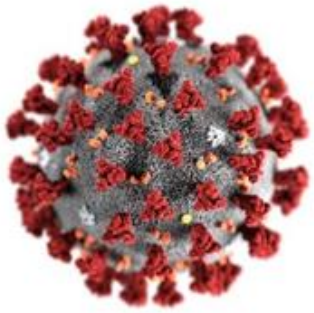
McMaster University

COVID–19



Survival Guide - 1st Edition
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Foreword to the 2020 First Edition
Dr. Hira Amir along with the staff physicians are pleased to contribute to the McMaster Internal Medicine Survival Guide for their peers.
Thank you to the staff physicians for their dedicated time and invaluable help in contributing and editing the content and updates: Dr. Ally Prebtani, Dr. Roman Jaeschke and Dr. Zain Chagla.
We would also like to acknowledge and thank Dr. Jim Douketis for his input on the thrombosis & coagulopathy sections.
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1.0 Epidemiology

1.1 Demographic Distribution

- A novel coronavirus COVID-19 (Corona Virus Disease-2019), identified as cause of pneumonia cases in Wuhan, Hubei Province of China, late 2019
- Outbreak began in China but has since spread to many other countries; it was officially declared by WHO to be a pandemic on March 11, 2020
- Cases in all continents, except Antarctica, are steadily rising in many countries

1.2 General Modes of Transmission for Respiratory Infections

- Droplets – small droplet particles with microbes > 5-10 μm in diameter which usually fall within 2meters/6 feet distance
- Airborne/Aerosol – microbes within droplet nuclei, smaller < 5 μm in diameter which remain in the air for extended time and disseminated at > 1meter distance

1.3 Route of Transmission for COVID-19

- Initial mode of transmission: Zoonotic (seafood market)
- Current mode of transmission: Person-to-person mainly via respiratory droplets (resembles Influenza spread) & less likely airborne/aerosol except in certain circumstances eg. Intubation, BIPAP/CPAP ventilation, bronchoscopy,etc
- In poorly ventilated, close contact settings, particularly with heavy exertion and singing, predominant aerosol transmission events have occurred
- SARS-CoV-2 RNA has been detected in blood & stool specimens. Live virus has been cultured in stool, according to a joint WHO-China report, fecal-oral transmission is not a significant factor for the disease spread

1.3.1 Factors for Viral Transmission

- Two parameters that assist to quantify the estimate of viral transmission rate are as follows (understanding their limitations):
    1. *Basic reproduction number (R_0)*
        - the average number of 2º infections by a typical case in a population where <u>everyone is susceptible</u>
        - R_0 is affected by
            - Rate of contacts in the host population
            - Probability of infection being transmitted during contact
            - Duration of infectiousness
        - $R_0 > 1$ leads to increased number of cases for an epidemic to occur in a susceptible population
    2. *Effective reproductive number (R_e)*
        - Average number of 2º infections per case in a population made up of <u>BOTH susceptible and non-susceptible hosts</u> due to immunity from past infection, vaccines, and other interventions. Hence, not all contacts will become infected and the average number of 2º cases per infectious case will be < than the R_0
        - R_e can be used as a parameter to assess the effect of vaccination, immunity from past infection, other interventions in a given population
        - If $R_e > 1$, the number of cases will increase, such as at the start of an epidemic & If $R_e < 1$ results in a decline in the number of cases

- The R_e can be estimated by the product of the R_0 and the fraction of susceptible host population
- To successfully eliminate a disease from a population, $\mathbf{R_e}$ must be < 1

1.4 Incubation Period

- The incubation period is within 2 weeks after exposure. The median incubation period is estimated to be 5.1 days. 97.5% will develop symptoms within 11.5 days of exposure

1.4.1 Asymptomatic and Pre-symptomatic Transmission

- Pre-symptomatic Case - an individual who has COVID19 infection but does not exhibit symptoms at the time of testing/diagnosis however, exhibit symptoms *later* during the course of infection
- Asymptomatic Case – an individual who has COVID 19 infection, who *does not* exhibit symptoms during the course of the infection
- Viral shedding in the upper respiratory tract during the incubation period has been associated with asymptomatic transmission in many individuals (median of 8 days versus 19 days in symptomatic individuals). Peak infectiousness seems to be *at one day* preceding symptoms with maximum viral load
- Distinction between asymptomatic and pre-symptomatic cases can be difficult

2.0 Viral Classification

- Coronaviruses belong to a family within *Nidovirale* order that use a nested set of mRNAs to replicate
- The virus family has four genera: alpha, beta, gamma and delta; human coronavirus is in two of these genera – alpha and beta coronaviruses
- Pathogen is a beta coronavirus that has characteristics similar to the agents of SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome)
- Designated as SARS-CoV-2 (severe acute respiratory syndrome corona virus 2)
- Coronavirus uses ACE-2 receptors for human cell entry

3.0 Clinical Presentation

3.1 History

- Common/typical symptoms: Fever, dry cough, myalgias, anorexia, fatigue and dyspnea
- Clinical evidence of pneumonia
- Less common symptoms:
    - Other URTI symptoms: Sore throat, rhinorrhea/nasal congestion (without another explanation e.g. allergic rhinitis, post-nasal drip)
    - Anosmia/taste disturbances
    - Headache
    - GI symptoms: nausea/vomiting/diarrhea/abdominal pain
- Moderate to severe disease: Hemoptysis and dyspnea
- Patients may report exposure to infected individual, travel to an area of outbreak, or recent travel (within 2 weeks) to widespread infection area
- Many without travel history

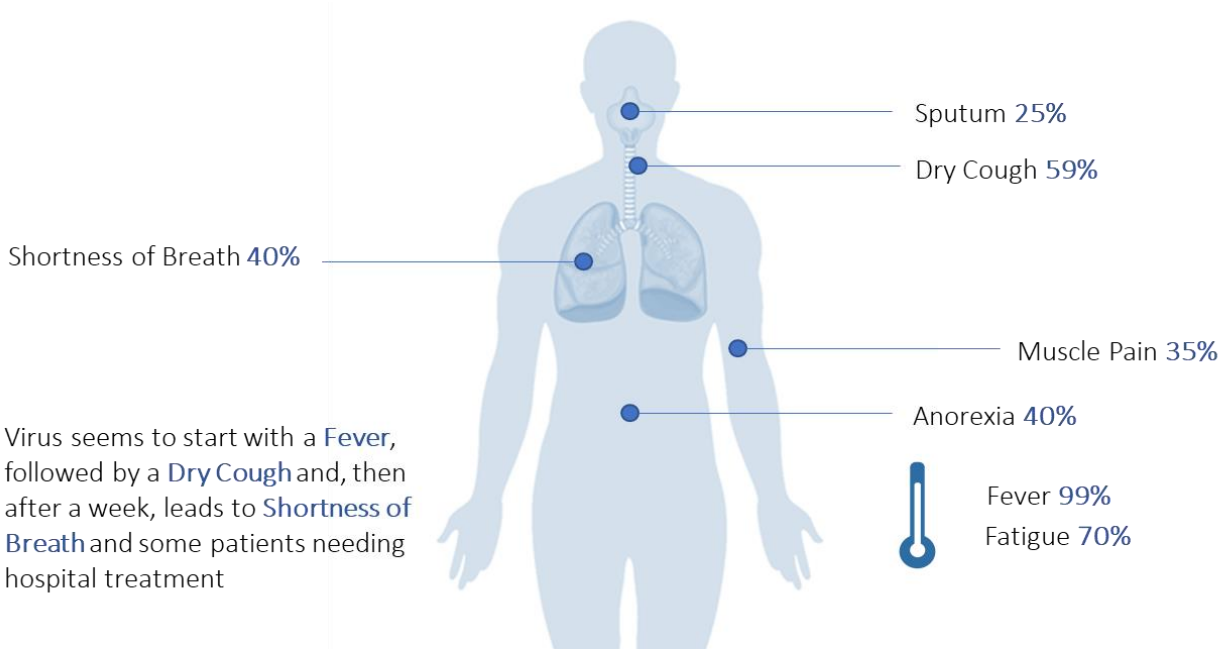

Figure 1: Symptoms of Covid-19

3.1.1 Atypical clinical presentation

Children, elderly and individuals with developmental disability can present with atypical signs and symptoms in COVID 19, listed as follows:

Atypical symptoms	*Atypical signs*
• Unexplained fatigue/malaise/chills • Croup (hoarseness) • Conjunctivitis • Headaches • Falls • Delirium • Acute functional decline • Worsening of pre-existing chronic medical conditions • Multisystem Inflammatory Syndrome in Children & Adolescents* (Kawasaki Disease overlap; causal effect not proven yet)	• Unexplained tachycardia • Hypotension • Unexplained hypoxemia (O2 Sat <90%) • Lethargy and difficulty feeding in infants (if no other diagnosis)

3.1.2 Multisystem Inflammatory Syndrome (MIS-C)*

a) Children and adolescents of 0 – 19 years with fever for >/= 3 days **AND** 2 of the following:

a. Rash or bilateral non-purulent conjunctivitis or mucocoutaneous inflammatory signs (oral/hands/feet)
b. Hypotension/Shock
c. Features suggestive of Myocardial dysfunction, percarditidis, valvulitis or coronary abnormalities (ECHO findings/elevated Troponins/NT-proBNP)
d. Evidence of coagulopathy (by PT, PTT, elevated D-Dimers)
e. Acute gastrointestinal complaints (Nausea/vomiting/Diarrhea)

AND

a. Elevated inflammatory markers (CRP, ESR)

AND

a. No other obvious microbial cause of bacterial sepsis, staphylococcal or streptococcal shock syndromes

AND

a. Laboratory evidence of COVID 19 infection (RT-PCR, antigen test or postive serology) OR likely contact with COVID 19 patients

NOTE: Consider MIS in children with typical or atypical Kawasaki Disease or Toxic Shock Syndrome

3.2 Physical Examination

- General: Severe disease – tachypnea, laboured breathing and cold clammy skin
- Vital signs: tachycardia, hypotension, fever (often 39°C); Children and elderly can present with hypothermia
- Indicators of Severe disease: Hemodynamic shock (Hypotension, tachycardia and cold clammy extremities), respiratory distress and ARDS

4.0 Spectrum of Disease Severity

- This viral illness has varied clinical course and ranges from asymptomatic to symptomatic respiratory illness and severe ARDS
    - Mild (none or mild pneumonia) 81%: non-specific clinical presentations including fever, cough ± dyspnea, sore throat, myalgia/fatigue and headache. Children and elderly can present with atypical signs/symptoms
    - Severe Disease 14%: Dyspnea (RR > 30/min), Hypoxemia (SpO2 < 90% on room air) or > than 50% lung involvement on CT imaging within 1 to 2 days
    - Critical Disease 5%: Respiratory failure, ARDS, shock and multi-organ dysfunction
- Overall global case fatality rate (CFR) among those diagnosed is about 5% and ranges from 1-14% (varies with asymptomatic case detection, time & region)
- Currently in Canada, the CFR is 7%
- Data on Infection Fatality Rate (IFR) is unknown due to likely many undiagnosed cases

5.0 Risk Factors for Disease Severity

Most of the fatal/severe cases were reported in patients with following clinical risk factors:

- Advanced age
- Cardiovascular disease
- Diabetes Mellitus
- Chronic lung disease
- Hypertension
- Malignancy
- Immunosuppression
- Smoking status
- Cerebrovascular disease/Stroke
- Obesity
- Black ethnicity
- Male Gender
- Blood group A
- Chronic Kidney Disease
- Sickle cell Disease
- Pregnancy

- Children with congenital heart disease
- Children with complex medical conditions (genetic, neurologic, metabolic)

6.0 Risk Assessment Tool

A Risk Assessment Tool (http://118.126.104.170/) to predict ICU admission, invasive ventilation or death has been developed in China taking into account several variables (age, clinical factors, laboratory investigations & CXR findings) for predicting severity of COVID-19 infection. These were studied primarily in the population in China with a relatively small cohort.

The 4C mortality score recently proved that the high risk patient factors such as age, gender, respiratory rate, comorbidities, CRP, Urea levels, peripheral O2 saturation and level of consciousness (GCS) can be utilized as a reliable tool for stratifying risk of hospital admission and in-hospital mortality. (https://www.mdcalc.com/4c-mortality-score-covid-19)

7.0 Diagnostic Investigations

7.1 Most Accurate Tests

PCR or RT-PCR

- NPS of respiratory tract specimens of non-intubated patients
    - Technique is important, video link of how to perform: https://www.nejm.org/doi/full/10.1056/NEJMvcm2010260?query=RP
- Non-induced Sputum & endotracheal aspirates (ETAs) or BAL of intubated patients

Pearls:

- ***NPS SN 90-95% within first 5 days of symptom onset (URTI) and SN 70% 5-7 days after symptom onset with illness progression & pneumonia (LRTI)***
- ***Sputum, BAL & ETAs: SN increases after 5-7 days with illness progression and pneumonia (LRTI) while NPS SN decreases***

Recent Evidence:

- Postive PCR specimens are unable to culturally grow the viable virus after 5 to 7 days of symptom onset/or post testing
- Most secondary cases occur after 5-10 days of symptom onset in primary cases, highlighting that primary cases are no longer infectious after 10 days of symptom onset
- No transmission has been confirmed after 14 days of symptoms from primary cases

Serologic Testing

- Possibly explains the vital role of cellular immunity in addition to a humoral immune response. Antibody (IgG) response may develop approximately 7 – 14 days after symptom-onset with some individuals with no response
- Duration of antibody response is not well established but some studies show detectable antibodies from 40 days up to 7 months post-infection, with higher levels in patients with more severe disease
- Positive titers DO NOT necessarily confer immunity for a second infection

- Serology tetsing is currently not licensed for the diagnosis, infectivity or recovery from COVID 19 but may be useful in epidemiologic studies of prior infection
- Serology testing maybe used clinically as an adjunct to the PCR testing in pediatric population with suspected MIS with a negative, inconclusive or indeterminant PCR test result or who did not undergo the PCR testing
- **Interpretation**
    - Positive IgG test: recent/prior COVID 19 infection (FP due to cross reaction from past infection with other human coronaviruses e.g., SARS-CoV-1)
    - Negative IgG test: Does NOT r/o current or past infectivity with SARS-CoV-2. (High clinical suspicion – repeat IgG testing in 2 – 3 weeks)
    - Inconclusive IgG test: Occurs when IgG levels too low or from non-specific binding of antibody to the antigen. (High clinical suspiscion – repeat IgG testing in 2 – 3 weeks)

Rapid Diagnostic Antigen Tests

- Measure external antigen to COVID-19 – usually through lateral flow assays. Has advantage of more rapid and point of care testing, however, sensitivity is compromised – the Abbott PanBio is approved in Canada, and has a sensitivity of 70-75%, with specificity of 95%.
- Can't be used for treatment and management decisions - Provides preliminary results ONLY
- Can't be used as a donor screening test for SARS-CoV-2

7.2 Laboratory Tests

Following laboratory results can be related to worse outcomes:

- CBC (leukopenia, lymphocytopenia, thrombocytopenia)
- Elevated inflammatory markers (CRP, LDH and Ferritin)
- Elevated serum aminotransferase levels (AST, ALT)
- Elevated CK & troponins
- Elevated prothrombin time (PT)/INR
- Normal serum Procalcitonin levels, despite pneumonia (limited availability)
- High D-Dimers
    - Although D-dimer level not predictive of VTE, do not forget PE/DVT if clinical suspicion high

NOTE: High D-dimers + Lymphopenia = ↑ Mortality (due to cytokine release or thrombotic phenomena)

7.3 Chest Imaging

- CXR – features consistent with viral pneumonia (*bilateral ground glass*); 50-60% have normal CXR early on in illness
- CT scan – (SN 97%, SP 25%) ground glass opacification with or without consolidation; mostly B/L lung involvement with predilection to RLL; peripheral > central

7.4 Routine Monitoring

Patients should be monitored for the following parameters during the acute phase of hospitalization:

- Vitals: BP, HR, RR
- Pulse oximetry for SpO2
- Quick Sequential Organ Failure Assessment (qSOFA)
  - *SBP < 100, RR > 22, Altered Mental Status GCS < 15*
- Myocardial dysfunction
- Clinical worsening to respiratory failure often on *day 4-5* post-symptom onset

7.5 Guide to COVID 19 Testing

Four important considerations before ordering COVID-19 only testing versus Full Respiratory Viral Panel are as follows:

1. Type of symptoms – typical or atypical, mild or severe
2. Type of patient – healthy patients without comorbidities or immunocompromised patients or with comorbidities
3. Inpatient or outpatient
4. Symptomatic or Asymptomatic

7.5.1 Full Viral Respiratory Panel	Full Viral Respiratory Panel
a) Typical Symptoms ○ All inpatients/or being admitted	**b) New Atypical Symptoms-unexplained** ○ All inpatient and out-patient if: i) Immunocompromised ii) Co-morbidities iii) Neonates < 3mo iv) From respiratory outbreak ward with unknown pathogen
Rationale: Impact antibiotic choices with influenza treatment decisions requiring admission for resp concerns and virus identification in outbreak facilities for outpatients	

7.5.2 COVID ONLY Test	COVID ONLY Test
a) Atypical/Mild symptoms ○ Healthy patients ○ Outpatients/Being discharged: v) HCW and house-hold contacts of HCW vi) Residents or working in communal settings (LTC/shelters/remote and indigenous communities et…c) vii) Essential workers viii) Cross-border workers *Most low risk outpatients do not require testing for COVID 19 or NPS*	**b) Asymptomatic individuals** ○ From LTC or ward with COVID 19 outbreak ○ Neonates whose mom COVID 19 +ve ○ Request by IPAC for contact racing/outbreak management ○ Chronic AGMP on D8 to D14 to consider stopping N95 use ○ Screen 24-48 hrs before planned AGMP if indicated* ○ Transfer to or from LTC* **These asymptomatic patients do not need isolation*
Rationale: Knowing COVID 19 status has public health and IPAC implications	

7.6 COVID 19 Testing Guidance & Clearance or Transfer – New Trends

The following changes have been made in testing protocols for COVID 19 positive patients by Public Health Ontario

- COVID 19 positive patients who have been cleared via a symptom-based approach ie. *symptom improvement for 24 hours and 10 days after symptom onset or negative testing for asymptomatic* will NO LONGER require additional isolation precautions and repeat testing
- COVID 19 postive individuals being transferred to congregate settings or LTCF, who have already been cleared via symptom-based approach DO NOT require repeat testing before transfer
- Individuals who are candidates for transfer to LTCF or congregate settings, who have never had COVID 19 will CONTINUE to be tested prior to transfer

8.0 Diagnostic Criteria

Case definitions by MOH Ontario as of May 11, 2020 for COVID 19

8.1 Probable Case

b) A person (who has not had laboratory test) with symptoms compatible with COVID 19 **AND**:
   a. Travelled to an affected area in 14 days prior to symptom onset; **OR**
   b. Close contact with a confirmed case of COVID 19; **OR**
   c. Lived in or worked in a facility with an outbreak of COVID 19 (e.g., LTCF, prison)

OR

c) A person with symptoms compatible with COVID 19 **AND** in whom laboratory diagnosis of COVID 19 is inconclusive

8.2 Presumptive Confirmed Case

a) Based on evolving situation with symptoms compatible with COVID 19 there is no longer a presumptive confirmed case definition for surveillance purposes

8.3 Confirmed Case

b) A person with laboratory confirmation of COVID 19 infection using a validated assay, consisting of positive nucleic acid amplification test (NAAT; e.g. real time PCR or nucleic acid sequencing) on at least one specific genome target

The case definitions should be followed according to country's epidemiologic data

8.4 Contact

a) A close contact is defined as follows:
   a. A person who has provided care for the patient, including healthcare workers, family members or other caregivers; **OR**
   b. A person who had other similar close physical contact; **OR**
   c. A person who lived with or had otherwise close, prolonged contact with a probable or confirmed case while the case was ill

9.0 Differential Diagnosis

Most common overlapping diagnoses are:

- Influenza
- Common cold
- Other viral pneumonia (parainfluenza, metapneumovirus…)
- Bacterial & Fungal pneumonia (Mycoplasma Pneumoniae, PJP/PCP)

Pearl: As COVID – 19 cannot often be differentiated from other pneumonias, travel or contact history remains an important risk factor

10.0 Treatment

10.1 Goals

- Adequate oxygenation and hemodynamic stability during acute phase of COVID – 19

10.2 Disposition

10.2.1 General criteria for Hospital Admission	10.2.2 General criteria for ICU Admission
• Non-severe pneumonia – Radiographic evidence of pneumonia; worsening clinical status • Risk factors for severe disease • Inadequate care at home • Inability to isolate at home	• Severe Pneumonia – WHO criteria ○ Tachypnea (resp. rate > *30* breaths per min), severe respiratory distress, inadequate oxygenation (e.g., FIO2 > 0.50 & *spO2 </=93%*) • Presence of severe complications – septic shock, ARDS

10.2.3 Specialist Referral

- All patients should be managed in consultation with public health authorities
- Consider Infectious disease specialist consult to coordinate diagnosis and management
- Respirologist/Intensivist to help in collecting deep specimens for Dx and managing mechanical ventilation if necessary, *using strict airborne protection precautions while obtaining airway specimens and during intubation*
- Critical care MD to help in fluid management, mechanical ventilation, and hemodynamic support as needed
- Consider enrolling in a research trial if available

10.3 Treatment options

10.3.1 Potential Specific Therapies

Multiple drugs/therapies are or have undergone Clinical trials for COVID-19 treatment:

1. Approved therapies:
    - Dexamethasone
    - Remdesivir
    - Monoclonal antibodies
    - Baricitinib
2. Therapies still undergoing clinical trials:
    - Convalescent Plasma
    - Tociluzimab – mixed benefits amongst studies
    - Inhaled interferon
    - Full dose anticoagulation
    - ACEI/ARBs
    - Vitamin D
    - Colchicine
    - DPP-4 Inhibitors
3. Therapies with no benefit:
    - Lopinavir Ritonavir
    - Hydroxy/Chloroquine
    - Systemic Interferons

Investigators at centers interested in becoming ACTCOVID-19 Sites or for more information (COVID-19 Clinical Trial at McMaster), email ACT.ProjectTeam@phri.ca

RECOVERY Trial – Dexamethasone arm:

- For details, see section on "*Role of Corticosteroids for Severe COVID 19 Infection"*

ACTT-Trial results for Remdesivir:

- Recommended use for 5 days in patients at early stages of severe COVID 19 (those with GFR < 30mL/min were excluded from studies)

- Improved recovery times in patients on supplemented oxygen but not in the subgroup of intubated patients
- Longer follow-ups needed to measure benefits in mechanically ventilated patients
- No signficant difference in mortality rates than placebo group (the absolute difference 7.1% versus 11.9% was still not statistically significant)
- No substantial difference in adverse events between the Remdesivir and the placebo group: Anemia, Acute Kidney Injury, Pyrexia, Hyperglycemia, Elevated liver enzymes

SOLIDARITY interim trial:

- Trial results (Oct 2020) showed that all 4 treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had LITTLE or NO effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients. Solidarity Trial investigators interrupted the trials with immediate effect.

10.3.2 Management of Mild COVID - 19 Disease

- Do not hospitalize the patients with mild illness
- Provide Symptomatic treatment e.g. antipyretics for fever (acetaminophen preferable over NSAIDs) prn
- Counsel the patient for the signs/symptoms of severe disease and that they should seek urgent hospital care
- Education on home isolation and reporting to public health

10.3.3 Management of Severe COVID–19 Disease

- Supportive therapy
- Immediate supplemental O2 therapy (target 92-96%; if CO2 retainer, then 88-92%)
    - Nasal cannula up to 6L/min (non-humidified low flow)
    - Venturi or Non-Rebreather Mask FIO2 up to 0.50 or 10L/min
        - If above methods fail to maintain adequate oxygenation, low threshold for consultation with respirology or critical care for potential use of HFNC (High Flow Nasal Cannula Oxygen) or NIV (Non-Invasive Ventilation) in proper ventilation rooms or endotracheal intubation by experienced operator using strict airborne protection precautions
- Adults with signs of respiratory distress, shock and convulsions – Airway management and O2 therapy with SpO2 92-96%
- NIV (e.g. BIPAP/CPAP) and HFNC (e.g. Opti flow) use is evolving if negative pressure rooms and/or HEPA filters available (use without latter measures is associated with increased risk of aerosol exposure)
- Avoid fans & nebulized therapy due to risk of aerosolization
- Maintenance targets for Oxygen therapy
        - Adults– SpO2 target 92-96% in non-pregnant adults (88-92% if CO2 retainer)
        - Pregnant Patients - SpO2 target ≥ 92–95%
        - Children – SpO2 ≥ 94% during resuscitation and ≥ 90% once stable
- Link: Hypoxemia management flowchart

- Conservative/Cautious fluid management with balanced crystalloid (Normal Saline/Ringer's lactate) if without signs and symptoms of shock due to risk of pulmonary edema
- Use norepinephrine as first-line vasoactive agent for shock. Vasopressin or epinephrine can be used as an alternative if norepinephrine not available and if fluid administration does not achieve adequate tissue perfusion (dopamine not recommended)
- Adding vasopressin as a second-line agent is suggested if the target (60-65 mmHg) mean arterial pressure cannot be achieved by norepinephrine
- In a recent UK randomized study (RECOVERY Trial), in COVID-19 patients, published in July 2020, Dexamethasone ***6mg iv/po for 10 days*** was found to lower the moratlity by one-third in ventilated patients and by one-fifth in patients on supplementary oxygen. Patients who were not on ventilatory support/oxygen did not benefit from Dexamethasone use.
- In order to prevent one death, 8 ventilated patients and 25 patients on supplementary oxygen need to be treated with Dexamethasone
- Consider Remdesivir use ***(5 or 10 days: 200mg iv on day 1 then 100mg iv daily for days 2 -10)*** for hospitalized patients with severe disease (requiring supplemental oxygen but not critically ill) - shown to improve recovery times according to ACTT -1 trial (in conflict with data from SOLIDARITY trial)

10.3.4 Management of Severe COVID–19 Disease and Co-Infections

- Treating co-infections
    - Broad spectrum antimicrobials – within one hour of presentation with sepsis
- Empiric antimicrobial therapy should be adjusted or discontinued based on clinical and microbiology results
- Consider empiric therapy with neuraminidase inhibitor (Oseltamivir/Tamiflu) for seasonal influenza for patients with influenza (dose could be given before the results are available)

10.3.5 Management of Critical COVID–19 Disease and ARDS

- Provide advanced oxygen and ventilatory support
- Perform Endotracheal intubation as needed, *using strict airborne precautions* with most experienced operator
- Implement mechanical ventilation using low tidal volumes (4-8 ml/kg estimated body weight) and lower inspiratory pressures (plateau pressure < 30 cm of H2O)
- Prone ventilation x 12-16 hours/day suggested in adult patients with severe ARDS
- Conservative fluid management for patients with ARDS without tissue hypoperfusion
- Careful PEEP application with attention to response and lung compliance
- in patients with moderate to severe ARDS – suggest use of intermittent neuromuscular blockade as needed rather than continuous use
- Use of Dexamethasone in COVID-19 patients on ventilatory or oxygenation support is widely utilized based on current data and incorporation into practice guidelines is pending; the balance of risks and benefits depending on the phase of the disease and its severity may still change;

- Glucocorticoids could also be considered in refractory shock or if indicated for other medical reasons (e.g. known adrenal insufficiency, rheumatic diseases, etc.)

10.3.6 Management & Prevention of Coagulopathy/Thrombosis – Thromboprophylaxis

- COVID 19 is a hypercoagulable state with increased risk of venous thromboembolism (VTE) and arterial thromboembolism (Venous > Arterial), ranging between 20-40% in hospitalized patients (2-3 x higher vs Influenza/ICU patients) despite receiving prophylactic doses of anticoagulation
- Similar pathogenesis as HIT & DIC
- Acute PE: a possible cause of right heart failure in critical disease. Consider acute cor pulmonale leading to obstructive shock in critically-ill COVID 19 patients
- All hospitalized COVID-19 patients should receive VTE prophylaxis (LMWH preferably)
- Avoid DOACs to prevent possible drug interactions with potential investigational COVID-19 drugs in critically ill and avoid warfarin
- Typical laboratory findings:
    - Increased D-dimer (4-6 x ULN)
    - Mild-moderate thrombocytopenia (100-150 x 10^9/L)
    - INR or prolonged PT (15-16 sec)
    - may also have mildly elevated PTT
    - Elevated fibrinogen levels

  Pearl: Repeat **every 2-3 days** for sick patients
- Thromboprophylaxis suggested dosing:
  Standard doses to be used in all patients, with following *suggested* adjustments (no RCT data)
    - Increase dose by 50% if EBW > 100kg or BMI > 30
        - For example, dalteparin 7,500 IU daily or enoxaparin 30 mg bid
    - Increase dose by 100% if EBW > 140kg or BMI > 40, D-dimer > 5,000 or additional risk factors e.g. prior VTE, active cancer, ICU admission
        - For example, dalteparin 5,000 IU bid or enoxaparin 40 mg bid or tinzaparin 10,000 IU daily
    - Empiric use of ***therapeutic-dose*** LMWH/UFH is appropriate if clinical/respiratory decompensation & diagnostic testing for suspected pulmonary embolism is problematic/difficult

End of Life Care (EOL) Discussions & Palliative Care

- Goals of care discussions should be done by the healthcare professional with the patients and their families during the **initial clinical encounter** with a sensitive and empathetic approach before the patient develops critical COVID-19 disease with increased mortality & potential lack of resources (ICU, ventilators…) in a surge status
- Usual recommendations for palliative care if patient deemed palliative

10.3.7 Special Populations

Patients with Cardiovascular Disease

According to Canadian Cardiovascular Society and Hypertension Canada (March 2020):

- Patients with confirmed or suspected COVID 19 infection should not stop taking ACEIs (angiotensin-converting enzyme inhibitors), ARBs (angiotensin receptor blockers or (ARNIs) angiotensin-receptor/neprilysin inhibitors for HTN and/or CHF since in general the benefits outweighs the risks unless justified medical events such as hypotension, AKI or hyperkalemia are present
- Patients on low-dose ASA for CVD should continue it unless advised by the responsible physician
- Acetaminophen is preferred over NSAIDS for fever & myalgias but if on NSAIDs, should consult with their doctor to decide if to continue or not
- Patients with CVD and CKD should take acetaminophen over NSAIDS to avoid deterioration in CV & renal status (CHF, HTN, AKI)

Safety of RAAS blockade (ACEI/ARB/ANRI) Use

- Several recent studies (observational) have shown no concerning harm issues:
  - NO correlation with COVID 19 infection risk
  - No increase in the severity of COVID-19 illness
  - Underlying cardiovascular disease is *independently* associated with severe COVID 19 illness leading to increased in-patient mortality
  - In fact, some studies show a beneficial effect, but this is still to be proven

Pregnant Women

- Pregnant women are at a higher risk for severe COVID19 illness with significantly higher ICU admission rate (2.5%) and mechanical ventilation (0.5%) as compared to non-pregnant women in one study. However, mortality rate shows no differences. Therefore, measures to prevent COVID-19 in this group should be a prime objective of care throughout pregnancy
- Pregnant patients receive same supportive care as non-pregnant adults
- In pregnant COVID19 positive women, consider corticosteroids if requiring oxygen support or mechanical ventilation (persistent SpO2 < 94%):
  - if needed for Fetal lung maturity (24-36 weeks GA) use Dexamethasone 6mg IM q12h x 4 doses over 2 days) then switch to Methylprednisone as below
  - if not needed for Fetal lung maturity, use Methylprednisone (32 mg/day PO or IV x 10 day course OR until discharge whichever comes first
- For breastfeeding women, use Methylprednisone (32 mg/day PO or IV x 10 day course OR until discharge (whichever comes first) – limited data on effects of dexamethasone in breastfeeding infants
- Determine mode of delivery by obstetrical indication and patient preference; caesarean delivery *only* recommended for medically indicated reason
- There is limited evidence to suggest significant vertical transmission from mother to neonate; Vertical transmission is a rare mode of transmission for COVID19
- WHO and SOGC suggestions for breast feeding in mothers who have or are suspected to have COVID 19
  - SOGC – if/when considering breast feeding, mother should follow strict hand and respiratory hygiene i.e., hand washing and wearing a mask. Cleansing of the breast/chest should be considered as well as maintaining good hydration status in the setting of fever has been recommended

- WHO - supports breast feeding within 1 hour of birth with strict protective measures before and after infant care as well as during feeding, in mothers with any symptoms suggestive of or proven COVID 19. These includes frequent hand washing with soap and water, wearing face masks, and routinely disinfecting all contact surfaces
- Mothers with severe COVID 19 should express breast milk for safe feeding of the neonate/infant if possible.
- One small recent study showed no virus in breast milk
- Limited evidence for the proven protective effect of SARS-CoV-2 antibodies in the neonates via breast milk;

Patients with HIV

- Recommendations for management of patients with HIV who develop COVID-19 do not differ from standard recommendations
- Empiric addition of lopinavir-ritonavir (for possible efficacy against or protection from SARS-CoV-2) is ***no longer*** recommended

Peri-Operative SARS-CoV-2 Infection

- Patients with COVID 19 in the peri-operative period carry *24% mortality risk* 30-days post-operatively mainly due to pulmonary complications, higher than expected vs pre-pandemic baseline rate
- Therefore, the threshold for surgical procedures should be even higher especially, in patients > 70 years of age, in men, patients with co-morbidities and those undergoing non-urgent major surgical procedures
- Consider non-operative treatment options or delay surgery if deemed non-urgent or nor time-sensitive

11.0 Complications and prognosis

11.1 Complications

- ARDS – most common
- Septic shock
- Acute Kidney Injury
- Myocardial Injury – Fulminant myocarditis, heart failure
- Neurologic Injury – complete/severe anosmia, encephalitis, myelitis, ataxia, large vessel strokes; ischemic strokes most common
- Secondary Infections – bacterial and fungal
- Multi-organ Dysfunction (liver, pancreas)
- Coagulopathy: Venous and arterial thromboembolism
- Multisystem Inflammatory Syndrome in Children and Adolescents

11.2 Prognosis

- Patients requiring ICU admission often have prolonged hospital stay, > 20 days
- Recovery of pulmonary infection in short and long term remains to be seen with time
- **> 50%** mortality if requiring ventilatory support (initial experience) but probably the numbers are lower with recent data but varies with region
- Mortality rate ranges between 2-3 % but varies by country, age and co-morbidities

- Advanced age continues to be most consistent predictor of mortality in ICU patients

12.0 Screening and/or Testing

12.1 Clinical Screening

- All returning travellers
- Anyone with symptoms & signs of suspicious of COVID-19
- Anyone with history of exposure/close contact with COVID-19 case

12.2 Low Threshold for Diagnostic Lab Testing for COVID-19

- Hospitalized patients
- Long-term care & Retirement home patients

- Other communal settings e.g. shelters, group homes, and jails
- Patients undergoing procedures with increased risk of aerosolization
- Essential workers (person working directly with the public) who have COVID-19 **symptoms or who have been exposed without protection**
- Healthcare workers or a household member of a healthcare worker who has **symptoms or who has been exposed without protection**
- Pregnant **women** in third trimester and have **symptoms or who have been exposed**

The recommendations for screening & testing are changing daily!

Pearl: *Anyone with a positive clinical screen or positive laboratory testing must be isolated*

13.0 Prevention

13.1 Specific Prevention

So far, several vaccines for COVID–19 are in phase 3 trials, pending approval for use. Interim analyses have shown to be promising with approximately 70-95% efficacy.

13.2 General Prevention

13.2.1 Advise to General Public

- If mild illness, stay home, call your doctor, public health agency, telehealth or fill online screening tool
- Practice physical distancing – avoid large and unnecessary gatherings; stay home except for critical needs – resupply food and medicine (stay at *2 meters* distance when in public)
- Greet without touching, nod instead of handshake and hugging
- Work from home if possible
- Frequent hand washing technique for at least 20 seconds with soap and water
- Use of alcohol-based hand sanitizer (> 60%) until next possible hand washing
- Cover your cough. Use the tissue and throw it away; second choice is sleeve not hand
- Avoid touching face
- **STAY AT HOME if possible**

Face Masks

- Non-medical/home made cotton face mask use in the community to reduce ongoing viral transmission. They are ***NOT a substitute*** for physical distancing!
- Use of non-medical face masks has ***not been proven*** to protect the person wearing it, but can be a measure to reduce the spread to others where it could be difficult to
- Eye protective shields in addition to face mask (increased protection) based on data

13.2.2 House-hold Members and Caregivers

- Wear face masks, gloves and gowns when caring for a patient with COVID-19,; remove and dispose upon leaving the room. DO NOT REUSE; wearing eye protection (face shields/goggles) provides enhanced protection and should be worn additionally
- Wash hands for at least 20 seconds after all contact; an alcohol-based hand sanitizer (at least 60% alcohol) is acceptable alternative to soap and water, if not available
- Do not share personal items such as towels, dishes, utensils before proper cleaning
- Wash laundry & high touch surfaces frequently; wear disposable gloves while handling dirty laundry
- Restrict contact to minimum number of caregivers

13.2.3 Healthcare Settings

- Provide the patient with a face mask and place the patient in a closed room
- Persons entering the room should follow standard contact and droplet precautions
- Follow infection prevention and control (IPC) guidelines and routine practices for preventing transmission of infection

Routine Practices

- Use of alcohol-based hand rub (> 60% alcohol) at point of care in healthcare settings
- Preference to single in-patient rooms with attached toilet and patient sinks
- Implementation of respiratory hygiene
- Use of simple respirator/N95 masks or disposable surgical masks in HCWs; according to a recent review, former is potentially more effective in *enhanced* prevention of viral transmission, particularly when high risk for aerosolization
- Eye protective shields in addition to face mask (increased protection) based on data
- Distance of 2 meters (6 feet) between a coughing patient with suspected COVID and another patient without infection
- Strategies for preventing infection spread while performing aerosol generating medical procedures (AGMPs) – enhanced PPE with standard transmission precautions
- Point-of-care risk assessments by healthcare workers before each patient interaction

13.2.4 Personal Protective Equipment – PPE

Definition

"Specialized clothing or equipment worn by an employee for protection against infectious materials" (OSHA)

Types of PPE in Healthcare Settings:

- Gloves – Hand protection
- Gowns/aprons – Skin and clothing protection
- Mask/respirators – Mouth and nose protection
    - Surgical/procedure masks for droplets
    - N95/respirator mask for aerosol risk
- Goggles – Eyes protection
- Face shields – Face with eyes, nose and mouth protection

Factors for PPE Selection

- **Type of exposure -** determined by the probable exposure type such as touch, splashes or sprays or large amount of body fluids/blood
- **Type of isolation precaution -** Combination of PPE is determined by the patient's isolation type such as airborne, droplet or contact precautions
- **Task appropriateness -** Choice of PPE is determined by type of patient interaction such as a gown or an apron should be fluid resistant, fluid proof or neither.
- **Appropriate size -** PPE must fit the individual user

Key Points for PPE Use

- Don before patient contact and entry into patients' room
- Avoid spreading contamination while PPE use
- Remove and discard PPE after use, discard immediately at the doorway or outside the patients' room
- Remove respirator outside patients' room
- Perform immediate hand hygiene before going to the next patient

PPE Sequence & Instructions on Donning & Doffing

The following link provides the pictorial order for donning and doffing personal protective equipment for use in healthcare settings: PPE Sequence

Video link: Droplets and PPE https://www.youtube.com/watch?v=Ww0Rf079MZ4
Video link: Aerosols & PPE https://www.youtube.com/watch?v=syh5UnC6G2k

PPE Extended Use

- Continued PPE use for more than one patient encounter without removing and with additional use of protective devices is recommended in contingency or crisis capacity (limited or critical supplies lacking)

PPE reuse

- Use of PPE that is removed after each patient encounter and re-used after some time and/or a processing step is recommended in contingency or crisis capacity (limited or critical supply lacking)

PPE Requirements

The following document entails the pictorial description of types of PPE products recommended for use in various patient encounters in a COVID 19 patient

PPE Requirements Graphic.pdf

Aerosol Generating Medical Procedures (AGMPs)

Use: Droplet + Contact + Enhanced PPE (N95 + Full Face Shield, Level 2 gown and gloves) in the following situations:

- Cardio-pulmonary resuscitation (CPR)
  - Chest compressions on their own NOT considered AGMPs
- Endotracheal Intubation (ETT)
- Open suctioning (e.g. "deep" insertion for nasopharyngeal or tracheal suctioning, not inclusive of oral suction)
- Tracheotomy
- High frequency oscillating ventilation
- Bronchoscopy (Diagnostic or Therapeutic)
- Non-invasive positive pressure ventilation (NIV)
  - CPAP/BiPAP
- Large volume nebulizers for humidity
- High flow oxygen therapy (HFNC)

Patient placement for AGMPs: 4-walled single room with a door only, ensure door is closed with essential staff only. If possible use airborne precaution room.

13.2.5 Discontinuation of Transmission-based Precautions

In-Home Isolation and in Healthcare settings for "Symptomatic" Patients

There are two main strategies (non-test based & test based) to help decide the time of discontinuation of isolation precautions (airborne & droplet) to prevent the spread of infection. These can be used for persons who have COVID 19 symptoms and are staying at home self-isolating themselves and for patients requiring hospital admission (in consultation with public health authority +/- healthcare team in hospital)

In-Home isolation for "Asymptomatic" individuals (Positive COVID 19 testing)

- 10 days after the date of their first positive swab testing and have no subsequent sickness

Strategies for discontinuation

Strategies for clearance	***Who to use in?***	***How to use?***
<u>Non test based strategies</u> Wait 10 days from symptom onset OR Wait 10 days from date of specimen collection – if constantly asymptomatic	Individuals recovered from mild to moderate illness (never hospitalized) including: • HCW (unless directed by facility or Occupational health) • Residents in communal settings e.g. LTC facility, shelters etc. • Non immunocompromised patients outside of a critical care unit	May discontinue isolation once afebrile with symptom improvement for at least 24 hours (without antipyretic use) @ 10 days from symptom onset Note: *Absence of cough is not mandatory with patients from chronic cough or post – infectious reactive airways*

Non test base strategies Wait 20 days from symptom onset	Individuals in ICU or with major immunocompromising conditions* (*Medical treatment with immunosuppressive agents, bone-marrow or solid organ transplant recipients, inherited immunodeficiency, poorly controlled HIV infection)*	May discontinue isolation once afebrile with symptom improvement for 20 days from symptom onset Note: *Absence of cough is not mandatory with patients from chronic cough or post – infectious reactive airways*
Test based strategies Two consecutive negative specimens collected at least 24 hours apart	Individuals who continue to have symptoms consistent with COVID-19 or an intercurrent illness/infection with symptoms that overlap with COVID-19 e.g., severe ARDS	May discontinue isolation after 2 negative specimen taken at least 24 hours apart If swab +ve: re-test in 3-4 days If swab –ve: re-test in 1-2 days (at least 24 hours apart) Note: *Clear instructions and lab requisitions as 'for clearance of disease'*

Pearl: Mass testing is proposed in LTC facilities to avoid asymptomatic transmission to the individuals that are at high risk of exposure and appropriate isolation. This includes residents and healthcare providers or caregivers in the facility

When testing is NOT available?

- Healthcare settings should use the non-test-based strategy **OR**
- Extend beyond the duration for non-test-based strategy on individual basis and clinical assessment in consultation with public health authorities

13.2.6 Self-Assessment Tool

- This tool is a designed questionnaire for helping the general public to assess their risk factors for COVID – 19 and is based on the best possible resources from Canadian public health agencies
- This tool could also be used by the healthcare providers to assess the spread of infection: Link to the COVID Self-Assessment Tool

14.0 Mental health wellness in COVID 19 Pandemic

The COVID 19 pandemic has disrupted daily routines in most people's life resulting in stress and mental health concerns for all at once.

14.1 Coping Strategies for Stress and Anxiety

Centre for addiction and Mental Health (CAMH) recommends following strategies to manage stress while considering the importance of limiting infection transmission

- Accept that certain degree of stress & anxiety is a normal response; make organized plans

- Follow authentic, credible sources for seeking COVID 19 updates (local medical institution, WHO, Health Canada, Ontario Ministry of Health) and limit checking sources to ONCE per day
- Seek support – online support groups, distress lines, community, religious resources
- Acquire a healthy lifestyle – balanced diet, sleep hygiene, physical exercise, cognitive exercise, intentional unplugging of electronic devices and practice relaxation techniques
- AVOID substance abuse – alcohol, vaping/smoking and medication overdose

14.2 How to Address Social Stigma

Play your role

- *Spreading facts + amplify voices:* collect, consolidate and disseminate accurate country and community-specific information. Amplify the stories/images of the people who have recovered or who helped patients through recovery from COVID 19 disease
- *Engaging social influencers* (community/religious leaders/respected celebrities) to address stigmatization and provide support measures for them.
- *Portray diverse ethnic groups + Practice ethical journalism:* Materials should include diverse communities impacted and working together for preventing the COVID 19 spread
- *Link up:* Initiate activities to address stereotyping hence creating an empathetic and positive environment

Communication tips

- *Correct* misconceptions about COVID 19 disease and promote the significance of preventative measures to reduce infection spread
- *Share* sympathetic narratives and address the sufferers in a sensitive and empathetic manner

Communicate support for all frontline responders (HCWs, volunteers and community leaderships)

15.0 References

1 Kenneth McIntosh, MD. 'Coronavirus disease 2019 (COVID-19).' Last modified April 10, 2020. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19?search=covid-19-2019-novel-coronavirus-the-basics&topicRef=8298&source=related_link#H3504376427

2 Rodgers R. Ayebare. March 11, 2020. 'Adoption of COVID-19 triage strategies for low-income settings.' *The Lancet – Respiratory Medicine, vol. 8(4), PE22.* https://doi.org/10.1016/S2213-2600(20)30114-4

3 Ontario Health, Toronto. 'COVID-19 Self-Assessment Tool.' Last modified April 9, 2020. https://covid19toronto.ca/?fbclid=IwAR3PAHQ8T5BqrhIsBHHYZeAAg8mwNDluUTg-J0lQj4_SojVkkRoEPqK90F0

4 Centres for disease control and prevention (CDC). 'PPE Sequence PDF.' Retrieved from: https://www.cdc.gov/hai/pdfs/ppe/ppe-sequence.pdf

5 Centres for disease control and prevention (CDC). 'Guidance for the selection and use of Personal protective equipment in healthcare settings.' Retrieved from: https://www.cdc.gov/hai/pdfs/ppe/ppeslides6-29-04.pdf
6 Loeb M, Alhazzani W, Mertz D, Jaeschke R, Rymer W, Wroczyńska A. 'Coronavirus Disease 2019 (COVID-19).' Last modified April 03, 2020. *McMaster Textbook of Internal Medicine*. Kraków: Medycyna Praktyczna. https://empendium.com/mcmtextbook/chapter/B31.II.18.1.12.
7 Dr. Andrew Krahn. 'Guidance from the CCS COVID-19 rapid response team.' March 20, 2020. *Canadian Cardiovascular Society (CCS).* Retrieved from: https://www.ccs.ca/images/Images_2020/CCS_CHFS_Update_COVID__CV_medications_Mar20.pdf
8 Dr. Stanley Perlman, MD, PhD. 'Coronavirus: novel coronavirus (COVID-19) infection.' Last modified April 07, 2020. *Elsevier*. Retrieved from: https://www.elsevier.com/__data/assets/pdf_file/0010/977698/Novel-coronavirus-COVID-19-infection_2020-04-07.pdf
9 World Health Organization (WHO). 'Clinical management of severe acute respiratory infection when COVID-19 is suspected: interim guidance V 1.2.' March 13, 2020. Retrieved from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
10 Canadian Cardiovascular Society (CCS). 'Practical advice for implementing recommendation from the CCS COVID-19 Rapid Response Team.' March 20, 2020. Retrieved from: http://ccs.ca/en/
11 Centres for disease control and prevention (CDC). 'Discontinuation of transmission-based precautions and disposition of patients with COVID 19 in healthcare settings.' Last modified April 10, 2020. Retrieved from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html
12 Government of Canada. 'Routine practices and additional precautions for preventing the transmission of infection in healthcare settings. Last modified September 2014.' Retrieved from: https://www.canada.ca/en/public-health/services/infectious-diseases/nosocomial-occupational-infections/routine-practices-additional-precautions-preventing-transmission-infection-healthcare-settings.html
13 London Health Sciences Centre. 'Guidelines for Aerosol generating medical procedures (AGMPs) for confirmed COVID 19.' April 07, 2020. Retrieved from: https://www.lhsc.on.ca/media/8476/download
14 Centre for addiction and mental health (CAMH). 'Strategies to maintain mental wellness during COVID 19 pandemic.' Retrieved from: https://www.camh.ca/en/health-info/mental-health-and-covid-19#coping
15 World Health Organization (WHO). 'Social stigma associated with COVID 19.' Last modified February 24, 2020. Retrieved from: https://www.who.int/docs/default-source/coronaviruse/covid19-stigma-guide.pdf
16 Amit Arya MD, Sandy Buchman MD, Bruno Gagnon MD MSc, James Downar MDCM MHSc (Bioethics). 'Pandemic palliative care: beyond ventilators and saving lives.' *Canadian medical association journal (*CMAJ 2020). doi: 10.1503/cmaj.200465; early-released March 31, 2020

17 World Health Organization (WHO). 'Advice on the use of masks in the context of COVID-19: interim guidance.' April 06, 2020. Retrieved from: https://www.who.int/publications-detail/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak
18 Government of Canada. 'Considerations in the use of homemade masks to protect against COVID 19.' Last modified April 12, 2020. Retrieved from: https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/activities/announcements/covid19-notice-home-made-masks.html
19 Alhazzani, Waleed, Møller, Morten Hylander; Arabi, Yaseen M, Mark Loeb. 'Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19).' *Critical Care Medicine Journal (CCMJ)*. Last modified March 27, 2020. Retrieved from: https://journals.lww.com/ccmjournal/Abstract/onlinefirst/Surviving_Sepsis_Campaign__Guidelines_on_the.95707.aspx
20 Jason T. Poston, MD; Bhakti K. Patel, MD; Andrew M. Davis, MD, MPH. 'Management of critically ill adults with COVID 19.' *JAMA. 2020; doi: 10.1001/jama.2020.4914*; released March 26, 2020.
21 Chelsea Elwood MD, Isabelle Boucoiran MD, Julie VanSchalkwyk MD, Deborah Money MD, Mark Yudin MD, Vanessa Poliquin MD, SOGC Committee Opinion – COVID-19 in Pregnancy, *Journal of Obstetrics and Gynaecology Canada (2020)*, doi: https://doi.org/10.1016/j.jogc.2020.03.012
22 Public Health Ontario. 'IPAC Recommendations for Use of Personal Protective Equipment for Care of Individuals with Suspect or Confirmed COVID-19.' April 06, 2020. Retrieved from: https://www.publichealthontario.ca/-/media/documents/ncov/updated-ipac-measures-covid-19.pdf?la=en
23 Sanchis-Gomar F, Lavie CJ, Perez-Quilis C, et al. Angiotensin-Converting Enzyme 2 and Anti-Hypertensives (Angiotensin Receptor Blockers and Angiotensin Converting Enzyme Inhibitors) in Coronavirus Disease 2019 (COVID-19). *Mayo Clinic Proceedings June* volume 95, issue 6
24 Marty FM, Chen K, Verrill KA. Videos in Clinical Medicine, How to Obtain a Nasopharyngeal Swab Specimen. *NEJM. April 17, 2020*.
25 Misra DP, Agarwal V, Gasparyan AY, Zimba O. 'Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets.' *Clinical Rheumatology (April 2020).* DOI: 10.1007/s10067-020-05073-9.
26 Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, Wang LF, Gao H, Wang Y, Dong CF, Li YJ, Xie XJ, Feng C, Liu L. 'First case of COVID-19 complicated with fulminant myocarditis: a case report and insights.' *Infection (April 2020*). doi: 10.1007/s15010-020-01424-5
27 Wang F et al. Pancreatic injury patterns in patients with COVID-19 pneumonia. *Gastroenterology 2020 Apr 1*; S0016-5085(20)30409-1; [e-pub]. https://doi.org/10.1053/j.gastro.2020.03.055
28 Roengrudee Patanavanich1, 2 MD LLM PhD Stanton A. Glantz1 PhD. 'Smoking is Associated with COVID-19 Progression: A Meta-Analysis.' *MedRxiv (April 2020).* doi: https://doi.org/10.1101/2020.04.13.20063669

29 Grasselli G et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA 2020 Apr 6*; [e-pub]. https://doi.org/10.1001/jama.2020.5394
30 Rubin GD et al. The role of chest imaging in patient management during the COVID-19 pandemic: A multinational consensus statement from the Fleischner Society. *Chest 2020* Apr 7; [e-pub]. https://doi.org/10.1016/j.chest.2020.04.003
31 Robert M. Hayden, MD, Edy Yong Kim, MD, Jessica C. Stuart, MD. 'COVID 19 Primer – review page.' *The New England Journal of Medicine. April 2020.* Retrieved from: https://interactives.nejm.org/external/covid_simulation/review.html
32 World Health Organization (WHO). 'Immunity passports in the context of COVID 19.' April 24, 2020. Retrieved from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf
33 Public Health Ontario. 'COVID-19: Aerosol Generation from Coughs and Sneezes.' April 10, 2020. Retrieved from: https://www.publichealthontario.ca/-/media/documents/ncov/ipac/report-covid-19-aerosol-generation-coughs-sneezes.pdf?la=en
34 John B. Lynch, Perica Davitkov. 'Infectious Diseases Society of America Guidelines on Infection Prevention in Patients with Suspected or Known COVID-19.' *The New England Journal of Medicine. April 2020*. Retrieved from: https://www.idsociety.org/practice-guideline/covid-19-guideline-infection-prevention/
35 Thomas J. Oxley, M.D. 'Large vessel stroke as a presenting feature of COVID 19 in young.' The New England Journal of Medicine (NEJM). April 28, 2020. DOI: 10.1056/NEJMc2009787 https://www.nejm.org/doi/full/10.1056/NEJMc2009787?query=recirc_mostViewed_railB_article
36 World Health organization. 'Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations.' March 2020. https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations
37 Jarcho John A., Ingelfinger Julie R., Hamel Mary Beth, D'Agostino Ralph B., Harrington David P. (2020) Inhibitors of the Renin–Angiotensin–Aldosterone System and Covid-19. N Engl J Med DOI: 10.1056/NEJMe2012924.
38 Mandeep R. Mehra, M.D., Sapan S. Desai, M.D., Ph.D., SreyRam Kuy, M.D., M.H.S., Timothy D. Henry, M.D., Amit N. Patel, M.D. 'Cardiovascular disease drug therapy and mortality in COVID 19.' The New England Journal of Medicine (NEJM). May 2020. DOI: 10.1056/NEJMoa2007621.
39 Harmony R. Reynolds, M.D., Samrachana Adhikari, Ph.D., Claudia Pulgarin, M.A., M.S., Andrea B. Troxel, Sc.D., Eduardo Iturrate, M.D., M.S.W., Stephen B. Johnson, Ph.D., Anaïs Hausvater, M.D., Jonathan D. Newman, M.D., M.P.H., Jeffrey S. Berger, M.D., Sripal Bangalore, M.D., Stuart D. Katz, M.D., Glenn I. Fishman, M.D., Dennis Kunichoff, M.P.H., Yu Chen, M.P.H., Ph.D., Gbenga Ogedegbe, M.D., M.P.H., Judith S. Hochman, M.D. 'renin-Angiotensin-Aldosterone system and Risk of COVID 19.' The New England Journal of Medicine (NEJM). May 2020. DOI: 10.1056/NEJMoa2008975
40 ScienceDirect. 'COVID 19 and thrombotic and thromboembolic disease: implications for prevention, anti-thrombotic therapy and follow-up.' April 2020. Retrieved from: https://doi.org/10.1016/j.jacc.2020.04.031

41 Ontario Ministry of health *(MOH)*. 'COVID 19 reference document for symptoms.' May 2020. Retrieved from: http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/2019_guidance.aspx
42 Bikdeli B et al. *JACC* 2020;doi: https://doi.org/10.1016/j.jacc.2020.04.031
43 Ontario Ministry of health (MOH). 'COVID 19 quick reference for Public Health guidance on testing and clearance.' May 2020. Retrieved from: http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_testing_clearing_cases_guidance.pdf
44 Osterholm. T. Michael. 'The future of COVID 19 pandemic: lessons from pandemic influenza.' Centres for infectious disease research and policy *CIDRAP*. April 2020. Retrieved from: https://www.cidrap.umn.edu/sites/default/files/public/downloads/cidrap-covid19-viewpoint-part1_0.pdf
45 Berlin D, Gulick R and Martinez F. 'Severe COVID-19.' The New England Journal of Medicine (NEJM), May 15, 2020. DOI: 10.1056/NEJMcp2009575 Retrieved from: https://www.nejm.org/doi/full/10.1056/NEJMcp2009575
46 Ontario Ministry of Health (MOH). 'Reference document for COVID 19 Symptoms.' May 11, 2020. Retrieved from: http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_case_definition.pdf
47 Ontario Ministry of Health (MOH). 'Reference document for Case Definitions for Coronavirus (COVID 19).' May 11, 2020. Retrieved from: http://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/2019_case_definition.pdf
48 Hung I, Lung C, Tso E, Liu R, Chung T, Chu M. 'Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial.' *The Lancet*, May 8, 2020. https://doi.org/10.1016/ S0140 -6736(20)31101-6. Retrieved from: https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31042-4.pdf
49 Liang W, Liang H, Ou L, et al. 'Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19.' *JAMA* Intern Med. Published online May 12, 2020. doi:10.1001/jamainternmed.2020.2033. retrieved from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2766086
50 Ye Z, Wang Y, Colunga-Lozano L, Prasad M, Tangamornsuksan W, Rochwerg B, Yao L, Motaghi S, Couban RJ, Ghadimi M, Bala MM, Gomaa H, Fang F, Xiao Y, Guyatt G. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ 2020. DOI: 10.1503/cmaj.200645; early-released May 14, 2020. Retrieved from: https://www.cmaj.ca/content/cmaj/early/2020/05/14/cmaj.200645.full.pdf
51 Li H, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Leukemia. 2020 May 5.

52 Levi M, Thachil J, Iba T, Levy J. Coagulation abnormalities and thrombosis in patients with COVID 19. *The Lancet Haematology*, May 2020. Retrieved form: https://doi.org/10.1016/ S2352-3026(20)30145-9
53 COVID 19 Testing Guide. *Hamilton Health Sciences*. Retrieved from: https://www.hamiltonhealthsciences.ca/covid19/staff-physician/safety/
54 World Health Organization *(WHO).* 'Multisystem Inflammatory Syndrome in Children and Adolescents.' May 15, 2020. Retrieved from: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
55 Price-Haywood E, Burton J, Fort D, and Seoane L. 'Hospitalization and Mortality among Black Patients and White Patients with Covid-19.' The New Englang Journal of Medicine, *The NEJM*. May27, 2020. DOI: 10.1056/NEJMsa2011686
56 Goldman J, Lye D, Hui D, Marks k, Bruno R, Montejano R, Christoph S, Galli M, Ahn Y, Nahass R, Chen Y, SenGupta D, et al. 'Remedesivir for 5 to 10 days in Patients with Severe COVID 19.' The New England Journal of Medicine, *The NEJM*. May 27, 2020. DOI: 10.1056/NEJMoa2015301
57 Beigel J, Tomashek K, Dodd E, Mehta A, Zingman B, Kalil A, Hohmann E, Chu H, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg R, et al. 'Remdesivir for the treatment of COVID 19 – Preliminary Report.' The New England Journal of Medicine, *The NEJM*. May 22, 2020. DOI: 10.1056./NEJMoa2007764
58 Zhu F, Li Y, Guan X, Hou L, Wang W, Li J, Wu S, Wang **B**, Wang Z, Wang L, Jia S, Jiang H, Wang L, Jiang T, Hu Y, Gou J, Xu S, Xu J, Wang X, Wang W, Chen W. 'Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial.' *The Lancet*. May 22, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31208-3
59 Yang R, Gui X, Xiong Y. 'Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China.' *JAMA* Netw*ork Open*. May 27, 2020;3(5):e2010182. DOI:10.1001/jamanetworkopen.2020.10182
60 Tang C, Wang Y, Lv H, Guan Z, Gu J. 'Caution against corticosteroid-based COVID-19 treatment.' *The Lancet.* May 25, 2020. DOI: https://doi.org/10.1016/ S0140-6736(20)30749-2
61 World Health Organization *(WHO).* 'Breast feeding advice during the COVID 19 outbreak.' May, 2020. Retrieved from: http://www.emro.who.int/nutrition/nutrition-infocus/breastfeeding-advice-during-covid-19-outbreak.html
62 Nepogodiev D, Glasbey J, Li E, Omar O, Simoes J, Abbott T, Alser O, Arnaud A, Bankhead-Kendall B, Breen K, Cunha M, Davidson G, Saverio S, Gallo G, Griffiths A et al. 'Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study.' *The Lancet*. May 29, 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31182-X
63 Chu D, Akl E, Duda S, Solo K, Yaacoub S, Schünemann H. 'Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis.' *The Lancet*. May 2020. DOI: https://doi.org/10.1016/S0140-6736(20)31142-9
64 Hernandes A, Roman Y, Pasupuleti V. 'Hydroxychloroquine or Chloroquine for treatment or prophylaxis of COVID 19: A living systematic review.' *Annals of Internal Medicine*. May 2020. DOI: https://doi.org/10.7326/M20-2496 DOI:https://doi.org/10.1016/S0140-6736(20)31208-3

65 Ellington S, Strid P, Tong VT, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United States, January 22–June 7, 2020. MMWR Morb Mortal Wkly Rep 2020;69:769–775. DOI: http://dx.doi.org/10.15585/mmwr.mm6925a1
66 Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernández J, Prati D, Baselli G, Asselta R, Grimsrud M, Milani C, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. NEJM. June 17, 2020. DOI: 10.1056/NEJMoa2020283
67 Centres for Disease control and prevention *CDC*. 'People of any age with underlying health conditions.' June 2020. Retrieved from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
68 Randomised evaluation of COVID 19 therapy RECOVERY. 'Low-cost dexamethasone reduces mortality by one-third in hospitalized patients with severe respiratory complications of COVID19.' June 16, 2020. Retrieved from: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19
69 Public Health Ontario. 'Coronavirus disease 2019 – Serology.' August 06, 2020. Retrieved from: https://www.publichealthontario.ca/en/laboratory-services/test-information-index/covid-19-serology#:~:text=As%20of%20August%206%2C%202020,is%20immune%20to%20COVID%2D19
70 World Health Organization. 'Multisystem Inflammatroy Syndrome in Children and Adolescents with COVID-19.' May 15, 2020. Retrieved from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19
71 Public Health Ontario. 'COVID19 routes of transmission – what do we know so far.' July 16, 2020. Retrieved from: https://www.publichealthontario.ca/-/media/documents/ncov/wwksf-routes-transmission-mar-06-2020.pdf?la=en
72 Vivanti, A.J., Vauloup-Fellous, C., Prevot, S. et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 11, 3572 (2020). https://doi.org/10.1038/s41467-020-17436-6
73 SOGC. 'Updated SOGC committee opinion – COVID 19 in pregnancy.' May 14, 2020. Retrieved from: https://sogc.org/common/Uploaded%20files/SOGC%20Committee%20Opinion200514may2020Final.pdf
74 Anne-Lise B, Aileen M, Malcom J, Stephane P. 'Systematic review of registered trials of Hydroxychloroquine prophylaxis for COVID-19 health-care workers at the first third of 2020.' Elevier. May 19, 2020. https://doi.org/10.1016/j.onehlt.2020.100141
75 Chambers C et al. Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women. JAMA. August 19, 2020 doi:10.1001/jama.2020.15580
76 Saad, A. F; Chappell, L; Saade, George R.; Pacheco, L. D. 'Corticosteroids in the Management of Pregnant Patients With Coronavirus Disease (COVID-19).' Obstetrics & Gynecology: October 2020 – Vol 136 - Issue 4 - p 823-826 doi:10.1097/AOG.0000000000004103

77 Wajnberg A, Amanat F, Rirpo A, Deena R. A, Mark J B. 'Robust neutralizing antibodies to SARS-CoV-2 infection persist for months.' Science 28 Oct 2020: eabd7728. doi: 10.1126/science.abd7728
78 Stephen R K, Antonio H, Rinuu P, Gail C, Iain B, Thomas M d, Jake D. 'Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score.' BMJ 2020; 370:m3339 doi: https://doi.org/10.1136/bmj.m3339 (Published 09 September 2020)
79 WHO. "SOLIDARITY" clinical trial for COVID-19 treatments.' October 2020. Retrieved from : https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments
80 Unicef. Panbio COVID-19 Ag rapid testing. Retrieved from: https://www.unicef.org/supply/media/5581/file/Abbott-Panbio-COVID-19-Ag-rapid-test-product-reference-note.pdf
81 Beigel, J H, Tomashek, K M, Dodd, L E, Mehta, A K, Zingman, B S, Kalil, A C, Hohmann, E, Chu, H Y, Luetkemeyer, A, Kline, S, Lopez de Castilla,D, et al. 'Remdesivir for the treatment of Covid-19 – Final report.' NEJM. Nov 05,2020. N Engl J Med 2020; 383:1813-1826. doi: 10.1056/NEJMoa2007764
CDC. October 2020. Retrieved from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html