The Daily COVID-19 Literature Surveillance Summary

June 13, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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

EXECUTIVE SUMMARY

Climate

- According to a study in France, initial signs of pressure on the emergency medical system (EMS) preceded the hospital influx of critical patients by approximately 30 days and identification of similar measures in other countries' EMS may be critical for pandemic preparation.

Epidemiology

- A study using a novel method based on statistical physics to predict the transmission/incubation time and global recovery trajectories during the COVID-19 pandemic found that the COVID-19 transmission/incubation rate was approximately five days, and different countermeasures (i.e., social isolation, distancing) led to different growth/decline trajectories worldwide.
- A retrospective study of 72 non-hospitalized COVID-19 patients who presented to the emergency department (ED) and underwent chest CT-scans with CT pulmonary angiography protocols found that thirteen patients (18%) were diagnosed with acute pulmonary embolisms (APE), suggesting associations between COVID-19 and APEs, even in non-severe and non-hospitalized patients.
- Researchers at University of California San Diego Health performed a cross-sectional study and found that 23 out of the 46 COVID-19 patients reported olfactory dysfunction; 18 of those 23 reported persistent subjective loss of smell despite two consecutive negative RT-PCR tests, suggesting that olfactory loss can persist even after significant viral load reduction.

Understanding Pathology

- A qualitative study evaluating antibody responses of rabbits to various SARS-CoV-2 spike protein antigens, including the receptor-binding domain (RBD), S1 domain, S2 domain, and S1+S2 domain, found the RBD immunogen elicited a much higher antibody response with greater affinity compared to other antigens, and the S2 domain produced the weakest response, suggesting that vaccine development based on the RBD may be a promising area of further research.

Adjusting Practice During COVID-19

- Guidelines and recommendations for adjusting practice include a triphasic response to COVID-19 with phase-specific recommendations to minimize adverse effects of delaying care for gastrointestinal diseases during the earlier part of the pandemic.
- A Health Belief Model and self-reporting questionnaire sent to 90 residents (mean age 84.9 years) across three nursing home facilities in Israel to determine the accuracy of self-reporting in the elderly found the difference between true BMI values and self-reported values varied by an average of 1.43, which would have a minimal impact on the physician's clinical evaluation of a patient, and the positive predictive value for self-reporting normal blood pressures was 77.78% and 78.57% for abnormal blood pressures.
    - In the COVID-19 era where minimizing physical encounters remains necessary, elderly self-reporting on health measures may potentially become an essential telehealth tool.

R&D: Diagnosis & Treatments

- In a case series of 105 COVID-19 patients in Germany 14 patients had severe hyperinflammation associated with COVID-19 by a COVID-19 Inflammation Score (CIS) and were subsequently treated with the Janus kinase (JAK) 1/2 inhibitor drug ruxolitinib of which 12 demonstrated statistically significant reduction in CIS on the seventh day, suggesting that ruxolitinib may be efficacious in patients with hyperinflammation in the setting of COVID-19. A phase II clinical trial for this drug is underway.
- A scoping review of clinical trials for treatments of COVID-19 registered with the WHO or clinicaltrials.gov, completed on 26 March 2020 by epidemiologists at Johns Hopkins University (United States), found:
    - A total 92 different experimental agents tested as either single or combination therapies
    - 201 ongoing clinical trials, of which 75.7% (152) were randomized trials

- Within the randomized trials group, only 36.2% (55) were at least single-blinded studies.
- Thus, while there are a wide variety of drugs undergoing testing, results of most studies are expected to only provide preliminary information on efficacy.

TABLE OF CONTENTS

CLIMATE

GLOBAL

COVID-19 EPIDEMIC IN THE SEINE-SAINT-DENIS DEPARTMENT OF GREATER PARIS: ONE MONTH AND THREE WAVES FOR A TSUNAMI

Lapostolle F, Goix L, Vianu I, Chanzy E, De Stefano C, Gorlicki J, Petrovic T, Adnet F.. Eur J Emerg Med. 2020 Jun 8. doi: 10.1097/MEJ.0000000000000723. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

This observational study examined the chronology of COVID-19 cases from 17 February to 28 March 2020 in Seine-Saint-Denis, France. The authors reported that the initial signs of pressure on the emergency medical system (EMS) preceded the hospital influx of critical patients by approximately 30 days (Figure 1). Although these initial signs are specific to the French EMS, identification of similar measures in other countries' EMS may be critical for pandemic preparation.

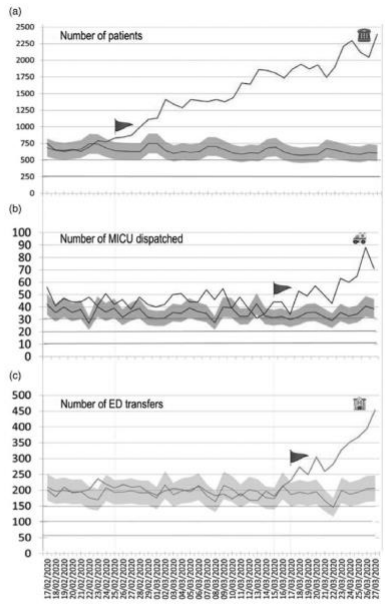
SUMMARY

In France, individuals who need urgent care can call Service d'Aide Médicale Urgente (SAMU, or Emergency Medical Service [EMS]) and speak to a physician. The physician will then determine the type of care to be provided, which may include medical advice, non-emergency transport ambulance, emergency transport, or dispatching a general practitioner to the patient's home. In severe cases, pre-hospital care consists of a mobile intensive care unit (MICU) staffed by an emergency physician, nurse, and a paramedic.

- A 20% increase in the daily number of patients managed by SAMU EMS compared to the previous 5-year mean is considered as a sensitive indicator of a public health crisis.
- This threshold was first crossed on 25 February 2020 in Seine-Saint-Denis, indicating the initial signs of pressure on the SAMU EMS.
- Approximately 30 days later, the number of MICUs dispatched and the daily admissions in the intensive care unit (ICU) reached its maximum (Table 1).

FIGURES

Fig. 1



(a) Evolution of the number of patients managed: red curve. Blue curve: average over the reference period (5-year mean); blue zone: 20% variation defined as the threshold for public health crisis; $R^2 = 0.95$ (linear). (b) Evolution of the number of MICUs dispatched: Blue curve. Purple curve: average over the reference period (5-year mean); pink zone: 20%; $R^2 = 0.77$ (exponential). Red flag: date the threshold was crossed (5-year mean +20%). (c) Evolution of the number of patients transferred to emergency departments: green curve. Brown curve: average over the reference period (5-year mean); green zone: 20% variation; $R^2 = 0.90$ (exponential). Primary end-point: lapse of time between the day the threshold of patients managed was crossed and the day the number of MICUs dispatched crossed its threshold. Secondary end-point: lapse of time between the day the number of patients managed crossed its threshold and the day the number of MICUs dispatched reached its maximum.

Table 1 Key dates of the chronology of the epidemic in France

13 January 2020: health warning issued by the Ministry of Health on the propagation of a virus in the Wuhan region of China
24 January 2020: first cases in France in patients returning from Wuhan
23 February 2020: Health warning by the Ministry of Health regarding the circulation of the virus in several Italian provinces end of a school vacation period in France
13 March 2020: French President announces lockdown decision
27 March 2020: Daily hospital admissions in France reach their peak (N = 2365)
26 March 2020: Daily admissions in intensive care units in France reach their peak (N = 548)
01 April 2020: patients hospitalized in intensive care units are transferred from the Greater Paris as maximum capacities are reached
06 April 2020: Daily hospital deaths in France reach their peak (N = 605)
08 April 2020: Number of patients hospitalized in intensive care units in France reach their peak (N = 7148)

COVID-19: RISK OF SECOND WAVE IS VERY REAL, SAY RESEARCHERS

Wise J.. BMJ. 2020 Jun 9;369:m2294. doi: 10.1136/bmj.m2294.
Level of Evidence: Other - Opinion

BLUF

An author from London briefly reviewed current literature on the likelihood of a severe second wave of COVID-19. It was referenced that an estimated 530 million lives have been saved by lockdown interventions. The author emphasized that continued adherence and implementation of anti-contagion policies are vital to minimizing risk of a second wave.

SUMMARY

Summarizing Excerpt:
"Lockdown measures may have averted 3.1 million deaths from covid-19[sic] across 11 European countries, including 470 000 in the UK...However, the researchers warn that European countries are very far from achieving herd immunity, as less than 4% of their populations were infected with SARS-CoV-2 up to 4 May, when lockdowns started to be lifted...[one] model found that lockdown measures had successfully reduced the reproduction number (R value) to less than 1 in all the countries studied, ranging from a mean of 0.44 for Norway to 0.82 for Belgium. The average R value across the 11 countries was 0.66, an 82%

reduction from the figure before the lockdowns...A second study...estimated that lockdown policies implemented in China, South Korea, Italy, Iran, France, and the US prevented or delayed around 530 million covid-19[sic] infections."

EPIDEMIOLOGY

MODELING

PREGNANCY AND PANDEMIC DISEASE

Beckerman KP.. Clin Infect Dis. 2020 Jun 10:ciaa741. doi: 10.1093/cid/ciaa741. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This commentary from the University of California, San Francisco describes the historical utility of tuberculosis screening and HIV testing during pregnancy as a tool to study disease presentation, prevalence, and transmission in a community. The author argues that earlier testing for COVID-19 in pregnant women could have allowed scientists to characterize the presentation and transmission of SARS-CoV-2 earlier and may have prevented some of the consequences of the pandemic, but they do not elaborate on recommendations for implementation of these testing/screening procedures.

PREDICTION OF COVID-19 INFECTION, TRANSMISSION AND RECOVERY RATES: A NEW ANALYSIS AND GLOBAL SOCIETAL COMPARISONS

Duffey RB, Zio E.. Saf Sci. 2020 Sep;129:104854. doi: 10.1016/j.ssci.2020.104854. Epub 2020 May 28.
Level of Evidence: Other - Modeling

BLUF

This study uses a novel method based on statistical physics to predict the transmission/incubation time and global recovery trajectories during the COVID-19 pandemic. The results of these new analyses suggest that the COVID-19 transmission/incubation rate was approximately five days, and different countermeasures (i.e., social isolation, distancing) led to different growth/decline trajectories worldwide (Figures 2-4).

ABSTRACT

We analyze the process of infection rate growth and decline for the recent global pandemic, applying a new method to the available global data. We describe and utilize an original approach based on statistical physics to predict the societal transmission timescale and the universal recovery trajectory resulting from the countermeasures implemented in entire societies. We compare the whole-society infection growth rates for many countries and local regions, to illustrate the common physical and mathematical basis for the viral spread and infection rate reduction, and validate the theory and resulting correlations. We show that methods traditionally considered for the numerical analysis and the control of individual virus transmission (e.g. R0 scaling) represent one special case of the theory, and also compare our results to the available IHME computer model outcomes. We proceed to illustrate several interesting features of the different approaches to the mitigation of the pandemic, related to social isolation and "lockdown" tactics. Finally, we use presently available data from many countries to make actual predictions of the time needed for securing minimum infection rates in the future, highlighting the differences that emerge between isolated "islands" and mobile cities, and identifying the desired overall recovery trajectory.

FIGURES

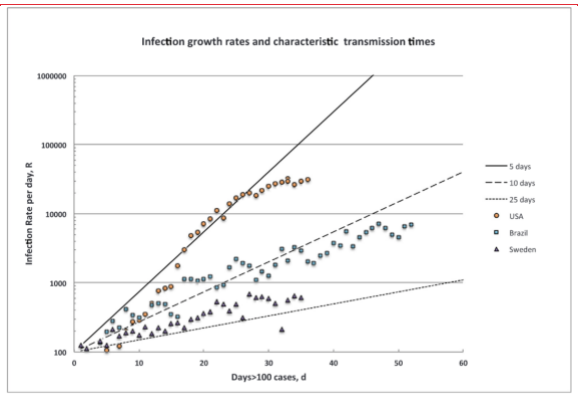


Fig. 2. Typical characteristic growth trajectories of societal infection rates (semi- logarithmic plot).

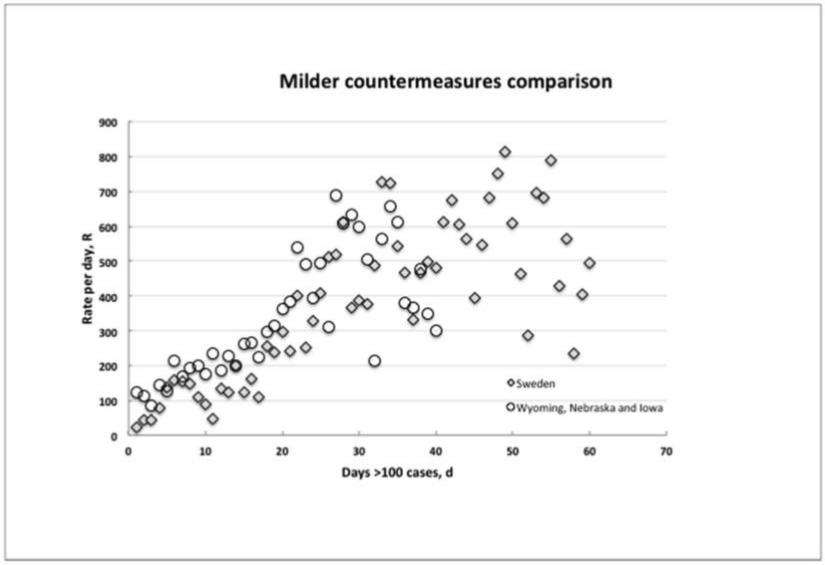


Fig. 3. Comparison of trajectories of infection rate growth in relatively little densely populated regions of two continents where mild countermeasures have been applied.

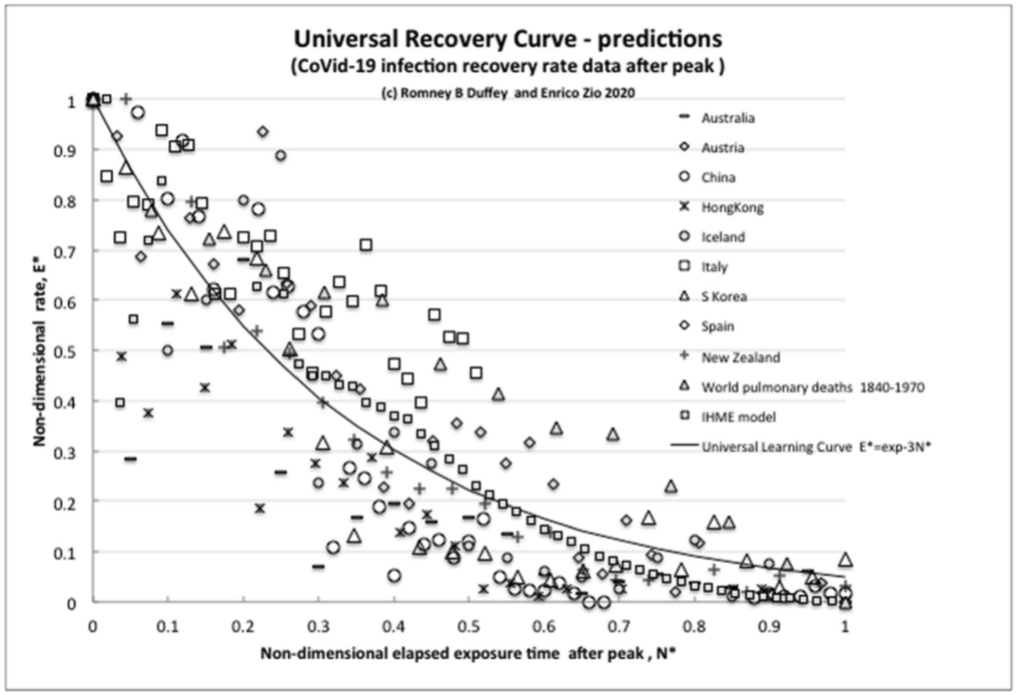


Fig. 4. Predictions of recovery in agreement with the analytical exponential trend of learning theory.

SYMPTOMS AND CLINICAL PRESENTATION

ACUTE PULMONARY EMBOLISM IN NON-HOSPITALIZED COVID-19 PATIENTS REFERRED TO CTPA BY EMERGENCY DEPARTMENT

Gervaise A, Bouzad C, Peroux E, Helissey C.. Eur Radiol. 2020 Jun 9. doi: 10.1007/s00330-020-06977-5. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective study of 72 non-hospitalized, COVID-19 positive (confirmed on RT-PCR and/or typical radiologic chest CT findings) patients who presented to the emergency department (ED) and underwent chest CT-scans with CT pulmonary angiography protocols was conducted between March 14 and April 6, 2020 to assess the prevalence of acute pulmonary embolisms (APE) in patients referred to the ED. Thirteen patients (18%) were diagnosed with APEs (Table 2), confirming the associations between COVID-19 and APEs, even in non-severe and non-hospitalized patients.

ABSTRACT

OBJECTIVES: To evaluate the prevalence of acute pulmonary embolism (APE) in non-hospitalized COVID-19 patients referred to CT pulmonary angiography (CTPA) by the emergency department.
METHODS: From March 14 to April 6, 2020, 72 non-hospitalized patients referred by the emergency department to CTPA for COVID-19 pneumonia were retrospectively identified. Relevant clinical and laboratory data and CT scan findings were collected for each patient. CTPA scans were reviewed by two radiologists to determinate the presence or absence of APE. Clinical classification, lung involvement of COVID-19 pneumonia, and CT total severity score were compared between APE group and non-APE group.
RESULTS: APE was identified in 13 (18%) CTPA scans. The mean age and D-dimer of patients from the APE group were higher in comparison with those from the non-APE group (74.4 vs. 59.6 years, p = 0.008, and 7.29 vs. 3.29 mug/ml, p = 0.011). There was no significant difference between APE and non-APE groups concerning clinical type, COVID-19 pneumonia lung lesions (ground-glass opacity: 85% vs. 97%; consolidation: 69% vs. 68%; crazy paving: 38% vs. 37%; linear reticulation: 69% vs. 78%), CT severity score (6.3 vs. 7.1, p = 0.365), quality of CTPA (1.8 vs. 2.0, p = 0.518), and pleural effusion (38% vs. 19%, p = 0.146).
CONCLUSIONS: Non-hospitalized patients with COVID-19 pneumonia referred to CT scan by the emergency departments are at risk of APE. The presence of APE was not limited to severe or critical clinical type of COVID-19 pneumonia.
KEY POINTS: Acute pulmonary embolism was found in 18% of non-hospitalized COVID-19 patients referred by the emergency department to CTPA. Two (15%) patients had main, four (30%) lobar, and seven (55%) segmental acute pulmonary embolism. Five of 13 (38%) patients with acute pulmonary embolism had a moderate clinical type. Severity and radiological features of COVID-19 pneumonia showed no significant difference between patients with or without acute pulmonary embolism.

FIGURES

	All patients (*n* = 72)	APE group (*n* = 13)	Non-APE group (*n* = 59)	*p* value
CTPA quality score	2.0 ± 0.9 (1–3)	1.8 ± 1.0 (1–3)	2.0 ± 0.8 (1–3)	0.518
Chest CT severity score	7.0 ± 3.5 (0–15)	6.3 ± 3.7 (1–15)	7.1 ± 3.4 (0–15)	0.365
Lobe involvement (*n*)				
Left upper lobe	59 (82%)	8 (62%)	51 (86%)	0.05
Left lower lobe	64 (89%)	12 (92%)	52 (88%)	1
Right upper lobe	64 (89%)	10 (77%)	54 (92%)	0.151
Right middle lobe	58 (81%)	8 (62%)	50 (85%)	0.114
Right lower lobe	68 (94%)	13 (100%)	55 (93%)	1
More than two lobes	65 (90%)	12 (92%)	53 (90%)	1
Radiological findings (*n*)				
GGO	68 (94%)	11 (85%)	57 (97%)	0.147
Consolidation	49 (68%)	9 (69%)	40 (68%)	1
Crazy paving	27 (38%)	5 (38%)	22 (37%)	1
Linear reticulation	55 (76%)	9 (69%)	46 (78%)	0.490
Radiological pattern (*n*)				
GGO > consolidation	40	7 (54%)	33 (56%)	1
Consolidation > GGO	31	6 (46%)	25 (42%)	1
Normal CT scan	1	0 (0%)	1 (2%)	
Pleural effusion (*n*)	16 (22%)	5 (38%)	11 (19%)	0.146

Except for *p* value, continuous variables are presented as mean ± standard deviation and extreme values in parentheses and compared by means of the Mann-Whitney *U* test between the APE group and non-APE group. Categorical variables are presented as numbers and percentage in parentheses and compared by means of Fisher's exact test between the two groups
APE, acute pulmonary embolism; *CTPA*, computed tomography pulmonary angiography; *GGO*, ground-glass opacity

Table 2. Chest CT findings for all patients and for APE vs. non-APE groups

PERSISTENT SMELL LOSS FOLLOWING UNDETECTABLE SARS-COV-2

Yan CH, Prajapati DP, Ritter ML, DeConde AS.. Otolaryngol Head Neck Surg. 2020 Jun 9:194599820934769. doi: 10.1177/0194599820934769. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers at University of California San Diego Health performed a cross-sectional study by reviewing medical records and implementing phone-based questionnaires to COVID-19 patients diagnosed between 9 March and 29 April 2020. 23 out of the 46 patients studied reported olfactory dysfunction; 18 of those 23 reported persistent subjective loss of smell despite two consecutive negative RT-PCR tests, suggesting that olfactory loss can persist even after significant viral load reduction (Figure 1).

ABSTRACT

The association of smell and taste loss with COVID-19 has been well demonstrated with high prevalence rates. In certain cases, chemosensory loss may be the only symptom of COVID-19 and may linger while other symptoms have resolved. The significance of persistent smell and taste loss and its relationship to ongoing viral shedding has yet to be investigated. In this cross-sectional study, of the 316 laboratory test-confirmed COVID-19 cases at our institution, 46 had subsequent test-based confirmation of viral clearance with 2 consecutive negative RT-PCR test results (reverse transcriptase polymerase chain reaction). Olfactory dysfunction was reported by 50% of the patients (23 of 46), with 78% (18 of 23) having subjective persistent smell loss despite negative RT-PCR test results. These preliminary data demonstrate the persistence of self-reported smell loss despite otherwise clinical resolution and undetectable nasal viral RNA.

FIGURES

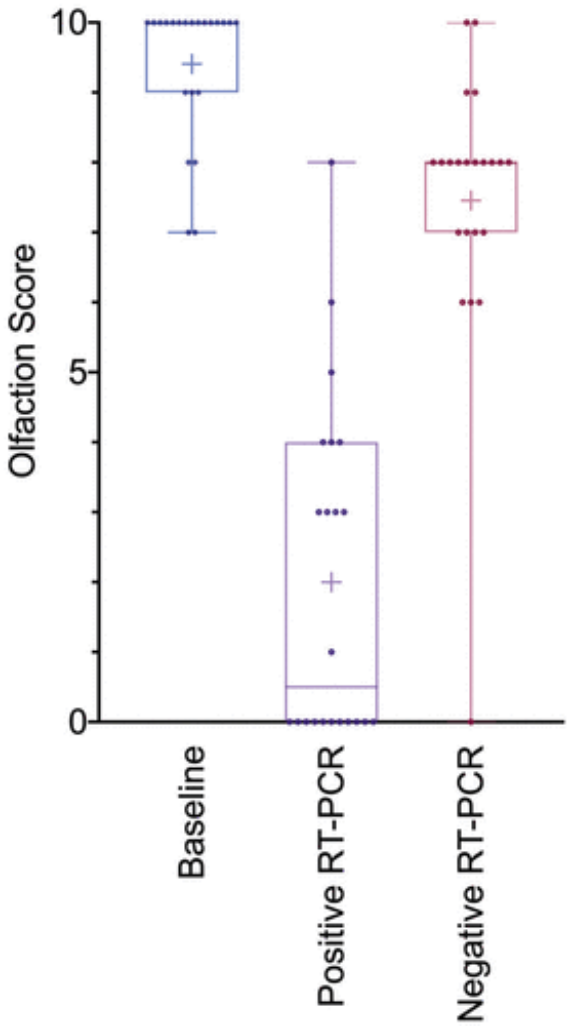


Figure 1: Relationship between olfaction scores and COVID-19 RT-PCR status. Box and whisker plot show olfaction scores at baseline, time of positive RT-PCR testing, and time of survey (following negative RT-PCR results). Whiskers represent minimum and maximum values; boxes indicate interquartile range; and the horizontal line within the box represents the median value. The mean value is denoted by the plus sign, +. RT-PCR, reverse transcriptase polymerase chain reaction.

ADULTS

TASTE AND SMELL IMPAIRMENT IN COVID-19: AN AAO-HNS ANOSMIA REPORTING TOOL-BASED COMPARATIVE STUDY

Sayin İ, Yaşar KK, Yazici ZM.. Otolaryngol Head Neck Surg. 2020 Jun 9:194599820931820. doi: 10.1177/0194599820931820. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A comparative study in Istanbul, Turkey investigated 128 symptomatic patients, mean age 38.63 +/- 10.8 years, half of whom tested COVID-19 positive. The AAO-HNS Anosmia Reporting Tool was used to gather responses by phone call to compare taste and smell impairment between both groups. It was found that COVID-19-positive patients experienced smell impairment at a significantly higher rate than COVID-19-negative patients (71.9% versus 26.6%, p = 0.001) (Table 3). Thus the authors suggest that smell impairment may be a useful screening tool for patients with symptoms of COVID-19.

ABSTRACT

OBJECTIVE: To identify the taste and smell impairment in coronavirus disease 2019 (COVID-19)-positive subjects and compare the findings with COVID-19-negative subjects using the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Anosmia Reporting Tool.
SETTING: Tertiary referral center/COVID-19 pandemic hospital.
STUDY DESIGN: Comparative study.
SUBJECTS AND METHODS: After power analysis, 128 subjects were divided into 2 groups according to real-time polymerase chain reaction (RT-PCR) COVID-19 testing results. Subjects were called via telephone, and the AAO-HNS Anosmia Reporting Tool was used to collect responses.
RESULTS: The mean age of the study group was 38.63 +- 10.08 years. At the time of sampling, rhinorrhea was significantly high in the COVID-19-negative group, whereas those complaints described as "other" were significantly high in the COVID-19-positive group. There was a significant difference in the smell/taste impairment rates of the groups (n = 46% [71.9%] for the COVID-19-positive group vs n = 17 [26.6%] for the COVID-19-negative group, P = .001). For subjects with a smell impairment, anosmia rates did not differ between the groups. The rates of hyposmia and parosmia were significantly high in the COVID-19-positive group. For the subjects with taste impairment, ageusia rates did not differ between groups. The rate of hypogeusia and dysgeusia was significantly high in the COVID-19-positive group. Logistic regression analysis indicates that smell/taste impairment in COVID-19-positive subjects increases the odds ratio by 6.956 (95% CI, 3.16-15.29) times.
CONCLUSION: COVID-19-positive subjects are strongly associated with smell/taste impairment.

FIGURES

Table 3. Comparison of Smell/Taste Impairment Between Groups.

Characteristic	COVID-19 Positive (n = 64)	COVID-19 Negative (n = 64)	*P* Value
Did the patient have smell/taste impairment? No. (%)			
Absent	18 (28.1)	47 (73.4)	.001[a,b]
Present	46 (71.9)	17 (26.6)	
Definition of smell impairment, No. (%)[c]			
Anosmia	8 (12.5)	3 (4.7)	.115[a]
Hyposmia	33 (51.6)	10 (15.6)	.001[a,b]
Parosmia	11 (17.2)	2 (3.1)	.008[a,b]
Normal	21 (32.8)	51 (79.7)	.001[a,b]
VAS of subjects with hyposmia			
Minimum-maximum (median)	2-9 (5)	2-9 (7.5)	.049[d,e]
Mean ± SD	5.48 ± 2.18	7.00 ± 2.05	
Definition of taste impairment, No. (%)[c]			
Ageusia	8 (12.5)	3 (4.7)	.115[a]
Hypogeusia	36 (56.3)	10 (15.6)	.001[a,b]
Dysgeusia	16 (25.0)	4 (6.3)	.003[a,b]
Normal	18 (28.1)	49 (76.6)	.001[a,b]
VAS of subjects with hypogeusia			
Minimum-maximum (median)	2-9 (5)	3-9 (7.5)	.145[e]
Mean ± SD	5.61 ± 2.09	6.70 ± 2.26	
Any other symptoms before the development of smell/taste impairment? No. (%)			
Yes	32 (69.6)	15 (88.2)	.195[f]
No	14 (30.4)	2 (11.8)	
What symptoms did the patient have at the time of smell/taste impairment? No. (%)[c]			
Fever	11 (23.9)	7 (41.2)	.216[f]
Chills	14 (30.4)	2 (11.8)	.195[f]
Malaise	24 (52.2)	9 (52.9)	.957[a]
Cough	18 (39.1)	10 (58.8)	.163[a]
Headache	18 (39.1)	9 (52.9)	.325[a]
Nasal congestion	11 (23.9)	5 (29.4)	.747[f]
Rhinorrhea	6 (13.0)	5 (29.4)	.149[f]
Gastrointestinal	6 (13.0)	4 (23.5)	.438[f]
Pneumonia	9 (19.6)	5 (29.4)	.498[f]
Other	4 (8.7)	1 (5.9)	1.000[f]
Did the patient's condition worsen or improve after the smell/taste impairment was observed? No. (%)			
Worsen	19 (41.3)	4 (23.5)	.193[a]
Improved	27 (58.7)	13 (76.5)	
Did the smell/taste impairment resolve? No. (%)			
Yes	21 (45.7)	11 (64.7)	.179[a]
No	25 (54.3)	6 (353)	

Table 3. Comparison of Smell/Taste Impairment Between Groups.

DIAGNOSIS OF COVID-19 PNEUMONIA DESPITE MISSING DETECTION OF VIRAL NUCLEIC ACID AND INITIALLY INCONSPICUOUS RADIOLOGIC FINDINGS

Schiller M, Wydra S, Kerl HU, Kick W.. J Med Virol. 2020 Jun 10. doi: 10.1002/jmv.26153. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

This case report describes a 79-year-old male patient in Germany with a past medical history significant for hypertension, diabetes, and peripheral vascular disease, who presented with cough and fever. He was suspected to have pneumonia due to SARS-CoV-2 infection, but the patient's initial PCR testing was negative, while his labs showed no lymphocytopenia and a CT scan showed only minimal ground glass opacity in the left upper lung lobe. Repeat testing for anti-SARS-CoV-2 immunoglobulin 14 days later was able to identify SARS-CoV-2 infection, suggesting that the virus may be missed with initial serology, lab, and imaging studies, and repeat testing is warranted when there is strong clinical suspicion for COVID-19.

ABSTRACT

The diagnosis of coronavirus disease 2019 (COVID-19) is mainly based on a positive SARS-CoV-2 polymerase chain reaction (PCR) result. PCR samples are obtained from upper or lower respiratory tract specimens. However, the sensitivity of PCR is known to have some limitations. We report on a patient who was admitted to our hospital with dyspnea, fever, cough and history of contact to a SARS-CoV-2 infected relative. The initial chest computed tomography (CT) showed only minimal changes and SARS-CoV-2 PCR from a nasopharyngeal swab sample was negative. PCR results obtained from further nasopharyngeal swabs, qualified sputum samples, and from a lower respiratory tract specimen also remained negative. At day 13 after admission, a second chest CT showed radiological findings suspicious for viral pneumonia. Finally, serologic results showed high levels of IgG and IgA antibodies against the S1 domain of the SARS-CoV-2 spike protein and the patient was diagnosed with COVID-19 pneumonia.

GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH LEPTOMENINGEAL ENHANCEMENT FOLLOWING SARS-COV-2 INFECTION

Sancho-Saldaña A, Lambea-Gil Á, Liesa JLC, Caballo MRB, Garay MH, Celada DR, Serrano-Ponz M.. Clin Med (Lond). 2020 Jun 9:clinmed.2020-0213. doi: 10.7861/clinmed.2020-0213. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

A case study of a 56-year-old woman in Zaragoza, Spain with new-onset paraesthesia in both hands, later diagnosed as Guillain-Barre syndrome, fifteen days after complaining of fever, dry cough, and shortness of breath. Upon admission, her chest X-ray showed lobar pneumonia, she tested positive for COVID-19 and was started on azithromycin and hydroxychloroquine. Within the first 48 hours of admission her neurological symptoms progressively worsened with "lumbar pain and weakness of the proximal lower extremities, progressing to bilateral facial nerve palsy, oropharyngeal weakness and severe proximal tetraparesis with cervical flexion 2/5 on the MRC scale." At this time, SARS-CoV-2 was not found in her cerebrospinal fluid, however, MRI showed brainstem and cervical leptomeningeal enhancement (Figure 1). Intravenous immunoglobulin treatment was started (2g/kg over 5 days) and patient began recovering on day 7 of admission, though there were still significant nerve conduction delays on day 11. This case study may suggest the existence of a causal relationship between SARS-CoV-2 infection and Guillain-Barre syndrome but more cases are necessary to verify this relationship exists.

ABSTRACT

INTRODUCTION: Patients with coronavirus disease 2019 (COVID-19) typically present with respiratory symptoms, but little is known about the disease's potential neurological complications. We report a case of Guillain-Barre syndrome (GBS) following a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, in association with leptomeningeal enhancement.
CASE PRESENTATION: A 56-year-old woman presented with recent unsteadiness and paraesthesia in both hands. Fifteen days earlier, she complained of fever, dry cough and shortness of breath. Her chest X-ray showed a lobar consolidation and PCR was positive for SARS-CoV-2; she was admitted due to mild COVID-19 pneumonia.In the first 48 hours of hospitalisation, she started to experience lumbar pain and weakness of the proximal lower extremities, progressing to bilateral facial nerve palsy, oropharyngeal weakness and severe proximal tetraparesis with cervical flexion 2/5 on the MRC scale. A full spine magnetic resonance imaging (MRI) scan showed a brainstem and cervical leptomeningeal enhancement. Analysis of cerebrospinal fluid (CSF) revealed albumin-cytological dissociation. Microbiological studies on CSF, including SARS-CoV-2, were negative. Nerve conduction studies were consistent with demyelinating neuropathy. She was treated with intravenous immunoglobulin, with significant neurological improvement noted over the next 2 weeks.
CONCLUSION: Leptomeningeal enhancement is an atypical feature in GBS, but could be a marker of its association with SARS-CoV-2 infection.

FIGURES

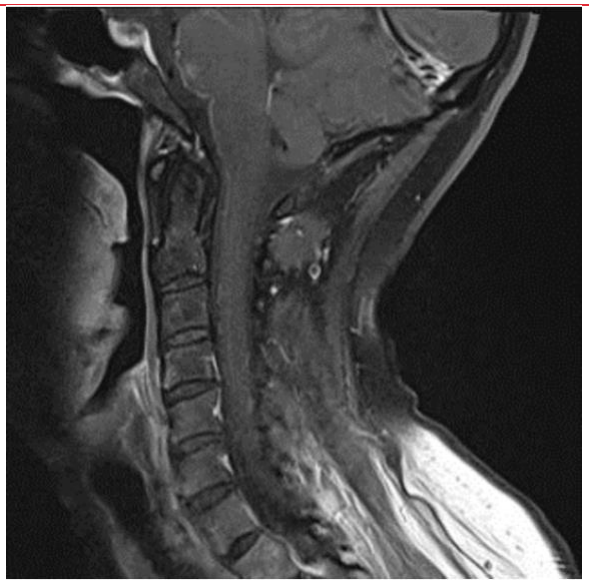


Figure 1. T1-weighted sagittal imaging after gadolinium, showing an anterior brainstem and cervical leptomeningeal enhancement.

PEDIATRICS

ANOSMIA AND AGEUSIA: NOT AN UNCOMMON PRESENTATION OF COVID-19 INFECTION IN CHILDREN AND ADOLESCENTS

Mak PQ, Chung KS, Wong JS, Shek CC, Kwan MY.. Pediatr Infect Dis J. 2020 Jun 8. doi: 10.1097/INF.0000000000002718. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

In this article, authors affiliated with Princess Margaret Hospital in Hong Kong, China present a case series of three patients (17, 15, and 14-year-old respectively, additional case details summarized below) returning to Hong Kong from study abroad trip in the UK. All three patients reported anosmia and ageusia without other respiratory symptoms and tested positive for COVID-19 by RT-PCR. In light of these findings, the authors recommend seeking healthcare professionals immediately on experiencing "new-onset anosmia/ ageusia" and performing SARS-CoV-2 testing for these patients to reduce further transmission.

SUMMARY

This article presents a series of three COVID-19 positive adolescents returning from UK to Hong Kong.

1. 17-year-old girl presented with anosmia and ageusia on the day of arrival. She had no other respiratory symptoms, prior history of allergic rhinitis, any medications, or contact with COVID-19 patients. Four days after symptom onset she tested positive for SARS-CoV-2 by RT-PCR and was admitted on the 8th day of illness where she had full recovery of anosmia/ageusia, mild chest discomfort and headache, and normal chest x-ray. The patient remained stable throughout the hospital stay with conservative management and Paracetomol as needed for pain until the chest discomfort and headache resolved.
2. 15-year-old girl who underwent compulsory home quarantine upon her return from the UK where she was exposed to a COVID-19 positive patient in the same inbound flight. RT-PCR returned positive for SARS-CoV-2 where she endorsed anosmia, ageusia, and mild rhinorrhea two days after saliva collection. She denied any history of fever, respiratory symptoms, allergic rhinitis or medication use. Physical examination and chest x-ray were normal. The patient received conservative management and on the eighth day of illness taste sensation started to return. Anosmia persisted until the thirteenth day.
3. 14-year-old boy who underwent compulsory home quarantine after his return from the UK where he denied any contact with COVID-19 patients. He was admitted due to positive RT-PCR for SARS-CoV-2. The patient also had transient anosmia with mild rhinorrhea three days before admission. He had a history of allergic rhinitis and no history of medication use. Physical examination and chest x-ray were normal. He was managed conservatively and vitals remained stable vitals without new symptoms.

ABSTRACT

Since the emergence of a cluster of viral pneumonia cases in Wuhan, Hubei Province, People's Republic of China, at the end of December 2019, caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2), a novel coronavirus also known as "coronavirus disease 2019 (COVID-19)," as of 7 April 2020, more than 1,214,466 cases of COVID-19 have been reported in more than 200 countries and territories, resulting in more than 67,767 deaths. The disease was recognized by World Health Organization (WHO) as a pandemic on 11 March 2020. Published reports of adult patients with COVID-19 infection described symptoms including fever, cough, fatigue, sputum production, headache, dyspnoea and diarrhoea. Children usually showed milder respiratory symptoms or were asymptomatic, while loss of taste or sensation of smell were seldom reported. In this paper, we report three cases of pediatric patients with COVID-19 infection who presented with anosmia and/or ageusia.

UNDERSTANDING THE PATHOLOGY

POTENTIAL ROLE FOR TISSUE FACTOR IN THE PATHOGENESIS OF HYPERCOAGULABILITY ASSOCIATED WITH IN COVID-19

Bautista-Vargas M, Bonilla-Abadía F, Cañas CA.. J Thromb Thrombolysis. 2020 Jun 9. doi: 10.1007/s11239-020-02172-x. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Researchers in Colombia review the pathologic mechanisms by which SARS-CoV-2 may cause hypercoagulability and increased risk of thrombosis. They argue that after binding and entering epithelial cells via angiotensin-converting enzyme 2 (ACE-2) receptors, ACE-2 receptor production is downregulated, levels of Angiotensin-2 (AT-2) increase, and immune dysfunction occurs, causing increased Tissue Factor (TF) expression inducing a hypercoagulable state (Figure 1).

ABSTRACT

In December 2019, a new and highly contagious infectious disease emerged in Wuhan, China. The etiologic agent was identified as a novel coronavirus, now known as Severe Acute Syndrome Coronavirus-2 (SARS-CoV-2). Recent research has revealed that virus entry takes place upon the union of the virus S surface protein with the type I transmembrane metallo-carboxypeptidase, angiotensin converting enzyme 2 (ACE-2) identified on epithelial cells of the host respiratory tract. Virus triggers the synthesis and release of pro-inflammatory cytokines, including IL-6 and TNF-alpha and also promotes downregulation of ACE-2, which promotes a concomitant increase in levels of angiotensin II (AT-II). Both TNF-alpha and AT-II have been implicated in promoting overexpression of tissue factor (TF) in platelets and macrophages. Additionally, the generation of antiphospholipid antibodies associated with COVID-19 may also promote an increase in TF. TF may be a critical mediator associated with the development of thrombotic phenomena in COVID-19, and should be a target for future study.

IN VITRO

CULTURE-BASED VIRUS ISOLATION TO EVALUATE POTENTIAL INFECTIVITY OF CLINICAL SPECIMENS TESTED FOR COVID-19

Huang CG, Lee KM, Hsiao MJ, Yang SL, Huang PN, Gong YN, Hsieh TH, Huang PW, Lin YJ, Liu YC, Tsao KC, Shih SR.. J Clin Microbiol. 2020 Jun 9:JCM.01068-20. doi: 10.1128/JCM.01068-20. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A study conducted in Taoyuan, Taiwan utilizing collected samples from January 25, 2020 through the end of March, 2020 found that among 60 nasopharyngeal (NP), oropharyngeal (OP), and sputum (SP) samples of real-time reverse transcription (RT)-PCR confirmed SARS-CoV-2 cases, the 23 samples which could be cultured had higher numbers of genomic copies, lower cycle thresholds (Ct), and a linear relationship to the number of structural and non-structural genes, indicating that culturability and infectiousness of SARS-CoV-2 may be determined by the integrity of the genome as well as the number of gene copies.

- This study evaluated genes encoding envelope (E), nucleocapsid (N), and RNA-dependent RNA polymerase (nsp12) proteins
- 23 samples were cultured, 12 from OP, 9 from NP, and 2 from SP samples
- Table 1 and Figure 2 demonstrate the Ct and genomic copies for each gene, culturable and non-culturable
- The lowest viral isolation copy number was 5.4 log10 genome copies/mL, lower than previous studies

ABSTRACT

Real-time reverse transcription (RT)-PCR is currently the most sensitive method to detect severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19). However, the correlation between detectable viral RNA and culturable virus in clinical specimens remains unclear. Here, we performed virus culture for 60 specimens that were confirmed to be positive for SARS-CoV-2 RNA by real-time RT-PCR. The virus could be successfully

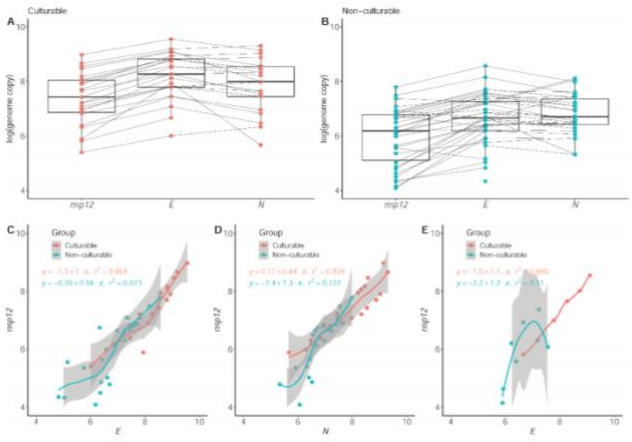
isolated from 12 throat and nine nasopharyngeal swabs, and two from sputum specimens. The lowest copy number required for virus isolation was determined to be 5.4, 6.0, and 5.7 log10 genome copies/mL sample for detecting the nsp12, E, and N gene, respectively. We further examined the correlation of genome copy number and virus isolation in different regions of the viral genome, demonstrating that culturable specimens are characterized by high copy numbers with a linear correlation observed between copy numbers of amplicons targeting structural and non-structural regions. Overall, these results indicate that in addition to the copy number, the integrity of the viral genome should be considered when evaluating the infectivity of clinical SARS-CoV-2 specimens.

FIGURES

TABLE 1. Cycle threshold (Ct) values and genome copy numbers (log_{10} copies/mL) of three SARS-CoV-2 genes from specimens with and without isolation of the virus

		Ct value			Log_{10} Genome copies/mL		
Gene	Sample (number)	Mean ± SEM	Highest	Lowest	Mean ± SEM	Highest	Lowest
Culturable (n = 23)							
nsp12	Total (23)	23.90 ± 0.78	31.47	17.75	7.37 ± 0.20	8.98	5.40
	OP (12)	24.21 ± 0.89	31.47	19.69	7.29 ± 0.23	8.47	5.40
	NP (9)	24.67 ± 1.37	29.87	18.94	7.17 ± 0.36	8.67	5.82
	SP (2)	18.57 ± 0.82	19.38	17.75	8.76 ± 0.21	8.98	8.55
E	Total (23)	22.39 ± 0.75	31.46	16.85	8.21 ± 0.18	9.55	6.01
	OP (12)	22.79 ± 1.01	31.46	18.85	8.11 ± 0.24	9.07	6.01
	NP (9)	22.89 ± 1.19	28.74	18.36	8.09 ± 0.28	9.19	6.67
	SP (2)	17.77 ± 0.92	18.68	16.85	9.33 ± 0.22	9.55	9.11
N	Total (21)	27.29 ± 0.77	35.20	22.14	7.87 ± 0.21	9.30	5.67
	OP (11)	27.21 ± 0.85	32.81	23.13	7.89 ± 0.24	9.03	6.33
	NP (8)	28.01 ± 1.61	35.20	22.14	7.67 ± 0.45	9.30	5.67
	SP (2)	24.8 ± 2.07	26.86	22.73	8.56 ± 0.58	9.14	7.99
Non-culturable (n = 37)							
nsp12	Total (34)	29.26 ± 0.69	36.52	22.32	5.98 ± 0.18	7.78	4.09
	OP (15)	30.32 ± 1.03	36.52	23.47	5.70 ± 0.27	7.49	4.09
	NP (15)	28.06 ± 0.91	35.60	23.92	6.29 ± 0.24	7.37	4.32
	SP (4)	29.74 ± 2.78	34.43	22.32	5.85 ± 0.72	7.78	4.63
E	Total (37)	28.92 ± 0.65	38.33	20.89	6.62 ± 0.16	8.57	4.34
	OP (17)	29.61 ± 0.97	38.33	22.61	6.46 ± 0.23	8.15	4.34
	NP (15)	28.22 ± 0.97	36.31	24.39	6.79 ± 0.24	7.72	4.83
	SP (5)	28.68 ± 2.13	32.93	20.89	6.68 ± 0.52	8.57	5.65
N	Total (31)	31.49 ± 0.59	42.47	26.39	6.70 ± 0.17	8.12	3.64
	OP (13)	32.81 ± 0.99	42.47	29.55	6.33 ± 0.28	7.54	3.64
	NP (13)	29.86 ± 0.62	33.34	26.39	7.15 ± 0.17	8.12	6.18
	SP (5)	32.27 ± 1.60	36.45	26.89	6.48 ± 0.45	7.98	5.32

454 Figure 2



455

456 **Figure 2.** Distributions of genome copies in SARS-CoV-2 non-structural (nsp12) and
457 structural (E and N) genes of (A) culturable and (B) non-culturable specimens.
458 Correlations of nsp12 genome copies with those of the (C) E and (D) N genes in
459 samples without a freeze-thaw cycle, and with (E) E gene copy numbers in
460 freeze-thawed samples, along with the respective regression equations and R square.

IN ANIMAL MODELS

ANTIBODY SIGNATURE INDUCED BY SARS-COV-2 SPIKE PROTEIN IMMUNOGENS IN RABBITS

Ravichandran S, Coyle EM, Klenow L, Tang J, Grubbs G, Liu S, Wang T, Golding H, Khurana S.. Sci Transl Med. 2020 Jun 8:eabc3539. doi: 10.1126/scitranslmed.abc3539. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

In this qualitative study, a group of researchers evaluated antibody responses of rabbits to various SARS-CoV-2 spike protein antigens including the receptor-binding domain (RBD), S1 domain, S2 domain, and S1+S2 domain. They found the RBD immunogen elicited a much higher antibody response with greater affinity compared to other antigens, and the S2 domain produced the weakest response (Figures 1-2). This suggests that vaccine development based on the RBD may be a promising area of further research.

ABSTRACT

Multiple vaccine candidates against SARS-CoV-2 based on viral spike protein are under development. However, there is limited information on the quality of antibody responses generated with these vaccine modalities. To better understand antibody responses induced by spike protein-based vaccines, we performed a qualitative study by immunizing rabbits with various SARS-CoV-2 spike protein antigens: S-ectodomain (S1+S2) (aa 16-1213), which lacks the cytoplasmic and transmembrane domains (CT-TM), the S1 domain (aa 16-685), the receptor-binding domain (RBD) (aa 319-541), and the S2 domain (aa 686-1213, lacking the RBD, as control). Resulting antibody quality and function were analyzed by enzyme linked immunosorbent assay (ELISA), receptor binding domain (RBD) competition assay, surface plasmon resonance (SPR) against different spike proteins in native conformation, and neutralization assays. All three antigens (S1+S2 ectodomain, S1 domain, and RBD), but not S2, generated strong neutralizing antibodies against SARS-CoV-2. Vaccination-induced antibody repertoire was analyzed by SARS-CoV-2 spike genome fragment phage display libraries (SARS-CoV-2 GFPDL), which identified immunodominant epitopes in the S1, S1-RBD, and S2 domains. Furthermore, these analyses demonstrated that the RBD immunogen elicited a higher antibody titer with 5-fold higher affinity antibodies to native spike antigens compared with other spike antigens; and antibody affinity correlated strongly with neutralization titers. These findings may help guide rational vaccine design and facilitate development and evaluation of effective therapeutics and vaccines against COVID-19 disease.

FIGURES

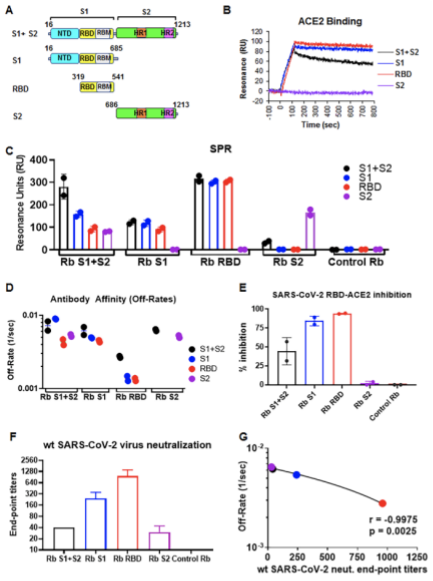


Fig. 1. SARS-CoV-2 spike binding and SARS-CoV-2 neutralization by serum antibodies generated following rabbit immunization with spike antigens.

A) Schematic representation of the SARS-CoV-2 spike protein and subdomains. Spike S1+S2 ectodomain (aa 16-1213) lacks the cytoplasmic and transmembrane domains (CT-TM), S1 domain (aa 16-685), RBD domain (aa 319-541), and S2 domain (aa 686-1213), all containing 6x His tag at C terminus, were commercially produced in either HEK 293 mammalian cells (S1 and RBD) or insect cells (S1+S2 ectodomain and S2 domain). The receptor-binding motif (RBM) encompasses residues 437-508. (B) Binding of purified proteins to human ACE2 (hACE2) proteins in SPR. Sensorgrams represent binding of purified spike proteins on low-density His-captured chips to 5 µg/mL human ACE2 protein. (C) SPR binding of antibodies from two rabbits each immunized twice with SARS-CoV-2 antigens to spike protein and domains from SARS-CoV-2 (S1+S2, black; S1, blue; RBD, red; and S2, purple). Total antibody binding is represented in maximum resonance units (RU) in this figure for 10-fold serum dilution. All SPR experiments were performed twice and the researchers performing the assay were blinded to sample identity. The variations for duplicate runs of SPR was <5%. The data shown are average values of two experimental runs. (D) Antibody off-rate constants were determined directly from the serum sample interaction with SARS-CoV-2 spike ectodomain (S1+S2), S1, S2, and RBD using SPR in the dissociation phase only for the sensorgrams with Max RU in the range of 20–100 RU. (E) RBD-hACE2 competition assay. Percent inhibition of hACE2 binding to RBD in presence of 1:50 dilutions of post-second vaccination rabbit serum was measured by SPR. (F) End-point virus neutralization titers for one rabbit from each group using wild type SARS-CoV-2 virus in a classical BSL3 neutralization assay based on CPE (Cytopathic effect) was performed as described in Materials and Methods. (G) Anti-spike ectodomain (S1+S2) binding antibody affinity as measured by antibody dissociation rates (off-rates) of post-vaccinated rabbit polyclonal antibodies correlated with the wt SARS-CoV-2 virus end-point neutralization titers ($r = -0.9975$, $p < 0.005$). Pearson two-tailed correlations are reported for the calculation of correlations between anti-S1+S2 antibody affinity and end-point titers for one rabbit per immunogen. The color scheme in panel G is the same as in panel D/F.

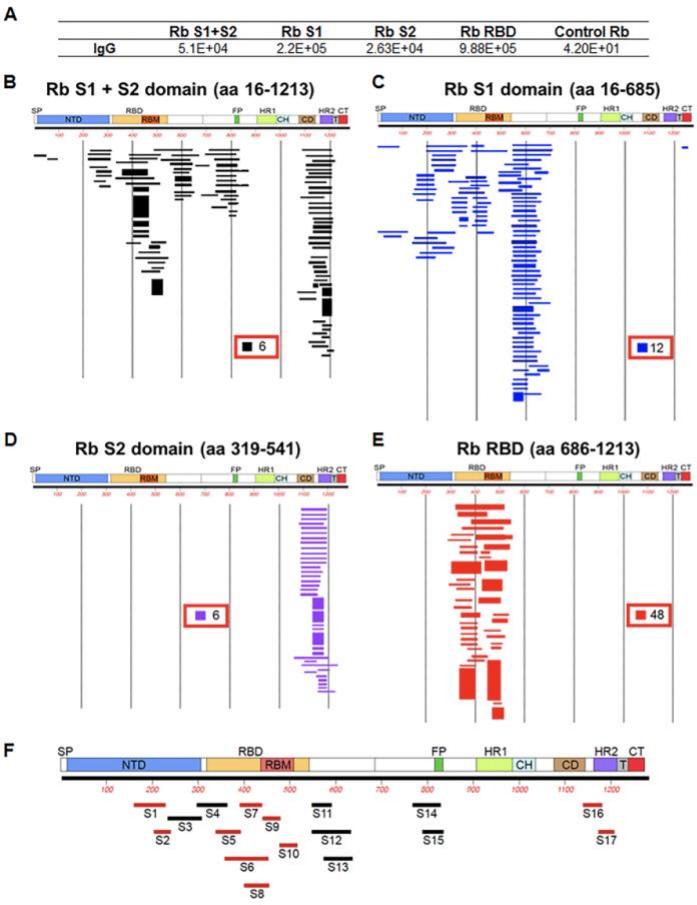


Fig. 2. Antibody epitope repertoires generated by different SARS-CoV-2 spike antigens. (A) Number of IgG-bound SARS-CoV-2 GFPDL phage clones using the post-second vaccination rabbit polyclonal sera. (B-E) Graphical distribution of representative clones with a frequency of ≥2, obtained after affinity selection, and their alignment to the spike protein of SARS-CoV-2 are shown for the four vaccine groups: S1+S2 ectodomain (B), S1 (C), S2 domain (D) and S1-receptor binding domain (RBD) (E). The thickness of each bar represents the frequency of repetitively isolated phage, with the scale shown enclosed in a red box in the respective alignments in each panel. (F) Elucidation of the antibody epitope profile in SARS-CoV-2 spike following rabbit vaccination. Antigenic sites within the SARS-CoV-2 spike protein recognized by serum antibodies following rabbit vaccination (based on data presented in Fig. 1B-E). The amino acid designation is based on the SARS-CoV-2 spike protein sequence (fig. S4). The antigenic regions/sites are depicted below the spike schematic and are color coded. Epitopes of each protein are numbered in a sequential fashion indicated in black. The antigenic epitopes are color coded unique to this study (red bars) or if they were predicted by algorithms (black bars) previously by Grifoni *et al*. (*19*). Sequence residues for each antigenic site and their sequence conservation with other human coronaviruses is shown in table S1. The GFPDL affinity selection data was performed twice. Similar numbers of phage clones and epitope repertoire were observed in both phage display analyses.

TRANSMISSION & PREVENTION

PREVENTION IN THE HOSPITAL

DISPOSITION OF PATIENTS WITH COVID-19 INFECTION WHOSE RESPIRATORY SPECIMENS REMAIN SARS-COV-2 PCR-POSITIVE

Mermel LA.. Infect Control Hosp Epidemiol. 2020 Jun 10:1-8. doi: 10.1017/ice.2020.286. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

An Infectious Disease specialist from Brown University argues that immunocompetent patients with COVID-19 can be removed from isolation precautions once they are 9 days beyond a) symptom onset or b) the first positive RT-PCR test in asymptomatic patients. By following this criteria, the author indicates that unnecessary PPE use, occupancy of single patient rooms, RT-PCT testing, social isolation, delays in patients re-entering their careers, and personnel redistribution in the fields of infection control and public health can be avoided.

SUMMARY

Dr. Leonard D. Mermel of the Warren Alpert Medical School of Brown University argues the following regarding decision-making for repeat RT-PCR testing and isolation precautions in patients recovering from COVID-19:

- Patients with COVID-19 who are not severely immunocompromised can be removed from isolation precautions after 9 days from symptom onset or 9 days from the first positive RT-PCR test in asymptomatic cases.
- If RT-PCR is positive on a respiratory specimen shortly after removal from isolation (i.e., within several months), immunocompetent patients should be allowed to have procedures and clinical services without the precautions used for individuals with active COVID-19 disease.
- RT-PCR should not be repeated for those who meet criteria for removal from isolation precautions unless it has been several months since symptom onset/initial asymptomatic presentation or the patient is severely immunocompromised.
- For severely immunocompromised patients, prolonged viral shedding is anticipated, so decisions regarding isolation precaution removal should be based on testing with a COVID-19 RT-PCR cycle threshold of greater than or equal to 34, which other studies suggest would not be associated with live virus in the respiratory system.

EMERGENCY MEDICINE

TREAT ALL COVID 19-POSITIVE PATIENTS, BUT DO NOT FORGET THOSE NEGATIVE WITH CHRONIC DISEASES

Mauro V, Lorenzo M, Paolo C, Sergio H.. Intern Emerg Med. 2020 Jun 9. doi: 10.1007/s11739-020-02395-z. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective analysis at San Giuseppe Hospital MultiMedica IRCCS in Milan found that emergency department (ED) admissions decreased by 53% in March and 63% in April 2020, especially in certain medical departments (trauma, cardiology, dermatology, etc.), when compared to data from December 2019 to February 2020 (Table 1). Based on this observation and currently available literature, the authors suggest there has been an overall reduction in patient care for non-COVID-19 conditions in Italy and recommend utilizing telemedicine to triage patients, ensure access to care, and avoid increased morbidity and mortality from chronic conditions.

ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) has distressed our working practice. Infectious disease specialists, pneumologists and intensivists were not enough to face the enormous amount of patients that needed hospital care; therefore, many doctors have been recruited from other medical specialties trying to take care of as many patients as possible. The 'call to duty' of such doctors for urgent COVID-19 cases, however, diverted the attention from the care of patients with chronic conditions, which might have been neglected or undervalued. In this extremely difficult time, the standard of care of chronic patients has been reduced and this might have determined an increased rate of complications secondary to undermanagement. Thousands of patients with acute and chronic non-COVID-19 conditions have not accessed specialist care in the last weeks in Italy. Moreover, even those patients who have had scheduled an outpatient visit did not attend it for fear of leaving their home or due to the inability to go. During the pandemic, there was a drastic reduction in the number of hospital admissions for any medical conditions different from COVID-19. Self-presentation to the emergency department (ED) has been discouraged and the patients' own fear of being infected by going to the hospital led to also a significant decrease in ED access. During the lockdown, in San Giuseppe Hospital MultiMedica IRCCS, Milan, the ED admissions dropped from the mean of 2361/month in December 2019-February 2020 to 1102 (- 53%) and 861 (- 63%) in March and April 2020, respectively. For all the above-mentioned reasons, it is possible that some clinical conditions will further progress with a significant increase in morbidity and mortality. To prevent this, it is essential that patients with chronic conditions should be at least monitored and managed with telephone or online health consultation, identifying those who need urgent access to care, prioritizing outpatient visits based on disease severity. Patients with mild conditions could be managed outside the hospital by implementing telemedicine and creating networks of general practitioners who can consult with in-hospital specialists.

FIGURES

	December 2019	January 2020	February 2020	March 2020	April 2020
ED access, no. (%)					
Cardiology	88 (4)	100 (4)	97 (4.2)	28 (2.6)	22 (2.6)
Dermatology	114 (5)	148 (6)	150 (6.4)	36 (3.3)	5 (0.6)
Gastroenterology/hepatology	298 (13)	300 (12)	314 (13.5)	124 (11.2)	81 (9.4)
Gynaecology/obstetrics	306 (13.5)	293 (11.8)	261 (11)	128 (11.6)	151 (17.5)
Musculoskeletal	325 (14.4)	256 (10.3)	114 (5)	24 (2.2)	23 (2.7)
Neumology	283 (12)	215 (8.7)	227 (9.8)	98 (8.9)	71 (8.2)
Other	308 (13.5)	461 (18.5)	553 (24)	184 (16.7)	197 (22.9)
Respiratory	196 (8.6)	297 (12)	321 (14)	397 (36)	249 (29)
Traumatology	264 (12)	325 (13)	190 (8.1)	33 (3)	22 (2.5)
Urology	97 (4)	91 (3.7)	91 (4)	50 (4.5)	40 (4.6)
Total	2279	2486	2318	1102	861
Symptoms at triage, no. (%)*					
Fever	48 (2.1)	86 (3.4)	105 (4.5)	115 (10.4)	92 (10.6)
Cough	60 (2.6)	89 (3.6)	78 (3.3)	107 (9.7)	18 (2)
Dyspnoea	98 (4.3)	52 (2)	138 (6)	118 (10.7)	110 (12.8)
Chest pain	66 (2.9)	67 (2.7)	67 (2.9)	18 (1,6)	12 (1,4)
Severity code at triage, no. (%)					
Red	31 (1.4)	38 (1.5)	36 (1.6)	43 (3.9)	23 (2.7)
Yellow	359 (15.7)	412 (17)	365 (15.7)	250 (22.7)	129 (15)
Green	1245 (54.6)	1431 (57.5)	1174 (50.7)	666 (60.4)	542 (63)
White	644 (28.3)	605 (24)	743 (32)	143 (13)	167 (19.3)
Men, no. (%)	948 (41.6)	1019 (41)	987 (42.6)	513 (46.5)	328 (38)
Median age, years	52	53	51	58	57
Death in ED, no. (%)	7 (0.3)	12 (0.5)	16 (0.7)	48 (4.3%)	28 (3.2)
Hospitalization rate, no. (%)	294 (13)	302 (12.1)	305 (13.1)	290 (26.3)	241 (28)

*As the predominant presentation symptom

Table 1. Variations in the emergency department (ED) admittances from March/April 2020 compared to December 2019–February 2020.

MEDICAL SUBSPECIALTIES

GASTROENTEROLOGY

"IT AIN'T OVER … . TILL IT'S OVER!" RISK-MITIGATION STRATEGIES FOR PATIENTS WITH GASTROINTESTINAL DISEASES IN THE AFTERMATH OF THE COVID-19 PANDEMIC

Holtmann G, Quigley EM, Shah A, Camilleri M, Tan VP, Gwee KA, Sugano K, Sollano JD, Fock KM, Ghoshal UC, Chen M, Dignass A, Cohen H.. J Gastroenterol Hepatol. 2020 Jun 8. doi: 10.1111/jgh.15133. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

An international group of authors describe a triphasic response to COVID-19 and provide the following phase-specific recommendations to minimize adverse effects of delaying care for gastrointestinal diseases during the earlier part of the pandemic (Figures 1-3).

SUMMARY

Acute phase:

- Pause all non-essential services including clinical surveillance, non-emergent follow-up, surgical and elective endoscopic procedures.
- Sustain urgent and emergency services.
- Prioritize safety of staff in the setting of scarce but critical resources, such as PPE.

Adaptation and Consolidation phases:

- Treat emergent gastrointestinal cases based on guidelines and recommendations for management in the setting of the pandemic.
- Begin developing strategies to manage clinical practice in a variety of scenarios for COVID-19 spread.
- Increase allocation of community resources to assist patients before their conditions become urgent.
- Move all possible services to technology-enabled encounters.
- Redesign physical spaces where in-person care is required to optimize safety.
- Develop robust quality assurance measures to optimize the care offered to patients.

ABSTRACT

The available COVID-19 literature has focussed on specific disease manifestations, infection control, and delivery or prioritisation of services for specific patient groups in the setting of the acute COVID-19 pandemic. Local health systems aim to contain the COVID-19 pandemic and hospitals and health care providers rush to provide the capacity for a surge of COVID-19 patients. However, the short, medium- and long-term outcomes of patients with gastrointestinal (GI) diseases without COVID-19 will be affected by the ability to develop locally adapted strategies to meet their service needs in the COVID-19 setting. To mitigate risks for patients with GI diseases, it is useful to differentiate three phases: 1) the acute phase, 2) the adaptation phase and 3) the consolidation phase. During the acute phase, service delivery for patients with GI disease will be curtailed to meet competing health care needs of COVID-19 patients. During the adaptation phase, GI-services are calibrated towards a 'new normal' and the consolidation phase is characterised by rapid introduction and ongoing refinement of services. Proactive planning with engagement of relevant stakeholders including consumer representatives is required to be prepared for a variety of scenarios that are dictated by thus far undefined long-term economic and societal impacts of the pandemic. Since substantial changes -to the delivery of services are likely to occur, it is important that these changes are embedded into quality and research frameworks to ensure that data are generated that support evidence-based decision-making during the adaptation and consolidation phases.

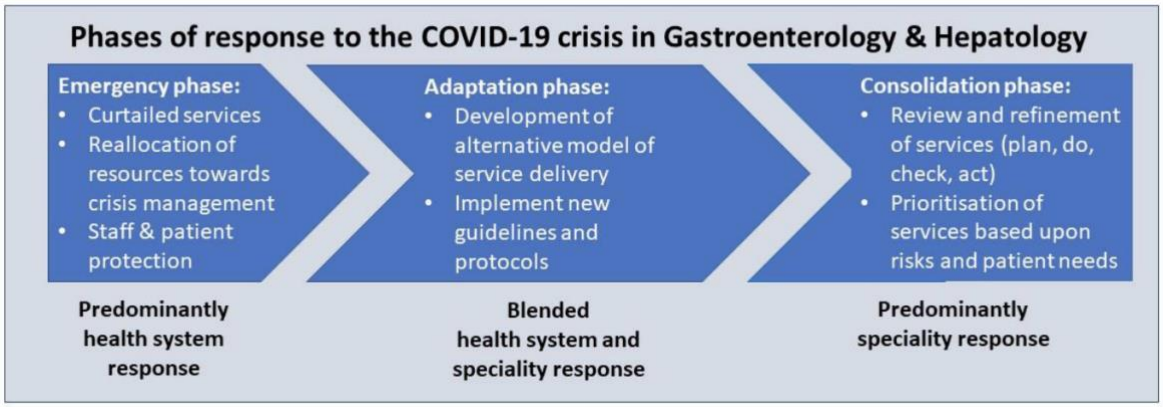


Figure 1: Phases of the response to the COVID-19 crisis. The initial emergency phase is characterized by reallocation of resources to augment capacity in the field of emergency and intensive care. As a consequence elective services in other areas including gastroenterology are curtailed. During the adaption phase alternative models of care (mainly for consulting services are developed and implemented). At the same time national and international guidelines will emerge that guide service delivery for the emergency phase. The Consolidation phase is characterized by review and refinement of the services. Emphasis will be given to prioritization of services. It is critical that the consolidation phase is accompanied by appropriate quality assurance and research activities to generate the evidence that is required to guide decision making in relation to service development.

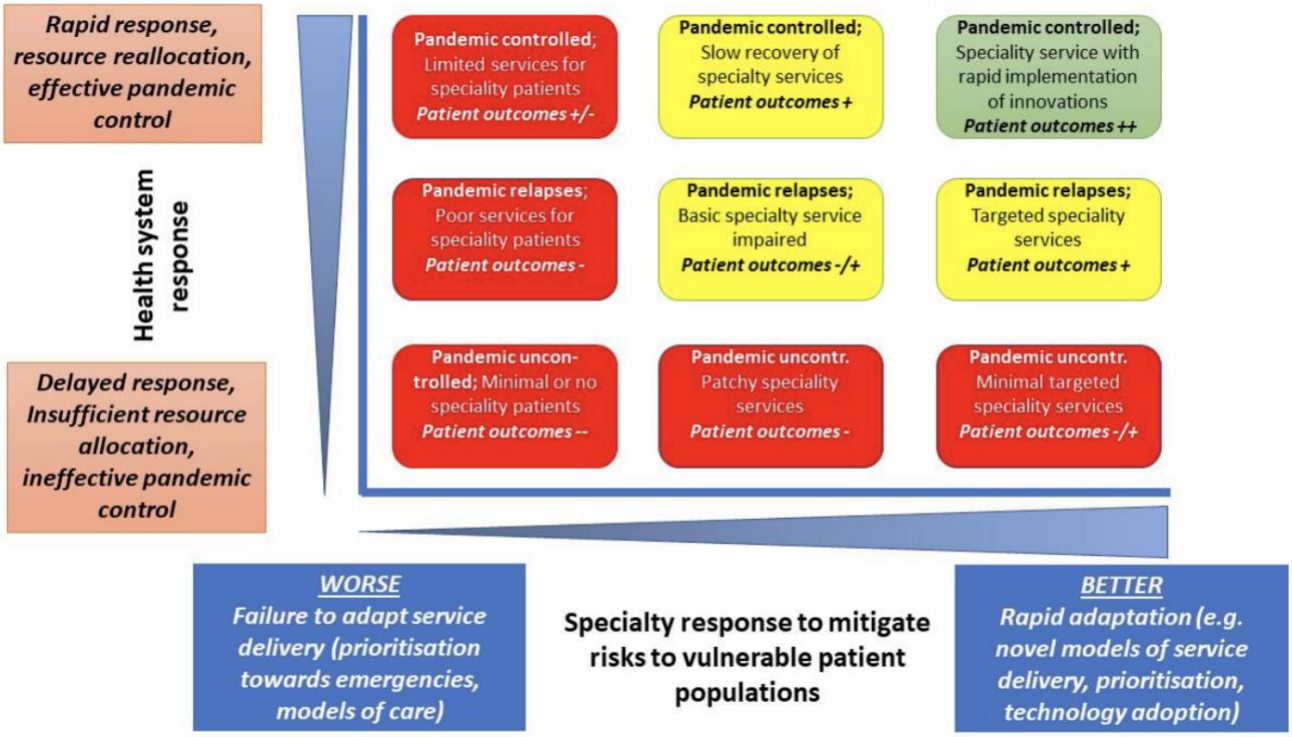
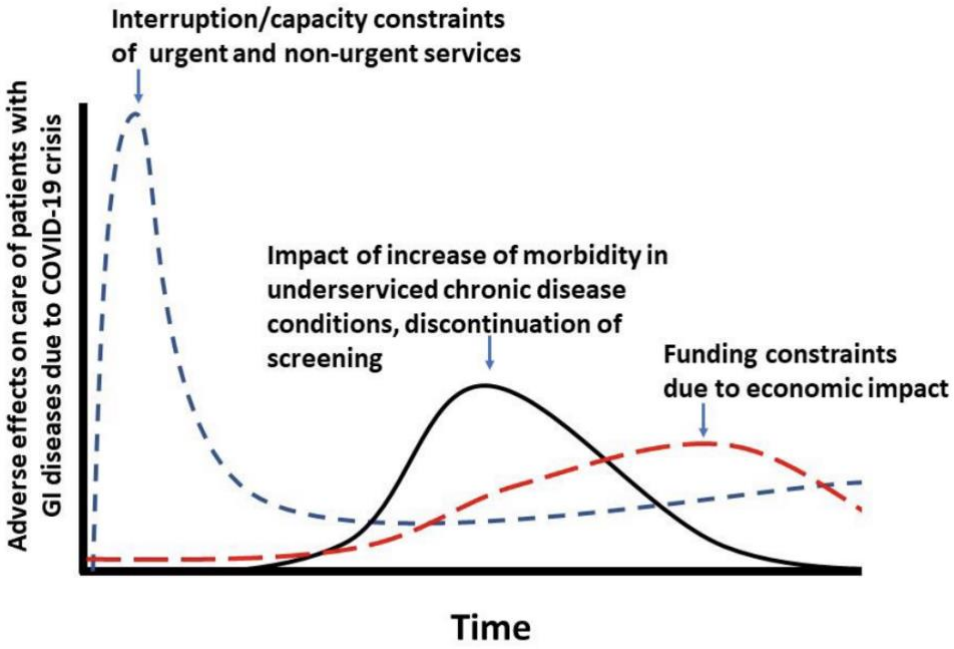


Figure 2: Interrelation of the health system response and the responses of the specialty Gastroenterology with regard to system performance in relation to patient outcomes. The health system response is aimed towards rapid containment of the pandemic (while resources are made available for the treatment of COVID-19 patients). In the changed environment of the COVID-19 crisis, specialties such as Gastroenterology are required to adapt and innovate service models and prioritize service allocation to meet patient needs and mitigate risks. If specialties fail (or are unable) to develop mitigation strategies excess morbidity and mortality will be the consequence.



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GERIATRICS

CREDIBILITY OF SELF-REPORTED HEALTH PARAMETERS IN ELDERLY POPULATION

Amster R, Reychav I, McHaney R, Zhu L, Azuri J.. Prim Health Care Res Dev. 2020 Jun 10;21:e20. doi: 10.1017/S1463423620000201.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Israeli investigators sent a Health Belief Model and self-reporting questionnaire to 90 residents (mean age 84.9 years) across three nursing home facilities to determine the accuracy of self-reporting of height, weight, and blood pressure values. The results show that the difference between true BMI values and self-reported values varied by an average of 1.43 which would have a minimal impact on the physician's clinical evaluation of a patient (Table 2). Additionally, the positive predictive value for self-reporting normal blood pressures was 77.78% and 78.57% for abnormal blood pressures (Table 3). In the COVID-19 era where minimizing physical encounters remains necessary, the authors suggest that elderly self-reporting on health measures may potentially become an essential telehealth tool.

ABSTRACT

AIM: Examining the credibility of self-reported height, weight, and blood pressure by the elderly population using a tablet in a retirement residence, and examining the influence of health beliefs on the self-reporting credibility.
BACKGROUND: Obesity is a major problem with rising prevalence in the western world. Hypertension is also a significant risk factor for cardiovascular diseases. Self-report, remotely from the clinic, becomes even more essential when patients are encouraged to avoid visiting the clinic as during the COVID-19 pandemic. Self-reporting of height and weight is suspected of leading to underestimation of obesity prevalence in the population; however, it has not been well studied in the elderly population. The Health Belief Model tries to predict and explain decision making of patients based on the patient's health beliefs.

METHODS: Residents of a retirement home network filled a questionnaire about their health beliefs regarding hypertension and obesity and self-reported their height, weight, and blood pressure. Blood pressure, height, and weight were then measured and compared to the patients' self-reporting.
FINDINGS: Ninety residents, aged 84.90 +- 5.88, filled the questionnaire. From a clinical perspective, the overall gap between the measured and the self-reported BMI (M = 1.43, SD = 2.72), which represents an absolute gap of 0.74 kilograms and 2.95 centimeters, is expected to have only a mild influence on the physician's clinical evaluation of the patient's medical condition. This can allow the physician to estimate their patient's BMI status before the medical consultation and physical examination upon the patient's self-reporting. Patients' dichotomous (normal/abnormal) self-report of their blood pressure condition was relatively credible: positive predictive value (PPV) of 77.78% for normal blood pressure (BP) and 78.57% for abnormal BP. The relatively high PPV of BP self-reporting demonstrates an option for the physician to recognize patients at risk. Regression analysis found no correlation between the anthropometric parameters and the Health Belief Model.

FIGURES

Table 2. Self-report, actual measurements and gap of height, weight and body mass index

	N	Mean	SD	Min	Q1	Median	Q3	Max
Self-reported weight	89	68.07	12.99	45.00	60.00	66.00	76.00	100.00
Self-reported height	89	158.82	8.61	140.00	152.00	158.00	165.00	180.00
Self-reported BMI	89	26.92	4.30	17.26	23.53	26.64	29.64	39.03
Measured weight	89	68.81	13.04	46.20	59.10	67.10	77.80	100.00
Measured height	89	155.87	8.10	132.00	150.00	156.00	160.00	179.00
Measured BMI	89	28.35	5.15	18.05	24.65	27.82	31.54	47.41
Weight gap	89	0.74	3.98	−10.20	−0.40	1.00	2.50	20.00
Height gap	89	−2.95	5.64	−21.00	−6.00	−2.00	0.00	15.00
BMI gap	89	1.43	2.72	−6.68	0.17	1.28	2.65	10.67

BMI – Body Mass Index.
Self-reported BMI refers to the calculation of the self-reported measurements.
We excluded one self-reported height of a 162 cm woman who said she doesn't know her height, but because it was mandatory to self-report she wrote she is 115 cm.

Table 2. Self-report, actual measurements and gap of height, weight and body mass index

Table 3. The relationship between self-reported blood pressure normality to actual blood pressure measurements

	Self-reported blood pressure	*N*	Missing	Mean	*SD*	Min	Q1	Median	Q3	Max
Measured SBP	Normal	72	0	146.93	24.59	104	126.5	146.0	159.5	215
	Abnormal	14	0	168.71	35.80	130	145.0	157.5	181.0	243
	I don't know	4	0	145.50	15.67	127	132.5	148.0	158.5	159
Measured DBP	Normal	72	0	80.32	12.85	57	70.0	79.0	87.5	122
	Abnormal	14	0	86.29	12.47	72	78.0	82.0	88.0	118
	I don't know	4	0	78.25	14.06	66	67.0	75.5	89.5	96
Self-reported SBP	Normal	36	36	133.39	14.23	115	120.0	130.0	140.0	170
	Abnormal	5	9	146.00	22.75	110	140.0	150.0	165.0	165
	I don't know	0	4	non	NA	NA	NA	NA	NA	NA
Self-reported DBP	Normal	36	36	72.14	6.80	60	66.5	70.0	78.0	90
	Abnormal	5	9	81.60	11.84	70	73.0	80.0	85.0	100
	I don't know	0	4	non	NA	NA	NA	NA	NA	NA

SBM – Systolic Blood Pressure; DBP-Diastolic Blood Pressure.

Table 3. The relationship between self-reported blood pressure normality to actual blood pressure measurements

THE JANUS KINASE 1/2 INHIBITOR RUXOLITINIB IN COVID-19 WITH SEVERE SYSTEMIC HYPERINFLAMMATION

La Rosée F, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, Fellhauer M, Henkes M, Kumle B, Russo SG, La Rosée P.. Leukemia. 2020 Jun 9. doi: 10.1038/s41375-020-0891-0. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A retrospective case series conducted at a large hospital in Germany examined 105 patients with COVID-19 between 30 March 2020 and 15 April 2020. Fourteen of these patients were determined to have severe hyperinflammation associated with COVID-19 by a COVID-19 Inflammation Score (CIS) and were subsequently treated with the Janus kinase (JAK) 1/2 inhibitor drug ruxolitinib. While treatment regimen involving ruxolitinib was tailored to each individual patient (Table 3), 12 patients demonstrated statistically significant reduction in CIS on the seventh day (Figure 2), suggesting that ruxolitinib may be efficacious in patients with hyperinflammation in the setting of COVID-19. A phase II clinical trial for this drug is underway.

ABSTRACT

A subgroup of patients with severe COVID-19 suffers from progression to acute respiratory distress syndrome and multiorgan failure. These patients present with progressive hyperinflammation governed by proinflammatory cytokines. An interdisciplinary COVID-19 work flow was established to detect patients with imminent or full blown hyperinflammation. Using a newly developed COVID-19 Inflammation Score (CIS), patients were prospectively stratified for targeted inhibition of cytokine signalling by the Janus Kinase 1/2 inhibitor ruxolitinib (Rux). Patients were treated with efficacy/toxicity guided step up dosing up to 14 days. Retrospective analysis of CIS reduction and clinical outcome was performed. Out of 105 patients treated between March 30th and April 15th, 2020, 14 patients with a CIS >= 10 out of 16 points received Rux over a median of 9 days with a median cumulative dose of 135 mg. A total of 12/14 patients achieved significant reduction of CIS by >=25% on day 7 with sustained clinical improvement in 11/14 patients without short term red flag warnings of Rux-induced toxicity. Rux treatment for COVID-19 in patients with hyperinflammation is shown to be safe with signals of efficacy in this pilot case series for CRS-intervention to prevent or overcome multiorgan failure. A multicenter phase-II clinical trial has been initiated (NCT04338958).

FIGURES

	Total ($N = 14$)
Treatment since hospitalization, no. (%)	
Invasive ventilation	3 (21)
Non-invasive ventilation	13 (93)
Renal-replacement therapy	1 (7)
Antibiotic agent	12 (86)
Hydroxychloroquine	13 (93)
Vasopressors	4 (29)
Tocilizumab	2 (14)
Glucocorticoid therapy	11 (79)
Days of glucocorticoid therapy, median (IQR)	3 (3–15)
Ruxolitinib dosage and therapy length	
Cumulative dosage, median (IQR)—mg	135 (52.5–285)
Length of treatment, median (IQR)—days	9 (5–17)
Days from illness onset to Ruxolitinib treatment, median (IQR)	15.5 (5–24)
Days from illness onset to hospitalization, median (IQR)	9 (4–19)[a]

[a]One patient suffered from in hospital SARS-CoV-2 transmission.

Table 3: Patient clinical assessment and treatments received.

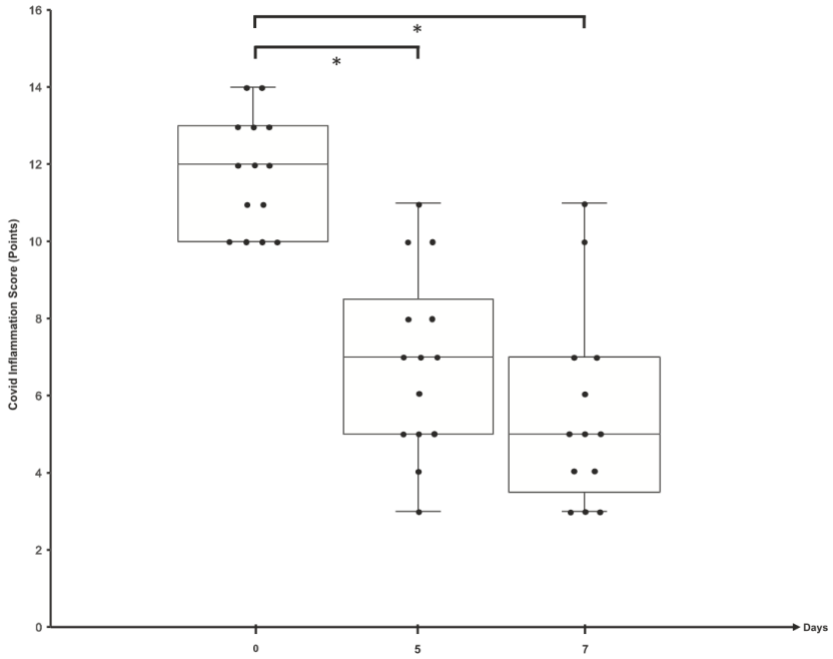
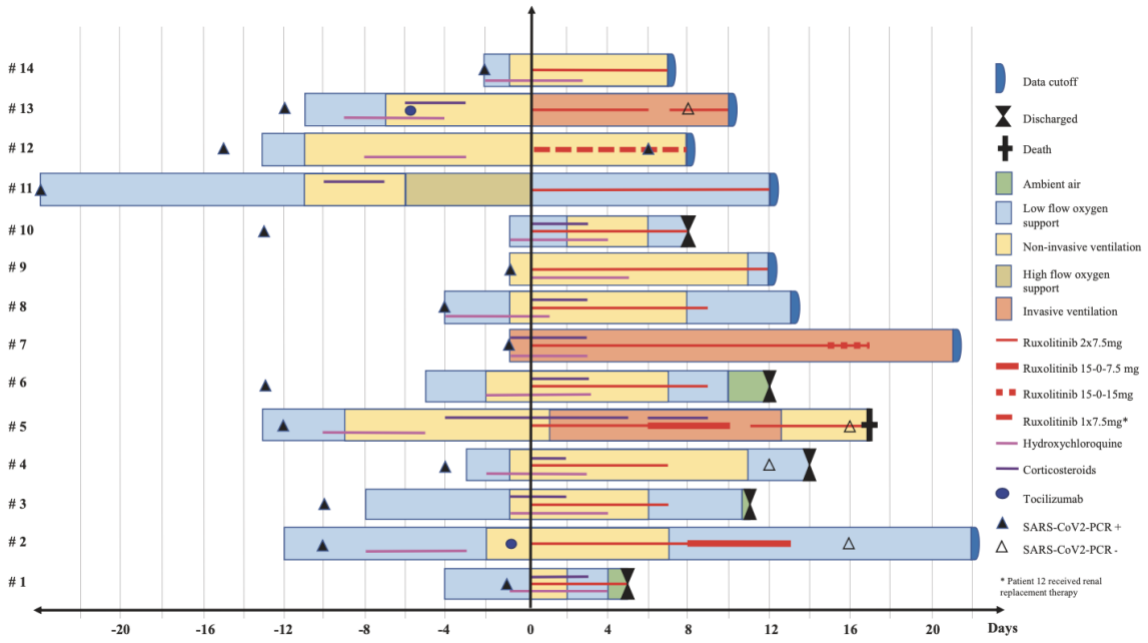


Figure 2: COVID inflammation score at baseline, day 5 and day 7 after Rux [ruxolitinib] treatment initiation. Dots represent individual patient results. Median and IQR are provided by box plots. *p < 0.01.



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HEPARIN AS A THERAPY FOR COVID-19: CURRENT EVIDENCE AND FUTURE POSSIBILITIES

Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP.. Am J Physiol Lung Cell Mol Physiol. 2020 Jun 10. doi: 10.1152/ajplung.00199.2020. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

This literature review from researchers in Colorado discusses the anticoagulant, anti-inflammatory, and antiviral effects of unfractionated and low molecular weight heparin (Figure 1, Figure 3). Additionally, it covers potential harms in COVID-19

patients, as well as compares the coagulopathic differences between sepsis and COVID-19 (Figure 2). The authors highlight how previous randomized clinical trials (RCT), cohort, and in-vitro studies have reported conflicting findings regarding the clinical effectiveness and safety (bleeding risk) with prophylactic and therapeutic Heparin in COVID-19 patients. Despite these concerns, they call for urgent evaluation of its therapeutic possibilities via RCTs as this drug has shown some promise in battling the effects of COVID-19.

ABSTRACT

Coronavirus Disease 2019 (COVID-19), the clinical syndrome associated with infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has impacted nearly every country in the world. Despite an unprecedented focus of scientific investigation, there is a paucity of evidence-based pharmacotherapies against this disease. Due to this lack of data-driven treatment strategies, broad variations in practice patterns have emerged. Observed hypercoagulability in COVID-19 patients has created debate within the critical care community on the therapeutic utility of heparin. We seek to provide an overview of the data supporting the therapeutic use of heparin, both unfractionated and low molecular weight, as an anticoagulant for the treatment of SARS-CoV-2 infection. Additionally, we review preclinical evidence establishing biological plausibility for heparin and synthetic heparin-like drugs as therapies for COVID-19 through anti-viral and anti-inflammatory effects. Finally, we discuss known adverse effects and theoretical off-target effects that may temper enthusiasm for the adoption of heparin as a therapy in COVID-19 without confirmatory prospective randomized controlled trials. Despite previous failures of anticoagulants in critical illness, plausibility of heparin for COVID-19 is sufficiently robust to justify urgent randomized controlled trials to determine the safety and effectiveness of this therapy.

FIGURES

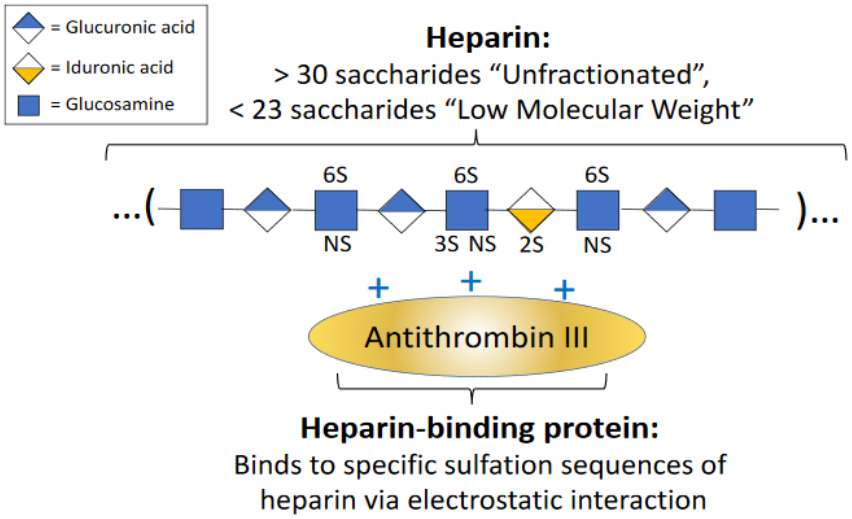


Figure 1. Structure and Function of Heparin. Heparins are a heterogeneous mix of heparan sulfate (HS) glycosaminoglycans. Each HS strand is composed of repeating disaccharide units of N-acetylglucosamine (GlcNAc) and Glucoronic Acid (GlcA) or Iduronic Acid (IdoA). GlcNAc can be sulfated at three distinct sites (-6S, -NS, and -3S) and IdoA at one (-2S). Unfractionated heparin is composed of HS chains that are greater than 30 saccharides in length whereas low molecular weight heparin constituent HS chains are 22 saccharides or less (3). The charge distribution of heparin imparted by the presence of the precise pentasaccharide sequence shown allows for the binding of heparin to serine protease inhibitor antithrombin-III (AT3), conferring its primary anticoagulant effect. Innumerable other sulfation sequences are found in heparin preparations, which leads to binding and biologically relevant activity modulation of many other proteins. Abbreviations: GlcNAc = N-acetylglucosamine, GlcA = Glucoronic Acid, IdoA = Iduronic Acid, AT3 = Antithrombin-III

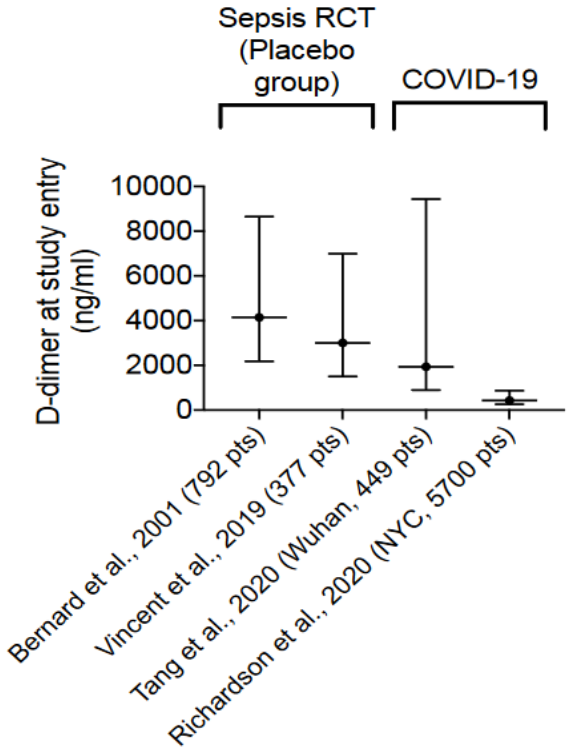
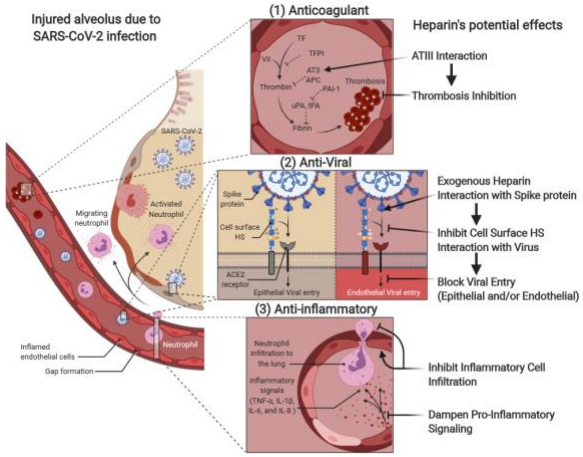


Figure 2. Coagulopathy in Sepsis compared to COVID-19. Circulating levels of d-dimer, a marker of coagulopathy, have been found to be significantly and similarly elevated in sepsis and COVID-19. This panel represents median and inter-quartile ranges. Abbreviations: RCT = Randomized Controlled Trial, NYC = New York City



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CHARACTERISTICS OF REGISTERED CLINICAL TRIALS ASSESSING TREATMENTS FOR COVID-19: A CROSS-SECTIONAL ANALYSIS

Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC.. BMJ Open. 2020 Jun 9;10(6):e039978. doi: 10.1136/bmjopen-2020-039978.

Level of Evidence: Other - Review / Literature Review

BLUF

A scoping review of clinical trials for treatments of COVID-19 registered with the WHO or clinicaltrials.gov, completed on 26 March 2020 by epidemiologists at Johns Hopkins University (United States), found:

1. Two hundred and one ongoing clinical trials, of which 75.7% (152) were randomized trials

2. A total 92 different experimental agents tested as either single or combination therapies
3. Within the randomized trials group, only 36.2% (55) were at least single-blinded studies (Figure 2)
   Thus, while there are a wide variety of drugs undergoing testing, results of most studies are expected to only provided preliminary information on efficacy.

ABSTRACT

OBJECTIVES: The coronavirus disease 2019 (COVID-19) pandemic has prompted many initiatives to identify safe and efficacious treatments, yet little is known regarding where early efforts have focused. We aimed to characterise registered clinical trials assessing drugs or plasma treatments for COVID-19.
DESIGN, SETTING AND PARTICIPANTS: Cross-sectional analysis of clinical trials for the treatment of COVID-19 that were registered in the USA or in countries contributing to the WHO's International Clinical Trials Registry Platform. Relevant trial entries of drugs or plasma were downloaded on 26 March 2020, deduplicated, verified with reviews of major medical journals and WHO websites and independently analysed by two reviewers.
MAIN OUTCOMES: Trial intervention, sponsorship, critical design elements and specified outcomes
RESULTS: Overall, 201 clinical trials were registered for testing the therapeutic benefits of 92 drugs or plasma, including 64 in monotherapy and 28 different combinations. Only eight (8.7%) products or combinations involved new molecular entities. The other test therapies had a wide range of prior medical uses, including as antivirals, antimalarials, immunosuppressants and oncology treatments. In 152 trials (75.7%), patients were randomised to treatment or comparator, including 55 trials with some form of blinding and 97 open-label studies. The 49 (24.4%) of trials without a randomised design included 29 single armed studies and 20 trials with some comparison group. Most trial designs featured multiple endpoints. Clinical endpoints were identified in 134 (66.7%) of trials and included COVID-19 symptoms, death, recovery, required intensive care and hospital discharge. Clinical scales were being used in 33 (16.4%) trials, most often measures of oxygenation and critical illness. Surrogate endpoints or biomarkers were studied in 88 (42.3%) of trials, primarily assays of viral load. Although the trials were initiated in more than 17 countries or regions, 100 (49.8%) were registered in China and 78 (37.8%) in the USA. Registered trials increased rapidly, with the number of registered trials doubling from 1 March to 26 March 2020.
CONCLUSIONS: While accelerating morbidity and mortality from the COVID-19 pandemic has been paralleled by early and rapid clinical investigation, many trials lack features to optimise their scientific value. Global coordination and increased funding of high-quality research may help to maximise scientific progress in rapidly discovering safe and effective treatments.

FIGURES

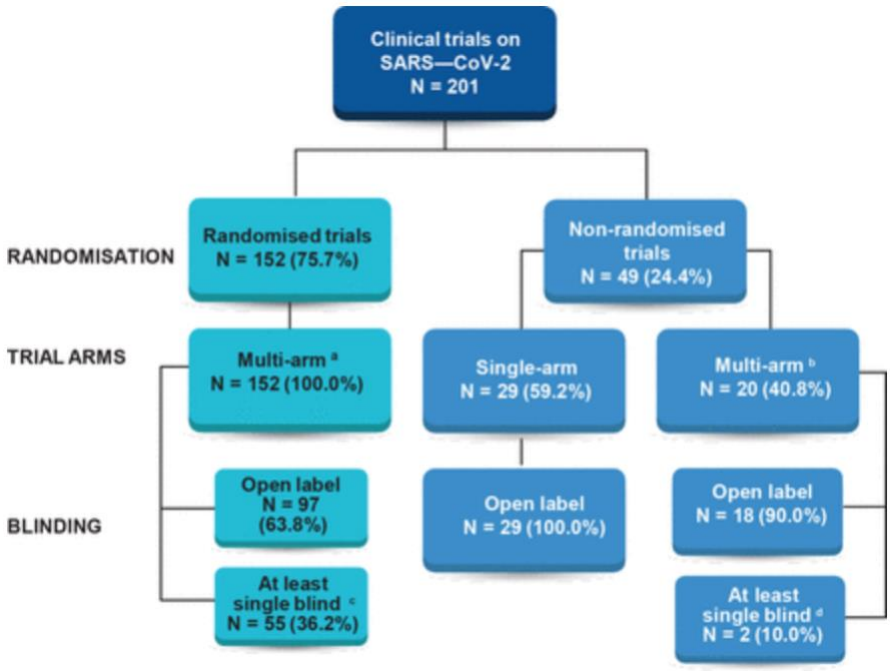

Figure 2: Study designs of registered clinical trials of products for SARS-CoV-2 infection (n=201 trials). a Includes 147 parallel, 1 platform and 4 sequential trials; b includes 1 crossover, 1 factorial, 17 parallel and 1 historical control arm trials; c includes 14 single, 5 at least single, 16 double, 2 triple and 18 quadruple blinded trials; d includes two double-blind trials. Sources: WHO and ClinicalTrials.gov (as of 26 March 2020). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

RESOURCES

INFOGRAPHIC. COOLING STRATEGIES TO ATTENUATE PPE-INDUCED HEAT STRAIN DURING THE COVID-19 PANDEMIC

Bongers CC, de Korte JQ, Catoire M, Greefhorst J, Hopman MTE, Kingma B, Eijsvogels TMH.. Br J Sports Med. 2020 Jun 10:bjsports-2020-102528. doi: 10.1136/bjsports-2020-102528. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

This infographic (Figure 1) illustrates the problem of increased heat strain and thermoregulatory challenges for healthcare workers as a result of prolonged personal protective equipment (PPE) wear. It provides information on and advocates for the benefit of cooling strategies before, during, and after COVID-19 work activities in order to decrease PPE-induced heat stress.

FIGURES

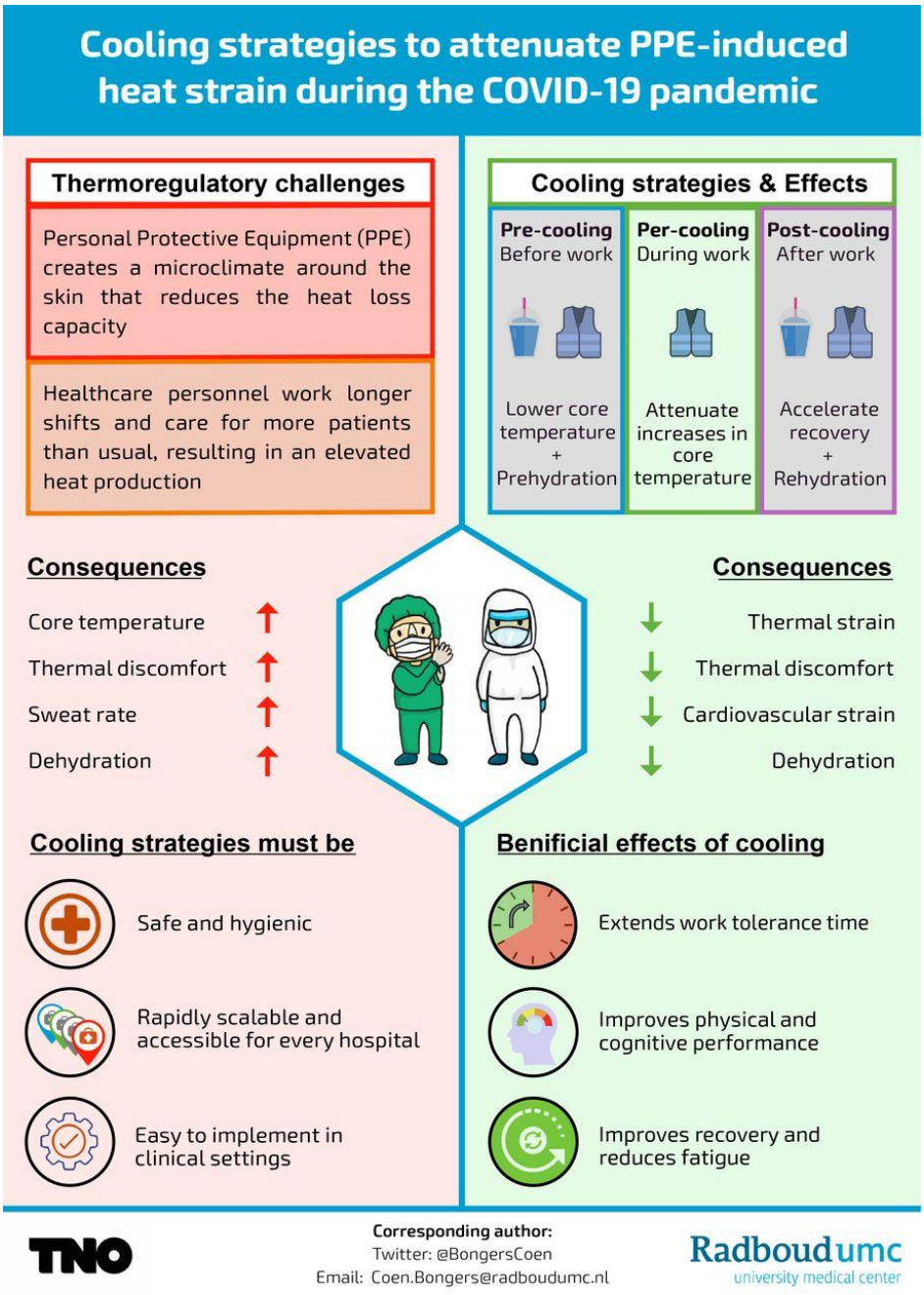

Figure 1. Infographic.

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