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7th Edition

COVID-19 Report

Finding the evidence for you

A weekly report to answer clinically relevant questions by summarizing the most recent evidence.

This information is intended for health care professionals.

Clinical Description & Epidemiology

Is there any data available or theories on why patients with hypertension develop more severe disease?

- A recent meta-analysis showed that hypertension correlates with increased risk of severe COVID-19, however causation has yet to be proven, with age and lifestyle as potential confounding factors.[1,2]
- Previous literature suggests a theoretical increased risk of infection associated with the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), due to the upregulation of angiotensin-converting enzyme II, the receptor through which SARS-CoV-2 invades host cells.[2] However, a study of patients with hypertension and admitted for COVID-19 (n=1,128) found that the use of ACEI/ARBs was associated with reduced all-cause mortality.[3] An additional study (n=362) found no association between ACEI/ARB use and outcome of COVID-19 infection.[4]
- Presently, there is no definitive answer as to why hypertension may increase the risk of severe COVID-19, or if hypertension is simply a surrogate for age.[2] Current Canadian guidelines recommend the continuation of ACEI/ARBs for control of hypertension in patients with COVID-19.[5]

What are the reported neurologic manifestations of COVID-19?

- In a retrospective case series of 214 patients hospitalized with COVID-19, common neurologic features included dizziness (17%), headache (13%), skeletal muscle injury (10.7%), impaired consciousness (7.5%), and impaired taste (5.6%) or smell (5.1%).[1] Other features included stroke (2.8%), nerve pain (2.3%), impaired vision (1.4%), ataxia (0.5%), and seizure (0.5%). In a prospective study of 41 hospitalized patients with COVID-19, 3/38 (8%) patients had headache.[2]
- An observational study of 58 patients published as a letter to the editor reported encephalopathy, agitation and corticospinal tract signs associated with acute respiratory distress syndrome due to SARS-CoV-2 infection.[3] Published case studies have also reported meningitis/encephalitis[4] and Guillain-Barré syndrome[5] with COVID-19.
- There is evidence that other coronaviruses, including SARS and MERS, may be capable of CNS invasion through a transsynaptic pathway from respiratory airways, thereby inducing neurological disease. Given the high homogeneity between SARS-CoV-2 and SARS-CoV, it is possible SARS-CoV-2 is capable of neuroinvasion and that neurologic factors may contribute to respiratory failure in infected patients.[6]

What do we know about the development of immunity post SARS-CoV-2 infection? Does data on immunity after infection with other coronaviruses provide any insight into the degree of protection conferred?

- The development of long-term immunity to viruses is estimated by serology testing for establishment of virus-specific antibodies. A letter describing a study which followed 34 Chinese patients admitted to hospital for COVID-19 in early February found a typical humoral response of IgM followed by the emergence of IgG antibodies.[1] In the third week after symptom onset, all patients were positive for IgM and IgG antibodies with sustained IgG levels out to seven weeks after symptom onset, the end of the observation period. Another preprint study found similar results reaffirming the presence of SARS-CoV-2 specific IgM and IgG following symptomatic COVID-19 infection.[2]
- 56 patients who recovered from SARS in 2003 were followed for several years to determine long-term immunity. The studies showed antibodies peaked four months post-infection and in the initial study, nearly 90% of patients still had detectable IgG levels at two years post-infection.[3] Follow-up studies from the same group showed that the presence of detectable antibodies tapered from roughly 80% of recovered patients at three years[4] to less than 10% at 6 years.[5]
- Notably, the immune system is complex and antibody presence alone does not guarantee immunity. Despite antibody development, the question of post-infectious

SARS-CoV-2 immunity is inconclusive given the lack of long-term immunological and epidemiological data.

Diagnostics & Surveillance

What is the diagnostic use of serology for SARS-CoV-2? Can it be used to measure individual immunity?

- The use of serology to measure SARS-CoV-2 antibodies is debated among countries worldwide. At this time, Canada has decided to not utilize the presence of IgG or IgM as a diagnostic tool to rule out COVID-19.[1] This is primarily due to the delay between symptom onset and serological detection,[2,3,4] suggesting that testing would be less reliable in the first week after symptom onset. Also, cross-reactivity of IgG against other endemic coronaviruses does occur,[3] leading to false positivity.
- The detection of IgG and/or IgM does not correlate with individual immunity. A plaque reduction assay is critical to determining the percentage of neutralizing antibodies in a specimen[4] (i.e. antibodies that can actually eliminate a viral pathogen). Canada's National Microbiology Laboratory (NML) is currently in the process of validating such assays, but these assays require biosafety level 3 facilities and are highly laborious to perform. In time, ELISA's that detect IgG and/or IgM may be used as a measure of seroprevalence and may act as an imperfect surrogate for immunity.
- Notably, in a study of 175 patients with mild illness, 30% did not develop adequate quantities of neutralizing antibodies either during or after infection with SARS-CoV-2.[4] Furthermore, a preprint study showed that prior exposure to other human coronaviruses does not confer any discernible cross-reactivity to SARS-CoV-2.[5]

What is the viral structure of SARS-CoV-2? How is the angiotensin-converting enzyme 2 (ACE2) involved in the pathophysiology of COVID-19 compared to SARS?

- SARS-CoV-2 is an enveloped single-stranded RNA virus. Starting from the outside of the virion towards the center, the key proteins used in diagnostic testing include:[1]
  - Spike (S) proteins, giving its classical "crown" appearance in images taken by electron microscopy
  - Envelope (E) proteins
  - Phosphorylated nucleocapsid (N) proteins that enclose the central RNA
- SARS-CoV specifically targeted ACE2 found in the lower respiratory tract (LRT),[2] even though higher expression of ACE2 has been demonstrated in the nasal epithelial cells.[3] The virus uses ACE2 as a receptor for cell entry. ACE2 is also found

throughout the body, with highest levels appearing in the small intestine, testis, kidneys, heart, thyroid, and adipose tissue.[4]

- SARS-CoV-2 has a broader clinical picture, affecting both the LRT and the upper respiratory tract (URT). One hypothesis suggests that SARS-CoV-2's binding interface contains more Van der Waals forces and hydrogen bonds with ACE2, which increases its likelihood of binding to ACE2 and thereby allowing for cell entry.[5]
- Another theory involves the presence of an unique polybasic cleavage site within SARS-CoV-2, which may improve pathogenicity by synthesizing added O-linked glycans.[6] These O-linked glycans may function to shield key residues on the S protein and allow for immunoevasion.

During the national shortage of specimen collection supplies, what alternatives are available for diagnostic use?

- Nationally there has been an ongoing shortage of nasopharyngeal (NP) swabs for many weeks, as described in our March 21, 2020 newsletter. This is primarily due to limitations in production, supply-chain disruptions and swab contaminations.
- As a result, various countries have adopted strategies to overcome this concern. Recently, the provincial lab in Manitoba has utilized ethylene oxide to sterilize many of their contaminated NP swabs. Ethylene oxide has been previously shown to be effective in decontamination.[1]
- Canada, USA and other countries are also exploring 3D printed swabs as an alternative to the traditionally used flocked swab. These could be easily mass-produced,[2,3] but their diagnostic utility is still to be determined.
- Very recently, the Canada's National Microbiology Laboratory (NML) has shown that non-standard swabs (wood, cotton and 3D-printed plastic), previously thought to be inhibitory to RT-PCR, had Ct values equitable to standard NP swabs (note: data being submitted for publication).

Therapeutics

What is the evidence for remdesivir in treating COVID-19?

- Remdesivir (RDV) is an adenosine analog antiviral medication that was initially developed for the Ebola outbreak in 2016.[1]

- While RDV is not yet FDA approved for the treatment of SARS-CoV-2, promising preliminary research led to RDV being distributed by the manufacturer, Gilead Sciences, for compassionate use for COVID-19.[2,3] Due to high volume of requests

and limited supply, Gilead Sciences ceased RDV distribution for compassionate use on March 22, 2020, to maintain availability for randomized controlled trials.[4]

- A multinational observational study investigated patients treated with compassionate use RDV: 35 of 53 patients (68%) had clinical improvement.[5] However, this study is limited by lacking a control group, thereby significantly diminishing the quality of the evidence.
- A randomized, double-blind, placebo-controlled trial of RDV found that of the 237 patients enrolled (158 given RDV and 79 placebo), RDV was not associated with time to clinical improvement (hazard ratio 1.23) in patients hospitalized with severe COVID-19.[6] In a subgroup analysis, they found that patients who received RVD within 10 days of symptom onset had a shorter time to clinical improvement, but this was not statistically significant.
- Several other double-blinded, randomized, placebo-controlled trials are currently underway.[7,8,9,10]

Does the use of intranasal steroids (e.g.: for allergic rhinitis) influence the risk of acquiring COVID-19? What is the evidence for other respiratory viruses?

- Guidelines from the European Academy of Allergy and Clinical Immunology (EAACI) maintain that, in the current pandemic, intranasal steroid prescribing should be continued as per usual standard of care.[1] This recommendation is based on expert opinion and anecdotal evidence from Wuhan. Proposed harms of avoiding intranasal steroids when indicated include increased sneezing which may perpetuate virus spread in asymptomatic carriers, as well as the risk of mistaking allergic rhinitis for COVID-19.
- No other data exist in COVID-19 or other coronavirus outbreaks with regards to intranasal steroid use and susceptibility to infection.
- Existing safety data for both acute and chronic use of intranasal steroids suggests no increased risk of infection and no significant systemic absorption.[2]
- In a trial of intranasal steroids for common cold symptoms in healthy young adults, intranasal steroid use was associated with prolonged shedding of viable rhinovirus as determined by growth in cell culture, but no difference in rhinovirus detection by PCR.[3] As well, intranasal steroid use did not significantly impact severity or duration of symptoms.

Is there any evidence regarding the use of inhaled bronchodilators for the management of COVID-19?

- There is presently no published evidence regarding the use of inhaled bronchodilators for the management of SARS-CoV-2, MERS-CoV or SARS-CoV.

- Limited evidence is published on the utility of inhaled or intravenous bronchodilators in patients with ARDS.[1] The BALTI-2 trial[2] (n=273) and the ALTA trial[3] (n=282) are randomized controlled trials studying the use of intravenous and inhaled bronchodilators respectively, for the treatment of ARDS. Despite biological plausibility, there was no mortality benefit and both trials were terminated early due to adverse effect or futility.[1,2,3]
- Evidence for the use of bronchodilators in pneumonia is extrapolated from the treatment of acute cough or acute bronchitis with bronchodilators, which showed limited utility. The Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community acquired pneumonia do not mention the use of bronchodilators for treatment of pneumonia.[4]

Infection Prevention & Control

What is the risk of SARS-CoV-2 transmission for dental healthcare personnel? What are the recommended infection prevention and control measures in dentistry?

Why is there risk?

- Dental healthcare personnel (DHCP) are at high risk for acquiring and transmitting diseases such as COVID-19 due to their close contact with the nose and oral cavity of patients.
- Many tools used in dental procedures generate bioaerosols. More specifically, ultrasonic scaler tips and high-speed handpieces with a burr cause the greatest emission of aerosols and splatter during dental procedures.[1]
- The oral cavity, in particular, may put DHCP at high risk for infection with SARS-CoV-2, as the oral mucosa and tongue express ACE2 (the main receptor for SARS-CoV-2 entry).[2] In patients with COVID-19, saliva has relatively high levels of viral RNA, is a source of live virus particles and may facilitate transmission.[3,4]

What do we know about transmission?

- There is no clinical data quantifying the risk of SARS-CoV-2 transmission during dental practice. However, early in the pandemic, a dental school in Wuhan reported 9 cases of COVID-19 among staff.[5] In response, they introduced stringent infection control measures and since then, no DHCP have been infected despite 169 staff members treating >700 patients for dental emergencies.
- In the United States, no DHCP have been infected to date.[6]

What are Manitoba Guidelines for dental practice in the COVID-19 pandemic?

- The Manitoba Dental Association (MDA) has released infection prevention and control (IP&C) guidelines for COVID-19 in dental settings. See guidelines released on April 30, 2020 for the full list of recommendations or their website for the latest updates. Key points are:
    - Strong recommendation that only emergent and urgent dental procedures should proceed with appropriate IP&C measures. Aerosol generating procedures should be reduced where possible.
    - Triage by phone: only asymptomatic patients with urgent or emergent dental conditions seen in person.
    - Patients with suspected or confirmed COVID-19: dental treatment should be provided in a hospital/facility with airborne precautions, not a regular dental operatory.
    - Reduce cross-contamination: strict hand hygiene, disinfect all surfaces and equipment and consider alternating operatory use to allow for time for proper air exchange between patients.
- The Government of Manitoba has announced that dental offices are allowed to reopen as of May 4, 2020, with measures to ensure patient safety. Some added restrictions include the use of the self-screening tool prior to patients booking an appointment and maintaining physical distancing while in waiting rooms.

Can SARS-CoV-2 be transmitted via food or food packing?

- There is no evidence of SARS-CoV-2 transmission via food or food packaging to date.[1] Similarly, there were no SARS or MERS cases associated with food in previous outbreaks.[2]
- While coronaviruses cannot replicate in food, food can act as a fomite, like any other surface, and it is important to practice proper hand hygiene in the preparation and handling of all food products.

What updates are there about the surface stability of SARS-CoV-2?

- As we discussed on March 20, 2020, following the dispersion of concentrated aerosols of SARS-CoV-2, viable virus was recovered from plastics and stainless steel for up to 72 hours, and from cardboard and copper for up to 24 hours.[1] However, these experiments were conducted under ideal lab conditions, using a selected particle size and viral inoculum.[2] As such, they may not be reflective of real life conditions.
- Other coronaviruses (e.g. SARS-CoV and MERS-CoV) persist on plastic in experimental conditions for 8 hours up to 9 days, depending on the viral strain and

titer studied.[3] Furthermore, the capsid protein structure of SARS-CoV-2 may help it persist longer in bodily fluids and in the environment.[4]

- Studies in natural environments like hospital wards have found SARS-CoV-2 RNA on numerous surfaces.[5,6] However, they have not reported on the presence or absence of live virus in these settings, nor the exact role of these fomites in transmission of the virus.
- Fortunately, routine hospital cleaning with ethanol-based products effectively reduces surface contamination by SARS-CoV-2 and other coronaviruses.[3,6]

Is there evidence for fecal-oral transmission of SARS-CoV-2?

- Fecal-oral transmission has not been documented for SARS-CoV-2. However, gastrointestinal symptoms have been observed in some COVID-19 cases.[1] Fecal shedding of SARS-CoV-2 has been detected by RT-PCR (56% in one prospective study)[2] even in patients presenting with only respiratory symptoms.[2,3] Successful culturing of live virus from fecal samples has also been reported.[3]
- The overall significance of fecal-oral transmission in the COVID-19 pandemic is still under investigation. Regardless, hand hygiene and surface decontamination protect against both fecal-oral and droplet routes of transmission.

Public Health Interventions

What is the transmission risk of SARS-CoV-2 with reusable grocery bags?

- Most reusable grocery bags are made from cloth or recycled plastic; brown paper bags are sometimes also used. SARS-CoV-2 can remain viable for up to 3[1] to 7[2] days on plastic, up to two days on cloth,[2] and up to 3 hours on paper.[2] No data exist for SARS-CoV-2 stability on recycled plastic and extrapolation from smooth plastic surfaces may not be possible as SARS-CoV-2 seems to be more stable on smooth surfaces,[2] whereas recycled plastic surfaces are rough. The authors note that these times should not be understood to indicate real world transmissibility of the virus from casual contact with a surface because they eluted the virus by soaking the material in viral transport medium for 30 minutes[2] or eluted with 1mL of viral culture medium.[1]
- Based on the above data, if people follow current advice not to go shopping frequently, any viral particles picked up by their reusable bag should become non-viable before the next shopping trip.
- The possibility of SARS-CoV-2 transmission on reusable bags cannot be ruled out. However, in the context of physical distancing, shoppers with contaminated bags

most likely inoculated the bags themselves, and so the concern would be the theoretical transmission to others. In any case, good hand hygiene during grocery shopping should be observed and anyone who is ill should stay home.

What is the transmission risk of SARS-CoV-2 in outdoors settings?

- There is currently very little evidence regarding outdoor transmission of SARS-CoV-2. A preprint study in China examining outbreak cases found that of the 7,324 cases of COVID-19, only one outbreak occurred outdoors.[1] This cluster involved two cases that was linked to a conversation held outdoors. Another preprint study from Japan postulated that indoor transmission of SARS-CoV-2 was 18.7 times more likely than outdoor transmission.[2]
- Besides the outdoors being an open space, other variables include temperature, humidity, and UV index. As mentioned in April 17, 2020 newsletter, it is difficult to predict the impact of variations in temperature and humidity on SARS-CoV-2 transmission. UV radiation is effective at inactivating SARS-CoV[3] and is known to inactivate influenza, thus we can likely extrapolate this to SARS-CoV-2. However, these experiments were done in a lab and it is unclear what the real-world effect of sunlight is on the virus.
- A preprint study postulated that viral particles may be able to travel in droplets further than 1.5 meters behind a person when released in a slipstream of air currents generated by runners or bikers.[4] The authors, however, noted that this was done using a simulation that assumed there was no wind. Given that the simulation was only focused on the physics aspect of droplet transmission, it is difficult to predict if there would be enough viable viral particles to cause infection. The infectious dose, ID_{50}, (amount of virions required to produce infection in 50% of exposed people) for SARS-CoV-2 is currently unknown. For SARS-CoV the ID_{50} was estimated to be 280 plaque forming units.[5] SARS-CoV-2's ID_{50} has been postulated to be lower given its higher infectivity.
- Overall, although it seems that outdoor spread of SARS-CoV-2 is relatively lower than in other scenarios, there is little evidence that provides a clear understanding of the factors involved and how they interact. Environmental conditions may play a role in reducing spread, but factors such as crowding and contact with contaminated surfaces may increase risk. Therefore, precautions such as physical distancing and diligent hand hygiene continue to be important.

What is the evidence regarding transmission of SARS-CoV-2 on university campuses? Are there special considerations for rearranging residences to allow students to stay?

- Numerous university campuses have closed to decrease potential transmission. There is limited evidence about transmission of SARS-CoV-2 on university campuses. Studies of transmission dynamics from previous pandemics may offer insight.
- There is data on intra-campus transmission during the 2009 H1N1 Influenza pandemic.[1,2] Transmission was likely due to high contact activities and congregate settings on campus such as student clubs, lectures, labs, and the use of common areas (e.g. libraries and canteens). Closure of campuses and cancellation of classes would limit these routes of transmission. Studies also observed a moderate degree of transmission from the general community into the campus.[1,3]
- There are conflicting results in studies about the transmission of influenza in campus housing (e.g. residence halls and dormitories). Some data indicates clustering of cases was present at residence sites,[1] but other studies suggest that no clustering was found there.[3] Currently, measures regarding student residences vary from school to school. Some institutions are allowing some students to stay in their current residence, but enforcing proper hygiene and social distancing measures.[4]

Pediatric Corner

What is the evidence regarding the use of antivirals in the treatment of pediatric patients with COVID-19?

- There is currently no evidence that antiviral treatment improves outcomes in pediatric patients with COVID-19.[1,2] As well, the use of antivirals is not recommended for pediatric patients outside the context of a clinical trial.
- A recent guidance from a panel of North American pediatric infectious disease physicians and pharmacists suggests that supportive care alone is appropriate for almost all children with COVID-19.[3] According to the guidance, antivirals could be considered in a child with severe disease and should be considered in critical disease. If an antiviral is used, preferably in the context of a clinical trial, the panelists recommend remdesivir as the preferred agent and hydroxychloroquine as an alternative. There was no consensus on whether lopinavir-ritonavir should be

considered for the treatment of any pediatric patient with COVID-19. It is important to remember that at this time, all these drugs are investigational for COVID-19 and so far, none have proven to be effective.

- Currently, there is one active clinical trial in Canada investigating antivirals that includes pediatrics. Lopinavir-ritonavir is being investigated for post-exposure prophylaxis (CORIPREV-LR trial) and is actively recruiting in British Columbia and Ontario.
- Health Canada has also authorized an expanded access treatment protocol for remdesivir that includes pediatric patients >12 years and >40 kg who require mechanical ventilation.[4] The protocol is connected to clinical trials outside of Canada investigating remdesivir for those with moderate and severe COVID-19.[5,6] There is also a clinical trial outside Canada that accepts pediatric patients investigating hydroxychloroquine, azithromycin, or both for the treatment of COVID-19.[7]

Are there considerations for pediatric patients requiring inhaled or oral steroids for another indication in the setting of the COVID-19 pandemic? What about children on immunosuppressant medications for chronic illnesses?

- For children with asthma, the Canadian Pediatric Society (CPS) recommends that current management plans be continued including short course of oral corticosteroids for acute exacerbations if indicated.[1] Furthermore, for children with suspected exposure or confirmed infection with SARS-CoV-2 and an acute exacerbation of asthma, concerns regarding risk of oral corticosteroid use should be balanced with the general consensus that aggressive management of asthma exacerbations is beneficial. A previously conducted meta-analysis of children with asthma on inhaled corticosteroids (ICS) versus placebo found no increase in non-COVID-19 respiratory infections between groups.[2] Data specific to risk of COVID-19 infection is not available.
- Whenever possible, asthma medications should be administered using metered dose inhaler (MDI) to avoid the aerosolization associated with nebulized medications.[1]
- For children diagnosed with croup during the COVID-19 pandemic, the CPS recommends against oral corticosteroids for treatment of mild cases in older children who are not distressed.[3] This is a change from their usual guidance to consider oral corticosteroid treatment in all children presenting with croup.
- Small numbers of children with inflammatory bowel disease (IBD) have been diagnosed with COVID-19 while continuing immunosuppressive medications without reported adverse outcomes.[4] Consensus guidelines for IBD and rheumatological conditions in pediatrics recommend continuing immunosuppressant therapy as usual, during the pandemic, to prevent disease flare.[4,5] Further recommendations

are that corticosteroids should be considered to treat IBD flares during the pandemic,[4] while children with juvenile idiopathic arthritis (JIA) on corticosteroids are advised to consult their rheumatologist for possible dose adjustment.[5] Children with IBD or JIA presenting with acute febrile illnesses should generally have immunosuppressive treatment suspended, in consultation with their specialist, until fever subsides, irrespective of SARS-COV-2.

The information presented reflects the data that is currently available to us. In the context of a pandemic where rapid dissemination of information is essential, we have included information from evolving medical literature which may be awaiting peer-review.

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