The Daily COVID-19 Literature Surveillance Summary

July 9, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

EXECUTIVE SUMMARY

Climate

- A survey of 195 faculty at a large academic radiology department found that 23% respondents with children reported having major gaps in their childcare needs while 53% reported minor gaps during the pandemic highlighting the need for supporting healthcare workers.

Epidemiology

- A series of acral chilblain lesion cases collected in France found that 7 of 121 cases tested positive for COVID-19 via RT-PCR and 5 of 75 tested positive via serology. Based on their findings, the investigators suggest that chilblains do not have diagnostic or prognostic value for SARS-CoV-2 infection, though the authors do not dismiss that some acral lesions could be related to COVID-19.

Understanding the Pathology

- Comparison of RNA-seq data from bronchoalveolar lavage samples from 9 COVID-19 patients found an increase in ACE2 expression and a resultant bradykinin storm leading to increased vascular permeability, infiltration of inflammatory cells, formation of hyaluronic acid membranes in the lungs, and electrolyte imbalances when compared to controls. This analysis helps characterize the mechanism of inhibited gas exchange in COVID-19.

Transmission and Prevention

- Researchers affiliated with Oxford, Harvard, Johns Hopkins, North Carolina State University, and the University of Haifa discuss the importance of human challenge trials in SARS-CoV-2 vaccine development and argue that these trials should be initiated immediately due to the lengthy process involved in conducting them.

Management

- A group of pediatricians describes recommendations for breastfeeding infants for mothers with suspected or confirmed COVID-19 citing the lack of consensus from national OB/GYN organizations in the US and UK.
- A study involving 140 patients in Singapore discusses and validates a proposed "Rule-of-6" which involves using early-infection levels of ferritin above 600 ug/L, LDH above 600 U/L, and CRP above 60 mg/L as predictors of COVID-19 disease progression and deterioration.

Adjusting Practice During COVID-19

- A retrospective cross-sectional analysis in Boston, MA found that among 327 patients who are taking systemic immunomodulatory medications for dermatologic conditions, there were 5 COVID-19 positive infections and 1 hospitalization, which is in-line with Boston's general population infection and hospitalization rate suggesting that long term immunomodulatory medications likely do not affect COVID-19 infection and outcomes.
- A 40-question survey filled out by 509 interventional cardiologists found a significant decrease in procedures, an increase in personal safety measures, suboptimal COVID-19 pre-testing, a limited amount of FIT-tested N95 masks, and adoption of telemedicine during the pandemic helping identify areas of improvement for interventional cardiology departments.

R&D: Diagnosis and Treatments

- Chinese researchers investigated the SARS-CoV-2 immune response using prospectively collected samples from all hospitalized patients with RT-PCR confirmed COVID-19 in four hospitals in Guangdong Province. They found that severely ill patients demonstrated longer viral shedding, had higher neutralizing antibody titers, and were more likely to demonstrate IgM response than mildly ill patients. Additionally, they also found SARS-CoV-2 S and N proteins did not cross react with MERS-CoV.
- Researchers at Johns Hopkins, Mayo Clinic, and Albert Einstein College of Medicine cite prior research indicating a lack of antibody response to SARS-CoV-2 in the first 10 days of COVID-19 infection and suggest that administration of convalescent antibody via plasma therapy in early stages of disease course could support viral clearance, improve function in immune modulation, limit viral proliferation, and dampen the detrimental inflammatory response.
- In response to a press release about the preliminary results of clinical trials evaluating dexamethasone's possible mortality benefit for COVID-19 treatment, a group of clinicians at Harvard propose a set of minimum requirements for disseminating clinical results during the COVID-19 pandemic citing the importance of facilitating scientific scrutiny before allowing limited, potentially rushed, study results to influence clinical practice.

Mental Health and Resilience Needs

- A survey of 233 psycho-oncology patients and 41 of their family members found that although patients had increased fear of infection and feelings of loneliness, about half of patients and family members had an increased sense of peace and belonging to society as a result of the lockdown and subsequently reduced pressures of daily living.

CLIMATE

RETHINKING THE IMPORTANCE OF THE INDIVIDUAL WITHIN A COMMUNITY OF DATA

Spector-Bagdady K, Beever J.. Hastings Cent Rep. 2020 Jul 7. doi: 10.1002/hast.1112. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Two American professors of ethics argue that principles regarding informed consent and other research protocols should take into account what is best for the community rather than the individual, specifically when it pertains to low-risk secondary research. The authors believe that large, community-driven databases are crucial to the benefit of future patients, are important during the COVID-19 pandemic, and have benefits that outweigh the small risk to the individual in these studies. As new regulations are created, the authors encourage:
1) consideration of the public opinion
2) consideration of new research protocols, including big data
3) a direct response to concerns regarding identifiable individual biological specimens.

ABSTRACT

The Covid-19 crisis has underscored the importance of the collection and analysis of clinical and research data and specimens for ongoing work. The federal government recently completed a related revision of the human subjects research regulations, founded in the traditional principles of research ethics, but in this commentary, we argue that the analysis underpinning this revision overemphasized the importance of informed consent, given the low risks of secondary research. Governing the interests of a community is different from governing the interests of individuals, and here we suggest that, moving forward, the analyses of the risks of secondary research protocols be assessed from the perspective of the former.

AFFECTING THE HEALTHCARE WORKFORCE

CHILDCARE FOR RADIOLOGY WORKERS DURING THE COVID-19 PANDEMIC: NO SMALL MATTER

Joshi A, Garver KA, Balasubramanian S, Lee EM, Gaetke-Udager K, Agarwal PP.. J Am Coll Radiol. 2020 Jun 18:S1546-1440(20)30648-7. doi: 10.1016/j.jacr.2020.06.008. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

An 8-question anonymous survey conducted at the Department of Radiology, University of Michigan Medical School (April 24, 2020, to May 2, 2020) with 195 respondents found that reliable childcare is a significant need during the COVID-19 pandemic (92%) that extends across all professions of the team (e.g. residents, faculty, technologists). These findings suggest that enabling solutions for reliable childcare, such as assisting employees to locate childcare facilities or providing free childcare, are critical towards supporting the radiology workforce during the COVID-19 pandemic.

DISPARITIES

COVID-19: WE MUST NOT FORGET ABOUT INDIGENOUS HEALTH AND EQUITY

McLeod M, Gurney J, Harris R, Cormack D, King P.. Aust N Z J Public Health. 2020 Jul 6. doi: 10.1111/1753-6405.13015. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

An opinion article by researchers in New Zealand discusses the negative impact of the COVID-19 pandemic on the indigenous Maori people, specifically concerns about disproportionately higher household transmission rates, inequalities in healthcare,

institutional racism, and increased rates of comorbidities than their European counterparts (Figure 1 and 2). The researchers recommend the New Zealand government work in partnership with the Maori to assure equity in all healthcare decisions, especially surrounding COVID-19.

SUMMARY

In New Zealand, the indigenous Maori may be at a higher risk of contracting and dying from COVID-19. Despite this, it appears many decisions were made without accounting for the Maori perspective. The Maori may be at a higher risk of transmission based on historical context; rates of transmission from the 2009 H1N1 pandemic were twice as high in Maoris. Additionally, the impact of COVID-19 may be disproportionately high for Maoris due to higher burden of disease in this population, such as cardiovascular and pulmonary diseases (Figure 1 and 2). Finally, existing health inequalities and institutional racism may lead to differences in COVID-19 detection, this may be amplified with a stressed healthcare system. Overall, the authors recommend the government form a partnership with the Maori to assure health equity in COVID-19 and beyond.

FIGURES

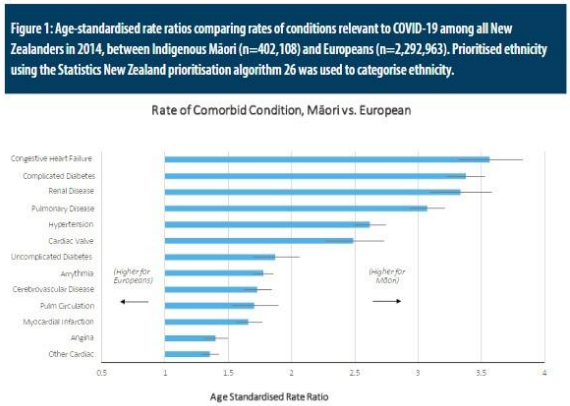

Figure 1. Age-standardised rate ratios comparing rates of conditions relevant to COVID-19 among all New Zealanders in 2014, between Indigenous Māori (n=402,108) and Europeans (n=2,292,963). Prioritised ethnicity using the Statistics New Zealand prioritisation algorithm 26 was used to categorise ethnicity.

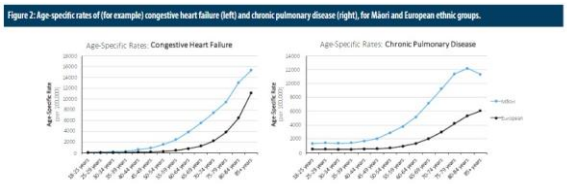

Figure 2: Age-specific rates of (for example) congestive heart failure (left) and chronic pulmonary disease (right), for Māori and European ethnic groups.

MOST CHILBLAINS OBSERVED DURING THE COVID-19 OUTBREAK OCCUR IN PATIENTS WHO ARE NEGATIVE FOR COVID-19 ON PCR AND SEROLOGY TESTING

Le Cleach L, Dousset L, Assier H, Fourati S, Barbarot S, Boulard C, Bourseau Quetier C, Cambon L, Cazanave C, Colin A, Kostrzewa E, Lesort C, Levy Roy A, Lombart F, Marco-Bonnet J, Monfort JB, Samimi M, Tardieu M, Wolkenstein P, Sbidian E, Beylot-Barry M; French Society of Dermatology.. Br J Dermatol. 2020 Jul 6. doi: 10.1111/bjd.19377. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A national survey by the French society of dermatology of 311 physician-reported acral lesion cases between March 30 and May 4, 2020 found that chilblains on the dorsum of the toes (Figure 2b) were the most common acral manifestation among the respondents, with 202 chilblains classified from the 245 respondents who sent photographs. Of the total cases, only 150 were tested for SARS-CoV-2 with 7 of 121 testing positive via RT-PCR and 5 of 75 testing positive via serology. Based on their findings, the authors suggest that chilblains do not have diagnostic or prognostic value for SARS-CoV-2 infection, although this study does not dismiss that some acral lesions could be related to COVID-19.

ABSTRACT

INTRODUCTION: Acral lesions, mainly chilblains, are the most frequently reported cutaneous lesions associated with COVID-19. In more than 80% of tested patients, nasopharyngeal swabs were negative on RT-PCR for SARS-CoV-2 when performed, and serology was generally not performed. MATERIALS AND METHODS: A national survey was launched on March 30, 2020 by the French society of dermatology asking physicians to report cases of skin manifestations in patients with suspected or confirmed COVID-19 by using a standardized questionnaire. We report the results for acral manifestations. RESULTS: We collected 311 cases of acral manifestations (58.5% females, median age 25.7 years [range 18-39]). The most frequent clinical presentation (65%) was typical chilblains. In total, 93 cases (30%) showed clinical suspicion of COVID-19, 67 (22%) had only less specific infectious symptoms, and 151 (49%) had no clinical signs preceding or during the course of acral lesions. Histology of skin biopsies was consistent with chilblains (n= 26/29). Twelve patients showed significant immunological abnormalities. Ten patients were positive among the 150 (48%) who were tested (RT-PCR and/or serology). Seven of 121 RT-PCR-tested patients were positive and 5 of 75 serology-tested patients were positive (IgG) among them RT-PCR and serology were both positive for two patients. Seven of 121 RT-PCR-tested patients were positive for SARS-CoV-2 (6%), and 5 of 75 serology-tested patients had IgG anti- SARS-CoV-2 (7 %). Tested and untested patients or those with and without confirmed COVID-19 did not differ in age, sex, history or acral-lesion clinical characteristics. CONCLUSION: The results of this survey do not rule out that SARS-CoV-2 could be directly responsible for some cases of chilblains but found no evidence of SARS-CoV-2 infection in large majority of patients with acral lesions during the COVID-19 lockdown period in France.

FIGURES

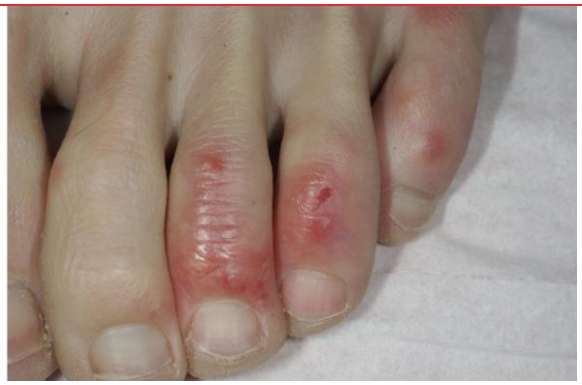

Figure 2b. Typical lesions observed in a majority of patients

ADULTS

RAPIDLY FATAL OUTCOME OF COVID-19 AFTER SUCCESSFUL EMERGENCY SURGERY DURING PANDEMIC OUTBREAK IN NORTHERN ITALY

Montali F, Palmieri G, Casali L, Pagliai L, Costi R.. Int J Surg Case Rep. 2020 Jun 20;73:9-12. doi: 10.1016/j.ijscr.2020.06.073. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

Authors in Italy present a case report of an 83-year-old male who developed COVID-19 interstitial pneumonitis after Hartmann's procedure for acute diverticulitis. They report an uneventful post-operative course aside from persistent hyperleukocytosis and increased CRP serum levels, then symptoms (fever and cough) suddenly developed on post-operative day (POD) 8, leading to respiratory failure and death 36 hours later. Upon initial ICU admission, a previous COVID-19 sick contact was identified and the patient was found to have diffuse bilateral interstitial pneumonitis (Figure 2) as well as a positive SARS-CoV-2 oropharyngeal swab test. Authors suggest that nonspecific markers of infection in patients recovering from surgery as seen in this case warrants further investigation/management (imaging, oropharyngeal swab, isolation) of SARS-CoV-2 infection, even in the absence of typical symptoms.

SUMMARY

Post-operative hospital course of an 83 year-old male with chronic obstructive pulmonary disease (COPD), arterial hypertension chronic and ischemic heart disease following Hartmann's procedure (sigmoid resection and descending colon terminal stoma) as treatment for acute diverticulitis:
- Patient with first flatus on POD 3 and solid food resumption on POD 4.
- Persistent hyperleukocytosis (WBC count between 17 × 103/μL and 20 × 103/μL) was noted through POD 8, despite antibiotic therapy (piperacillin/tazobactam and metronidazole).
- POD 8: Patient developed dry cough, sore throat, dyspnea, fever (temperature: 38.5 °C) and hypoxemia (SaO2: 88–90% on room air). He was transferred to the ICU where shortly thereafter it was discovered that his 70-year-old partner had similar symptoms one week before (on patient's POD 2) and underwent oropharyngeal swab which ultimately resulted positive for SARS-CoV-2 (POD 7). Oropharyngeal swab was then collected from the patient and a high-resolution computed tomography (HRCT) scan identified extensive bilateral interstitial pneumonitis (Figure 2).
- POD 9: Patient's respiratory function deteriorated rapidly. He underwent intubation and mechanical ventilation.
- POD 10: Oropharyngeal swab test (real-time reverse-transcriptase-polymerase-chain-reaction [rRT-PCR]) resulted positive for SARS-CoV-2. The patient died few hours later owing to respiratory failure refractory to any treatment.

SARS-CoV-2 infection seemingly did not affect surgery outcome in this particular case and postoperative course was uneventful until respiratory breakdown. The persistent increase of nonspecific inflammatory markers (hyperleukocytosis and increased CRP) were the only warning signs for days before symptom onset. Authors suggest these observations should be considered in future COVID-19 protocols to identify infected patients while also limiting viral spread within surgical units and that during a pandemic outbreak (as seen presently with COVID-19), surgeons should collect history of contagious contacts from all patients.

ABSTRACT

INTRODUCTION: A pandemic outbreak of novel coronavirus, named SARS-CoV-2 and responsible of Coronavirus Disease 2019 (COVID-19), has rapidly spread from China to Europe, being Northern Italy the first focus outside Asia. Little is known about the evolution of SARS-CoV-2 infection in patients undergoing surgery. PRESENTATION OF CASE: Here we report the first confirmed case of early postoperative SARS-CoV-2 infection in a patient recovering after Hartmann's procedure for acute diverticulitis. After an otherwise unevenful postoperative course, on post-operative day 8, the patient suddenly presented hyperpyrexia and cough, rapidly evolving to respiratory failure and death 36 h after symptoms onset. CT-scan identified bilateral, diffuse, interstitial pneumonitis and oropharyngeal swab test confirmed the presence of SARS-CoV-2. A previous contact with the partner, developing the same symptoms, remained unrecognized until ICU admission. DISCUSSION: During a pandemic outbreak, the early identification of SARS-CoV-2 infection of an inside patient initially considered to be infection-free has a pivotal importance not only for the prompt patient's management, but also to avoid infection spreading to other patients and hospital personnel.In the reported case, a more precise information to the patient regarding the imperative necessity to inform the medical personnel of any person of his entourage presenting, at any time, any tell-tale sign, symptom or examination which may be attributed to COVID-19, may have had allowed to anticipate patient's isolation and examinations

and procedures aimed at identifying such an infection. CONCLUSION: Persistent hyperleucocytosis and increased CRP serum level in spite of uneventful postoperative course were the only, aspecific markers of an ongoing SARS-CoV-2 infection before symptoms' onset, and should be considered in future clinical practice in order to adopt the prompt and appropriate patient management and limit COVID-19 contagion in surgical units.

FIGURES

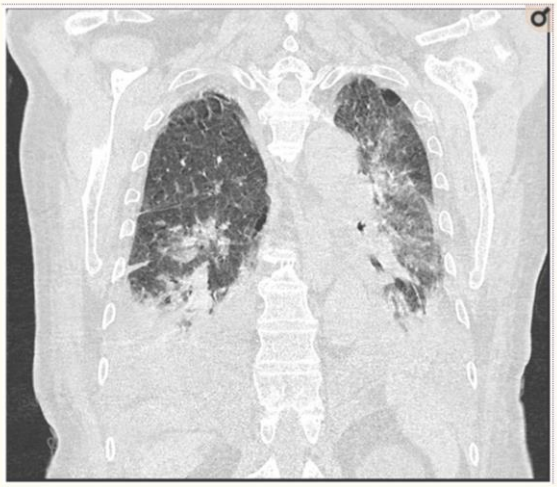

Fig. 2

High-resolution computed tomography scan of lung showing extensive bilateral interstitial pneumonitis.

PREGNANT PERSONS

COVID-19 INFECTION PRESENTING AS PANCREATITIS IN A PREGNANT WOMAN: A CASE REPORT

Rabice SR, Altshuler PC, Bovet C, Sullivan C, Gagnon AJ.. Case Rep Womens Health. 2020 Jul;27:e00228. doi: 10.1016/j.crwh.2020.e00228. Epub 2020 May 29.
Level of Evidence: Other - Case Report

BLUF

This article describes a case study involving a 36-year-old G4P2 (33-week gestation) woman with a history of type 1 diabetes mellitus, mild intermittent asthma, maternal obesity, and preeclampsia on previous pregnancy, who was admitted to the hospital three times with a SARS-CoV-2 infection over the course of two weeks due to complications with acute pancreatitis, mastitis, and preeclampsia respectively. The authors suggest that COVID-19 may incite episodes of acute pancreatitis in pregnant patients and should be an area of future study.

ABSTRACT

Background: The coronavirus 2019 (COVID-19) pandemic has posed unique challenges in healthcare. In obstetrics, there is little information available to guide practice. As new data emerge, the spectrum of initial presenting symptoms has expanded from fever, cough, and dyspnea to gastrointestinal and other symptoms in both pregnant and non-pregnant patients. Case: A 36-year-old woman, G4P2, at 33 weeks of gestation presented very early in the COVID-19 course with four days of cough and fever, without recent travel or known exposure. She appeared well, with stable vital signs, and was sent home to self-quarantine after a specimen for COVID-19 testing was collected. Two days later, she presented with nausea, vomiting, and abdominal pain, and was diagnosed with acute pancreatitis. Conclusion: To date, no cases of human pancreatitis have been identified as related to a COVID-19 infection, although multiple other gastrointestinal symptoms have been described. Given the lack of other etiology, we consider the possibility that patient's acute pancreatitis could be secondary to COVID-19 infection.

A MECHANISTIC MODEL AND THERAPEUTIC INTERVENTIONS FOR COVID-19 INVOLVING A RAS-MEDIATED BRADYKININ STORM

Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Aronow B, Jacobson D.. Elife. 2020 Jul 7;9:e59177. doi: 10.7554/eLife.59177. Online ahead of print.
Level of Evidence: 4 - Mechanism-based reasoning

BLUF

A case-control study conducted at the Oak Ridge National Laboratory found a critical imbalance in the RAAS system (Figure 4) when observing human RNA-seq data from bronchoalveolar lavage samples of 9 COVID-19 patients compared to controls. The study found an increase in ACE2 expression, which serves as the entry-point for SARS-CoV-2, and a resultant bradykinin storm leading to increased vascular permeability, infiltration of inflammatory cells, formation of hyaluronic acid membranes in the lungs, and electrolyte imbalances, all of which contribute to inhibited gas exchange in COVID-19 patients (Figure 3). Identification of these imbalances presents opportunities for clinical trials investigating the effects of targeted pharmaceutical interventions (Table 1).

ABSTRACT

Neither the disease mechanism nor treatments for COVID-19 are currently known. Here we present a novel molecular mechanism for COVID-19 that provides therapeutic intervention points that can be addressed with existing FDA-approved pharmaceuticals. The entry point for the virus is ACE2, which is a component of the counteracting hypotensive axis of RAS, that produces the nonapeptide angiotensin1-9 from angiotensin I. Bradykinin is a potent, but often forgotten, part of the vasopressor system that induces hypotension and vasodilation 1, and is regulated by ACE and enhanced by angiotensin1-9 2. Here we perform a completely new analysis on gene expression data from cells of bronchoalveolar lavage samples from COVID-19 patients that were used to sequence the virus, but the host information was discarded 3. Comparison with lavage samples from controls identify a critical imbalance in RAS represented by decreased expression of ACE in combination with increases in ACE2, renin (REN) , angiotensin (AGT), key RAS receptors (AGTR2, AGTR1), kinogen (KNG) and the kallikrein enzymes (KLKB1, many of KLK-1-15) that activate it, and both bradykinin receptors (BDKRB1, BDKRB2). This very atypical pattern of the RAS is predicted to elevate bradykinin levels in multiple tissues and systems that will likely cause increases in vascular dilation, vascular permeability and hypotension. These bradykinin-driven outcomes explain many of the symptoms being observed in COVID-19.

FIGURES

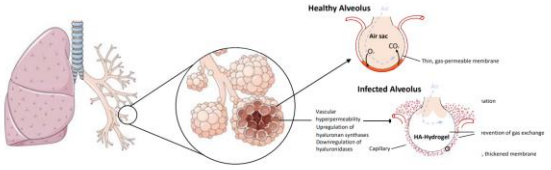

Figure 3. The upregulation of hyaluronan synthases and downregulation of hyaluronidases combined with the BK-induced hyperpermeability of the lung microvasculature leads to the formation of a HA-hydrogel that inhibits gas exchange in the alveoli of COVID-19 patients.

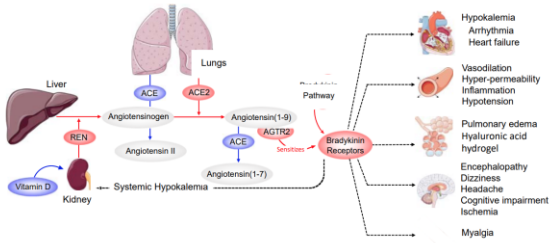

Figure 4. Systemic-level effects of critically imbalanced RAS and BK pathways. The gene expression patterns from COVID BAL samples reveal a RAS that is skewed toward low levels of ACE that result in higher levels of Ang_{1-9} and BK. High levels of ACE normally present in the lungs are responsible for generating system-wide angiotensin-derived peptides. As detailed in Figure 2, the Bradykinin-Storm is likely to affect major organs that are regulated by angiotensin derivatives. These include altered electrolyte balance from affected kidney and heart tissue, arrhythmia in dysregulated cardiac tissue, neurological disruptions in the brain, myalgia in muscles and severe alterations in oxygen uptake in the lung itself. Red colors indicate upregulation and blue downregulation.

Drug	Target	Predicted Effect
Danazol, Stanasolol	SERPING1	Reduce Bradykinin production
Icatibant	BKB2R	Reduce Bradykinin signaling
Ecallantide	KLKB1	Reduce Bradykinin production
Berinert,Cinryze,Haegarda	SERPING1	Reduce Bradykinin production
Vitamin D	REN	Reduce Renin production
Hymecromone	HAS1,HAS2, HAS3	Reduce hyaluronan
Timbetasin	TMSB4X	Increase fibrinolysis

INTEGRATED APPROACHES TO REVEAL MECHANISMS BY WHICH RNA VIRUSES REPROGRAM THE CELLULAR ENVIRONMENT

Haddad C, Davila-Calderon J, Tolbert BS.. Methods. 2020 Jul 1:S1046-2023(20)30124-9. doi: 10.1016/j.ymeth.2020.06.013. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Authors from Case Western Reserve University, Ohio summarize experimental techniques that inform on physiochemical features and protein interactions of RNA viruses such as SARS-CoV-2 (Figure 1) to better understand virus-host interactions for accelerated development of novel therapies. They describe techniques such as ScanFold, dimethyl sulfate mutational profiling and sequencing (DMS-MaP seq), antisense probing of RNA structure accessibility, crosslinking immunoprecipitation coupled with sequencing (CLIP-seq), and nuclear magnetic resonance (NMR) spectroscopy as being critical in developing comprehensive descriptions of virus-host interactions (Figure 2). Authors suggest that obtaining detailed knowledge via these integrative (collaborative) approaches will allow for advancement in the development of COVID-19 therapeutic strategies.

SUMMARY

Summary of experimental techniques as follows:

ScanFold: single-sequence computational method used to identify RNA structural motifs, helpful for studying RNA sequences with poor sequence alignment
- Identification of evolutionarily conserved functional regions can be identified using ScanFold with complementary sequence alignment data.

- ScanFold is limited in that predicted structures must be experimentally validated.

DMS-MaP seq: probes RNA secondary structure in vivo and in vitro
- As a reliable method to generate quantitative analysis of RNA secondary structures in vivo, DMS-Map seq has the advantage of providing insights into viral RNA structures under physiological conditions.
- DMS-Map seq is limited in that only the exposed A and C bases are modified, therefore obtained information is most reliable for determining which bases are not involved in stable Watson-Crick base pairs.

Antisense probing: studies effects of environmental factors on the accessibility of RNA structure
- Useful in understanding translation of viral proteins after cellular entry, replication pathways, RNA accessible regions and RNA-binding proteins (RBPs) in coronaviruses.
- A limitation of antisense RNA probing is that it requires theoretical knowledge on RBPs to efficiently study these interactions.

CLIP-seq: identifies RNA-binding protein (RBP) binding sites on RNA to better understand host-virus interactions
- It is useful to pair CLIP-seq with other structural approaches to provide detailed RNA physiochemical mechanisms.
- CLIP-seq is limited by its inability to obtain information on the surrounding RNA structural environment, which weakens interpretations of the influence of RNA-RNA interactions on RNA-protein binding.

NMR spectroscopy: produces high-resolution three-dimensional RNA to study structure and conformational dynamics
- Reconstructing RNA functional structures via NMR is helpful in understanding viral pathogenesis. Titration experiments can also be used to map binding sites and post-binding dynamics along an RNA surface.
- NMR is obviously limited due to restriction of studying molecular systems less than ~50 kDa and in buffer conditions that approximate the cellular environment.

ABSTRACT

RNA viruses are major threats to global society and mass outbreaks can cause long-lasting damage to international economies. RNA and related retro viruses represent a large and diverse family that contribute to the onset of human diseases such as AIDS; certain cancers like T cell lymphoma; severe acute respiratory illnesses as seen with COVID-19; and others. The hallmark of this viral family is the storage of genetic material in the form of RNA, and upon infecting host cells, their RNA genomes reprogram the cellular environment to favor productive viral replication. RNA is a multifunctional biomolecule that not only stores and transmits heritable information, but it also has the capacity to catalyze complex biochemical reactions. It is therefore no surprise that RNA viruses use this functional diversity to their advantage to sustain chronic or lifelong infections. Efforts to subvert RNA viruses therefore requires a deep understanding of the mechanisms by which these pathogens usurp cellular machinery. Here, we briefly summarize several experimental techniques that individually inform on key physicochemical features of viral RNA genomes and their interactions with proteins. Each of these techniques provide important vantage points to understand the complexities of virus-host interactions, but we attempt to make the case that by integrating these and similar methods, more vivid descriptions of how viruses reprogram the cellular environment emerges. These vivid descriptions should expedite the identification of novel therapeutic targets.

FIGURES

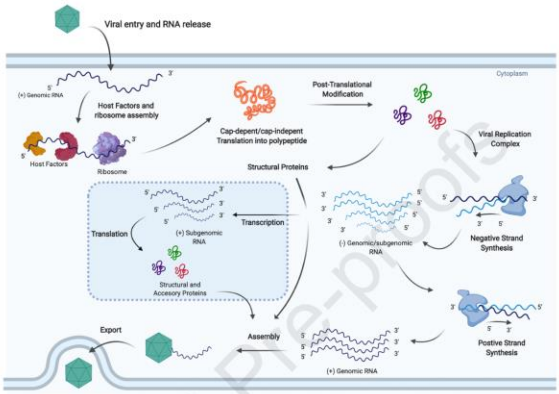

Figure 1: Generalized replication cycle for positive-sense RNA viruses depicting viral pathways by which these viruses reprogram the cellular environment.

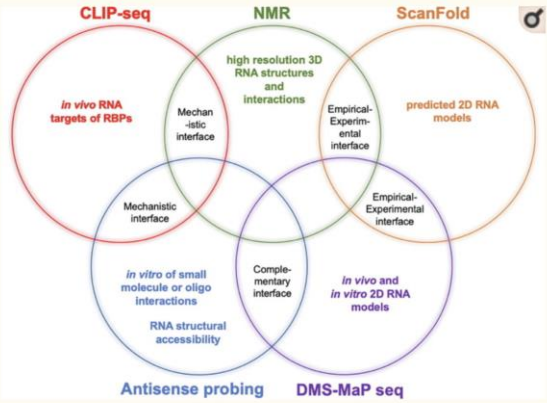

Figure 2

Integrated approaches to develop comprehensive descriptions of virus-host interactions essential for viral replication

TRANSMISSION & PREVENTION

EVALUATING USE CASES FOR HUMAN CHALLENGE TRIALS IN ACCELERATING SARS-COV-2 VACCINE DEVELOPMENT

Nguyen LC, Bakerlee CW, McKelvey TG, Rose SM, Norman AJ, Joseph N, Manheim D, McLaren MR, Jiang S, Barnes CF, Kinniment M, Foster D, Darton TC, Morrison J; 1Day Sooner Research Team.. Clin Infect Dis. 2020 Jul 6:ciaa935. doi: 10.1093/cid/ciaa935. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This paper written by researchers affiliated with Oxford, Harvard, Johns Hopkins, North Carolina State University, and the University of Haifa discusses the importance of human challenge trials (HCTs) in SARS-CoV-2 vaccine development. They suggest that HCT modeling for COVID-19 should be initiated immediately because it will require several of months before any meaningful modeling data on the pathophysiology and immune response to the virus could be generated and applied on a large-scale. The performance of an HCT is expected to take a minimum of eight months and would entail:
1. Working with vaccine manufacturers to identify an appropriate candidate in the current pipeline for use in an HCT,
2. Manufacturing the challenge virus following good manufacturing practices,
3. Dose-finding studies in order to determine the viral load necessary to produce and infection in seronegative patients, and
4. Completing the HCT itself, including at least two weeks of isolation prior to the challenge to ensure that the participants have not been previously infected and surveillance for at least another two weeks after the viral challenge.

ABSTRACT

Human challenge trials (HCTs) have been proposed as a means to accelerate SARS-CoV-2 vaccine development. We identify and discuss three potential use cases of HCTs in the current pandemic: evaluating efficacy, converging on correlates of protection, and improving understanding of pathogenesis and the human immune response. We outline the limitations of HCTs and find that HCTs are likely to be most useful for vaccine candidates currently in preclinical stages of development. We conclude that, while currently limited in their application, there are scenarios in which HCTs would be extremely beneficial. Therefore, the option of conducting HCTs to accelerate SARS-CoV-2 vaccine development should be preserved. As HCTs require many months of preparation, we recommend an immediate effort to (1) establish guidelines for HCTs for COVID-19; (2) take the first steps toward HCTs, including preparing challenge virus and making preliminary logistical arrangements; and (3) commit to periodically re-evaluating the utility of HCTs.

PREVENTION IN THE COMMUNITY

IT IS TIME TO ADDRESS AIRBORNE TRANSMISSION OF COVID-19

Morawska L, Milton DK.. Clin Infect Dis. 2020 Jul 6:ciaa939. doi: 10.1093/cid/ciaa939. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A commentary from July 2020 with support from 239 scientists highlights that SARS-CoV-2 can survive in the form of microdroplets released when an infected person exhales, coughs, or talks even from distances 1 to 2 meters away. They urge increased precautions to reduce COVID-19 spread (detailed below).

SUMMARY

The authors advocate for increased transmission precautions against airborne spread through 1) effective ventilation (ie., in public buildings, workplaces, transportation, care homes), 2) airborne infection controls (ie., exhaust, air filtration, germicidal ultraviolet lights), and 3) overcrowding prevention (ie., in public transport and buildings) (Figure 1).

FIGURES

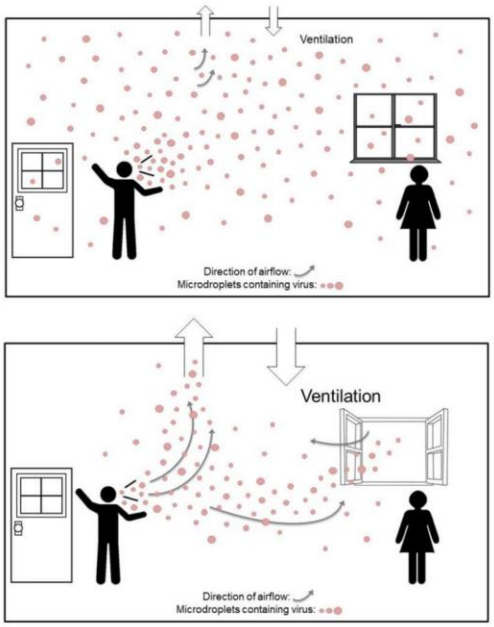

Figure 1. Illustration of SARS-CoV-2 transmission via airborne microdroplets in an enclosed environment with inadequate vs adequate ventilation.

MANAGEMENT

ACUTE CARE

SIMPLE 'RULE-OF-6' PREDICTS SEVERE COVID-19 DISEASE

Lee Dickens BS, Lim JT, Low JW, Lee CK, Sun Y, Nasir HBM, Yan G, Oon J, Yan B, Cook AR, Tambyah PA, Chai LYA.. Clin Infect Dis. 2020 Jul 6:ciaa938. doi: 10.1093/cid/ciaa938. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A two-cohort study (140 patients; discovery cohort and validation cohort) conducted in Singapore by the National University Health System discusses the "Rule-of-6" which involves using early-infection levels of ferritin above 600 ug/L, LDH above 600 U/L, and CRP above 60 mg/L as predictors of COVID-19 disease progression and deterioration to the ICU (Figure 1). This suggests a method for healthcare systems to "assist in patient treatment pathway determination, and alleviate equipment and ICU demands more effectively."

FIGURES

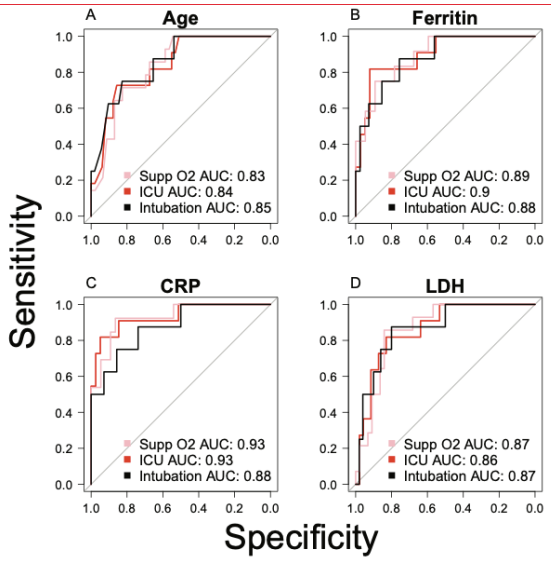

Figure 1

PEDIATRICS

SETTING REALISTIC GOALS FOR FEEDING INFANTS WHEN THEIR MOTHERS HAVE SUSPECTED OR CONFIRMED COVID-19

Mosalli R, Paes B.. Acta Paediatr. 2020 Jul 6. doi: 10.1111/apa.15459. Online ahead of print.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

Authors within the field of pediatrics provide recommendations (listed below) on breastfeeding infants for mothers with suspected or confirmed COVID-19, citing the lack of consensus from national OB/GYN organizations in the US and UK. Given the limited data on breast-feeding for mothers with confirmed or suspected COVID-19, the authors suggest that healthcare providers practice shared decision-making on breastfeeding with patients/families and provide proper education on mother-infant contact.

SUMMARY

Recommendations include, but are not limited to, the following:

For an infant born to a COVID-19 positive mother:
•Test the infant for SARS-CoV-2 at 24 and 48 hours after birth.
•The infant should be placed in a single, air-filtered room or admitted to the NICU in a single, negative pressure room if clinically unstable.
•Direct breastfeeding requires strict infection control protocols.

For a COVID-19 positive mother who wishes to pump or express breast milk:
•The mother can express breastmilk after carefully washing both her breasts and hands. Breastmilk can then be fed to the infant by a non-infected caregiver.
•Breast pumps should be cleaned thoroughly.

If a COVID-19 positive mother is discharged and the baby remains in the NICU:
•The mother cannot visit her baby until she has had two negative virus tests, 24-hours apart.
•The infant can be fed expressed breast milk, donor breast milk, or formula. Breast milk pumped at home can only be used once the mother is clinically cleared from the virus.

For an infant with a mother who may have COVID-19:
•The mother should be temporarily separated from her child right after birth while waiting on test results.
•The infant should be placed in an isolated negative pressure room.

ABSTRACT

The pandemic is a stressful time for everyone, including mothers and healthcare providers who are concerned about the best and safest way to feed babies born to mothers with suspected or confirmed COVID-19. There is lack of consensus regarding mother-infant contact, unless the mother definitely has COVID-19 and even then there is a distinct lack of data to devise protocols for everyday clinical practice.1,2.

DERMATOLOGY

RISK OF COVID-19 IN DERMATOLOGIC PATIENTS ON LONG-TERM IMMUNOMODULATORY THERAPY

Holcomb ZE, Santillan MR, Morss-Walton PC, Salian P, Her MJ, Giannotti NM, Kimball AB, Porter ML.. J Am Acad Dermatol. 2020 Jul 1:S0190-9622(20)32099-5. doi: 10.1016/j.jaad.2020.06.999. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cross-sectional analysis conducted by various medical institutions in Boston, MA found among 327 patients who are taking systemic immunomodulatory medications for dermatologic conditions, there were 5 COVID-19 positive infections and 1 hospitalization, which is in-line with Boston's general population infection rate (~1%) and hospitalization rate (slightly < 10% of cases). Their results suggest "COVID-19 and poor outcomes are minimally impacted by long term immunomodulatory medications" (Table 1). Of note, the authors acknowledge their study was limited by their inability to test for potential asymptomatic cases.

FIGURES

Table 1. Baseline characteristics of patients on immunosuppressive therapy.

Characteristic	All Patients (n=412)	Positive and Presumed Positive Patients (n=5)
Demographics		
Mean Age (years) ± SD	48.2 ± 15.9	48.4
Male – number (%)	196 (48)	2 (40)
Female – number (%)	216 (52)	3 (60)
Live in Massachusetts – number (%)	382 (93)	5 (100)
Medications		
Biologics		
TNFα Inhibitor	117 (28.4%)	2 (40%)
IL-17 Inhibitor	29 (7%)	0
IL-23 Inhibitor	30 (7.3%)	0
IL-12/23 Inhibitor	54 (13.2%)	1 (20%)
JAK Inhibitor	12 (2.9%)	0
Traditional Immunosuppressives		
Methotrexate	48 (11.7%)	1 (20%)
Cyclosporine	5 (1.2%)	0
Mycophenolate mofetil	8 (1.9%)	0
Other Immunomodulatory Therapies		
IL-4Rα Inhibitor	65 (15.8%)	0
Apremilast	26 (6.3%)	1 (20%)
Multiple Medications (combination of multiple biologics, traditional immunosuppressives and/or other immunomodulatory therapies)	18 (4.4%)	0
COVID-19 Infection Outcomes		
COVID-related Hospitalization	1 (0.2%)	1 (20%)
Any Cause of Death	0	0
Degree of Contact with Others		
	All Patients (n=260)	Positive and Presumed Positive Patients (n=5)
None (patient generally not leaving home)	158 (60.8%)	1 (33%)
Patient with minimal degree of contact at work	31 (11.9%)	0
Patient with minimal degree of contact at home	31 (11.9%)	1 (33%)
Patient with minimal degree of contact both at work and home	9 (3.5%)	0
Patient with high degree of contact at work and home	22 (8.5%)	1 (33%)

Table 1: Baseline characteristics of patients on immunosuppressive therapy

CARDIOLOGY

CORONAVIRUS DISEASE 2019 (COVID-19) CATHETERIZATION LABORATORY SURVEY

Banerjee S, Tarantini G, Abu-Fadel M, Banerjee A, Little BB, Sorajja P, Shishehbor MH, Brilakis ES.. J Am Heart Assoc. 2020 Jun 9:e017175. doi: 10.1161/JAHA.120.017175. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

A 40 question survey filled out by 509 interventional cardiologists between April 1st and April 11th found a significant decrease in procedures, an increase in personal safety measures, changes in scheduling, a limited amount of FIT-tested N95 masks, and adoption of telemedicine. "The findings of this survey may help identify and address improvements that can be made regarding institutional and personal responses to COVID-19 pandemic."

ABSTRACT

Background The Coronavirus Disease 2019 (COVID-19) pandemic is expected to affect operations and lifestyles of interventional cardiologists (ICs) around the world in unprecedented ways. Timely gathering of information on this topic can provide valuable insight and improve the handling of the ongoing and future pandemic outbreaks. Methods and Results A survey instrument developed by the authors was disseminated via email, text messaging, WhatsAppTM and social media to ICs between April 6 and April 11, 2020. A total of 509 responses were collected from 18 countries, mainly from the U.S. (51%) and Italy (36%). Operators reported significant decline in coronary, structural heart and endovascular procedure volumes. Personal protection equipment (PPE) was available to 95% of respondents, however FIT-tested N95 or equivalent masks were available to only 70% and 74% indicated absence of COVID-19 pre-testing. Most (83%) operators expressed concern when asked to perform cardiac catheterization on a suspected or confirmed COVID-19 patient, primarily due to fear of viral transmission (88%). While the survey demonstrated significant compliance with social distancing, high use of telemedicine (69%) and online education platforms (80%), there was concern over impending financial loss. Conclusions Our survey indicates significant reduction in invasive procedure volumes and concern for viral transmission. There is near universal adoption of PPEs, however COVID-19 pre-testing and access to FIT-tested N95 masks is suboptimal. While there is concern over impending financial loss, substantial engagement in telemedicine and online education is reported.

KINETICS OF VIRAL LOAD AND ANTIBODY RESPONSE IN RELATION TO COVID-19 SEVERITY

Wang Y, Zhang L, Sang L, Ye F, Ruan S, Zhong B, Song T, Alshukairi AN, Chen R, Zhang Z, Gan M, Zhu A, Huang Y, Luo L, Mok CK, Al Gethamy MM, Tan H, Li Z, Huang X, Li F, Sun J, Zhang Y, Wen L, Li Y, Chen Z, Zhuang Z, Zhuo J, Chen C, Kuang L, Wang J, Lv H, Jiang Y, Li M, Lin Y, Deng Y, Tang L, Liang J, Huang J, Perlman S, Zhong N, Zhao J, Malik Peiris JS, Li Y, Zhao J.. J Clin Invest. 2020 Jul 7:138759. doi: 10.1172/JCI138759. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Chinese researchers investigated SARS-CoV-2 immune response using prospectively collected samples from all hospitalized patients with RT-PCR confirmed COVID-19 in four hospitals in Guangdong Province from January 28-February 24, 2020 (n=23, Table 1). They found severely ill patients demonstrated longer viral shedding, had higher neutralizing antibody titers, and were more likely to demonstrate IgM response than mildly ill patients (Summary; Figure 1,2,6); they also found SARS-CoV-2 S and N proteins did not cross react with MERS-CoV (Summary). The authors suggest their findings can aid in interpretation of laboratory diagnostics and augment broader understanding of immunologic response to SARS-CoV-2.

SUMMARY

The authors analyzed nasal, throat, sputum, fecal, urine, plasma, and gastric juice sample(s) from 23 patients during their admissions. While the authors do not provide an explicit definition, they group patients as "severely ill" versus "mildly ill," presumably ascribing "severely ill" to ICU patients based on their demographic table (Table 1). Comparison samples were from 96 plasma donors from 2017-2018.
They conducted a variety of analyses:
1. Viral shedding was monitored with RT-PCR. Patients with severe disease shed virus for 30-40 days post-disease onset; most mild patients did not have detectable viral loads after 15 days (Figure 1). While they mainly detected virus in respiratory samples, virus was also present in fecal samples from severely ill patients.
2. ELISA assays were used for serologic analysis. Patients with severe disease demonstrated plasma IgM response within 1-2 weeks, while most mild patients had no IgM response (Figure 2). Most patients had an IgG response after 10-15 days, which endured for at least six weeks. Only in severe patients was antibody detected in other body fluids (sputum, urine). All patients seroconverted against spike proteins S (aa 1-1213) and S2 (aa 686-1213) seven to 14 days after onset.
3. Using SARS-CoV-2 spike protein fragments, the authors tested plasma response to different antigens via ELISA. All patients seroconverted against spike proteins S (aa 1-1213) and S2 (aa 686-1213) seven to 14 days after onset. They also tested cross reactivity between all six human respiratory coronaviruses and found SARS-CoV-2 S and N proteins did not cross react with MERS-CoV but did with SARS-CoV.
4. Neutralization activity was assessed via a luciferase reporter-based pseudotype neutralization assay and focus reduction neutralization test. Severely ill patients developed higher neutralizing antibody titers than mildly ill patients, without correlation between viral load and neutralizing titer.

ABSTRACT

The SARS-CoV-2 is the causative agent for COVID-19 pneumonia. Little is known about the kinetics, tissue distribution, cross-reactivity and neutralization antibody response in COVID-19 patients. Two groups of RT-PCR confirmed COVID-19 patients were enrolled in this study, including 12 severe patients in ICUs who needed mechanical ventilation and 11 mild patients in isolation wards. Serial clinical samples were collected for laboratory detection. Results showed that most of the severe patients had viral shedding in a variety of tissues for 20~40 days post onset of disease (8/12, 66.7%); while the majority of mild patients had viral shedding restricted to the respiratory tract and had no detectable virus RNA after 10 days post-onset (9/11, 81.8%). Mild patients showed significantly lower IgM response compared with that of the severe group. IgG responses were detected in most patients in both severe and mild groups at 9 days post onset and remained high level throughout the study. Antibodies cross-reactive to SARS-CoV and SARS-CoV-2 were detected in COVID-19 patients but not in MERS patients. High-levels of neutralizing antibodies were induced after about 10 days post onset in both severe and mild patients which were higher in the severe group. SARS-CoV-2 pseudotype neutralization test and focus reduction neutralization test with authentic virus showed consistent results. Sera from COVID-19 patients, but not convalescent SARS and MERS patients inhibited SARS-CoV-2 entry. Anti-SARS-CoV-2 S and N IgG level exhibited moderate correlation with neutralization titers in patients' plasma. This study improves our understanding of immune response in human after SARS-CoV-2 infection.

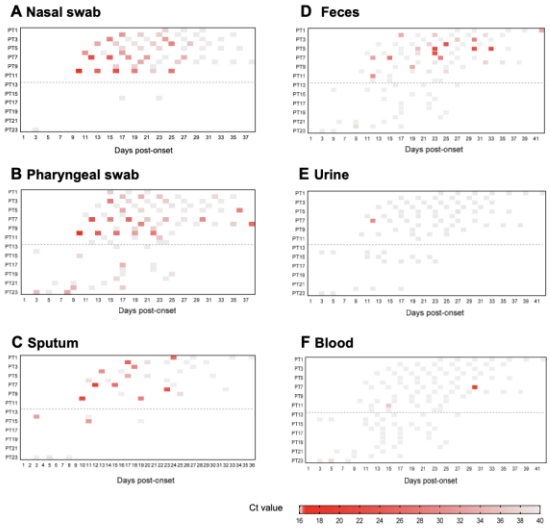

Figure 1. Temporal profile of serial viral load from different tissue samples. Viral loads in patients in the ICU (PT1~PT12) and mild patients with mild disease (PT13~PT23) in nasal swabs (**A**), pharyngeal swabs (**B**), sputum (**C**), feces (**D**), urine (**E**) and blood (**F**) were measured. X-axis indicates the days post-onset, y-axis indicates patient numbers. Heat map of Ct values of viral loads were shown. Ct value < 37 indicates the presence of SARS-CoV-2 nucleic acid in the samples. Each square represents one sample detected and gray squares indicate viral nucleotide acid negative.

Figure 2

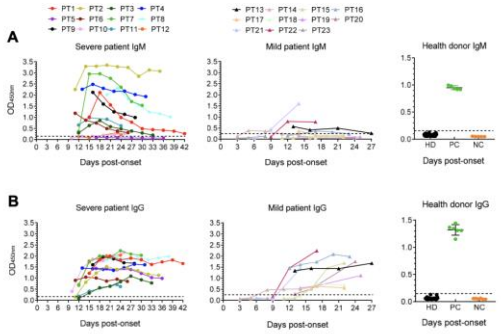

Figure 2. Kinetics of IgM and IgG responses against SARS-CoV-2 in severe and mild patients. IgM (**A**) and IgG (**B**) antibody response against the N protein of SARS-CoV-2 in plasma were detected. Serial plasma samples were collected from 12 severe and 11 mild SARS-CoV-2 infected patients. Forty-eight plasma previously collected from healthy voluntary donors in 2017-2018 were used as healthy donor group (HD). Positive (PC) and negative (NC) controls provided by detection kit were included to ensure test validity.

Table 1. Demographic and clinical outcomes of SARS-CoV-2 infected patients

	Patient number	Gender[1]	Age	City, Country	Visited Wuhan Hubei, China[2]	Direct contact with confirmed cases[3]	Receiving mechanical ventilation[4]	Clinical outcome
Group A: Severe patients (n=12)	PT1	M	67	Guangzhou, China	Y	N	Y	Still in ICU
	PT2	M	49	Guangzhou, China	Y	Y	Y	Still in ICU
	PT3	M	50	Guangzhou, China	Y	NA	Y	Still in ICU
	PT4	M	53	Guangzhou, China	N	Y	Y	Still in ICU
	PT5	M	61	Guangzhou, China	Y	N	Y	Still in ICU
	PT6	M	42	Guangzhou, China	Y	NA	Y	Transferred out of ICU
	PT7	M	72	Guangzhou, China	N	Y	Y	Still in ICU
	PT8	M	58	Guangzhou, China	N	Y	Y	Still in ICU
	PT9	M	42	Guangzhou, China	Y	Y	Y	Transferred out of ICU
	P10	M	79	Guangzhou, China	N	Y	Y	Still in ICU
	PT11	M	61	Yangjiang, China	Y	Y	Y	Still in ICU
	PT12	F	60	Yangjiang, China	Y	Y	Y	Still in ICU
Group B: mild patients (n=11)	PT13	F	56	Yangjiang, China	Y	Y	N	Discharged
	PT14	F	25	Guangzhou, China	N	Y	N	Discharged
	PT15	M	50	Guangzhou, China	N	N	N	Isolation ward
	PT16	F	82	Guangzhou, China	N	Y	N	Isolation ward
	PT17	M	24	Yangjiang, China	Y	N	N	Discharged
	PT18	M	35	Yangjiang, China	Y	Y	N	Discharged
	PT19	M	69	Yangjiang, China	Y	N	N	Discharged
	PT20	M	77	Yangjiang, China	Y	Y	N	Discharged
	PT21	M	52	Qingyuan, China	Y	NA	N	Discharged
	PT22	M	50	Qingyuan, China	Y	NA	N	Discharged
	PT23	M	65	Qingyuan, China	Y	NA	N	Isolation ward

[1]Gender: M male, F female
[2]Visited Wuhan Hubei, China. Y yes, N no, NA not available.
[3]Direct contact with confirmed cases. Y yes, N no, NA not available
[4]Receiving mechanical ventilation

CORONAVIRUSES AND INTEGRIN AVB3: DOES THYROID HORMONE MODIFY THE RELATIONSHIP?

Davis PJ, Lin HY, Hercbergs A, Keating KA, Mousa SA.. Endocr Res. 2020 Aug;45(3):210-215. doi: 10.1080/07435800.2020.1767127.
Level of Evidence: 5 - Review / Literature Review

BLUF

Researchers from the US and Taiwan performed a literature review to evaluate the cell uptake of the porcine epidemic diarrhea α-coronavirus (PEDV; a virus proposed as a model for other coronaviruses) following binding to integrin av-beta-3. They found that the thyroid hormone L-thyroxine may enhance the uptake of integrin av-beta-3 and PEDV through increasing gene expression of integrin monomers and aiding cell uptake of the integrin. Based on this possible role of T4 in coronavirus internalization, the authors suggest that thyroid analogues, such as deaminated T4, may be considered for potential therapeutics in blocking SARS-CoV-2 uptake.

ABSTRACT

BACKGROUND: Uptake of coronaviruses by target cells involves binding of the virus by cell ectoenzymes. For the etiologic agent of COVID-19 (SARS-CoV-2), a receptor has been identified as angiotensin-converting enzyme-2 (ACE2). Recently it has been suggested that plasma membrane integrins may be involved in the internalization and replication of clinically important coronaviruses. For example, integrin alphavbeta3 is involved in the cell uptake of a model porcine enteric alpha-coronavirus that causes human epidemics. ACE2 modulates the intracellular signaling generated by integrins. OBJECTIVE: We propose that the cellular internalization of alphavbeta3 applies to uptake of coronaviruses bound to the integrin, and we evaluate the possibility that clinical host T4 may contribute to target cell uptake of coronavirus and to the consequence of cell uptake of the virus. DISCUSSION AND CONCLUSIONS: The viral binding domain of the integrin is near the Arg-Gly-Asp (RGD) peptide-binding site and RGD molecules can affect virus binding. In this same locale on integrin alphavbeta3 is the receptor for thyroid hormone analogues, particularly, L-thyroxine (T4). By binding to the integrin, T4 has been shown to modulate the affinity of the integrin for other proteins, to control internalization of alphavbeta3 and to regulate the expression of a panel of cytokine genes, some of which are components of the 'cytokine storm' of viral infections. If T4 does influence coronavirus uptake by target cells, other thyroid hormone analogues, such as deaminated T4 and deaminated 3,5,3'-triiodo-L-thyronine (T3), are candidate agents to block the virus-relevant actions of T4 at integrin alphavbeta3 and possibly restrict virus uptake.

LABORATORY DIAGNOSIS OF CORONAVIRUS DISEASE-2019 (COVID-19)

Li C, Zhao C, Bao J, Tang B, Wang Y, Gu B.. Clin Chim Acta. 2020 Jul 1:S0009-8981(20)30309-0. doi: 10.1016/j.cca.2020.06.045. Online ahead of print.
Level of Evidence: 3 - Review / Literature Review

BLUF

A literature review written by a group of researchers from China and the US that discusses the variety of different laboratory tests available for COVID-19 diagnosis (Table 1). They found that
1. Portable benchtop tests such as Xpert Express assay and ID NOW are suitable for quick, infection control decision making situations,
2. Highly accurate tests such as RT-PCR may be more useful in controlled situations to see the extent of infection spread in the population, and
3. Both molecular and immunological tests were not suitable for point-of-care use due to their "time-consuming, expensive equipment and biosafety requirements."
Together, these results indicate that a combination of serological testing (which is faster, cheaper, and easy to use) employed at point-of-care locations alongside molecular testing mechanisms (which is slower and expensive but more accurate) at large hub locations could enable effective detection and potentially control of the spread of SARS-CoV-2.

ABSTRACT

The outbreak of Coronavirus Disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has threatened health worldwide. As of the end of 2020, there were nearly 10 million confirmed cases and nearly 5 million deaths associated with COVID-19. Rapid and early laboratory diagnosis of COVID-19 is the main focus of treatment and control. Molecular tests are the basis for confirmation of COVID-19, but serological tests for SARS-CoV-2 are widely available and play an increasingly important role in understanding the epidemiology of the virus and in identifying populations at higher risk for infection. Point-of-care tests have the advantage of rapid, accurate, portable, low cost and non-specific device requirements, which provide great help for disease diagnosis and detection. This review will discuss the performance of different laboratory diagnostic tests and platforms, as well as suitable clinical samples for testing, and related biosafety protection. This review shall guide for the diagnosis of COVID-19 caused by SARS-CoV-2.

FIGURES

Table 1. Advantages and disadvantages of the laboratory diagnostic methods for SARS-CoV-2

Diagnostic approach	Method	Testing scenarios	Advantages	Disadvantages	Reference
Neutralization tests	VNT and PVNT	BSL-2 or BSL-3 laboratories, pathogen laboratories	Authoritative, simple, low cost, reliable, high sensitivity	Time-consuming, long-period, laborious, perform in BSL-3 or BSL-2 lab	[78, 80, 94, 95]
PCR	qRT-PCR	BSL-2 laboratories, public health institutes, quarantine depots	High specificity, not require expensive equipment, time-saving	Complex pretreatment steps, requires skillful, false negative	[104, 105]
	Nested RT-PCR	BSL-2 laboratories, prefectural and municipal public health institutes, quarantine depots	High sensitivity, specificity was higher than that of RT-PCR, suitable for detect low-copy-number viruses, time-saving	Complex pretreatment steps, requires skillful, manpower, the second PCR amplification may caused cross-contamination	[51, 52]
	ddPCR	BSL-2 laboratories, public health institutes, quarantine depots	Quantitative, sensitive, suitable for detect samples with low viral load, independent of a traditional standard curve	Susceptible to exogenous contamination, expensive than qRT-PCR, calibrant materials need to be defined	[54, 55]
	Nanoparticles - based amplification	BSL-2 laboratories, environmental testing institutions	High sensitivity, adopted in fully-automated RNA extraction systems, excellent RNA binding performances	Complex pretreatment steps, requires skillful, expensive than qRT-PCR, with the risk of photobleaching	[57, 59, 60]
	RT-LAMP	Basic laboratories,	Time-saving,	Easy to be contaminated	[56-58]

Table 1. Advantages and disadvantages of the laboratory diagnostic methods for SARS-CoV-2. Neutralization Tests and PCR.

		community nursing sites	thermostatic, sensitive, user-friendly, sophisticated equipment-free	and cause false-positive, nonspecific amplification cannot be easily identified, requires skillful	
	Portable benchtop-sized analyzers	Clinical laboratories, physicians' office, emergency departments	Automatic, portable, rapid, not requires trained staff	Inconsistent performance, may lack sensitivity in weakly positive samples	[62-68]
Immunological diagnostic	ELISA	Clinical laboratories, public health institutes	Quantitative detection, simple, a low risk of infection, convenient, stable reagent	Time-consuming, low sensitivity, cross-reactivity, expensive monoclonal antibody, low-throughput	[78, 79]
	IFA	Clinical laboratories, pathogen laboratories, public health institutes	Avoid the interference of endogenous biotin and contamination of antigens in the blood	Non-specific fluorescence, subjective, low-throughput, time-consuming	[78, 80].
	CLIA	Clinical laboratories, public health institutes	Automatic, rapid, quantitative, high sensitivity, broad linear range, stable results	Sophisticated instruments, high requirements for equipment and environment, not suitable for detect whole blood samples,	[81-84]
	LFA	Clinical laboratories, physicians' offices, emergency departments, community service stations	Rapid, convenient, on-site screening, inexpensive, small sample volume	Low sensitivity, cross-reactivity, inconsistent performance, not suitable for early diagnosis, low-throughput	[85-88]

Table 1. Advantages and disadvantages of the laboratory diagnostic methods for SARS-CoV-2. Immunologic Diagnostics.

	Microarray and microfluidic chip	Clinical laboratories, emergency departments, community service stations	Small size, high sensitivity, automatic, high-throughput, portable	Core technologies lack norms and standards, high cost, nonspecific binding of proteins	[89-92]
Genome sequencing	Metatranscriptomic sequencing	BSL-2 laboratories, genetic testing centres, research laboratories	Simple, reduce the cost, does not claim a reference sequence	Increase cost, sophisticated instruments, insufficient coverage and depth	[11, 13]
	Nanopore targeted sequencing	BSL-2 laboratories, genetic testing centres, research laboratories	Broad detection range, rapid turnaround time, long-read, high-accuracy, monitor the variation	Increase cost, sophisticated instruments, requires skillful	[97]
	Amplicon se quencing	BSL-2 laboratories, genetic testing centres, research laboratories	Convenient, high sensitivity, suitable for detect samples with low viral load, economical	Sophisticated instruments, not be used to sequence highly diverse or recombinant viruses	[96]
	Hybrid capture - based sequencing	BSL-2 laboratories, genetic testing centres, research laboratories	High sensitivity, suitable for detect intra-individual variations	Sophisticated instruments, not be used to sequence highly diverse or recombinant viruses	[96]

Table 1. Advantages and disadvantages of the laboratory diagnostic methods for SARS-CoV-2. Immunologic Diagnostics.

DEVELOPMENTS IN TREATMENTS

SARS-COV-2 VIRAL LOAD AND ANTIBODY RESPONSES: THE CASE FOR CONVALESCENT PLASMA THERAPY

Casadevall A, Joyner MJ, Pirofski LA.. J Clin Invest. 2020 Jul 7:139760. doi: 10.1172/JCI139760. Online ahead of print.
Level of Evidence: 4 - Expert Opinion

BLUF

An expert opinion by authors at Johns Hopkins, Mayo Clinic, and Albert Einstein College of Medicine cites prior research indicating lack of antibody response to SARS-CoV-2 in the first 10 days of COVID-19 infection. They suggest that administration of convalescent antibody via plasma therapy in early stages of disease course could support viral clearance,

improve function in immune modulation, limit viral proliferation, and dampen the detrimental inflammatory response (Figure 1).

ABSTRACT

Most patients with COVID-19 lack antibody to SARS-CoV-2 in the first 10 days of illness while the virus drives disease pathogenesis. SARS-CoV-2 antibody deficiency in the setting of a tissue viral burden suggests that using an antibody as a therapeutic agent would augment the antiviral immune response. In this issue of the JCI, Wang and collaborators describe the kinetics of viral load and antibody responses of 23 individuals with COVID-19 with mild and severe disease. The researchers found: 1) individuals with mild and severe disease produced neutralizing IgG to SARS-CoV-2 10 days after disease onset; 2) SARS-CoV-2 persisted longer in those with severe disease; and 3) there was cross-reactivity between antibodies to SARS-CoV-1 and SARS-CoV-2, but only antibodies from patients with COVID-19 neutralized SARS-CoV-2. These observations provide important information on the serological response to SARS-CoV-2 of hospitalized patients with COVID-19 that can inform the use of convalescent plasma therapy.

FIGURES

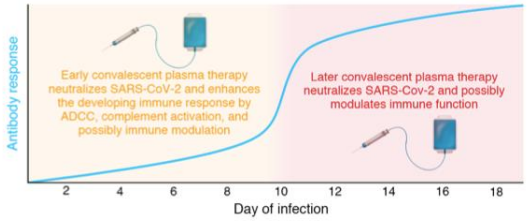

Figure 1. Early and later administration of convalescent plasma in the context of the developing antibody response. Patients with COVID-19 mount measurable antibody responses around day 10, which peaks by day 15, suggesting that convalescent plasma may benefit patients early in the disease course.

RNA-DEPENDENT RNA POLYMERASE OF SARS-COV-2 AS A THERAPEUTIC TARGET

Wang Y, Anirudhan V, Du R, Cui Q, Rong L.. J Med Virol. 2020 Jul 7. doi: 10.1002/jmv.26264. Online ahead of print.
Level of Evidence: 4 - Review / Literature Review

BLUF

Authors from Shandong University of Traditional Chinese Medicine and the University of Illinois at Chicago review the therapeutic potential of several RNA-dependent RNA polymerase (RdRp) inhibitors for SARS-CoV-2, including: sofosbuvir and galidesivir (anti-HCV drugs), ribavirin (broad spectrum antiviral), favipiravir (anti-influenza drug), remdesivir and EIDD-2801 (Ebola/coronavirus agents). The authors suggest that remdesivir is not an effective cure for COVID-19 based on findings from recent clinical and randomized double-blind controlled trials; however, the other RdRp inhibitors should be further evaluated as treatment options for SARS-CoV-2.

ABSTRACT

The global pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), named coronavirus disease 2019 (COVID-19), has infected more than 8.9 million people worldwide. This calls for urgent effective therapeutic measures. RNA-dependent RNA polymerase (RdRp) activity in viral transcription and replication has been recognized as an attractive target to design novel antiviral strategies. Although SARS-CoV-2 shares less genetic similarity with SARS-CoV (~79%) and Middle East respiratory syndrome (MERS)-CoV (~50%), the respective RdRps of the three coronaviruses are highly conserved, suggesting that RdRp is a good broad-spectrum antiviral target for CoVs. In this review, we discuss the antiviral potential of RdRp inhibitors (mainly nucleoside analogues) with an aim to provide a comprehensive account of drug discovery on SARS-CoV-2. This article is protected by copyright. All rights reserved.

PROPOSING MINIMUM REQUIREMENTS FOR ANNOUNCING CLINICAL TRIAL RESULTS DURING THE COVID-19 PANDEMIC

Siedner MJ, Gandhi RT.. Clin Infect Dis. 2020 Jul 8:ciaa945. doi: 10.1093/cid/ciaa945. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

In response to a press release on June 13 about the preliminary results of clinical trials evaluating dexamethasone's possible mortality benefit for COVID-19 treatment, the authors propose a set of minimum requirements for disseminating clinical results during the COVID-19 pandemic (Table 1). They also present recommendations to have the following: updated in-trials registry, release of full study protocol, informal webinar, pre-print/publication, and an approved data safety monitoring board (DSMB) report. These proposals provide more support to preliminary results by allowing an opportunity for scientific scrutiny before allowing limited, potentially rushed, study results to influence clinical practice.

FIGURES

Table 1. Minimum suggested data elements to report at the time of initial public dissemination of clinical trial results

Data Element	Minimal Reporting	Relevance	Examples for COVID-19 Clinical Trials
Study design	-Randomization and arms -Control design -Blinding -Geographic locations -Study timing and duration	Provides context on study quality, strengths, and potential weaknesses	-Open-label versus blinded (placebo and/or dummy description) -Components of standard of care -Nature of standard of care -Location and timing to put in context of epidemic trends
Participant characteristics	-Sample size in each arm -Sociodemographic characteristics -Comorbidities and clinical characteristics	Required to determine generalizability of study population and patient selection for clinical use	-Age -Sex -Co-morbidities (diabetes, obesity, immunosuppression) -Concurrent therapies (other antiviral agents or immunosuppression)
Primary findings	-Protocol-specified primary outcome including absolute and relevant events and confidence intervals -Major pre-specified secondary outcomes including sub-groups and secondary outcomes are welcome, but not in lieu of the primary outcome in the total study population	Required to determine effect size	-Depending on protocol, mortality, requirement for mechanical ventilation, duration of disease -If secondary outcomes are reported they should be labeled as such -Sub-group analyses should include interaction terms
Toxicity and Safety Data	-Major adverse events by arm, including deaths -Protocol-specified adverse events	Required for patient monitoring and safety assessments	-For antivirals these should include standard FDA-defined adverse events -For immunosuppressive agents, data on secondary infections should be included
Study Limitations	-Study-dependent	Permits public and scientific community to understand the scope and potential interpretation concerns	-Generalizability -Issues related to open-label designs -Consideration of balance between randomized arms or in sub-groups

FDA: Food and drug administration

Table 1. Minimum suggested data elements to report at the time of initial public dissemination of clinical trial results

LONELINESS AND BELONGING: EXPLORING EXPERIENCES WITH THE COVID-19 PANDEMIC IN PSYCHO-ONCOLOGY

Schellekens MPJ, van der Lee ML.. Psychooncology. 2020 Jul 6. doi: 10.1002/pon.5459. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A survey of 233 psycho-oncology patients and 41 of their family members (demographics available in Table 1) was conducted at the Helen Dowling Institute evaluating the psychological burden of the COVID-19 pandemic. The survey found that although patients had increased fear of infection and feelings of loneliness, some patients (45.5%) and family members (41.5%) had an increased sense of peace and belonging to society as a result of the lockdown and subsequently reduced pressures of daily living. The results of this survey may assist in improving communication between patients and healthcare professionals to reduce the psychological burden on patients during the COVID-19 pandemic.

FIGURES

	233 patients n (%)	**41 family members** n (%)
Sex, female	172 (73.8)	28 (68.3)
Age		
<30	8 (3.4)	1 (2.4)
30-39	25 (10.7)	8 (19.5)
40-49	40 (17.2)	8 (19.5)
50-59	77 (33.0)	12 (29.3)
60-69	62 (26.6)	10 (24.4)
≥70	21 (9.0)	2 (4.9)
Living situation		
Alone	45 (19.3)	11 (26.8)
With partner	76 (32.6)	11 (26.8)
With partner and children	98 (42.1)	14 (34.1)
With children	12 (5.2)	4 (9.8)
With parents	1 (0.4)	1 (2.4)
Education		
Primary/lower secondary	12 (5.2)	3 (7.3)
Upper secondary	90 (39.1)	12 (29.3)
Higher vocational training/university	124 (53.3)	25 (61.0)
Start psychological treatment		
Prior 2019	52 (22.3)	15 (36.6)
Since 2019	94 (40.3)	15 (36.6)
Since 2020	87 (37.3)	11 (26.8)

Table 1. Demographic characteristics of the 274 survey respondents.

ACKNOWLEDGEMENTS

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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