The Daily COVID-19 Literature Surveillance Summary

February 19, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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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

** 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

Transmission & Prevention

- Researchers from Shenzhen Third People's Hospital in China evaluated potential environmental fomites by taking serum samples from 66 hospitalized patients with COVID-19 (46 symptomatic and 20 asymptomatic) and samples from a number of environmental sources (squat toilets, cups, straws, oxygen catheters, breathing exercisers, and atomizing nozzles), analyzed using qRT-PCR. The researchers found that environmental contamination presents in both symptomatic and asymptomatic patients but an increased viral load (detected by nasopharyngeal swab) was associated with increased likelihood of environmental spread regardless of symptoms, especially to toilets (28.6% asymptomatic - 33.3% symptomatic), suggesting further evidence in support of hand hygiene and toilet disinfection to reduce risk of fecal-oral transmission of COVID-19.

Management

- A multicenter, double-blind, randomized clinical trial by Hospital das Clinicas HCFMUSP, Sao Paulo, Brazil evaluated the efficacy of single high dose vitamin D3 supplementation on the hospital length of stay for patients with COVID-19. 240 hospitalized COVID-19 patients with moderate to severe course of the disease were given a single oral dose of 200,000 IU of vitamin D3. The study did not find a significant reduction (p=0.59) in the length of hospital stay between the group that received intervention versus the placebo group indicating the lack of clinical benefit of Vitamin D3 for treatment of COVID-19.

R&D: Diagnosis & Treatments

- Physician investigators from various institutions across the US present the primary results of the BLAZE-1 study. This is an ongoing randomized phase 2/3 double-blinded trial involving 577 outpatients with mild to moderate COVID-19 across 49 US medical centers, comparing placebo vs. treatment with anti-spike neutralizing monoclonal antibody monotherapy (bamlanivimab), vs. combination therapy (bamlanivimab + etesevimab). The results revealed a statically significant (p= .01) difference in the primary outcome of decreased SARS-CoV-2 viral load at day 11 with combination therapy, suggesting a possible efficacious treatment option for patients with mild to moderate COVID-19.

TABLE OF CONTENTS

CLIMATE

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.. Clin Infect Dis. 2021 Feb 16;72(4):710-715. doi: 10.1093/cid/ciaa935.
Level of Evidence: 5 - Review / Literature Review

BLUF

This collaboration by an international group of physicians and legal experts discusses the ethics and utility of Human Challenge Trials (HCTs) in accelerating SARS-CoV-2 vaccine development. The authors highlight the potential utility of HCTs for evaluating vaccine efficacy and understanding correlates of protection (CoP), which are biomarkers related to specific disease outcomes. HCTs could also provide real-time efficacy data for down-selecting candidates and rapid confirmation of any CoP indicated in phase 2 trials. However, many ethical considerations regarding HCTs would need to be addressed before implementation (outlined summary below). This topic has significant implications and urgency, as HCTs have the potential to considerably shorten the COVID-19 pandemic, which would save lives and improve the economy.

SUMMARY

Recommended necessary considerations/preparations:

1. Convening experts to discuss the ethical and practical considerations associated with HCTs for COVID-19, concluding in a set of recommendations and guidelines for their use in the present pandemic and their role in the licensure process. The WHO and the National Institutes of Health have already started this process. (Notably, this could provide useful guidance in the event of future pandemics as well.)
2. Taking the first practical steps toward HCTs, including preparing challenge virus and making preliminary arrangements with volunteers, vaccine developers, regulators, academic institutions, and clinical researchers to run HCTs in situations where they are expected to be highly useful.
3. Periodically conducting a systematic re-evaluation, and adjusting course based on the progress of the pandemic and the first drug and vaccine trials.

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.

CLINICAL COURSE OF SARS-COV-2 INFECTION IN PATIENTS WITH SEVERE ACQUIRED BRAIN INJURY AND A DISORDER OF CONSCIOUSNESS: AN OBSERVATIONAL STUDY

Caronni A, Liaci E, Bianchi A, Viganò A, Marenco F, Comanducci A, Cabrini DM, Meloni M, Alberoni M, Farina E, Bianco M, Galeri S, Devalle G, Navarro J.. Brain Inj. 2021 Feb 15:1-10. doi: 10.1080/02699052.2021.1887937. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

Clinicians and scientists from Fondazione IRCCS, a national institute of tumor research and study center in Milan, investigated patterns of SARS-CoV-2 infection in 11 patients with severe acquired brain injury (SABI) (Tables 1, 2) hospitalized on the rehabilitation unit in March 2020. Six patients contracted SARS-CoV-2, four of whom developed symptoms. None developed severe symptoms and none died. Authors suggest morbidity from COVID-19 was unexpectedly low in patients with SABI, but reiterate the limited scope of their study due to sample size and recommend further monitoring of this population.

FIGURES

Patient	Gender	Age (years)	BMI	Aet	Inj to ad (days)	Ad to test (days)	1st pos	DTN1	TNNT	COVID	LCF ad	DRS ad	CRS-R ad	LCF test	DRS test
P1	M	60	20.5	HS	24	10	-	-	2	-	3	20	17, MCS+	3	18
P2	M	66	15.4	TBI	105	5	-	-	4	-	2	26	5, UWS	3	26
P3	F	73	23.3	HS	107	57	-	-	4	-	2	24	11, UWS	2	24
P4	F	58	25.6	HS	47	37	-	-	4	-	2	25	5, MCS	3	22
P5	M	44	18.4	HS	92	68	-	-	2	-	3	24	16, MCS	5	18
Negative patients		60 (44–73)	20.5 (15.4–25.6)		92 (24–107)	37 (5–68)					2 (2–3)	24 (20–26)		3 (2–5)	22 (18–26)
P6	M	73	17.5	TBI	156	58	03–23	39	-	Yes	2	24	6, UWS	2	24
P7	F	55	18.2	HS	73	16	03–23	25	-	No	3	23	9, MCS+	4	21
P8	F	63	17.5	HS	97	90	03–30	18	-	No	3	20	14, MCS-	4	20
P9	F	56	17.7	HS	231	121	03–14	73	-	Yes	2	24	17, MCS+	6	20
P10	F	68	25.1	HS	48	119	03–17	97	-	Yes	2	24	8, MCS-	6	18
P11	M	51	17.4	IS	59	9	03–23	120	-	Yes	3	21	18, UWS	3	21
Positive patients		59.5 (51–73)	17.6 (17.4–25.1)		85 (48–231)	74 (9–121)		56 (18–97)			2.5 (2–3)	23.5 (20–24)		4 (2–6)	20.5 (18–24)
Whole sample		60 (44–73)	18.2 (15.4–25.6)		92 (24–231)	57 (5–121)					2 (2–3)	24 (20–26)		3 (2–6)	21 (18–26)
P12	F	77	28.0	HS	33	-	-	-	-	-	2	26	13, MCS	-	-

Table 1:

Gender: M and F for males and females, respectively; Age: age at the time of the brain injury; BMI: BMI at the time of the RNA testing; Aet: etiology of the brain injury (TBI, traumatic brain injury, HS, hemorrhagic stroke; IS, ischemic stroke); Inj to ad: days from brain injury to admission; Ad to test: days from admission to the first RNA test; 1st pos: day of the first RNA test positive for SARS-CoV-2 (month – day); DTN1: days to the first negative test in a row of three consecutive negative tests, at least 24 hours apart (P11 was still positive 120 days from his first positive test, see text); TNNT: total number of negative RNA tests collected in the 30 days period after the first RNA test (negative patients only); COVID: patients who developed the COVID; LCF ad, LCF test: levels of cognitive functioning (LCF) at admission and at the time of the first RNA test, respectively; DRS ad, DRS test: disability rating scale (DRS) at admission and at the time of the first RNA test, respectively; CRS-R ad: coma recovery scale – revised at admission (total score and consciousness impairment); UWS: unresponsive wakefulness syndrome; MCS: minimally conscious state and MCS plus (+) and minus (-) variants. Median and range (min-max) are given for positive and negative patients and for the whole sample (gray rows). Data for the single dropout are given in the last row.

	Patient	TT	IC	TF	FiO2	CIRS CI	HT	Smoke	Cancer
Negative patients	P1	1	1	1	21	8	1	1	0
	P2	1	1	1	21	7	0	0	0
	P3	1	0	1	24–28	5	0	0	0
	P4	1	1	1	24–28	6	1	1	0
	P5	0	0	1	21	9	1	1	0
Positive patients	P6	1	1	1	21	9	0	0	1
	P7	1	1	1	24–28	6	0	0	0
	P8	0	0	1	21	9	1	0	0
	P9	0	1	1	24–28	8	0	0	0
	P10	0	1	1	21	7	1	0	0
	P11	1	1	1	21	8	0	1	1
	P12	1	1	1	21	7	1	0	0

Table 2

TT, IC, TF, FiO2: tracheostomy tube, indwelling catheter, tube feeding and fraction of inspired oxygen at the time of the first RNA test, respectively; CIRS CI: CIRS comorbidity index on ward admission, i.e. number of items scored 2 or higher (item 14 included). Preexisting medical conditions at the time of the brain injury: hypertension (HT), smoking and cancer. No patient had diabetes mellitus. Data for the single dropout patient are given in the last row.

ADULTS

DUAL-ENERGY CT ANGIOGRAPHY REVEALS HIGH PREVALENCE OF PERFUSION DEFECTS UNRELATED TO PULMONARY EMBOLISM IN COVID-19 LESIONS

Le Berre A, Boeken T, Caramella C, Afonso D, Nhy C, Saccenti L, Tardivel AM, Gerber S, Frison Roche A, Emmerich J, Marini V, Zins M, Toledano S.. Insights Imaging. 2021 Feb 17;12(1):24. doi: 10.1186/s13244-021-00972-0.
Level of Evidence: 3 - Local non-random sample

BLUF

Radiologists from Fondation Hôpital Saint Joseph in Paris, France conducted a retrospective single center study comparing the frequency and characteristics of perfusion defects (PD) on dual-energy computed tomography pulmonary angiography (DE-CTPA) in 67 COVID-19 patients (admitted March-May 2020) verses 79 non-COVID-19 pneumonia patients (admitted January 2017-September 2019) who all underwent imaging for suspected pulmonary embolism. The results revealed PDs in 59.7% of the COVID-19 patients with the majority being heterogenous consolidations, compared to 26.6% in the non-COVID-19 group (p-value < 0.001), suggesting diagnostic characteristics specific to COVID-19 pneumonia (Figure 2) compared to non-COVID-19 pneumonia (Figure 3 and 4).

ABSTRACT

BACKGROUND: Lung perfusion defects (PDs) have been described in COVID-19 using dual-energy computed tomography pulmonary angiography (DE-CTPA). We assessed the prevalence and characteristics of PDs in COVID-19 patients with suspected pulmonary embolism (PE) and negative CTPA. METHODS: This retrospective study included COVID-19 and non-COVID-19 pneumonia groups of patients with DE-CTPA negative for PE. Two radiologists rated the presence of PD within the lung opacities and analyzed the type of lung opacities and PD pattern (i.e. homogeneous or heterogeneous). The clinical, biological, radiological characteristics including time from first symptoms and admission to DE-CTPA, oxygen requirements, CRP, D-dimer levels, duration of hospital admission and death were compared within the COVID-19 group between patients with (PD +) or without PD (PD-). RESULTS: 67 COVID-19 and 79 non-COVID-19 patients were included. PDs were more frequent in the COVID-19 than in the non-COVID-19 group (59.7% and 26.6% respectively, p < 0.001). Patterns of PDs were different, with COVID-19 patients exhibiting heterogenous PDs (38/40, 95%) whereas non-COVID-19 patients showed mostly homogeneous perfusion defects (7/21 heterogeneous PDs, 33%), p < 0.001. In COVID-19 patients, most consolidations (9/10, 90%) exhibited PDs while less than a third of consolidations (19/67, 28%) had PDs in non-COVID-19 patients. D-dimer, oxygen levels and outcome were similar between COVID-19 PD + and PD- patients; however, time between admission and DE-CTPA was longer in PD + patients (median [IQR], 1 [0-7] and 0 [0-2]; p = 0.045). CONCLUSION: Unlike in bacterial pneumonia, heterogeneous PDs within lung opacities are a frequent feature of COVID-19 pneumonia in PE-suspected patients.

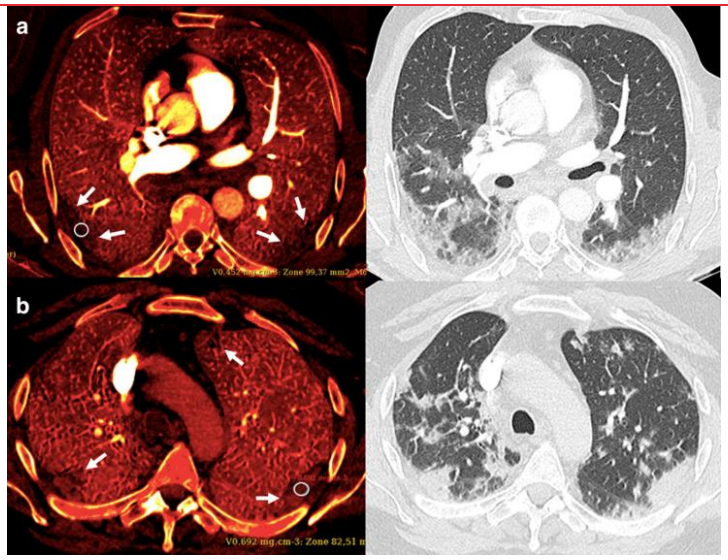


Figure 2. a 66-year-old male with COVID-19 related pneumonia at hospital day 7. A rt-PCR assay confrmed the diagnosis. DE-CTPA was performed for increased D-dimer (640 ng/mL) and oxygen requirement levels. Heterogeneous iodine distribution (PD+) is seen with sub-pleural perfusion defects (iodine map, left) partially matching the consolidations in the lower lobes (conventional lung images, right). Iodine concentration was measured at 0.452 mg/cm3 using a 1 cm2 ROI within the circle and at 0.873 mg/cm3 within the normal-appearing parenchyma. b 57-year-old-male with a rt-PCR confrmed COVID-19 pneumonia also at hospital day 7. The D-dimer level was increased at 1160 ng/mL. Heterogeneous perfusion defects (PD+) are seen in the sub-pleural areas (iodine map, left), partially matching the lung opacities (right). Iodine concentration was measured at 0.692 mg/cm3 within the circle and at 0.928 mg/cm3 within the normal-appearing parenchyma.

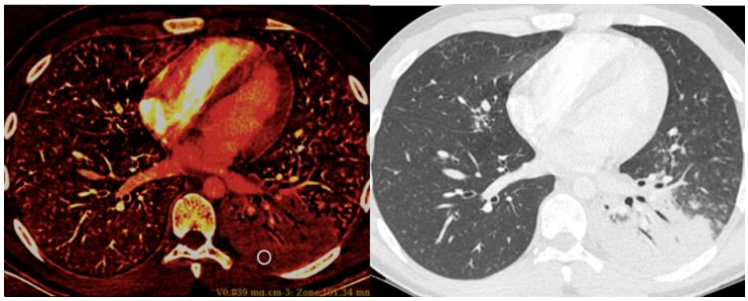


Figure 3. 19-year-old male with hemoptysis and chest pain. A homogeneous perfusion defect (PD+) is seen (iodine map, left) matching a left basal consolidation (conventional lung images, right). Tuberculous pneumonia was confrmed by PCR assay performed a on sputum sample. Iodine concentration was measured at 0.839 mg/cm3 within the circle and at 0.686 mg/cm3 within the normal-appearing parenchyma.

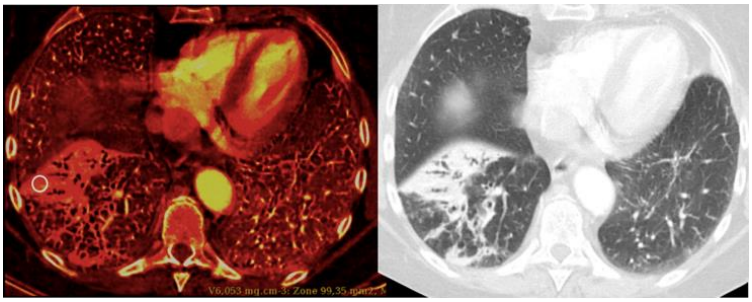


Figure 4. 75-year-old female with bronchopneumonia and suspected PE. No perfusion defect was detected (PD-). Instead, a homogeneous high iodine distribution is seen (iodine map, left) matching consolidations in the right anterior basal segment (conventional lung images, right). The patient was treated with Ceftriaxone with a favorable outcome. Iodine concentration was measured at 6.053 mg/cm3 within the circle and at 0.723 mg/cm3 within the normal-appearing parenchyma.

AUTOPSY AND HISTOLOGIC FINDINGS OF PATIENTS WITH NEW CORONAVIRUS PNEUMONIA: THE PATHOLOGIC ASSOCIATIONS WITH HYPOXEMIA

Zhang H, Zhou J, Chen R, Ren Y, Cai J, Zhao L, Fei X, Liu Z, Zhang Y, Yuan L, Wang C.. Med Sci Monit. 2021 Feb 13;27:e928837. doi: 10.12659/MSM.928837.
Level of Evidence: 4 - Case-series

BLUF

Pathologists from Shanghai Jiaotong University School of Medicine, China conducted systemic autopsies on four SARS-CoV-2 positive individuals to investigate the pathophysiology of hypoxemia in SARS-CoV-2. Lung biopsies showed prominent fibroblastic proliferation (Figure 1A,1B), viral inclusions in the alveolar cavity with hyperplastic macrophage activity (Figure 4A, 4B) and evidence of mucus plugs on alveolar ducts due to exfoliated ciliary cells in the epithelium lining (Figure 2A,2B). Authors suggest that insufficient air exchange due to microscopic findings in the respiratory system, mechanical obstruction due to mucus plugs, and loss of ciliated epithelial cells in the small bronchi likely influence the hypoxemia observed in COVID-19.

ABSTRACT

BACKGROUND Coronavirus 2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) in March 2020. To further reveal the pathologic associations between coronavirus and hypoxemia, we report the findings of 4 complete systematic autopsies of severe acute respiratory syndrome coronavirus 2-positive individuals who died of multiple organ failure caused by severe hypoxemia. MATERIAL AND METHODS We examined the donated corpses of 4 deceased patients who had been diagnosed with severe acute respiratory syndrome coronavirus 2. A complete post-mortem examination was carried out on each corpse, and multiple organs were macroscopically examined. RESULTS The 4 corpses were 2 males and 2 females, with an average age of 69 years. Bilateral lungs showed various degrees of atrophy and consolidation, with diffusely tough and solid texture in the sections. A thromboembolism was found in the main pulmonary artery extending into the atrium in 1 corpse, and significant atherosclerotic plaques tagged in the inner wall of the aortic arch were found in 2 corpses. Two corpses were found to have slightly atrophied bilateral renal parenchyma. Atrophic changes in the spleen were found in 2 corpses. Notably, there were significantly expanded alveolar septa and prominent fibroblastic proliferation. CONCLUSIONS The laboratory data of these corpses showed a progressive decrease in blood oxygen saturation, followed by refractory and irreversible hypoxemia. Clinical and laboratory information and autopsy and histologic presentations of multiple organs showed insufficient air exchange due to abnormalities in the respiratory system, and reduced erythropoiesis in bone marrow may play a role.

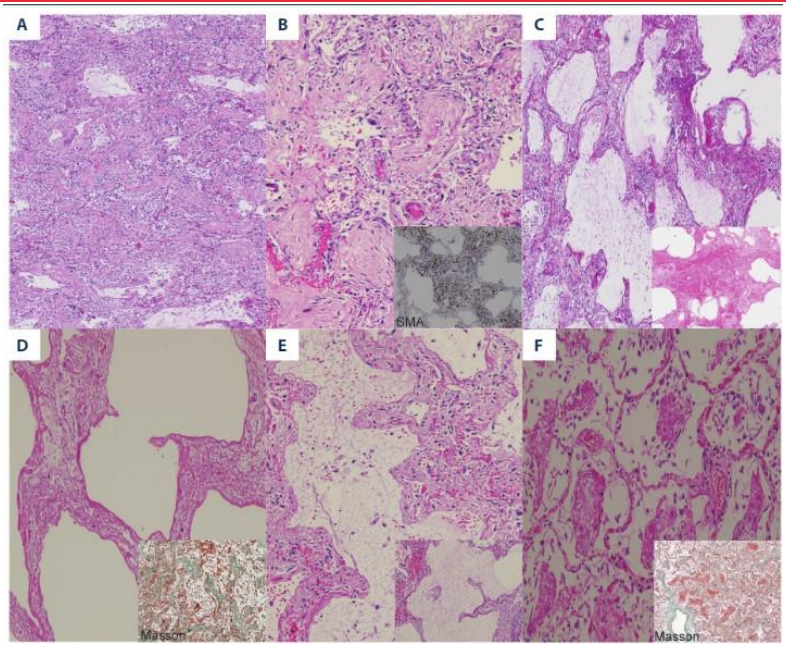


Figure 1. (A) Lung consolidation. (B) Lung consolidation (SMA showed a hyperplasia of myoﬁbroblasts). (C) Lung injury, pulmonary bullae. (D) Hyaline membrane (brown color highlighted by Masson’s stain). (E) Abundant serous exudation in the alveoli.(F) Cellulose exudation in the alveoli (brown color stained by Masson’s stain)

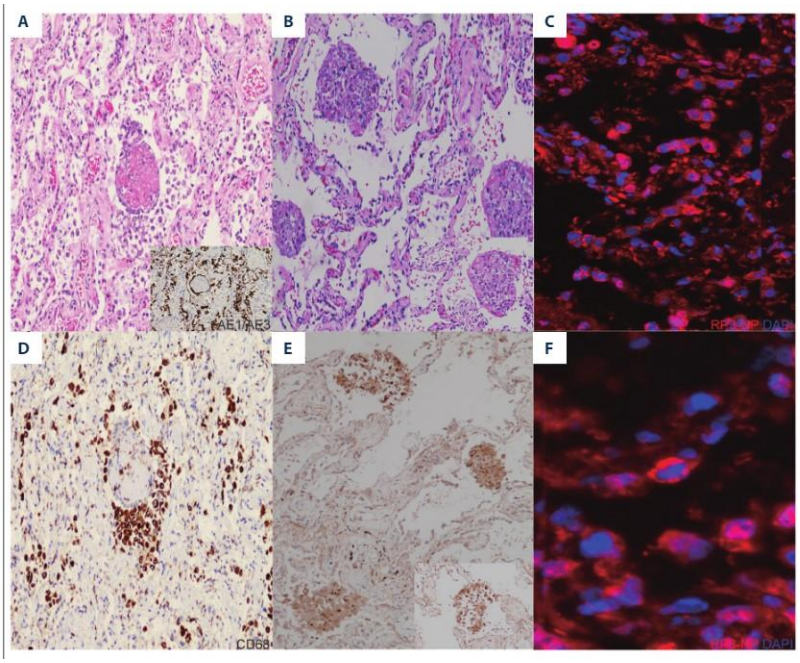


Figure 4. (A, B) Macrophage aggregation was found in the alveolar cavity, and type II alveolar epithelial cells were surrounded by
cellulose exudates (type II alveolar epithelial cells labeled by AE1/AE3). (D) Macrophages were stained by CD68. (C, E, F) The 2019-nCoV-speciﬁc marker RN3-NP was expressed in hyperplastic macrophage

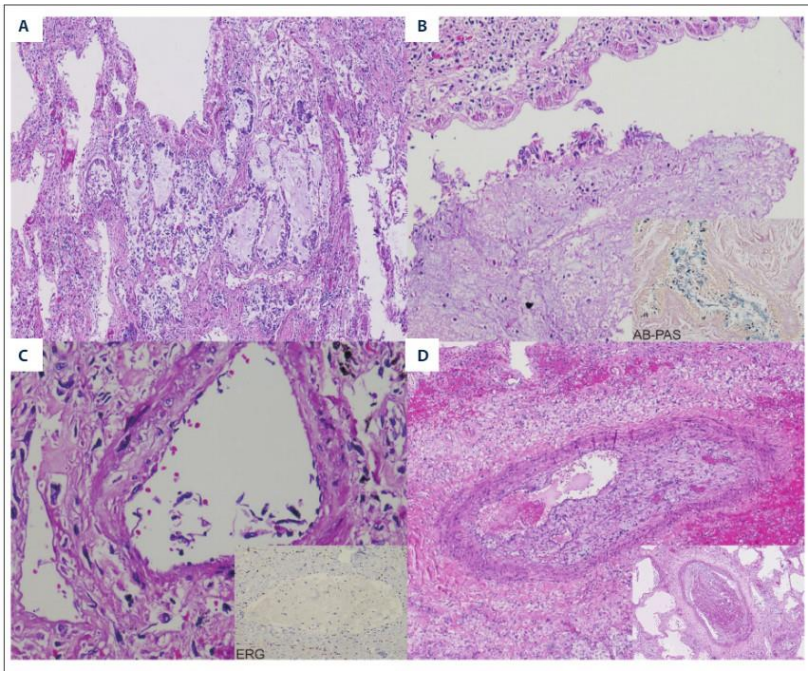


Figure 2. (A) Mucus plugs located in the small airway. (B) Mucus plugs were blue when stained by AB-PAS. (C) Capillary endothelial cells shed (ERG was negative). (D) Thrombosis in the interstitial blood vessels and organization and recanalization was seen

A GENOME-WIDE CRISPR SCREEN IDENTIFIES HOST FACTORS THAT REGULATE SARS-COV-2 ENTRY

Zhu Y, Feng F, Hu G, Wang Y, Yu Y, Zhu Y, Xu W, Cai X, Sun Z, Han W, Ye R, Qu D, Ding Q, Huang X, Chen H, Xu W, Xie Y, Cai Q, Yuan Z, Zhang R.. Nat Commun. 2021 Feb 11;12(1):961. doi: 10.1038/s41467-021-21213-4.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Molecular virologists from Shanghai Medical College, among others, created a SARS-CoV-2 clone with disruptions to the S1/S2 site (Sdel) and examined its effect on cell entry. While virus with intact spike protein entered via plasma fusion, Sdel entered via endocytosis and had decreased infectivity in an animal model (Figure 1). They also used CRISPR to identify several endosomal entry-specific regulators that affect viral entry, transmission and infectivity (Figures 2, 4). Authors suggest modulation to the spike protein can change entry pathways and transmission and that identifying factors involved may have implications for treatment development.

ABSTRACT

The global spread of SARS-CoV-2 is posing major public health challenges. One feature of SARS-CoV-2 spike protein is the insertion of multi-basic residues at the S1/S2 subunit cleavage site. Here, we find that the virus with intact spike (Sfull) preferentially enters cells via fusion at the plasma membrane, whereas a clone (Sdel) with deletion disrupting the multi-basic S1/S2 site utilizes an endosomal entry pathway. Using Sdel as model, we perform a genome-wide CRISPR screen and identify several endosomal entry-specific regulators. Experimental validation of hits from the CRISPR screen shows that host factors regulating the surface expression of angiotensin-converting enzyme 2 (ACE2) affect entry of Sfull virus. Animal-to-animal transmission with the Sdel virus is reduced compared to Sfull in the hamster model. These findings highlight the critical role of the S1/S2 boundary of SARS-CoV-2 spike protein in modulating virus entry and transmission and provide insights into entry of coronaviruses.

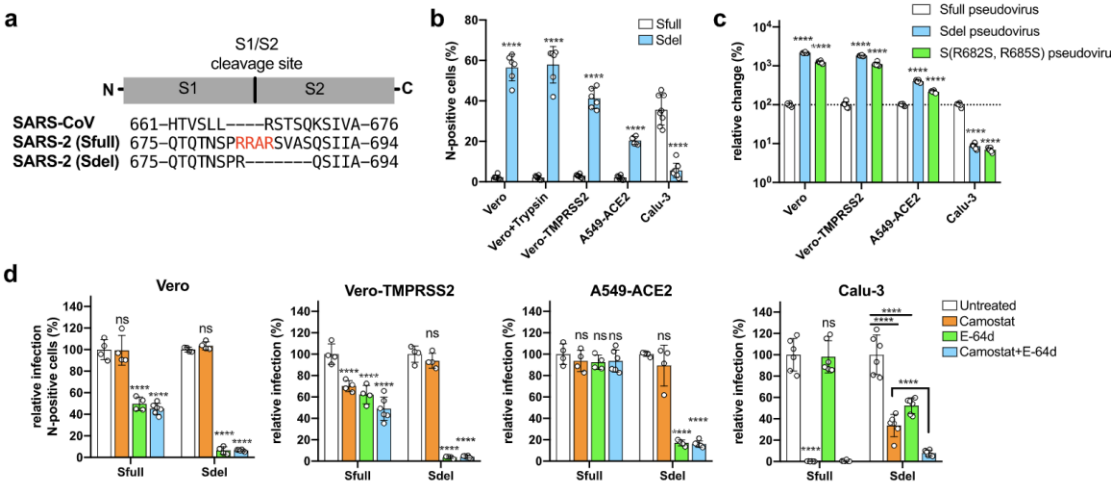


Fig. 1 The deletion at the S1/S2 boundary of spike protein propels the virus to enter cells through the endosomal pathway. aSequence alignment ofspike protein encompassing the cleavage site between S1 and S2 subunits. The spike proteins of SARS-CoV-2 without (Sfull strain) and with (Sdel strain)deletion were used to compare with that of SARS-CoV. The insertion of multi-basic amino acids in spike protein of SARS-CoV-2 was shown in red.bComparison of the replication property between Sfull and Sdel strains in different cell lines. The percentage of nucleocapsid (N) protein-positive cells was analyzed by imaging-based analysis following virus infection (two or more experiments;n=6 except for Calu-3 in which n=8; one-way ANOVA with Dunnett’s test; mean ± s.d.).cEvaluation of entry efficiency in different cell lines infected with pseudoviruses bearing spike protein Sfull, Sdel, or S mutant(R682S, R685S). Data are normalized to the Sfull of individual experiments (two experiments;n=6; one-way ANOVA with Dunnett’s test; mean ± s.d.).dEffect of TMPRSS2 serine protease inhibitor Camostat and cysteine protease inhibitor E-64d on Sfull or Sdel infection in different cell lines (two experiments;n=4 or 6; one-way ANOVA with Dunnett’s test; mean ± s.d.). Data shown were normalized to the untreated group of individual experiments.****P< 0.0001; n.s. not significant.

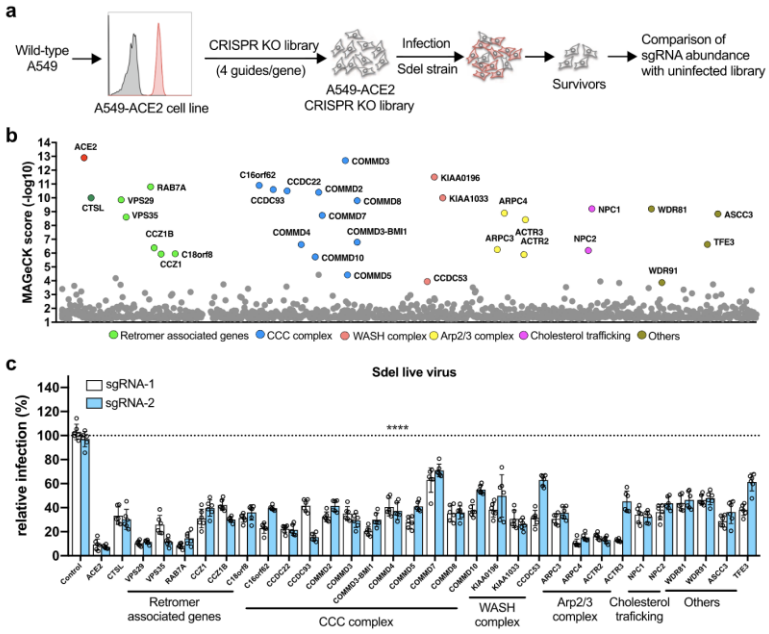


Fig. 2 Genome-wide CRISPR/Cas9 screen identifies host factors using Sdel virus as model. aSchematic of the screening process. A549 cells expressing the human ACE2 were used to generate the CRISPR sgRNA knockout cell library. The library was infected with Sdel strain of SARS-CoV-2, and cells survived were harvested for genomic extraction and sequence analysis.bGenes and complexes identified from the CRISPR screen. The top 32 (FDR < 0.15)genes were indicated based the MAGeCK score.cThe top 32 genes were selected for experimental validation in A549-ACE2 cells using two independents gRNAs by Sdel live virus infection. Data shown are an average of two independent experiments performed in triplicate and are normalized to the controls of individual experiments. One-way ANOVA with Dunnett’s test;n=6; mean ± s.d.; ****P< 0.0001.

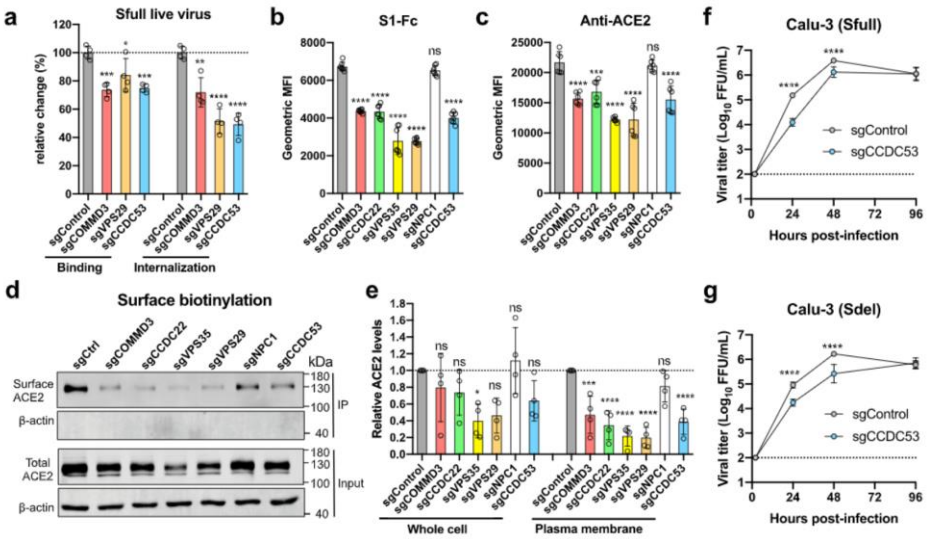


Fig. 4 Host genes that regulate the surface expression of receptor ACE2 are identified. aThe effect on virion binding and internalization in gene-editedcells. A549-ACE2 cells were incubated with SARS-CoV-2 Sfull infectious virus on ice for binding or then switched to 37 °C for internalization. Viral RNA was extracted for RT-qPCR analysis (two experiments;n=4; one-way ANOVA with Dunnett’s test; mean ± s.d.).b,c Surface expression of receptor ACE2was decreased in gene-edited cells as measured byflow cytometry using S1-Fc recombinant protein or anti-ACE2 antibody (2 experiments;n=7(b)or6(c); one-way ANOVA with Dunnett’s test; mean ± s.d.).d,eSurface and total expression of receptor ACE2 were decreased in gene-edited cells. Theplasma membrane proteins were biotin-labeled and immunoprecipitated by streptavidin beads for western blotting. One representative blot was shown(d) and data are pooled from four independent experiments, quantified, and normalized to the controls of individual experiments (e) (four experiments;n=4; one-way ANOVA with Dunnett’s test; mean ± s.d.).f,gThe impact on viral production inCCDC53gene-edited Calu-3 cells. The mixed cellpopulation was infected with Sfull (f) or Sdel (g) to assess the virus yield (two experiments;n=6; two-way ANOVA with Sidak’s test). *P< 0.05; **P<0.01; ***P< 0.001; ****P< 0.0001; n.s. not significant.

PROSPECTIVE OBSERVATIONAL STUDY AND SEROSURVEY OF SARS-COV-2 INFECTION IN ASYMPTOMATIC HEALTHCARE WORKERS AT A CANADIAN TERTIARY CARE CENTER

Ferreira VH, Chruscinski A, Kulasingam V, Pugh TJ, Dus T, Wouters B, Oza A, Ierullo M, Ku T, Majchrzak-Kita B, Humar ST, Bahinskaya I, Pinzon N, Zhang J, Heisler LE, Krzyzanowski PM, Lam B, Lungu IM, Manase D, Pace KM, Mashouri P, Brudno M, Garrels M, Mazzulli T, Cybulsky M, Humar A, Kumar D.. PLoS One. 2021 Feb 16;16(2):e0247258. doi: 10.1371/journal.pone.0247258. eCollection 2021.
Level of Evidence: 3 - Local non-random sample

BLUF

Immunologists, molecular biologists and infectious disease physicians from the University Health Network in Toronto, Canada investigated the prevalence of asymptomatic SARS-CoV-2 infection in healthcare workers (HCWs) via RT-PCR between April 17 – May 29, 2020. They found 29/5776 asymptomatic HCWs had positive swabs (0.50%, 95%CI 0.32-0.75) and 54/1597 (3.4%) symptomatic HCWs tested positive for SARS-CoV-2 (Figure 1). Because they identified asymptomatic infections in HCWs, authors suggest routinely screening HCWs could allow infected individuals to isolate and minimize COVID-19 spread in medical settings.

ABSTRACT

Health care workers (HCWs) are at higher risk for SARS-CoV-2 infection and may play a role in transmitting the infection to vulnerable patients and members of the community. This is particularly worrisome in the context of asymptomatic infection. We performed a cross-sectional study looking at asymptomatic SARS-CoV-2 infection in HCWs. We screened asymptomatic HCWs for SARS-CoV-2 via PCR. Complementary viral genome sequencing was performed on positive swab specimens. A seroprevalence analysis was also performed using multiple assays. Asymptomatic health care worker cohorts had a combined swab positivity rate of 29/5776 (0.50%, 95%CI 0.32-0.75) relative to a comparative cohort of symptomatic HCWs, where 54/1597 (3.4%) tested positive for SARS-CoV-2 (ratio of symptomatic to asymptomatic 6.8:1). SARS-CoV-2 seroprevalence among 996 asymptomatic HCWs with no prior known exposure to SARS-CoV-2 was 1.4-3.4%, depending on assay. A novel in-house Coronavirus protein microarray showed differing SARS-CoV-2 protein reactivities and helped define likely true positives vs. suspected false positives. Our study demonstrates the utility of routine screening of asymptomatic HCWs, which may help to identify a significant proportion of infections.

FIGURES

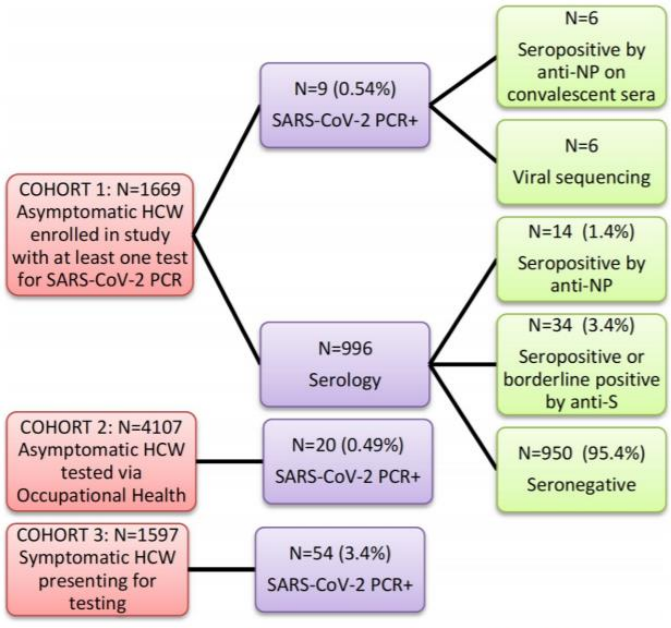


Fig 1. Study flow and outcomes. Abbreviations: HCW—healthcare workers, NP—nucleoprotein, S—spike.

EVIDENCE OF FOODBORNE TRANSMISSION OF THE CORONAVIRUS (COVID-19) THROUGH THE ANIMAL PRODUCTS FOOD SUPPLY CHAIN

Hu L, Gao J, Yao L, Zeng L, Liu Q, Zhou Q, Zhang H, Lu D, Fu J, Liu QS, Li M, Zhao X, Hou X, Shi J, Liu L, Guo Y, Wang Y, Ying GG, Cai Y, Yao M, Cai Z, Wu Y, Qu G, Jiang G.. Environ Sci Technol. 2021 Feb 16. doi: 10.1021/acs.est.0c06822. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

Environmental and toxicology experts from the Research Center for Eco-Environmental Sciences in Beijing argue for more extensive surveillance of SARS-CoV-2 in the meat, seafood, and general produce industry. Referencing several articles that suggest potential transmission of SARS-CoV-2 from imported frozen seafood and poultry, authors raise concern about food-associated transmission routes (Figure 1). They note current research on the food-based transmission is limited and based mostly on other coronaviruses, such as SARS-CoV-1 and MERS-CoV-4, and suggest further investigation into whether packaging, shipping materials, and viral screening methods need modification.

FIGURES

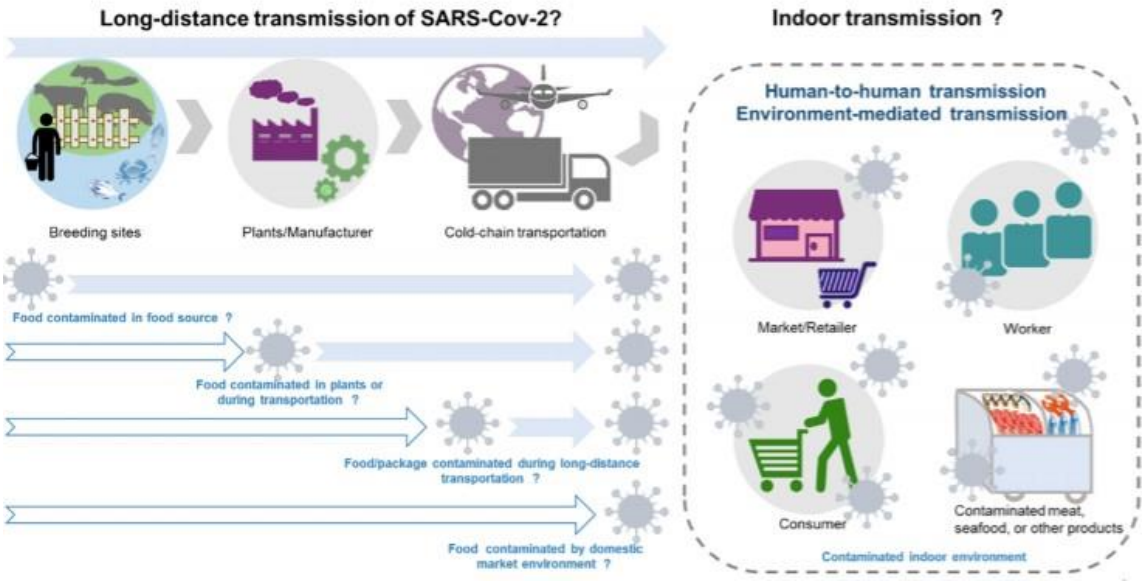


Figure 1. Possible food-associated transmission routes of COVID-19

FAMILIAL THROMBOCYTOPENIA FLARE-UP FOLLOWING THE FIRST DOSE OF MRNA-1273 COVID-19 VACCINE

Toom S, Wolf B, Avula A, Peeke S, Becker K.. Am J Hematol. 2021 Feb 13. doi: 10.1002/ajh.26128. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Hematologists, internists and critical care physicians from Maimonides Medical Center and Saint Barnabas Hospital in New York recount the case of a 36-year-old female with history of immune thrombocytopenia purpura (baseline platelet count 40-60K/μL) who presented with diffuse petechiae, easy bruising, and bleeding gums 2 weeks after receiving the first dose of the SARS-CoV-2 mRNA-1273 (Moderna) vaccine. On presentation, platelet count was 3,000/μL and recovered to 28,000/μL after 3 days of dexamethasone and IVIG. The patient had previously been without flare-up for 12 years. Authors suggest this is the first reported case of exacerbation of an underlying thrombocytopenia after vaccination with the mRNA-1273 vaccine and should be investigated further.

SARS-COV-2 DETECTED ON ENVIRONMENTAL FOMITES FOR BOTH ASYMPTOMATIC AND SYMPTOMATIC COVID-19 PATIENTS

Yang M, Li L, Huang T, Li S, Zhang M, Yang Y, Jiang Y, Li X, Yuan J, Liu Y.. Am J Respir Crit Care Med. 2020 Dec 16. doi: 10.1164/rccm.202006-2136LE. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from Shenzhen Third People's Hospital in China evaluated potential environmental fomites by taking serum samples from 66 hospitalized patients with COVID-19 (46 symptomatic and 20 asymptomatic) and samples from a number of environmental sources (squat toilets, cups, straws, oxygen catheters, breathing exercisers, and atomizing nozzles), analyzed using qRT-PCR (Table 1). The researchers found that environmental contamination presents in both symptomatic and asymptomatic patients but an increased viral load (detected by nasopharyngeal swab) was associated with increased likelihood of environmental spread regardless of symptoms (Figure 1), especially to toilets (28.6% asymptomatic - 33.3% symptomatic), suggesting further evidence in support of hand hygiene and toilet disinfection to reduce risk of fecal-oral transmission of COVID-19.

FIGURES

Table 1. Sample collection details and viral RNA detection results.

Characteristic	COVID-19 cases				
	Patient Number=66(Total samples)	Asymptomatic (Patient Number=20)		Symptomatic (Patient Number=46)	
Male (N, %)	41 (57.7)	8 (40.0)		29 (63.0)	
Median sample collection day after patient's Admission[a]/ Symptom[b] Onset (range)	9 (1-48)	6 (1-20)		12 (1-48)	
Median number of samples for each patient (range)	8 (1-36)	8 (7-16)		8 (1-36)	
Sample types	555	179		376	
		Positive Samples/ Total Samples	Positive Patients[c]/Total Patients	Positive Samples/Total Samples	Positive Patients[d]/Total Patients
Inside the mask	28	1/13	1/12	3/15	3/15
Hand/foot	47	2/22	2/18	2/25	2/23
Cell phone	54	1/23	1/20	1/31	1/30
Mouth/nose contacts	68	4/30	3/20	6/38	6/36
Squat toilet around	22	2/7	2/7	5/15	5/15
Mouse and nose around	27	1/17	1/17	2/10	2/10
Bedclothes[e]	68	0/17	0/12	1/51	1/30
Other electronic products	30	0/16	0/14	0/14	0/13
Various handles	27	0/4	0/4	0/23	0/21
Clothes/shoes	6	0/5	0/5	0/1	0/1
Wash supplies	12	0/7	0/7	0/5	0/5
Daily necessities[f]	24	0/10	0/10	1/14	1/14
Medical supplies[g]	63	0/7	0/7	1/56	1/41
Others	79	0/2	0/2	0/78	0/41[h]

Table 1. Sample collection details and viral RNA detection results.. COVID-19: Coronavirus disease 2019. a: Sample collection from asymptomatic patients started from admission onset. b: Sample collection from symptomatic patients started from symptom onset. c&d: Positive patients represent the patients whose environmental fomites were detectable with SARSCoV-2. e: One positive sample from a symptomatic patient’s pillow was detected. f: One positive sample from a symptomatic patient’s glasses was detected. g: One positive sample from a symptomatic patient’s infusion pump was

detected. h: Except for 2 positive samples of mouse/nose contacts collected from the same patient, for all the rest of positive environmental samples, each of them was collected from a different participant.

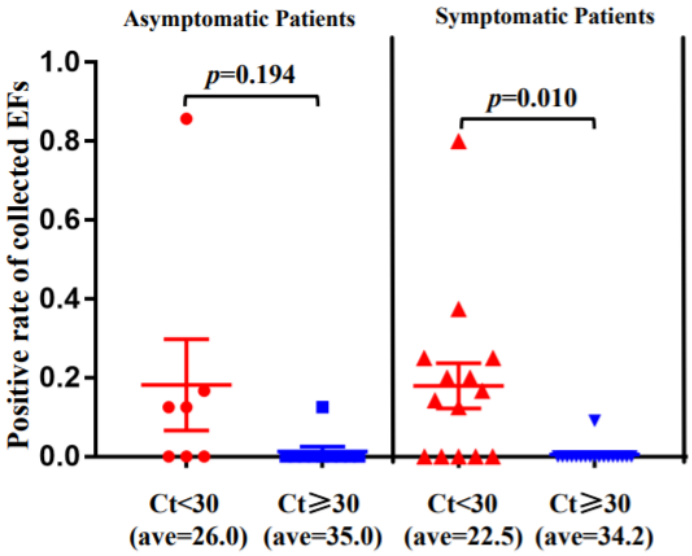


Figure 1

Figure 1. Correlation of the viral loads from patient samples with the positive rates of environmental samples from COVID-19 patients. EFs: environmental fomites. Positive rate of collected EFs represents the ratio of the number of positive types of EFs collected from a patient to the total number of types of EFs collected from the specific patient. The positive EFs include squat toilet around, water cup, breathing exerciser, straw, oxygen catheter and atomizing, inside the mask, hand/foot, cell phone, pillow and glasses as shown in Table 1. Within both asymptomatic patient group and symptomatic patient group, patients were further divided according to the Ct values of SARS-CoV-2 RNA qRT-PCR from nasopharyngeal swab samples, as high viral load group for Ct < 30, and low viral load group for Ct  30, determined from the distribution of patient nasopharyngeal sample Ct values. Positive rates of collected EFs were compared between the high vs. low viral load patient groups for the number of positive EFs/ the number of total tested EFs. $p < 0.050$ is considered statistically significant. Spearman rank coefficient correlation analysis showed that the positive SARS-CoV-2 RNA detection rate of EFs from both symptomatic and asymptomatic patients were highly correlated with the specific patient’s nasopharyngeal viral load assessed by Ct values (asymptomatic : $r = -0.630$, $p = 0.0070$; symptomatic: $r = -0.600$, $p=0.0003$).

VALIDATION OF CDC 3-LEVEL RISK CLASSIFICATION FOR HEALTHCARE WORKERS EXPOSED TO COVID-19

Gragnani CM, Fernandes P, Waxman DA.. Infect Control Hosp Epidemiol. 2020 Dec 7:1-9. doi: 10.1017/ice.2020.1353. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers at University of California at Los Angeles (UCLA) between March 9 - 27, 2020, used prospective risk classification to quantify the infection probability by categorizing health care workers (HCWs) at UCLA health centers into high risk (n=98, 14.7%), medium risk (n=192, 28.8%) and low risk (n=377, 56%) based on exposure description. These categories saw positive post-exposure COVID-19 RT-PCR tests in 9.2%, 4.7%, and 1.6%, respectively (Table 1), suggesting that the CDC 3-Level Risk Classification is a valid assessment of risk probability.

FIGURES

Variable	% Tested With PCR for SARS-CoV-2	CDC Exposure Risk Level, No. (% of Risk Level)		
		High	Medium	Low
Population (N=667)	48.1	98	192	377
Age in y, Mean ± SD (N=576)		36.6±9.4	38.6±10.5	39.3±10.3
Sex (N=572)[a]				
Female (N=375)	53.3	53 (62.4)	110 (67.1)	212 (65.6)
Male (N=197)	41.6	32 (37.7)	54 (32.9)	111 (34.4)
Employee job description				
Nurse (N=274)	50.7	38 (38.8)	83 (43.2)	153 (40.6)
Resident physician (N=37)	67.6	5 (5.1)	12 (6.3)	20 (5.3)
Attending physician (N=47)	46.8	7 (7.1)	15 (7.8)	25 (6.6)
Respiratory therapist (N=28)	67.9	11 (11.2)	7 (3.7)	10 (2.7)
Other (clinical and support staff) (N=281)	41.3	37 (37.8)	75 (39.1)	169 (44.8)
Employee job site				
Inpatient (N=478)	50.8	82 (83.7)	140 (72.9)	256 (67.9)
Outpatient/other (N=189)	47.1	16 (16.3)	52 (27.1)	121 (32.1)
Days between exposure and enrollment, median [IQR] (N=667)		3 [2–6]	4 [3–6]	4 [2–7]
Days between enrollment and testing, median [IQR] (N=321)		3 [2–7]	4 [2–7]	4 [3–5]
Tested (N=321)		64 (65.3)	102 (53.1)	155 (41.1)
Outcome				
Positive COVID-19 PCR (N=24)[b]		9	9	6
As % of enrolled (95% CI)		9.2 (4.3–16.7)	4.7 (2.2–8.7)	1.6 (0.6–3.4)
As % of tested (95% CI)		14.1 (6.6–25.0)	8.8 (4.1–16.1)	3.9 (1.4–8.2)

Table 1. Description of Healthcare Worker (HCW) Population with Centers for Disease Control and Prevention (CDC)–Risk Classified, Work-Related SARS-CoV-2 Exposures Enrolled in Symptom Monitoring (N=667) NOTE. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory coronavirus virus 2; PCR, polymerase chain reaction; SD, standard deviation; IQR, interquartile range; CI, confidence interval.

EARLY INITIATION OF PROPHYLACTIC ANTICOAGULATION FOR PREVENTION OF CORONAVIRUS DISEASE 2019 MORTALITY IN PATIENTS ADMITTED TO HOSPITAL IN THE UNITED STATES: COHORT STUDY

Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, Skanderson M, Brittain E, King JT Jr, Ho YL, Eden S, Kundu S, Lann MF, Greevy RA Jr, Ho PM, Heidenreich PA, Jacobson DA, Douglas IJ, Tate JP, Evans SJW, Atkins D, Justice AC, Freiberg MS.. BMJ. 2021 Feb 11;372:n311. doi: 10.1136/bmj.n311.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A multidisciplinary team of physicians and epidemiologists compared the outcomes of 4297 patients hospitalized with SARS-CoV-2 infection between March 1 and July 31, 2020 (Table 1) based on whether they received early prophylactic anticoagulation (see summary). They found patients who received anticoagulation had a 27% decreased risk of death (HR: 0.73, 95%CI: 0.66-0.81)(Figure 3), though 30-day mortality rates were not statistically different (14.3% [95%CI: 3.1-15.5%] vs. 18.7% [95%CI:15.1- 22.9%)(Table 3). Authors suggest early initiation of prophylactic anticoagulation in COVID-19 patients may confer a mortality benefit.

SUMMARY

Early initiation was defined as anticoagulation initiated within 24 hr of hospital admission, with subcutaneous heparin and enoxaparin the most commonly used drugs. In the study cohort, 3627 patients (84.4%) received early prophylactic anticoagulation.

ABSTRACT

OBJECTIVE: To evaluate whether early initiation of prophylactic anticoagulation compared with no anticoagulation was associated with decreased risk of death among patients admitted to hospital with coronavirus disease 2019 (covid-19) in the United States. DESIGN: Observational cohort study. SETTING: Nationwide cohort of patients receiving care in the Department of Veterans Affairs, a large integrated national healthcare system. PARTICIPANTS: All 4297 patients admitted to hospital from 1 March to 31 July 2020 with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and without a history of anticoagulation. MAIN OUTCOME MEASURES: The main outcome was 30 day mortality. Secondary outcomes were inpatient mortality, initiating therapeutic anticoagulation (a proxy for clinical deterioration, including thromboembolic events), and bleeding that required transfusion. RESULTS: Of 4297 patients admitted to hospital with covid-19, 3627 (84.4%) received prophylactic anticoagulation within 24 hours of admission. More than 99% (n=3600) of treated patients received subcutaneous heparin or enoxaparin. 622 deaths occurred within 30 days of hospital admission, 513 among those who received prophylactic anticoagulation. Most deaths (510/622, 82%) occurred during hospital stay. Using inverse probability of treatment weighted analyses, the cumulative incidence of mortality at 30 days was 14.3% (95% confidence interval 13.1% to 15.5%) among those who received prophylactic anticoagulation and 18.7% (15.1% to 22.9%) among those who did not. Compared with patients who did not receive prophylactic anticoagulation, those who did had a 27% decreased risk for 30 day mortality (hazard ratio 0.73, 95% confidence interval 0.66 to 0.81). Similar associations were found for inpatient mortality and initiation of therapeutic anticoagulation. Receipt of prophylactic anticoagulation was not associated with increased risk of bleeding that required transfusion (hazard ratio 0.87, 0.71 to 1.05). Quantitative bias analysis showed that results were robust to unmeasured confounding (e-value lower 95% confidence interval 1.77 for 30 day mortality). Results persisted in several sensitivity analyses. CONCLUSIONS: Early initiation of prophylactic anticoagulation compared with no anticoagulation among patients admitted to hospital with covid-19 was associated with a decreased risk of 30 day mortality and no increased risk of serious bleeding events. These findings provide strong real world evidence to support guidelines recommending the use of prophylactic anticoagulation as initial treatment for patients with covid-19 on hospital admission.

Table 1 Personal and clinical characteristics of 4297 patients admitted to hospital with coronavirus disease 2019 (covid-19) who received prophylactic anticoagulation within 24 hours of hospital admission, before and after weighting. Values are numbers (percentages) unless stated otherwise

Characteristics	Unweighted			IPT weighted*		
	No anticoagulation (n=670)	Prophylactic anticoagulation (n=3627)	SMD	No anticoagulation (n=2141)	Prophylactic anticoagulation (n=2156)	SMD
Personal characteristics						
Median (interquartile range) age (years)	69.0 (58.0-76.5)	68.1 (58.2-74.8)	0.04	69.4 (59.7-76.5)	68.3 (58.2-75.0)	0.04
Age groups (years):						
20-49	89 (13.3)	446 (12.3)	0.03	239 (11.2)	265 (12.3)	0.04
50-59	105 (15.7)	619 (17.1)	0.04	313 (14.6)	363 (16.8)	0.06
60-69	161 (24.0)	951 (26.2)	0.05	554 (25.9)	558 (25.9)	0.00
70-79	188 (28.1)	1056 (29.1)	0.02	652 (30.5)	626 (29.0)	0.03
≥80	127 (19.0)	555 (15.3)	0.10	383 (17.9)	343 (15.9)	0.05
Race or ethnicity:						
White	256 (38.2)	1347 (37.1)	0.02	832 (38.9)	806 (37.4)	0.03
Black	291 (43.4)	1649 (45.5)	0.04	940 (43.9)	974 (45.2)	0.03
Hispanic	74 (11.0)	432 (11.9)	0.03	238 (11.1)	252 (11.7)	0.02
Other	22 (3.3)	102 (2.8)	0.03	76 (3.6)	63 (2.9)	0.04
Unknown	27 (4.0)	97 (2.7)	0.08	55 (2.6)	61 (2.8)	0.02
Men	620 (92.5)	3395 (93.6)	0.04	2019 (94.3)	2014 (93.4)	0.04
Urban residence	587 (87.6)	3181 (87.7)	0.00	1915 (89.5)	1893 (87.8)	0.05
Census region:						
Midwest	79 (11.8)	724 (20.0)	0.22	343 (16.0)	400 (18.6)	0.07
Northeast	139 (20.7)	622 (17.1)	0.09	432 (20.2)	383 (17.8)	0.06
South	314 (46.9)	1703 (47.0)	0.00	998 (46.6)	1012 (46.9)	0.01
West	138 (20.6)	578 (15.9)	0.12	367 (17.2)	361 (16.7)	0.01
Month of admission:						
March	116 (17.3)	518 (14.3)	0.08	323 (15.1)	316 (14.7)	0.01
April	169 (25.2)	868 (23.9)	0.03	491 (22.9)	522 (24.2)	0.03
May	70 (10.4)	429 (11.8)	0.04	277 (12.9)	250 (11.6)	0.04
June	110 (16.4)	616 (17.0)	0.02	361 (16.9)	364 (16.9)	0.00
July	205 (30.6)	1196 (33.0)	0.05	689 (32.2)	704 (32.6)	0.01
Clinical conditions						
Acute myocardial infarction	11 (1.6)	66 (1.8)	0.01	45 (2.1)	39 (1.8)	0.02
Asthma	33 (4.9)	176 (4.9)	0.00	117 (5.5)	105 (4.9)	0.03
Cancer, any	97 (14.5)	494 (13.6)	0.02	318 (14.9)	298 (13.8)	0.03
Cerebrovascular disease	85 (12.7)	369 (10.2)	0.08	223 (10.4)	230 (10.7)	0.01
Chronic kidney disease	136 (20.3)	694 (19.1)	0.03	436 (20.4)	421 (19.5)	0.02
COPD	105 (15.7)	544 (15.0)	0.02	359 (16.8)	328 (15.2)	0.04
Coronary artery disease	25 (3.7)	90 (2.5)	0.07	65 (3.0)	59 (2.7)	0.02
Dementia	104 (15.5)	378 (10.4)	0.15	261 (12.2)	244 (11.3)	0.03
Diabetes	269 (40.1)	1573 (43.4)	0.07	859 (40.1)	924 (42.9)	0.06
Heart failure	77 (11.5)	375 (10.3)	0.04	265 (12.4)	232 (10.8)	0.05
Hypertension	446 (66.6)	2470 (68.1)	0.03	1380 (64.5)	1462 (67.8)	0.07
Liver disease	71 (10.6)	322 (8.9)	0.06	209 (9.8)	199 (9.2)	0.02
Peripheral arterial disease	70 (10.4)	387 (10.7)	0.01	236 (11.0)	229 (10.6)	0.01
Charlson comorbidity index score:						
0	130 (19.4)	765 (21.1)	0.04	404 (18.9)	450 (20.9)	0.05
1	110 (16.4)	723 (19.9)	0.09	388 (18.1)	423 (19.6)	0.04
2	119 (17.8)	657 (18.1)	0.01	403 (18.8)	384 (17.8)	0.03
3	74 (11.0)	394 (10.9)	0.01	252 (11.8)	235 (10.9)	0.03
4	69 (10.3)	324 (8.9)	0.05	217 (10.2)	194 (9.0)	0.04
≥5	168 (25.1)	764 (21.1)	0.10	476 (22.2)	470 (21.8)	0.01
Drug history						
ACE inhibitor	119 (17.8)	807 (22.2)	0.11	422 (19.7)	463 (21.5)	0.04
ARB	78 (11.6)	481 (13.3)	0.05	261 (12.2)	283 (13.1)	0.03
NSAID	144 (21.5)	731 (20.2)	0.03	408 (19.1)	438 (20.3)	0.03
Oral corticosteroid	156 (23.3)	875 (24.1)	0.02	514 (24.0)	516 (24.0)	0.00
In-hospital treatments						
Dexamethasone:						
<24 hours	74 (11.0)	588 (16.2)	0.15	309 (14.4)	332 (15.4)	0.03
>24 hours	115 (17.2)	892 (24.6)	0.18	463 (21.6)	508 (23.6)	0.05
Remdesivir:						
<24 hours	35 (5.2)	437 (12.0)	0.24	204 (9.5)	236 (10.9)	0.05
>24 hours	89 (13.3)	791 (21.8)	0.23	341 (15.9)	447 (20.7)	0.12
Substance use						
Alcohol consumption status:						
Abstinent	51 (7.6)	300 (8.3)	0.02	178 (8.3)	177 (8.2)	0.00
Low risk	360 (53.7)	1831 (50.5)	0.07	1059 (49.4)	1098 (50.9)	0.03
At risk	148 (22.1)	965 (26.6)	0.11	574 (26.8)	557 (25.8)	0.02
Hazardous	28 (4.2)	161 (4.4)	0.01	79 (3.7)	94 (4.4)	0.03
Alcohol use disorder	3 (0.4)	19 (0.5)	0.01	11 (0.5)	11 (0.5)	0.00
Missing	80 (11.9)	351 (9.7)	0.07	241 (11.3)	219 (10.1)	0.04
Smoking status:						
Never	17 (2.5)	63 (1.7)	0.06	42 (2.0)	41 (1.9)	0.00
Former	258 (38.5)	1431 (39.5)	0.02	753 (35.1)	842 (39.1)	0.08
Current	225 (33.6)	1355 (37.4)	0.08	905 (42.3)	793 (36.8)	0.11
Missing	170 (25.4)	778 (21.5)	0.09	442 (20.6)	479 (22.2)	0.04
Vital signs						
Body mass index:						
<26	206 (30.7)	938 (25.9)	0.11	630 (29.4)	576 (26.7)	0.06
26-32	258 (38.5)	1436 (39.6)	0.02	940 (43.9)	854 (39.6)	0.09
≥33	169 (25.2)	1113 (30.7)	0.12	494 (23.1)	637 (29.5)	0.15
Missing	37 (5.5)	140 (3.9)	0.08	78 (3.6)	89 (4.1)	0.03
Oxygen saturation (%):						
<93	72 (10.7)	582 (16.0)	0.16	315 (14.7)	329 (15.2)	0.02
93-96	182 (27.2)	1147 (31.6)	0.10	669 (31.3)	666 (30.9)	0.01
≥96	396 (59.1)	1775 (48.9)	0.21	1077 (50.3)	1091 (50.6)	0.01
Missing	20 (3.0)	123 (3.4)	0.02	80 (3.7)	71 (3.3)	0.02
Pulse (beats/min):						
<90	438 (65.4)	2200 (60.7)	0.10	1327 (62.0)	1327 (61.6)	0.01
≥90	232 (34.6)	1427 (39.3)	0.10	814 (38.0)	828 (38.4)	0.01
Systolic blood pressure (mm Hg):						
<140	446 (66.6)	2360 (65.1)	0.03	1347 (62.9)	1405 (65.2)	0.05
≥140	224 (33.4)	1267 (34.9)	0.03	794 (37.1)	751 (34.8)	0.05
Temperature (°C):						
≤37	356 (53.1)	1701 (46.9)	0.12	1045 (48.8)	1033 (47.9)	0.02
37·37·9	244 (36.4)	1292 (35.6)	0.02	737 (34.4)	771 (35.8)	0.03
≥38	70 (10.4)	634 (17.5)	0.20	359 (16.8)	352 (16.3)	0.01

IPT=inverse probability of treatment; SMD=absolute value of the standardized mean difference; COPD=chronic obstructive pulmonary disease; ACE=angiotensin converting enzyme; ARB=angiotensin II receptor blocker; NSAID=non-steroidal anti-inflammatory drug;
* Counts after IPT weighting were calculated by multiplying weights by constant factor k, where k was the ratio of observed sample size to number in the pseudopopulation after weighting; in this study, k=4297/8576.

Table 1

Personal and clinical characteristics of 4297 patients admitted to hospital with coronavirus disease 2019 (covid-19) who received prophylactic anticoagulation within 24 hours of hospital admission, before and after weighting. Values are numbers (percentages) unless stated otherwise

Table 3 Absolute and relative risks associated with prophylactic anticoagulation in the first 24 hours of hospital admission with coronavirus disease 2019

Outcomes	No of patients	No of events	Unweighted		IPT weighted	
			Hazard ratio (95% CI)		Cumulative incidence (95% CI)	Hazard ratio (95% CI)
30 day mortality:						
Prophylactic anticoagulation	3627	513	0.85 (0.69 to 1.05)		14.3 (13.1 to 15.5)	0.73 (0.66 to 0.81)
No anticoagulation	670	109	Ref		18.7 (15.1 to 22.9)	Ref
Inpatient mortality:						
Prophylactic anticoagulation	3627	418	0.82 (0.66 to 1.03)		11.7 (10.7 to 12.8)	0.69 (0.61 to 0.77)
No anticoagulation	670	92	Ref		16.4 (13.0 to 20.5)	Ref
Initiating therapeutic anticoagulation:						
Prophylactic anticoagulation	3627	573	1.14 (0.91 to 1.42)		15.6 (14.4 to 16.8)	0.81 (0.73 to 0.90)
No anticoagulation	670	92	Ref		18.8 (15.2 to 23.1)	Ref

IPT=inverse probability of treatment.

Table 3
Absolute and relative risks associated with prophylactic anticoagulation in the first 24 hours of hospital admission with coronavirus disease 2019

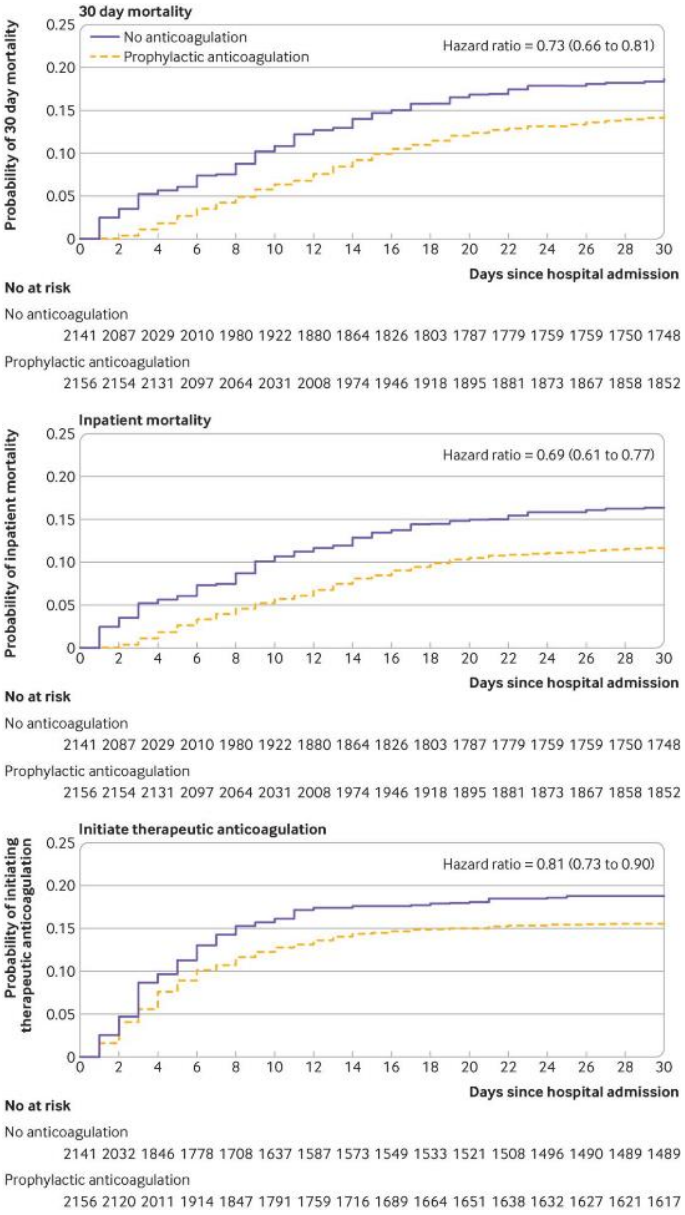


Fig 3

Inverse probability treatment weighted Kaplan-Meier plots. Numbers at risk were calculated by multiplying weights by constant factor k, where k was the ratio of observed sample size to number in the pseudopopulation after inverse probability treatment weighting; in this study, k=4297/8576

PREVALENCE AND PREDICTORS OF VENOUS THROMBOEMBOLISM OR MORTALITY IN HOSPITALIZED COVID-19 PATIENTS

Cohen SL, Gianos E, Barish MA, Chatterjee S, Kohn N, Lesser M, Giannis D, Coppa K, Hirsch J, McGinn T, Goldin M, Spyropoulos A.. Thromb Haemost. 2021 Jan 20. doi: 10.1055/a-1366-9656. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Investigators from various academic and medical institutions in New York conducted a retrospective cohort study of 9407 COVID-19 patients admitted to numerous hospitals throughout New York from March 1 - April 27, 2020, analyzing the frequency of venous thromboembolism (VTE) and resulting mortality. They found the rate of VTE to be 2.4% in the medical ward and 4.9% in the ICU, with an overall rate of 2.9%, with increased risk associated with age 60 or older, increasing number of comorbidities, larger BMI, elevated d-dimer level, steroid use or anti-rheumatologic medications, suggesting the need for prophylactic anticoagulation (supplemental table) in hospitalized COVID-19 patients, especially in high-risk subgroups.

ABSTRACT

OBJECTIVES: To identify the prevalence and predictors of VTE or mortality in hospitalized COVID-19 patients. METHODS: A retrospective cohort study of adult COVID-19 patients admitted to an integrated health care network in the New York metropolitan region between March 1, 2020 and April 27, 2020. The final analysis included 9407 patients with an overall VTE rate of 2.9% (2.4% in the medical ward and 4.9% in the ICU) and a VTE or mortality rate of 26.1%. Most patients received prophylactic-dose thromboprophylaxis. Multivariable analysis showed significantly reduced VTE or mortality with Black race, history of hypertension, angiotensin converting enzyme/angiotensin receptor blockers use, and initial prophylactic anticoagulation. It also showed significantly increased VTE or mortality with age 60 years or greater, Charlson Comorbidity Index (CCI) of 3 or greater, patients on Medicare, history of heart failure, history of cerebrovascular disease, body mass index greater than 35, steroid use, anti-rheumatologic medication use, hydroxychloroquine use, maximum D-dimer 4 times or greater than the upper limit of normal (ULN), ICU level of care, increasing creatinine, and decreasing platelet counts. CONCLUSION: In our large cohort of hospitalized COVID-19 patients, the overall in-hospital VTE rate was 2.9% (4.9% in the ICU) and a VTE or mortality rate of 26.1%. Key predictors of VTE or mortality included advanced age, increasing CCI, history of cardiovascular disease, ICU level of care, and elevated maximum D-dimer with a cutoff at least 4 times the ULN. Use of prophylactic-dose anticoagulation but not treatment-dose anticoagulation was associated with reduced VTE or mortality.

FIGURES

Anticoagulation	Prophylaxis dose	Treatment dose
Subcutaneous heparin, any dose	X	
Fondaparinox any dose < 7.5 mg daily	X	
Fondaparinox any dose ≥ 7.5 mg daily		X
Unfractionated heparin IV		X
Argatroban IV		X
Apixaban any dose < 10 mg daily	X	
Apixaban any dose ≥ 10 mg daily		X
Dabigatran 150 mg twice a day		X
Coumadin/warfarin any dose		X
Rivaroxaban any dose < 20 mg daily	X	
Rivaroxaban any dose ≥ 20 mg daily		X
Lovenox any dose < 80mg daily	X	
Lovenox any dose ≥ 80mg daily		X
Tissue plasminogen activator		X

Supplemental Table. Anticoagulation Medications.

EFFECT OF A SINGLE HIGH DOSE OF VITAMIN D3 ON HOSPITAL LENGTH OF STAY IN PATIENTS WITH MODERATE TO SEVERE COVID-19: A RANDOMIZED CLINICAL TRIAL

Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, Silva CBR, Franco AS, Macedo MB, Dalmolin HHH, Baggio J, Balbi GGM, Reis BZ, Antonangelo L, Caparbo VF, Gualano B, Pereira RMR.. JAMA. 2021 Feb 17. doi: 10.1001/jama.2020.26848. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A multicenter, double-blind, randomized clinical trial by Hospital das Clinicas HCFMUSP, Sao Paulo, Brazil evaluated the efficacy of single high dose vitamin D3 supplementation on the hospital length of stay for patients with COVID-19. 240 hospitalized COVID-19 patients (Figure 1) with moderate to severe course of the disease were given a single oral dose of 200,000 IU of vitamin D3. The study did not find a significant reduction (p=0.59) in the length of hospital stay between the group that received intervention versus the placebo group indicating the lack of clinical benefit of Vitamin D3 for treatment of COVID-19.

SUMMARY

-This study was conducted between June 2, 2020 to August 27, 2020.

-240 participants were recruited from the Clinical Hospital of the School of Medicine of the University of Sao Paulo and from the Ibirapuera field hospital in Sao Paulo, Brazil.

-Patients were assigned in a 1:1 ratio to the placebo or the high dose vitamin D3 group.

-Medium length of hospital stay between the groups were not significantly different (p=0.59; Figure 2).

-Furthermore, there were no significant differences seen between the two groups for in-hospital mortality, admission to the ICU, ventilation use, or the mean duration of ventilation use (Table 2).

ABSTRACT

Importance: The efficacy of vitamin D3 supplementation in coronavirus disease 2019 (COVID-19) remains unclear. Objective: To investigate the effect of a single high dose of vitamin D3 on hospital length of stay in patients with COVID-19. Design, Setting, and Participants: This was a multicenter, double-blind, randomized, placebo-controlled trial conducted in 2 sites in Sao Paulo, Brazil. The study included 240 hospitalized patients with COVID-19 who were moderately to severely ill at the time of enrollment from June 2, 2020, to August 27, 2020. The final follow-up was on October 7, 2020. Interventions: Patients were randomly assigned to receive a single oral dose of 200 000 IU of vitamin D3 (n = 120) or placebo (n = 120). Main Outcomes and Measures: The primary outcome was length of stay, defined as the time from the date of randomization to hospital discharge. Prespecified secondary outcomes included mortality during hospitalization; the number of patients admitted to the intensive care unit; the number of patients who required mechanical ventilation and the duration of mechanical ventilation; and serum levels of 25-hydroxyvitamin D, total calcium, creatinine, and C-reactive protein. Results: Of 240 randomized patients, 237 were included in the primary analysis (mean [SD] age, 56.2 [14.4] years; 104 [43.9%] women; mean [SD] baseline 25-hydroxyvitamin D level, 20.9 [9.2] ng/mL). Median (interquartile range) length of stay was not significantly different between the vitamin D3 (7.0 [4.0-10.0] days) and placebo groups (7.0 [5.0-13.0] days) (log-rank P = .59; unadjusted hazard ratio for hospital discharge, 1.07 [95% CI, 0.82-1.39]; P = .62). The difference between the vitamin D3 group and the placebo group was not significant for in-hospital mortality (7.6% vs 5.1%; difference, 2.5% [95% CI, -4.1% to 9.2%]; P = .43), admission to the intensive care unit (16.0% vs 21.2%; difference, -5.2% [95% CI, -15.1% to 4.7%]; P = .30), or need for mechanical ventilation (7.6% vs 14.4%; difference, -6.8% [95% CI, -15.1% to 1.2%]; P = .09). Mean serum levels of 25-hydroxyvitamin D significantly increased after a single dose of vitamin D3 vs placebo (44.4 ng/mL vs 19.8 ng/mL; difference, 24.1 ng/mL [95% CI, 19.5-28.7]; P < .001). There were no adverse events, but an episode of vomiting was associated with the intervention. Conclusions and Relevance: Among hospitalized patients with COVID-19, a single high dose of vitamin D3, compared with placebo, did not significantly reduce hospital length of stay. The findings do not support the use of a high dose of vitamin D3 for treatment of moderate to severe COVID-19. Trial Registration: ClinicalTrials.gov Identifier: NCT04449718.

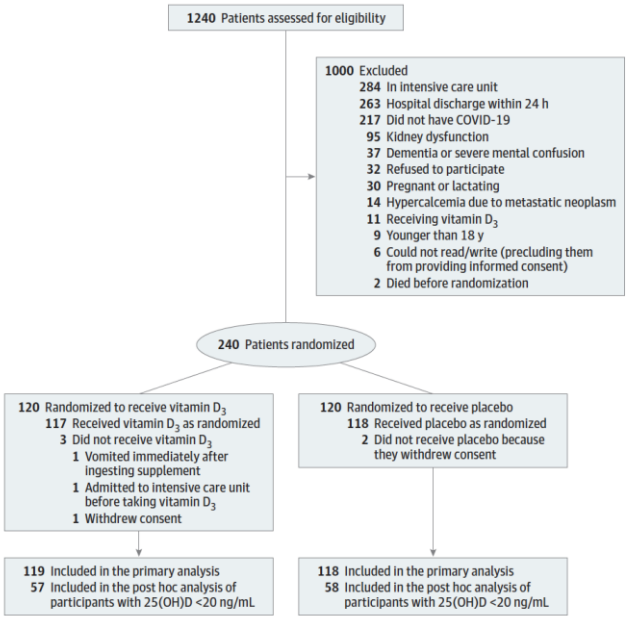
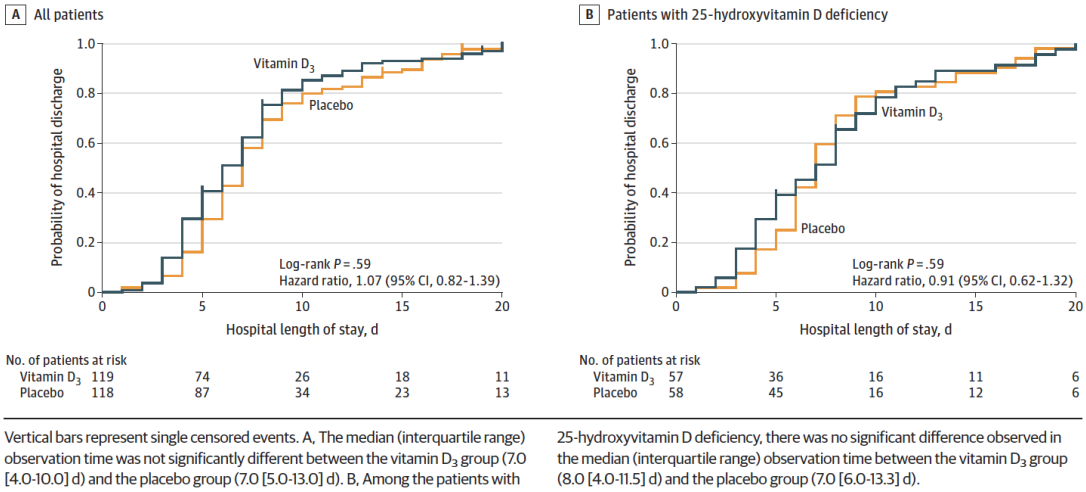


Figure 1. Flow of Patients in a Study of the Effect of a High Dose of Vitamin D3 on Patients With Moderate to Severe Coronavirus Disease 2019 (COVID-19).



Vertical bars represent single censored events. A, The median (interquartile range) observation time was not significantly different between the vitamin D_3 group (7.0 [4.0-10.0] d) and the placebo group (7.0 [5.0-13.0] d). B, Among the patients with 25-hydroxyvitamin D deficiency, there was no significant difference observed in the median (interquartile range) observation time between the vitamin D_3 group (8.0 [4.0-11.5] d) and the placebo group (7.0 [6.0-13.3] d).

Figure 2. Hospital Discharge in Study of the Effect of a High Dose of Vitamin D3 on Patients with Moderate to Severe Coronavirus Disease 2019.

Outcome	Patients (95% CI), %		Between-group difference (95% CI), %	*P* value
	Vitamin D_3 group	Placebo group		
All patients	n = 119	n = 118		
In-hospital mortality	7.6 (3.5 to 13.9)	5.1 (1.9 to 10.7)	2.5 (-4.1 to 9.2)	.43
Admission to intensive care unit	16.0 (9.9 to 22.5)	21.2 (14.2 to 29.7)	-5.2 (-15.1 to 4.7)	.30
Mechanical ventilation requirement	7.6 (3.5 to 13.9)	14.4 (8.6 to 22.1)	-6.8 (-15.1 to 1.2)	.09
Patients with 25-hydroxyvitamin D deficiency (<20 ng/mL)	n = 57	n = 58		
In-hospital mortality	7.0 (1.9 to 17.0)	1.7 (0.04 to 9.2)	5.3 (-3.3 to 15.1)	.21
Admission to intensive care unit	19.3 (10.0 to 31.9)	15.5 (7.4 to 27.4)	3.8 (-10.3 to 17.8)	.59
Mechanical ventilation requirement	7.0 (1.9 to 17.0)	8.6 (2.9 to 19.0)	-1.6 (-12.5 to 9.2)	>.99

Table 2. Secondary Outcomes in a Study of the Effect of a High Dose of Vitamin D3 on Patients With Moderate to Severe Coronavirus Disease 2019

GENERAL SURGERY

RECONSTRUCTION OF COVID-19 VASCULITIS-RELATED THUMB NECROSIS WITH A MICROSURGICAL FREE FLAP

Morales-Perez MJ, Gallardo-Calero I, Rivas-Nicolls D, Gelabert Mestre S, Garcia Forcada I, Soldado F.. Microsurgery. 2021 Feb 13. doi: 10.1002/micr.30719. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Physician and doctorate researchers form various institutions in Spain highlight the vascular complications of COVID-19 by presenting a case of a woman diagnosed with SARS-CoV-2 on March 19, 2020, with subsequent ischemia and necrosis of her right distal thumb (Figure 1a, 1b). Biopsy suggested a COVID-19 related vasculitis with elevated levels of C3 compliment (Figure 1c), and she later underwent successful auto transplant microsurgical flap reconstruction (Figure 1d, 1e, 1f, 1g). This study suggests that microsurgical reconstructions may be possible for patients with acral necrosis resulting from COVID-19 vasculitis.

FIGURES

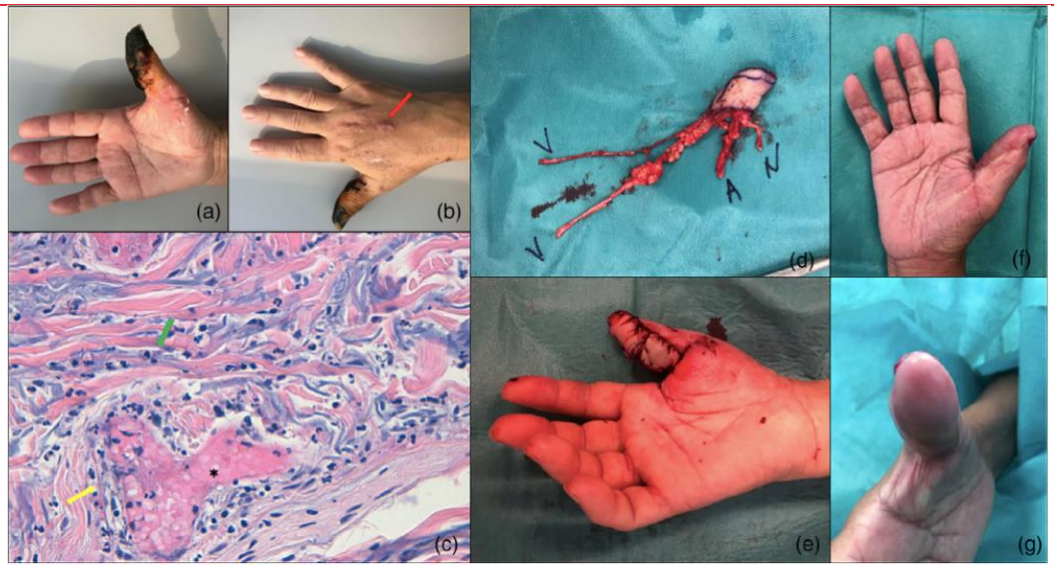


Figure 1. (a,b) Vasculitic lesions appeared during COVID-19 active disease: acral-ischemia at right thumb that progressed to necrosis and residual scar at the dorsum of the hand secondary a liveoid lesion (red arrow). (c) High magnification (×40) histologic section of hand lesion biopsy with Hematoxylin and Eosin staining showed perivascular inflammatory infiltrate at dermal vessels (green arrow), with vessel wall thickening(yellow arrow), lumen sclerosis and fibrin thrombus (*). (d,e) Intraoperatively images of the thumb-tip reconstruction with lateral hemi-pulp toe transfer. (f,g) Hemi-pulp toe transfer to right thumb at 8 weeks postoperatively.

MODIFIED FULL-FACE SNORKEL MASKS AS REUSABLE PERSONAL PROTECTIVE EQUIPMENT FOR HOSPITAL PERSONNEL

Kroo L, Kothari A, Hannebelle M, Herring G, Pollina T, Chang R, Peralta D, Banavar SP, Flaum E, Soto-Montoya H, Li H, Combes K, Pan E, Vu K, Yen K, Dale J, Kolbay P, Ellgas S, Konte R, Hajian R, Zhong G, Jacobs N, Jain A, Kober F, Ayala G, Allinne Q, Cucinelli N, Kasper D, Borroni L, Gerber P, Venook R, Baek P, Arora N, Wagner P, Miki R, Kohn J, Kohn Bitran D, Pearson J, Arias-Arco B, Larrainzar-Garijo R, Herrera CM, Prakash M.. PLoS One. 2021 Jan 13;16(1):e0244422. doi: 10.1371/journal.pone.0244422. eCollection 2021.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An experiment conducted at Stanford University by the Department of Mechanical Engineering evaluated modified full-face snorkel masks (Pneumasks) compared to N95 masks and found that the Pneumasks outperformed N95 masks in sealing capability, filter performance, and CO2 buildup (Figure 1). Speech was muffled by the Pneumasks, which the authors suggest mitigating by utilizing a Bluetooth relay to cell phone speakers, but the Pneumask can serve as a long-lasting and efficacious alternative to N95s in the face of PPE shortages.

ABSTRACT

Here we adapt and evaluate a full-face snorkel mask for use as personal protective equipment (PPE) for health care workers, who lack appropriate alternatives during the COVID-19 crisis in the spring of 2020. The design (referred to as Pneumask) consists of a custom snorkel-specific adapter that couples the snorkel-port of the mask to a rated filter (either a medical-grade ventilator inline filter or an industrial filter). This design has been tested for the sealing capability of the mask, filter performance, CO2 buildup and clinical usability. These tests found the Pneumask capable of forming a seal that exceeds the standards required for half-face respirators or N95 respirators. Filter testing indicates a range of options with varying performance depending on the quality of filter selected, but with typical filter performance exceeding or comparable to the N95 standard. CO2 buildup was found to be roughly equivalent to levels found in half-face elastomeric respirators in literature. Clinical usability tests indicate sufficient visibility and, while speaking is somewhat muffled, this can be addressed via amplification (Bluetooth voice relay to cell phone speakers through an app) in noisy environments. We present guidance on the assembly, usage (donning and doffing) and decontamination protocols. The benefit of the Pneumask as PPE is that it is reusable for longer periods than typical disposable N95 respirators, as the snorkel mask can withstand rigorous decontamination protocols (that are standard to regular elastomeric respirators). With the dire worldwide shortage of PPE for medical personnel, our conclusions on the performance and efficacy of Pneumask as an N95-alternative technology are cautiously optimistic.

FIGURES

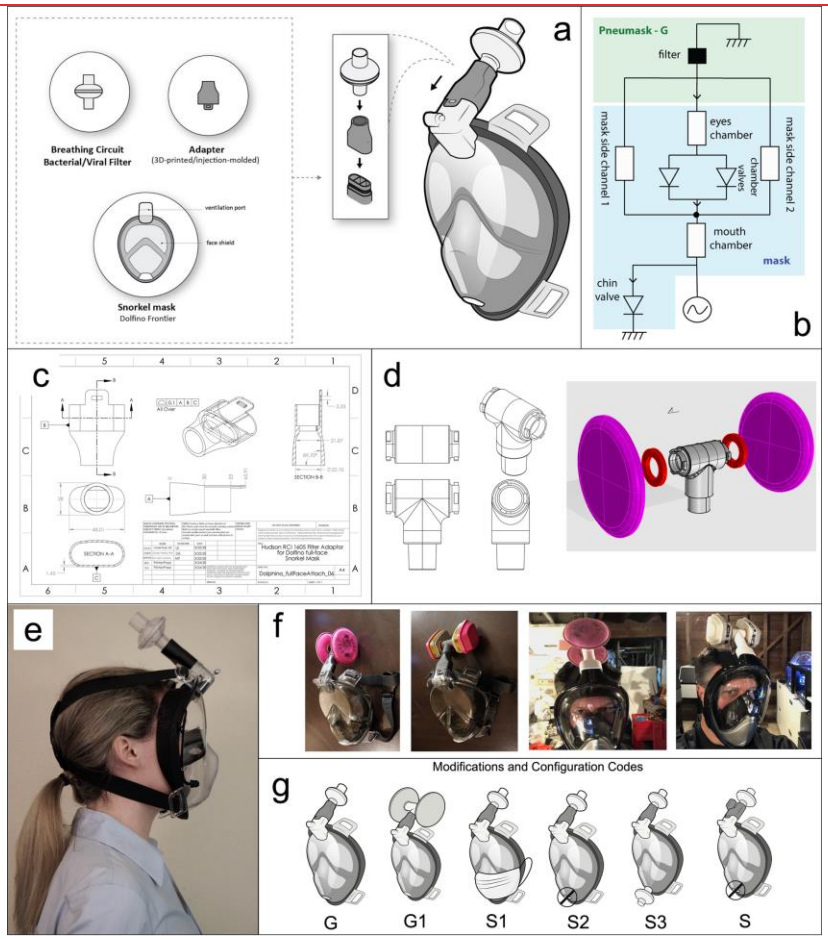


Fig 1. Concept of a modified snorkel-mask or "Pneumask" as PPE. The device consists of a full-face snorkel mask, an adapter, and an FDA or NIOSH-rated filter. b) Air Pathway for the Pneumask. Notation: diodes = valves; ground = atmospheric pressure. c) Original Pneumask adapter from the Prakash Lab was initially designed to be 3D-printed from Carbon RPU-70, a biocompatible resin. Latter versions of the adapter were made and edited by Eric Gagner for injection molding, which allowed for high-tolerance quality parts to be manufactured at high volume. d) A second, option piece designed by Dominic Peralta of Stellar Designs, allows for two quarter-turn NIOSH filters to attach a standard ISO 22mm female port. e) Side view of the Pneumask-G device on an author. f) Industrial filters in the Pneumask-G1 configuration are shown. g) Configurations Pneumask-G and Pneumask-G1 are the main topic of this study. However, we have heard anecdotal reports from the community of people modifying the system to allow for use in "sterile-field" environments, such as by using a surgical mask over the chin valve (S1), taping shut the chin valve (S2), replacement of the chin valve with a second filter (S3), or designing a more complex top adapter part that keeps exhale channels and inhale channels separated; typically also used in conjunction with additional one-way valves. We do not provide recommendations or evaluate the efficacy of Pneumask-S(1–3) designs in this study.

EFFECT OF BAMLANIVIMAB AS MONOTHERAPY OR IN COMBINATION WITH ETESEVIMAB ON VIRAL LOAD IN PATIENTS WITH MILD TO MODERATE COVID-19: A RANDOMIZED CLINICAL TRIAL

Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Kumar P, Adams AC, Van Naarden J, Custer KL, Durante M, Oakley G, Schade AE, Holzer TR, Ebert PJ, Higgs RE, Kallewaard NL, Sabo J, Patel DR, Klekotka P, Shen L, Skovronsky DM.. JAMA. 2021 Feb 16;325(7):632-644. doi: 10.1001/jama.2021.0202.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

Physician investigators from various institutions across the US present the primary results of the BLAZE-1 study. This is an ongoing randomized phase 2/3 double-blinded trial involving 577 outpatients with mild to moderate COVID-19 across 49 US medical centers, comparing placebo vs. treatment with anti-spike neutralizing monoclonal antibody monotherapy (bamlanivimab), vs. combination therapy (bamlanivimab + etesevimab). The results revealed a statically significant (p= .01) difference in the primary outcome of decreased SARS-CoV-2 viral load at day 11 with combination therapy (Figure 2), suggesting a possible efficacious treatment option for patients with mild to moderate COVID-19.

ABSTRACT

Importance: Coronavirus disease 2019 (COVID-19) continues to spread rapidly worldwide. Neutralizing antibodies are a potential treatment for COVID-19. Objective: To determine the effect of bamlanivimab monotherapy and combination therapy with bamlanivimab and etesevimab on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load in mild to moderate COVID-19. Design, Setting, and Participants: The BLAZE-1 study is a randomized phase 2/3 trial at 49 US centers including ambulatory patients (N = 613) who tested positive for SARS-CoV-2 infection and had 1 or more mild to moderate symptoms. Patients who received bamlanivimab monotherapy or placebo were enrolled first (June 17-August 21, 2020) followed by patients who received bamlanivimab and etesevimab or placebo (August 22-September 3). These are the final analyses and represent findings through October 6, 2020. Interventions: Patients were randomized to receive a single infusion of bamlanivimab (700 mg [n = 101], 2800 mg [n = 107], or 7000 mg [n = 101]), the combination treatment (2800 mg of bamlanivimab and 2800 mg of etesevimab [n = 112]), or placebo (n = 156). Main Outcomes and Measures: The primary end point was change in SARS-CoV-2 log viral load at day 11 (+-4 days). Nine prespecified secondary outcome measures were evaluated with comparisons between each treatment group and placebo, and included 3 other measures of viral load, 5 on symptoms, and 1 measure of clinical outcome (the proportion of patients with a COVID-19-related hospitalization, an emergency department [ED] visit, or death at day 29). Results: Among the 577 patients who were randomized and received an infusion (mean age, 44.7 [SD, 15.7] years; 315 [54.6%] women), 533 (92.4%) completed the efficacy evaluation period (day 29). The change in log viral load from baseline at day 11 was -3.72 for 700 mg, -4.08 for 2800 mg, -3.49 for 7000 mg, -4.37 for combination treatment, and -3.80 for placebo. Compared with placebo, the differences in the change in log viral load at day 11 were 0.09 (95% CI, -0.35 to 0.52; P = .69) for 700 mg, -0.27 (95% CI, -0.71 to 0.16; P = .21) for 2800 mg, 0.31 (95% CI, -0.13 to 0.76; P = .16) for 7000 mg, and -0.57 (95% CI, -1.00 to -0.14; P = .01) for combination treatment. Among the secondary outcome measures, differences between each treatment group vs the placebo group were statistically significant for 10 of 84 end points. The proportion of patients with COVID-19-related hospitalizations or ED visits was 5.8% (9 events) for placebo, 1.0% (1 event) for 700 mg, 1.9% (2 events) for 2800 mg, 2.0% (2 events) for 7000 mg, and 0.9% (1 event) for combination treatment. Immediate hypersensitivity reactions were reported in 9 patients (6 bamlanivimab, 2 combination treatment, and 1 placebo). No deaths occurred during the study treatment. Conclusions and Relevance: Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11; no significant difference in viral load reduction was observed for bamlanivimab monotherapy. Further ongoing clinical trials will focus on assessing the clinical benefit of antispike neutralizing antibodies in patients with COVID-19 as a primary end point. Trial Registration: ClinicalTrials.gov Identifier: NCT04427501.

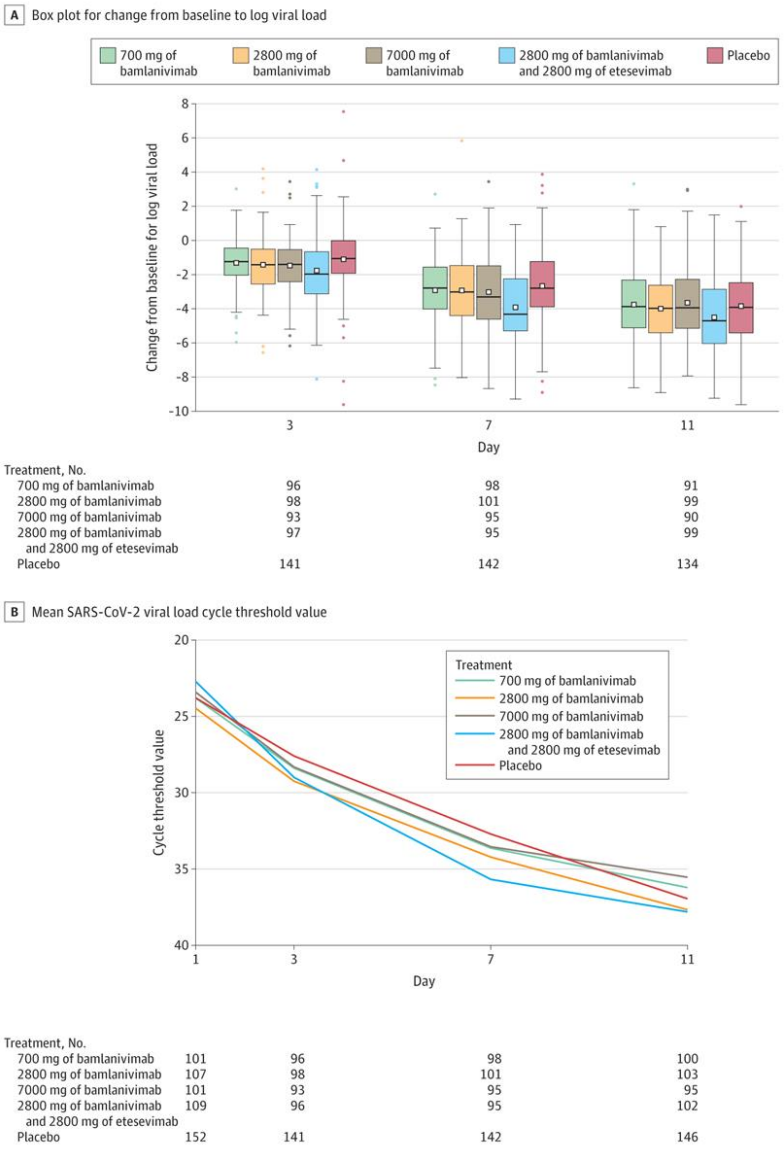


Figure 2. Change in Log Viral Load and in Viral Load Cycle Threshold Over Time With Bamlanivimab Monotherapy and Bamlanivimab and Etesevimab Combination Therapy.

NEUTRALIZING MONOCLONAL ANTIBODY FOR MILD TO MODERATE COVID-19

Malani PN, Golub RM.. JAMA. 2021 Feb 16;325(7):644-645. doi: 10.1001/jama.2021.0585.
Level of Evidence: 5 - Review / Literature Review

BLUF

A report of the ongoing BLAZE-1 (Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies) trial conducted at the University of Michigan during early 2021 by the Division of Infectious Diseases found that, in investigating the efficacy of novel monoclonal antibodies for treating COVID-19 infections, bamlanivimab did not exert statistically significant differences from the placebo treatment 11 days post-administration, but was significant when combined with etesevimab. Further research is necessary to investigate more complex clinical outcomes.

SUMMARY

- Importantly, findings from the interim analysis of the trial differ from the current study's final analyses with regards to effect sizes, doses, and differences in primary outcomes, due to incomplete follow-up for the placebo group at the time of it's report.

- The findings suggest that significant differences in outcomes may only occur if intervention with novel monoclonal antibodies occurs early in the course of the illness.

CARRAGEENAN CONTAINING OVER-THE-COUNTER NASAL AND ORAL SPRAYS INHIBIT SARS-COV-2 INFECTION OF AIRWAY EPITHELIAL CULTURES

Schütz D, Conzelmann C, Fois G, Groß R, Weil T, Wettstein L, Stenger S, Zelikin A, Hoffmann TK, Frick M, Müller JA, Münch J.. Am J Physiol Lung Cell Mol Physiol. 2021 Feb 9. doi: 10.1152/ajplung.00552.2020. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An experiment conducted at Ulm University Medical Center during early 2021 by the Institute of Molecular Virology analyzed nasal and oral sprays being developed to treat COVID-19 infection and found that certain carrageenans (polyanionic ι- and κ-carrageenans) in the sprays possessed virucidal activity. This suggests these carrageenan containing spray interventions could reduce acquisition and spread of COVID-19, though clinical verification is warranted.

SUMMARY

- In total, the researchers analyzed one oral, and five nasal sprays for virucidal and antiviral activity, for COVID-19 (Table 1)

- carrageenans are sulfated polysaccharides which are isolated from red seaweeds, and, prior to this study, were known for exerting antiviral effects.

- the efficacy of the two carrageenan containing products, A and B, was based on reduced intensity in signal intensities measuring the amount of spike protein of COVID-19 (Figure 2)

ABSTRACT

Pharmaceutical interventions are urgently needed to prevent SARS-CoV-2 infection and transmission. As SARS-CoV-2 infects and spreads via the nasopharyngeal airways, we analyzed the antiviral effect of selected nasal and oral sprays on virus infection in vitro. Two nose sprays showed virucidal activity but were cytotoxic precluding further analysis in cell culture. One nasal and one mouth spray suppressed SARS-CoV-2 infection of TMPRSS2-Vero E6 cells and primary differentiated human airway epithelial cultures. The antiviral activity in both sprays could be attributed to polyanionic iota- and kappa-carrageenans. Thus, application of carrageenan containing nasal and mouth sprays may reduce the risk of acquiring SARS-CoV-2 infection and may limit viral spread, warranting further clinical evaluation.

Table 1: Overview and composition of tested products A-F.

Product	Trade name	Active agent	Additives
A	Viruseptin (nasal)	ι- and κ-carrageenan (1.2 and 0.4 mg/ml)	sodium chloride
B	Viruseptin (oral)	ι-carrageenan (1.2 mg/ml)	sodium chloride, xylitol, cherry flavor
C	Nasic (nasal)	xylometazoline hydrochloride (0.1%), dexpanthenol (5%)	benzalkonium chloride, monopotassium phosphate, disodium phosphate dodecahydrate
D	Rhinospray (nasal)	tramazoline hydrochloride (1.264 mg/ml)	sodium chloride, citric acid, benzalkonium chloride, menthol, cineol, camphor racemic, sodium hydroxide, magnesium sulfate, magnesium chloride, calcium chloride, sodium hydrogen carbonate, povidone-iodine glycerol 85%, hyromellose
E	Wick Erste Abwehr (nasal)	hydroxypropyl methylcellulose	succinic acid, disodium succinate, pyroglutamic acid
F	Wick Sinex Avera (nasal)	oxymetazoline hydrochloride (0.5 mg/ml)	sorbitol, trisodium citrate, polysorbat 80, benzyl alcohol, citric acid, benzalkonium chloride, acesulfame potassium, menthol, cineol, sodium edetate, aloe dry extract, L-carvone

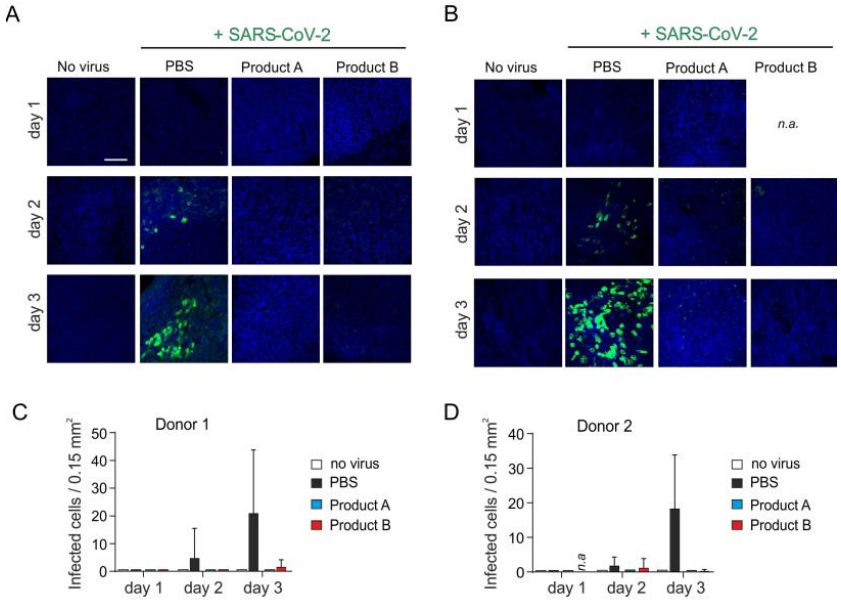


Figure 2: Product A and B inhibit SARS-CoV-2 infection of primary human airway epithelial cultures (HAEC). A, B.

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