The Daily COVID-19 Literature Surveillance Summary

September 04, 2020

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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

Climate

- An online survey of gay, bisexual and other men who have sex with men assessed changes in sexual behavior, prophylaxis use, and disease testing during the COVID-19 lockdown. Findings included a mean increase of 2.3 sexual partners during lockdown, HIV and other STI screenings were decreased in about a third of respondents, and lockdown prevented 8.9% of respondents from accessing HIV PrEP. This study suggests the need to help ensure that populations needing these services will have access to them, especially during the pandemic.

Epidemiology

- Post-discharge surveillance of 285 adult patients with COVID-19 in China showed that RT-PCR retested positive (RP) events occurred in 10% of cases within 15 days of discharge and were unlikely due to reinfection. The RP incidence, as well as clinical features and risk factors for RP patients found in this study, can inform COVID-19 post-discharge management in other developing countries.

Management

- Intensivists in Italy describe two COVID-19 patients admitted to the ICU who developed acute liver failure secondary to herpes simplex virus 1 (HSV-1). During their clinical course, both patients received hydroxychloroquine and tocilizumab, required ventilation assistance, developed signs of confusion or delirium, and succumbed to death. Based on these two cases, the authors suggest that "unbalanced use" of immunosuppressive agents in COVID-19 could contribute to secondary infections and argue for research into COVID-19 and its typical therapies in HSV-1 infection or reactivation.

Adjusting Practice During COVID-19

- A survey of 277 neonatal intensive care units (NICUs) globally found that the number of NICUs allowing 24-hour parental presence declined from 83% pre-COVID-19 to 53% during COVID-19 and 43% of NICUs reported a decrease in services for therapy, lactation, and/or social work. The authors warn against limiting parental presence, which can adversely impact the well-being and health of infants and their families.

R&D: Diagnosis & Treatments

- Medical researchers in Thailand conducted a study to explore the viability of saliva pooling as a cost-effective, less invasive alternative SARS-CoV-2 specimen for RT-PCR. The authors analyzed 40 pools of 5 samples and 20 pools of 10 samples. Their findings suggest that saliva pools are able to detect SARS-CoV-2 and, thus, may be an effective testing option in low prevalence areas. The authors note, however, that saliva pooling may be limited by viral RNA breakdown during storage protocol and freeze-thawing, leading to possible false negative results.

- Researchers affiliated with Novavax report findings from phase 1 of their randomized, placebo-controlled, phase 1-2 trial of the NVX-CoV2372 vaccine, a recombinant nanoparticle vaccine consisting of SARS-CoV-2 spike glycoprotein and Matrix-M1 adjuvant. They found the following:
  - Reactogenicity was mild or absent in most participants; no serious adverse events were reported.
  - The vaccine yielded greater IgG anti-spike protein response compared to controls.
  - Participants who received the Matrix-M1 adjuvant showed significant Th1-driven immune response compared to the non-adjuvant vaccine group.

- Investigators affiliated with Mayo Clinic working in collaboration with the United States Food and Drug Administration provide a safety update of the US Convalescent Plasma Expanded Access Program after transfusing 20,000 hospitalized patients with severe or life-threatening COVID-19 with convalescent plasma. Based on the results of these 20,000 patients, the authors suggest that the use of convalescent plasma is safe and carries no excess risk of complications. The authors also share that a future report will describe the efficacy of COVID-19 convalescent plasma therapy.

TABLE OF CONTENTS

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SEX IN THE TIME OF COVID-19: RESULTS OF AN ONLINE SURVEY OF GAY, BISEXUAL AND OTHER MEN WHO HAVE SEX WITH MEN'S EXPERIENCE OF SEX AND HIV PREVENTION DURING THE US COVID-19 EPIDEMIC

Stephenson R, Chavanduka TMD, Rosso MT, Sullivan SP, Pitter RA, Hunter AS, Rogers E.. AIDS Behav. 2020 Sep 2. doi: 10.1007/s10461-020-03024-8. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Experts in epidemiology and sexual health disparities from University of Michigan performed a cross-sectional online survey of gay, bisexual and other men who have sex with men (GBMSM) (n=696) between April and May of 2020 to assess changes in sexual behavior, prophylaxis use, and disease testing during the COVID-19 lockdown. Some key findings that the researchers found include:

- A mean increase of 2.3 sexual partners was reported by participants during COVID-19 lockdown (Table 3).
- HIV and other STI screenings were prevented by COVID-19 lockdown measures in approximately one-third of the group (32.2% and 29.3% respectively) (Table 3).
- COVID-19 lockdown prevented 8.9% of respondents from accessing HIV PrEP (Table 3).
- Participants reported an increase in number of anal sex partners, with a mean increase of 2.1 during COVID-19 lockdown (Table 4).

This study shows high levels of sexual activity in the GBMSM group during the COVID-19 lockdown and the lack of basic health service or access, such as routine STI testing and HIV PrEP, suggesting for the implementation of strategies to ensure that populations needing these services will have access to them, even during a pandemic.

ABSTRACT

This paper presents data from a recent cross-sectional survey of gay, bisexual and other men who have sex with men (GBMSM) in the US, to understand changes in sexual behavior and access to HIV prevention options (i.e. condoms and pre-exposure prophylaxis (PrEP)) during the COVID-19 lockdown period. The Love and Sex in the Time of COVID-19 survey was conducted online from April to May, 2020. GBMSM were recruited through advertisements featured on social networking platforms, recruiting a sample size of 518 GBMSM. Analysis considers changes three in self-reported measures of sexual behavior: number of sex partners, number of anal sex partners and number of anal sex partners not protected by pre-exposure prophylaxis (PrEP) or condoms. Approximately two-thirds of the sample reported that they believed it was possible to contract COVID-19 through sex, with anal sex reported as the least risky sex act. Men did not generally feel it was important to reduce their number of sex partners during COVID-19, but reported a moderate willingness to have sex during COVID-19. For the period between February and April-May 20,202, participants reported a mean increase of 2.3 sex partners during COVID-19, a mean increase of 2.1 anal sex partners (range - 40 to 70), but a very small increase in the number of unprotected anal sex partners. Increases in sexual behavior during COVID-19 were associated with increases in substance use during the same period. High levels of sexual activity continue to be reported during the COVID-19 lockdown period and these high levels of sexual activity are often paralleled by increases in substance use and binge drinking. There is a clear need to continue to provide comprehensive HIV prevention and care services during COVID-19, and telehealth and other eHealth platforms provide a safe, flexible mechanism for providing services.

Table 3 Engagement in HIV prevention, COVID-19 testing and perceptions of COVID-19 prevalence among an online sample of gay, bisexual and other men who have sex with men (n = 518)

From: Sex in the Time of COVID-19: Results of an Online Survey of Gay, Bisexual and Other Men Who Have Sex with Men's Experience of Sex and HIV Prevention During the US COVID-19 Epidemic

	% (N) or mean (range)
Received test for COVID-19 in past 3 months	7.9 (41)
Received a HIV test	
Past 6 months	37.8 (176)
6–12 months	34.0 (158)
1–3 years	14.0 (65)
> 3 years	8.2 (38)
Never	6.0 (28)
COVID-19 prevented you from testing for HIV	32.2 (166)
Likelihood of receiving a HIV test during COVID-19	3.5 (1–5)
COVID-19 prevented you from testing for STIs	29.3 (150)
Likelihood of receiving a STI test during COVID-19	3.5 (1–5)
Has taken PrEP in the past 3 months	27.3 (123)
Currently taking PrEP	18.0 (93)
COVID-19 has prevented access to PrEP prescription	8.9 (11)
Perceived prevalence of COVID-19 among US population	13.9 (0–100)
Perceived prevalence of COVID-19 among state population	12.9 (0–94)
Perceived prevalence of COVID-19 among county population	11.6 (0–100)
Perceived prevalence of COVID-19 among friends	4.7 (0–100)
Perceived prevalence of COVID-19 among sex partners	3.3 (0–100)

Table 4 Regression models for self-reported changes in number of sexual partner, number of anal sex partner and number of unprotected anal sex partners in an online sample of gay, bisexual and other men who have sex with men (GBMSM) (n = 518)

From: Sex in the Time of COVID-19: Results of an Online Survey of Gay, Bisexual and Other Men Who Have Sex with Men's Experience of Sex and HIV Prevention During the US COVID-19 Epidemic

Characteristic	Change in number of sex partners	Change in number of anal sex partners	Change in number of unprotected anal sex partners
	Beta (SE)	Beta (SE)	Beta (SE)
Age (18–24)			
25–34	− 0.615 (0.697)	*2.201 (0.134)*	0.120 (0.163)
35–44	0.899 (0.791)	*4.981 (1.459)*	0.106 (0.185)
> 45	1.443 (0.989)	2.544 (1.852)	− 0.705 (0.232)
Education (high school)			
Some college	*1.633 (0.601)*	0.021 (1.109)	0.044 (0.141)
College graduate or graduate school	*1.141 (0.364)*	− *2.492 (1.123)*	− 0.011 (0.156)
Employed (No)			
No	− *1.159 (0.205)*	0.948 (1.115)	− 0.051 (0.141)
Race (Black/African American)			
White	− 1.463 (1.317)	1.268 (2.301)	0.255 (0.292)
Other	− 1.762 (1.247)	0.097 (2.430)	0.363 (0.309)
Sexual identity (Gay/homosexual)			
Bisexual	0.183 (0.734)	0.524 (1.355)	0.060 (0.172)
Other	*2.298 (1.052)*	*3.780 (1.432)*	*0.991 (0.247)*
HIV sero-status (HIV-negative)			
HIV-positive	− *0.888 (0.104)*	1.635 (1.688)	− 0.143 (0.214)
Relationship status (Single)			
Has partner (i.e. boyfriend)	− 0.167 (0.712)	1.365 (0.935)	0.805 (0.119)
Married to male partner	− 1.182 (0.606)	0.848 (1.313)	− 0.051 (0.167)
Change in substance use during lockdown (stayed the same)			
Increased	*0.722 (0.210)*	*1.243 (0.034)*	*0.124 (0.034)*
Decreased	− 0.034 (0.056)	− 0.147 (0.217)	− 0.078 (0.189)
Change in binge drinking during lockdown (stayed the same)			
Increased	− 0.305 (0.545)	− 0.630 (1.007)	0.014 (0.128)
	− 0.214 (0.412)	− 0.146 (0.317)	− 0.154 (0.214)
Have skipped meals due to COVID-19 (No)			
Yes	− *2.297 (0.799)*	− 0.845 (1.474)	0.072 (0.187)
Have experienced homelessness during COVID-19 (No)			
Yes	− *1.456 (0.210)*	− *1.765 (0.076)*	− *0.217 (0.043)*
Perceived prevalence of COVID-19 among US population	− 0.033 (0.038)	− *0.115 (0.045)*	− *0.154 (0.034)*
Perceived prevalence of COVID-19 among state population	− 0.035 (0.037)	0.028 (0.065)	− *0.321 (0.063)*
Perceived prevalence of COVID-19 among county population	0.049 (0.026)	0.034 (0.045)	0.089 (0.056)
Perceived prevalence of COVID-19 among friends	0.009 (0.032)	0.036 (0.050)	0.082 (0.098)
Perceived prevalence of COVID-19 among sex partners	− 0.046 (0.028)	− 0.038 (0.048)	− *0.239 (0.091)*

Italic values represent significance at the 5% level

EPIDEMIOLOGY

INCIDENCE, CLINICAL COURSE AND RISK FACTOR FOR RECURRENT PCR POSITIVITY IN DISCHARGED COVID-19 PATIENTS IN GUANGZHOU, CHINA: A PROSPECTIVE COHORT STUDY

Zheng J, Zhou R, Chen F, Tang G, Wu K, Li F, Liu H, Lu J, Zhou J, Yang Z, Yuan Y, Lei C, Wu X.. PLoS Negl Trop Dis. 2020 Aug 31;14(8):e0008648. doi: 10.1371/journal.pntd.0008648. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Investigators affiliated with the School of Public Health at Southern Medical University and Guangzhou Center for Disease Control and Prevention conducted a prospective cohort study of 285 adult patients with COVID-19 who were admitted to Guangzhou Eighth People's Hospital between January 20 and February 18, 2020. Post-discharge surveillance (within 15 days after discharge) showed that RT-PCR retested positive (RP) events occurred in 10% of cases and were unlikely due to reinfection. The RP incidence, as well as clinical features and risk factors for RP patients (summarized below) found in this study, can inform COVID-19 post-discharge management in other developing countries.

SUMMARY

•The clinical course and the duration of viral shedding for COVID-19 RP patients and non-RP (NRP) patients are shown in Figure 2. The results suggest that a prolonged duration of viral shedding during the first hospitalization was a risk factor for the RP result (Table 4).

•RP patients, compared with the first hospitalization, had shorter length of stay (7.0 days [5.0–11.0] vs. 18.0 [13.0–24.0], p less than 0.001), more asymptomatic persons (17 [62.9%] vs. 5 [18.5%], p = 0.013), and higher cyclic threshold (Ct) value of N gene (37.5 [36.0–38.5] vs. 35.0 [33.0–37.0], p = 0.042).

•Elder RP patients (60 years of age and older), compared to younger RP patients, were more likely to be symptomatic (7/8, 87.5% vs. 3/19, 18.8%, p = 0.001) at readmission (Figure 3).

ABSTRACT

The phenomenon of COVID-19 patients tested positive for SARS-CoV-2 after discharge (redetectable as positive, RP) emerged globally. The data of incidence rate and risk factors for RP event and the clinical features of RP patients may provide recommendations for virus containment and cases management for COVID-19. We prospectively collected and analyzed the epidemiological, clinical and virological data from 285 adult patients with COVID-19 and acquired their definite clinical outcome (getting PCR positive or not during post-discharge surveillance). By March 10, 27 (9.5%) discharged patients had tested positive for SARS-CoV-2 in their nasopharyngeal swab after a median duration of 7 0 days (IQR 5 0-8 0). Compared to first admission, RP patients generally had milder clinical symptoms, lower viral load, shorter length of stay and improved pulmonary conditions at readmission (p<0.05). Elder RP patients (>= 60 years old) were more likely to be symptomatic compared to younger patients (7/8, 87.5% vs. 3/19, 18.8%, p = 0.001) at readmission. Age, sex, epidemiological history, clinical symptoms and underlying diseases were similar between RP and non-RP patients (p>0.05). A prolonged duration of viral shedding (>10 days) during the first hospitalization [adjusted odds ratio [aOR]: 5.82, 95% confidence interval [CI]: 2.50-13.57 for N gene; aOR: 9.64, 95% CI: 3.91-23.73 for ORF gene] and higher Ct value (ORF) in the third week of the first hospitalization (aOR: 0.69; 95% CI: 0.50-0.95) were associated with RP events. In conclusion, RP events occurred in nearly 10% of COVID-19 patients shortly after the negative tests, were not associated with worsening symptoms and unlikely reflect reinfection. Patients' lack of efficiency in virus clearance was a risk factor for RP result. It is noteworthy that elder RP patients (>= 60 years old) were more susceptible to clinical symptoms at readmission.

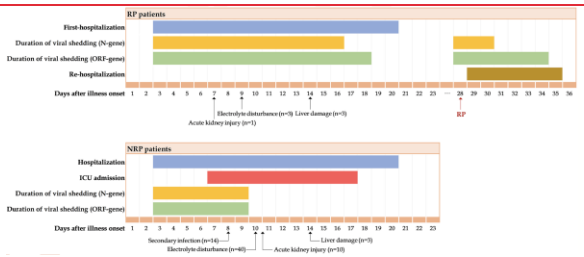


Figure 2. Clinical course, complications and duration of viral shedding from illness onset in patients hospitalized with COVID-19. Figure shows median duration of hospitalization and positive nucleic acid Ct value and onset of several complications. RP = redetectable as positive. NRP = non-redetectable as positive.

	Univariate OR	p value	Adjusted OR*	p value
Basic information				
Age, years	0.99 (0.97–1.02)	0.458	..	..
Male (vs. female)	0.98 (0.44–2.17)	0.959	..	..
Clinical severity				
Mild	1 (reference)		1 (reference)	
Moderate	0.65 (0.18–2.37)	0.522	0.72 (0.19–2.69)	0.632
Comorbidity				
Any comorbidity	0.91 (0.38–2.17)	0.832	0.89 (0.12–5.02)	0.711
Diabetes	0.39 (0.05–3.03)	0.370	..	..
Hypertension	1.35 (0.52–3.54)	0.539	..	..
Liver diseases	0.90 (0.20–4.08)	0.894	..	..
Laboratory findings				
Median Ct value (N gene)	0.96 (0.87–1.07)	0.496	0.96 (0.86–1.07)	0.487
Week1	0.96 (0.87–1.05)	0.367	0.96 (0.87–1.06)	0.385
Week2	0.95 (0.84–1.07)	0.380	0.94 (0.82–1.08)	0.368
Week3	0.85 (0.71–1.03)	0.103	0.88 (0.70–1.10)	0.256
Median Ct value (ORF gene)	0.91 (0.82–1.01)	0.071	0.89 (0.80–0.99)	0.042
Week1	0.93 (0.84–1.04)	0.193	0.93 (0.83–1.03)	0.167
Week2	0.90 (0.79–1.04)	0.144	0.87 (0.75–1.02)	0.078
Week3	0.76 (0.60–0.97)	0.030	0.69 (0.50–0.95)	0.022
Eosinophil,×10^9 /L	0.84 (0.63–1.11)	0.213	1.59 (0.24–10.75)	0.633
Week1	9.42 (0.07–54.09)	0.374	9.30 (0.06–49.06)	0.390
Lactate dehydrogenase, U/L	0.99 (0.99–1.00)	0.133	0.99 (0.99–1.00)	0.165
Week1	0.99 (0.99–1.00)	0.065	0.99 (0.99–1.00)	0.072
Week3	0.99 (0.98–1.00)	0.122	0.99 (0.98–1.00)	0.193
C-reactive protein, mg/L	0.98 (0.93–1.02)	0.303	0.98 (0.93–1.03)	0.392
Week1	0.97 (0.94–1.01)	0.102	0.97 (0.94–1.01)	0.108
Clinical course				
Duration of viral shedding from admission, days				
N gene				
≤10	1 (reference)		1 (reference)	
>10	5.49 (2.39–12.62)	<0.001	5.82 (2.50–13.57)	<0.001
ORF gene				
≤10	1 (reference)		1 (reference)	
>10	8.77 (3.64–21.09)	<0.001	9.64 (3.91–23.73)	<0.001

OR = odds ratio.
*Adjusted for age, sex, hypertension, diabetes and liver disease. OR value in continuous variables is the risk related to per 1 unit increase.

Table 4. Univariable and multivariable analysis of risk factors associated with RP events

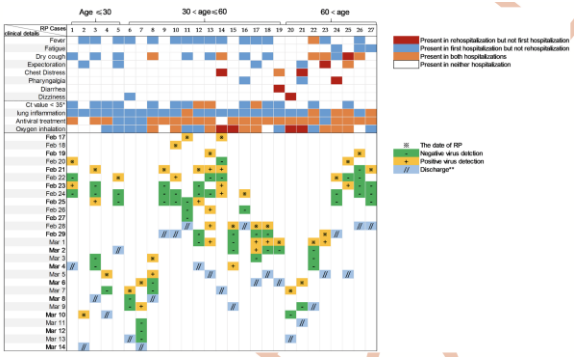


Figure 3. Comparison of the two hospitalization courses of 27 RP patients and result of series SARS-CoV-2 RNA test in nasopharyngeal swab specimens during the second hospitalization.

Comparisons of clinical condition between first and second hospitalization are shown for each RP patient (upper panels). Timeline of series SARS-CoV-2 RNA test (lower panels) during rehospitalization are shown. *Ct value <35 refers to whether the lowest Ct value during hospitalization is lower than 35. **Discharge indicates two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24 h apart. This figure showed that elder RP patients (greater than or equal to 60 years old) were more likely to be symptomatic compared to younger RP patients (7/8, 87.5% vs. 3/19, 18.8%, p = 0.001) at readmission. RP = redetectable as positive. NRP = non-redetectable as positive.

THE IMPLICATIONS OF COVID-19 INFECTION ON THE ENDOTHELIUM: A METABOLIC VASCULAR PERSPECTIVE

Dalan R, Boehm BO.. Diabetes Metab Res Rev. 2020 Sep 1:e3402. doi: 10.1002/dmrr.3402. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review study by endocrinologists at Tan Tock Seng Hospital in Singapore outlines the pathophysiology of SARS-CoV-2, particularly investigating how diabetic patients are at higher risk of severe COVID-19 infection due to increased expression of CD147 and angiotensin II receptors, which facilitates viral entry into endothelial cells leading to increased endothelial cytokine and marker production (Figure 1). This study highlights the importance of understanding the pathway of this endothelial dysfunction and demonstrates the need to monitor patients with metabolic disorders for developing micro-and-macrovascular complications, particularly in endocrine organs, following COVID-19 infection.

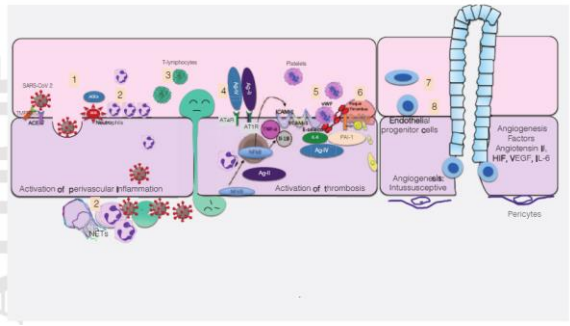
ABSTRACT

FIGURES

Figure 1. Schema elaborating the endothelial dysfunction pathways in diabetes, COVID-19 Infections and potential areas of exacerbation in diabetes

	Diabetes	COVID-19	Diabetes & COVID-19
1.	Advanced glycation end products (AGEs) increases oxidative stress and reactive oxygen species leading to endothelial cell activation.	SARS-CoV-2 enters the endothelium through the ACE-2, TMPRSS2, CD-147 receptors and activates the endothelium.	The SARS-CoV-2 enters a chronically activated endothelium and since it uses the ACE-2 enzyme receptor it further upsets the balance between ACE-2 and ACE-AngII-AT1R pathways.
2.	Even in the chronic state the innate immune response is affected in terms of neutrophils and monocytes activation, increased cytokines and interleukins , formation of neutrophil extracellular traps, leading to a low grade inflammatory state.	innate immune response in terms of inflammation and neutrophilic activation with formation of neutrophil extracellular traps. This has the propensity to activate inflammatory, thrombotic and angiogenesis pathways.	There is a risk of a hyperinflammatory response as there is already ongoing low grade inflammatory response. This exaggerated response –"Cytokine Storm" has been attributed to lead to more severe disease.
3.	In diabetes, the adaptive immune response is lowered.	Adaptive immune response is stimulated in terms of T lymphocytes which is required for resolution of infection.	The adaptive immune response may be lower compared to non-diabetes patients thus affecting prognosis.
4.	The ACE-2-Ang1-7 pathway is downregulated with upregulation in Angiotensin II-AT1R pathways.	The loss of counter regulatory response from ACE-2-Ang1-7 with increased Angiotensin II and IV can stimulate AT1R and AT4R receptors.	The use of the ACE-2 receptor further downregulates ACE-2-Ang1-7 pathway with upregulation of ACE-AngII-AT1R pathways which has the potential to activate thrombosis.

5.	The platelets are activated in patients with diabetes	SARS-CoV-2 can cause genetic alteration of platelets leading to activation & thrombosis.	The platelets are already activated in patients with diabetes and the process is exacerbated
6.	The activated platelets, in the setting of activated endothelium with expression of ICAM-1, VCAM-1, E-selectin von-Willebrand factor, plasminogen activator inhibitor-1 (PAI-1) and other thrombotic markers leads to downstream activation of thrombotic pathways and is responsible for plaques in atherosclerosis.	Thrombosis and plaque formations can occur especially when a typical Virchow's triad of stasis (immobility like in any illness), endothelial injury (endothelialitis) and hypercoagibility with activated platelets, increased angiotensin-II, PAI-1, von-Willebrand factor amongst other factors.	In the setting or a low grade activation of the thrombotic pathways, these pathways will be exacerbated and has the potential for affecting pre-existing plaques in terms of rupture or sudden increase in size.
7.	In patients with diabetes, potential angiogenic factors including angiotensin-II, hypoxia inducing factor (HIF-1α), vascular endothelial growth factor (VEGF), interleukins 6 and 8 are classically activated and is responsible for angiogenesis at sites like the eyes.	In some vessels like the pulmonary vessels, a propensity towards angiogenesis is present with potential angiogenic factors including angiotensin-II, hypoxia inducing factor (HIF-1α), vascular endothelial growth factor (VEGF), interleukins 6 and 8 classically activated and exacerbated in adaptive immune response.	Although the exact effect on angiogenesis in pulmonary vessels is unclear there is potential for exacerbation.
8.	The angiogenesis phenomenon is very similar to the one seen in patients with choroidal neovascularisation in acute macular degeneration in the initial stages before sprouting angiogenesis occurs.	Intussusception type of angiogenesis with a cylindrical microstructure that spans the lumen of the small vessels is seen.	Increased angiogenesis is associated with a worse prognosis and in patients with diabetes the potential for exacerbation is there.



TWO FATAL CASES OF ACUTE LIVER FAILURE DUE TO HSV-1 INFECTION IN COVID-19 PATIENTS FOLLOWING IMMUNOMODULATORY THERAPIES

Busani S, Bedini A, Biagioni E, Serio L, Tonelli R, Meschiari M, Franceschini E, Guaraldi G, Cossarizza A, Clini E, Maiorana A, Gennari W, De Maria N, Luppi M, Mussini C, Girardis M; Modena Covid-19 Working Group (MoCo19).. Clin Infect Dis. 2020 Aug 25:ciaa1246. doi: 10.1093/cid/ciaa1246. Online ahead of print.
Level of Evidence: 4 - Case Report

BLUF

Researchers affiliated with the University of Modena and Reggio Emilia in Italy describe two COVID-19 cases admitted to the intensive care unit between February 25 and April 25, 2020 who developed acute liver failure secondary to herpes simplex virus 1 (HSV-1). During their clinical course, both patients received hydroxychloroquine and tocilizumab, required ventilation assistance, developed signs of mental confusion (patient 1) or delirium (patient 2), were diagnosed with HSV-1 by real-time PCR assay, and succumbed to death (Figure 1). Based on these two cases, the authors suggest that "unbalanced use" of immunosuppressive agents in COVID-19 could contribute to secondary infections and argue for research into COVID-19 and its typical therapies in HSV-1 infection or reactivation.

ABSTRACT

We reported two fatal cases of acute liver failure secondary to Herpes Simplex Virus 1 infection in COVID-19 patients, following tocilizumab and corticosteroid therapy.Screening for and prompt recognition of Herpes Simplex Virus 1 reactivation in these patients, undergoing immunomodulatory treatment, may have potentiallyrelevant clinical consequences.

FIGURES

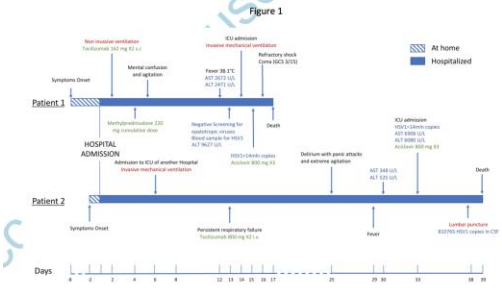


Figure 1. The clinical course of the two COVID-19 patients who developed acute liver failure following Herpes Simplex Virus 1 infection.

NEONATAL/PEDIATRIC INTENSIVE CARE

IMPACT OF RESTRICTIONS ON PARENTAL PRESENCE IN NEONATAL INTENSIVE CARE UNITS RELATED TO CORONAVIRUS DISEASE 2019

Darcy Mahoney A, White RD, Velasquez A, Barrett TS, Clark RH, Ahmad KA.. J Perinatol. 2020 Sep;40(Suppl 1):36-46. doi: 10.1038/s41372-020-0753-7.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers within the field of pediatrics conducted a cross-sectional survey between April 21 and April 30, 2020 of 277 medical facilities regarding neonatal intensive care units' (NICUs) restrictions and policies during the COVID-19 pandemic (Table 2). They found that:
- the number of NICUs allowing 24-hour parental presence reduced from 83% pre-COVID-19 to 53% during COVID-19
- NICUs using single family rooms maintained 24/7 parental presence more than NICUs with open bays and hybrid room designs (Table 3).
- 43% of NICUs related a decrease in services for therapy, lactation, and/or social work.
- Overall, 47% of the NICUs had parental restrictions in place for the pandemic (Figure 3).
The authors caution on limiting parental presence, which can have adversely impact the well-being and health of the infants and their families. The author suggests further evaluation of these policy changes in addition to considering single-family rooms to maintain parental presence.

ABSTRACT

OBJECTIVES: To determine the relationship between the emergence of COVID-19 and neonatal intensive care unit (NICU) family presence as well as how NICU design affects these changes. STUDY DESIGN: A cross-sectional survey from April 21 to 30, 2020. We queried sites regarding NICU demographics, NICU restrictions on parental presence, and changes in ancillary staff availability. RESULTS: Globally, 277 facilities responded to the survey. NICU policies preserving 24/7 parental presence decreased (83-53%, p < 0.001) and of preserving full parental participation in rounds fell (71-32%, p < 0.001). Single-family room design NICUs best preserved 24/7 parental presence after the emergence of COVID-19 (single-family room 65%, hybrid-design 57%, open bay design 45%, p = 0.018). In all, 120 (43%) NICUs reported reductions in therapy services, lactation medicine, and/or social work support. CONCLUSIONS: Hospital restrictions have significantly limited parental presence for NICU admitted infants, although single-family room design may attenuate this effect.

FIGURES

	Pre-COVID $n = 277$ No. (%)	During COVID $n = 277$ No. (%)	P value[a]
Hospital entry policies			
Screening questions for travel history	25 (9)	220 (79)	<0.001
Screening questions for fever and illness	91 (33)	268 (97)	<0.001
Screening temperature check	11 (4)	226 (82)	<0.001
NICU entry policies			
Screening questions for travel history	78 (28)	212 (77)	<0.001
Screening questions for fever and illness	214 (77)	263 (95)	<0.001
Screening temperature check	66 (24)	200 (72)	<0.001
Any restrictions on parental visitation	48 (17)	130 (47)	<0.001
NICU rounding policy			
Full team and parental participation	197 (71)	89 (32)	<0.001
Limited team and parental participation	33 (12)	114 (41)	<0.001
No formal procedure or other procedure	47 (17)	74 (27)	<0.001

[a]False discovery rate adjusted p value.

Table 2 Hospital and NICU policy changes during the COVID-19 pandemic.

Table 3 The effect of NICU design on the changes in NICU entry and rounding policies.

	Single-family room			Hybrid design			Open bay design		
	$n = 76$			$n = 67$			$n = 134$		
	Pre- COVID n (%)	During COVID n (%)		Pre- COVID n (%)	During COVID n (%)		Pre-COVID n (%)	During COVID n (%)	
NICU entry policies									
Screening questions for travel history	23 (30)	58 (76)	***	18 (27)	52 (78)	***	37 (28)	102 (76)	***
Screening questions for fever and illness?	61 (80)	73 (96)	**	50 (75)	64 (96)	**	103 (77)	126 (94)	***
Screening temperature check	18 (24)	55 (72)	***	17 (25)	48 (72)	***	31 (23)	97 (72)	***
Parents always welcome (24/7)	64 (84)	49 (64)	**	61 (91)	38 (57)	***	104 (78)	60 (45)	***
NICU rounding policy									
Full team and parent participation	63 (83)	28 (37)	***	49 (73)	23 (34)	***	85 (63)	38 (28)	***
Limited team and parent participation	2 (3)	32 (42)	***	10 (15)	26 (39)	**	21 (16)	56 (42)	***
No formal procedure or other procedure	11 (14)	16 (21)		8 (12)	18 (27)	**	28 (21)	40 (30)	**

False discovery rate adjusted p values

NICU neonatal intensive care unit.

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

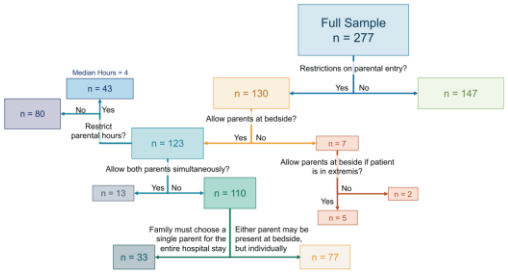


Figure 3. Flow diagram of restrictions to parental presence in the NICU after the emergence of COVID-19. Overall, 130 of 277 NICUs (47%) had restrictions to NICU parental in the NICU during the Covid-19 pandemic. Of these, most allowed only a single parent at the bedside and 33 NICUs required families to choose a single parent for the entire hospital stay. Prohibition of parental presence in the NICU was rare but occurred at 7 sites (3%).

SALIVA SAMPLE POOLING FOR THE DETECTION OF SARS-COV-2

Pasomsub E, Watcharananan SP, Watthanachockchai T, Rakmanee K, Tassaneetrithep B, Kiertiburanakul S, Phuphuakrat A.. J Med Virol. 2020 Aug 25. doi: 10.1002/jmv.26460. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

Medical researchers at the Mahidol University in Thailand conducted a study to explore the viability of saliva pooling as a cost-effective, less invasive alternative SARS-CoV-2 specimen for RT-PCR (Table 1). The authors used 105 saliva samples grouped in pools of 5 and 150 samples grouped into pools of 10, totaling 40 pools of 5 samples and 20 pools of 10 samples. Based on their findings (illustrated below), the authors suggest that saliva pools of either 5 or 10 samples are able to detect SARS-CoV-2 and, thus, may be an effective testing option in low prevalence areas. The authors note, however, that saliva pooling may be limited by viral RNA breakdown during storage protocol and freeze-thawing, leading to possible false negative results.

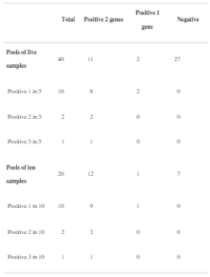
SUMMARY

The findings regarding SARS-CoV-2 detection in the different pools of saliva samples include, but are not limited to, the following:
-Median cycle threshold (Ct) value of SARS-CoV-2 ORF1ab gene in the 5 sample pools and the individual specimens were 37.6 (IQR: 34.8-40.7) and 35.1 (IQR: 30.9-36.5; p=0.007)
-Median Ct value of the SARS-CoV-2 N gene in the 5 samples pools and the individual specimens were 34.9 (IQR: 32.4-35.2) and 36.7 (IQR: 32.4-37.5; p=0.138)
- Ct values of both ORF1ab and N genes of the 5 sample pools that contained 2 or 3 positive specimens were lower than those of the individual specimens (Figure 1).
- Ct values of the ORF1ab gene in the 10 sample pools was 36.7 (IQR: 33.7-39.1), which was considerably higher than that of the individual specimens (p=0.001).
- Median Ct value of the N gene in the 10 sample pools was 34.7 (IQR: 32.1-38.9) and Ct values of both ORF1ab and N genes of the 10 sample pools that contained 2 or 3 positive specimens were lower than those of the individual specimens (Figure 2).

ABSTRACT

As the battle against coronavirus disease 2019 pandemic continues, an increase in workload and medical expenses have been a concern to the health care system worldwide. Developing a measure that helps to conserve the health care resource is, therefore, highly desirable, and the pooling of the specimens for testing is one of the attractive strategies. Recently we showed that saliva could be a potential alternative specimen for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time polymerase chain reaction (RT-PCR). In the present study, we performed the pooling of saliva specimens for testing by SARS-CoV-2 RT-PCR. We showed that the saliva pool of either five or ten samples, by allowing the detection of either gene in the pool at an increased cycle threshold cut-off value, further performing individual sample testing in the positive pools did not compromise the detection of SARS-CoV-2. This article is protected by copyright. All rights reserved.

FIGURES



	Total	Positive 2 genes	Positive 1 gene	Negative
Pools of five samples	40	11	2	27
Positive 1 in 5	10	8	2	0
Positive 2 in 5	2	2	0	0
Positive 3 in 5	1	1	0	0
Pools of ten samples	20	12	1	7
Positive 1 in 10	10	9	1	0
Positive 2 in 10	2	2	0	0
Positive 3 in 10	1	1	0	0

Table 1: Summary of the SARS-CoV-2 gene detection by specimen pooling

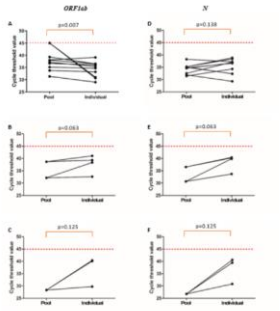


Figure 1: Cycle threshold values of ORF1ab (A-C) and N genes (D-F) in the SARS-CoV-2 detectable pools of five and individual samples. A and D, B and E, and C and F show the pools that contained one, two, and three positive samples, respectively.

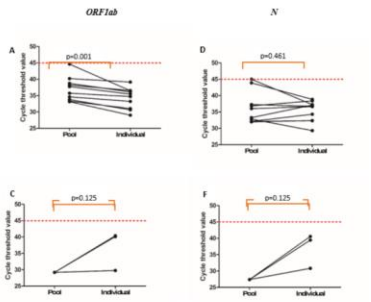


Figure 2: Cycle threshold values of ORF1ab (A-C) and N genes (D-F) in the SARS-CoV-2 detectable pools of ten and individual samples. A and D, B and E, and C and F show the pools that contained one, two, and three positive samples, respectively

DEVELOPMENTS IN TREATMENTS

PHASE 1-2 TRIAL OF A SARS-COV-2 RECOMBINANT SPIKE PROTEIN NANOPARTICLE VACCINE

Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, Plested JS, Zhu M, Cloney-Clark S, Zhou H, Smith G, Patel N, Frieman MB, Haupt RE, Logue J, McGrath M, Weston S, Piedra PA, Desai C, Callahan K, Lewis M, Price-Abbott P, Formica N, Shinde V, Fries L, Lickliter JD, Griffin P, Wilkinson B, Glenn GM.. N Engl J Med. 2020 Sep 2. doi: 10.1056/NEJMoa2026920. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

Authors affiliated with Novavax and physicians from University of Maryland School of Medicine, Baylor College of Medicine, Nucleus Network and Q-Pharm of Australia report findings from phase 1 of their randomized, placebo-controlled, phase 1-2 trial of the NVX-CoV2372 vaccine, a recombinant nanoparticle vaccine consisting of SARS-CoV-2 spike glycoprotein and Matrix-M1 adjuvant (Figure 1). They found the following:
- Reactogenicity was mild or absent in most participants; no serious adverse events were reported.
- The vaccine yielded greater IgG anti-spike protein response compared to controls (Figure 3).
- Participants who received the Matrix-M1 adjuvant showed significant Th1-driven immune response compared to the non-adjuvant vaccine group (Figure 5).
These findings suggest NVX-CoV2373 is a safe and promising candidate for COVID-19 vaccination. Phase 2 of the trial is currently active and phase 3 is in preparation.

ABSTRACT

BACKGROUND: NVX-CoV2373 is a recombinant severe acute respiratory syndrome coronavirus 2 (rSARS-CoV-2) nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant. METHODS: We initiated a randomized, placebo-controlled, phase 1-2 trial to evaluate the safety and immunogenicity of the rSARS-CoV-2 vaccine (in 5-mug and 25-mug doses, with or without Matrix-M1 adjuvant, and with observers unaware of trial-group assignments) in 131 healthy adults. In phase 1, vaccination comprised two intramuscular injections, 21 days apart. The primary outcomes were reactogenicity; laboratory values (serum chemistry and hematology), according to Food and Drug Administration toxicity

scoring, to assess safety; and IgG anti-spike protein response (in enzyme-linked immunosorbent assay [ELISA] units). Secondary outcomes included unsolicited adverse events, wild-type virus neutralization (microneutralization assay), and T-cell responses (cytokine staining). IgG and microneutralization assay results were compared with 32 (IgG) and 29 (neutralization) convalescent serum samples from patients with Covid-19, most of whom were symptomatic. We performed a primary analysis at day 35. RESULTS: After randomization, 83 participants were assigned to receive the vaccine with adjuvant and 25 without adjuvant, and 23 participants were assigned to receive placebo. No serious adverse events were noted. Reactogenicity was absent or mild in the majority of participants, more common with adjuvant, and of short duration (mean, <=2 days). One participant had mild fever that lasted 1 day. Unsolicited adverse events were mild in most participants; there were no severe adverse events. The addition of adjuvant resulted in enhanced immune responses, was antigen dose-sparing, and induced a T helper 1 (Th1) response. The two-dose 5-mug adjuvanted regimen induced geometric mean anti-spike IgG (63,160 ELISA units) and neutralization (3906) responses that exceeded geometric mean responses in convalescent serum from mostly symptomatic Covid-19 patients (8344 and 983, respectively). CONCLUSIONS: At 35 days, NVX-CoV2373 appeared to be safe, and it elicited immune responses that exceeded levels in Covid-19 convalescent serum. The Matrix-M1 adjuvant induced CD4+ T-cell responses that were biased toward a Th1 phenotype. (Funded by the Coalition for Epidemic Preparedness Innovations; ClinicalTrials.gov number, NCT04368988).

FIGURES

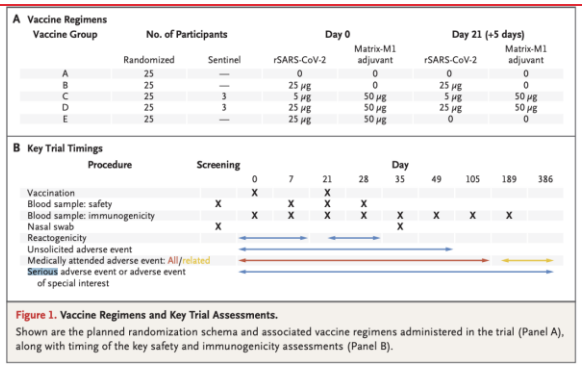


Figure 1. Vaccine Regimens and Key Trial Assessments.
Shown are the planned randomization schema and associated vaccine regimens administered in the trial (Panel A), along with timing of the key safety and immunogenicity assessments (Panel B).

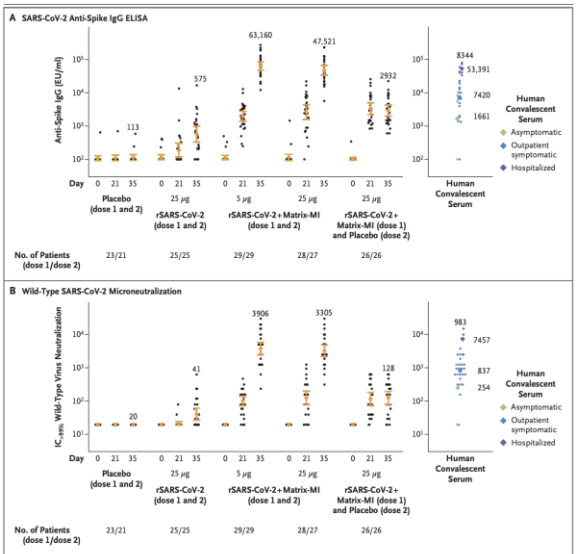


Figure 3. SARS-CoV-2 Anti-Spike IgG and Neutralizing Antibody Responses.
Shown are geometric mean anti-spike IgG enzyme-linked immunosorbent assay (ELISA) unit responses to recombinant severe acute respiratory syndrome coronavirus 2 (rSARS-CoV-2) protein antigens (Panel A) and wild-type SARS-CoV-2 microneutralization assay at an inhibitory concentration greater than 99% (MN $IC_{>99\%}$) titer responses (Panel B) at baseline (day 0), 3 weeks after the first vaccination (day 21), and 2 weeks after the second vaccination (day 35) for the placebo group (group A), the 25-μg unadjuvanted group (group B), the 5-μg and 25-μg adjuvanted groups (groups C and D, respectively), and the 25-μg adjuvanted and placebo group (group E). Diamonds and whisker endpoints represent geometric mean titer values and 95% confidence intervals, respectively. The Covid-19 human convalescent serum panel includes specimens from PCR-confirmed Covid-19 participants, obtained from Baylor College of Medicine (29 specimens for ELISA and 32 specimens for MN $IC_{>99\%}$), with geometric mean titer values according to Covid-19 severity. The severity of Covid-19 is indicated by the colors of the dots for hospitalized patients (including those in intensive care), symptomatic outpatients (with samples collected in the emergency department), and asymptomatic patients who had been exposed to Covid-19 (with samples collected during contact and exposure assessment). Mean values (in black) for human convalescent serum are depicted next to (and of same color as) the category of Covid-19 patients, with the overall mean shown above the scatter plot (in black). For each trial vaccine group, the mean at day 35 is depicted above the scatterplot.

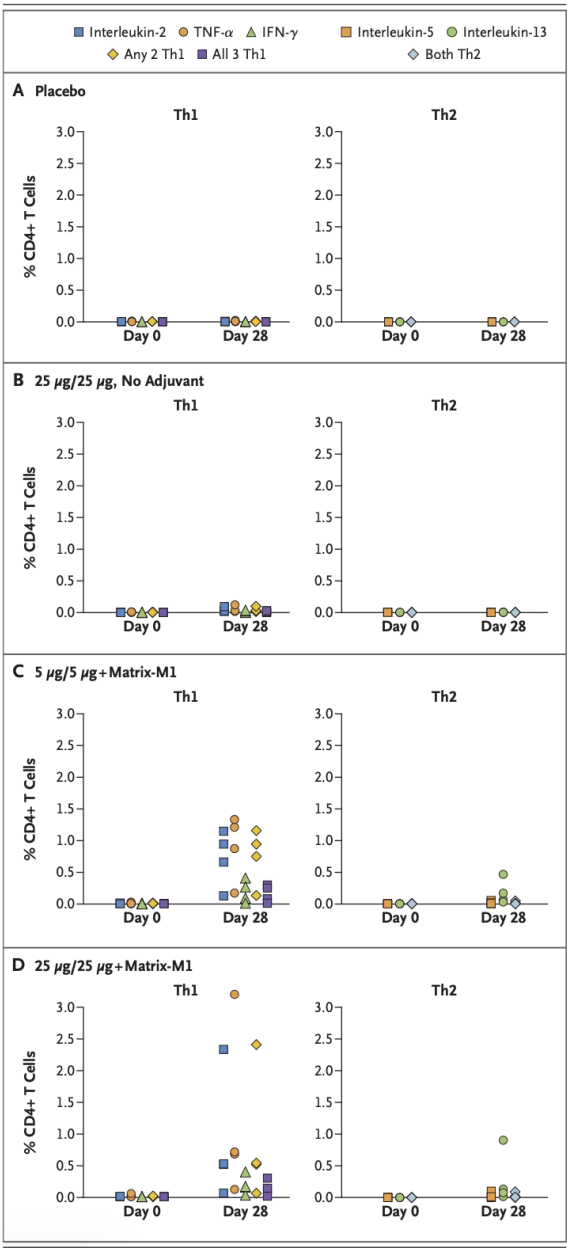


Figure 5. rSARS-CoV-2 CD4+ T-cell Responses with or without Matrix-M1 Adjuvant.
Frequencies of antigen-specific CD4+ T cells producing T helper 1 (Th1) cytokines interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-2 and for T helper 2 (Th2) cytokines interleukin-5 and interleukin-13 indicated cytokines from four participants each in the placebo (group A), 25-μg unadjuvanted (group B), 5-μg adjuvanted (group C), and 25-μg adjuvanted (group D) groups at baseline (day 0) and 1 week after the second vaccination (day 28) after stimulation with the recombinant spike protein. "Any 2Th1" indicates CD4+ T cells that can produce two types of Th1 cytokines at the same time. "All 3 Th1" indicates CD4+ T cells that produce IFN-γ, TNF-α, and interleukin-2 simultaneously. "Both Th2" indicates CD4+ T cells that can produce Th2 cytokines interleukin-5 and interleukin-13 at the same time.

SAFETY UPDATE: COVID-19 CONVALESCENT PLASMA IN 20,000 HOSPITALIZED PATIENTS

Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, Wiggins CC, Senefeld JW, Klompas AM, Hodge DO, Shepherd JRA, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, van Buskirk CM, Winters JL, Stubbs JR, van Helmond N, Butterfield BP, Sexton MA, Diaz Soto JC, Paneth NS, Verdun NC, Marks P, Casadevall A, Fairweather D, Carter RE, Wright RS.. Mayo Clin Proc. 2020 Sep;95(9):1888-1897. doi: 10.1016/j.mayocp.2020.06.028. Epub 2020 Jul 19.
Level of Evidence: 2 - Individual randomized trial or (exceptionally) observational study with dramatic effect

BLUF

Investigators affiliated with Mayo Clinic who are working in collaboration with the United States (US) Food and Drug Administration provide a safety update of the US Convalescent Plasma Expanded Access Program (EAP) after transfusing 20,000 hospitalized patients with severe or life-threatening COVID-19 with convalescent plasma. Based on the results of these 20,000 patients (summarized below), the authors suggest that the use of convalescent plasma is safe and carries no excess risk of complications. The authors also share that a future report will describe the efficacy of COVID-19 convalescent plasma therapy.

SUMMARY

• The patient characteristics and clinical symptoms defining severe or life-threatening COVID-19 can be found in Table 1.
• The authors report that the overall frequency of serious adverse events (SAEs) was low (less than 1% of all transfusions), and the 7-day mortality rate in this high-risk cohort was 13.0% (Table 2, Figure 2).

ABSTRACT

OBJECTIVE: To provide an update on key safety metrics after transfusion of convalescent plasma in hospitalized coronavirus 2019 (COVID-19) patients, having previously demonstrated safety in 5000 hospitalized patients. PATIENTS AND METHODS: From April 3 to June 2, 2020, the US Food and Drug Administration Expanded Access Program for COVID-19 convalescent plasma transfused a convenience sample of 20,000 hospitalized patients with COVID-19 convalescent plasma. RESULTS: The incidence of all serious adverse events was low; these included transfusion reactions (n=78; <1%), thromboembolic or thrombotic events (n=113; <1%), and cardiac events (n=677, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=75) and cardiac events (n=597) were judged to be unrelated to the plasma transfusion per se. The 7-day mortality rate was 13.0% (12.5%, 13.4%), and was higher among more critically ill patients relative to less ill counterparts, including patients admitted to the intensive care unit versus those not admitted (15.6 vs 9.3%), mechanically ventilated versus not ventilated (18.3% vs 9.9%), and with septic shock or multiple organ dysfunction/failure versus those without dysfunction/failure (21.7% vs 11.5%). CONCLUSION: These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

FIGURES

	April	May	Total
Characteristic			
N	6214	13,786	20,000
Age, y			
18-39	449 (7.2)	1083 (7.9)	1,532 (7.7)
40-59	2056 (33.1)	4320 (31.3)	6,376 (31.9)
60-69	1798 (28.9)	3611 (26.2)	5,409 (27.0)
70-79	1260 (20.3)	2859 (20.7)	4,119 (20.6)
≥80	651 (10.5)	1913 (13.9)	2,564 (12.8)
Sex			
Female	2262 (36.4)	5499 (39.9)	7761 (38.8)
Male	3924 (63.2)	8241 (59.8)	12,165 (60.8)
Intersex or transgender	22 (0.4)	35 (0.3)	57 (0.3)
Undisclosed	6 (0.1)	11 (0.1)	17 (0.1)
Weight status[b]			
Underweight	61 (1.2)	249 (1.8)	310 (1.7)
Normal weight	868 (17.3)	2454 (18.0)	3322 (17.8)
Overweight	1502 (30.0)	3802 (27.8)	5304 (28.4)
Obese	2587 (51.6)	7166 (52.4)	9753 (52.2)
Race			
Asian	408 (6.6)	591 (4.3)	999 (5.0)
Black	1132 (18.2)	2784 (20.2)	3916 (19.6)
White	2993 (48.2)	6741 (48.9)	9734 (48.7)
Other or unknown	1681 (27.1)	3670 (26.6)	5351 (26.8)
Ethnicity			
Hispanic or Latino	2142 (34.5)	4794 (34.8)	6936 (34.7)
Not Hispanic or Latino	4072 (65.5)	8992 (65.2)	13,064 (65.3)
Clinical status			
Current severe or life-threatening COVID-19	4963 (79.9)	9274 (67.3)	14,237 (71.2)
High risk of severe or life-threatening COVID-19	1251 (20.1)	4512 (32.7)	5763 (28.8)
Intensive care unit admission	4038 (65.0)	7522 (55.0)	11,560 (58.1)
Mechanical ventilation[c]	2709 (48.5)	4155 (30.4)	6864 (35.6)
Clinical symptoms[d]			
Respiratory failure	3574 (72.0)	6155 (66.4)	9729 (68.3)
Dyspnea	3152 (63.5)	6561 (70.7)	9713 (68.2)
Blood oxygen saturation ≤93%	3092 (62.3)	6663 (71.8)	9755 (68.5)
Lung infiltrates >50% within 24 to 48 h	2105 (42.4)	4021 (43.4)	6126 (43.0)
Respiratory frequency ≥30/min	1937 (39.0)	4014 (43.3)	5951 (41.8)
$P_AO_2FiO_2$[e] <300	1642 (33.1)	3014 (32.5)	4656 (32.7)
Multiple organ dysfunction or failure	936 (18.9)	1212 (13.1)	2148 (15.1)
Septic shock	734 (14.8)	987 (10.6)	1721 (12.1)

[a]Values shown are n (%).
[b]These data include a subset of the sample (n=18,689).
[c]These data include a subset of the sample (n=19,256).
[d]These data include a subset of the sample (n=14,237), only those patients that currently have severe or life-threatening COVID-19.
[e]$P_AO_2FiO_2$ the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ratio.

Table 1. Patient Characteristics Stratified by Month of COVID-19 Convalescent Plasma Transfusion (See superscript "a" below)

SAE: Transfusion reactions	Reported	Related	% Estimate[b] (95% CI)
Mortality within four hours of transfusion	63	10	0.05 (0.03-0.09)
TACO	36	36	0.18 (0.13-0.25)
TRALI	21	21	0.10 (0.07-0.16)
Severe allergic transfusion reaction	21	21	0.10 (0.07-0.16)
7-day SAE reports			
Thrombolic or thromboembolic complication	113	38	0.19 (0.14-0.26)
Sustained hypotension[c]	457	54	0.27 (0.21-0.35)
Cardiac events[d]	677	80	0.40 (0.32-0.50)
7-day mortality	Reported		
Crude Estimate	2592		12.96 (12.50-13.44)
Clinical status			
No ICU admission (n=8323)	772		9.28 (8.67-9.92)
ICU admission (n=11,560)	1806		15.62 (14.97-16.30)
No mechanical ventilation (n=12,147)	1220		9.85 (9.34-10.38)
Mechanical ventilation (n=6864)	1258		18.33 (17.43-19.26)
Clinical symptoms			
No MOF or septic shock (n=17,081)	1952		11.45 (10.98-11.94)
MOF or septic shock (n=2919)	640		21.72 (20.27-23.24)

[a]ICU = intensive care unit; MOF = multiple organ failure or dysfunction; SAE = severe adverse event; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury.
[b]Point estimate of related serious adverse event incidence relative to 20,000 transfusions.
[c]Sustained hypotension included events requiring intravenous pressor support.
[d]Cardiac events included ventricular or atrial fibrillation or arrhythmia requiring treatment, and cardiac arrest.

Table 2. SAE Characteristics in Patients Transfused With COVID-19 Convalescent Plasma (N1/420,000) (See superscript "a" below)

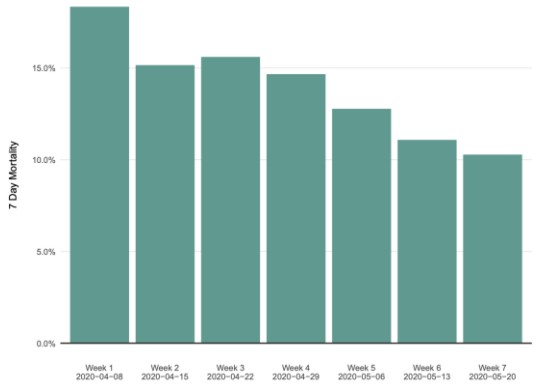


Figure 2. Seven-day mortality rate in patients transfused with COVID-19 convalescent plasma stratified by week since initiation of the US COVID-19 Convalescent Plasma Expanded Access Program (EAP). Each green bar indicates the 7-day mortality rate stratified by the patients enrolled during a given week since the initiation of the EAP.

REMDESIVIR: FIRST APPROVAL

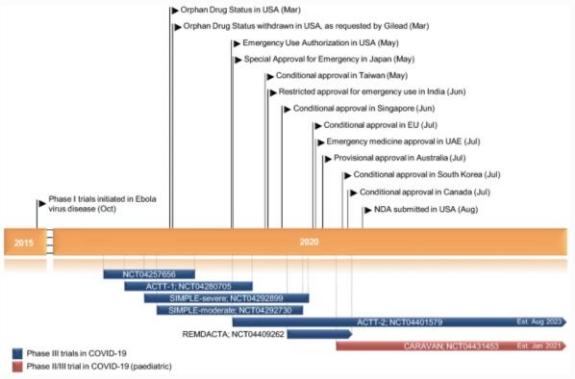
Lamb YN.. Drugs. 2020 Sep 1. doi: 10.1007/s40265-020-01378-w. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A New Zealand-based medical writer for Springer Nature summarizes the progress of clinical trials of remdesivir as therapy for COVID-19. Remdesivir, a nucleotide analog prodrug, has been conditionally approved for treatment of COVID-19 in several countries, and in August 2020, a New Drug Application was submitted to the U.S. Food and Drug Administration (Figure 1). Multinational phase III clinical trials (Figure 2) have shown promising results of clinical improvement with remdesivir treatment, and currently active phase III clinical trials are investigating remdesivir with adjuvant baricitinib or tocilizumab.

ABSTRACT

The antiviral agent remdesivir (Veklury ; Gilead Sciences), nucleotide analogue prodrug, has broad-spectrum activity against viruses from several families. Having demonstrated potent antiviral activity against coronaviruses in preclinical studies, remdesivir emerged as a candidate drug for the treatment of the novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, during the current global pandemic. Phase III evaluation of remdesivir in the treatment of COVID-19 commenced in early 2020 and has thus far yielded promising results. In late May 2020, Taiwan conditionally approved the use of remdesivir in patients with severe COVID-19. This was followed by a rapid succession of conditional approvals in various countries/regions including the EU and Canada. Preceding these conditional approvals, an emergency use authorization for remdesivir had been granted in the USA (on 1 May 2020) and a special approval for emergency use was granted in Japan (on 7 May 2020). This article summarizes the milestones in the development of remdesivir leading to its first conditional approval for the treatment of COVID-19.



Key milestones in the development of remdesivir for use in COVID-19. NDA New Drug Application.

Drug(s)	Phase	Status	Location(s)	Identifier	Sponsor (Collaborator)
Remdesivir	II/III	Recruiting	Multinational	NCT04431453 (CARAVAN)	Gilead Sciences
Remdesivir, placebo	III	Terminated	China	NCT04257656	Capital Medical University
Remdesivir, SOC	III	Completed	Multinational	NCT04292730 (SIMPLE-moderate)	Gilead Sciences
Remdesivir, SOC	III	Completed	Multinational	NCT04292899 (SIMPLE-severe)	Gilead Sciences
Remdesivir, placebo	III	Completed	Multinational	NCT04280705 (ACTT-1)	NIAID
Remdesivir, baricitinib, placebo	III	Active	Multinational	NCT04401579 (ACTT-2)	NIAID
Remdesivir, tocilizumab, placebo	III	Recruiting	Multinational	NCT04409262 (REMDACTA)	Hoffmann-La Roche (Gilead Sciences)

NIAID National Institute of Allergy and Infectious diseases, SOC standard of care

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