# The Daily COVID-19 Literature Surveillance Summary

## November 19, 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

# 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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# EXECUTIVE SUMMARY

**Understanding the Pathology**

- An vitro study by microbiologists from University of Kansas Medical Center monitored long-term SARS-CoV-2 replication in polarized human airway epithelium cells (HAE) of lung bronchi sampled from 4 donors to model the human mucociliary airway epithelium, suggesting that epithelial cell regeneration may provide opportunity for maintenance and recurrent infection by SARS-CoV-2.

**Management**

- Hematologists at the Italian National Blood Centre in Rome, Italy review literature regarding management of SARS-CoV-2 induced coagulopathy and outline proposed pathophysiology, laboratory studies (inflammatory markers [IL-6, CRP, procalcitonin, ferritin], coagulopathy markers [D-Dimer, platelet count, fibrinogen]), and potential usefulness of prophylactic treatment with low molecular weight heparin (LMWH). They recommend anticoagulant prophylaxis should be personalized according to each patient's disease course and thrombotic risk profile.

**Adjusting Practice During COVID-19**

- Microbiology and flow cytometry researchers suggest new guidelines for modifying regulations in Shared Resource Laboratories (SRLs) in response to the COVID-19 pandemic by providing a risk assessment and proposed mitigation measures. Overall, the authors recommend limiting access to laboratories and modifying behaviors within the laboratories (such as equipment use, mask wearing, etc.) to make these typically high-trafficked SRL areas safer in the context of the pandemic.

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# UNDERSTANDING THE PATHOLOGY

## POTENTIAL INFLUENCE OF OLFACTORY, GUSTATORY, AND PHARYNGOLARYNGEAL SENSORY DYSFUNCTIONS ON SWALLOWING PHYSIOLOGY IN COVID-19

Vergara J, Lirani-Silva C, Brodsky MB, Miles A, Clavé P, Nascimento W, Mourão LF.. Otolaryngol Head Neck Surg. 2020 Nov 10:194599820972680. doi: 10.1177/0194599820972680. Online ahead of print.
Level of Evidence: Other - Expert Opinion

### BLUF

A commentary article by an international group of specialists in speech-language pathology and PM&R examined recent literature illustrating how SARS-CoV-2 interacts with angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) in the oral cavity, tongue, and olfactory epithelium. They describe potential for SARS-CoV-2 to act as a neurologic invader and negatively affect swallowing via pharyngolaryngeal sensitivity alterations, absence of gag reflex, silent aspiration, and impaired pharyngeal constriction. Authors suggest patients with COVID-19 may be at increased risk for dysphagia or compromised airway protection via these mechanisms, and advocate for further research on pathophysiology of SARS-CoV-2 for better understanding of its effects on modified deglutition.

### ABSTRACT

Persistent smell and taste disorders have been reported as some of the most common symptoms after COVID-19 (coronavirus disease 2019). Sensory, olfactory, and gustatory functions perform an important role in the initiation and modulation of oropharyngeal swallow biomechanics and salivation as well as in mealtime enjoyment and appetite. Yet, the details of this interaction remain relatively unknown in patients who are infected with and recovering from COVID-19. In this commentary, we discuss the possible impacts of SARS-CoV-2 on the central and peripheral nervous system and consider the pathophysiology of olfactory, gustatory, and pharyngolaryngeal sensory deficits and its influence on deglutition, describing hypotheses and offering guidance for future research.

# IN VITRO

## LONG-TERM MODELING OF SARS-COV-2 INFECTION OF IN VITRO CULTURED POLARIZED HUMAN AIRWAY EPITHELIUM

Hao S, Ning K, Kuz CA, Vorhies K, Yan Z, Qiu J.. mBio. 2020 Nov 6;11(6):e02852-20. doi: 10.1128/mBio.02852-20.
Level of Evidence: Other - Mechanism-based reasoning

### BLUF

This in vitro study by microbiologists from University of Kansas Medical Center monitored long-term SARS-CoV-2 replication in polarized human airway epithelium cells (HAE) of lung bronchi sampled from 4 donors to model the human mucociliary airway epithelium. Authors suggest their findings demonstrated how epithelial cell regeneration may provide opportunity for maintenance and recurrent infection by SARS-CoV-2 (see summary).

### SUMMARY

Further details of study findings below:
Authors found SARS-CoV-2 viral load >2.5 x 10^5 virions per cm^2 of epithelium was necessary for infection. Peak viral replication occurred between 7-10 days (Figure 1), with infection primarily in ciliated and goblet cells while sparing basal and club cells. The virus did not infect basolateral epithelial cells, and authors suggest a protective role conferred at the cellular level by tight-junction-associated proteins. They also report these proteins (ZO-1, occludin and claudins) may be disturbed by SARS-CoV-2 induced cytokine storm via epithelial permeability alteration. Authors further propose that as airway epithelium repairs itself after destruction via basal cell proliferation to ciliated or goblet cells (Figure 8), the SARS-CoV-2 viral remains from prior virion release may have the capacity to infect these newly differentiated cells and produce a new round of replication. Thus, they highlight how tissue regeneration may initiate recurrent SARS-CoV-2 infection of HAE.

## ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replicates throughout human airways. The polarized human airway epithelium (HAE) cultured at an airway-liquid interface (HAE-ALI) is an in vitro model mimicking the in vivo human mucociliary airway epithelium and supports the replication of SARS-CoV-2. Prior studies characterized only short-period SARS-CoV-2 infection in HAE. In this study, continuously monitoring the SARS-CoV-2 infection in HAE-ALI cultures for a long period of up to 51 days revealed that SARS-CoV-2 infection was long lasting with recurrent replication peaks appearing between an interval of approximately 7 to 10 days, which was consistent in all the tested HAE-ALI cultures derived from 4 lung bronchi of independent donors. We also identified that SARS-CoV-2 does not infect HAE from the basolateral side, and the dominant SARS-CoV-2 permissive epithelial cells are ciliated cells and goblet cells, whereas virus replication in basal cells and club cells was not detected. Notably, virus infection immediately damaged the HAE, which is demonstrated by dispersed zonula occludens-1 (ZO-1) expression without clear tight junctions and partial loss of cilia. Importantly, we identified that SARS-CoV-2 productive infection of HAE requires a high viral load of >2.5 x 105 virions per cm2 of epithelium. Thus, our studies highlight the importance of a high viral load and that epithelial renewal initiates and maintains a recurrent infection of HAE with SARS-CoV-2.IMPORTANCE The pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to >35 million confirmed cases and >1 million fatalities worldwide. SARS-CoV-2 mainly replicates in human airway epithelia in COVID-19 patients. In this study, we used in vitro cultures of polarized human bronchial airway epithelium to model SARS-CoV-2 replication for a period of 21 to 51 days. We discovered that in vitro airway epithelial cultures endure a long-lasting SARS-CoV-2 propagation with recurrent peaks of progeny virus release at an interval of approximately 7 to 10 days. Our study also revealed that SARS-CoV-2 infection causes airway epithelia damage with disruption of tight junction function and loss of cilia. Importantly, SARS-CoV-2 exhibits a polarity of infection in airway epithelium only from the apical membrane; it infects ciliated and goblet cells but not basal and club cells. Furthermore, the productive infection of SARS-CoV-2 requires a high viral load of over 2.5 x 105 virions per cm2 of epithelium. Our study highlights that the proliferation of airway basal cells and regeneration of airway epithelium may contribute to the recurrent infections.

## FIGURES

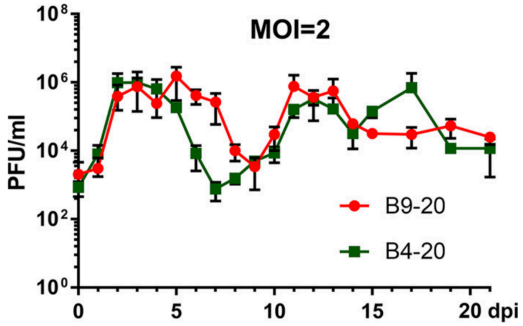


Figure 1. SARS-CoV-2 replication in primary human bronchial airway epithelium (HAE) over a course of 21 days. HAE-ALIB4-20 and HAE-ALIB9-20 cultures were infected with SARS-CoV-2 at an MOI of 2 from the apical side. At the indicated days postinfection (dpi), the apical surface was washed with 100 l of D-PBS to collect the released virus. Plaque-forming units (PFU) were determined (y axis) and plotted to the day postinfection. Values represent means +/- standard deviations (SD) (error bars).

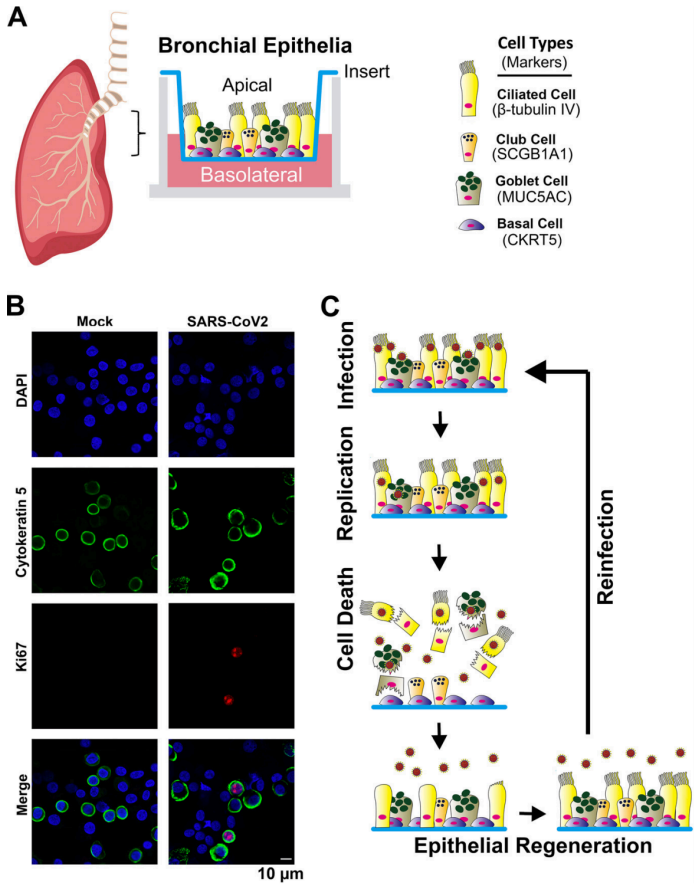


Figure 8. Diagram of HAE-ALI and model of the SARS-CoV-2 recurrent infection in HAE. (A) HAE-ALI model. Epithelial cells are taken from bronchia from the lungs of healthy donors and plated onto Transwell inserts at an air-liquid interface (ALI) for 4 weeks. Four major types of epithelial cells in the welldifferentiated polarized HAE cultures, basal, ciliated, goblet, and club cells, are diagrammed in the Transwell insert, and their expression markers are indicated. (B) Basal cells in proliferation. Epithelial cells of the mock- and SARS-CoV-2-infected HAE-ALIB9-20 cultures at 9 dpi (MOI = 0.2) were dissociated from the Transwell insert and cytospun onto slides. The cells on the slides were fixed, permeabilized, and immunostained with anti-Ki67 and together with anti-CKRT5. Confocal images were taken at a magnification of 63. Nuclei were stained with DAPI (blue). (C) Model of airway cell regeneration of SARS-CoV-2 recurrent infections. SARS-CoV-2 infects apical ciliated and goblet cells, where it replicates to produce infectious progeny and causes the death of the infected cells. The destructive lesion of epithelium induces basal cell proliferation and differentiation to regenerate ciliated and goblet cells, which are readily infected by SARS-CoV-2 in the next cycle of the recurrent infections.

# COVID-19-ASSOCIATED COAGULOPATHY

Franchini M, Marano G, Cruciani M, Mengoli C, Pati I, Masiello F, Veropalumbo E, Pupella S, Vaglio S, Liumbruno GM.. Diagnosis (Berl). 2020 Nov 18;7(4):357-363. doi: 10.1515/dx-2020-0078.
Level of Evidence: Other - Review / Literature Review

## BLUF

Hematologists at the Italian National Blood Centre in Rome, Italy review literature regarding management of SARS-CoV-2 induced coagulopathy. They outline proposed pathophysiology, laboratory studies (inflammatory markers [IL-6, CRP, procalcitonin, ferritin], coagulopathy markers [D-Dimer, platelet count, fibrinogen]), and potential usefulness of prophylactic treatment with low molecular weight heparin (LMWH) (Table 1). Authors suggest anticoagulant prophylaxis should be personalized according to each patient's disease course and thrombotic risk profile, and recommend further analysis of data from clinical trials to better manage SARS-CoV-2 induced coagulopathies.

## ABSTRACT

Coronavirus disease 2019 (COVID-19), a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been recently recognized as a systemic disorder inducing a prothrombotic state. The molecular mechanisms underlying the hypercoagulable state seen in patients with COVID-19 is still incompletely understood, although it presumably involves the close link between inflammatory and hemostatic systems. The laboratory coagulation monitoring of severely ill COVID-19 patients is mandatory to identify those patients at increased thrombotic risk and to modulate thromboprophylaxis accordingly. In this review, we summarize the current understanding on the pathogenesis, epidemiology, clinical and laboratory features and management of coagulopathy associated with COVID-19.

## FIGURES

**Table 1:** Management of coronavirus disease 2019 (COVID-19) coagulopathy.

| Assessment of thromboembolic risk | References | Thromboprophylaxis | References |
|---|---|---|---|
| – Laboratory monitoring: platelet count, fibrinogen, PT, D-dimer, CRP, ferritin, IL-6. | [19, 23, 57] | – Use of standard prophylactic doses of LMWH, UFH or fondaparinux in all COVID-19 hospitalized patients (use mechanical thromboprophylaxis if pharmacological prophylaxis is contraindicated). | [19, 23, 41, 57, 58] |
| – Assessment of individual risk factors: immobilization, ICU setting; patients' age, previous VTE, BMI >30, active cancer or chronic comorbidities. | [19, 25, 41, 57] | – Use of intermediate dose of LMWH or UFH on an individual basis, considering patients' risk factors. | [19, 57, 58] |
| | | – Use of prophylaxis for the entire duration of the hospital stay and for 7–14 after discharge in case of persisting VTE risk. | [25, 41, 57, 58] |

PT, prothrombin time; CRP, C-reactive protein; IL-6, interleukin 6; BMI, body mass index; VTE, venous thromboembolism; LMWH, low molecular weight heparin; UFH, unfractionated heparin; ICU, intensive care unit.

# MODIFYING REGULATORY PRACTICES TO CREATE A SAFE AND EFFECTIVE WORKING ENVIRONMENT WITHIN A SHARED RESOURCE LABORATORY (SRL) DURING A GLOBAL PANDEMIC

Filby A, Haviland DL, Jones DD, López AB, Orlowski-Oliver E, Rieger AM.. Cytometry A. 2020 Nov 15. doi: 10.1002/cyto.a.24264. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

## BLUF

Microbiology and Flow Cytometry researchers suggest new guidelines for modifying regulations in Shared Resource Laboratories (SRLs) in response to the COVID-19 pandemic by providing a risk assessment and proposed mitigation measures (Table 2). Overall, the authors recommend limiting access to laboratories and modifying behaviors within the laboratories (such as equipment use, mask wearing, etc.) to make these typically high-trafficked SRL areas safer in the context of the pandemic.

## ABSTRACT

Shared Resource Laboratories (SRLs) present a very unique set of problems with respect to operating safely and effectively during the current COVID-19 global pandemic caused by the SARS-CoV-2 virus. By nature, they are often high-footfall, multi-user environments where surfaces are touched and instruments interacted with by many different people. As such, it is essential that the SRL management and team look carefully at their regulatory procedures in order to be able to operate effectively and minimize/eliminate all associated risks from the SARS-CoV-2 virus. This paper presents some suggestions for simple modifications to SRL regulatory practices that can greatly reduce the risks from SARS-CoV-2 and still allow for the SRL to be accessed and utilized effectively. These include three major areas of consideration: (i) regulation of access to the SRL; (ii) regulation of SRL space; (iii) regulation of behaviors within the SRL (users and staff). Finally, we discuss risk-management with examples and the potential risks. As there is no "one size fits all" solution, the aim of this article is to provoke discussion and forethought so that individual SRLs can make specific plans and implement the needed safeguards to minimize risk while continuing to operate. 

## FIGURES

**Table 2. Risk assessment for operating a SRL during the COVID-19 pandemic.**

| Risk | Risk Level | Breach/issue | Mitigation measures |
|---|---|---|---|
| Continuous flow of people in the SRL | High | Physical distancing<br>Room capacity | -Staggered schedules for SRL staff<br>-Use of equipment with defined intervals and time between users.<br>-Floor tape and Perspex screens to restrict area access<br>-Constant disinfection of high traffic surfaces.<br>-Use of appropriate PPE |

Table 2 Continued

| | | | |
|---|---|---|---|
| Confirmed COVID-19 case within the SRL/Building | High | Confirmed virus exposure to users and areas | -Prepare SOP for such an event<br>-Include a business continuity plan<br>- Instigate contact tracing using instrument booking records |
| Ventilation system with air recirculation | High | Recycled air not clearing potential viral particles | -Turn off ventilation system, open windows<br>-Use of appropriate PPE |
| User Training | High | Physical distancing<br>Room capacity | -Remote training using programs such as "team viewer"<br>-If not possible; Use of appropriate PPE<br>-Laser pointers to allow physical distancing<br>-Use of training videos and other educational material |
| Sorting | High | Physical distancing<br>Room capacity | -Remote sorting using programs such as "team viewer" for sample/gating checks<br>-Use of appropriate PPE<br>-Sample drop off and pick up locations outside the sorting area/room |
| Sorting untested primary human sample | High | Possibly infectious Aerosol generation during blockages, spills and handling | - Sorting to be carried out in BCL3/PC3 level area<br>- Aerosol management system attached to sorter<br>- Alternative, use a sorter that doesn't generate aerosols. |
| Biometric lock to enter the SRL | Medium | High traffic/risk surface for transmission | -Provide sanitation station for frequent disinfection of the lock and hand disinfection before and after contact |
| Entrance and exit at the same door. | Medium | Physical distancing restrictions<br>High traffic/risk surface for transmission | -Staggered schedules/bookings<br>-Keep the door open during normal hours to minimize transfer risk |
| Inadequate instrument spacing | Medium | Physical distancing restriction<br>Room capacity restrictions | -Space out instruments within the room<br>-Move instruments to different rooms if not possible, stagger availability of instruments to comply with room capacity and/or physical distancing restrictions |
| Reception of suppliers and signing of printed documents. | Medium | Physical distancing restrictions<br>High traffic/risk surface transmission | -Schedule defined hours for reception of suppliers.<br>-Use of appropriate PPE<br>-Move to digital if possible, if not practice good hand hygiene |
| Staff and users unaware of new rules | Medium | Staff or users failing to follow the rules and putting others at risk | -Send out new SOP's to all users and institute OH&S teams<br>-Ensure received and read through declaration document<br>-Add signage to all rooms (physical distancing, room capacity limits, ect) |
| Analyzing untested unfixed primary human samples | Medium | Increased risk of transmission<br>Resuspension method generating aerosols<br>Spills | -Impose all untested/unfixed primary human samples be fixed with an approved method before acquisition on instruments.<br>- If not possible due to functional or time course experiments move an instrument into a BCL2/PC2 hood. |

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