The Daily COVID-19 Literature Surveillance Summary

July 8, 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:

- A cross-sectional survey of 812 Sudanese residents assessed their knowledge, attitude, and practices towards COVID-19. While 78.2% exhibited accurate comprehension, there was significant variance between demographics and only 34.1% report wearing masks in public, highlighting the need for increase education especially in vulnerable population in order to improve public health outcomes.
- The Italian Ministry of Justice published measures implemented to limit the spread of COVID-19 in Italian prisons. These include widespread testing and rapid identification, isolation, and treatment of infected individuals. Legal and bioethics researchers argue that these initiatives fell short in effectively protecting the prisoners and urge legislators to decrease the prison population by providing alternative sentences, such as house arrest during the COVID-19 pandemic.

EPIDEMIOLOGY:

- Chinese researchers created a statistical model using COVID-19 transmission data from 367 Chinese cities to estimate the "COVID-19 spreading profile" (i.e. peak infection time, rate of infection, etc) for any given population. Applying their model to early case spread in South Korea, Italy, and Iran, the authors accurately predicted peak surges in mid-April, late March, and the end of May. The authors believe this model may be used by public health officials to predict COVID-19 surges after initial infection in cities.
- A cross-sectional study of COVID-19 patients in Italy (n=202) found 64% reported altered taste/smell, and of those, 89% had complete or partial recovery of taste/smell after 4 weeks. Higher degree of olfactory and gustatory impairment correlated with a lower likelihood of recovery after 4 weeks, suggesting these symptoms may be a useful prognostic factor in addition to screening tool.

UNDERSTANDING THE PATHOLOGY:

- Researchers from India hypothesize that early onset pulmonary edema in COVID-19 is due to a SARS-CoV-2 mediated insult to the nucleus tractus solitarius (NTS), leading to a loss of inhibition of sympathetic outflow. This increased sympathetic activity may result in neurogenic pulmonary edema by injuring lung vasculature and inducing a hypercoagulable state.

TRANSMISSION AND PREVENTION:

- A case series of 51 COVID-19 patients in India found the median duration of viral persistence in asymptomatic individuals was 8.87 days, with 10 of the 44 cases lasting beyond 2 weeks, leading authors to propose the quarantine duration should be extended from 17 to 21 days regardless of symptoms.
- Researchers from Harvard and Stanford University propose a feasible method for decontaminating N95 respirators. This strategy involves heating the masks in a convection oven at 85 degrees C with 60-85% humidity for 30 minutes. They found no significant decrease in filtration after five cycles of decontamination, offering a safe way to reuse these masks in resource-limited settings.
- Researchers from a 150-bed Skilled Nursing Facility (SNF) generated heat maps to track the spread of SARS-CoV-2 infection among residents and staff. They observed "rapid dissemination within 3 weeks of the first confirmed case despite adequate protection measures", suggesting the need for increased testing and appropriate isolation precautions to prevent further transmission, and recommend increasing staff reserve to compensate for the predicted increase in employees requiring self-quarantine.

MANAGEMENT:

- A retrospective study from Italy (n=115) found that therapeutic anticoagulation was an independent predictor of survival (OR 0.055). Additional findings include age (OR 1.1), D-dimer (OR: 1.0), and albuminuria (OR: 11.6) were found to be independent predictors of death

R&D DIAGNOSIS AND TREATMENT:

- Research from the Institute of Virology in Germany suggests that utilizing IgG binding avidity may improve characterization of SARS-CoV-2 infection status. Current data shows IgM responses are highly variable with IgG status, making it difficult to distinguish past infection vs. early infections. However, understanding that low avidity = new infection and high avidity = past infection may improve contact tracing, vaccination programs, and epidemiological data.
- A retrospective cohort study conducted in Wuhan, China examined 64 COVID-19 patients with Influenza A/B co-infection alongside age and sex matched COVID-19 positive controls to understand the effect of co-infection on COVID-19 and the use of lopinavir/ritonavir. Resolution of lung involvement demonstrated a hazard ratio of 1.878 (p=0.020) for patients treated with lopinavir/ritonavir compared to those not treated with this regiment, and viral shedding time was significantly longer (17 days versus 12 days) for patients with Influenza co-infection than those without co-infection (p=0.001).

MENTAL HEALTH AND RESILIENCE:

- The COVID Trauma Response Group and the Institute of Mental Health at University College London offer guidance on providing psychological support to hospital staff during the COVID-19 pandemic. The authors suggest that implementing these recommendations may help maintain morale in the workplace while possibly avoiding the need for formal psychological interventions in the future. Interventions include:
    - Meeting basic needs of access to personal protective equipment, nutrition, rest and sleep.
    - Alternating high and low-stress jobs.
    - Avoid psychological debriefing (PD), critical incident stress debriefing (CISD) or any other single session intervention which involves mandating staff to talk about their thoughts or feelings.
    - Partnering less experienced staff with more experienced mentors.

KNOWLEDGE, ATTITUDES, AND PRACTICES OF SUDANESE RESIDENTS TOWARDS COVID-19

Hezima A, Aljafari A, Aljafari A, Mohammad A, Adel I.. East Mediterr Health J. 2020 Jun 24;26(6):646-651. doi: 10.26719/emhj.20.076.

Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

This cross-sectional study surveyed 812 Sudanese residents living in the capital of Khartoum who were recruited via social media (67%) and manual survey distribution (33%) from March 5th, 2020 to March 26th, 2020, in order to determine their knowledge (Table 1), attitude (Table 3), and practices (Table 4) towards COVID-19. The average correct rate on knowledge questions was 78.2%, with significant differences between different demographics, suggesting a need for increased education in order to improve public health compliance during this pandemic. The results also revealed only 34.1% of participants have been wearing masks in public, which the authors hypothesize may be attributed to the economic state of the Sudan and the inability of the government to provide adequate protective equipment.

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Sufficient knowledge, positive attitudes, and correct practices are crucial for the prevention of COVID-19. Aims: This study aimed at assessing the knowledge, attitudes and practices of a sample of Sudanese residents towards COVID-19. Methods: A cross-sectional community-based survey was conducted on 812 participants, including both sexes and aged 18 years and above, with the exclusion of health care workers. Considerable care was taken to include people with different education levels. Results: Among the survey respondents (n=812), 45.8% were women, 40.4% held a bachelor's degree, 5.7% were uneducated, and 51.1% were aged 18-25 years. The overall correct rate of the knowledge questionnaire was 78.2%; 66.9% agreed that religious gatherings and events should be cancelled to prevent the spread of COVID-19; 34.1% of respondents wore medical masks; and 57.9% avoided shaking hands in recent days. Conclusion: This study showed that sampled Sudanese residents have incomplete knowledge and poor practices towards COVID-19. However, we found that women and people aged 18-25 years were more knowledgeable and had more positive attitudes towards COVID-19. We hope that concerned authorities will establish awareness programmes to improve the ability to combat this disease.

FIGURES

Table 1 **Knowledge of Sudanese residents towards COVID-19**

Question	Correct rate, % of the total sample
K1. The main clinical symptoms of COVID-19 are fever, dry cough, and body aches?	88.1
K2. Unlike the common cold, sneezing and runny nose are less common in persons infected with the SARS-CoV-2 virus?	67.1
K3. All infected individuals are symptomatic?	15.8
K4. The disease can be transmitted from asymptomatic individuals?	62.3
K5. Avoiding crowded places can prevent the infection by SARS-CoV-2?	95.5
K6. Wearing medical masks and washing hands can prevent the infection by SARS-CoV-2?	95.1
K7. SARS-CoV-2 can be transmitted through respiratory droplets?	87.9
K8. Touching contaminated surfaces can facilitate the transmission of SARS-CoV-2?	94.9
K9. Elderly and those who have chronic illnesses are more likely to be severe cases?	96.7

Table 1. Knowledge of Sudanese residents towards COVID-19.

Table 3 **Attitudes of Sudanese residents towards COVID-19 (n=812)**

Question	No. of positive responses	%
A1. Do you agree that COVID-19 is a serious threat to public health?	759	93.4
A2. Do you agree that suspected and infected patients should be isolated and restricted from social contact?	786	96.7
A3. Do you agree that religious gatherings and events should be cancelled temporarily to prevent the spread of SARS-CoV-2?	544	66.9
A4. Do you agree that universities and schools should be closed temporarily to prevent the spread of SARS-CoV-2?	766	94.3
A5. Do you agree that your country should close their borders with other countries that have an outbreak of COVID-19?	781	96.1
A6. Do you agree with the country lockdown to combat COVID-19?	714	87.9

Table 3. Attitudes of Sudanese residents towards COVID-19 (n=812).

Table 4 **Practices of Sudanese residents towards COVID-19 (n=812)**

Question	Yes n(%)	No n(%)
P1. Have you been wearing medical masks when leaving your house in recent days?	277(34.1)	535(65.9)
P2. Have you been frequently washing your hands in recent days?	698(86.0)	114(14.0)
P3. Did you go to any crowded place in recent days?	281(34.6)	531(65.4)
P4. Have you been avoiding handshaking with others in recent days?	470(57.9)	342(42.1)

Table 3. Attitudes of Sudanese residents towards COVID-19 (n=812).

THE COVID-19 EPIDEMIC AND THE PRISON SYSTEM IN ITALY

Cingolani M, Caraceni L, Cannovo N, Fedeli P.. J Correct Health Care. 2020 Jul 6:1078345820929733. doi: 10.1177/1078345820929733. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

This report summarizes the two strategies that the Italian Ministry of Justice has established to limit the spread of COVID-19 in Italian prisons: progressive isolation from the external world and adoption of practices to identify and treat infected prisoners. Legal and bioethics researchers argue that these initiatives fall short in effectively protecting the prisoners. Instead, the authors urge the legislators to decrease the prison population by providing alternative sentences, such as house arrest during the COVID-19 pandemic.

SUMMARY

- With the increasing number of COVID-19 cases in Italy, the Justice Ministry developed initiatives that limited opportunities that potentially could introduce the SARS-CoV-2 virus into the prisons. In-person visits with relatives or individuals other than defense lawyers outside of the prison were halted and changed to remote contact (i.e., telephone, videoconference). Additionally, a legislation decree allowed those with sentences under 18 months, or sentences with less than 18 months left to serve, to be placed under house arrest.
- The Justice ministry also passed an initiative to develop pre-triage for prisoners with three classifications. Symptomatic prisoners (i.e., fever, sore throat, respiratory difficulty, and COVID-19 related pneumonia) will be treated according to guidelines developed by the Health Ministry. Prisoners with few symptoms, but a negative COVID-19 test, will be evaluated by the penitentiary physician and local health care providers. Lastly, asymptomatic prisoners with a positive COVID-19 test will be subjected to isolation for 14 days in a designated area while the penitentiary physician actively monitors the individual.
- The authors believe not only that these initiatives have reduced the individual health rights of prisoners, but also that they do not effectively prevent the risk of COVID-19 transmission. The authors argue that prisons cannot truly isolate from the external world, as numerous workers, health care staff, and prison guards enter and exit the prisons daily. Moreover, due to overcrowding and structural limitation, prisoners could not effectively follow the social distancing recommendations.

ABSTRACT

The Italian Ministry of Justice and that of Health have established two strategies to limit the spread of COVID-19 in prisons: progressive isolation from the external world and adoption of practices to identify possible cases and to treat infected subjects. After the announcement of regulations revolts erupted in numerous Italian prisons. The motivations and effects of these strategy are discussed critically into the search for a balance between the right to health and other rights of prisoners in Italian prisons with the problem of an occupancy level of 121.75%.

PREDICTION OF COVID-19 SPREADING PROFILES IN SOUTH KOREA, ITALY AND IRAN BY DATA-DRIVEN CODING

Zhan C, Tse CK, Lai Z, Hao T, Su J.. PLoS One. 2020 Jul 6;15(7):e0234763. doi: 10.1371/journal.pone.0234763. eCollection 2020.
Level of Evidence: Other - Modeling

BLUF

Authors affiliated with several universities in China created a statistical model using COVID-19 transmission data from 367 Chinese cities to estimate the "COVID-19 spreading profile" (i.e. peak infection time, rate of infection, etc) for any given population. Applying their model to early case spread in South Korea (Figure 2), Italy (Figure 3), and Iran (Figure 4), the authors predicted, with decent accuracy, peak case loads near mid-April, the end of March, and the end of May with expected maximum case loads per region or city being less than 0.01%, 0.5%, and 0.5%, respectively. The authors believe this model may be used by public health officials to predict COVID-19 surges after initial infection in cities.

ABSTRACT

This work applies a data-driven coding method for prediction of the COVID-19 spreading profile in any given population that shows an initial phase of epidemic progression. Based on the historical data collected for COVID-19 spreading in 367 cities in China and the set of parameters of the augmented Susceptible-Exposed-Infected-Removed (SEIR) model obtained for each city, a set of profile codes representing a variety of transmission mechanisms and contact topologies is formed. By comparing the data of an early outbreak of a given population with the complete set of historical profiles, the best fit profiles are selected and the corresponding sets of profile codes are used for prediction of the future progression of the epidemic in that population. Application of the method to the data collected for South Korea, Italy and Iran shows that peaks of infection cases are expected to occur before mid April, the end of March and the end of May 2020, and that the percentage of population infected in each city or region will be less than 0.01%, 0.5% and 0.5%, for South Korea, Italy and Iran, respectively.

FIGURES

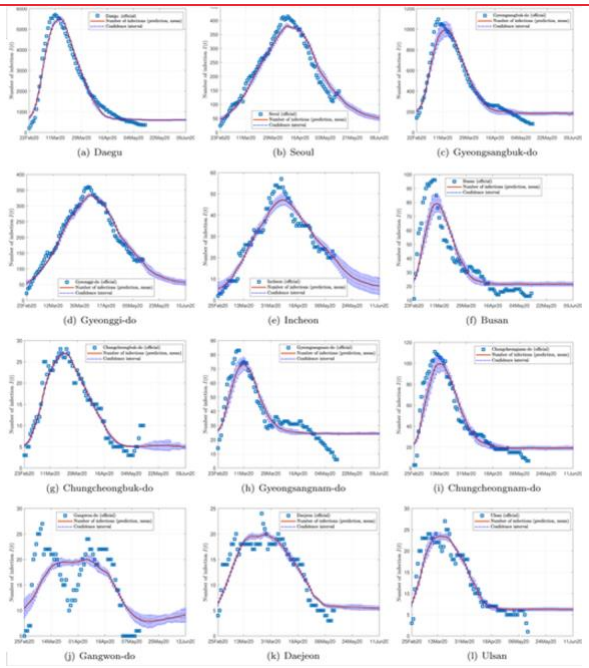


Figure 2. Official and estimated number of infected individuals in some cities or regions in South Korea.

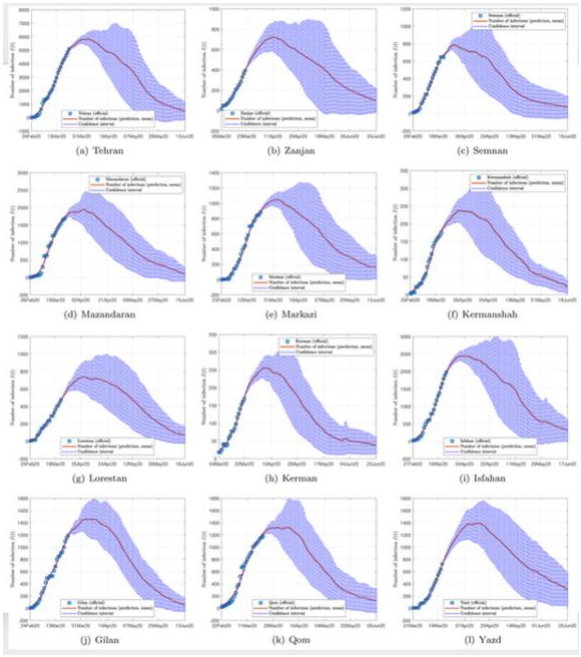


Figure 3. Official and estimated number of infected individuals in some provinces in Iran.

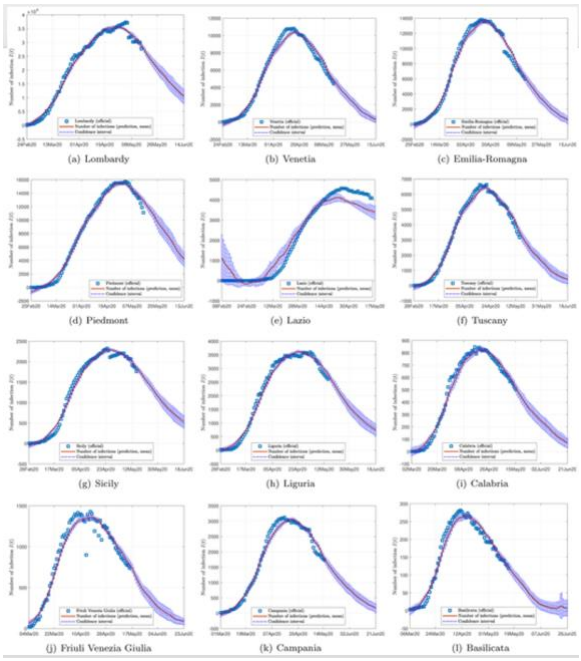


Figure 3. Official and estimated number of infected individuals in some provinces in Iran.

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

EVOLUTION OF ALTERED SENSE OF SMELL OR TASTE IN PATIENTS WITH MILDLY SYMPTOMATIC COVID-19

Boscolo-Rizzo P, Borsetto D, Fabbris C, Spinato G, Frezza D, Menegaldo A, Mularoni F, Gaudioso P, Cazzador D, Marciani S, Frasconi S, Ferraro M, Berro C, Varago C, Nicolai P, Tirelli G, Da Mosto MC, Obholzer R, Rigoli R, Polesel J, Hopkins C.. JAMA Otolaryngol Head Neck Surg. 2020 Jul 2. doi: 10.1001/jamaoto.2020.1379. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross-sectional study conducted in Italy between 3/19-3/22/2020 surveyed 202 COVID-19 positive patients and found 64% reported altered taste/smell, and of those, 89% had complete or partial recovery of taste/smell after 4 weeks (Tables 1-2). Higher severity of impaired taste/smell was associated with lower likelihood of recovery after 4 weeks; however, "persistent loss of smell/taste was not associated with persistent SARS-CoV-2 infection."

ABSTRACT

Importance: An altered sense of smell and taste has been reported to be associated with coronavirus disease 2019 (COVID-19). To understand the evolution of these symptoms during the course of the disease is important to identify patients with persistent loss of smell or taste and estimate the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the burden of olfactory and gustative dysfunctions. Objective: To evaluate the evolution of the loss of sense of smell and taste in a case series of mildly symptomatic patients with SARS-CoV-2 infection. Design, Setting, and Participants: This cross-sectional survey-based study included 202 mildly symptomatic adults (>=18 years) consecutively assessed at Treviso Regional Hospital, Italy, between March 19 and March 22, 2020, who tested positive for SARS-CoV-2 RNA by polymerase chain reaction on nasopharyngeal and throat swabs. Main Outcomes and Measures: Prevalence of altered sense of smell and taste at follow-up and their variation from baseline. Results: Of 202 patients completing the survey at baseline, 187 (92.6%) also completed the follow-up survey (103 [55.1%] women; median age, 56 years). The evaluation of the evolution of altered sense of smell or taste in the 113 patients reporting sudden onset of these symptoms at baseline showed that 55 patients (48.7%; 95% CI, 39.2-58.3) reported complete resolution of smell or taste impairment, 46 (40.7%; 95% CI, 31.6-50.4) reported an improvement in the severity, and only 12 (10.6%; 95% CI, 5.6-17.8) reported the symptom was unchanged or worse. Persistent loss of smell or taste was not associated with persistent SARS-CoV-2 infection. Conclusions and Relevance: At 4 weeks from the onset, 89% of the SARS-CoV-2-positive mildly symptomatic patients who had had a sudden onset of altered sense of smell or taste experienced a complete resolution or improvement of these symptoms. Persistent loss of smell or taste was not associated with persistent SARS-CoV-2 infection.

FIGURES

Table 2. Evolution of Alteration of Sense of Smell or Taste in 113 Patients Positive for SARS-CoV-2

Alteration of sense of smell or taste at baseline[a]	No. (%)						
		Alteration of sense of smell or taste after 4 weeks[a]					
	Total	0: No	1: Very mild	2: Mild or slight	3: Moderate	4: Severe	5: As bad as it can be
1: Very mild	5 (4.4)	4	0	0	0	1	0
2: Mild or slight	15 (13.3)	10	1	2	1	1	0
3: Moderate	26 (23.0)	10	10	3	0	3	0
4: Severe	24 (21.2)	12	6	3	3	0	0
5: As bad as it can be	43 (38.1)	19	4	4	8	4	4
Total	113	55 (48.7)	21 (18.6)	12 (10.6)	12 (10.6)	9 (8.0)	4 (3.5)

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus.
[a] According to Sino-Nasal Outcome Test 22 (SNOT-22), item "sense of smell or taste."

Table 1. Symptom Evolution From Baseline to the 4-week Follow-up in 187 Patients Positive for SARS-CoV-2

Symptom	No. (%)			
	Symptomatic at baseline	Symptom evolution in 4 weeks		Onset during follow-up
		Recovered	Still present	
Fever	104	99 (95.2)	5 (4.8)	3
Dry cough or coughing up mucus	116	70 (60.3)	46 (39.7)	8
Blocked nose	70	54 (77.1)	16 (22.9)	12
Problems breathing	77	47 (61.0)	30 (39.0)	14
Headache	80	61 (76.3)	19 (23.7)	4
Sore throat	59	51 (86.4)	8 (13.6)	5
Muscle or joint pains	85	68 (80.0)	17 (20.0)	13
Chest pain	29	27 (93.1)	2 (6.9)	9
Sinonasal pain	31	28 (90.3)	3 (9.7)	3
Loss of appetite	101	87 (86.1)	14 (13.9)	6
Felt tired	130	101 (86.1)	29 (13.9)	0
Diarrhea	84	74 (88.1)	10 (11.9)	1
Nausea	38	37 (97.4)	1 (2.6)	1
Vomiting	12	12 (100)	0 (0.0)	1
Abdominal pain	23	21 (91.3)	2 (8.7)	5
Dizziness	25	22 (88.0)	3 (12.0)	2
Altered sense of smell or taste	113	55 (48.7)	58 (51.3)	11

PULMONARY EDEMA IN COVID19-A NEURAL HYPOTHESIS

U R A, Verma K.. ACS Chem Neurosci. 2020 Jul 2. doi: 10.1021/acschemneuro.0c00370. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

An expert opinion written by a pair of researchers from the UR Anoop Research Group in Pondicherry, India proposes that the early onset pulmonary edema seen in some COVID-19 patients is due to a SARS-CoV-2 mediated insult to the nucleus tractus solitarius (NTS), leading to a loss of inhibition of sympathetic outflow. The acute increase in sympathetic outflow may cause a neurogenic pulmonary edema as a result of impacts on lung vasculature and potentially could also lead to a hypercoaguable state through interactions with coagulation and fibronolysis pathways (Figure 2). This hypothesis needs further evaluation but suggests that future treatments must provide early intervention for both the neurogenic and pulmonary pathologies underlying SARS-CoV-2-related pulmonary edema.

ABSTRACT

In COVID-19, lung manifestations present as a slowly evolving pneumonia with insidious early onset interstitial pulmonary edema that undergoes acute exacerbation in the late stages and microvascular thrombosis. Currently, these manifestations are considered to be only consequences of pulmonary SARS-CoV-2 virus infection. We are proposing a new hypothesis that neurogenic insult may also play a major role in the pathogenesis of these manifestations. SARS-CoV-2 mediated inflammation of the nucleus tractus solitarius (NTS) may play a role in the acute exacerbation of pulmonary edema and microvascular clotting in COVID-19 patients.

FIGURES

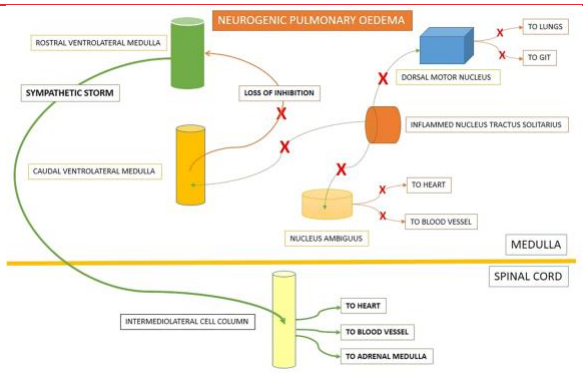


Figure 2. Inflamed NTS with loss of relay to the vagal parasympathetic nuclei and loss of inhibition of rostral ventrolateral medulla.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

PROLONGED PERSISTENCE OF SARS-COV-2 IN THE UPPER RESPIRATORY TRACT OF ASYMPTOMATIC INFECTED INDIVIDUALS

Saurabh S, Kumar R, Gupta MK, Bhardwaj P, Nag VL, Garg MK, Misra S.. QJM. 2020 Jul 1:hcaa212. doi: 10.1093/qjmed/hcaa212. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A case series of 51 COVID-19 positive patients (44 of whom were asymptomatic) conducted at All India Institute of Medical Sciences from March 19th - May 21st, 2020 found the median virus persistence in asymptomatic individuals to be 8.87 days, with 10 of the 44 cases lasting beyond 2 weeks (Figure 1). Based on these findings, the authors propose that the quarantine duration of SARS-CoV-2 infected individuals be extended from 17 to 21 days in India, regardless of symptom status.

ABSTRACT

BACKGROUND: Duration of persistence of SARS-CoV-2 in the upper respiratory tract of infected individuals has important clinical and epidemiological implications. AIM: We aimed to establish the duration and risk factors for persistence of SARS-CoV-2 in the upper respiratory tract of asymptomatic infected individuals. METHODS: Data of repeat rRT-PCR test done for SARS-CoV-2 infected individuals at our institute at Jodhpur, India was analysed from 19 March- 21 May 2020. Duration of virus persistence was estimated with parametric regression models based on Weibull, Log-normal, Log-logistic, Gamma and Generalized Gamma distributions. Factors associated with prolonged viral persistence were analysed with the best fitting model. RESULTS: 51 SARS-CoV-2 infected individuals with repeat rRT-PCR test were identified with 44 asymptomatics. The asymptomatic individuals had median virus persistence duration of 8.87 days (95%CI: 7.65 - 10.27) and 95 percentile duration of 20.70 days (95% CI: 16.08 -28.20). The overall median virus persistence including both symptomatic and asymptomatic individuals was found to be 9.18 days (95 CI 8.04 - 10.48). Around one-fourth asymptomatics (10/44) demonstrated SARS-CoV-2 persistence beyond 2 weeks. Age < 60 years and local transmission were found to be significantly associated with longer virus persistence among asymptomatic individuals on univariate regression but not in multivariate analysis. CONCLUSION: Recommended home isolation duration for SARS-CoV-2 infected individuals in India should be extended from 17 days to at least three weeks. Prolonged persistence of SARS-CoV-2 in a proportion of asymptomatic individuals merits attention with regard to ensuring universal infection prevention precautions irrespective of symptomatic status.

FIGURES

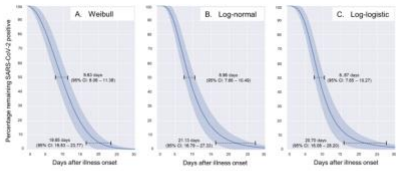


Figure 1. Duration of persistence of SARS-CoV-2 in the upper respiratory tract of asymptomatic individuals as fitted to Weibull, Log-normal and Log-logistic distributions (n = 44)

A SCALABLE METHOD OF APPLYING HEAT AND HUMIDITY FOR DECONTAMINATION OF N95 RESPIRATORS DURING THE COVID-19 CRISIS

Anderegg L, Meisenhelder C, Ngooi CO, Liao L, Xiao W, Chu S, Cui Y, Doyle JM.. PLoS One. 2020 Jul 1;15(7):e0234851. doi: 10.1371/journal.pone.0234851. eCollection 2020.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Researchers from Harvard and Stanford University propose a scalable method for decontaminating N95 respirators by applying heat and humidity in a convection oven at 85 degrees C with 60-85% humidity for 30 minutes. They studied the effects of five cycles of decontamination and found no significant decrease in filtration efficacy or fit (Tables 1-2), offering a safe way to reuse these masks in light of the worldwide shortage due to the COVID-19 pandemic.

ABSTRACT

A lack of N95 Filtering Facepiece Respirators (FFRs) during the COVID-19 crisis has placed healthcare workers at risk. It is important for any N95 reuse strategy to determine the effects that proposed protocols would have on the physical functioning of the mask, as well as the practical aspects of implementation. Here we propose and implement a method of heating N95 respirators with moisture (85 C, 60-85% humidity). We test both mask filtration efficiency and fit to validate this process. Our tests focus on the 3M 1860, 3M 1870, and 3M 8210 Plus N95 models. After five cycles of the heating procedure, all three respirators pass both quantitative fit testing (score of >100) and show no degradation of mask filtration efficiency. We also test the Chen Heng V9501 KN95 and HKYQ N95 finding no degradation of mask filtration efficiency, however even for unheated masks these scored <50 for every fit test. The heating method presented here is scalable from individual masks to over a thousand a day with a single industrial convection oven, making this method practical for local application inside health-care facilities.

FIGURES

Table 1. Quantitative Fit Testing results measured with a TSI PortaCount Respirator Fit Tester 8038. Red shaded cells indicate an overall fit factor <100, indicating failure of the fit test. Green shaded cells indicate successful fit tests. The cycle number indicates the number of heating cycles the test group had undergone at the time of fit testing.

Mask Type	Control or Test	Overall Fit Factor							
		Initial	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 Test 1	Cycle 5 Test 2	Cycle 5 Test 3
HKYQ N95	Control	28	9	6	9	19	26	NA	NA
HKYQ N95	Test	5	NA	NA	NA	NA	NA	NA	NA
Chen Heng V9501 KN95	Control	9	19	11	45	31	43	NA	NA
Chen Heng V9501 KN95	Test	4	NA	NA	NA	NA	NA	NA	NA
3M 8210 Plus	Control	127	200+	200+	200+	200+	200+	NA	NA
3M 8210 Plus	Test	163	186	200+	200+	200+	200+	200+	200+
3M 1860	Control	153	193	138	112	200+	200+	NA	NA
3M 1860	Test	154	200+	200+	200+	200+	200+	200+	200+
3M 1870	Control	102	200+	200+	200+	200+	200+	NA	NA
3M 1870	Test	193	118	177	111	187	133	163	112

Table 2. Filtration testing results. Initial filtration performance of 0.26 μm (mass mean diameter) NaCl at a flow rate of 85 L/min is reported. Filtration efficiency and pressure drop shown for the test group masks is an average of the two masks of each type tested. Variation between the two samples was minimal. Testing performed with a TSI Inc. Automated Filter Tester 8130A.

Mask Type	Control Group		5 Cycles at 85°C + 60-85% Humidity	
	Filtration Efficiency (%)	Pressure Drop (Pa)	Filtration Efficiency (%)	Pressure Drop (Pa)
3M 1860	99.79[2]	86	99.51	71.5
3M 1870	99.97	97	99.84	99.8
3M 8210 Plus	99.78	84	99.63	71.5
Chen Heng V9501 KN95	97.99	119.3	97.73	110.3
HKYQ N95	98.91	125.7	98.88	144.3

PREVENTION IN THE COMMUNITY

HOW TO SAFELY REOPEN COLLEGES AND UNIVERSITIES DURING COVID-19: EXPERIENCES FROM TAIWAN

Cheng SY, Wang CJ, Shen AC, Chang SC.. Ann Intern Med. 2020 Jul 2. doi: 10.7326/M20-2927. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Researchers at National Taiwan University, Taipei discuss college reopening guidelines put forth by the Ministry of Education (MOE) beginning 26 February 2020. Campus-based guidelines led by university COVID-19 task force and health center managed matters such as risk screening, quarantine protocols, hygiene, sanitation, ventilation, suspected case reporting, and school closures. Authors report proactive containment efforts and comprehensive contact tracing have kept COVID-19 case numbers low with a total of 7 confirmed cases in 6 Taiwanese universities. They suggest low COVID-19 case numbers overall may have contributed to Taiwan's success in university prevention and containment, but implementation of these guidelines could allow for safe reopening of universities elsewhere.

SUMMARY

Summary of guideline structure below:
- COVID-19 task force: members (led by university vice president) met regularly to coordinate online learning, supervise isolation/quarantine, monitor public assembly, address financial concerns, and ensure adequate supply of personal protective equipment (PPE).

- University health center: medical professionals provided outpatient clinics, health check-ups, urgent/emergent care,

psychological consultations, and infectious disease surveillance. Risk screening was conducted based on travel history, occupation, contacts, and clusters (TOCC) to assess need for 14 day home isolation/quarantine.

- General hygiene measures: focused on travel restrictions, PPE/sanitization utilization, hand washing, social distancing (5 feet indoors, 3.3 feet outdoors), and wearing masks indoors. Dormitories were regulated closely via restricted entry/exit at a single checkpoint with a screening station (temperature checks). Transparent dividers were also placed on each table of the cafeteria.

- Ventilation and sanitization: introduced ventilation policy to leave doors open (CO2 concentration maintained at <1000ppm). Detailed guidance on cleaning procedures (areas requiring particular attention, cleaning chemical formulas) was implemented.

- Suspected case reporting: When a confirmed/suspected case was present, university health center staff reported to the local health department and the school conducted contact tracing with health status monitoring of all contacts.

- School closures and make-up classes: If 1 confirmed case was identified, all of that person's classes were to be suspended. If a university had 2 confirmed cases, it was to close altogether and initiate online courses for at least 14 days. Students were allowed to apply for delayed registration/tuition payment, return of tuition, or online courses. The university also offered an extension to fulfill graduation requirements.

-Quarantine implementation: For international students, universities were responsible for transporting students from the airport to the quarantine location (independent dormitory or other private room). 14 day isolation was initiated, and temperatures were checked twice daily. Quarantined students were allowed to live at home if they had a single room and private bathroom but were required to move to a designated hotel if at risk individuals (elderly, those with chronic disease, children) were in their household.

ABSTRACT

Reopening colleges and universities during the coronavirus disease 2019 (COVID-19) pandemic poses a special challenge worldwide. Taiwan is one of the few countries where schools are functioning normally. To secure the safety of students and staff, the Ministry of Education in Taiwan established general guidelines for college campuses. The guidelines delineated creation of a task force at each university; school-based risk screening based on travel history, occupation, contacts, and clusters; measures on self-management of health and quarantine; general hygiene measures (including wearing masks indoors); principles on ventilation and sanitization; regulations on school assemblies; a process for reporting suspected cases; and policies on school closing and make-up classes. It also announced that a class should be suspended if 1 student or staff member in it tested positive and that a school should be closed for 14 days if it had 2 or more confirmed cases. As of 18 June 2020, there have been 7 confirmed cases in 6 Taiwanese universities since the start of the pandemic. One university was temporarily closed, adopted virtual classes, and quickly reopened after 14 days of contact tracing and quarantine of possible contacts. Taiwan's experience suggests that, under certain circumstances, safely reopening colleges and universities this fall may be feasible with a combination of strategies that include containment (access control with contact tracing and quarantine) and mitigation (hygiene, sanitation, ventilation, and social distancing) practices.

IMPORTANCE OF FACE MASKS FOR COVID-19 - A CALL FOR EFFECTIVE PUBLIC EDUCATION

Tso RV, Cowling BJ.. Clin Infect Dis. 2020 Jul 2:ciaa593. doi: 10.1093/cid/ciaa593. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Authors from The Education University of Hong Kong and the University of Hong Kong reviewed public health authorities' recommendations on mask-wearing prior to April 6, 2020 to understand the ongoing debates and confusion on mask use in the general population. They found that countries and authorities that originally did not support community mask-wearing stated supply shortages, inadequate public knowledge on mask use, and a possible reduction in public compliance to other measures as their main concerns. The authors suggest that more public health education on basic microbiology and on proper mask use may help increase community mask-wearing behaviors.

ABSTRACT

Considerable debates about the general community use of face masks for protection against COVID-19 stemmed out from differing views taken by health authorities. Misconceptions and stigmatization towards the use of face masks may hinder the containment of the COVID-19 pandemic. We address this previous debate by analyzing the advice on the community use of masks across different credible health authorities: countries that promoted the use of masks acknowledged that masks are effective, but also explained the importance of their proper use along with other hygiene measures. In contrast, authorities that recommended against the community use of masks mainly cited shortage of supplies, the argument that the public do not have the adequate skills to wear them, or that wearing masks might reduce compliance with other important behaviors. We suggest promoting effective behavioral changes in personal protective measures by teaching microbiological knowledge instead of just listing out the "dos-and-don'ts".

PREVENTION IN THE HOSPITAL

AN ILLUSTRATION OF SARS-COV-2 DISSEMINATION WITHIN A SKILLED NURSING FACILITY USING HEAT MAPS

Blackman C, Farber S, Feifer RA, Mor V, White EM.. J Am Geriatr Soc. 2020 Jun 13. doi: 10.1111/jgs.16642. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A 150-bed Skilled Nursing Facility (SNF) for those with cognitive impairment generated heat maps to track the spread of infection and SARS-CoV-2 test results among its residents and staff. They observed "rapid SARS-CoV-2 dissemination in the SNF within 3 weeks of the first COVID-19 confirmed case in the dementia unit despite adequate[sic] protection measures: visitor exclusion, regular symptom screening of residents and staff, PPE use, social distancing policies". Widespread SARS-CoV-2 transmission from asymptomatic patients may lead to significant morbidity and mortality, suggesting the need for early rapid SARS-CoV-2 testing and appropriate isolation to prevent further transmission. The authors encourage collaboration with with SNF's and other care providers to maintain increased testing. They also recommend "adequate staffing reserve to support the current staff" as increased testing will likely yield increased positive cases requiring self-quarantine.

ABSTRACT

OBJECTIVES: To illustrate dissemination and asymptomatic transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during a skilled nursing facility (SNF) outbreak. DESIGN: Case report. SETTING AND PARTICIPANTS: Residents of a 150-bed SNF. MEASUREMENTS: Heat maps generated by the SNF's infection prevention team to track staff and resident symptoms and SARS-CoV-2 test results to identify infection patterns. RESULTS: The SNF experienced a severe outbreak of SARS-CoV-2 early in the pandemic. The initial cluster of residents with symptoms and the first confirmed case occurred on the SNF's dementia care unit. The insufficient availability and prolonged turnaround time of testing for both residents and staff at the outset of the outbreak prevented timely and accurate identification and cohorting of cases. Despite extensive other infection control measures being in place, SARS-CoV-2 disseminated widely through the facility within 3 weeks of the first confirmed case, resulting in significant morbidity and mortality. CONCLUSION: Early, rapid, universal SARS-CoV-2 testing of both SNF residents and staff at the outset of an outbreak and then repeatedly thereafter is critical to mitigate viral transmission. This will become even more important as states relax stay-at-home orders and SNF staff intermingle with communities that are increasingly mobile. Increased testing will inevitably result in more staff testing positive and having to self-quarantine at home, meaning that states must partner with SNFs and other long-term care providers to coordinate and support strategic staffing reserves that can supplement current frontline staff.

EVALUATION OF SEX-RELATED HORMONES AND SEMEN CHARACTERISTICS IN REPRODUCTIVE-AGED MALE COVID-19 PATIENTS

Ma L, Xie W, Li D, Shi L, Ye G, Mao Y, Xiong Y, Sun H, Zheng F, Chen Z, Qin J, Lyu J, Zhang Y, Zhang M.. J Med Virol. 2020 Jul 4. doi: 10.1002/jmv.26259. Online ahead of print.
Level of Evidence: 4 - Case-series or casecontrol studies, or poor quality prognostic cohort study

BLUF

Authors from Wuhan University in China performed a retrospective study at Wuhan Leishenshan Hospital comparing sex-related hormone profiles between 119 reproductive-aged male COVID-19 patients (admitted between March 5-March 31, 2020) and 273 age-matched control patients. They found that the COVID-19 group had higher serum luteinizing hormone (LH) levels (p less than 0.0001) and a lower serum testosterone to LH ratio (T:LH; p less than 0.0001; Table 4); the T:LH ratio was negatively associated with white blood cell counts (p=0.0069) and C-reactive protein (p=0.0285; Table 5). Additionally, analysis of semen samples from 12 COVID-19 patients (March 26-April 23, 2020) were negative for SARS-CoV-2 via qRT-PCR. While mechanisms of these phenomena remain unclear, authors recommend including reproductive function evaluation in COVID-19 follow-up for men.

ABSTRACT

In the past several months, the outbreak of SARS-CoV-2-associated infection (coronavirus disease 2019, COVID-19) developed rapidly and has turned into a global pandemic. Although SARS-CoV-2 mainly attacks respiratory systems, manifestations of multiple organs have been observed. Great concern was raised about whether COVID-19 may affect male reproductive functions. In this study, we collected semen specimens from twelve male COVID-19 patients for virus detection and semen characteristics analysis. No SARS-CoV-2 was found in semen specimens. 8 out of 12 patients had normal semen quality. We also compared the sex-related hormone levels between 119 reproductive-aged men with SARS-CoV-2 infection and 273 age-matched control men. A higher serum luteinizing hormone (LH) and a lower ratio of testosterone (T) to LH were observed in the COVID-19 group. Multiple regression analysis indicated that serum T:LH ratio was negatively associated with white blood cell counts (WBC) and c-reactive protein (CRP) level in COVID-19 patients. It's the first report about semen assessment and sex-hormone evaluation in reproductive-aged male COVID-19 patients. Although further study is needed to clarify the reasons and underlying mechanisms, our study presents an abnormal sex hormone secretion among COVID-19 patients, suggesting that attention should be paid to reproductive function evaluation in the follow-up.

FIGURES

	Men with COVID-19 (n=119)	Age-matched control group (n=273)	*p* value
Age - yrs	39 (35.0~44.0)	39 (35.0~42.0)	0.1585
Testosterone (ng/mL)	3.97(3.14~5.74)	4.43 (3.53~5.24)	0.1886
FSH (mIU/mL)	4.57(3.15~6.67)	4.64 (3.51~6.38)	0.5585
LH (mIU/mL)	6.36(4.63~8.37)	3.38 (2.48~4.52)	<0.0001*
T: LH	0.68 (0.43~0.96)	1.24(0.92~1.84)	<0.0001*
FSH: LH	0.80 (0.53~1.04)	1.40 (1.04~1.94)	<0.0001*

Table 4. Sex-related Hormone Profiles in the COVID-19 group and the control group.

Data are presented as medians (IQR). * statistically significant.

	95% CI			*p* value
Age	-0.0200	~	0.0040	0.1871
Severity †	-0.2414	~	0.1919	0.8213
WBC (×10^9/L)	-0.1669	~	-0.02729	0.0069*
Lymphocyte count (× 10^9/L)	-0.1327	~	0.2941	0.4549
Lymphocyte percentage (%)	-0.02297	~	0.006507	0.2707
CRP (mg/L)	-0.01190	~	-0.0006757	0.0285*
ALT(IU/L)	-0.003524	~	0.002383	0.7025
AST (IU/L)	-0.008145	~	0.009696	0.8635
Serum abbulmin (g/L)	-0.03309	~	0.02713	0.8449
Creatinine (μmol/L)	-0.001961	~	0.001260	0.6674
Urea nitrogen (mmol/L)	-0.05946	~	0.04560	0.7943
D-dimer(mg/L)	-0.1740	~	0.06645	0.3771

Table 5. Multiple Linear regression for association of clinical characteristics of COVID-19 patients with serum T:LH ratio

95% CI: 95% confidence interval. * statistically significant

ACUTE CARE

A POSSIBLE BENEFIT FROM THERAPEUTIC ANTICOAGULATION IN COVID-19: THE DOLO HOSPITAL EXPERIENCE IN VENETO, ITALY

Secco E, Pasqualetto MC, Bombardini T, Picano E, Rigo F.. Kardiol Pol. 2020 Jul 6. doi: 10.33963/KP.15489. Online ahead of print.
Level of Evidence: 4 - Case-series or casecontrol studies, or poor quality prognostic cohort study

BLUF

A retrospective study conducted by researchers in Veneto, Italy of 115 confirmed patients with COVID-19 at Doro Hospital (admitted to intermediate care unit from March 13-April 13, 2020) found that therapeutic anticoagulation (oral anticoagulants or high dose heparin; OR 0.055, P=0.03) was an independent predictor of survival when comparing patients who died (n=19) to those who were discharged (n=96). Age (OR 1.109; p = 0.007), D-dimer on last day (OR: 1.000, P = 0.006), and albuminuria (OR: 11.612, P = 0.04) were found to be independent predictors of death. The authors recognize the limitations of the observational study and highlight the importance of further large, randomized studies to explore the benefits of therapeutic anticoagulation in COVID-19.

PRACTICAL CONSIDERATIONS IN PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM IN HOSPITALIZED PATIENTS WITH COVID-19

Smith K, Krajewski KC, Krajewski MP.. Am J Health Syst Pharm. 2020 Jul 6:zxaa245. doi: 10.1093/ajhp/zxaa245. Online ahead of print.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

Pharmaceutical researchers from Buffalo, NY propose practical anticoagulation strategies for the management of challenging COVID-19 related coagulopathies. In the absence of specific COVID-19 evidence-based guidelines, the authors include patient, agent, post-discharge and approach selection factors, including the use of a tiered approach in their proposal of both active and prophylactic management strategies.

SUMMARY

Proposed recommendations included, but not limited to:

• Prophylactic anticoagulation is recommended for all patients who require hospital admission for COVID-19 in the absence of any contraindications such as active bleeding and a platelet count less than 250 × 103 /μL.
• Low-molecular-weight heparin (LMWH) as the anticoagulant of choice with Fondaparinux as an alternative in patients with a history of heparin-induced thrombocytopenia (HIT) or aversion to receipt of porcine derivatives.
• Consider a 3-tiered approach to stratifying anticoagulation intensity. This includes low-intensity anticoagulation (tier I), intermediate-intensity anticoagulation (tier II), and therapeutic-dose anticoagulation (tier III).
• In the setting of renal dysfunction, use of intravenous unfractionated heparin (UFH) along with anti–factor Xa (anti-Xa) monitoring may be preferable.
• Transition patients on oral anticoagulation at home to therapeutic-dose LMWH or parenteral UFH infusion for the duration of hospitalization unless contraindications exist

Patient selection for tiered anticoagulation therapy:

• Tier I anticoagulation: Low acuity patients, those without known thrombi or known malignancy; D-dimer levels less than 3 times the ULN that are not trending upward. Dose examples include enoxaparin 40mg sc once daily to q12hourly; renal adjustments of enoxaparin 30 mg sc daily.
• Tier II anticoagulation: Higher risk patients (clinically deteriorating, with an upward trend in inflammatory marker and/or D-dimer levels). Risk stratification models (Caprini score, IMPROVE risk score, and Padua Prediction Score models) can be used to determine suitability. Enoxaparin 40 mg sc every 12 hours may be an option for patients with a BMI of <40.
• Tier III anticoagulation: Patients with COVID-19 with known or strongly suspected venous thromboembolism (VTE), presenting with acute coronary syndrome or D-dimer greater than 6 times the ULN. Enoxaparin 1 mg/kg sc q12hrly (for patients with creatinine clearance [CLcr] above 30 mL/min).
• In clinically brittle patients with increasing oxygen needs, mechanical ventilation or organ failure, consider prophylactic treatment.

Agent selection for tiered anticoagulation therapy (Figure 1):

• Tier I anticoagulation: LMWH at standard prophylactic doses with dose considerations for obese patients (BMI >40) and renal disease. Assaying anti-Xa levels therapeutic levels may be done in obese patients. Fondaparinux may replace heparin where needed.
• Tier II anticoagulation: Consider higher-than-standard doses as needed. Initiate VTE doses in suspected cases until ruled out.
• Tier III anticoagulation: Stepped up dosing recommendations for high-intensity anticoagulation in critically ill patients with COVID-19.

Discharge considerations:

• Regardless of tier, assess all patients for need for prophylaxis and ongoing anticoagulation therapy. Factors to consider include prolonged immobility while in quarantine, D-dimer, CRP, ferritin, and lactate dehydrogenase levels.
• Consider patient-specific factors such as insurance and cost considerations, duration of prophylactic therapy and bleeding risk.
• Extending prophylaxis up to 45 days may be appropriate in patients at increased risk for VTE who are at low risk for bleeding.
• Upon discharge of patients with confirmed or suspected VTE, continuation of anticoagulation treatment for minimum 3 months for provoked VTE can be chosen. Treatment with therapeutic-dose LMWH or DOAC therapy can be considered in preference to warfarin, in accordance with current guidelines.
• If VTE is not confirmed at time of discharge due to lack of test availability, the clinician may wish to treat according to conventional protocols for VTE.
• Follow-up with primary care or specialty providers for ongoing re-evaluation and extension of therapy.

ABSTRACT

DISCLAIMER: In an effort to expedite the publication of articles related to the COVID-19 pandemic, AJHP is posting these manuscripts online as soon as possible after acceptance. Accepted manuscripts have been peer-reviewed and copyedited, but are posted online before technical formatting and author proofing. These manuscripts are not the final version of record and will be replaced with the final article (formatted per AJHP style and proofed by the authors) at a later time. PURPOSE: There are increasing reports in the literature of high rates of coagulopathy and venous thromboembolism (VTE) among hospitalized patients with coronavirus disease 2019 (COVID-19). Understanding of these abnormalities is continually evolving, but these conditions may pose a risk to COVID-19 patients beyond the risk typically seen in critically ill patients. SUMMARY: There are currently no widely accepted evidence-based guidelines regarding specifics related to treatment and prevention of COVID-19-related coagulopathies. Areas of management requiring clinical equipoise include agent selection and dosing, continuation vs interruption of home oral anticoagulant therapy during hospital admission, and postdischarge VTE prophylaxis. Clinicians may wish to consider use of a stratified, 3-tiered approach of low-intensity anticoagulation, intermediate-intensity anticoagulation, and therapeutic-dose anticoagulation. Patients can be categorized by tier depending on their risk factors for VTE, acuity of illness, and laboratory values such as D-dimer level. CONCLUSION: Practical guidance on anticoagulation considerations and dosing suggestions are provided to assist clinicians faced with challenging anticoagulation-related situations in caring for hospitalized COVID patients until formal evidence-based guidelines become available.

FIGURES

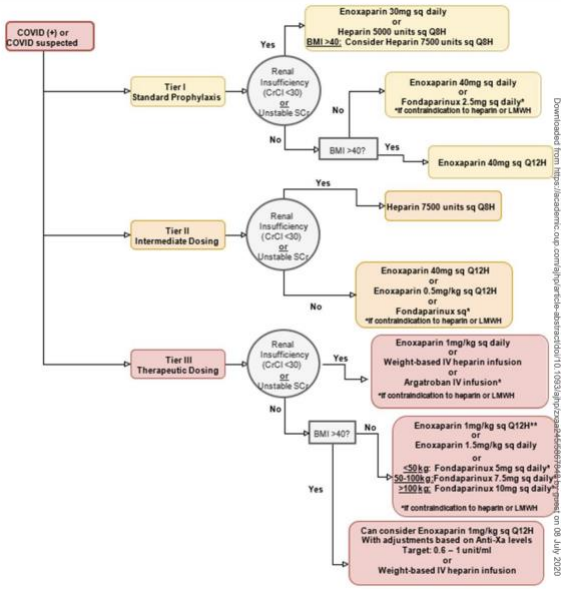


Figure 1. Flowchart of 3-tiered approach to stratification of anticoagulation intensity. Anti-Xa indicates anti–factor Xa; BMI, body mass index; CrCl, creatinine clearance; IV, intravenous; LMWH, low-molecular-weight heparin; SCr, serum creatinine; sq, subcutaneously.

MEDICAL SUBSPECIALTIES

CARDIOLOGY

A PROPOSED STRATEGY FOR MANAGEMENT OF IMMUNOSUPPRESSION IN HEART TRANSPLANT PATIENTS WITH COVID-19

Ahluwalia M, Givertz MM, Mehra MR.. Clin Transplant. 2020 Jul 4:e14032. doi: 10.1111/ctr.14032. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

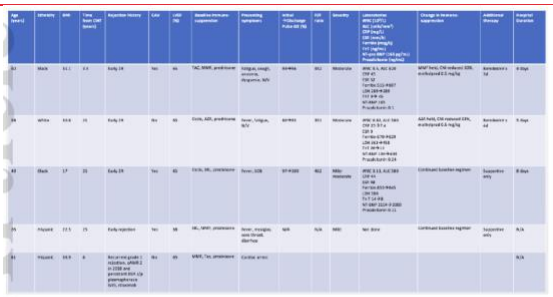
Researchers at Brigham and Women's Hospital present a case series of 19 patients with orthotopic heart transplant who were evaluated in their program from March 10 through May 15. Five of those patients were confirmed positive for COVID-19: one patient died prior to presentation due to cardiac arrest and the remaining four showed marked improvement in the four weeks after hospital discharge (Table 1). The authors hypothesize that the immune suppressive treatment these patients received, which includes mycophenolate mofetil, prednisone, sirolimus, aziothioprine, and tacrolimus, suppressed T cell

response, leading to a decreased inflammatory response that may have been protective against severe COVID-19 disease in these patients. They propose monitoring principles for heart transplant patients with COVID-19 (Figure 1) and recommend further studies with large cohorts to better understand the risks of COVID-19 in transplant patients.

ABSTRACT

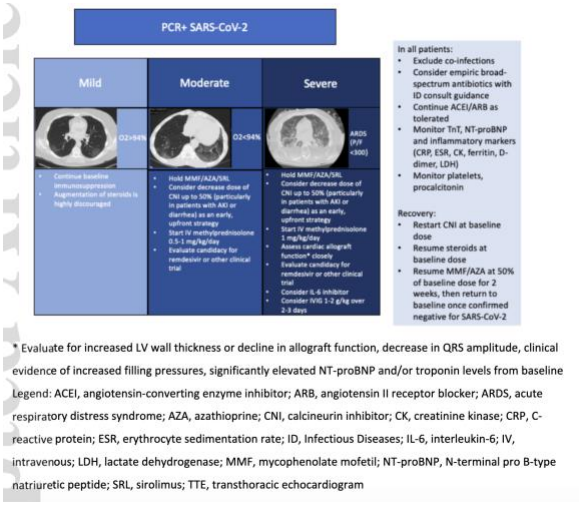
There is limited experience in management of orthotopic heart transplant (OHT) patients with COVID-19. In this study, we present our initial experience using a standardized management algorithm. Data collection was performed on OHT patients with COVID-19 after March 10, 2020 (declaration of state-of-emergency in Massachusetts). Among the 358 OHT patients currently followed at our program, 5 patients (1.4%) tested positive for COVID-19 (median age 50 years [IQR, 49-58], duration post-OHT 21 years [IQR, 6-25], and 4 of 5 (80%) were men). Among the 5 OHT patients, 2 of 5 (20%) had mild disease, and had no change in baseline immunosuppression therapy. Two of 5 (20%) had moderate disease, and received remdesivir as part of a clinical trial, and reduced immunosuppression therapy. One patient (20%) died prior to presenting to the hospital, consistent with 20% case fatality rate.

FIGURES



Legend: ALC, absolute lymphocyte count; AZA, azathioprine; BMI, body mass index; CNI, calcineurin inhibitor, CRP; c-reactive protein; Cyclo, cyclosporine; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase test; MMF, mycophenolate mofetil; NT-proBNP, N-terminal pro b-type natriuretic peptide; N/V, nausea/vomiting, O2, oxygen; Procal, procalcitonin; SRL, sirolimus; Tac, tacrolimus; TnT, high sensitivity Troponin-T; WBC, white blood cell count

Table 1. Clinical characteristics of heart transplant patients with COVID-19



* Evaluate for increased LV wall thickness or decline in allograft function, decrease in QRS amplitude, clinical evidence of increased filling pressures, significantly elevated NT-proBNP and/or troponin levels from baseline

Legend: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARDS, acute respiratory distress syndrome; AZA, azathioprine; CNI, calcineurin inhibitor; CK, creatinine kinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ID, Infectious Diseases; IL-6, interleukin-6; IV, intravenous; LDH, lactate dehydrogenase; MMF, mycophenolate mofetil; NT-proBNP, N-terminal pro B-type natriuretic peptide; SRL, sirolimus; TTE, transthoracic echocardiogram

Figure 1. Management principles for heart transplant patients with COVID-19

THE VARIABILITY OF THE SEROLOGICAL RESPONSE TO SARS CORONA VIRUS-2: POTENTIAL RESOLUTION OF AMBIGUITY THROUGH DETERMINATION OF AVIDITY (FUNCTIONAL AFFINITY)

Bauer G.. J Med Virol. 2020 Jul 7. doi: 10.1002/jmv.26262. Online ahead of print.
Level of Evidence: 3 - Review / Literature Review

BLUF

A proposal authored by Georg Bauer of the Institute of Virology in Germany suggests utilizing IgG avidity to better characterize SARS-CoV-2 infection status based on analysis of 16 recent reports. Current data shows that IgM responses are highly variable with IgG status (Figure 1), making interpretation difficult to determine past infection vs. early infections that could be easily identified with IgG avidity (low avidity = new infection, high avidity = past infection; see Figure 4). While authored by one expert, this recommendation could be beneficial for contact tracing, vaccination programs, and epidemiology.

ABSTRACT

Data on the serological response towards SARS CoV-2 in 16 recent reports were analyzed and a high degree of variability was shown. IgM responses were either found earlier than IgG, or together with IgG, later than IgG or were missing. Therefore, clear distinctions between early, intermediate and past infections are obviously not possible merely on the basis of IgM and IgG determinations. The review of publications on the serology of other virus groups shows that variable IgM responses can be found as well and therefore are not specific for SARS CoV-2 infections. A model to explain this variability is proposed. The inclusion of avidity determination into regular diagnostic procedures has allowed to resolve such "atypical" serological constellations. The potential use of avidity determination for the diagnosis of Covid-19, for risk assessment, epidemiological studies, analysis of cross reactions, as well as for the control of vaccination programs is suggested and discussed.

FIGURES

Figure 1

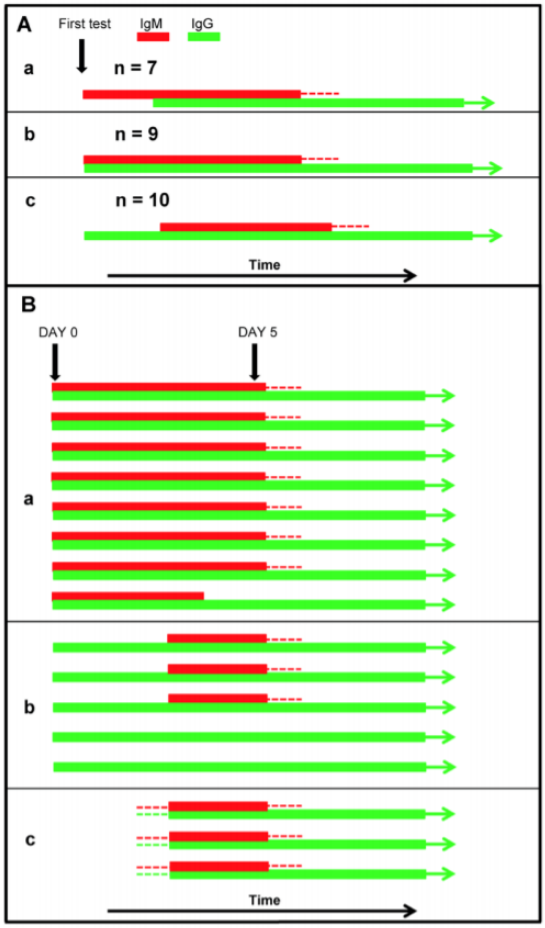


Figure 1. Variability of the serological response to SARS-CoV-2 infection

A. Schematic presentation of key findings presented in Long et al. The analysis of the variability of the serological response in 26 cases of PCR confirmed cases of SARS-CoV-2 infection shows that in 7 cases IgM preceded IgG (a), in 9 cases IgM and IgG seroconversion was determined at the same time (b) and in 10 cases the IgM response was detected after the IgG response (c).
B. Schematic presentation of key findings presented in Zhang et al. The serological response in16 PCR-confirmed cases of SARS-CoV-2 infections was analyzed on day 0 and day 5 after the onset of clinical symptoms. Group a: Eight cases showed positivity for IgM and IgG in parallel on day 0. Parallel positivity of IgG and IgM was maintained on day 5 except for one serum. Group b: Five cases showed IgG, but not IgM on day 0. In three of these cases, the IgM response was detectable on day 5 ("delayed IgM response"). In two cases, no IgM response was detectable at day 5, but acute infection was confirmed by the increase in the IgG response between day 0 and day 5. Group c: In three cases with confirmed infection, no serological response was detectable on day 0. Serum conversion both for IgM and IgG was detectable on day 5.

The data from A and B demonstrate the high variability of the IgM and IgG response after acute SARS-CoV-2 infection. The number of cases with parallel or delayed IgM response (A) and the number of cases with parallel, delayed, negative IgM response (B) compared to the number of expected cases with preceding IgM (according to an outdated classical view) is highly significant ($p = 0.0079$ for A, 0.0005 for B, determined by the Yates continuity corrected chi-square test).

Figure 4

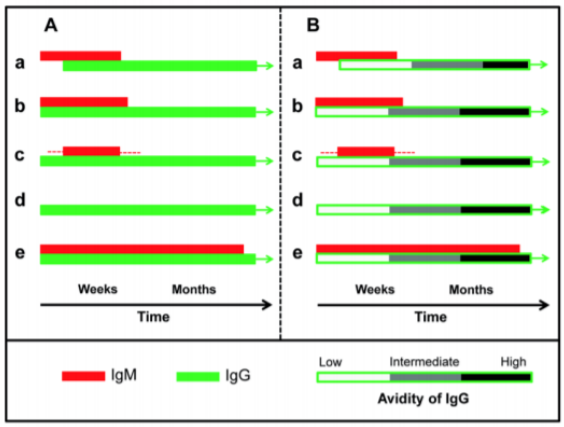


Figure 4: Proposed resolution of serological ambiguity through determination of avidity (functional affinity)

A: Possible serological IgM/IgG constellations following primary viral infection are schematically summarized. In serological practice, the "text book constellation" with IgM seroconversion preceding IgG seroconversion (a) is rather rare. Parallel determination of IgM and IgG usually represents the most frequent case (b). Delayed occurrence of IgM is less frequent (c). In several cases of acute infections, the detection of the IgM may be missed (d). This may be due to low expression of IgM response, problems of sensitivity of the assay used, competition of IgM by IgG during the assay or missing the right time point of positivity of the response. In few cases, IgM responses may persist for long times after primary infection (e). As discussed in the text, constellations a-d have been reported for SARS-CoV-2 infections. Based on the experience with SARS CoV-1 and many other viral systems, constellation e can be predicted to occur as well and may be detected as soon as longer follow up studies will have been performed. Part A shows that the determination of IgM and IgG does not allow to draw an unequivocal conclusion on the time point of infection or beginning of clinical symptoms.

B. The inclusion of IgG avidity allows an unambiguous determination of early, intermediate and past infection, irrespective of the variability of the IgM response. The diagnostic power of avidity determination has been shown for many viral systems. It is suggested to include this general immunological feature into routine diagnostics of SARS-CoV-2 infections.

DEVELOPMENTS IN TREATMENTS

LOPINAVIR/RITONAVIR IS ASSOCIATED WITH PNEUMONIA RESOLUTION IN COVID-19 PATIENTS WITH INFLUENZA COINFECTION: A RETROSPECTIVE MATCHED-PAIR COHORT STUDY

Yu C, Zhang Z, Guo Y, Shi J, Pei G, Yao Y, Liao W, Zeng R.. J Med Virol. 2020 Jul 4. doi: 10.1002/jmv.26260. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A retrospective matched-pair cohort study conducted at Tongji Hospital in Wuhan, China from January 28 to February 18, 2020 examined 64 COVID-19 patients with Influenza A/B co-infection alongside 64 age and sex matched COVID-19 positive controls to understand the effect of co-infection on COVID-19 and the use of lopinavir/ritonavir in these patients. Resolution of lung involvement demonstrated a hazard ratio of 1.878 (p=0.020) for patients treated with lopinavir/ritonavir compared to those not treated with this regiment (95% CI: 1.103, 3.196), suggesting that lopinavir/ritonavir may be beneficial in the treatment of COVID-19 patients with lung involvement (Figures 1-2). Additional findings of the study include:

-Symptoms of fever, cough, hypertension, diabetes, coronary heart disease, and dyspnea were not significantly different between the co-infected and not co-infected groups (All with p>0.199).

-Patients infected with both Influenza A/B and COVID-19 received more lopinavir/ritonavir therapy than patients infected only with COVID-19 (p=0.001).

-Viral shedding time was significantly longer (17 days versus 12 days) for patients with Influenza co-infection than those without co-infection (p=0.001).

ABSTRACT

BACKGROUND: During the early stages of the pandemic, some coronavirus disease (COVID-19)patients were misdiagnosed as having influenza, which aroused the concern that some deaths attributed to influenza were actually COVID-19-related. However, little is known about whether coinfection with influenza contributes to severity of COVID-19 pneumonia, and the optimal therapeutic strategy for these patients. METHODS: We retrospectively studied 128 hospitalized patients with COVID-19 pneumonia. All patients were positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)positive by nucleic acid detection. 64 cases were co-infected with influenza A/B and the other 64 were influenza negative, matched by age, sex, and days from onset of symptoms. RESULTS: Among the 64 co-infected patients, 54 (84.4%) were co-infected with influenza A, and 10 (15.6%) with influenza B. The median duration of viral shedding time from admission was longer for patients with influenza coinfection (17.0 days) than for those without influenza coinfection (12.0 days) (P<0.001). The multivariable Cox proportional hazards model showed that the hazard ratio HR of resolution in lung involvement was 1.878 (P=0.020) for patients administered lopinavir/ritonavir, compared with those not administered lopinavir/ritonavir (95% confidence interval (CI) 1.103, 3.196). Among influenza co-infected patients, those treated with lopinavir/ritonavir exhibited faster pneumonia resolution within two weeks after symptom onset (37% vs 1%, P=0.001). CONCLUSIONS: There was no difference in lung involvement between influenza co-infected and non-infected groups. Lopinavir/ritonavir eliminated the difference of lung involvement between influenza co-infected and non-infected groups, indicating that lopinavir/ritonavir is associated with pneumonia resolution in COVID-19. This article is protected by copyright. All rights reserved.

FIGURES

Table 3. Results of Cox proportional hazards regression model

	B	SE	Wald	df	P	Exp(B)	95.0% CI for Exp(B) Lower	Upper
Influenza (with vs without)	-0.140	0.277	0.257	1	0.612	0.869	0.505	1.495
Oseltamivir (used vs unused)	0.518	0.414	1.564	1	0.211	1.678	0.746	3.778
Lopinavir/ritonavir (used vs unused)	**0.630**	**0.271**	**5.386**	**1**	**0.020**	**1.878**	**1.103**	**3.196**
SARS-CoV-2 turned into negative in 28 days	0.333	0.443	0.564	1	0.453	1.395	0.585	3.327

Note: all variables passed the proportional hazard assumption test (*P*>0.05)

Figures

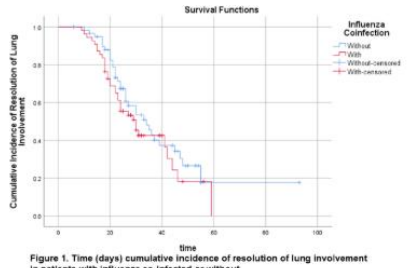


Figure 1. Time (days) cumulative incidence of resolution of lung involvement in patients with influenza co-infected or without.

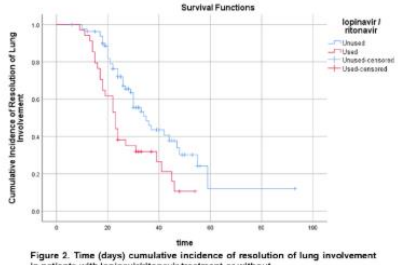


Figure 2. Time (days) cumulative incidence of resolution of lung involvement in patients with lopinavir/ritonavir treatment or without.

CORRIGENDUM TO: SUPPORTING HOSPITAL STAFF DURING COVID-19: EARLY INTERVENTIONS

Billings J, Greene T, Kember T, Grey N, El-Leithy S, Lee D, Kennerley H, Albert I, Robertson M, Brewin CR, Bloomfield MAP.. Occup Med (Lond). 2020 Jul 2:kqaa121. doi: 10.1093/occmed/kqaa121. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

The COVID Trauma Response Group, a joint effort of UK clinicians and the Institute of Mental Health at University College London, offers guidance on providing psychological support to hospital staff during the COVID-19 pandemic. The authors suggest that implementing these recommendations (listed below) may help maintain morale in the workplace while possibly avoiding the need for formal psychological interventions in the future.

SUMMARY

Recommendations include, but are not limited to, the following:

• Meet basic physical needs of access to personal protective equipment, nutrition, rest and sleep. Support staff in attending to self-care.
• Keep lines of communication open, relevant and updated.
• Alternate high and low-stress jobs and be sensitive to workers' personal circumstances.
• Provide clinical and crisis training with an emphasis on mental health consequences.
• Set up regular feedback and staff-check in sessions. Ensure that timely measures are implemented where needed or communicate accordingly over delays.
• Be sensitive and aware of staff with mental health conditions or previous traumas that may be triggered on the job, and address accordingly with additional support.
• Encourage social and peer support within and between teams.
• Implement a buddy system and partner less experienced staff with more experienced members.
• Facilitate team cohesion and strong supportive links between team members and managers and provide opportunities for staff to discuss their experiences.
• Monitor and support staff, providing psychological support and referrals to formal psychological or psychiatric services where needed, such as where symptoms of acute stress disorder (ASD) or post-traumatic stress disorder (PTSD) may be evident.
• Avoid psychological debriefing (PD), critical incident stress debriefing (CISD) or any other single session intervention which involves mandating staff to talk about their thoughts or feelings.
• Avoid non-specific training programs or unproven approaches to psychological treatment.
• Avoid offering formal psychological interventions too soon; instead, first perform proper assessment and monitoring

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