The Daily COVID-19 Literature Surveillance Summary

August 5, 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

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Epidemiology

- Investigators at the CDC performed an analysis of COVID-19 cases from early in the pandemic and found that among the first case reported in each of 99 countries, 60% were in individuals with a history of travel to China, Italy, or Iran.

Understanding the Pathology

- A retrospective study conducted in Spain found that a cohort of 134 COVID-19 patients had significantly elevated levels of uroporphyrin I, coproporphyrin I, and coproporphyrin III when compared to patients with COVID-19 negative pneumonia. These findings provide evidence to suggest that the accumulation of these markers may exacerbate heme shortages while also promoting oxidative damage and mitochondrial dysfunction in patients with COVID-19.

Transmission and Prevention

- A literature review by authors at John Hopkins and the University of California argues that wearing masks reduces disease severity by reducing the viral inoculum exposure of the wearer. The authors cite several countries, including South Korea, Singapore, Hong Kong, Taiwan, Japan, that have practiced population-level mask wearing and have low case fatality rates, suggesting the dual benefit of mask-wearing in allowing generation of herd immunity while preventing severe disease.

Management

- Investigators used data from 17 COVID-19 patients to assess differences in pulse oximetry (SpO2) and arterial oxygen saturation (SaO2) levels and found that SpO2 underestimated the SaO2 value by an average of 5.3%, which could cause overestimation of hypoxia in COVID-19 patients and administration of a higher inspired oxygen fraction than necessary.

Adjusting Practice during COVID-19

- A group of otolaryngologists reviewed 15 international recommendations to compile guidelines for sinus and anterior skull base surgery during the pandemic which include postponing elective surgeries, postoperative COVID-19 testing, and designating COVID-19 operating rooms.

R&D: Diagnosis and Treatments

- Researchers in Germany developed a novel in-cell enzyme-linked immunosorbent assay (ELISA) that can effectively quantify de novo synthesis of SARS-CoV-2 spike protein in fixed and permeabilized cells to offer a rapid and quantifiable detection method of the virus for use in future research.

CONTENTS

EPIDEMIOLOGY

OBSERVATIONS OF THE GLOBAL EPIDEMIOLOGY OF COVID-19 FROM THE PREPANDEMIC PERIOD USING WEB-BASED SURVEILLANCE: A CROSS-SECTIONAL ANALYSIS

Dawood FS, Ricks P, Njie GJ, Daugherty M, Davis W, Fuller JA, Winstead A, McCarron M, Scott LC, Chen D, Blain AE, Moolenaar R, Li C, Popoola A, Jones C, Anantharam P, Olson N, Marston BJ, Bennett SD.. Lancet Infect Dis. 2020 Jul 29:S1473-3099(20)30581-8. doi: 10.1016/S1473-3099(20)30581-8. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

Authors affiliated with the Centers for Disease Control and Prevention (CDC) conducted a web-based surveillance of 32,459 pre-pandemic COVID-19 cases occurring between December 31st, 2019 and March 10th, 2020 to analyze the global spread of COVID-19. Characteristics of early versus late COVID-19 cases and trends seen among COVID-19 clusters found in affected countries were investigated. By continuing to analyze COVID-19 characteristics, risk factors, and transmission, the authors argue that management and containment of the virus can be improved.

SUMMARY

Main findings gathered from data analysis include:
1. Ninety-nine countries reported cases of COVID-19 between December 31st, 2019 and March 10th, 2020, 75% of which identified their initial cases in individuals with a history of travel to China, Italy, Iran, and several other countries (Figure 3).
2. 1,200 of the 32,456 cases studied included information about patient sex and age (Table 2) allowing for further analysis. The authors found that:
- Early cases - up to the first 100 cases reported in a country - represented 874 of the 1,200 cases
- The median age of 762 of the early cases was 51 years
- In the 826 early cases, 460 of the patients were male
- The 326 late cases were found to have fewer links to travel or exposure to COVID-19 confirmed individuals when compared to the 874 early cases
3. 386 of the 1,200 cases including sex and age information were linked to known clusters (Table 3), and household transmission was identified to be the most common transmission method among the clusters.

ABSTRACT

Background Scant data are available about global patterns of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread and global epidemiology of early confirmed cases of COVID-19 outside mainland China. We describe the global spread of SARS-CoV-2 and characteristics of COVID-19 cases and clusters before the characterisation of COVID-19 as a pandemic. METHODS: Cases of COVID-19 reported between Dec 31, 2019, and March 10, 2020 (ie, the prepandemic period), were identified daily from official websites, press releases, press conference transcripts, and social media feeds of national ministries of health or other government agencies. Case characteristics, travel history, and exposures to other cases were abstracted. Countries with at least one case were classified as affected. Early cases were defined as those among the first 100 cases reported from each country. Later cases were defined as those after the first 100 cases. We analysed reported travel to affected countries among the first case reported from each country outside mainland China, demographic and exposure characteristics among cases with age or sex information, and cluster frequencies and sizes by transmission settings. FINDINGS: Among the first case reported from each of 99 affected countries outside of mainland China, 75 (76%) had recent travel to affected countries; 60 (61%) had travelled to China, Italy, or Iran. Among 1200 cases with age or sex information, 874 (73%) were early cases. Among 762 early cases with age information, the median age was 51 years (IQR 35-63); 25 (3%) of 762 early cases occurred in children younger than 18 years. Overall, 21 (2%) of 1200 cases were in health-care workers and none were in pregnant women. 101 clusters were identified, of which the most commonly identified transmission setting was households (76 [75%]; mean 2 6 cases per cluster [range 2-7]), followed by non-health-care occupational settings (14 [14%]; mean 4 3 cases per cluster [2-14]), and community gatherings (11 [11%]; mean 14 2 cases per cluster [4-36]). INTERPRETATION: Cases with travel links to China, Italy, or Iran accounted for almost two-thirds of the first reported COVID-19 cases from affected countries. Among cases with age information available, most were among adults aged 18 years and older. Although there were many clusters of household transmission among early cases, clusters in occupational or community settings tended to be larger, supporting a possible role for physical distancing to slow the progression of SARS-CoV-2 spread. FUNDING: None.

FIGURES

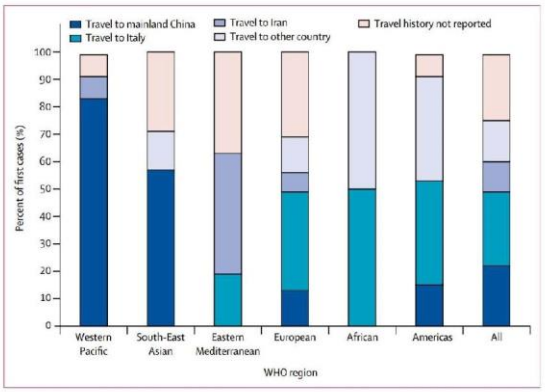

Figure 3. Travel exposure of first cases reported from 99 countries and locations outside of mainland China by WHO region

	Early cases* in each country (n=874)	Later cases† in each country (n=326)	p value
Country income level‡			
High income	690 (79%)	326 (100%)	<0·0001
Upper middle income	129 (15%)	0	..
Lower middle income	53 (6%)	0	..
Low income	2 (<1%)	0	..
Age, years§	51 (35-63)	55 (45-65)	<0·0001
<18	25/762 (3%)	11/324 (4%)	<0·0001
18–49	339/762 (44%)	99/324 (31%)	..
≥50	398/762 (52%)	214/324 (66%)	..
Sex	..	..	0·21
Male	460/826 (56%)	145/282 (51%)	..
Female	366/826 (44%)	137/282 (49%)	..
Special populations¶	..	..	..
Health-care workers	16 (2%)	5 (2%)	0·73
Pregnant women	0	0	..
Exposure history	..	..	..
Travel from affected countries	375 (43%)	17 (5%)	<0·0001
Contact with previously confirmed case	244 (28%)	27 (8%)	..
No travel history or contact with a previously confirmed case	130 (15%)	59 (18%)	..
Insufficient information	125 (14%)	223 (68%)	..
Deaths‖	48 (5%)	4 (1%)	0·0012

Data are n or n/N (%) or median (IQR). p values are for the comparison between early and late cases. Analyses were restricted to cases with available data about patient age or sex and exclude cases associated with an outbreak among passengers on the *Diamond Princess* cruise ship in Yokohama Bay, Japan. *Defined as cases among the first 100 reported from each country and location. †Defined as cases reported after the first 100 in each country and location. ‡Defined based on World Bank gross national income per capita classification.[3] §Age data were available for 762 of 874 cases among the first 100 cases reported from countries and 324 of 326 cases among later cases reported from countries. ¶Health-care worker status and pregnancy status might have been underascertained because of under-reporting. ‖Deaths might have been underascertained because of incomplete follow-up reporting.

Table 2. Demographic characteristics of early COVID-19 cases compared with later cases in each affected country outside mainland China

UNDERSTANDING THE PATHOLOGY

ABNORMAL CONCENTRATION OF PORPHYRINS IN SERUM FROM COVID-19 PATIENTS

San Juan I, Bruzzone C, Bizkarguenaga M, Bernardo-Seisdedos G, Laín A, Gil-Redondo R, Diercks T, Gil-Martínez J, Urquiza P, Arana E, Seco M, García de Vicuña A, Embade N, Mato JM, Millet O.. Br J Haematol. 2020 Aug 3. doi: 10.1111/bjh.17060. Online ahead of print.
Level of Evidence: 4 - Cohort study or control arm of randomized trial

BLUF

A retrospective cohort study conducted by the Precision Medicine and Metabolism Laboratory in Derio, Spain found that a cohort of COVID-19 patients (n=134) had significantly elevated levels of uroporphyrin I (URO I), coproporphyrin I (COP I), and coproporphyrin III (COP III) (Figure 1) when compared to COVID-19 negative controls (60 patients with pneumonia and 54 asymptomatic individuals). These findings suggest that the accumulation of URO I, COP I, and COP III may exacerbate the heme shortage while also promoting oxidative damage and mitochondrial dysfunction in patients with COVID-19.

ABSTRACT

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is not only a lung disease but rather a systemic syndrome where blood alterations may play a key role (1). Severe cases show a marked variation in the red blood cell distribution width (2), which agrees well with reduced erythrocyte turnover and would function as a compensatory mechanism to maintain the circulating red blood cell and oxygen levels (3).

FIGURES

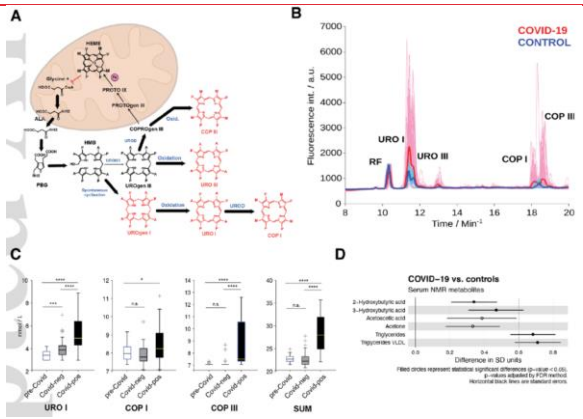

Figure 1: (A) The heme biosynthesis pathway. The enzymatic reactions for the heme production are shown in black; compounds in red are likewise generated by-products. Thick arrows indicate reactions that are upregulated during erythropoiesis. Legend: A = acetyl; M = methyl; P = propionyl; V = vinyl. (B) High performance liquid chromatography (HPLC) chromatography results of COVID-19 patients (red) and control individuals (blue). Solid lines correspond to the average intensity values along the chromatography whereas the colored shadows indicate the standard deviation. RB (10.3 min), URO I (11.3 min), URO III (11.5 min), COP I (18.0 min) and COP III (18.6 min) are easily detected. (C) Boxplot representation of the indicated porphyrin concentrations found in the pre-COVID, COVID-neg and the COVID-pos patient sera. P-values of 0.01, 0.0001 and beyond 0.0001 are represented by *,*** and **** respectively while n.s. means no statistically significant. (D) Summary of statistical analysis for a selection of metabolites and lipoprotein subclasses of interest. Metabolite mean concentrations (pre-COVID): 2-Hydroxybutirin 23 ?M, 3-hydroxybutiric 267 ?M, acetoacetic 11 ?M , acetone 28 ?M, triglycerides 110 mg/dL, TG-VLDL 32 mg/dL. Points represent the average increase (positive) or decrease (negative), in standard deviation (SD) units, for individuals with COVID-19, after controlling for gender and age. Filled points indicate that the value is significantly different from zero (p-value < 0.05). Horizontal black lines represent the 95% confidence interval.

IGGS DRIVE COVID-19 MYELOID HYPERINFLAMMATION

Park MD.. Nat Rev Immunol. 2020 Jul 31. doi: 10.1038/s41577-020-00415-9. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This "In-Brief" report summarizes a publication by Hoepel et al. 2020, which posed a mechanism describing how alveolar macrophages contribute to hyperinflammation. Specifically, Hoepel et al. 2020 revealed that serum Anti-Spike protein IgGs from severe COVID-19 patients lead to a strong pro-inflammatory response in macrophages, especially through FcγRII. A kinase SYK inhibitor, which can block this pathway, counteracted the production of IL-6, IL-1β, and TNF. The author of this correspondence highlights that these results provide an explanation for the "abnormal myeloid response in COVID-19 and identify a potential therapeutic target."

MASKS DO MORE THAN PROTECT OTHERS DURING COVID-19: REDUCING THE INOCULUM OF SARS-COV-2 TO PROTECT THE WEARER

Gandhi M, Beyrer C, Goosby E.. J Gen Intern Med. 2020 Jul 31. doi: 10.1007/s11606-020-06067-8. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A literature review by authors affiliated with John Hopkins Bloomberg School of Public Health and the University of California argues that wearing masks reduces disease severity by reducing the viral inoculum exposure of the wearer. The authors cite several countries (South Korea, Singapore, Hong Kong, Taiwan, Japan) that have practiced population-level mask wearing and have low case fatality rates, suggesting the dual benefit of mask-wearing in allowing generation of herd immunity while preventing severe disease.

ABSTRACT

Although the benefit of population-level public facial masking to protect others during the COVID-19 pandemic has received a great deal of attention, we discuss for one of the first times the hypothesis that universal masking reduces the "inoculum" or dose of the virus for the mask-wearer, leading to more mild and asymptomatic infection manifestations. Masks, depending on type, filter out the majority of viral particles, but not all. We first discuss the near-century-old literature around the viral inoculum and severity of disease (conceptualized as the LD50 or lethal dose of the virus). We include examples of rising rates of asymptomatic infection with population-level masking, including in closed settings (e.g., cruise ships) with and without universal masking. Asymptomatic infections may be harmful for spread but could actually be beneficial if they lead to higher rates of exposure. Exposing society to SARS-CoV-2 without the unacceptable consequences of severe illness with public masking could lead to greater community-level immunity and slower spread as we await a vaccine. This theory of viral inoculum and mild or asymptomatic disease with SARS-CoV-2 in light of population-level masking has received little attention so this is one of the first perspectives to discuss the evidence supporting this theory.

MANAGEMENT

ACUTE CARE

DISCREPANCY BETWEEN S(P) O(2) AND S(A) O(2) IN PATIENTS WITH COVID-19

Wilson-Baig N, McDonnell T, Bentley A.. Anaesthesia. 2020 Aug 1. doi: 10.1111/anae.15228. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Authors from Manchester University Hospital used data from 17 COVID-19 patients to assess differences in pulse oximetry (SpO2) and arterial oxygen saturation (SaO2) levels. They found that SpO2 underestimated the SaO2 value by an average of 5.3%, which could cause overestimation of hypoxia in COVID-19 patients and administration of a higher inspired oxygen fraction than necessary.

OTOLARYNGOLOGY

SINUS AND ANTERIOR SKULL BASE SURGERY DURING THE COVID-19 PANDEMIC: SYSTEMATIC REVIEW, SYNTHESIS AND YO-IFOS POSITION

Radulesco T, Lechien JR, Sowerby LJ, Saussez S, Chiesa-Estomba C, Sargi Z, Lavigne P, Calvo-Henriquez C, Lim CM, Tangjaturonrasme N, Vatanasapt P, Puya DM, Fakhry N, Ayad T, Michel J.. Eur Arch Otorhinolaryngol. 2020 Jul 24. doi: 10.1007/s00405-020-06236-9. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Otolaryngologists from the Young Otolaryngologist of IFOS (YO-IFOS) summarizes the recommendations for sinus and skull base surgeries during the COVID-19 pandemic by reviewing 15 international recommendation publications (Table 3), which include:

- postponing elective surgeries unless urgent (Table 2)
- providing preoperative COVID-19 testing with reverse transcription polymerase chain reaction (RT-PCR)
- using negative pressure rooms and designated COVID-19 operating rooms
- optimizing PPE use to reduce risk of exposure to potential aerosolization of the SARS-CoV-2 viral particles

The authors suggest that these recommendations can protect health care workers but note that these recommendations may depend on local availability of PPE/supplies and may change overtime with the pandemic.

ABSTRACT

PURPOSE: The COVID-19 pandemic has caused significant confusion about healthcare providers' and patients' pandemic-specific risks related to surgery. The aim of this systematic review is to summarize recommendations for sinus and anterior skull base surgery during the COVID-19 pandemic. METHODS: PubMed/MEDLINE, Google Scholar, Scopus and Embase were searched by two independent otolaryngologists from the Young Otolaryngologists of IFOS (YO-IFOS) for studies dealing with sinus and skull base surgery during COVID-19 pandemic. The review also included unpublished guidelines edited by Otolaryngology-Head and Neck Surgery or Neurosurgery societies. Perioperative factors were investigated including surgical indications, preoperative testing of patients, practical management in operating rooms, technical aspects of surgery and postoperative management. The literature review was performed according to PRISMA guidelines. The criteria for considering studies or guidelines for the review were based on the population, intervention, comparison, outcome, timing and setting (PICOTS) framework. RESULTS: 15 International publications met inclusion criteria. Five references were guidelines from national societies. All guidelines recommended postponing elective surgeries. An algorithm is proposed that classifies endonasal surgical procedures into three groups based on the risk of postponing surgery. Patients' COVID-19 status should be preoperatively assessed. Highest level of personal protective equipment (PPE) is recommended, and the use of high-speed powered devices should be avoided. Face-to-face postoperative visits must be limited. CONCLUSIONS: Sinus and skull base surgeries are high-risk procedures due to potential aerosolization of SARS-CoV-2 virus. Protection of health care workers by decreasing exposure and optimizing the use of PPE is essential with sinus and anterior skull base surgery.

Group	Disease or surgery
Group A	
Urgent surgery	Sinusitis with complications (cavernous sinus thrombophlebitis, neuromeningeal or ophthalmologic involvement, significant bone destruction)
	Sinusitis in immunocompromised patient
	Invasive fungal infection
	Mucocele with complications
	Foreign body
	Epistaxis without arterial embolization possible
	Sinonasal malignant tumor*
	CSF leak*
	Biopsy for suspicion of malignant tumor
	Highly displaced nasal bone fracture
Group B	
Treatment within a maximum of 1 month	Fungal sinusitis in immunocompromised patients
	Purulent sinusitis resisting medical treatment
Group C	
Non-urgent surgery	Sinonasal polyposis
	Mycetoma in immunocompetent patient
	Non-malignant tumor (e.g. hamartoma, hemangiopericytoma…)
	Non-complicated mucoceles
	Inverted papilloma without bone destruction
	Septoplasty or rhinoplasty
	Endonasal dacryocystorhinostomy
	Turbinate reduction
	Nasal valve repair

AFR Association Française de Rhinologie, The French Rhinology Association

*Case-by-case discussion

Table 2. Classifcation of surgical procedures according to postponing risk, derived from AFR proposition [14].

Recommendations	YO-IFOS approval
Before hospitalization	
Prioritize according to postponing risk	Yes
Perform only urgent procedures (group A)	Yes
Assess COVID-19 patient status preoperatively	Yes
Consider COVID-19 positive a patient with only one RT-PCR test negative (high risk of false negatives)	Yes
In operative room (OR)	
Negative pressure for COVID-19 positive patients	Yes
Designated OR	Yes
Reduced team	Yes
Team trained to use of PPE	Yes
HEPA filters	Yes
High frequency of air change	Yes
Carefully consider involvement of trainees or fellow	Yes
Protective personnel equipment (PPE)	
N95 masks	Yes
Google	Yes
Gown	Yes
Double gloves	Yes
Hat	Yes
PAPR	Option
Technical specificities for sinus and anterior skull base surgery	
Allow endonasal surgery with highest level PPE	Yes
Avoid high-speed powered devices	Yes
Postoperative visits	
Preference given to phone or video consultation	Yes

Summary of YO-IFOS recommendation regarding sinus and anterior skull base surgery

OR operative room, *HEPA* high-efficiency particulate air, *PAPR* powered air-purifying respirators, *PPE* personal protective equipment

Table 3. Summary of YO-IFOS recommendation

REVIEW OF MATERNAL COVID-19 INFECTION: CONSIDERATIONS FOR THE PEDIATRIC OPHTHALMOLOGIST

DiSciullo A, Mokhtari N, Fries M.. J AAPOS. 2020 Jul 29:S1091-8531(20)30153-1. doi: 10.1016/j.jaapos.2020.07.003. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

In this review, OBGYNs from MedStar Washington Hospital in Washington DC describe recommendations for labor and delivery, neonatal care, and pediatric ophthalmology care for patients infected with COVID-19 (summarized below), providing clear guidance on reducing the risk of transmission for these patient populations and their providers.

SUMMARY

The recommendations for labor and delivery are as follows:
- Restricted hospital visits for pregnant persons with confirmed COVID-19 or those who are persons under investigation (PUI).
- Placement in isolation rooms with droplet and contact precautions and using isolation rooms for vaginal deliveries.
- Appropriate personal protective equipment (PPE) for healthcare workers working with these patients including N95 masks, gowns, and eye protection.
- Infants born to pregnant persons with confirmed COVID-19 should be isolated and tested for COVID-19 every 28-72 hours until they have two consecutive negative tests.
- Pediatric ophthalmologists should assume patients born to pregnant persons with confirmed COVID-19 to be infected and should wear appropriate PPE when caring for these patients.
- Add plexiglass to an indirect ophthalmoscope to reduce risk of transmission to the ophthalmologist.
- Ophthalmologists should wash hands and wear gloves for retinopathy of prematurity exams, and wash hands again after the exam.
- Ophthalmologists should defer elective examinations for patients who may be infected.

AN ENZYME-BASED IMMUNODETECTION ASSAY TO QUANTIFY SARS-COV-2 INFECTION

Conzelmann C, Gilg A, Groß R, Schütz D, Preising N, Ständker L, Jahrsdörfer B, Schrezenmeier H, Sparrer KMJ, Stamminger T, Stenger S, Münch J, Müller JA.. Antiviral Res. 2020 Jul 29:104882. doi: 10.1016/j.antiviral.2020.104882. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

A mechanism based study by researchers in Germany found a novel in cell enzyme-linked immunosorbent assay (ELISA) had the ability to quantify de novo synthesis of SARS-CoV-2 spike protein in fixed cells (Figure 1) and to determine median tissue culture infectious dose (TCID50; Figure 4) as well as half maximal inhibitory concentration (IC50; Figure 5). Authors suggest in cell ELISA may be useful in rapid and measurable SARS-CoV-2 detection and studying SARS-CoV-2 infection and inhibition for advancement of COVID-19 therapeutics.

ABSTRACT

SARS-CoV-2 is a novel pandemic coronavirus that caused a global health and economic crisis. The development of efficient drugs and vaccines against COVID-19 requires detailed knowledge about SARS-CoV-2 biology. Several techniques to detect SARS-CoV-2 infection have been established, mainly based on counting infected cells by staining plaques or foci, or by quantifying the viral genome by PCR. These methods are laborious, time-consuming and expensive and therefore not suitable for a high sample throughput or rapid diagnostics. We here report a novel enzyme-based immunodetection assay that directly quantifies the amount of de novo synthesized viral spike protein within fixed and permeabilized cells. This in-cell ELISA enables a rapid and quantitative detection of SARS-CoV-2 infection in microtiter format, regardless of the virus isolate or target cell culture. It follows the established method of performing ELISA assays and does not require expensive instrumentation. Utilization of the in-cell ELISA allows to e.g. determine TCID50 of virus stocks, antiviral efficiencies (IC50 values) of drugs or neutralizing activity of sera. Thus, the in-cell spike ELISA represents a promising alternative to study SARS-CoV-2 infection and inhibition and may facilitate future research.

FIGURES

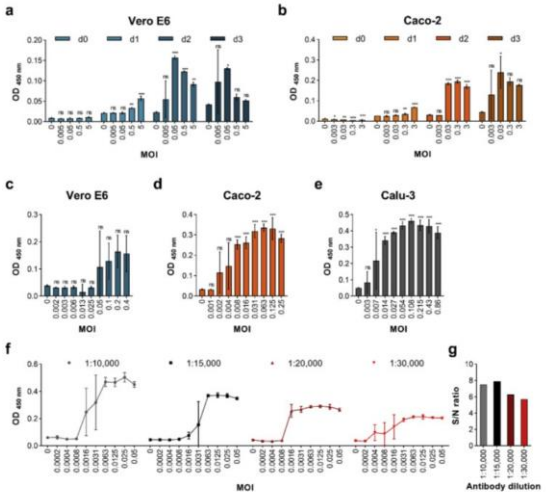

Figure 1. Establishment of an in-cell S protein ELISA to quantify SARS-CoV-2 infection. a, b) Time course of S protein expression in infected Vero E6 and Caco-2 cells as detected by in-cell ELISA. Vero E6 (a) and Caco-2 (b) cells were inoculated with increasing MOIs of a SARS-CoV-2 isolate from France. In-cell ELISA (1:5,000 (10 ng/well) 1A9 antibody; 1:20,000 (2.5 ng/well) HRP-antibody) was performed after 2 h (d0) or 1, 2 or 3 days post infection. c, d, e) ELISA signal correlates with viral input dose. Vero E6 (c), Caco-2 (d), or Calu-3 (e) cells were inoculated with serial two-fold dilutions of SARS-CoV-2 and infections rates were determined 2 days later by in-cell ELISA. f) Titration of secondary antibody to optimize assay sensitivity

applying 5 (1:10,000), 3.3 (1:15,000), 2.5 (1:20,000) or 1.7 ng/well (1:30,000). Caco-2 cells infected with indicated MOIs of SARS-CoV-2 and stained 2 days later with anti-S protein antibody were treated with four dilutions of the HRP-coupled secondary antibody before OD was determined. g) Corresponding maximum signal-to-noise (S/N) ratios observed in Fig. 1f. All values show in panels a–e are means of raw data obtained from technical triplicates ±sd. ns not significant, *P < 0.01, **P < 0.001, ***P < 0.0001 (by one-way ANOVA with Bonferroni's post-test).

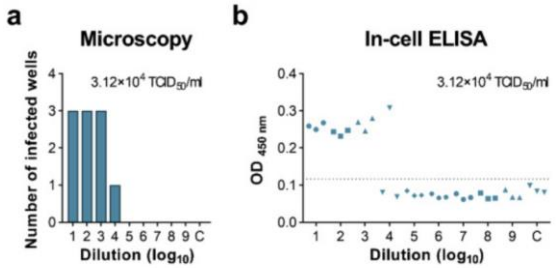

Figure 4. Utilization of the in-cell ELISA to determine the TCID50 of SARS-CoV-2 stocks. A stock of the French SARS-CoV-2 isolate was titrated 10-fold and used to inoculate Vero E6 cells in triplicates. At day 4 post infection, the number of infected wells was determined by a) microscopically evaluating the CPE or b) performing the SARS-CoV-2 S protein in-cell ELISA. Grey line illustrates the threshold of 0.117 (three times the sd added to the uninfected control) used to determine infected wells. The corresponding titer determined according to Reed and Muench is shown as inlet in both figures.

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