend against the use of NSAIDS[23]

2. ACEi/ARB use

- **Recommendation 1:** Patients with hypertension, heart failure or ischemic heart disease *should not* stop taking ACE inhibitors, ARBS or angiotensin receptor neprilysin inhibitors.
  - There is no clinical data that ACEi and ARB therapy increases the risk of COVID-19[24]
  - This recommendation is supported by Hypertension Canada[26] Canadian Cardiovascular Society[27]
- **Background**
  - Coronavirus binds to target cells through ACE2
  - A letter in *Lancet Respiratory Medicine* by Fang et al. proposed that ACE inhibitors and ARBs could increase the risk for developing severe COVID-19 because ACE2 expression is increased when patients take ACEi or ARBs[22]
  - There is no clinical data to support the hypothesis that RAAS blockers could increase the ability of the virus to enter the lungs
  - ACE inhibitors and ARBs were shown to upregulate ACE2 in animal studies *but* upregulation was not seen in limited human studies

- **Recommendation 2:** It is unknown if ACEi and/or ARBs should be started during COVID-19 infection
- **Background**
    - Coronavirus binding to ACE2 leads to downregulation of ACE2
    - ACE2 is responsible for converting angiotensin to angiotensin 1-7, a vasodilator and anti-inflammatory heptapeptide
    - Decreased levels of ACE2 also allows for angiotensin II binding to AT1R, leading to vasoconstriction and increased lung permeability and increased lung injury
    - Elevated ACE2 levels may occur with prolonged ARB use, which may result in blocking excessive angiotensin-mediated AT1R activation and increasing production of angiotensin 1-7 with a COVID-19 infection
    - However, there is no clinical data to support this
    - **Ongoing clinical trial:**
        - Randomized Controlled Trial of Losartan for Patients with COVID-19 Requiring Hospitalization Trial Link

POTENTIAL COVID-19 THERAPIES (medicines) IN THE PIPELINE

Drug/ Therapy	Type	Mode of Action	Data Supporting Use	Clinical Trials
Remdesivir	Adenosine nucleotide analogue	Inhibits viral replication	* Broad-spectrum antiviral activity effective against SARS & MERS * Human safety trials already done	**YES** China: ongoing USA: ongoing
Camostat Mesilate	Protease inhibitor	Blocks enzyme (protease) needed by virus for maturation & entry into cells	Blocked entry of SARS-CoV-2 into lung cells *in vitro*	**NO** Approved in Japan to treat pancreatic inflammation
Lopinavir (LPV) & Ritonavir (RTV)	Protease inhibitor	Blocks enzyme (protease) needed by virus for cellular entry	* Effective against SARS-CoV-1 infection both *in vitro* & in patients * Less/not effective against MERS	(see below) Approved for use against HIV-1
Interferon beta (IFNb) + LPV/RTV		INFb alters host inflammatory response to inhibit virus replication		**YES** Saudi Arabia: ongoing MIRACLE trial (for use against MERS) China: ongoing against SARS-CoV-2
Ribavirin + IFN	Guanosine nucleotide analogue	Inhibits viral replication	Broad-spectrum anti-viral previously tested against MERS with mixed results	**NO** Approved for use against RSV and Hepatitis C
Hydroxychloroquine	4-aminoquinoline	Not fully resolved	* Inhibits infection of cells by SARS-CoV-2 *in vitro*	**YES** China: ongoing Approved to treat/prevent malaria
Actemra (Roche) **or Kevzara** (Sanofi, Regeneron)	IL-6 inhibitors		Reduced fevers & need for supplemental oxygen for COVID-19 patients	**YES** China: ongoing USA: starting phase 2/3 Approved by FDA for arthritis
Umifenovir	Fusion inhibitor	Inhibits fusion between viral & cellular membranes	Antiviral activity against several other coronaviruses	**YES** China: ongoing Approved in Russia & China for influenza
Favipiravir	RNA polymerase inhibitor	Inhibits viral RNA-dependent RNA polymerase	Broad-spectrum antiviral against influenza, arenavirus, bunyavirus & filovirus	**YES** China: ongoing Thailand: starting phase 2 Approved in Japan for influenza
Drug candidates blocking SARS-CoV-2 specific protease	Protease inhibitor	Blocks an enzyme (protease) needed by the virus for infectivity	Because the protease these drugs inhibit is not found in humans, hope for drugs with high potency & low side effects	**NO**
SARS-CoV-2 specific antibodies	Antibody	Bind to virus & block infection; bind to infected cells & signal the immune system	Sera from SARS patients inhibits SARS-CoV-2 entry into cells *in vitro*	**NO** Labs in Germany & USA working on recovering antibodies from recovered SARS & COVID-19 patients

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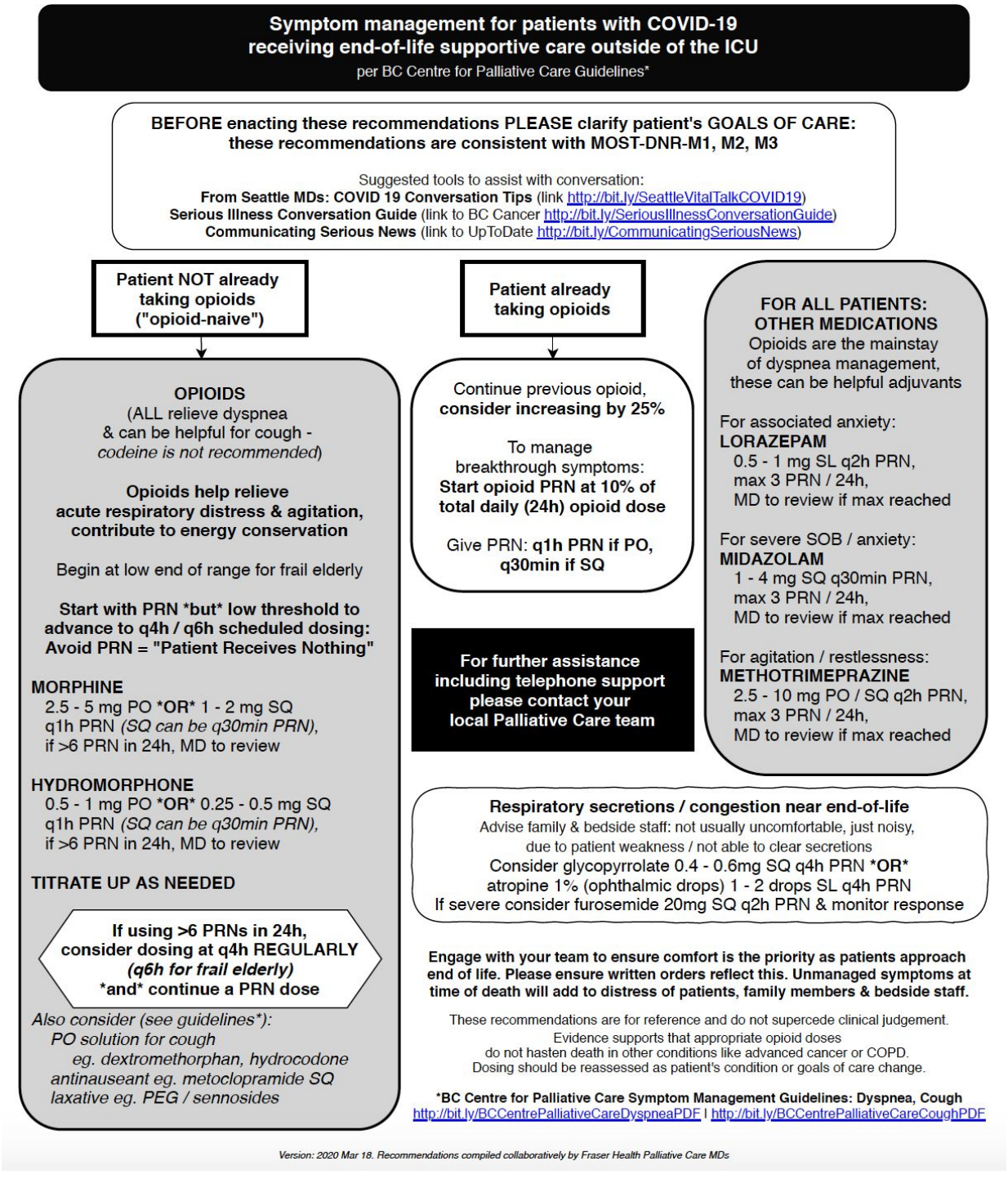
VIII. Supplementary Materials

End-of-life Care in COVID



Hospital Specific Links

1. Royal Columbian Hospital: RCH COVID Information
2. Vancouver General Hospital: VGH COVID Information
3. St. Paul's Hospital: SPH COVID Information