

The Daily COVID-19 Literature Surveillance Summary

June 22, 2020



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COVID-19 Daily Literature Surveillance

COVID19LST



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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

- Researchers from the University of Wisconsin-Madison propose [a framework for early communication of risks](#) for healthcare workers that can inform future communication in public health emergencies.
- An analysis of [the economic impact of COVID-19 on older adults](#) highlights that more than 1/3 of adults 65 years or older live in counties with a high cost of living and increased COVID-19 prevalence demonstrating an overlap between "infection rates and economic insecurities" during COVID-19 with nearly 25% of these adults relying on Social Security benefits that may be insufficient to meet financial needs during a pandemic. The authors encourage employment and economic recovery strategies to take into consideration the older population.

Epidemiology

- A survey was conducted in Israel of 140 ambulatory, non-hospitalized COVID-19 patients that found that while both sexes report common symptoms (ie., cough, weakness, and myalgia), symptoms overall were more frequent among women and olfactory dysfunction, and oral symptoms (dry mouth, taste dysfunction, facial pain, masticatory pain) were common, even in the absence of other symptoms (25.8%), placing increased emphasis in exploring [olfactory dysfunction and oral manifestations](#) to diagnose COVID-19.
- A two-center retrospective study at Wuhan Pulmonary Hospital and Tongji Hospital examining 1,018 COVID-19 patients found that [increased interleukin-6 \(IL-6\) levels \(>20 pg/mL; P<0.001\) and decreased CD8+ T cell levels \(<165 cells/mul; P<0.001\)](#) are both independently associated with increased mortality in patients with COVID-19, suggesting that both of these indicators may help clinicians in prognostication and clinical decision making.
- Researchers at an urban teaching hospital in Lombardy, Italy examined 69 cases of hospitalized [COVID-19 patients ≥80 years of age](#) with 23 patients who died found a significant association between severe dementia and increased mortality and independent risk factors for death in this population included a lactate dehydrogenase level >464 U/L and an oxygen saturation level ≤90% at admission.

Understanding the Pathology

- A [SARS-CoV-2 genomic and phylogenetic analysis](#) in India discovered four unique sequence regions that interact with the angiotensin converting enzyme (ACE)-2 receptor and may be potential targets for antibody vaccine design and revealed that bat SARS-CoV genome is the closest homolog of human SARS-CoV-2, supporting evidence that the COVID-19 outbreak originated from bat-to-human zoonotic transmission.

Management

- A case series of 63 [positive end-expiratory pressure \(PEEP\) titrations performed in 15 patients with COVID-19-related ARDS using electrical impedance tomography \(EIT\)](#) found that high PEEP were from personalized PEEP at the level of lowest relative alveolar overdistention and collapse, PEEP set was positively correlated to BMI ($p < 0.001$), and individualized PEEP titration could result in improved clinical outcomes but further research is needed to confirm whether this personalized PEEP titration approach is safe and effective.
- A case series of 21 [rheumatic patients with COVID-19](#) who were admitted to Tongji Hospital in Wuhan, China were found to have symptomatology and inflammatory biomarkers that also appeared similar to flares in rheumatic conditions, emphasizing the importance of distinguishing between the two ailments to ensure patients are treated appropriately.

Adjusting Practice During COVID-19

- Guidelines and recommendations for adjusting clinical practice include:
 - Practitioners from King County, Washington developed guidelines for management of [sexually transmitted infections \(STI\)](#).
 - The Department of Pediatrics at the University of California, Davis shares the institution's methodology of [stratifying pediatric patients who may need endoscopic procedures](#) and their recommendations on use of personal protective equipment (PPE) during aerosol-generating procedures.
 - Chinese authors present effective and protective measures for managing [urological diseases](#).

- The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition distributed surveys to participating centers (102 worldwide) to [determine global trends in patients with pediatric inflammatory bowel disease \(PIBD\)](#) during the pandemic and found eight cases of PIBD patients testing positive for SARS-CoV-2, all with mild presentation of symptoms and none-requiring hospital admission or disruption of current IBD treatment protocols.

R&D: Diagnosis & Treatments

- An experiment conducted at the University of Paris tested the efficacy of [the Orient Gene COVID-19 IgG/IgM Rapid Test Cassette](#) at multiple time points and compared it to a previously validated antibody test (Abbott SARS-CoV-2 IgG Immunoassay). In patients with known COVID-19 and results interpreted by unblinded clinical microbiologists, the Orient Gene test had a sensitivity of 95.8% and a specificity of 100%, suggesting clinical utility of this test with needed validation with a larger asymptomatic group.
- A retrospective cohort conducted at Daegu Catholic University School of Medicine in Korea found that 31 COVID-19-positive patients treated with [lopinavir-ritonavir had significantly shorter times to negative conversion of viral RNA than 34 COVID-19-positive patients treated with hydroxychloroquine](#) (median, 21 days vs. 28 days; Figure 2); however, time until clinical improvement was not found to be different between these groups.

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CLIMATE

GLOBAL

COVID-19 AND ANTIMICROBIAL RESISTANCE: PARALLEL AND INTERACTING HEALTH EMERGENCIES

Nieuwlaat R, Mbuagbaw L, Mertz D, Burrows L, Bowdish DME, Moja L, Wright GD, Schünemann HJ.. Clin Infect Dis. 2020 Jun 16:ciaa773. doi: 10.1093/cid/ciaa773. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

This expert opinion by researchers in Canada and Switzerland draws parallels between the COVID-19 pandemic and the increase in Antimicrobial Resistance (AMR), suggesting that the same urgency and international collaboration are necessary to combat AMR. The authors believe we should be learning lessons from the COVID-19 outbreak to apply to the issue of AMR, as well as understanding how the COVID-19 outbreak affects trends in AMR. They hypothesize that the current use of antibiotics to treat COVID-19 may increase AMR, while the policies of social distancing will likely decrease infectious disease transmission, possibly slowing down the rate of AMR. Ultimately, they recommend researchers begin collecting data to measure the impact of COVID-19 on AMR.

ABSTRACT

The COVID-19 pandemic and antimicrobial resistance are parallel and interacting health emergencies with opportunity for mutual learning. As their measures and consequences are comparable, the COVID-19 pandemic helps to illustrate the potential long-term impact of AMR, which is less acute but not less crucial. They may also impact each other as there is a push to resort to existing antimicrobials in critically ill COVID-19 patients in the absence of specific treatments, while attempts to manage the spread of COVID-19 may also lead to a slow down AMR. Understanding how COVID-19 affects AMR trends and what we can expect if these remain the same or worsen, will help us plan next steps to tackle AMR. Researchers should now start collecting data to measure the impact of current COVID-19 policies and programs on AMR.

AFFECTING THE HEALTHCARE WORKFORCE

CRISIS COMMUNICATION AND PUBLIC PERCEPTION OF COVID-19 RISK IN THE ERA OF SOCIAL MEDIA

Malecki K, Keating JA, Safdar N.. Clin Infect Dis. 2020 Jun 16:ciaa758. doi: 10.1093/cid/ciaa758. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Researchers from the University of Wisconsin-Madison discuss the manner in which healthcare providers communicate with the public regarding the dangers of COVID-19 and how this affects the public's perception of risk. They discuss cultural factors, the pervasive influence of social media, and the novelty of COVID-19 as sources that affect hazard (number of people exposed and infected) and subsequent outrage (public perception of risk and response to risk mitigation measures) (see Table 1). They propose a framework for early communication of risks that can inform future communication in public health emergencies (Figure 1).

ABSTRACT

A number of important principles in effective risk communication established in the late 20th century can provide important scientific insight into patient response to the risks posed by COVID-19 [1-3]. Early risk communication scholars studied public perceptions of risk in response to environmental disasters, or infectious disease outbreaks. They found acceptability of risk, and any limitations and acceptability of response by experts was shaped by two key components: hazard and outrage. The number of people who are exposed, infected and fall ill can be considered the hazard. How the public and patients perceive the risk and respond to messages regarding risk mitigation relates to outrage. Social and cultural factors, immediacy, uncertainty, familiarity, personal control, scientific uncertainty and trust in institutions and media all shape acceptability of response. These outrage factors influence the ever-changing public understanding of COVID-19 risk, as well as the public's acceptance of personal and societal mitigation strategies. Risk perceptions and acceptability of mitigation strategies are also largely shaped

in the context of culture and society. In concert, hazard and outrage along with cultural and economic context shape adherence to, and overall acceptance of, personal mitigation strategies including wearing facemasks, and social distancing among the general public. The spread of misinformation on social media in the context of crisis communication provides both challenges and opportunities for experts and officials to effectively communicate and influence these outrage factors. Social media offers an opportunity for experts to quickly convey true information about hazards, but offers others the opportunity to counter this with the spread of misinformation and exacerbate outrage. We propose strategies for infectious diseases clinicians to apply risk communication principles and frameworks to improve patient care and public message development in response to COVID-19.

FIGURES

Table 1. Outrage Factors Influencing Public Perceptions of Risk and Acceptability of Risk

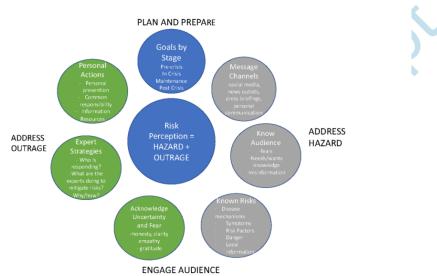
Mitigation Strategies over Time^A

Factors Influencing Public Perceptions of Risks*	Directionality of Increased Risk Perception (Increased outrage, lower acceptability of risk)	Changing Public Risk Perception Over Time in the US Regarding COVID-19 Pandemic (December 2019- April 2020)		
		Prevention	Pre-Crisis	Crisis
High Catastrophic Potential	Fatalities and injuries grouped in time and space rather than random and scattered	Low	Low/med	High
Familiarity	Unfamiliar	High	Med	Low
Understanding	Difficult to understand	High	High	High
Scientific Uncertainty	High scientific uncertainty	High	High	High
Controllable	Lack of personal control and agency	High	High	High/Low
Voluntariness	Involuntary vs. Voluntary	Low	High	Low
Trust in Institutions*	Lack of trust	Low	High/Low	High/Low
Media Attention	High vs. Low media attention	Low	High	High

*Note- the perception of risk can vary by context, and cultural beliefs of the public audience.

^A Adapted from Below From Appendix C – from ³ Covello VT, Sandman PM, Slovic P. Risk Communication, Risk Statistics, and Risk Comparison: A Manual for Plant Managers. Washington, D.C.: Chemical Manufacturers Association, 1988.

Figure 1. Crisis Communication: Addressing Hazard + Outrage During the COVID 19 Pandemic



HOW WE MAKE CHOICES AND SACRIFICES IN MEDICAL EDUCATION DURING THE COVID-19 PANDEMIC

Tolsgaard MG, Cleland J, Wilkinson T, Ellaway RH.. Med Teach. 2020 May 22:1-3. doi: 10.1080/0142159X.2020.1767769. Online ahead of print.

Level of Evidence: Other -

BLUF

In this commentary, the authors provide a broad framework for considering changes in healthcare education in the time during and following the COVID-19 pandemic. In order to maintain the integrity of the future healthcare workforce, the authors suggest "triaging" educational activities based on their necessity at present and their necessity to train a fruitful future healthcare workforce.

ABSTRACT

In this commentary, we highlight some of the pressing choices and sacrifices we must make in medical education during the COVID-19 pandemic.

DISPARITIES

OLDER ADULTS AND THE ECONOMIC IMPACT OF THE COVID-19 PANDEMIC

Li Y, Mutchler JE.. J Aging Soc Policy. 2020 Jun 16:1-11. doi: 10.1080/08959420.2020.1773191. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Authors affiliated with the University of Massachusetts, Boston present an analysis of the economic impact of COVID-19 on older adults. The authors highlight that more than one-third of adults 65 years or older live in counties with a high cost of living and increased COVID-19 prevalence demonstrating an overlap between "infection rates and economic insecurities" during COVID-19. Furthermore, nearly 25% of these adults rely on Social Security benefits, which, the authors explain, may be insufficient to meet financial needs during a pandemic. Thus, the authors encourage employment and economic recovery strategies should take into account the older population.

ABSTRACT

The COVID-19 pandemic has impacted communities throughout the United States and worldwide. While the implications of the concomitant economic downturn for older adults are just beginning to be recognized, past experience suggests that the consequences could be devastating for many. Analyses indicate that more than one out of five Americans aged 65 years or older live in counties where high infection rates and high economic insecurity risks occur simultaneously. These findings highlight the overlap between current infection patterns and subsequent challenges to economic security that are impacting older people. Strategies and supports for getting people back to work must take into account the large segment of older people who rely on earnings well into later life. Social Security serves as the foundation of economic security for older adults across the income continuum, but it is frequently insufficient in and of itself, let alone during a crisis. Recognizing the importance of cost of living in shaping economic security highlights the need for the federal and state governments and municipalities to take older people into account in the economic recovery effort.

SOCIAL JUSTICE, TRIAGE, AND COVID-19: IGNORE LIFE-YEARS SAVED

Stone JR.. Med Care. 2020 Jul;58(7):579-581. doi: 10.1097/MLR.0000000000001355.

Level of Evidence: Other - Expert Opinion

BLUF

A bioethics expert at Creighton University School of Medicine in Nebraska argues that triage decisions of life saving resources should not focus on life-years saved since that does not account for inequities that reduce life-years saved for certain populations. Instead they propose that a triage model should be consistent with a justice-respect-worth framework and triage decisions should be made by a diverse team including representatives of disenfranchised and oppressed groups.

A MULTICRITERIA APPROACH FOR RISK ASSESSMENT OF COVID-19 IN URBAN DISTRICT LOCKDOWN

Sangiorgio V, Parisi F.. Saf Sci. 2020 Oct;130:104862. doi: 10.1016/j.ssci.2020.104862. Epub 2020 Jun 6.

Level of Evidence: Other - Modeling

BLUF

Researchers in Italy used data from the COVID-19 outbreak in Italy to model the risk of reopening urban cities in Italy. The first phase of the modeling used a multicriteria approach to determine the parameters that may increase the risk of contracting COVID-19 (Figure 1). The researchers then determined the influence of each parameter, with age of inhabitants being the largest parameter (34%), followed by cafe/restaurant density, non-immune people, infected people, and population density which all had a 13% influence (Figure 3). Researchers then used two different analyses to determine the risk in 257 urban districts of the Apulia region of Italy. The authors suggest that many urban areas are at a higher risk of infection if they are partially or fully reopened as opposed to continuing full lockdown (Figure 4).

ABSTRACT

At the beginning of 2020, the spread of a new strand of Coronavirus named SARS-CoV-2 (COVID-19) raised the interest of the scientific community about the risk assessment related to the viral infection. The contagion became pandemic in few months forcing many Countries to declare lockdown status. In this context of quarantine, all commercial and productive activities are suspended, and many Countries are experiencing a serious crisis. To this aim, the understanding of risk of contagion in every urban district is fundamental for governments and administrations to establish reopening strategies. This paper proposes the calibration of an index able to predict the risk of contagion in urban districts in order to support the administrations in identifying the best strategies to reduce or restart the local activities during lockdown conditions. The objective regards the achievement of a useful tool to predict the risk of contagion by considering socio-economic data such as the presence of activities, companies, institutions and number of infections in urban districts. The proposed index is based on a factorial formula, simple and easy to be applied by practitioners, calibrated by using an optimization-based procedure and exploiting data of 257 urban districts of Apulian region (Italy). Moreover, a comparison with a more refined analysis, based on the training of Artificial Neural Networks, is performed in order to take into account the non-linearity of the phenomenon. The investigation quantifies the influence of each considered parameter in the risk of contagion useful to obtain risk analysis and forecast scenarios.

FIGURES

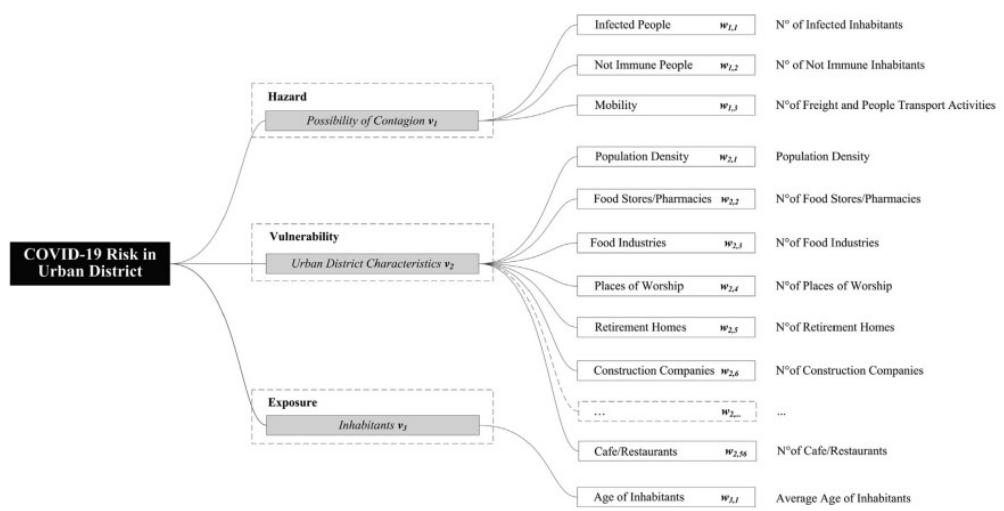


Fig. 1. Structure of the problem in Criteria, Sub-Criteria and Intensity.

Figure 1. Structure of the problem in Criteria, Sub-Criteria and Intensity

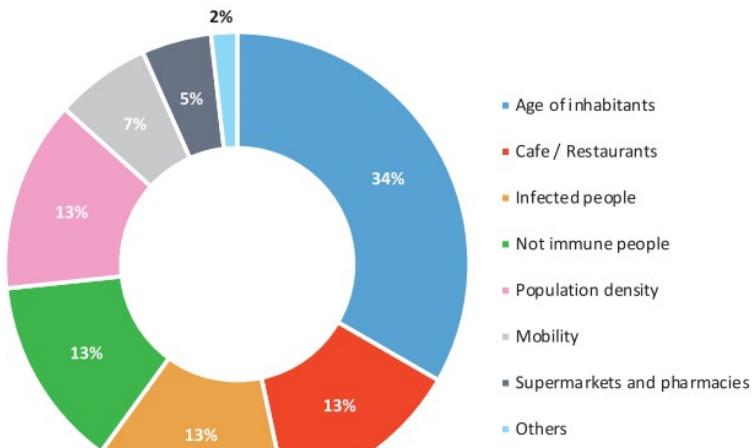


Fig. 3. Influence of each parameter in the risk of contagion for Covid-19.

Figure 3. Influence of each parameter in the risk of contagion for Covid-19.

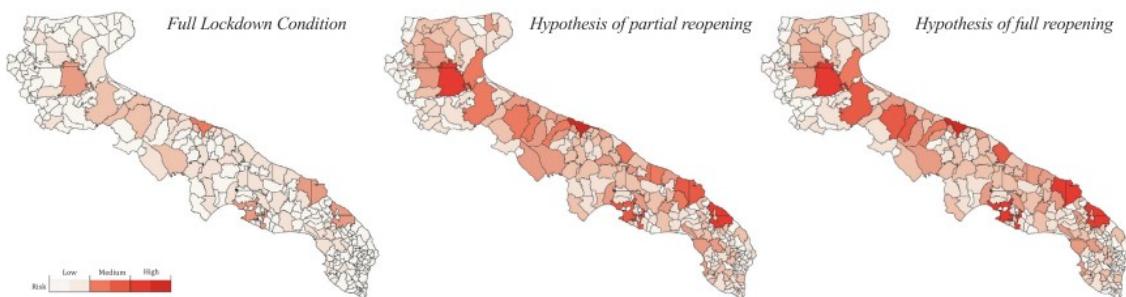


Fig. 4. Risk maps of contagion for Covid-19 for three regional scenarios.

Figure 3. Influence of each parameter in the risk of contagion for Covid-19.

SYMPTOMS AND CLINICAL PRESENTATION

OLFACTOORY AND GUSTATORY DYSFUNCTION AS AN EARLY IDENTIFIER OF COVID-19 IN ADULTS AND CHILDREN: AN INTERNATIONAL MULTICENTER STUDY

Qiu C, Cui C, Hautefort C, Haehner A, Zhao J, Yao Q, Zeng H, Nisenbaum EJ, Liu L, Zhao Y, Zhang D, Levine CG, Cejas I, Dai Q, Zeng M, Herman P, Jourdain C, de With K, Draf J, Chen B, Jayaweera DT, Denneny JC 3rd, Casiano R, Yu H, Eshraghi AA, Hummel T, Liu X, Shu Y, Lu H.. Otolaryngol Head Neck Surg. 2020 Jun 16:194599820934376. doi: 10.1177/0194599820934376. Online ahead of print.

Level of Evidence: 4 - Case-series

BLUF

A retrospective study conducted at five tertiary care hospitals (three in China and one each in France and Germany) examined the incidence and manifestation of olfactory and/or gustatory dysfunction in COVID-19 patients between 15 March and 5 April, 2020. Of 394 patients, 161 presented with these symptoms. The authors found the following:

- 12% of patients in China, 4% in Germany, and 9% in France had olfactory and gustatory symptoms as the first and only symptom (Table 1).
- 23% of patients in China, 15% in Germany, and 15% in France presented with olfactory or gustatory symptoms before any other symptom of COVID-19 (Table 1).
- In all three countries, 25% of children originally presented with only gustatory or olfactory symptoms (Table 3).

Overall, their findings suggest that olfactory and gustatory symptoms should play an important role in early screening and disease control. The authors call for the widespread use of screening questions related to gustatory and olfactory changes as part of early diagnosis of COVID-19.

ABSTRACT

OBJECTIVE: To evaluate the prevalence and characteristics of olfactory or gustatory dysfunction in coronavirus disease 2019 (COVID-19) patients.

STUDY DESIGN: Multicenter case series.

SETTING: Five tertiary care hospitals (3 in China, 1 in France, 1 in Germany).

SUBJECTS AND METHODS: In total, 394 polymerase chain reaction (PCR)-confirmed COVID-19-positive patients were screened, and those with olfactory or gustatory dysfunction were included. Data including demographics, COVID-19 severity, patient outcome, and the incidence and degree of olfactory and/or gustatory dysfunction were collected and analyzed. The Questionnaire of Olfactory Disorders (QOD) and visual analog scale (VAS) were used to quantify olfactory and gustatory dysfunction, respectively. All subjects at 1 hospital (Shanghai) without subjective olfactory complaints underwent objective testing.

RESULTS: Of 394 screened subjects, 161 (41%) reported olfactory and/or gustatory dysfunction and were included. Incidence of olfactory and/or gustatory disorders in Chinese (n = 239), German (n = 39), and French (n = 116) cohorts was 32%, 69%, and 49%, respectively. The median age of included subjects was 39 years, 92 of 161 (57%) were male, and 10 of 161 (6%) were children. Of included subjects, 10% had only olfactory or gustatory symptoms, and 19% had olfactory and/or gustatory complaints prior to any other COVID-19 symptom. Of subjects with objective olfactory testing, 10 of 90 demonstrated abnormal chemosensory function despite reporting normal subjective olfaction. Forty-three percent (44/102) of subjects with follow-up showed symptomatic improvement in olfaction or gustation.

CONCLUSIONS: Olfactory and/or gustatory disorders may represent early or isolated symptoms of severe acute respiratory syndrome coronavirus 2 infection. They may serve as a useful additional screening criterion, particularly for the identification of patients in the early stages of infection.

FIGURES

Characteristics	Countries			
	China	Germany	France	Total
Olfactory/gustatory dysfunction, No./total screened No. (%)	77/239 (32)	27/39 (69)	57/116 (49)	161/394 (41)
Symptoms, No./total screened No. (%)				
Only olfactory dysfunction	47/239 (20)	7/39 (18)	7/116 (6)	61/394 (15)
Only gustatory dysfunction	6/239 (3)	1/39 (3)	0/116 (0)	7/394 (2)
Olfactory and gustatory dysfunctions	24/239 (10)	19/39 (49)	50/116 (43)	93/394 (24)
Age of enrolled subjects, median ± SD (IQR)	30.5 ± 16.2 (20, 35)	43.1 ± 15.2 (32, 55.5)	48.1 ± 15.3 (33, 60)	38.8 ± 17.6 (23, 53)
Sex of enrolled subjects, No./total enrolled No. (%)				
Male	45/77 (58)	13/27 (48)	34/57 (60)	92/161 (57)
Female	32/77 (42)	14/27 (52)	23/57 (40)	69/161 (43)
COVID-19 severity in enrolled subjects, No./total enrolled No. (%)				
Asymptomatic	0/77 (0)	0/27 (0)	0/57 (0)	0/161 (0)
Mild	26/77 (34)	27/27 (100)	25/57 (44)	78/161 (48)
Moderate	40/77 (52)	0/27 (0)	0/57 (0)	40/161 (25)
Severe	11/77 (14)	0/27 (0)	22/57 (39)	33/161 (20)
Critical	0/77 (0)	0/27 (0)	10/57 (18)	10/161 (6)
Onset of olfactory/gustatory dysfunction, No./total enrolled No. (%)				
As the only symptom of COVID-19	9/75 (12) ^a	1/27 (4)	5/54 (9) ^b	15/156 (10) ^{a,b}
Before general symptoms of COVID-19	17/75 (23) ^a	4/27 (15)	8/54 (15) ^b	29/156 (19) ^{a,b}
At the same time as general symptoms of COVID-19	5/75 (7) ^a	4/27 (15)	21/54 (39) ^b	30/156 (19) ^{a,b}
After general symptoms of COVID-19	44/75 (59) ^a	18/27 (67)	20/54 (37) ^b	82/156 (53) ^{a,b}
Outcome of olfactory/gustatory symptoms, No./total enrolled No. (%)				
Improved	34/77 (44)	Unknown/27 ^c	10/25 (40) ^d	44/102 (43) ^e
Nonimproved	43/77 (56)	Unknown/27 ^c	15/25 (60) ^{d,f}	58/102 (57) ^e

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

^aTwo patients in China could not remember the date of onset of olfactory or gustatory dysfunction.

^bThree patients in France could not remember the date of onset of olfactory or gustatory dysfunction.

^cThe patients' improvement in Germany is unavailable.

^dOnly 25 patients were followed in France.

^eStatistics for China (77 cases) and France (25 cases).

^fThree critical patients died of COVID-19.

Table 1. Characteristics of COVID-19 Patients Presenting With Olfactory/Gustatory Dysfunction.

Characteristics	Children
Total enrolled No./total observed No. (%)	10/27 (37)
Age, median \pm SD (IQR), y	16.6 \pm 0.7 (16.3, 17)
Sex, No./total enrolled No. (%)	
Male	6/10 (60)
Female	4/10 (40)
COVID-19 severity classification, No./total enrolled No. (%)	
Asymptomatic	0/10 (0)
Mild	6/10 (60)
Moderate	4/10 (40)
Severe	0/10 (0)
Critical	0/10 (0)
Symptoms, No./total observed No. (%)	
Only olfactory dysfunction	3/27 (11)
Only gustatory dysfunction	0/10 (0)
Olfactory and gustatory dysfunctions	7/27 (26)
Onset of olfactory/gustatory dysfunction, No./total enrolled No. (%)	
As the only symptom of COVID-19	2/8 (25) ^a
Before general symptoms of COVID-19	0/8 (0) ^a
At the same time as general symptoms of COVID-19	1/8 (13) ^a
After general symptoms of COVID-19	5/8 (63) ^a
Outcome of olfactory/gustatory symptom, No./total enrolled No. (%)	
Improved	3/9 (33) ^b
Nonimproved	6/9 (67) ^b

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

^aTwo children could not remember the date of onset of olfactory or gustatory dysfunction.

^bFollow-up was not obtained for 1 child in the German cohort.

Table 3. Characteristics of COVID-19-Positive Children Presenting With Olfactory/Gustatory Dysfunction.

ADULTS

OLFACTORY AND ORAL MANIFESTATIONS OF COVID-19: SEX-RELATED SYMPTOMS-A POTENTIAL PATHWAY TO EARLY DIAGNOSIS

Biadsee A, Biadsee A, Kassem F, Dagan O, Masarwa S, Ormianer Z.. Otolaryngol Head Neck Surg. 2020 Jun 16:194599820934380. doi: 10.1177/0194599820934380. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A survey was conducted in Israel between March 25 and April 15, 2020 to analyze COVID-19 symptom differences between men and women ($n = 140$ ambulatory, nonhospitalized patients). Findings suggest that while both sexes report common symptoms (ie, cough, weakness, and myalgia), symptoms overall were more frequent among women (Figure 2). Additionally, olfactory dysfunction and oral symptoms (dry mouth, taste dysfunction, facial pain, masticatory pain) were common, even in the absence of other symptoms (25.8%). Thus, the authors advocate for further clinical studies exploring olfactory dysfunction and oral manifestations to diagnose COVID-19.

ABSTRACT

OBJECTIVE: The coronavirus disease 2019 (COVID-19) pandemic poses a threat to global health. Early diagnosis is an essential key to limit the outbreak of the virus.

STUDY DESIGN: Case series, study conducted between March 25, 2020, and April 15, 2020. **SETTING:** Ambulatory, nonhospitalized patients who were quarantined in a designated hotel for COVID-19 patients and were recruited by an advertisement at the hotel.

SUBJECTS AND METHODS: In total, 140 patients participated in a web-based questionnaire assessing initial symptoms of common viral diseases, olfactory and taste functions, xerostomia, and orofacial pain.

RESULTS: A total of 58 men and 70 women participated. Initial symptoms were cough (59.4%), weakness (47.7%), myalgia (46.9%), fever (42.2%), headache (40.6%), impaired sense of smell (38.3%), impaired sense of taste (32.8%), sore throat (26.6%), runny nose (26.6%), and nasal congestion (22.7%). All symptoms were more frequent among women; however, only runny nose was statistically significant ($P = .018$). The most common combination of symptoms was cough and weakness (37.5%). A total of 25.8% reported olfactory and taste dysfunctions in the absence of other symptoms. In a comparison between the sexes, cough and runny nose were the most common combination in women ($P = .018$). A total of 38.3% of patients reported olfactory dysfunction as an initial symptom. Anosmia and facial pain were more common among women ($P < .001$ and $P = .01$, respectively), and 56% of patients reported xerostomia.

CONCLUSION: A considerable number of patients presented with olfactory and oral disorders. Interestingly, women presented with a different cluster of symptoms than men, which may suggest a new clinical approach to diagnosing COVID-19 disease.

FIGURES

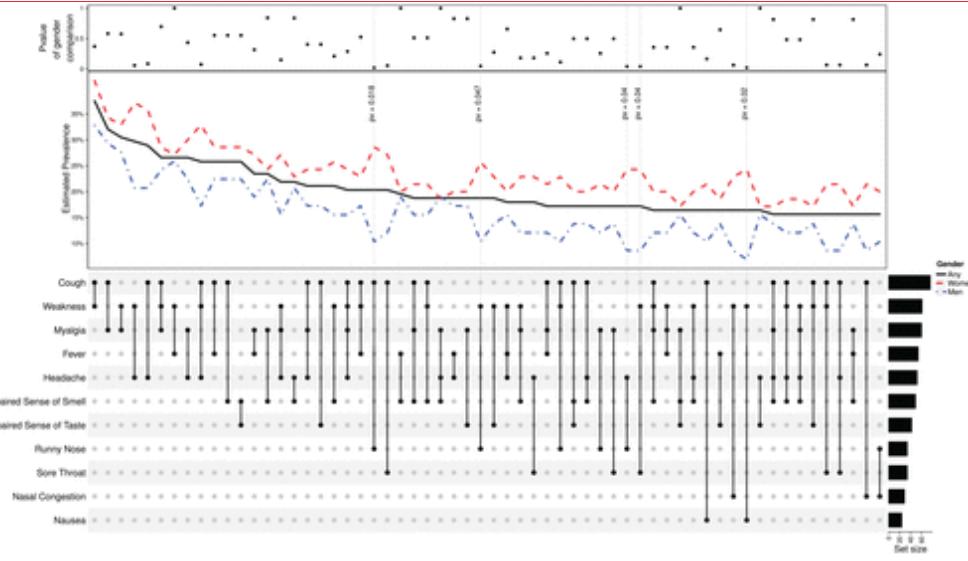


Figure 2. Combinations of initial symptoms. The grid in the lower part maps the combination of symptoms examined (x-axis); the corresponding value on the y-axis is the overall prevalence in the sample (black solid line), prevalence among men (blue dot-dashed line), and prevalence among women (red dashed line). The upper panel reports that Fisher's odds ratio test for the null odds ratio of men vs women is 1. For example, the far-left column shows the prevalence of patients who experienced both cough and weakness: ≈35% overall, ≈33% of women, and ≈41% of men. Odds ratio with $P \approx .4$. Sixty most frequent combinations are displayed; in 5 combinations, women had significantly increased odds compared to men with $P < .05$ (gray vertical lines).

IL-6 COMBINED WITH CD8+ T CELL COUNT EARLY PREDICT IN-HOSPITAL MORTALITY FOR PATIENTS WITH COVID-19

Luo M, Liu J, Jiang W, Yue S, Liu H, Wei S.. JCI Insight. 2020 Jun 16:139024. doi: 10.1172/jci.insight.139024. Online ahead of print.

Level of Evidence: 4 - Case-series

BLUF

A two-center retrospective study at Wuhan Pulmonary Hospital and Tongji Hospital examined 1018 cases of patients with COVID-19 confirmed via RT-PCR between 9 January and 31 March, 2020. They found that increased interleukin-6 (IL-6) levels ($P < 0.001$) and decreased CD8+ T cell levels ($P < 0.001$) are both independently associated with increased mortality in patients with COVID-19 (Table 3), suggesting that both of these indicators may help clinicians in prognostication and clinical decision making.

ABSTRACT

BACKGROUND: The numbers of fatal cases of Coronavirus Disease 2019 (COVID-19) continue to increase rapidly around the world. We aim to retrospectively investigate potential roles of factors, mainly immunologic parameters, in early predicting outcomes of patients with COVID-19.

METHODS: A total of 1,018 patients confirmed COVID-19 were enrolled in our retrospective study from two centers. The data of clinical features, laboratory tests, immunological tests, radiological findings, and outcomes were collected. Univariate and multivariable logistic regression analysis were performed to evaluate factors associated with in-hospital mortality. Receiver operator characteristic (ROC) curves and survival curves were plotted to evaluate the clinical usefulness.

RESULTS: Compared to the survival patients, the counts of all T lymphocytes subsets were markedly lower in non-survivors ($P < 0.001$), especially in CD8+ T cells (96.89 vs 203.98 cells/mul, $P < 0.001$). Among all tested cytokines, IL-6 elevated most significantly with an upward trend of more than ten times (56.16 vs 5.36 pg/mL, $P < 0.001$). By a multivariable logistic regression analysis, two immunological indicators were found to be associated with in-hospital mortality, including IL-6 > 20 pg/mL (OR = 9.781; 95%CI, 6.304-15.174; $P < 0.001$) and CD8+ T cell count < 165 cells/mul (OR = 5.930; 95%CI, 3.677-9.562; $P < 0.001$), after adjusting confounding factors (age, gender, and underlying diseases). All the patients were divided into four groups according to levels of IL-6 and CD8+ T cells. The group with IL-6 > 20 pg/mL and CD8+ T cell count < 165 cells/mul had more old and male patients, as well as more proportion of patients with comorbidities, ventilation, ICU admission, shock, and death than those of any other group ($P < 0.001$). Furthermore, the ROC curve of the model combining IL-6 (>20 pg/mL) and CD8+ T cell count(<165 cells/mul) displayed more favorable discrimination than that of CURB-65 score (area under curve

(AUC) = 0.907 vs 0.843, P < 0.001). Hosmer-Lemeshow test showed a good fitting of the model with no statistical significance (P = 0.581).

CONCLUSIONS: We firstly identify two reliable prognostic indicators, IL-6 (>20 pg/mL) and CD8+ T cell count (<165 cells/mul), which can accurately stratify patients into risk categories and predict mortality of patients with COVID-19. Those two indicators combined may guide clinicians to evaluate patient prognosis and make appropriate decisions.

FIGURES

Variables	Univariate				Multivariate [#]			
	β	OR	CI	P value	β	OR	CI	P value
IL6>20 pg/mL	2.954	19.176	12.815-28.696	<0.001	2.280	9.781	6.304-15.174	<0.001
CD8+<165 cells/ μ L	2.583	13.326	8.649-20.257	<0.001	1.780	5.930	3.677-9.562	<0.001

In adjusting for age, gender, and underlying diseases including hypertension, coronary heart disease, diabetes mellitus and underlying pulmonary diseases

Table 3. Univariable and multivariable logistic regression analysis of mortality related risks in patients with COVID-19.

BRAINSTEM INVOLVEMENT AND RESPIRATORY FAILURE IN COVID-19

Manganelli F, Vargas M, Iovino A, Iacovazzo C, Santoro L, Servillo G.. Neurol Sci. 2020 May 29. doi: 10.1007/s10072-020-04487-2. Online ahead of print.

Level of Evidence: 4 - Case-series

BLUF

A case series conducted May 2020 in Naples, Italy at Federico II Hospital suggests that the time COVID-19 patients spend mechanically ventilated may be associated with SARS-CoV-2 effects on the brain's respiratory centers. Based on three ICU cases they propose that, similar to SARS-CoV and MERS-CoV, the virus propagates along cranial nerves such as the olfactory and vagus nerves (damaging special afferents responsible for smell and taste). They hypothesize this propagation continues until the virus reaches the solitary nucleus where it damages brain centers responsible for respiration. (Please see the summary for further information on the cases).

SUMMARY

- Patient 1: 66 y.o. male intubated for 18 days, sedation interrupted for six days, generalized slow EEG activity, no gross structural changes on MRI (see Figure 1), failure to regain spontaneous respirations, died six days after neurological exam.
 - Patient 2: 47 y.o. female intubated for 22 days, sedation interrupted for six days, generalized slow EEG activity, no structural changes noted on MRI (see Figure 1), failure to regain spontaneous respirations, died four days after neurological exam.
 - Patient 3: 67 y.o. female intubated for 13 days, sedation interrupted for four days, generalized slow EEG activity, patient was able to maintain spontaneous respirations but not sufficiently to be taken off ventilator support.
- The authors were unable to identify any gross structural abnormalities on TC scan in any of the patients (imaging from Patient 3 not provided in paper). However, they did note "hyperintense punctiform gilotic foci in right pons" on the TC scan of Patient 3. The authors did not provide outcome of Patient 3, but do not report death after weaning of ventilation.

ABSTRACT

Respiratory failure is the most worrisome problem of COVID-19. Patients may develop severe pneumonia requiring invasive mechanical ventilation and a significant proportion of them dies. It has been suggested that brainstem might play a role in severe respiratory failure of COVID-19 patients. We described three COVID-19 patients in ICU at Federico II Hospital in Naples that, although had recovered from pneumonia, could not be weaned from invasive mechanical ventilation. Our clinical evaluation was consistent with an involvement of the brainstem and especially of respiratory centre thus possibly explaining the weaning failure in patients that were awake and had recovered from lung involvement. Our data, though limited, indicate that brainstem involvement may play a role in respiratory failure and perhaps in the high death rate of COVID-19 patients. Moreover, the weaning failure from mechanical ventilation due to central respiratory drive depression might underlie the unusual long stay in ICU reported for COVID-19 patients.

FIGURES

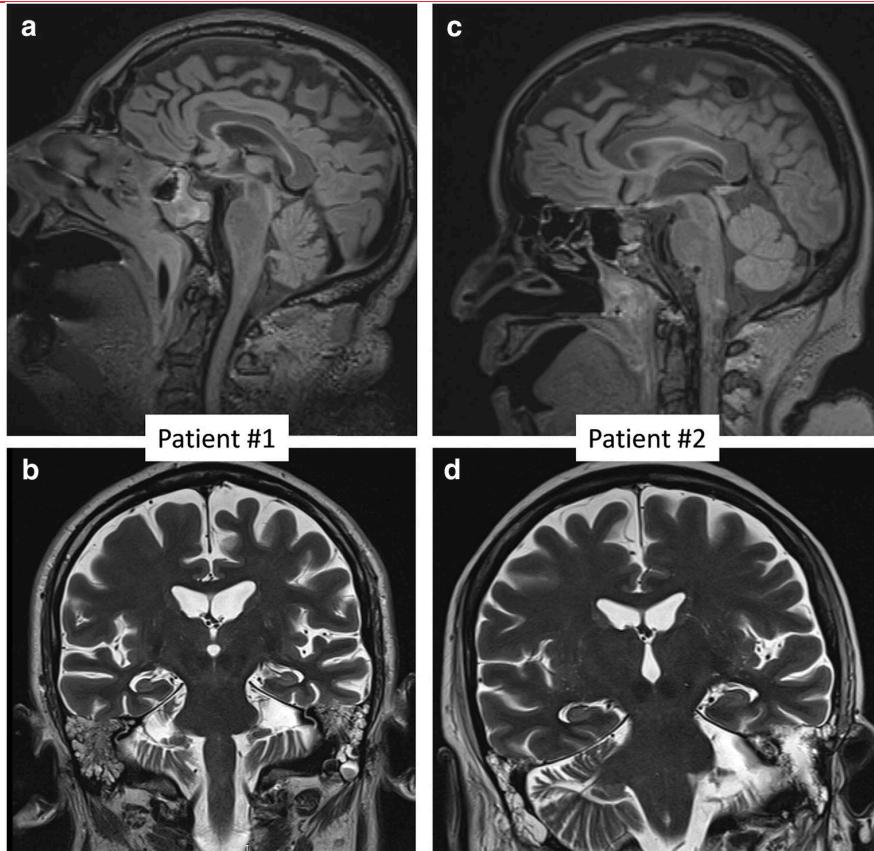


Figure 1: Brain MRI sagittal FLAIR (a, c) and coronal T2-weighted (b, d) images from patient #1 (a, b) and #2 (c, d). No structural changes are visible

ANTICARDIOLIPIN ANTIBODIES AND COVID-19 - A CASE REPORT FROM AMERICA

Manrique JV, Ghosh K, Boma N.. J Med Virol. 2020 Jun 4. doi: 10.1002/jmv.26135. Online ahead of print.

Level of Evidence: Other - Case Report

BLUF

A case report from the Metropolitan Hospital Center in New York describes an 82-year-old male with shortness of breath and a 1-week history of flu-like symptoms who developed a pulmonary embolism (PE) in the setting of COVID-19 pneumonia. Per the authors, at the time of this report, this was the first reported case in the US of synchronic presentation of PE and COVID-19 pneumonia and the authors believe additional research is needed to better understand the clinical presentation.

SUMMARY

An 82-year-old male with progressive shortness of breath and a 1-week history of distressed, desaturating, and tachypneic symptoms presented to the hospital with a synchronic presentation of pulmonary embolism in COVID-19 pneumonia. Below are the highlights of the patient's report:

- Initial workup: Mild leukocytosis with lymphopenia (Table 1), chest x-ray showed dense and mixed alveolar and interstitial infiltrate.
- Received hydroxychloroquine, azithromycin, and ceftriaxone for COVID-19 related pneumonia with hypoxic respiratory failure
- CT angiogram of the chest showed concomitant pulmonary embolism and tested positive for anticardiolipin antibodies (Figure 1).
- The patient expired on day 17 of hospitalization shortly after extubation.

ABSTRACT

In an effort to unravel the pathological mechanism of COVID-19, several reports and studies have been recently conducted in the frontlines around the world. Some initial clues have been obtained, and among them, the concern for clot formation and

the idea of an impaired coagulation has strongly increased. We report a case of pulmonary embolism in a COVID-19 patient who tested positive for anticardiolipin antibodies. This article is protected by copyright. All rights reserved.

FIGURES

Table 1. Laboratory findings

White cell count ($\times 10^3/\text{mcL}$)	11.11
Neutrophil abs ($\times 10^3/\text{mcL}$)	9.83
Lymphocyte abs ($\times 10^3/\text{mcL}$)	0.49
Hemoglobin (g/dL)	12.4
Platelets count ($\times 10^3/\text{mcL}$)	256
Alanine transaminase (U/L)	26
Aspartate transaminase (U/L)	34
Creatinine (mg/dL)	0.7
Procalcitonin (ng/mL)	0.950
Lactate dehydrogenase (U/L)	406
C-reactive protein (mg/dL)	20.46
D-dimer ($\mu\text{g/mL}$)	
Admission	39.863
day 3	2.435
day 5	2.903
day 11	0.880
day 13	0.605
Ferritin (ng/mL)	1064
Anticardiolipin antibodies	Positive
IgA (APL)	33.1
IgM (MPL)	16.7
IgG (GPL)	24.1

Table 1: Laboratory Findings

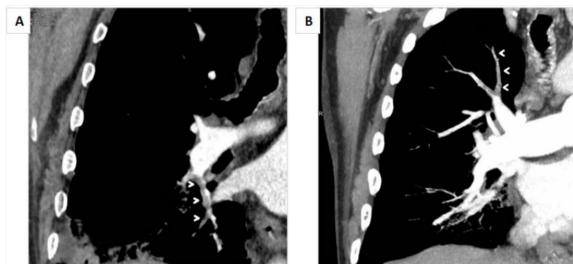


Figure 1: CT angiography of lungs. Note multiple small thrombus in the right middle lobe (panel A, white arrow heads) and right upper lobe (panel B, white arrow heads).

PEDIATRICS

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF PEDIATRIC SARS-COV-2 INFECTIONS IN CHINA: A MULTICENTER CASE SERIES

Zhang C, Gu J, Chen Q, Deng N, Li J, Huang L, Zhou X.. PLoS Med. 2020 Jun 16;17(6):e1003130. doi: 10.1371/journal.pmed.1003130. eCollection 2020 Jun.

Level of Evidence: 3 - Local non-random sample

BLUF

This retrospective observational study followed 34 pediatric COVID-19 patients enrolled from Jan 27 - Feb 23, 2020 in West China. Among this cohort, significant findings include fever and cough in most patients, lung CT abnormalities without ground glass opacities, and disease characterized as mild or moderate (Table 3). While the sample size of this study is small, it is useful to begin to compile data on the epidemiology of COVID-19 in pediatric patients, as such data is currently lacking.

ABSTRACT

BACKGROUND: As of April 18, 2020, over 2,000,000 patients had been diagnosed with coronavirus disease-2019 (COVID-19) globally, and more than 140,000 deaths had been reported. The clinical and epidemiological characteristics of adult patients have been documented recently. However, information on pediatric patients is limited. We describe the clinical and epidemiological characteristics of pediatric patients to provide valuable insight into the early diagnosis and assessment of COVID-19 in children.

METHODS AND FINDINGS: This retrospective, observational study involves a case series performed at 4 hospitals in West China. Thirty-four pediatric patients with COVID-19 were included from January 27 to February 23, 2020. The final follow-up visit was completed by March 16, 2020. Clinical and epidemiological characteristics were analyzed on the basis of demographic data, medical history, laboratory tests, radiological findings, and treatment information. Data analysis was performed for 34 pediatrics patients with COVID-19 aged from 1 to 144 months (median 33.00, interquartile range 10.00-94.25), among whom 14 males (41%) were included. All the patients in the current study presented mild (18%) or moderate (82%) forms of COVID-19. A total of 48% of patients were noted to be without a history of exposure to an identified source. Mixed infections of other respiratory pathogens were reported in 16 patients (47%). Comorbidities were reported in 6 patients (18%). The most common initial symptoms were fever (76%) and cough (62%). Expectoration (21%), vomiting (12%), and diarrhea (12%) were also reported in a considerable portion of cases. A substantial increase was detected in serum amyloid A for 17 patients (among 20 patients with available data; 85%) and in high-sensitivity C-reactive protein for 17 patients (among 29 patients with available data; 59%), whereas a decrease in prealbumin was noticed in 25 patients (among 32 patients with available data; 78%). In addition, significant increases in the levels of lactate dehydrogenase and alpha-hydroxybutyrate dehydrogenase were detected in 28 patients (among 34 patients with available data; 82%) and 25 patients (among 34 patients with available data; 74%), respectively. Patchy lesions in lobules were detected by chest computed tomographic scans in 28 patients (82%). Ground-glass opacities, which were a typical feature in adults, were rare in pediatric patients (3%). Rapid radiologic progression and a late-onset pattern of lesions in the lobules were also noticed. Lesions in lobules still existed in 24 (among 32 patients with lesions; 75%) patients that were discharged, although the main symptoms disappeared a few days after treatment. All patients were discharged, and the median duration of hospitalization was 10.00 (8.00-14.25) days. The current study was limited by the small sample size and a lack of dynamic detection of inflammatory markers.

CONCLUSIONS: Our data systematically presented the clinical and epidemiological features, as well as the outcomes, of pediatric patients with COVID-19. Stratified analysis was performed between mild and moderate cases. The findings offer new insight into early identification and intervention in pediatric patients with COVID-19.

FIGURES

Characteristics	All (n = 34)	Age ≤ 12 months (n = 10)	12 < Age ≤ 72 months (n = 13)	Age > 72 months (n = 11)
Demographics				
Sex				
Male, n (%)	14 (41)	6 (60)	3 (23)	5 (45)
Female, n (%)	20 (59)	4 (40)	10 (77)	6 (55)
Age, median (IQR), months	33.00 (10.00–94.25)	/	/	/
Clinical type				
Mild, n (%)	6 (18)	0	1 (8)	5 (45)
Moderate, n (%)	28 (82)	10 (100)	12 (92)	6 (55)
Exposure to suspected cases, n (%)	18 (52)	6 (60)	7 (54)	5 (45)
Family cluster, n (%)	13 (38)	5 (50)	5 (38)	3 (27)
Mixed infection, n (%)	16 (47)	2 (20)	8 (62)	6 (55)
Comorbidities				
Infectious mononucleosis, n (%)	2 (6)	/	2 (15)	/
Nephroblastoma, n (%)	1 (3)	/	1 (8)	/
Atrial septal defect, n (%)	1 (3)	1 (10)	/	/
Feverile convulsion, n (%)	1 (3)	/	/	1 (9)
Asthma, n (%)	1 (3)	/	/	1 (9)

Abbreviation: IQR, interquartile range

Table 1. Characteristics of patients on admission.

Laboratory findings	Normal range	Median (IQR)
Hematology		
White blood cell count, $\times 10^9$ /L	3.50–9.50	6.78 (5.74–8.66)
Neutrophil count, $\times 10^9$ /L	1.80–6.30	2.96 (2.02–4.34)
Lymphocyte count, $\times 10^9$ /L	1.10–3.20	3.19 (1.73–4.34)
Platelet count, $\times 10^9$ /L	150.00–350.00	231.50 (192.75–263.75)
Hemoglobin count, g /L	110.00–160.00	129.00 (116.75–135.00)
Blood biochemistry		
Albumin, g /L	40.00–55.00	44.70 (42.85–46.50)
Prealbumin, mg /L	170.00–420.00	138.65 (106.85–168.55)
ALT, IU /L	0.00–50.00	16.00 (12.75–25.25)
AST, IU /L	0.00–40.00	39.50 (27.00–57.25)
Total bilirubin, μmol /L	3.42–20.50	7.50 (6.10–10.35)
Creatinine, μmol /L	44.00–120.00	42.05 (32.53–49.35)
Potassium, mmol /L	3.50–5.50	4.45 (4.28–4.73)
Sodium, mmol /L	137.00–155.00	139.00 (137.88–141.13)
Alkaline phosphatase, IU /L	0.00–500.00	198.00 (161.00–266.50)
CK, IU /L	50.00–310.00	105.00 (73.75–167.50)
LDH, IU /L	100.00–240.00	327.00 (268.75–403.75)
α -HBDH, IU /L	72.00–182.00	237.00 (179.75–288.00)
CK-MB, IU /L	0.00–24.00	19.00 (14.00–33.50)
Procalcitonin, ng /ml	0.00–0.50	0.06 (0.03–0.07)
SAA, mg /L	0.00–8.00	36.59 (9.25–50.33)
hs-CRP, mg /L	0.00–5.00	7.56 (1.21–15.13)
ESR, mm /h	0.00–20.00	10.00 (8.00–26.00)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase-MB; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; SAA, serum amyloid A; α -HBDH, α -hydroxybutyrate dehydrogenase

Table 2. Laboratory findings of patients on admission (n = 34).

Clinical features	All (n = 34)	Mild (n = 6)	Moderate (n = 28)
Exposure history			
Exposure to suspected cases, n (%)			
Unidentified source of infection, n (%)	18 (52)	2	16
Mixed infection	16 (47)	4	12
Without mixed infection, n (%)	18 (53)	2	16
With mixed infection, n (%)	16 (47)	4	12
Adenovirus, n (%)	1 (3)	0	1
Influenza B virus, n (%)	6 (18)	0	6
Influenza A virus, n (%)	3 (9)	0	3
Respiratory syncytial virus, n (%)	2 (6)	0	2
Egyptian-Barr virus, n (%)	2 (6)	1	1
Parainfluenza virus, n (%)	1 (3)	0	1
Adenovirus, n (%)	1 (3)	0	1
Comorbidities			
With comorbidities, n (%)	6 (18)	1	5
Without comorbidities, n (%)	28 (82)	5	23
Signs and symptoms			
Fever, n (%)	26 (76)	3	23
Cough, n (%)	21 (62)	5	16
Expectoration, n (%)	7 (21)	0	7
Vomiting, n (%)	4 (12)	0	4
Diarrhea, n (%)	4 (12)	0	4
Tachypnea, n (%)	3 (9)	0	3
CT findings			
Distribution of patchy shadows	28 (82)	0	28
Ground-glass opacity ^a	1 (3)	0	1
Normal, n (%)	6 (18)	6	0
Treatments			
Interferon- α nebulization, n (%)	34 (100)	6	28
Traditional Chinese medicine, n (%)	20 (59)	4	16
Ribavirin, n (%)	15 (44)	3	12
Antibiotic therapy, n (%)	29 (85)	4	25
Corticosteroid therapy, n (%)	5 (15)	0	5
Oxygen inhalation, n (%)	3 (9)	0	3

^aA ground-glass opacity with patchy shadows was observed in 1 case.

Abbreviations: CT, computed tomography

Table 2. Laboratory findings of patients on admission (n = 34).

FULMINANT COVID-19-RELATED MYOCARDITIS IN AN INFANT

Kesici S, Aykan HH, Orhan D, Bayrakci B.. Eur Heart J. 2020 Jun 12:ehaa515. doi: 10.1093/eurheartj/ehaa515. Online ahead of print.

Level of Evidence: 5 - Case report

BLUF

A case study conducted at Hacettepe Universitesi Tip Fakultesi, Ankara, presents a 2-year-old COVID-19 positive male patient who developed concurrent dilated cardiomyopathy with evidence of direct viral cardiac tissue damage suggested by "COVID-19 RT-PCR positivity in the cardiac tissue." The authors report that this is the first case "describing COVID-19-related fatal fulminant myocarditis demonstrated with pathological work-up in an infant."

ADVANCED AGE

CLINICAL CHARACTERISTICS AND PROGNOSTIC FACTORS IN COVID-19 PATIENTS AGED ≥80 YEARS

Covino M, De Matteis G, Santoro M, Sabia L, Simeoni B, Candelli M, Ojetto V, Franceschi F.. Geriatr Gerontol Int. 2020 Jun 9. doi: 10.1111/ggi.13960. Online ahead of print.

Level of Evidence: 4 - Case-series

BLUF

In this retrospective study, researchers at an urban teaching hospital in Lombardy, Italy examined 69 cases of patients ≥80 years of age hospitalized with COVID-19 between 1 March and 31 March, 2020. A total of 23 patients died at the conclusion of the study, and they found a significant association between severe dementia and increased mortality. In addition to dementia, independent risk factors for death in this population included a lactate dehydrogenase level >464 U/L and an oxygen saturation level ≤90% at admission (Figure 1). Overall, the study may provide insight into the clinical risk factors for geriatric patients with regards to COVID-19 and may complicate the notion that age itself is a salient risk factor for severe disease progression.

ABSTRACT

AIM: The aim of the present study was to describe the clinical presentation of patients aged >=80 years with coronavirus disease 2019 (COVID-19), and provide insights regarding the prognostic factors and the risk stratification in this population.
METHODS: This was a single-center, retrospective, observational study, carried out in a referral center for COVID-19 in central Italy. We reviewed the clinical records of patients consecutively admitted for confirmed COVID-19 over a 1-month period (1-31 March 2020). We excluded asymptomatic discharged patients. We identified risk factors for death, by a uni- and multivariate Cox regression analysis. To improve model fitting and hazard estimation, continuous parameters were dichotomized by using Youden's index.

RESULTS: Overall, 69 patients, aged 80-98 years, met the inclusion criteria and were included in the study cohort. The median age was 84 years (82-89 years is interquartile range); 37 patients (53.6%) were men. Globally, 14 patients (20.3%) presented a mild, 30 (43.5%) a severe and 25 (36.2%) a critical COVID-19 disease. A total of 23 (33.3%) patients had died at 30 days' follow up. Multivariate Cox regression analysis showed that severe dementia, $\text{pO}_2 \leq 90$ at admission and lactate dehydrogenase >464 U/L were independent risk factors for death.

CONCLUSIONS: The present data suggest that risk of death could be not age dependent in patients aged >=80 years, whereas severe dementia emerged as a relevant risk factor in this population. Severe COVID-19, as expressed by elevated lactate dehydrogenase and low oxygen saturation at emergency department admission, is associated with a rapid progression to death in these patients.

FIGURES

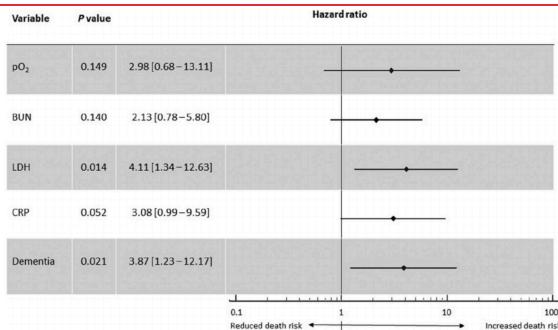


Figure 1. Multivariate Cox regression for prognostic factors. The forest plot graphically represents hazard ratios (95% confidence interval) for peripheral oxygen saturation (pO_2), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), C-reactive protein (CRP) and dementia. All parameters were assessed at emergency department admission.

UNDERSTANDING THE PATHOLOGY

SARS-COV2 MAY EVADE INNATE IMMUNE RESPONSE, CAUSING UNCONTROLLED NEUTROPHIL EXTRACELLULAR TRAPS FORMATION AND MULTI-ORGAN FAILURE

Thierry AR, Roch B.. Clin Sci (Lond). 2020 Jun 26;134(12):1295-1300. doi: 10.1042/CS20200531.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

Researchers from France propose that SARS-CoV-2 may activate Neutrophil Extracellular Traps (NETs), a part of innate immune defenses that can damage endothelial and parenchymal tissue as a result of toxic by-product buildup. Under this assumption, the immune system evasion allows the virus to produce a massive inflammatory response in an autoloop fashion secondary to NET dysregulation. They suggest that this mechanism may be responsible for many of the complications of COVID-19 and similar infections, and controlling or neutralizing NETs may help minimize complications.

ABSTRACT

We demonstrate that the general clinical conditions, risk factors and numerous pathological and biological features of COVID-19 are analogous with various disorders caused by the uncontrolled formation of neutrophil extracellular traps and their by-products. Given the rapid evolution of this disease's symptoms and its lethality, we hypothesize that SARS-CoV2 evades innate immune response causing COVID-19 progresses under just such an amplifier loop, leading to a massive, uncontrolled inflammation process. This work allows us to propose new strategies for treating the pandemic.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS IMPACT ON COVID-19 MORTALITY: WHAT'S NEXT FOR ACE2?

Patel AB, Verma A.. Clin Infect Dis. 2020 May 22:ciaa627. doi: 10.1093/cid/ciaa627. Online ahead of print.

Level of Evidence: Other -

BLUF

The authors discuss the effect of renin-angiotensin-aldosterone system inhibitor (RAASi) use on the incidence and severity of COVID-19 with a focus on a retrospective study conducted by [Jung et al] (<https://pubmed.ncbi.nlm.nih.gov/32442285/>) that showed no association between RAASi use and mortality in COVID-19 patients. The authors suggest that RAASi does not negatively impact COVID-19 and call for additional studies to investigate the pulmonary pathophysiology of SARS-CoV-2 in order to better understand the role RAASi could play in COVID-19 infection.

IN SILICO

EVOLUTIONARY RELATIONSHIPS AND SEQUENCE-STRUCTURE DETERMINANTS IN HUMAN SARS CORONAVIRUS-2 SPIKE PROTEINS FOR HOST RECEPTOR RECOGNITION

Guruprasad L.. Proteins. 2020 Jun 16. doi: 10.1002/prot.25967. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

A SARS-CoV-2 genomic and phylogenetic analysis conducted by a researcher in India during June 2020 discovered four unique sequence regions that interact with the angiotensin converting enzyme (ACE)-2 receptor and may be potential targets for antibody vaccine design: two N-terminal domain (NTD) spike protein regions "MESEFR" and "SYLTPG," and two receptor binding domain (RBD) regions "VGGNY" and "EIYQAGSTPCNGV" (Figure 2A-C). The phylogenetic analysis revealed that bat SARS-CoV genome is the closest homolog of human SARS-CoV-2, supporting evidence that the COVID-19 outbreak originated from bat-to-human zoonotic transmission.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a pandemic infectious disease caused by novel Severe Acute Respiratory Syndrome coronavirus-2 (SARS CoV-2). The SARS CoV-2 is transmitted more rapidly and readily than SARS CoV. Both, SARS CoV and SARS CoV-2 via their glycosylated spike proteins recognize the human angiotensin converting enzyme-2 (ACE-2) receptor. We generated multiple sequence alignments and phylogenetic trees for representative spike proteins of SARS CoV and SARS CoV-2 from various host sources in order to analyze the specificity in SARS CoV-2 spike proteins required for causing infection in humans. Our results show that among the genomes analysed, two sequence regions in the N-terminal domain (NTD); "MESEFR" and "SYLTPG" are specific to human SARS CoV-2. In the receptor binding domain (RBD), two sequence regions; "VGGNY" and "EIQAGSTPCNGV" and a disulfide bridge connecting 480C and 488C in the extended loop are structural determinants for the recognition of human ACE-2 receptor. The complete genome analysis of representative SARS CoVs from bat, civet, human host sources and human SARS CoV-2 identified the bat genome (GenBank code: MN996532.1) as closest to the recent novel human SARS CoV-2 genomes. The bat SARS CoV genomes (GenBank codes: MG772933 and MG772934) are evolutionary intermediates in the mutagenesis progression towards becoming human SARS CoV-2. This article is protected by copyright. All rights reserved.

FIGURES

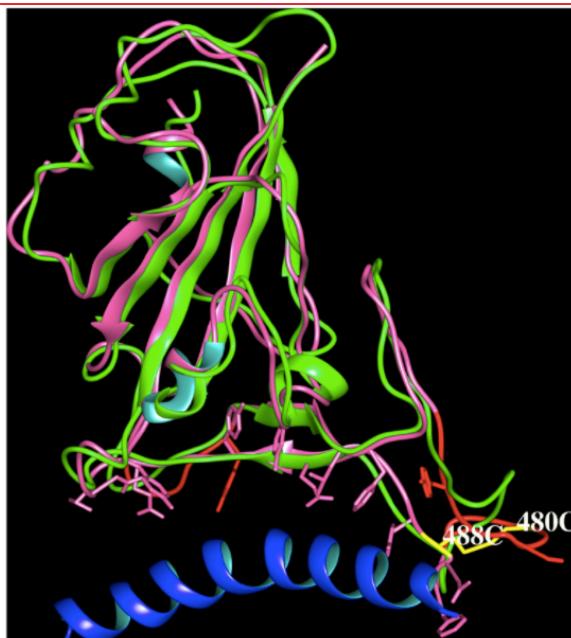


Figure 2C: Structural superposition of human SARS CoV (6ACG, green) and human SARS CoV-2 (6M17, magenta) and the long H1 helix in ACE-2 (blue). The side chains of amino acid residues in RBD that lie within 5 Å from ACE-2 are shown. The deletion region in RBD of bat SARS CoV is shown in the structure of 6M17 (red). The C480-C488 disulfide bond (yellow) connects the extended loop in 6M17.

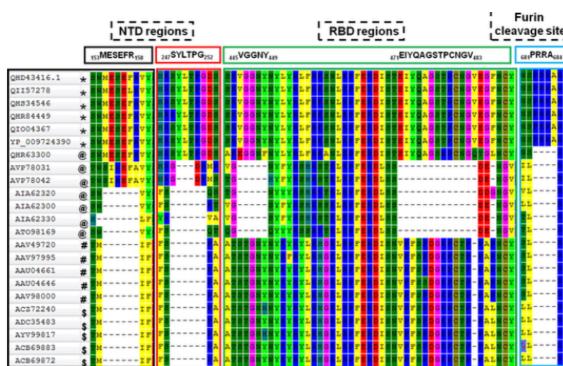


Figure 2A

Figure 2A: Portions of the alignment of spike proteins extracted from the multiple sequence alignment (Figure S1). Insertion sequence regions and their locations within the NTD, RBD and furin cleavage sites for human SARS CoV-2 (*), bat SARS CoV (@), civet SARS CoV (#), human SARS CoV (\$).

Figure 2B

Figure 2A: Portions of the alignment of spike proteins extracted from the multiple sequence alignment (Figure S1). Insertion sequence regions and their locations within the NTD, RBD and furin cleavage sites for human SARS CoV-2 (*), bat SARS CoV (@), civet SARS CoV (#), human SARS CoV (\$).

TRANSMISSION & PREVENTION

DO FACEMASKS PROTECT AGAINST COVID-19?

Isaacs D, Britton P, Howard-Jones A, Kesson A, Khatami A, Marais B, Nayda C, Outhred A.. J Paediatr Child Health. 2020 Jun 16. doi: 10.1111/jpc.14936. Online ahead of print.

Level of Evidence: Other - Opinion

BLUF

Australian authors wrote a brief communication letter to discuss the efficacy of facemasks (medical/surgical and N95/P2) during the COVID-19 pandemic. Their opinion is that there is "no good evidence that facemasks protect the public". They suggest healthcare workers conserve N95/P2 masks for aerosol-generating procedures and advise against facemasks while caring for low-risk patients as it might disrupt the quality of care.

SUMMARY

Summarizing excerpt:

"Evidence on the efficacy of masks is confounded by whether or not they are being used in a pandemic; whether by health-care workers or the public, and by the concomitant use of hand-washing, social distancing and other personal protective equipment. A meta-analysis of randomised controlled trials of pre-COVID-19[sic] showed that surgical masks or N95 respirators reduced clinical respiratory illness in health-care workers by 41% and influenza-like illness by 66%: they work but are far from perfect. N95 masks were not statistically better than surgical masks in preventing proven influenza, nor in preventing COVID-19, although the latter is based on weak data. N95 masks are more efficient filters of small particles, but these findings suggest it is reasonable to recommend that health-care workers use surgical masks when there is risk of droplet spread and reserve preciousN95 masks for health-care workers performing aerosol-generating procedures...As [surgical masks] become moist they become porous and no longer protect. Indeed, experiments have shown that surgical and cotton masks do not trap theSARS-CoV-2 (COVID-19) virus, which can be detected on the outer surface of the masks for up to 7 days. Thus, a pre-symptomatic or mildly infected person wearing a face mask for hours without changing it and without washing hands every time they touched the mask could paradoxically increase the risk of infecting others."

PREVENTION IN THE COMMUNITY

KNOWLEDGE AND PRACTICES REGARDING SAFE HOUSEHOLD CLEANING AND DISINFECTION FOR COVID-19 PREVENTION - UNITED STATES, MAY 2020

Gharpure R, Hunter CM, Schnall AH, Barrett CE, Kirby AE, Kunz J, Berling K, Mercante JW, Murphy JL, Garcia-Williams AG.. MMWR Morb Mortal Wkly Rep. 2020 Jun 12;69(23):705-709. doi: 10.15585/mmwr.mm6923e2.

Level of Evidence: 3 - Local non-random sample

BLUF

An internet survey of 502 U.S adults conducted during May 2020 by authors from the Centers for Disease Control and Prevention measured the understanding and usage of common household cleaners during the pandemic. Survey results showed a large proportion of adults using disinfectants improperly and unsafely (see below), suggesting a need for COVID-19 public health messaging that focuses on the safe use of household cleaners and evidence based practices to prevent transmission of COVID-19.

SUMMARY

Results from this online survey show:

- 58% and 35% of U.S. adults knew bleach should not be mixed with ammonia and vinegar, respectively, which indicates the limited knowledge in regards to safe storage and preparation of disinfectants (Figure 1).
- 39% of the respondents intentionally used disinfectants in non-CDC recommended ways to try and prevent transmission of COVID-19, including using bleach to wash food items, household disinfectants to clean bare skin, and inhaling household cleaning vapors (Figure 2).

ABSTRACT

A recent report described a sharp increase in calls to poison centers related to exposures to cleaners and disinfectants since the onset of the coronavirus disease 2019 (COVID-19) pandemic (1). However, data describing cleaning and disinfection practices within household settings in the United States are limited, particularly concerning those practices intended to prevent transmission of SARS-CoV-2, the virus that causes COVID-19. To provide contextual and behavioral insight into the reported increase in poison center calls and to inform timely and relevant prevention strategies, an opt-in Internet panel survey of 502 U.S. adults was conducted in May 2020 to characterize knowledge and practices regarding household cleaning and disinfection during the COVID-19 pandemic. Knowledge gaps were identified in several areas, including safe preparation of cleaning and disinfectant solutions, use of recommended personal protective equipment when using cleaners and disinfectants, and safe storage of hand sanitizers, cleaners, and disinfectants. Thirty-nine percent of respondents reported engaging in nonrecommended high-risk practices with the intent of preventing SARS-CoV-2 transmission, such as washing food products with bleach, applying household cleaning or disinfectant products to bare skin, and intentionally inhaling or ingesting these products. Respondents who engaged in high-risk practices more frequently reported an adverse health effect that they believed was a result of using cleaners or disinfectants than did those who did not report engaging in these practices. Public messaging should continue to emphasize evidence-based, safe practices such as hand hygiene and recommended cleaning and disinfection of high-touch surfaces to prevent transmission of SARS-CoV-2 in household settings (2). Messaging should also emphasize avoidance of high-risk practices such as unsafe preparation of cleaning and disinfectant solutions, use of bleach on food products, application of household cleaning and disinfectant products to skin, and inhalation or ingestion of cleaners and disinfectants.

FIGURES

FIGURE 1. Knowledge about safe use of cleaners and disinfectants,*† based on responses to an opt-in Internet panel survey§ (N = 502 respondents) — United States, May 2020

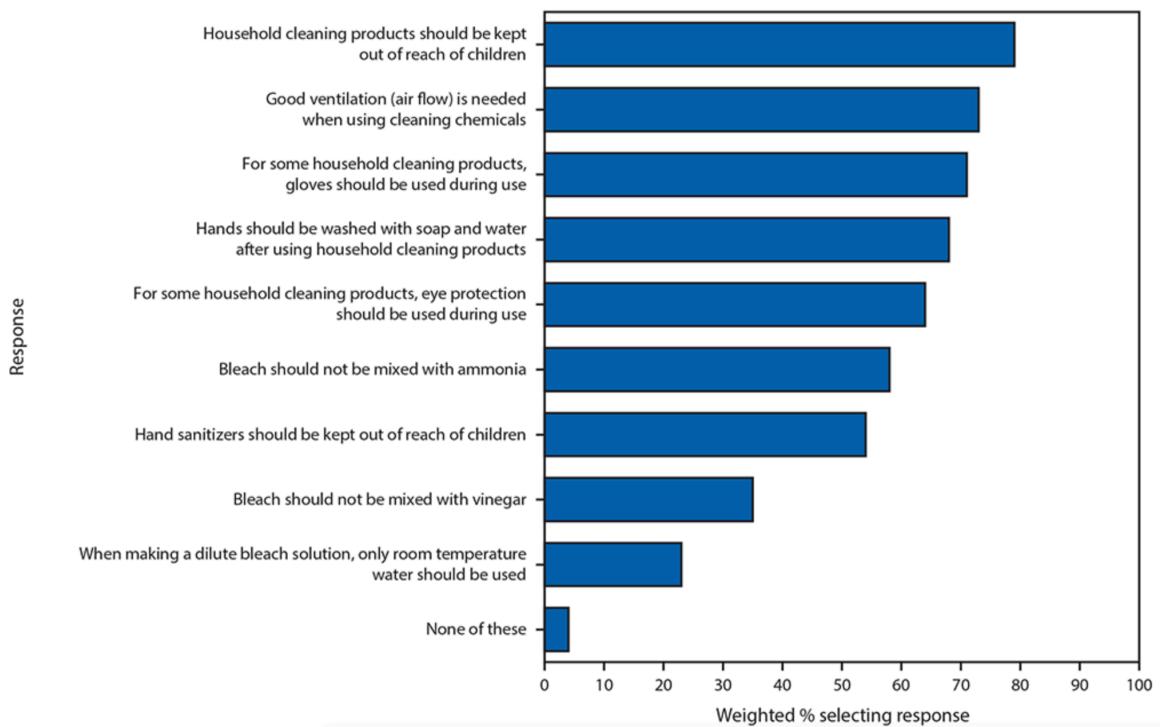
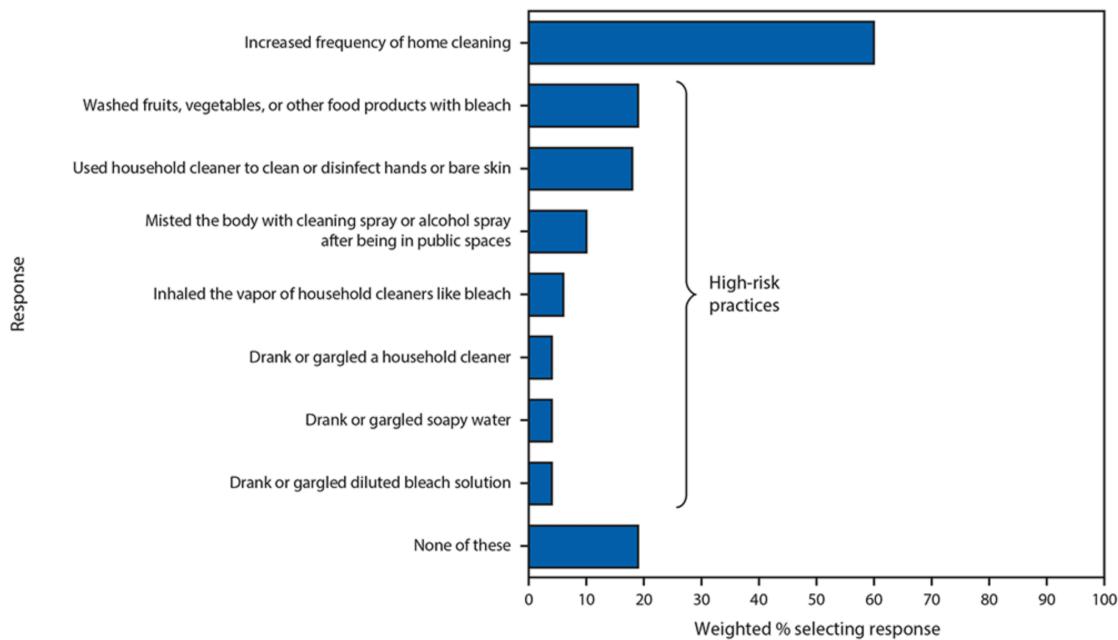


FIGURE 2. Cleaning and disinfection practices in the previous month with the intent of preventing SARS-CoV-2 infection,*† based on responses to an opt-in Internet panel survey[§] (N = 502 respondents) — United States, May 2020



TELEMEDICINE-ENABLED ACCELERATED DISCHARGE OF HOSPITALIZED COVID-19 PATIENTS TO ISOLATION IN REPURPOSED HOTEL ROOMS

Bruni T, Alvani A, Richeldi L.. Am J Respir Crit Care Med. 2020 Jun 16. doi: 10.1164/rccm.202004-1238OE. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

An expert opinion on how using nearby hotels for recovering COVID-19 patients discharged from overwhelmed hospitals may be an effective method to meet surging demands (see below). This strategy has been successfully employed in Italy (239 patients from 4/1/2020 - 5/1/2020, 126 discharged home with a median stay of 12 days, 0 patients readmitted). The authors believe this approach will minimize transmission rates and benefit hospitals which have limited staff, beds, and resources.

SUMMARY

This plan involves discharging stable COVID-19 patients and transferring them to a nearby hotel that is set up in a "reverse-triage" manner (Figure 1), with adequate supplies and nursing personnel to care for the patients (see below).

- Only available for patients who are clinically stable (no fever or relevant symptoms), resolving COVID-19 symptoms, and are able to use a smartphone.
- Patients will be attended by nursing staff and vitals checked via telemedicine while in the hotel rooms.
- Patients who have two consecutive negative SARS-CoV-2 PCR tests would be discharged home.
- Worsening condition would prompt visitation from a doctor and potential readmission.
- Limitations include difficult sanitation and cleaning compared to a hospital room, proper transportation to hotels, and potential negative psychological effects on patients during isolation.

FIGURES

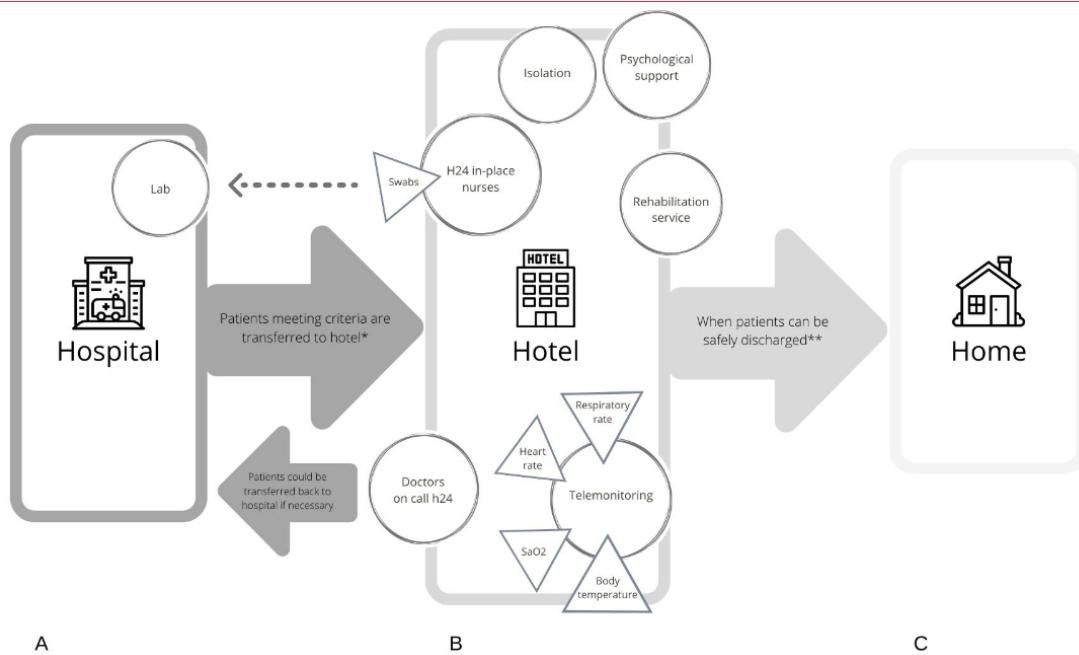


Figure 1: Patient flow between the various sites highlighting crucial check points and potential challenges. A. The hospital adopts a "Reverse triage" method to free up beds, discharging patients in order of greater clinical stability. Patients who need to continue isolation (when not possible at home, or when they live in a care home) or medical monitoring or both, are transferred to the hotel facility if medical stability is met. The proximity between the hotel and the hospital allows for rapid delivery of nasopharyngeal swabs to the laboratory and patients to the emergency room if necessary. B. Key functions provided in the hotel: isolation through accommodation in single rooms; telemonitoring; 24-hour present nurses; doctors on call; psychological assistance; physiotherapy services. C. Once two consecutive negative swabs are obtained, the patient can go home safely, without the risk of contagion to family members or care home residents or their carers.* Patient with a positive SARS-CoV-2 swab or a clinical diagnosis of COVID-19, clinically stable, with no need for oxygen therapy nor intravenous

therapy, able to use a smartphone, independent in daily routine activities and who cannot maintain effective home isolation can be admitted.** Patients undergo SARS-CoV-2 swabs in the hotel after 48-72 hours (if positive) or after 24 hours (if negative). After two consecutive negative swabs the patient is safely discharged from the hotel.

ACUTE CARE

CRITICAL CARE

ELECTRICAL IMPEDANCE TOMOGRAPHY FOR POSITIVE END-EXPIRATORY PRESSURE TITRATION IN COVID-19 RELATED ARDS

van der Zee P, Somhorst P, Endeman H, Gommers D.. Am J Respir Crit Care Med. 2020 Jun 1. doi: 10.1164/rccm.202003-0816LE. Online ahead of print.

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

BLUF

A group of Dutch authors discuss a case series conducted from March 1-31, 2020 in a tertiary ICU where they tested positive end-expiratory pressure (PEEP) titration in 15 patients with COVID-19-related ARDS using electrical impedance tomography (EIT) (Table 1). Noteworthy results:

- High PEEP measured by EIT were from personalized PEEP at the level of lowest relative alveolar overdistention and collapse (Figure 2a).
- PEEP set was positively correlated to BMI (p less than 0.001) (Figure 2b)
- Individualized PEEP titration could result in improved clinical outcomes
- Additional details on the titration trials below.

Further research is needed to confirm whether this personalized PEEP titration approach is safe and effective.

SUMMARY

The authors conducted 63 PEEP trials on 15 patients with COVID-19-related ARDS (median amount of PEEP trials per patient was 3). They found that "personalized PEEP at the level of lowest relative alveolar overdistention and collapse as measured with EIT resulted in high PEEP. These PEEP levels did not result in high driving pressure or transpulmonary pressure. In addition, PEEP trials did not result in relevant hemodynamic instability or pneumothorax. PEEP set corresponded better to the higher PEEP-FiO₂ table than the lower PEEP-FiO₂ table and was positively correlated with BMI."

FIGURES

Table 1. Patient characteristics

Gender (M/F)	Age (year)	BMI (kg/m ²)	APACHE IV Score	PaO ₂ /FiO ₂ ratio (mmHg)*	Baseline PEEP (cmH ₂ O) [†]	Duration of MV (days) [‡]	Prone positioning §	DP (cmH ₂ O) ^{**}	P _L (cmH ₂ O)		Compliance (mL/cmH ₂ O)			CRP ↑↑ (mg/L)	ARDS morphology
									Exp.	Insp.	Lung	CW	RS		
F	49	42	79	68	18	8	Yes	12	2	13	104	53	35	530	Diffuse
M	56	33	113	171	20	8	Yes	8	0	8	90	165	58	349	Diffuse
M	65	27	94	54	16	2	Yes	10	2	19	89	103	47	681	Diffuse
M	16	22	74	158	15	1	No	n.a. ^{††}	6	19	52	92	33	157	Focal to diffuse
M	72	26	99	163	16	1	No	8	4	12	114	175	69	673	Diffuse
F	59	28	73	116	18	1	Yes	10	5	14	54	189	42	563	Diffuse
F	73	18	125	105	16	0	No	8	2	10	82	134	51	401	Focal to diffuse
F	54	31	94	132	16	2	Yes	13	3	16	43	180	35	526	Diffuse
M	53	31	67	186	16	1	Yes	7	9	14	101	148	60	401	Diffuse
F	62	30	98	134	12	1	No	10	n.a. ^{§§}	n.a. ^{§§}	n.a. ^{§§}	n.a. ^{§§}	61	350	Focal to diffuse
M	66	36	124	118	18	1	No	4	4	13	77	88	41	638	Focal
M	68	34	94	134	18	2	Yes	6	-1	14	124	77	47	280	Diffuse
M	56	34	101	148	18	2	Yes	7	n.a. ^{§§}	n.a. ^{§§}	n.a. ^{§§}	n.a. ^{§§}	69	331	Diffuse
M	61	29	124	140	18	1	Yes	7	9	14	94	95	47	336	Diffuse
M	65	27	112	100	16	3	Yes	7	5	9	102	146	60	386	Diffuse

Table 1. Patient Characteristics.

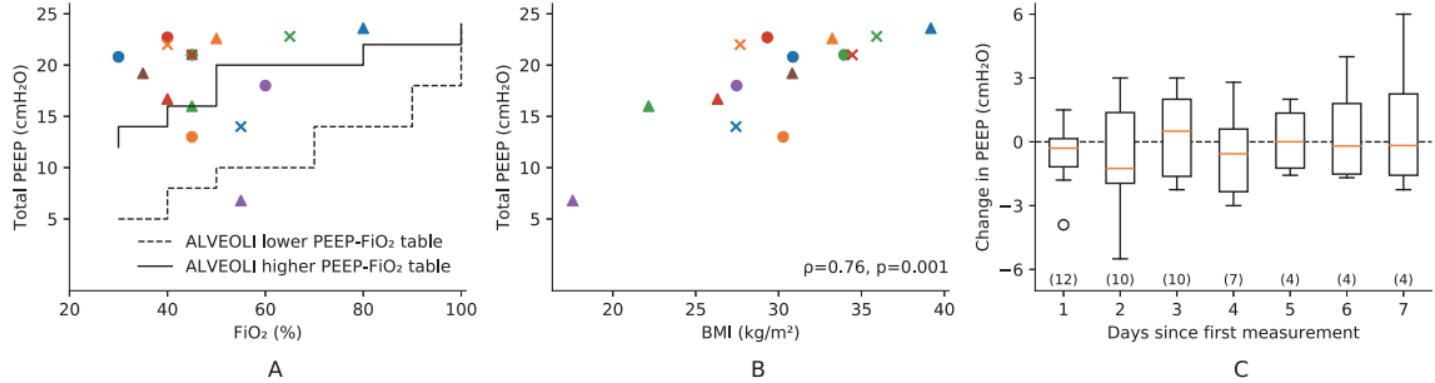


Figure 2a. PEEPset versus higher and lower PEEP-FiO₂ table. The solid and dashed lines represent the PEEP-FiO₂ combination to be used according to the lower and higher PEEP-FiO₂ tables from the ALVEOLI trial. Each marker represents PEEPset at the level of lowest relative alveolar overdistention and collapse as measured with electrical impedance tomography. Only the first PEEP trial of each patient is presented. The crosses indicate subjects that died within 28-days following ICU admission. There was no correlation between PEEPset and FiO₂ ($\rho = 0.11$, p-value 0.69).

Figure 2b. PEEPset versus body mass index

The correlation between BMI and PEEPset after the first PEEP trial for each patient. Spearman's rank correlation coefficient $\rho = 0.76$ with p-value 0.001. Similar markers in figure 2a and 2b represent the same patient.

Figure 2c. Change in PEEP as compared to the first PEEP trial. The change in PEEPset as compared to the first PEEP trial, represented by the median (orange line), interquartile range (box) and minimum/maximum values (whiskers). PEEPset did not change significantly over time. The number between parentheses represents the amount of patients measured at that day."

NEUROLOGY

CNS INFLAMMATORY VASCULOPATHY WITH ANTIMYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODIES IN COVID-19

Pinto AA, Carroll LS, Nar V, Varatharaj A, Galea I.. Neurol Neuroimmunol Neuroinflamm. 2020 Jun 10;7(5):e813. doi: 10.1212/NXI.0000000000000813. Print 2020 Sep.

Level of Evidence: 5 - Case report

BLUF

Researchers at the University of Southampton, United Kingdom present a case report of a 44-year-old woman who, seven days after the onset of respiratory symptoms and pruritus due to COVID-19, developed expressive and receptive aphasia, visual and sensory inattention, right arm and right leg weakness, and bilateral chest rash. She was subsequently diagnosed with CNS inflammatory vasculopathy with antimyelin oligodendrocyte glycoprotein (MOG) antibodies (Figure 1) and treated successfully with IV methylprednisolone and plasma exchange. The authors note that the perivascular enhancement on MRI and lack of acute disseminated encephalitis-like presentation is unusual for MOG antibody disease and suggest that this may be related to endothelial dysfunction from COVID-19, indicating the need for clinicians to consider COVID-19-related impacts in unusual neurological presentations such as this.

FIGURES

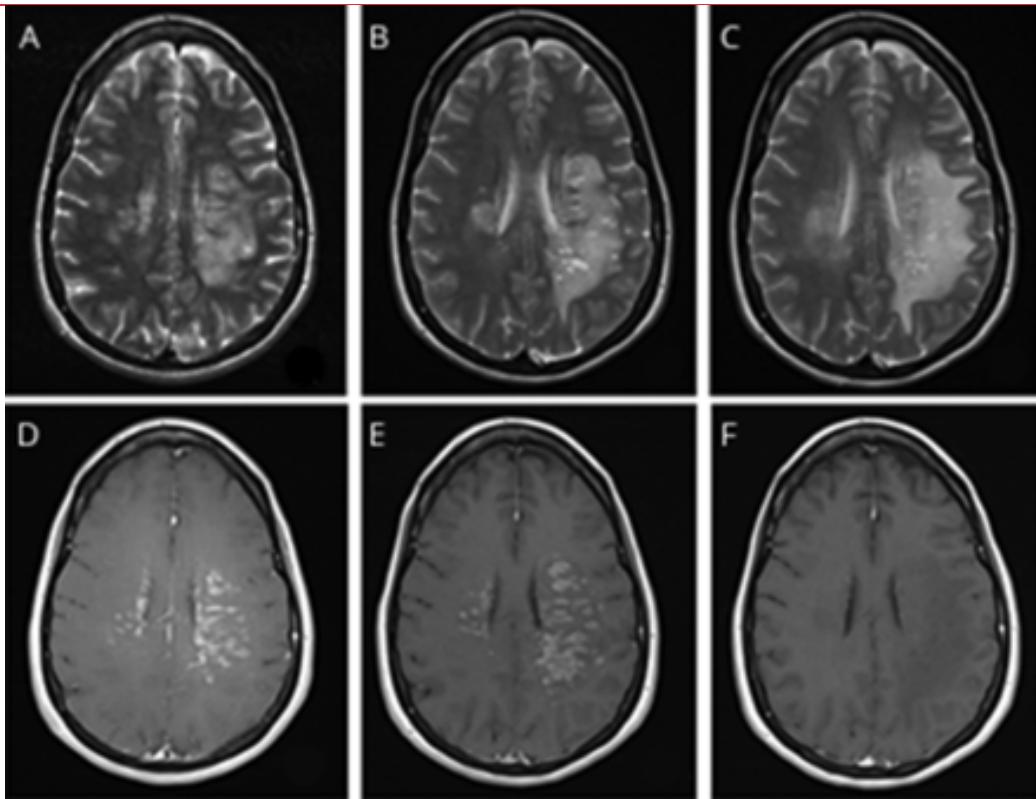


Figure 1: MRI appearances of CNS inflammatory vasculopathy with antimyelin oligodendrocyte glycoprotein antibodies in COVID-19. T2-weighted axial images at day 1 (A), day 6 (B), and post-treatment day 17 (C). Postcontrast axial images at day 1 (D), day 6 (E), and post-treatment day 17 (F).

COVID-19-WHITE MATTER AND GLOBUS PALLIDUM LESIONS: DEMYELINATION OR SMALL-VESSEL VASCULITIS?

Brun G, Hak JF, Coze S, Kaphan E, Carvelli J, Girard N, Stellmann JP.. Neurol Neuroimmunol Neuroinflamm. 2020 May 22;7(4):e777. doi: 10.1212/NXI.0000000000000777. Print 2020 Jul.

Level of Evidence: Other -

BLUF

Herein, the authors report the case of a 54-year-old female with COVID-19 who was managed successfully with mechanical ventilation in the prone position in combination with hydroxychloroquine, azithromycin, amoxicillin/clavulanic acid. Two days after cessation of sedation, she presented with delayed wake-up and Glasgow Coma Scale 6, and CT scan of the brain demonstrated hypodense lesions involving supratentorial white matter and pallidum bilaterally. MRI should be employed to explore neurologic symptoms in COVID-19 patients, and clinicians should be vigilant for demyelination or small-vessel vasculitis as neurologic complications.

SUMMARY

Neurologic manifestations of COVID-19 are not uncommon, however few studies have shown central nervous system abnormalities on MRI secondary to this disease. Herein, the authors detail a case from a 54-year-old woman who presented to the emergency department with fever, asthenia, symptoms of respiratory distress, and altered mental status, but without focal neurologic deficit. A RT-PCR test of nasopharyngeal swab sample for SARS-CoV-2 was positive, while a chest CT demonstrated pathologic findings to support the diagnosis. Her condition improved by day 2 after mechanical ventilation in the prone position and treatment with a combination of hydroxychloroquine, azithromycin, and amoxicillin/clavulanic acid. However, after stopping her sedation, she presented with wake-up delay. CT scan of the brain revealed hypodense lesions involving the supratentorial white matter and pallidum bilaterally. A cardiac ultrasound and ECG ruled out an embolic cause. On day 7, a brain MRI revealed lesions with restricted diffusion without any hemorrhagic or enhancement after gadolinium injection. Two days later, a lumbar puncture showed no relevant alterations, and RT-PCR for SARS-CoV-2 was negative. Hemiplegia was observed on day 10, while follow-up MRI did not reveal new lesions. Steroids were initiated on day 12 after another negative result on RT-PCR.

FIGURES

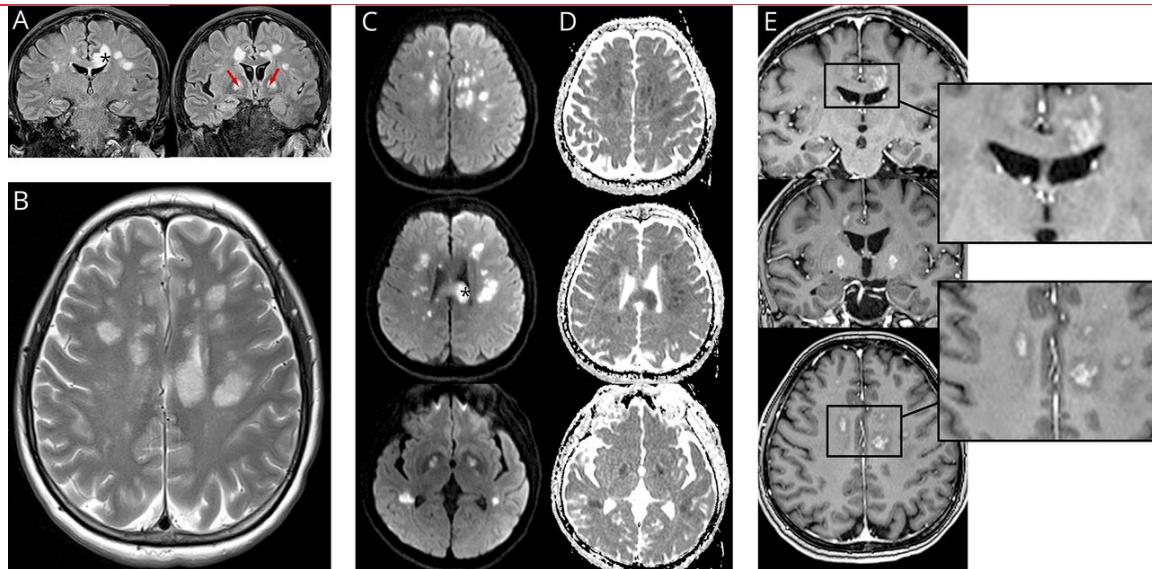


Figure 1. Brain MRI of SARS-CoV-2-related lesions. Multiple supratentorial punctiform and tumefactive lesions involving the white matter bilaterally and showing hypersignal on coronal fluid attenuation and inversion recovery (FLAIR; A), axial T2-weighted images (B), and diffusion-weighted imaging (C) with low apparent diffusion coefficient (ADC; D). Some lesions are periventricular or involve the corpus callosum with a mass effect on the left lateral ventricle (*). Note the restricted diffusion with hyperintensity on FLAIR images within the globus pallidum bilaterally (black arrows). On a follow-up brain MRI, the lesions demonstrate avid enhancement on postgadolinium coronal and axial T1-weighted images (E).

MEDICAL SUBSPECIALTIES

RHEUMATOLOGY

CLINICAL FEATURES OF RHEUMATIC PATIENTS INFECTED WITH COVID-19 IN WUHAN, CHINA

Ye C, Cai S, Shen G, Guan H, Zhou L, Hu Y, Tu W, Chen Y, Yu Y, Wu X, Chen Y, Zhong J, Dong L.. Ann Rheum Dis. 2020 May 22:annrheumdis-2020-217627. doi: 10.1136/annrheumdis-2020-217627. Online ahead of print.

Level of Evidence: 4 -

BLUF

Authors of this retrospective case series present 21 rheumatic patients with COVID-19 who were admitted to Tongji Hospital in Wuhan, China between 13 January and 15 March 2020. These patients were found to have symptomatology and inflammatory biomarkers that also appeared similar to flares in rheumatic conditions, emphasizing the importance of distinguishing between the two ailments to ensure patients are treated appropriately.

SUMMARY

Notable findings include:

- No difference in mortality rate between rheumatic and non-rheumatic patients (9.52% vs 9.54%, p>0.99; figure 1F).
- Rheumatic patients are predisposed to respiratory failure (38% vs 10%, p<0.001).
- The most common presenting symptoms among rheumatic patients were fever, fatigue, and diarrhea.
- Rheumatic patients had more length of stays greater than 20 days (57% vs 47%)
- The most common CT findings were ground-glass opacities.
- Authors suggest tocilizumab (TCZ) may be efficacious in controlling rheumatoid flares and preventing cytokine storm.

Collectively, these findings have important implications for clinical practice as many of the symptoms and laboratory indices used in the assessment of Coronavirus disease 2019 may lead to the misinterpretation of COVID-19 as a flare of rheumatic disease.

ABSTRACT

OBJECTIVE: The clinical features of rheumatic patients with coronavirus disease 2019 (COVID-19) have not been reported. This study aimed to describe the clinical features of COVID-19 in rheumatic patients and provide information for handling this situation in clinical practice.

METHODS: This is a retrospective case series study. Deidentified data, including gender, age, laboratory and radiological results, symptoms, signs, and medication history, were collected from 2326 patients diagnosed with COVID-19, including 21 cases in combination with rheumatic disease, in Tongji Hospital between 13 January and 15 March 2020.

RESULTS: Length of hospital stay and mortality rate were similar between rheumatic and non-rheumatic groups, while the presence of respiratory failure was more common in rheumatic cases (38% vs 10%, $p<0.001$). Symptoms of fever, fatigue and diarrhoea were seen in 76%, 43% and 23% of patients, respectively. There were four rheumatic patients who experienced a flare of rheumatic disease during hospital stay, with symptoms of muscle aches, back pain, joint pain or rash. While lymphocytopenia was seen in 57% of rheumatic patients, only one patient (5%) presented with leucopenia in rheumatic cases. Rheumatic patients presented with similar radiological features of ground-glass opacity and consolidation. Patients with pre-existing interstitial lung disease showed massive fibrous stripes and crazy-paving signs at an early stage. Five rheumatic cases used hydroxychloroquine before the diagnosis of COVID-19 and none progressed to critically ill stage.

CONCLUSIONS: Respiratory failure was more common in rheumatic patients infected with COVID-19. Differential diagnosis between COVID-19 and a flare of rheumatic disease should be considered.

TRIAL REGISTRATION NUMBER: ChiCTR2000030795.

FIGURES

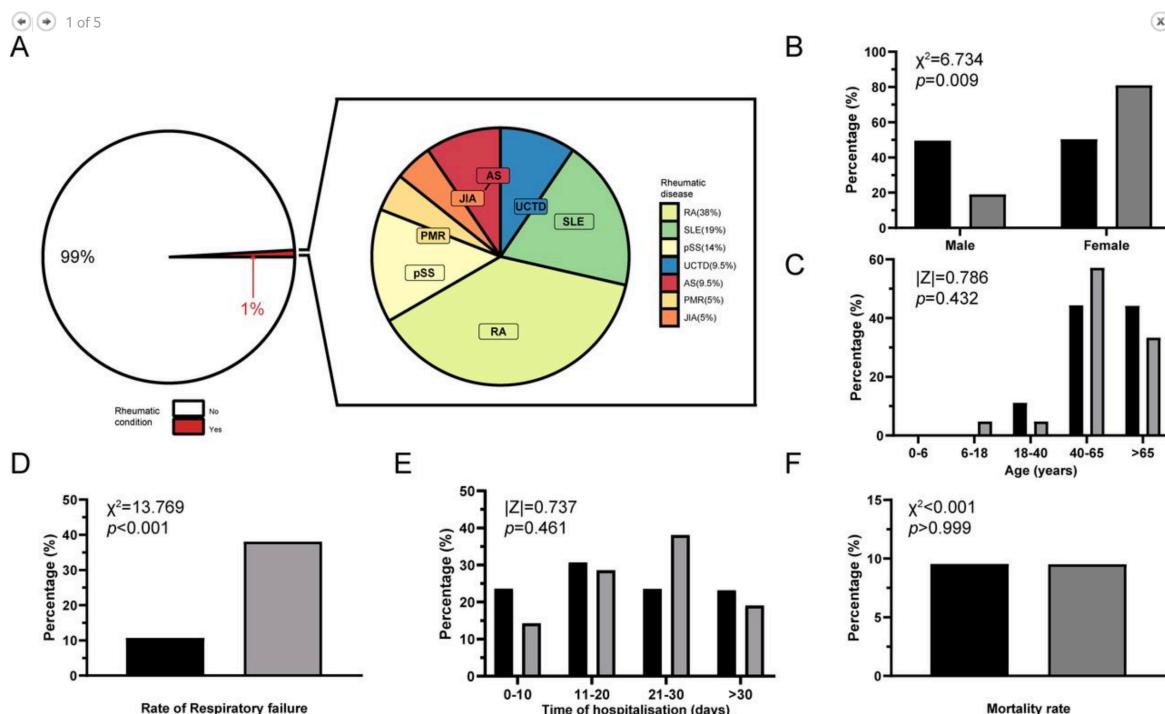
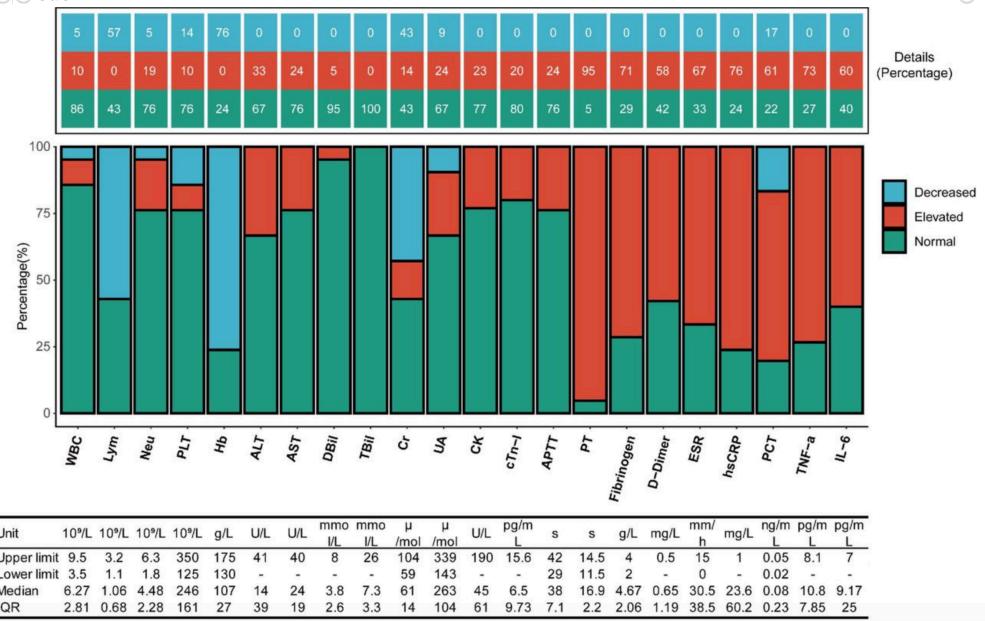


Figure 1: Basic information on rheumatic cases enrolled in this study. Ratio of rheumatic cases to the total number of patients with COVID-19 admitted to Wuhan Tongji Hospital (China), from 13 January 2020 to 15 March 2020 (left). Our series in this study consisted of eight RA cases, four SLE, three pSS, two UCTD, two AS, one JIA and one PMR (A). Gender distribution (B), age distribution (C), ratio of respiratory failure (D), hospitalisation [sic] time distribution (E) and mortality rate (F) of patients with COVID-19 with and without rheumatic diseases. Comparison of ordered categorical variables between two different groups was done using Mann-Whitney U test, while comparison of proportions for unordered categorical variables was realised [sic] using χ^2 test. $P<0.05$ was regarded as statistically significant. AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis; PMR, polymyalgia rheumatica; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease.



Unit	10 ⁹ /L	10 ⁹ /L	10 ⁹ /L	10 ⁹ /L	g/L	U/L	U/L	mmo _l	mmo _l	μ	μ	U/L	pg/m _l	s	s	g/L	mg/L	mm/ _h	mg/L	ng/m _l	pg/m _l	pg/m _l
Upper limit	9.5	3.2	6.3	350	175	41	40	8	26	104	339	190	15.6	42	14.5	4	0.5	15	1	0.05	8.1	7
Lower limit	3.5	1.1	1.8	125	130	-	-	-	-	59	143	-	-	29	11.5	2	-	0	-	0.02	-	-
Median	6.27	1.06	4.48	246	107	14	24	3.8	7.3	61	263	45	6.5	38	16.9	4.67	0.65	30.5	23.6	0.08	10.8	9.17
IQR	2.81	0.68	2.28	161	27	39	19	2.6	3.3	14	104	61	9.73	7.1	2.2	2.06	1.19	38.5	60.2	0.23	7.85	25

ADJUSTING PRACTICE DURING COVID-19

ACUTE CARE

NEUROLOGY

ISCHEMIC STROKE ASSOCIATED WITH NOVEL CORONAVIRUS 2019: A REPORT OF THREE CASES

Sharifi-Razavi A, Karimi N, Zarvani A, Cheraghmakan H, Baghbanian SM.. Int J Neurosci. 2020 Jun 16:1-5. doi: 10.1080/00207454.2020.1782902. Online ahead of print.

Level of Evidence: 4 - Case-series

BLUF

Researchers from Bou Ali Sina Hospital in Iran reviewed three cases of ischemic stroke in the setting of COVID-19 between 15 March and 7 April, 2020. Three adult patients (ages 55, 85, 88), diagnosed with COVID-19 via RT-PCR of nasopharyngeal swab sample, suffered ischemic strokes with involvement of large cerebral arteries. The authors posit inflammatory response to cytokine release due to SARS-CoV-2 infection as a potential underlying mechanism. They recommend that all patients who suffer from ischemic strokes during the pandemic be tested for SARS-CoV-2 infection and emphasize the need for further investigation of the link between strokes and COVID-19.

ABSTRACT

Introduction: There is limited evidence about the neurological manifestations of COVID-19 in infected patients. In this report, we describe three patients with ischemic stroke associated with COVID-19 infection.

Methods: We report 3 cases of adult patients with ischemic stroke and novel coronavirus 2019 infection. Case 1 is an 88-year-old female with acute left hemiplegia and right peripheral facial paresis that she had a fever along with stroke symptoms. Case 2 is an 85-year-old female with left hemiplegia and drowsiness who had a weakness, asthenia, and dry cough 3 days before appearing stroke signs. Case 3 is a 55-year-old male with acute Broca's aphasia and right hemiplegia who experience fever and respiratory problems 3 days after admission.

Results: The clinical symptoms of infected patients with COVID-19 have been associated with severe symptoms of ischemic stroke. Two patients were admitted to the ICU. RT-PCR of the oropharyngeal sample was positive in three cases. All patients had the involvement of large cerebral arteries.

Conclusion: The mechanism by which COVID-19 causes ischemic stroke is unknown but it is likely by production inflammatory cytokines or direct infection of cerebral arteries. Therefore, regarding the current situation of the COVID-19 pandemic, it is indispensable that the possible diagnosis of COVID-19 vasculopathy is considered in all ischemic strokes of unclear etiology.

MEDICAL SUBSPECIALTIES

"SEX IN THE TIME OF COVID": CLINICAL GUIDELINES FOR SEXUALLY TRANSMITTED DISEASE MANAGEMENT IN AN ERA OF SOCIAL DISTANCING

Barbee LA, Dombrowski JC, Hermann S, Werth BJ, Ramchandani M, Ocbamichael N, Barash E, Golden MR.. Sex Transm Dis. 2020 Jul;47(7):427-430. doi: 10.1097/OLQ.0000000000001194.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

The authors present the following guidelines for the management of sexually transmitted infections (STI) in King County, Washington during COVID-19:

- 1) Defer STI screening visits.
- 2) Treat patients with positive STI tests or known exposure via telemedicine using oral medications only.
- 3) Triage patients over the phone.
- 4) Provide in-person care for certain high-risk STI's such as patients with acute HIV and patients with complicated syphilis or syphilis during pregnancy.

Additional details on all recommendations is provided below.

SUMMARY

In order to reduce the risk of spreading COVID-19, practitioners from King County, Washington have developed guidelines for treating patients with an STI or a suspected STI while maintaining as much social distance as possible. It is also important to determine how to notify patients of the change in guidelines. Their recommendations are as follows:

1. Defer STI screening visits: For most patients, deferring an STI screening test is very low-risk because serious complications from most STIs are extremely rare, and generally do not develop over a short period of time. The authors suggest the risk of contracting COVID-19 is greater than the risk of a delayed STI screening test.
2. Treat patients with STIs or known exposure via telemedicine and oral medication: Oral medication is available for nearly every STI. Although first-line treatment for gonorrhea and syphilis are injectable both have highly efficacious oral alternatives. For recommendations on oral medications see Table 1.
3. Triage patients over the phone: Most patients with STI symptoms can be correctly diagnosed via telemedicine and with the practitioner using local epidemiological data. For treatment options for common STI symptoms see Table 2.
4. Provide in-person care to certain high-risk STI's such as patients with acute HIV and patients with complicated syphilis or syphilis during pregnancy: High-risk STI's require in-person visits for a variety of reasons. For individuals with syphilis during pregnancy, an injection of benzathine penicillin is required. Complicated syphilis, which includes systemic symptoms, can cause blindness and deafness if not properly treated. Currently, the only treatment available is intramuscular injections. For patients with suspected HIV, a laboratory diagnosis is required, which must be done in-clinic.

FIGURES

TABLE 1. Recommended Oral Therapies for Gonorrhea, Chlamydia, and Syphilis			
Infection	Type or Site of Infection	First Oral Option	Alternative Oral Option
Syphilis	Contact or early latent	Doxycycline 100 mg PO BID × 14 d	None
	Late latent	Doxycycline 100 mg PO BID × 28 d	
	In pregnancy	Not option Must be seen for benzathine penicillin	
Gonorrhea	Contact or nonpharyngeal	Ceftriaxone 1 g PO × 1 plus azithromycin 1 g PO × 1	Cefpodoxime 400 mg q12h × 2 doses, plus azithromycin 1 g × 1
	Pharyngeal*	Ceftriaxone 1 g PO q12h × 2, plus azithromycin 2 g PO × 1	Cefpodoxime 400 mg q12h × 4 doses, plus azithromycin 2 g PO × 1
	Cephalosporin allergy	Azithromycin 2 g PO × 1	Ciprofloxacin 500 mg PO daily × 7 days of cure
Chlamydia	Contact or nonrectal	Azithromycin 1 g or doxycycline 100 mg PO BID × 7 d	Levofloxacin 500 mg PO daily × 7 d
	Rectal chlamydia	Doxycycline 100 mg PO BID × 7 d	or Erythromycin base 500 mg q6h × 7 d

*We recommend home self-collected test of cure using nucleic-acid amplification test at 14 days after treatment.

†May separate the 2-g dose into two 1-g doses given with the first 2 doses of the cephalosporin.

‡Current ciprofloxacin resistance levels vary by jurisdiction.¹² In areas where ciprofloxacin resistance is >30%, use caution.

BID indicates twice a day; PO, per os; q6h, every 6 hours; q12h, every 12 hours.

Table 1. Recommended Oral Therapies for Gonorrhea, Chlamydia, and Syphilis

TABLE 2. Recommendations for Syndromic Management of STI Syndromes Over the Phone		
Symptoms	Syndromic Management	Other Considerations
Urethral discharge	Cefixime* 800 mg PO × 1 plus doxycycline 100 mg PO BID × 7 d	Can substitute aztreonam 1 g PO for persistent symptoms ¹³ ; consider adding moxifloxacin 400 mg daily × 10 d to cover Mycoplasma genitalium and/or metronidazole 2 g PO × 1 for Trichomonas ⁸
Vaginal discharge [‡]	Frothy or malodorous discharge: metronidazole 500 mg BID × 7 d Cottage cheese-like discharge: fluconazole 150 mg PO × 1, may repeat q4d for 3 doses Yellow/green discharge: cefixime [§] 800 mg PO × 1 plus azithromycin 1 g PO × 1 Doxycycline 100 mg PO BID × 14 d With pain: Azylovir 400 mg every 8 h × 7–10 d	Ask women with vaginal discharge about symptoms of pelvic inflammatory disease, abdominal or pelvic pain, and fever. If present, treat with cefixime 800 × 1, doxycycline × 14 d plus metronidazole 500 BID × 14 d.
Genital ulcer disease	Doxycycline 100 mg PO BID × 14 d plus cefixime [§] 800 mg PO × 1 plus doxycycline 100 mg PO BID × 7 d Pain: add azylovir 400 mg PO q8h × 7–10 d	All persons with suspect syphilis should be screened for symptoms of neurosyphilis.
Anorectal symptoms [‡]	Doxycycline 100 mg PO BID × 14 d plus azylovir 400 mg PO q8h × 7–10 d	
Body rash	Doxycycline 100 mg PO BID × 14 d	All persons with suspect syphilis should be screened for symptoms of neurosyphilis. Whenever possible, attempt to see the rash using videoconferencing or a picture [¶]

*If cefixime is unavailable, ciprofloxacin 400 mg every 12 hours × 2 doses can be substituted.

[‡]Local epidemiology of urethritis etiologies can assist second-line therapies for persistent urethritis.

[§]Use symptomatology to guide treatment.

[¶]Consider treatment for genital herpes particularly if painful or blisters.

[¶]Exchange of information needs to comply with federal privacy laws.

BID indicates twice a day; PO, per os; STI, sexually transmitted infection; q3d, every 3 days; q6h, every 6 hours; q8h, every 8 hours; q12, every 12 hours.

Table 2. Recommendations for Syndromic Management of STI Syndromes Over the Phone

GASTROENTEROLOGY

RISK STRATIFICATION AND PERSONAL PROTECTIVE EQUIPMENT USE IN PEDIATRIC ENDOSCOPY DURING THE CORONAVIRUS DISEASE 2019 OUTBREAK: A SINGLE-CENTER PROTOCOL

Say DS, de Lorimier A, Lammers CR, Natale J, Lakshminrusimha S, Wiedeman J, Partridge E.. J Pediatr Gastroenterol Nutr. 2020 Jun;70(6):751-754. doi: 10.1097/MPG.0000000000002731.

Level of Evidence: Other -

BLUF

This protocol released by the Department of Pediatrics at the University of California, Davis shares the institution's methodology of stratifying pediatric patients who may need endoscopic procedures and their recommendations on use of personal protective equipment (PPE) during aerosol-generating procedures during the COVID-19 pandemic (Figure 1 & 2).

SUMMARY

The University of California, Davis pediatric endoscopy protocol includes specific recommendations on risk stratification, procedures, scheduling, and appropriate PPE:

1. Stratify the patient's COVID-19 risk based on symptoms and sick contacts if SARS-CoV-2 tests are not available (Table 1)
2. Have no more than five individuals in endoscopy suite at a time
3. Use a negative pressure room for all endoscopic procedures
4. Use a neutral pressure room with the door closed if all personnel has a powered air-purifying respirator (PAPR), and leave the door closed for one hour after completing the procedure.
5. Perform essential endoscopic procedures (where a delay of 8 to 12 weeks predisposes to harm) if adequate supply of PPE are available.
6. If the availabilities of PPE or workforce were compromised, emergent procedures will be done, such as foreign body retrieval and evaluation of GI bleeding.
7. Schedule endoscopies according to the shared decision made by the gastroenterologist, patient, and the patient's family

PPE for all endoscopic procedures:

1. Minimum: gloves, water-resistant gowns, surgical face masks, eye protection, and hair coverings
2. Low-risk and high-risk patients with upper endoscopy and high-risk patients with colonoscopy: N95 respirators or equivalents.
3. PAPR may be used in lieu of surgical face masks, N95 respirators, eye protection, and hair covering.

ABSTRACT

SARS-CoV-2, the novel coronavirus causing coronavirus disease 2019 (COVID-19), is now a global pandemic. Human-to-human transmission has been documented to occur through respiratory secretions, feces, aerosols, and contaminated environmental surfaces. Pediatric patients present a unique challenge as they may have minimal symptoms and yet transmit disease. Endoscopists face risk for infection with viruses like SARS-CoV-2, as the aerosol generating nature of endoscopy diffuses respiratory disease that can be spread via an airborne and droplet route. We describe our center's methodology for pediatric patient risk stratification to facilitate responsible use of endoscopic resources during this crisis. We also describe our recommendations for use of personal protective equipment by endoscopists, with the goal of ensuring the safety of ourselves, our anesthesiology and endoscopy staff, and our patients.

FIGURES

TABLE 1. SARS-CoV-2 infection risk in pediatric patients requiring endoscopy	
Classification of potential COVID-19 infection risk in pediatric patients undergoing endoscopic evaluation	
Low risk	No symptoms (eg, cough, fever, shortness of breath) in the past 14 days AND No known contact with confirmed COVID-19 case
High risk	At least 1 symptom (eg, cough, fever, shortness of breath) in the past 14 days, with: Contact with confirmed COVID-19 case OR At least 1 symptom (eg, cough, fever, shortness of breath) in the past 14 days, with: No known contact with confirmed COVID-19 case OR No symptoms (eg, cough, fever, shortness of breath) in the past 14 days, but: Contact with confirmed COVID-19 case
Unknown risk	In an emergency setting, all procedures should be considered high risk if patient history cannot be properly assessed

COVID-19, corona virus disease 2019.

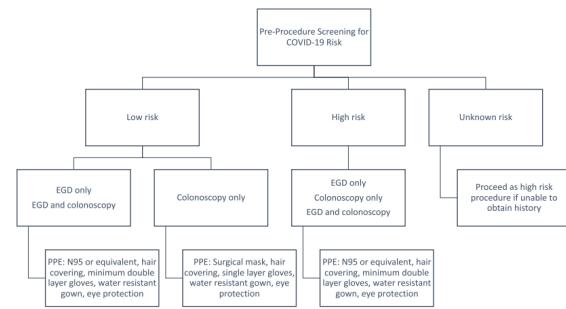


FIGURE 1. Personal protective equipment utilization algorithm for endoscopists.

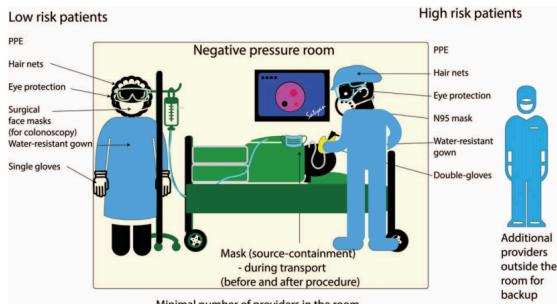


FIGURE 2. Personal protective equipment utilization in the endoscopy suite.

SURGICAL SUBSPECIALTIES

UROLOGY

SPECIAL STRATEGIES AND MANAGEMENT OF UROLOGICAL DISEASES DURING THE COVID-19 PANDEMIC: INITIAL EXPERIENCES FROM A MEDICAL CENTER OF CHINA

Chen W, Wang XM, Fu GQ, Fu GQ, Zeng X, Wu CP, Liang Y, Liu JH, Teoh JY.. Int Braz J Urol. 2020 Jun 17;46. doi: 10.1590/S1677-5538.IBJU.2020.S102. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Authors from China discuss their initial experiences with managing urological diseases in one Chinese hospital during the COVID-19 outbreak and formulate a set of guidelines and recommendations, highlighting effective and protective measures for managing urological diseases during the COVID-19 pandemic (Figures 1, 2, and 3). Adoption of similar measures in other countries may be critical in preventing COVID-19 in this population that consists of many elderly patients at a high risk of severe infection.

ABSTRACT

Although urological diseases are not directly related to coronavirus disease 2019 (COVID-19), urologists need to make comprehensive plans for this disease. Urological conditions such as benign prostatic hyperplasia and tumors are very common in elderly patients. This group of patients is often accompanied by underlying comorbidities or immune dysfunction. They are at higher risk of COVID-19 infection and they tend to have severe manifestations. Although fever can occur along with urological infections, it is actually one of the commonest symptoms of COVID-19; urologists must always maintain a high index of suspicion in their clinical practices. As a urological surgeon, how we can protect medical staff during surgery is a major concern. Our hospital had early adoption of a series of strict protective and control measures, and was able to avoid cross-infection and outbreak of COVID-19. This paper discusses the effective measures that can be useful when dealing with urological patients with COVID-19.

Figure 1 - Three levels of pre-examination for urology clinic.

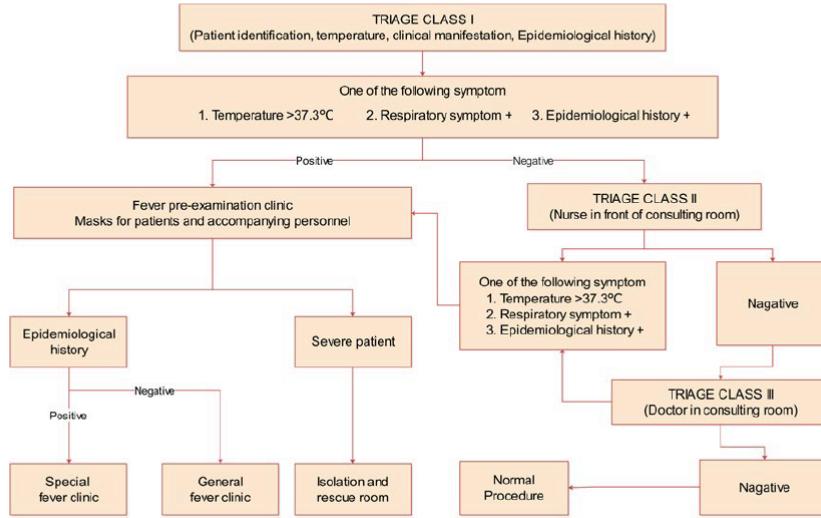


Figure 2 - General screening procedures for patients in urology ward.

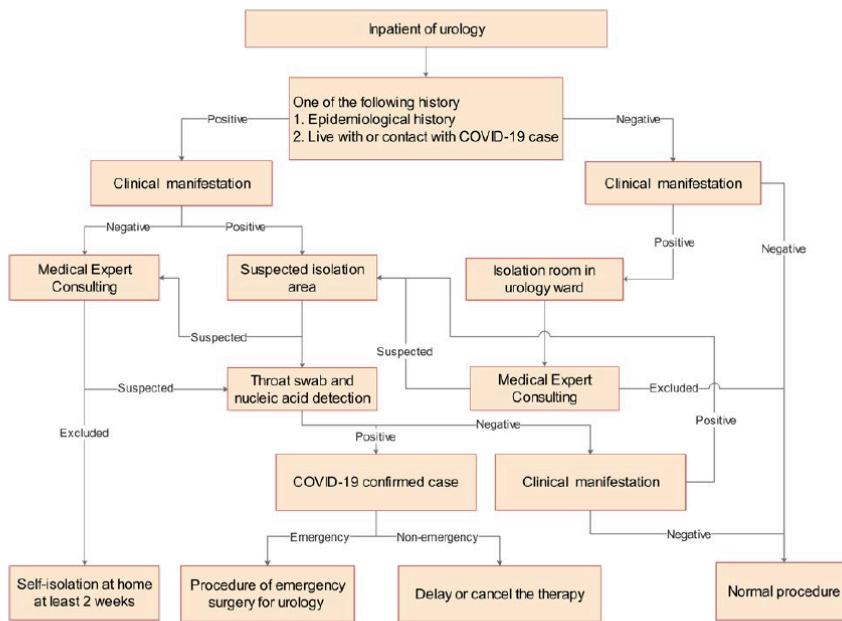
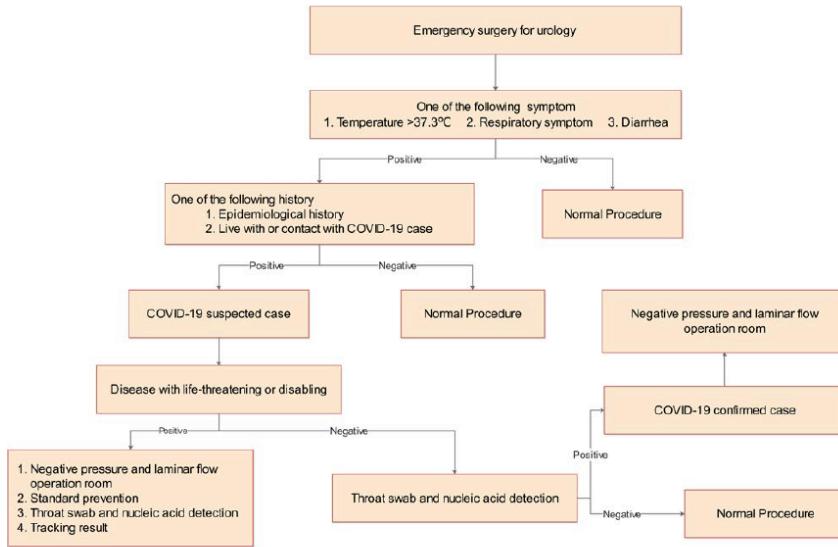


Figure 3 - Procedure for emergency surgery of urology during COVID-19 pandemic.



5

PEDIATRICS

CORONA VIRUS DISEASE 2019 AND PAEDIATRIC INFLAMMATORY BOWEL DISEASES: GLOBAL EXPERIENCE AND PROVISIONAL GUIDANCE (MARCH 2020) FROM THE PAEDIATRIC IBD PORTO GROUP OF EUROPEAN SOCIETY OF PAEDIATRIC GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION

Turner D, Huang Y, Martín-de-Carpi J, Aloia M, Focht G, Kang B, Zhou Y, Sanchez C, Kappelman MD, Uhlig HH, Pujol-Muncunill G, Ledder O, Lionetti P, Dias JA, Ruemmele FM, Russell RK; Paediatric IBD Porto group of ESPGHAN.. J Pediatr Gastroenterol Nutr. 2020 Jun;70(6):727-733. doi: 10.1097/MPG.0000000000002729.

Level of Evidence: 3 -

BLUF

The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition distributed surveys to participating centers (102 worldwide) to determine global trends in patients with pediatric inflammatory bowel disease (PIBD) during the pandemic. They report eight cases of PIBD patients testing positive for SARS-CoV-2, all with mild presentation of symptoms and none-requiring hospital admission or disruption of current IBD treatment protocols. Notably they recommend:

- continuing immunomodulating treatments even when diagnosed with COVID19.
- children with PIBD are not at a higher risk for infection with SARS-CoV-2 than the general pediatric population.
- full list in table 1.

ABSTRACT

INTRODUCTION: With the current coronavirus disease 2019 (COVID-19) pandemic, concerns have been raised about the risk to children with inflammatory bowel diseases (IBD). We aimed to collate global experience and provide provisional guidance for managing paediatric IBD (PIBD) in the era of COVID-19.

METHODS: An electronic reporting system of children with IBD infected with SARS-CoV-2 has been circulated among 102 PIBD centres affiliated with the Porto and Interest-group of ESPGHAN. A survey has been completed by major PIBD centres in China and South-Korea to explore management during the pandemic. A third survey collected current practice of PIBD treatment. Finally, guidance points for practice have been formulated and voted upon by 37 PIBD authors and Porto group members.

RESULTS: Eight PIBD children had COVID-19 globally, all with mild infection without needing hospitalization despite treatment with immunomodulators and/or biologics. No cases have been reported in China and South Korea but biologic treatment has been delayed in 79 children, of whom 17 (22%) had exacerbation of their IBD. Among the Porto group members, face-to-face appointments were often replaced by remote consultations but almost all did not change current IBD

treatment. Ten guidance points for clinicians caring for PIBD patients in epidemic areas have been endorsed with consensus rate of 92% to 100%.

CONCLUSIONS: Preliminary data for PIBD patients during COVID-19 outbreak are reassuring. Standard IBD treatments including biologics should continue at present through the pandemic, especially in children who generally have more severe IBD course on one hand, and milder SARS-CoV-2 infection on the other.

FIGURES

Statements	Consensus rate
1. IBD per-se does not currently seem to be a risk factor for acquiring SARS-CoV-2, nor for a more severe infection.	100%
2. For decreasing the risk of contracting SARS-CoV-2 in children with IBD, we recommend using the same measures as in the local population during the pandemic (eg, good hand hygiene, avoiding contact with anyone with respiratory symptoms and social distancing).	100%
3. When possible by local situation and resources, children should continue follow-up visits to ensure appropriate monitoring of the disease. Remote telemedicine consultations, along with the use of surrogate markers of inflammation (fecal calprotectin, C-reactive protein, patient-reported outcomes) may, however, be an alternative to face-to-face office visits during the epidemic, especially for those in remission. The option of delaying visits should be considered on an individual basis.	97%
4. Active IBD disease should be treated according to the standard guidance PIBD protocols as before the epidemics, as the risk of IBD complications in active IBD outweighs any risk of COVID-19 complications, especially in children.	97%
5. There is currently no concrete evidence that any of the IBD treatments increases the risk for acquiring SARS-CoV-2 or for a more severe infection once infected. Therefore, uninfected children should generally continue their medical treatment, including immunomodulators and biologic therapies, as the risk of a disease flare outweighs any estimated risk of SARS-CoV2 infection. This is especially true in children who have a much milder infection. Specific considerations are listed below.	97%
6. Corticosteroids can be used to treat disease relapses, but as always recommended in children, the drug should be weaned as soon as possible. In Crohn disease, exclusive enteral nutrition should be preferred.	92%
7. The use of anti-TNFs should be continued at the regular intervals and doses. Infusion centers should minimize crowding and implement screening procedures for suspected COVID-19.	97%
8. Switching from infliximab to adalimumab in a stable child should be discouraged unless impossible to provide intravenous infusions, as the risk of disease exacerbation after such a switch has been documented in the clinical trial setting.	97%
9. There is no clear indication to stop IBD treatment during COVID-19 infection, also because of the typical prolonged effect of IBD drugs. Nonetheless, we recommend suspending immunosuppressive treatment during an acute febrile illness until fever subsides and the child returns to normal health, irrespective of the SARS-CoV-2 testing status. In case of positive SARS-CoV-2 testing in an asymptomatic child, the decision of therapeutic changes should be individualized. Mesalamine should never be suspended.	100%
10. Elective surgeries and nonurgent endoscopies should be postponed during the epidemic.	97%

All statements are limited to children and are based on the emerging but limited data available upon March 2020; it is possible that statements may change as data on PIBD and COVID-19 will accumulate. The following 2 statements did not receive consensus of the Porto group, and thus were removed: "Up to one-third of patients with COVID-19 may present with gastrointestinal symptoms, mainly diarrhea or nausea. Therefore, these symptoms during an active infection do not necessarily indicate a flare of the underlying IBD" and "In children with suspected symptoms of COVID-19, SARS-CoV2 testing is recommended before any therapeutic change". COVID-19 = corona virus disease 2019; IBD = inflammatory bowel disease; PIBD = paediatric inflammatory bowel disease.

Table 1: Guidance points endorsed by the Paediatric Porto Group of ESPGHAN (37 voting experts).

LOPINAVIR PHARMACOKINETICS IN COVID-19 PATIENTS

Gregoire M, Le Turnier P, Gaborit BJ, Veyrac G, Lecomte R, Bouteille D, Canet E, Imbert BM, Bellouard R, Raffi F.. J Antimicrob Chemother. 2020 May 22:dkaa195. doi: 10.1093/jac/dkaa195. Online ahead of print.

Level of Evidence: 4 -

BLUF

A group of French clinicians track lopinavir plasma pharmacokinetics using liquid chromatography tandem mass spectrometry in 12 admitted patients with COVID-19 that received various dosages of lopinavir/ritonavir dual therapy 1 to 4 days post-admission (Figure 1). Few adverse effects were noted, including diarrhea (n=6, also taking amoxicillin/clavulanate), and nausea/vomiting (n=2), leading the authors to conclude that lopinavir/ritonavir was safe in their study, though they acknowledge that further study is needed on pharmacokinetic profile and routes of administration.

FIGURES

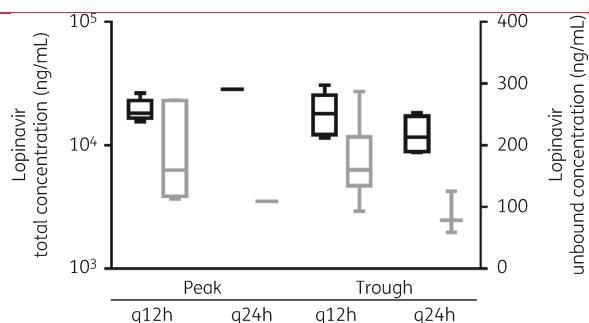


Figure 1. Lopinavir concentrations in SARS-CoV-2-infected patients after ritonavir-boosted lopinavir 400/100 mg once or twice daily. Total (black) and unbound (grey) concentrations are represented by medians, IQRs and ranges at peak (4 ± 1 h after intake) or trough (q12h: at least 10 h after intake; and q24h: at least 18 h after intake).

PRACTICE CONSIDERATIONS ON THE USE OF INVESTIGATIONAL ANTI-COVID-19 MEDICATIONS: DOSAGE, ADMINISTRATION AND MONITORING

Kang JE, Rhie SJ.. J Clin Pharm Ther. 2020 Jun 11. doi: 10.1111/jcpt.13199. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

Researchers in South Korea reviewed current medications used to treat patients with COVID-19, giving guidance on the method of administration, formulation, and adverse-reaction monitoring. The current medications being used to treat COVID-19 patients are Hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir, Tocilizumab, Ciclesonide, Niclosamide, and intravenous immunoglobulin. While none of these medications have been proven to be effective, studies are currently being conducted on all of these potential COVID-19 treatments.

SUMMARY

There are several medications currently being used for COVID-19 treatment. It is vitally important for physicians to be up to date on the details of these treatments and their side effects.

1. Hydroxychloroquine/Chloroquine: Several dosing regimens have been used, however, the FDA has recommended 800 mg on day 1 followed by 400 mg daily for 4-7 days. Hydroxychloroquine is recommended to be used in conjunction with azithromycin or zinc supplementation. Risk of QT prolongation and heart arrhythmia at high cumulative dosages.
2. Lopinavir/ritonavir: The main combination treatment used in Korea and was found to significantly reduce viral load. Current treatment with this drug is for 14 days at a dosage of 10/2.5 mg/kg respectively. There is a high risk of GI adverse events.
3. Remdesivir: Given as a 200 mg dose on the first day and then 100 mg for the following 5-10 days. Remdesivir has shown activity against SARS-CoV-2 in preclinical trials. Daily monitoring of liver and renal functions should be done, if possible.
4. Tocilizumab: Current evidence from a retrospective study (n=21) demonstrated possible decrease in mortality. Current dosages are 8 mg/kg every 12 hours or a single 200 mg IV dose. Providers should monitor for signs and symptoms of infection. Additionally, severe liver damage and intestinal perforation are potential risks requiring monitoring.

5. Ciclesonide: An inhaled steroid currently being tested for treatment with COVID-19 patients at a dosage of 320 mcg every 12 hours for 14 days.
6. Niclosamide: Originally used as an anthelmintic drug, it is being considered as a possible treatment via a single 2 gram dose.
7. High-dose intravenous immunoglobulin (IVIG): Recommended dosage is 0.2-0.5 g/kg/day, likely to be used only in critically ill patients.

ABSTRACT

WHAT IS KNOWN AND OBJECTIVE: Understanding investigational medications is important. Many older drugs are being investigated for repurposing against COVID-19. We comment on various drugs currently undergoing such trials to optimize their safe use.

COMMENT: We describe medications used during early COVID-19 outbreaks in South Korea, focusing on practice aspects including the method of drug administration, drug formulation, patient-monitoring for adverse reactions and drug interactions informed by our experience during the 2015 outbreak of Middle East respiratory syndrome (MERS). We comment on hydroxychloroquine, chloroquine, lopinavir/ritonavir with zinc supplement, remdesivir, tocilizumab, ciclesonide, niclosamide and high-dose intravenous immunoglobulin (IVIG).

WHAT IS NEW AND CONCLUSION: Effective therapies are urgently needed to manage COVID-19, and existing drugs such as antivirals and antimalarials are under investigation for repurposing to meet this need. This process requires up-to-date drug information to ensure optimum use, particularly safety and efficacy profiles of the medications, until convincing evidence is reported.

DEVELOPMENTS IN DIAGNOSTICS

EVALUATION OF COVID-19 IgG/IgM RAPID TEST FROM ORIENT GENE BIOTECH

Delliére S, Salmona M, Minier M, Gabassi A, Alanio A, Le Goff J, Delaugerre C, Chaix ML; Saint-Louis CORE (COvid REsearch) group.. *J Clin Microbiol.* 2020 Jun 9:JCM.01233-20. doi: 10.1128/JCM.01233-20. Online ahead of print.

Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

An experiment conducted at the University of Paris tested the efficacy of the Orient Gene COVID-19 IgG/IgM Rapid Test Cassette at multiple time points and compared it to a previously validated antibody test (Abbott SARS-CoV-2 IgG Immunoassay). In patients with known COVID-19 (Table 1) and results interpreted by unblinded clinical microbiologists, the Orient Gene test had a sensitivity of 95.8% and a specificity of 100% (IgG and IgM results shown in Figure 1); while the authors note that these results need validation with a larger asymptomatic group, these findings suggest clinical utility for this test.

ABSTRACT

While the COVID-19 pandemic has peaked in many countries already, the current challenge is to assess population immunity on large scale. Many serological tests are available and require urgent independent validation. Here we report performance characteristics of Orient Gene (OG) COVID-19 IgG/IgM Rapid Test Cassette compare it Abbott SARS-CoV-2 IgG immunoassay (ASIA). Patients (n=102) with a positive SARS-CoV-2 RT-PCR were tested. They were asymptomatic (n=2), had mild (n=37) or severe symptoms requiring hospitalization in medical (n=35) or intensive care unit (n=28). Specificity was evaluated on 42 patients with previous viral and parasitic diseases as well as high level of rheumatic factor. Sensitivity of OG was 95.8% (CI95% 89.6-98.8) for samples collected \geq 10 days after onset of symptoms which was equivalent to sensitivity of ASIA of 90.5% (IC95% 82.8-95.6). OG uncovered 6 false negative of ASIA, of which two had only IgM with OG. Specificity was 100% (CI95% 93.4-100) with both tests on samples including patients infected with endemic coronavirus. Overall, OG performance characteristics indicate that the test is suitable for routine use in clinical laboratories and performance is equivalent to immunoassay. Testing OG on a larger asymptomatic population may be needed to confirm these results.

FIGURES

Characteristics	n (%) Total n=102
Male	59 (57.8)
Disease severity	
Asymptomatic	2 (1.9)
Mild	37 (36.3)
Severe (Medical Unit)	35 (34.3)
Critical (ICU)	28 (27.5)
Patients with ≥2 consecutive sera	4 (3.9)
Mean age of the patient population was 52 (\pm 16)	
ICU: Intensive care unit	

Table 1. Clinical characteristics of 102 patients with a positive SARS-COV-2 RT-PCR

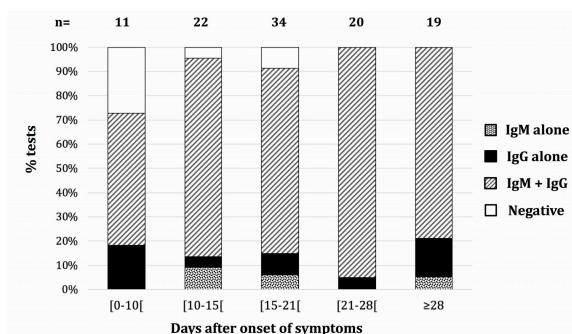


Figure 1. Percentage of Orient Gene tests displaying IgM alone, IgG alone or both IgM and IgG 189 according to days from onset of symptoms.

DEVELOPMENTS IN TREATMENTS

LOPINAVIR-RITONAVIR VERSUS HYDROXYCHLOROQUINE FOR VIRAL CLEARANCE AND CLINICAL IMPROVEMENT IN PATIENTS WITH MILD TO MODERATE CORONAVIRUS DISEASE 2019

Kim JW, Kim EJ, Kwon HH, Jung CY, Kim KC, Choe JY, Hong HL.. Korean J Intern Med. 2020 Jun 16. doi: 10.3904/kjim.2020.224. Online ahead of print.

Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A retrospective cohort conducted at Daegu Catholic University School of Medicine in Korea found that 31 COVID-19-positive patients treated with lopinavir-ritonavir had significantly shorter times to negative conversion of viral RNA than 34 COVID-19-positive patients treated with hydroxychloroquine (median, 21 days vs. 28 days; Figure 2); however, time until clinical improvement was not found to be different between these groups. This suggests that lopinavir-ritonavir treatment may have faster viral clearance in patients with COVID-19 than hydroxychloroquine therapy, although randomized controlled trials are needed to confirm this finding and investigate its clinical relevance.

ABSTRACT

Background/Aims: The efficacies of lopinavir-ritonavir or hydroxychloroquine remain to be determined in patients with coronavirus disease 2019 (COVID-19). To compare the virological and clinical responses to lopinavir-ritonavir and hydroxychloroquine treatment in COVID-19 patients. **Methods:** This retrospective cohort study included patients with COVID-19 treated with lopinavir-ritonavir or hydroxychloroquine at a single center in Korea from February 17 to March 31, 2020. Patients treated with lopinavir-ritonavir and hydroxychloroquine concurrently and those treated with lopinavir-ritonavir or hydroxychloroquine for less than 7 days were excluded. Time to negative conversion of viral RNA, time to clinical improvement, and safety outcomes were assessed after 6 weeks of follow-up. **Results:** Of 65 patients (mean age, 64.3 years; 25 men [38.5%]), 31 were treated with lopinavir-ritonavir and 34 were treated with hydroxychloroquine. The median duration of symptoms before treatment was 7 days and 26 patients (40%) required oxygen support at baseline. Patients treated with lopinavir-ritonavir had a significantly shorter time to negative conversion of viral RNA than those treated with hydroxychloroquine (median, 21 days vs. 28 days). Treatment with lopinavir-ritonavir (adjusted hazard ratio [aHR], 2.28;

95% confidence interval [CI], 1.24 to 4.21) and younger age (aHR, 2.64; 95% CI 1.43 to 4.87) was associated with negative conversion of viral RNA. There was no significant difference in time to clinical improvement between lopinavir-ritonavir- and hydroxychloroquine-treated patients (median, 18 days vs. 21 days). Lymphopenia and hyperbilirubinemia were more frequent in lopinavir-ritonavir-treated patients compared with hydroxychloroquine-treated patients. Conclusions: Lopinavir-ritonavir was associated with more rapid viral clearance than hydroxychloroquine in mild to moderate COVID-19, despite comparable clinical responses. These findings should be confirmed in randomized, controlled trials.

FIGURES

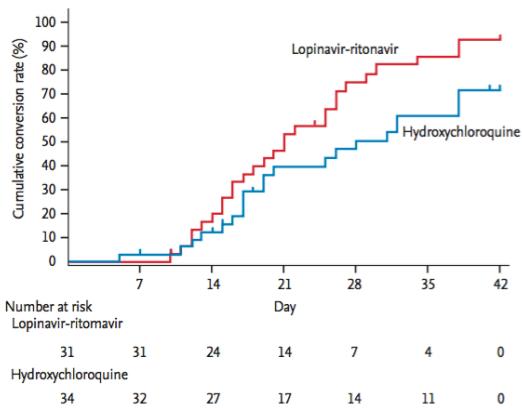


Figure 2. Kaplan-Meier curves showing time to negative conversion of viral RNA in nasopharyngeal and oropharyngeal specimens.

THE BROAD-SPECTRUM ANTIVIRAL RECOMMENDATIONS FOR DRUG DISCOVERY AGAINST COVID-19

Hazafa A, Ur-Rahman K, Haq IU, Jahan N, Mumtaz M, Farman M, Naeem H, Abbas F, Naeem M, Sadiqa S, Bano S.. Drug Metab Rev. 2020 Jun 17:1-17. doi: 10.1080/03602532.2020.1770782. Online ahead of print.

Level of Evidence: 5 - Review / Literature Review

BLUF

A review conducted by a multidisciplinary group of researchers from Pakistan discuss the use of interferons, ribavirin, remdesivir, chloroquine and hydroquinone, favipiravir, ritonavir, lopinavir, inhibitors, and monoclonal antibodies (mAbs) as potential treatments for COVID-19 until novel therapies can be developed due to their abilities to inhibit viral RNA replication and viral protein expression. The authors also emphasize the inhibition of TMPRSS2 as a potential target for upcoming drug discovery, as this protein plays a significant role in the activation of the SARS-CoV-2. Campostat, which targets TMPRSS2, has been shown in cell lines and mouse models to inhibit viral replication in the coronavirus family. In addition, direct and indirect-acting antivirals (DAA, IAAAs), which target various factors required for transmission of the coronavirus, have shown activity against coronaviruses such as MERS-CoV in past in-vitro and cell line studies.

ABSTRACT

Despite to outbreaks of highly pathogenic beta and alpha coronaviruses including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and human coronavirus, the newly emerged 2019 coronavirus (COVID-19) is considered as a lethal zoonotic virus due to its deadly respiratory syndrome and high mortality rate among the human. Globally, more than 3,517,345 cases have been confirmed with 243,401 deaths due to Acute Respiratory Distress Syndrome (ARDS) caused by COVID-19. The antiviral drug discovery activity is required to control the persistence of COVID-19 circulation and the potential of the future emergence of coronavirus. However, the present review aims to highlight the important antiviral approaches, including interferons, ribavirin, mycophenolic acids, ritonavir, lopinavir, inhibitors, and monoclonal antibodies (mAbs) to provoke the nonstructural proteins and deactivate the structural and essential host elements of the virus to control and treat the infection of COVID-19 by inhibiting the viral entry, viral RNA replication and suppressing the viral protein expression. Moreover, the present review investigates the epidemiology, diagnosis, structure, and replication of COVID-19 for better understanding. It is recommended that these proteases, inhibitors, and antibodies could be a good therapeutic option in drug discovery to control the newly emerged

coronavirus. Highlights COVID-19 has more than 79.5% identical sequence to SARS-CoV and a 96% identical sequence of the whole genome of bat coronaviruses. Acute respiratory distress syndrome (ARDS), renal failure, and septic shock are the possible clinical symptoms associated with COVID-19. Different antivirals, including interferons, ribavirin, lopinavir, and monoclonal antibodies (mAbs) could be the potent therapeutic agents against COVID-19. The initial clinical trials on hydroxychloroquine in combination with azithromycin showed an admirable result in the reduction of COVID-19. The overexpression of inflammation response, cytokine dysregulation, and induction of apoptosis could be well-organized factors to reduce the pathogenicity of COVID-19.

FIGURES

Inhibitor name	Inhibitor class	IC_{50}	
		SARS-CoV	MERS-CoV
Benztropine mesylate	Neurotransmitter inhibitors	21.6	1
Triflupromazine hydrochloride	Neurotransmitter inhibitors	6.39	5.75
Chlorpromazine hydrochloride	Neurotransmitter inhibitors	12.97	9.51
Thiothixene	Neurotransmitter inhibitors	5.31	9.29
Clomipramine hydrochloride	Neurotransmitter inhibitors	13.23	9.33
Gemcitabine hydrochloride	DNA metabolism inhibitor	4.95	1.21
Nilotinib	Kinase signaling inhibitor	2.10	5.46
Imatinib mesylate	Kinase signaling inhibitor	9.82	17.68
Toremifene citrate	Estrogen receptor inhibitor	11.96	12.91
Tamoxifen citrate	Estrogen receptor inhibitor	92.88	10.11
Mefloquine	Anti-parasite agent	15.53	7.41
Terconazole	Sterol metabolism inhibitor	15.32	12.20

This information is taken from the research of Frieman et al. (2019).

Table 1: The in vitro study of diverse classes of inhibitors against MERS and SARS-CoV with activity.

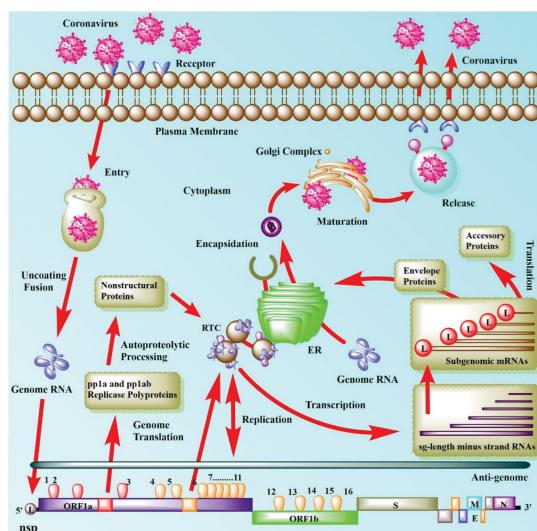


Figure 3: The schematic diagram of replication cycle of coronavirus. The virus (pink) across the plasma membrane (brown color) by receptor-mediated endocytosis (dark blue) and release into the cytosol of infected persons and yield in two replicate polyproteins including pp1a and pp1ab (in a light brown box) by genome translation. The viral nonstructural proteins (nsps) accumulates into RTC (dark brown ball with viral nsps) that resembled in minus-strand RNA formulation due to internal proteases like HAT, and TMPRSS2. The sub-genome mRNAs (brown lines with red balls), (sg)-length minus strands (purple) and full-length genome

produced, and accessory proteins exist in the 3'-proximal quarter of the genome. Finally, the encapsulation of viral RNA occurs by budding in the smooth endoplasm reticulum (green) and packed in the form of nucleocapsids (light blue) by the Golgi apparatus (orange) and released from the cell via an exocytic pathway (Snijder et al. 2016; de Wilde et al. 2017).

ANTIVIRAL EFFICACIES OF FDA-APPROVED DRUGS AGAINST SARS-COV-2 INFECTION IN FERRETS

Park SJ, Yu KM, Kim YI, Kim SM, Kim EH, Kim SG, Kim EJ, Casel MAB, Rollon R, Jang SG, Lee MH, Chang JH, Song MS, Jeong HW, Choi Y, Chen W, Shin WJ, Jung JU, Choi YK.. mBio. 2020 May 22;11(3):e01114-20. doi: 10.1128/mBio.01114-20.

BLUF

An in vivo model conducted in Cheongju, Republic of Korea by the Chungbuk National University College of Medicine and Medical Research Institute investigated different antiviral therapies (lopinavir/ritonavir, hydroxychloroquine sulfate, emtricitabine/tenofovir) and the immunosuppressive agent azathioprine in SARS-CoV-2 inoculated ferrets. Results are summarized in figures 1-3 and reveal:

- Antiviral therapies decreased overall clinical scores, with emtricitabine-tenofovir being the only therapy to reduce virus titers in nasal washes at 8 days post infection
- Delayed virus clearance and reduced serum neutralization antibody titers in the azathioprine-treated ferrets signifies that immunosuppressant drugs can elongate illness duration

ABSTRACT

Due to the urgent need of a therapeutic treatment for coronavirus (CoV) disease 2019 (COVID-19) patients, a number of FDA-approved/repurposed drugs have been suggested as antiviral candidates at clinics, without sufficient information. Furthermore, there have been extensive debates over antiviral candidates for their effectiveness and safety against severe acute respiratory syndrome CoV 2 (SARS-CoV-2), suggesting that rapid preclinical animal studies are required to identify potential antiviral candidates for human trials. To this end, the antiviral efficacies of lopinavir-ritonavir, hydroxychloroquine sulfate, and emtricitabine-tenofovir for SARS-CoV-2 infection were assessed in the ferret infection model. While the lopinavir-ritonavir-, hydroxychloroquine sulfate-, or emtricitabine-tenofovir-treated group exhibited lower overall clinical scores than the phosphate-buffered saline (PBS)-treated control group, the virus titers in nasal washes, stool specimens, and respiratory tissues were similar between all three antiviral-candidate-treated groups and the PBS-treated control group. Only the emtricitabine-tenofovir-treated group showed lower virus titers in nasal washes at 8 days postinfection (dpi) than the PBS-treated control group. To further explore the effect of immune suppression on viral infection and clinical outcome, ferrets were treated with azathioprine, an immunosuppressive drug. Compared to the PBS-treated control group, azathioprine-immunosuppressed ferrets exhibited a longer period of clinical illness, higher virus titers in nasal turbinate, delayed virus clearance, and significantly lower serum neutralization (SN) antibody titers. Taken together, all antiviral drugs tested marginally reduced the overall clinical scores of infected ferrets but did not significantly affect in vivo virus titers. Despite the potential discrepancy of drug efficacies between animals and humans, these preclinical ferret data should be highly informative to future therapeutic treatment of COVID-19 patients.

IMPORTANCE The SARS-CoV-2 pandemic continues to spread worldwide, with rapidly increasing numbers of mortalities, placing increasing strain on health care systems. Despite serious public health concerns, no effective vaccines or therapeutics have been approved by regulatory agencies. In this study, we tested the FDA-approved drugs lopinavir-ritonavir, hydroxychloroquine sulfate, and emtricitabine-tenofovir against SARS-CoV-2 infection in a highly susceptible ferret infection model. While most of the drug treatments marginally reduced clinical symptoms, they did not reduce virus titers, with the exception of emtricitabine-tenofovir treatment, which led to diminished virus titers in nasal washes at 8 dpi. Further, the azathioprine-treated immunosuppressed ferrets showed delayed virus clearance and low SN titers, resulting in a prolonged infection. As several FDA-approved or repurposed drugs are being tested as antiviral candidates at clinics without sufficient information, rapid preclinical animal studies should proceed to identify therapeutic drug candidates with strong antiviral potential and high safety prior to a human efficacy trial.

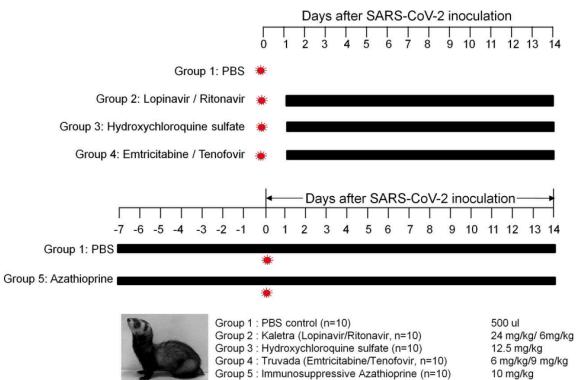
FIGURES

Figure 1. Schedule of drug treatments and SARS-CoV-2 infection in ferrets. To induce the immunosuppression condition, PBS or azathioprine was orally administered to ferrets for the entire experimental period. All groups of ferrets were administered each drug or PBS via oral gavage once, starting at 1 dpi.

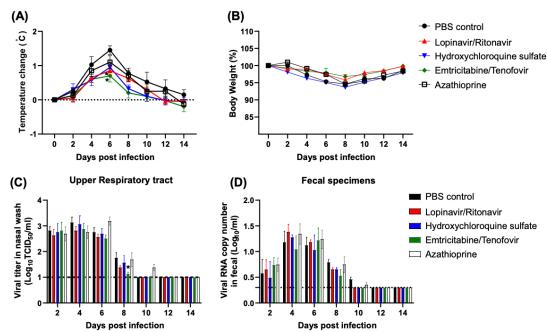


Figure 3. Comparison of serum neutralization antibody titers of drug-treated ferrets. Blood was collected at 10, 14, and 21 dpi from each group of ferrets (n=4), and serum neutralization antibody titers were measured in Vero cells. The serum neutralization titer of each ferret is represented by an individual dot in each bar graph. Asterisks indicate statistical significance between the control and each group, as determined by two-way ANOVA and subsequent Dunnett's test (*, P < 0.05; ***, P < 0.001).

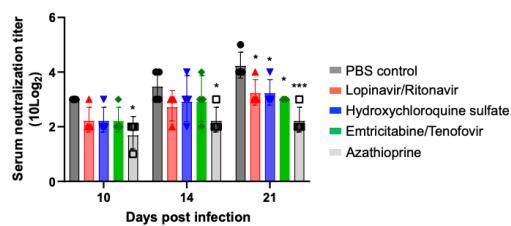


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DEVELOPMENT OF A SIMPLE, INTERPRETABLE AND EASILY TRANSFERABLE QSAR MODEL FOR QUICK SCREENING ANTIVIRAL DATABASES IN SEARCH OF NOVEL 3C-LIKE PROTEASE (3CLPRO) ENZYME INHIBITORS AGAINST SARS-COV DISEASES

Kumar V, Roy K.. SAR QSAR Environ Res. 2020 Jun 16:1-16. doi: 10.1080/1062936X.2020.1776388. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Researchers from the Department of Pharmaceutical Technology at Jadavpur University in Kolkata, India developed a 2D quantitative structure-activity relationship (2D-QSAR) using 3C-like protease (3CL-pro) enzyme inhibitors and chemoinformatic tools to identify the essential structural features of 3CLpro in SARS-CoV-2 (Figure 1)(see summary for details). The researchers believe the 2D-QSAR model and the 36,342 identified inhibitors will help develop a novel analog for treatment of COVID-19 by blocking 3CLpro enzyme activity in SARS-CoV-2 and inhibiting viral replication.

SUMMARY

The following are descriptions of the model and tests that were performed:

2D descriptor (2D-QSAR) Model

- To investigate structural features that inhibit 3CLpro enzyme in SARS-CoV-2 (Figure 2 relation of the observed and predicted values).
- The analysis revealed this model was not obtained by chance correlation (Avg r squared= - 0.155, Avg. Q squared = -0.240).
- Molecular Docking (Table 1)
- Observe COVID-19 main protease enzyme interaction with inhibitory activity of 3CLpro.
- Used a dataset of 69 heterocyclic molecules with 3CLpro enzyme inhibitory activity.
- Most active compounds #1, #4, and #5 formed interactive bonds (hydrogen bond, pi-bond, alkyl, and halogen) with active

-Least active compounds #83 ($\text{pIC}_{50} = -4.565$) and #84 ($\text{pIC}_{50} = -4.607$)

ABSTRACT

In the context of recently emerged pandemic of COVID-19, we have performed two-dimensional quantitative structure-activity relationship (2D-QSAR) modelling using SARS-CoV-3CLpro enzyme inhibitors for the development of a multiple linear regression (MLR) based model. We have used 2D descriptors with an aim to develop an easily interpretable, transferable and reproducible model which may be used for quick prediction of SAR-CoV-3CLpro inhibitory activity for query compounds in the screening process. Based on the insights obtained from the developed 2D-QSAR model, we have identified the structural features responsible for the enhancement of the inhibitory activity against 3CLpro enzyme. Moreover, we have performed the molecular docking analysis using the most and least active molecules from the dataset to understand the molecular interactions involved in binding, and the results were then correlated with the essential structural features obtained from the 2D-QSAR model. Additionally, we have performed in silico predictions of SARS-CoV 3CLpro enzyme inhibitory activity of a total of 50,437 compounds obtained from two anti-viral drug databases (CAS COVID-19 antiviral candidate compound database and another recently reported list of prioritized compounds from the ZINC15 database) using the developed model and provided prioritized compounds for experimental detection of their performance for SARS-CoV 3CLpro enzyme inhibition.

FIGURES

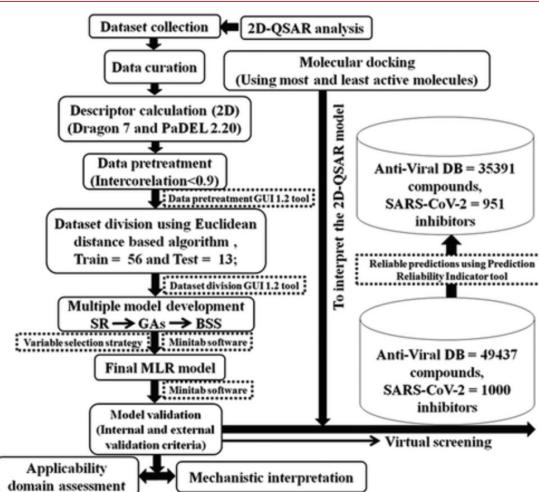


Figure 1. Schematic work flow for the methodologies adopted in this study. MLR = Multiple linear regression, SR = Stepwise regression, BSS = Best subset selection, GAs = Genetic algorithms.

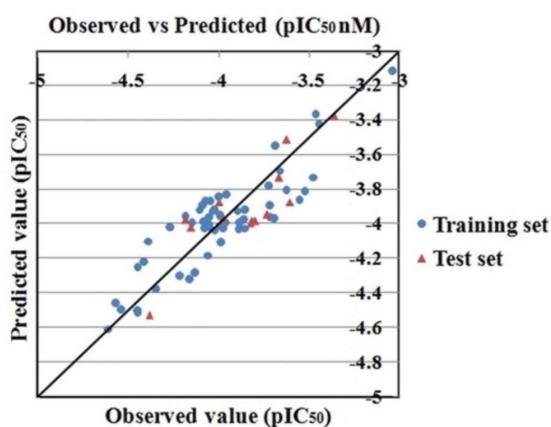


Figure 2. Scatter plot of observed and predicted values from the developed MLR model against 3CLpro enzyme.

N.	Concurrent coauthor	Bibliography (level of knowledge)	Interactions mechanisms	Interactions	Crosslinking with the QMAs mechanisms
S	5 (Dong et al.)	-0.67	CDR A-140, 200A-141, LSA-141, GGU-156, NSD-148	Hydrogen bonding, π-π堆积, π-疏水, π-极性, π-π堆积, π-疏水, π-极性	Phe6, Phe10, and Uuc
S	6 (Dong et al.)	-0.67	CDR A-140, 200A-141, LSA-141, GGU-156, NSD-148	Hydrogen bonding, π-π堆积, π-疏水, π-极性, π-π堆积, π-疏水, π-极性	Phe6, Phe10, and Uuc
S	7 (Dong et al.)	-0.67	CDR A-140, 200A-141, LSA-141, GGU-156, NSD-148, GLU-155	Hydrogen bonding, π-π堆积, π-疏水, π-极性, π-π堆积, π-疏水, π-极性	Phe6, Phe10, and Uuc
S	8 (Dong et al.)	-0.67	CDR A-140, 200A-141, LSA-141, GGU-156, NSD-148, GLU-155	Hydrogen bonding, π-π堆积, π-疏水, π-极性, π-π堆积, π-疏水, π-极性	Phe6, Phe10, and Uuc
S	9 (Dong et al.)	-0.62	CDR A-140, 200A-141, LSA-141, GGU-156, NSD-148	Carbon hydrogen bonding, 极性和疏水	Uue8ape, Uuc10, and Phe4

Figure 2. Scatter plot of observed and predicted values from the developed MLR model against 3CLpro enzyme.

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