COVID-19 Update
Medicine Grand Rounds
April 16, 2020

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Disclaimer

• No disclaimers to report

• Some of the views expressed in this presentation are my own and do not necessarily reflect those of LHSC, SJHC, or Western University
Outline

• Epidemiology
• PPE & Physical Distancing
• Phenomenology
• Diagnostics
• Pharmacotherapeutics
  • Potential Agents for COVID-19
  • Clinical Trial Update
  • IDSA Guidelines
  • Canadian Guidelines
• Final Reflections

Source: Getty Images
Emergence of Coronaviruses

- **SARS-CoV-2 (2019-Present)**
  - Likely the greatest global public health crisis since the 1918 influenza pandemic
  - Case fatality rate > 0.1% - < 9.5% (1.4% in Wuhan)

- **MERS-CoV (2012-2020)**
  - Middle Eastern Respiratory Syndrome Coronavirus
  - Over 2500 cases (34.4% fatality)
    - 2 cases in USA (2014); none in Canada
    - Sporadic cases in Saudi Arabia

- **SARS-CoV (2002-2004)**
  - Over 8000 cases worldwide (9.5% fatality)
  - Canada: 251 cases, 43 deaths (17.1% fatality)
COVID-19 Epidemiology: The Numbers

• Worldwide
  • Over 2 million cases
    • 25% have completely recovered
    • Over 130K deaths

• Canada
  • Over 28K cases
    • Over 9K recovered
    • Over 1000 deaths (almost half in LTC homes)
    • London: 247 cases; 108 resolved; 11 deaths

• USA
  • Over 645K cases, with about 30K deaths

Source: The Scientist Magazine
COVID-19 Cases in Ontario
(As of April 14, 2020)

- Cases: 8447
- Deaths: 385
  - 247 (64%): 80 years of age or older
  - 115 (30%): 60-79 year age group
  - 22 (6%): 40-59 year age group
  - 1: < 39 year age group
- Hospitalized: 795
- ICU: 254
- Mechanically ventilated: 188
Figure 4. Rate of confirmed cases of COVID-19 by public health unit: Ontario, January 15, 2020 to April 14, 2020

Data Source: integrated Public Health Information System (iPHIS) database
Flattening the Curve: Are we there yet?

- Effective Measures
  - Hand hygiene, PPE, physical distancing, limiting travel, working from home

- Early signs of flattening in some parts of Canada

- Relaxing physical distancing too early could lead to a resurgence of cases

The coronavirus path

COVID-19 cases for selected nations, starting at the day of the 100th case

Source: MacLean’s Magazine
April 14, 2020
Physical Distancing: For How Long?

- Prolonged or intermittent physical distancing may be necessary into 2022
  - Mitigates the possibility of a resurgence
  - 26% of Canadians are not practicing social distancing (Ipsos poll – April 8, 2020)

- Wintertime outbreaks expected over the next 2 years (post-pandemic period)
  - Depends on herd immunity and vaccine availability

Source: National Post

Kissler SM et al. Science. 2020
Concern about COVID-19 by Age Group and Lifestyle Changes Made

A. Concern about COVID-19 by generation

- Silent generation (≥76 y)
- Baby boomers (55-75 y)
- Gen X (40-54 y)
- Millennials (25-39 y)
- Gen Z (18-24 y)

B. Lifestyle changes in response to COVID-19

- Washing hands more
- Avoiding social gatherings
- Stocking up on food and supplies
- Avoiding or canceling domestic travel
- Working from home
- Avoiding gym and exercise classes
- Avoiding or canceling international travel
- Avoiding routine health care appointments
- Not attending classes

A, Responses to the question “How concerned do you feel about the novel coronavirus, COVID-19?” among each generation. Of 8891 respondents, 143 were from the silent generation, 2040 were baby boomers, 3075 were gen X, 3084 were millennials, and 549 were gen Z. B, Following the question, “Have you made any changes to your lifestyle or daily activities because of COVID-19?” respondents completed the survey question, “Which of the following are you doing? (Select all that apply).”

Mental Health “Pandemic” after COVID-19

• Physical distancing may have short-term & long-term effects on mental health and well being

• Previous large-scale disasters (including the SARS epidemic) have been associated with increased rates of depression, PTSD, and psychological distress

• Increased rates of anxiety/depression, substance use, domestic violence, and child abuse expected following COVID-19 pandemic

Economic Implications of COVID-19
(Source: World Bank)

(real GDP growth, percent change)
Are we running out of PPE?

Source: N. Elsayed
“Made in Canada” PPE Solution

• The Woodbridge Group (Canada) in collaboration with INOAC Corp (Japan) and McMaster University
  • Joint venture to produce surgical masks and N95 masks
  • Facility in Tennessee will manufacture PPE for US market

• Medicom (Montreal, PQ)
  • Face masks and gloves

• Canada Goose
  • Medical gowns – up to 1.5 million, at cost

• InkSmith
  • Health Canada-approved reusable face shields
# PPE Recommendations (Public Health Ontario)

## Healthcare Providers and Support Staff

<table>
<thead>
<tr>
<th>In-Patient Healthcare Facilities</th>
<th>Droplet &amp; Contact Precautions</th>
<th>Airborne Precautions</th>
<th>No PPE required</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient’s room</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Providing direct care to suspect or confirmed COVID-19 patients (including nasopharyngeal and oropharyngeal swab collection)</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Aerosol-generating procedures performed on suspect or confirmed COVID-19 patients</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><strong>Patient transit areas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any activity that does not involve contact with suspect or confirmed COVID-19 patients</td>
<td>✓</td>
<td></td>
<td>Routine practices and additional precautions based on risk assessment</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Triage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preliminary screening not involving direct contact</td>
<td>✓</td>
<td></td>
<td>PPE not required if separated by physical barrier or able to maintain 2m distance from patient</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Administrative areas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administrative tasks that do not involve contact with patients</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

## Ambulatory and Outpatient Healthcare Facilities

<table>
<thead>
<tr>
<th>Consultation room</th>
<th>Droplet &amp; Contact Precautions</th>
<th>Airborne Precautions</th>
<th>No PPE required</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician examination of patient with suspected or confirmed COVID-19</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

## Home Care

<table>
<thead>
<tr>
<th>In patient’s home</th>
<th>Droplet &amp; Contact Precautions</th>
<th>Airborne Precautions</th>
<th>No PPE required</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visiting clients/patients suspected or confirmed to have COVID-19</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

## Long Term Care Home

<table>
<thead>
<tr>
<th>Any location</th>
<th>Droplet &amp; Contact Precautions</th>
<th>Airborne Precautions</th>
<th>No PPE required</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providing direct care to suspect or confirmed COVID-19 residents (including nasopharyngeal and oropharyngeal swab collection)</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

## Visitors and Environmental Service Workers

<table>
<thead>
<tr>
<th>All Care Settings</th>
<th>Droplet &amp; Contact Precautions</th>
<th>Airborne Precautions</th>
<th>No PPE required</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s room</td>
<td>Entering the room of a suspect or confirmed COVID-19 person (including entering to clean after and between consultations)</td>
<td>✓</td>
<td></td>
<td>Visitors should be discouraged or limited</td>
</tr>
</tbody>
</table>
Respiratory Virus Shedding in Exhaled Breath: Efficacy of “Secondary” PPE

Homemade “PPE”

- Cloth/Non-medical masks have not been proven to provide protection against
- Not regulated by Health Canada
- Not a substitute for physical distancing and handwashing
- May be useful for short periods of time in public settings (e.g. grocery shopping, public transit)
- WHO recommends against routine wearing of PPE in community settings although CDC recommends it in high-risk states
Effectiveness of Hand-Sanitizer Compounds

Microbiologic Diagnosis of COVID-19

• Laboratory-Based Testing
  • Real-Time PCR
    • High throughput
    • Sensitivity & Specificity
      • ~70-90%
    • Lower Respiratory Tract > NP > Throat/Saliva

• Point-of-Care Testing
  • Spartan Cube System (Ottawa, Canada)
  • Health Canada Approved
  • 30 min test time
Viral Shedding after COVID-19 Symptoms

Zou L. et al. NEJM. 2020
Can I rely on a Negative COVID-19 Test?

• No perfect test for COVID-19

• Accuracy depends on many factors
  • Virus shedding
  • Specimen collection technique and site
  • Specimen handling and transport time
  • Analytic method and targets

• Up to 30% of tests may be negative
  • Patients can still be infectious

• Repeat testing may “enhance” sensitivity

• Some jurisdictions (e.g. B.C.) believe that mass testing is not necessary
Serology for COVID-19

• May be helpful with epidemiologic investigations and identification of asymptomatic cases

• Late seroconversion may limit the utility of serology in the early phase of illness

• Potential use to assess herd immunity and seroprotection
Status of Serological Assays for COVID-19

• FDA-approved assays
  • Celiex Inc lateral flow assay for detection of IgG and IgM
    • Sensitivity 93.8%; Specificity 95.6% when tested at two Chinese hospitals
  • Ortho Clinical Diagnostics VITROS Anti-SARS-CoV IgG+IgM assay
  • Chebio Diagnosis Systems point of care SARS-CoV-2 test

• FDA has loosened regulations
  • Companies can market their tests without approval as long as they have internal validation data

• No Health Canada approved assays

• Studies currently underway at LHSC and other centres
Pharmacotherapeutic for COVID-19

• Various agents with in-vitro activity against SARS-CoV-2

• Limited data to guide therapeutic decision making

• Clinical trials are ongoing
Antimalarials and COVID-19

• FDA
  • Emergency Use Authorization gives physicians the option to prescribe these drugs
    • Declared national drug shortage 3 days later

• EMA
  • Studies have not yet documented that these agents can effectively treat COVID-19

• WHO
  • Insufficient data to assess efficacy of these agents in prevention or treatment of COVID-19

Chloroquine

Hydroxychloroquine
Toxicity of Chloroquine/Hydroxychloroquine

- Cardiovascular – CHF, ↑QTc, other conduction disorders
- Ototoxicity
- Psychosis
- Ocular (long-term use)
Risks of Experimental COVID-19 Therapy

**Small Chloroquine Study Halted Over Risk of Fatal Heart Complications**

April 12, 2020 - A research trial of coronavirus patients in Brazil ended after 11 patients taking a higher dose of chloroquine drugs dies from lethal arrhythmias (New York Times)
Cytokine Storm

Cytokine Storm

- Increased concentration of proinflammatory cytokines
  - Corticosteroids are the conventional agents used in this setting
  - Important in pathogenesis of COVID-19
    - Increased levels of IL-2, IL-6, IL-7, and IL-10, INFγ, MCP1, MIP1A, and TNFα

- Progression to ARDS, cardiovascular collapse, MODS, and death due to increased alveolar-capillary blood-gas exchange dysfunction

- Early identification and management of cytokine storm may be an important therapeutic target in patients with COVID-19
Cytokine Storm

Immune Response

Non lethal infections

Immune recognition (DAMPS/PAMPs)

Immune recruitment and resolution (Appropriate immune response)

↑ IL-6
↑ TNF-α

Return to homeostasis (Clearance of infection)

↑ T_reg

Host Survival

Lethal infections

Immune evasion

Delayed and/or inappropriate immune response

↑ IL-6
↑ TNF-α

“Cytokine Storm”

Tissue damage “SEPSIS”

Host Death
IL-6 Inhibitors and Cytokine Storm

• Hypothesis that IL-6 inhibitors may be effective in a subgroup of patients who have cytokine storm

• Tocilizumab (monoclonal IL-6 soluble receptor inhibitor) included in 7th edition of Chinese Clinical Guidance document for COVID-19
  • Option for severe COVID-19 with extensive pulmonary changes and increased IL-6 levels
Tocilizumab and COVID-19

- Very limited published data
- Single centre retrospective case series of 15 patients in China
- Isolated case reports, mostly in non-critically ill patients
- Preclinical evidence suggests that IL-6 may be important in the early phase of viral infections

**Conclusion:** Efficacy and safety has NOT been demonstrated

Limitations of IL-6 Inhibitors

• Toxicity
  • Bacterial, mycobacterial, viral, and fungal superinfections
  • Reactivation of hepatitis B and C
  • GI perforation
  • Demyelinating disease (MS and CIDP)
  • Drug-induced liver injury/failure
  • Osteonecrosis of the jaw

• Cost
  • 4-8 mg/kg/dose IV q12h x 2 doses = $4000

• Recommendation
  • Avoid use in COVID-19 until clinical trial data available
Remdesivir

• Nucleotide analogue that inhibits viral RNA polymerases

• In-vitro broad spectrum activity against SARS-CoV, MERS, and Ebola

• Demonstrated in-vitro activity against SARS-CoV-2

• Favourable safety profile
Compassionate Use of Remdesivir for Patients with Severe Covid-19

Green, J. et al. 2020
Clinical Trial Update
(As of April 15, 2020)

• Solidarity Trial
  • International Clinical trial launched by WHO and partners (CATCO = Canadian arm)
  • Four treatment options (HCQ/CQ, lopinavir/ritonavir w/ or w/o INFβ, and remdesivir
  • Randomized but open label

• COVID-19-PEP
  • Post-exposure Prophylaxis/Pre-emptive Rx for SARS-CoV-2

• Remdesivir - 2 RCTs terminated due to poor enrolment; other randomized trials in progress

• Tocilizumab – 8 trials, with 6 recruiting

• Convalescent Plasma – trials underway
Convalescent Plasma

• Used for the treatment and prevention for several infectious diseases

• Has been used for SARS-CoV, MERS, and 2009-H1N1 pandemic
  • Safety and efficacy demonstrated

• Assumption that SARS-CoV-2 might be a promising treatment option

• Patients who have convalesced from COVID-19 may be potential donors

• Clinical trials underway

Duan K. et al. PNAS. 2020
The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis

Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how

Running title: COVID-19 convalescent plasma

Pierre Tiberghien, Xavier de Lambalerie, Pascal Morel, Pierre Gallian, Karine Lacombe, Yazdan Yazdanpanah
Figure 4. Forest plot of pooled odds ratios (ORs) of mortality following treatment with convalescent plasma or convalescent serum, excluding studies with <5 patients (n = 5 studies). Weights are from random-effects analysis. Abbreviation: CI, confidence interval.
Patient 9

Before CP

A

After CP

B

Patient 10

C

D

Duan K. et al. PNAS. 2020
Ethics of Using Unproven Therapies

• Is it ethically permissible to provide unproven interventions to seriously ill COVID-19 patients, such as
  • Experimental agents?
    • E.g. remdesivir
  • Agents currently approved for other indications?
    • E.g. hydroxychloroquine, azithromycin, tocilizumab

• Two considerations
  • Integrity of the medical profession (e.g. trying anything that might work)
  • Resource constraints
Guidance for Using Unproven Therapies

| Past phase II | Past phase I | Safe and effective in relevant animal models | Safe and effective in animal models but unclear extrapolation | Safe and effective in relevant animal models/repurposed drugs | No evidence to support use, but some reason to offer (e.g., plausible mechanism of action) |

**Figure 1. Spectrum of unproven interventions.**

Providing Access to Unproven Therapies: An Antimicrobial Stewardship Perspective

• Beneficence
  • If interventions can help and there is a chance for benefit, then treatment should be considered if a poor outcome is expected without any intervention

• Autonomy
  • Informed voluntary consent is required

• Non-Maleficence
  • Life-saving therapies may incur short-term and/or long-term harm

• Justice
  • The major obstacle to using experimental therapies
  • The cost of interventions being considered might be better spent in other ways
Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>43 In mechanically ventilated patients with COVID-19 and respiratory failure, we <strong>suggest</strong> using empiric antimicrobials/antibacterial agents, over no antimicrobials. <strong>Remark:</strong> if the treating team initiates empiric antimicrobials, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology results and the patient's clinical status.</td>
<td>Weak</td>
</tr>
<tr>
<td>44 For critically ill adults with COVID-19 who develop fever, we <strong>suggest</strong> using acetaminophen/paracetamol for temperature control, over no treatment.</td>
<td>Weak</td>
</tr>
<tr>
<td>45 In critically ill adults with COVID-19, we <strong>suggest against</strong> the routine use of standard intravenous immunoglobulins (IVIG).</td>
<td>Weak</td>
</tr>
<tr>
<td>46 In critically ill adults with COVID-19, we <strong>suggest against</strong> the routine use of convalescent plasma.</td>
<td>Weak</td>
</tr>
<tr>
<td>47.1 In critically ill adults with COVID-19: we <strong>suggest against</strong> the routine use of lopinavir/ritonavir.</td>
<td>Weak</td>
</tr>
<tr>
<td>47.2 <strong>There is insufficient evidence to issue a recommendation</strong> on the use of other antiviral agents in critically ill adults with COVID-19.</td>
<td>No recommendation</td>
</tr>
<tr>
<td>48 <strong>There is insufficient evidence to issue a recommendation</strong> on the use of recombinant rIFNs, alone or in combination with antivirals, in critically ill adults with COVID-19.</td>
<td>No recommendation</td>
</tr>
<tr>
<td>49 <strong>There is insufficient evidence to issue a recommendation</strong> on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19.</td>
<td>No recommendation</td>
</tr>
<tr>
<td>50 <strong>There is insufficient evidence to issue a recommendation</strong> on the use of tocilizumab in critically ill adults with COVID-19.</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>
IDSA Guidelines on the Treatment and Management of Patients with COVID-19
(Bhimraj A. et al., in press)

• Based on a systematic review of the peer and grey literature

• Seven treatment recommendations with narrative summaries of other treatments undergoing evaluations

• Acknowledgement of current “knowledge gap” and aim at avoiding premature favorable recommendations for potentially ineffective or harmful interventions

• Overarching goal that patients be recruited into ongoing trials to determine treatment efficacy and safety

• Unable to determine risk:benefit ratio for most treatments
IDSA Guidelines on the Treatment and Management of Patients with COVID-19

(Bhimraj A. et al., in press)

• Hospitalized COVID-19 patients
  • Hydroxychloroquine/chloroquine (HCQ/CQ) in the context of a clinical trial
  • HCQ/CQ + Azithromycin only in the context of a clinical trial
  • Lopinavir/ritonavir only in the context of a clinical trial
  • Tolicizumab only in the context of a clinical trial
  • Convalescent plasma in the context of a clinical trial

• Pneumonia due to COVID-19
  • Corticosteroids are NOT recommended

• ARDS due to COVID-19
  • Corticosteroids in the context of a clinical trial
Canadian (AMMI CANADA) Guidelines for COVID-19

Coming soon (late April 2020)
Potential New Therapeutic Agents


- Melatonin (Zhang R. et al. Life Sci. 2020)
  - Effects on cytokine storm and inflammation

- Drugs identified through 3D computer-assisted models
  - Atazanavir
  - Tiotropium
Putative pathogenesis of COVID-19 and potential adjuvant use of melatonin.

Zhang R. et al. Life Sci. 2020
Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model

Eo Ram Beck, Donggun Shin, Yoonjung Choi, Sungsoo Park*, Keunsoo Kang*
Preparing for the Next Pandemic

Scrabble picture
Summary

• COVID-19 is the single largest public health threat of our era

• Everyone from patients, HCWs, and the general public has been affected in some way, shape or form

• Detection, tracking, control, and treatment of COVID-19 are high priorities

• Results of clinical trials will help guide next steps
THANK YOU!