New Research

Basic Science / Virology / Pre-clinical


Findings: There are currently no antiviral drugs with proven clinical efficacy, nor are there vaccines for its prevention, and these efforts are hampered by limited knowledge of the molecular details of SARS-CoV-2 infection. To address this, we cloned, tagged and expressed 26 of the 29 SARS-CoV-2 proteins in human cells and identified the human proteins physically associated with each. Among these, we identify 66 druggable human proteins or host factors targeted by 69 compounds (29 FDA-approved drugs, 12 drugs in clinical trials, and 28 preclinical compounds). Further studies of these host factor targeting agents, including their combination with drugs that directly target viral enzymes, could lead to a therapeutic regimen to treat COVID-19.


Findings: SARS-CoV-2 requires concerted and global approaches to better understand the virus and stop the COVID-19 pandemic. Although SARS-CoV-2 primarily targets cells of the lung epithelium causing respiratory infection and pathologies, there is growing evidence that the intestinal epithelium is also infected. Here, using both colon-derived cell lines and primary non-transformed colon organoids, we engage in the first comprehensive analysis of SARS-CoV-2 lifecycle in human intestinal epithelial cells. Our results demonstrate that human intestinal epithelial cells fully support SARS-CoV-2 infection, replication and production of infectious de-novo virus particles. We found that viral infection elicited an extremely robust intrinsic immune response where, interestingly, type III interferon mediated response was significantly more efficient at controlling SARS-CoV-2 replication and spread compared to type I interferon. Taken together, our data demonstrate that human intestinal epithelial cells are a productive site of SARS-CoV-2 replication and suggest that the enteric phase of SARS-CoV-2 may participate in the pathologies observed in COVID-19 patients by increasing patient viremia and by fueling an exacerbated cytokine response.

Findings: Analysis of the transcriptional response to SARS-CoV-2 as it compares to other respiratory viruses. Cell and animal models of SARS-CoV-2 infections, in addition to transcriptional and serum profiling of COVID-19 patients, consistently revealed a unique and inappropriate inflammatory response. This response is defined by low levels of Type I and III interferons juxtaposed to elevated chemokines and high expression of IL6. Taken together, we propose that reduced innate antiviral defenses coupled with exuberant inflammatory cytokine production are the defining and driving feature of COVID-19.

Clinical Syndrome


   Findings: Despite frequent prescription of broad-spectrum empirical antimicrobials in patients with coronavirus associated respiratory infections, there is a paucity of data to support the association with respiratory bacterial/fungal co-infection. Generation of prospective evidence to support development of antimicrobial policy and appropriate stewardship interventions specific for the COVID-19 pandemic are urgently required.

   [https://cancerdiscovery.aacrjournals.org/content/early/2020/04/29/2159-8290.CD-20-0516](https://cancerdiscovery.aacrjournals.org/content/early/2020/04/29/2159-8290.CD-20-0516)

   Findings: A total of 218 COVID-19 positive patients from March 18th-April 8th, 2020 with a malignant diagnosis were identified. A total of 61 (28%) cancer patients died from COVID-19 with a case fatality rate (CFR) of 37% (20/54) for hematologic malignancies and 25% (41/164) for solid malignancies. 6/11 (55%) lung cancer patients died from COVID-19 disease. Increased mortality was significantly associated with older age, multiple comorbidities, need for ICU support, and elevated levels of D-Dimers, LDH and lactate on multivariable analysis. Age-adjusted CFRs in cancer patients compared to non-cancer patients at our institution and NYC reported a significant increase in case fatality for cancer patients. These data suggest the need for proactive strategies to reduce likelihood of infection and improve early identification in this vulnerable patient population.


   Findings: Multicenter retrospective cohort study that included 5,771 adult patients with COVID-19 pneumonia in Hubei Province. Longitudinal liver function tests were retrospectively analyzed and correlated with the risk factors and death. Liver injury dynamic patterns differed in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBIL). AST elevated first, followed by ALT, in severe patients. ALP modestly increased during hospitalization and largely remained in the normal range. The fluctuation in
TBIL levels was mild in the non-severe and the severe group. AST abnormality was associated with the highest mortality risk compared to other indicators of liver injury during hospitalization. Common factors associated with elevated liver injury indicators were lymphocyte count decrease, neutrophil count increase, and male gender.

Findings: Of the 213 patients with COVID-19, 41 (19.2%) were asymptomatic until admission. Among the remaining patients with mild COVID-19, the most common symptom was cough (40.1% [69/172]), followed by hyposmia (39.5% [68/172]) and sputum (39.5%, [68/172]). Of the 68 patients with hyposmia, 61 (90%) patients had accompanying symptoms such as hypogeusia, nasal congestion, or rhinorrhea. Fever (>37.5 °C) was only observed in 20 (11.6%). As much as one-fifth of patients with COVID-19 had remained asymptomatic from exposure to admission.

Findings: Our study confirmed previous observations suggesting that underlying cardiovascular disease is associated with an increased risk of in-hospital death among patients hospitalized with Covid-19. Our results did not confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital death in this clinical context.

Findings: Lesions may be classified as acral areas of erythema with vesicles or pustules (Pseudo-chilblain) (19%), other vesicular eruptions (9%), urticarial lesions (19%), maculopapular eruptions (47%) and livedo or necrosis (6%). Vesicular eruptions appear early in the course of the disease (15% before other symptoms). The pseudo-chilblain pattern frequently appears late in the evolution of the COVID-19 disease (59% after other symptoms), while the rest tend to appear with other symptoms of COVID-19. Severity of COVID-19 shows a gradient from less severe disease in acral lesions to most severe in the latter groups. Results are similar for confirmed and suspected cases, both in terms of clinical and epidemiological findings. Alternative diagnoses are discussed but seem unlikely for the most specific patterns (pseudo-chilblain and vesicular).

Findings: Renal abnormalities occurred in the majority of patients with COVID-19 pneumonia. Although proteinuria, hematuria, and AKI often resolved in such patients within 3 weeks after
the onset of symptoms, renal complications in COVID-19 were associated with higher mortality.


   Findings: patients with COVID-19 are at accelerated risk for delirium due to at least seven factors including (1) direct central nervous system (CNS) invasion, (2) induction of CNS inflammatory mediators, (3) secondary effect of other organ system failure, (4) effect of sedative strategies, (5) prolonged mechanical ventilation time, (6) immobilization, and (7) other needed but unfortunate environmental factors including social isolation and quarantine without family. Given early insights into the pathobiology of the virus, as well as the emerging interventions utilized to treat the critically ill patients, delirium prevention and management will prove exceedingly challenging, especially in the intensive care unit (ICU).


   Findings: The most common complications include arrhythmia, cardiac injury, fulminant myocarditis, heart failure, pulmonary embolism, and disseminated intravascular coagulation (DIC). Mechanistically, SARS-CoV-2, following proteolytic cleavage of its S protein by a serine protease, binds to the transmembrane angiotensin-converting enzyme 2 (ACE2) to enter type 2 pneumocytes, macrophages, perivascular pericytes, and cardiomyocytes. This may lead to myocardial dysfunction and damage, endothelial dysfunction, microvascular dysfunction, plaque instability, and myocardial infarction (MI). Early evaluation and continued monitoring of cardiac damage (cTnI and NT-proBNP) and coagulation (D-dimer) after hospitalization may identify patients with cardiac injury and predict COVID-19 complications. Cardiovascular considerations of therapies currently used, including remdesivir, chloroquine, hydroxychloroquine, tocilizumab, ribavirin, interferons, and lopinavir/ritonavir, as well as experimental therapies, such as human recombinant ACE2 (rhACE2), are discussed.


   Findings: The magnitude of the COVID-19 pandemic will result in substantial neurological disease, whether through direct infection (rare), para-infectious complications (less rare), or critical illness more generally (common). Here, we raise the importance of stringent diagnosis and data collection regarding neurological complications of COVID-19. We also outline the specific management of patients with neuroinflammatory diseases in the context of the pandemic.

**Diagnostics & Screening**


Findings: The current gold standard for COVID-19 diagnosis is real-time RT-PCR detection of SARS-CoV-2 from nasopharyngeal swabs. Low sensitivity, exposure risks to healthcare workers, and global shortages of swabs and personal protective equipment, however, necessitate the validation of new diagnostic approaches. To validate the use of saliva for SARS-CoV-2 detection, we tested nasopharyngeal and saliva samples from confirmed COVID-19 patients and self-collected samples from healthcare workers on COVID-19 wards. When we compared SARS-CoV-2 detection from patient-matched nasopharyngeal and saliva samples, we found that saliva yielded greater detection sensitivity and consistency throughout the course of infection. Furthermore, we report less variability in self-sample collection of saliva. Our findings demonstrate that saliva is a viable and more sensitive alternative to nasopharyngeal swabs and could enable at-home self-administered sample collection for accurate large-scale SARS-CoV-2 testing.


Findings: Many countries are currently in a lockdown state due to the SARS-CoV-2 pandemic. One key aspect to transition safely out of lockdown is to continuously test the population for infected subjects. Currently, detection is performed at points of care using quantitative reverse-transcription PCR (RT-qPCR) and requires dedicated professionals and equipment. Here, we developed a protocol based on Reverse Transcribed Loop-Mediated Isothermal Amplification (RT-LAMP) for detection of SARS-CoV-2, directly from crude nose and throat swabs. We applied this protocol to over 180 suspected patients, and determined its specificity and sensitivity by comparison to their RT-qPCR results. In addition, we further succeeded to apply the protocol on self-sampled saliva from confirmed cases. Since the proposed protocol provides results on-the-spot, and can detect SARS-CoV-2 from saliva, it can allow simple and continuous surveillance of the community.


18. **Preliminary support for a “dry swab, extraction free” protocol for SARS-CoV-2 testing via RT-qPCR.** Srivatsan, S, Han, PD, van Raay, K, et al. PREPRINT https://www.biorxiv.org/content/10.1101/2020.04.22.056283v1.full.pdf

Abstract: Using paired mid-turbinate swabs self-collected by 11 individuals with previously established SARS-CoV-2 positivity, we performed a comparison of conventional (swab → UTM → RNA extraction → RT-qPCR) vs. simplified (direct elution from dry swab → RT-qPCR) protocols. Our results suggest that dry swabs eluted directly into a simple buffered solution (TE) can support molecular detection of SARS-CoV-2 via endpoint RT-qPCR without substantially
compromising sensitivity. Although further confirmation with a larger sample size and variation of other parameters is necessary, these results are encouraging for the possibility of a simplified workflow that could support massively scaled testing for COVID-19 control. (U Washington).


**Epidemiology**


Findings: The clinical presentation of mild-to-moderate Covid-19 substantially varies according to the age and the sex characteristics of patients. Olfactory dysfunction seems to be an important underestimated symptom of mild-to-moderate Covid-19 that needs to be recognized as such by the WHO.


Findings: Data on viral load, as estimated by real-time RT-PCR threshold cycle values from 3,712 COVID-19 patients were analysed to examine the relationship between patient age and SARS-CoV-2 viral load. Analysis of variance of viral loads in patients of different age categories found no significant difference between any pair of age categories including children. In particular, these data indicate that viral loads in the very young do not differ significantly from those of adults. Based on these results, we have to caution against an unlimited re-opening of schools and kindergartens in the present situation. Children may be as infectious as adults.


Findings: The substantial variation in the rates for COVID-19 hospitalizations and deaths across the New York City boroughs is concerning. The Bronx, which has the highest proportion of racial/ethnic minorities, the most persons living in poverty, and the lowest levels of educational attainment had higher rates of hospitalization and death related to COVID-19 than the other 4 boroughs. In contrast, the rates for hospitalizations and deaths were lowest among residents of the most affluent borough, Manhattan, which is composed of a predominately white population. Manhattan has the highest population density, indicating that other factors, such as
underlying comorbid illnesses, occupational exposures, socioeconomic determinants, and race-based structural inequities may explain the disparate outcomes among the boroughs.


Findings: data indicate that millions of health workers likely to be exposed to SARS–CoV-2 have medical conditions that increase their risk for poor COVID-19 outcomes. Many lack health insurance and paid sick leave, and more than 600 000 live in poverty, potentially compromising their ability to maintain social distancing outside their workplace. Poverty, particularly when coupled with lack of sick pay, might push minimally symptomatic workers to attend work.

Healthcare Delivery


Therapeutics


Findings: In this cohort study, patients who received hydroxychloroquine for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation, and concurrent
treatment with azithromycin was associated with greater changes in QTc. Clinicians should carefully weigh risks and benefits if considering hydroxychloroquine and azithromycin, with close monitoring of QTc and concomitant medication usage.


   Findings: The document includes practice implications for evaluation of stroke patients with caution for stroke team members to avoid COVID-19 exposure, during clinical evaluation and performance of imaging and laboratory procedures with special considerations of intravenous thrombolysis and mechanical thrombectomy in stroke patients with suspected or confirmed COVID-19 infection. A total of 41 conclusions and practice implications have been developed.


   Findings: Based on the limited scientific data, CPT therapy in COVID-19 patient appears safe, clinically effective and reduces mortality. Well-designed large multi-center clinical trial studies should be conducted urgently to establish the efficacy of CPT to COVID-19 patients.


   Findings: Remdesivir use was not associated with a difference in time to clinical improvement. Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less. Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early. In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.

**Transmission / Infection Control**


   Findings: The most contaminated zones were the intensive care unit specialized for taking care of novel coronavirus pneumonia (31.9%), Obstetric Isolation Ward specialized for pregnant women with NCP (28.1%), and Isolation Ward for NCP (19.6%). We classified the 13 zones into four contamination levels. The most contaminated objects were self-service printers (20.0%), desktop/keyboard (16.8%), and doorknob (16.0%). Both hand sanitizer dispensers (20.3%) and gloves (15.4%) were the most contaminated PPE.

Findings: SARS-CoV-2 is highly contagious and stable in the environment and predominantly transmits among humans via the respiratory route. Accumulating evidence suggest that this virus, like many of its related viruses, may also be an enteric virus that can spread via the fecal-oral route. Such a hypothesis would also contribute to the rapidity and proliferation of this pandemic. Here we briefly summarize what is known about this family of viruses and literature basis of the hypothesis that SARS-CoV-2 is capable of infecting the gastrointestinal tract and shedding in the environment for potential human-to-human transmission.


Findings: Recent epidemiologic, virologic, and modeling reports support the possibility of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission from persons who are presymptomatic or asymptomatic. Critical knowledge gaps include the relative incidence of asymptomatic and symptomatic SARS-CoV-2 infection, the public health interventions that prevent asymptomatic transmission, and the question of whether asymptomatic SARS-CoV-2 infection confers protective immunity.


Findings: While the transmission of SARS-CoV-2 via human respiratory droplets and direct contact is clear, the potential for aerosol transmission is poorly understood. This study investigated the aerodynamic nature of SARS-CoV-2 by measuring viral RNA in aerosols in different areas of two Wuhan hospitals during the COVID-19 outbreak in February and March 2020. The concentration of SARS-CoV-2 RNA in aerosols detected in isolation wards and ventilated patient rooms was very low, but it was elevated in the patients’ toilet areas. Levels of airborne SARS-CoV-2 RNA in the majority of public areas was undetectable except in two areas prone to crowding, possibly due to infected carriers in the crowd. We found some medical staff areas had high concentrations of viral RNA with aerosol size distributions, but these levels were reduced to undetectable after implementation of rigorous sanitization procedures. Although we have not established the infectivity of the virus detected in these hospital areas, we propose that SARS-CoV-2 may have the potential to be transmitted via aerosols. Our results indicate that room ventilation, open space, sanitization of protective apparel, and proper use and disinfection of toilet areas can effectively limit the concentration of SARS-CoV-2 RNA in aerosols.

Findings: Personal protective equipment (PPE) has been an invaluable yet limited resource when it comes to protecting healthcare workers against infection during the COVID-19 pandemic. In the US, N95 respirator supply chains are severely strained and conservation strategies are needed. A multidisciplinary team at the Washington University School of Medicine, Barnes Jewish Hospital, and BJC Healthcare was formed to implement a program to disinfect N95 respirators. The process described extends the life of N95 respirators using vaporized hydrogen peroxide (VHP) disinfection and allows healthcare workers to retain their own N95 respirator across a large metropolitan health care system.


Findings: UV-C administered as a 1-minute cycle in a UV-C box or a 30-minute cycle by a room decontamination device reduced contamination but did not meet criteria for decontamination of the viruses from all sites on the N95s. The high-level disinfection cabinet was effective for decontamination of the N95s and achieved disinfection with an extended 31-minute cycle. Dry heat at 70°C for 30 minutes was not effective for decontamination of the bacteriophages. UV-C could be useful to reduce contamination on N95 respirators. However, the UV-C technologies studied did not meet pre-established criteria for decontamination under the test conditions used. The high-level disinfection cabinet was more effective and met criteria for disinfection with an extended cycle.

**Women & Children**


Findings: Among 9 pregnant women with severe COVID-19 disease, at the time of reporting 7 of 9 died, 1 of 9 remains critically ill and ventilator-dependent, and 1 of 9 recovered after prolonged hospitalization. We obtained self-verified familial/household cohort data in all 9 cases, and in each and every instance the maternal outcomes were more severe when compared to other high and low-risk familial/household members (n=33 members for comparison). We report herein maternal deaths due to COVID-19 disease. Until rigorously collected surveillance data emerges, it is prudent to be aware of the potential for maternal death among pregnant women diagnosed with COVID-19 disease in their latter trimester(s).


Findings: The clinical characteristics of pregnant women with COVID-19 are similar to those of non-pregnant adults. Fetal and neonatal outcomes appear good in most cases, but available
data only include pregnant women infected in their third trimesters. Further studies are needed to ascertain long-term outcomes and potential intrauterine vertical transmission.


Abstract: Suggestions to meet optimize the safety of patients and health care workers and to better conserve health care resources without impacting maternal or neonatal outcomes.


GUIDELINES & CONSENSUS STATEMENTS


https://www.cmaj.ca/content/early/2020/04/29/cmaj.200648.long

https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.120.048180

**FDA / CDC / NIH/ WHO Updates**

FDA Revised Policy on Antibody Tests: Prioritizing Access and Accuracy
https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy

FDA issues Emergency Use Authorization for remdesivir

FDA Recommendations for Investigational COVID-19 Convalescent Plasma

NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19

CDC COVID-19 Breastfeeding Guidance

**Commentary**

https://www.cidrap.umn.edu/covid-19/covid-19-cidrap-viewpoint


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