The Daily COVID-19 Literature Surveillance Summary

June 19, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

EXECUTIVE SUMMARY

Climate

- Policy advisors from the American Association of Retired Persons (AARP) highlight the importance of social and emotional connections between care facility residents and their family caregivers, especially as recent federal guidelines have restricted family visitation to limit the spread of COVID-19. The authors suggest increasing communication between care facilities and families to clarify restrictions and allow the continuation of meaningful connections, encouraging families to work together to provide emotional and logistical support to each other, and increasing geriatric social work to mitigate the emotional toll on residents of healthcare facilities.

Epidemiology

- A retrospective study of 98 convalescent patients with COVID-19 found that nucleic acids for SARS-CoV-2 were found in sputum or nasopharyngeal samples in 17 of the 98 patients (17.3%) after hospital discharge, despite two negative COVID-19 tests as a requirement for hospital discharge. This may suggest that continuous shedding or relapse of SARS-CoV-2 is possible post-discharge, making it incredibly important for continuous quarantine and follow-up for these patients.
- A retrospective chart review from 15 hospitals in China from January 19 to March 6, 2020 (n=252 patients with COVID-19) to highlight the high proportion of non-febrile patients with COVID-19 (55/252, 21.82%) who became critically ill and required oxygen supplementation (43/55, 78.18%) (Table 1). These findings emphasize that fever alone may not be an adequate measure of COVID-19 presence or progression.
- A retrospective analysis of 105 hospitalized patients with COVID-19 performed at 3 University of Washington found a high incidence of severe disease (49%) and mortality (33%) among hospitalized patients, in which 55% had 3 or more comorbidities. These two major findings suggest the need for rapid implementation of preventive measures, especially to protect elderly individuals with co-morbidities who may be the most susceptible to severe disease.

Understanding the Pathology

- Stanford researchers profiled peripheral blood mononuclear cells (PBMCs) via single-cell RNA sequencing (scRNA-seq) from seven patients hospitalized for COVID-19 and describe an immune cell phenotype with heterogeneous interferon-stimulated gene signature, HLA class II downregulation, and a developing neutrophil population that appears closely related to plasmablasts in the ARDS group, highlighting potential targets for immunopathologic study and therapeutic intervention (Figures 1, 2, and 4). Peripheral monocytes and lymphocytes did not produce notable inflammatory cytokines, suggesting they likely do not contribute to the cytokine storm seen in COVID-19.

Transmission and Prevention

- Italian Association of Human Milk Banks recommend
    - That mothers wear a surgical mask while breastfeeding or during intimate contact to mitigate infecting infants via respiratory route.
    - Emphasize the importance of hand hygiene, disinfecting surfaces as well as thoroughly cleaning plastic and glass milk containers as the virus can remain stable on these materials for several days.
    - Allocating human milk "to the smallest and most at risk preterm infants (e.g., birth weight <1500 grams or a gestational age <30 weeks) to prevent NEC and other severe illnesses occurring in these extremely fragile infants."
- Researchers in Hong Kong collected air and environmental samples inside airborne infection isolation rooms suggesting that COVID-19 is not predominantly transmitted via the airborne route, however, the researchers recommend additional investigation in the cohort ward setting or during aerosol generating procedures.

Management

- Today's report included guidelines and recommendations for management of
    - Effects of methylprednisolone on CT imaging lesion absorption COVID-19 patients under 50 years of age
    - Why, when, and how to use lung ultrasound during the COVID-19 pandemic: enthusiasm and caution
    - COVID-19-White matter and globus pallidum lesions
    - Heparin resistance in COVID-19 patients in the intensive care unit
    - SARS-COV-2 and Male Reproductive Health

Adjusting Practice during COVID-19

- Today's report included guidelines and recommendations for adjusting the practice
    - Hand Eczema Pandemic Caused by SARS-CoV-2 Hygiene Measures

- IL-16 as a possible indication for deeper targeting IL-6
- Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives
- Practical considerations and challenges in Cardio-Oncology services during the COVID-19 pandemic
- Risk Stratification and Personal Protective Equipment Use in Pediatric Endoscopy During the Coronavirus Disease 2019 Outbreak
- Procedural sedation in the COVID-19 era
- Practical recommendations for gynecologic surgery during the COVID-19 pandemic
- When Separation is not the Answer: Breastfeeding Mothers and Infants affected by COVID-19

R&D: Diagnosis and Treatments:

- 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.
- This study conducted by the University of Washington (UW) and Stanford University retested a percentage of 20,912 patients who initially tested negative for SARS-CoV-2 via RT-PCR between March 2nd, 2020 to April 7th, 2020. They were able to retest patients whose symptoms were persistent/worsening (Figure 1) and found that of the 4.1% of the patients from UW and 2.6% from Stanford they retested, 3.5% of these cases (22 patients) returned positive within 7 days, suggesting an initial false negative test that turned positive after a mean of 4 days.
- A study of different antiviral therapies (lopinavir/ritonavir, hydroxychloroquine sulfate, emtricitabine/tenofovir) and the immunosuppressive agent azathioprine in SARS-CoV-2 inoculated ferrets revealed
    - 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

TABLE OF CONTENTS

CLIMATE

GOOD DEEDS AND CHEAP MARKETING-THE FOOD INDUSTRY IN THE TIMES OF COVID-19

White M, Nieto C, Barquera S.. Obesity (Silver Spring). 2020 May 22. doi: 10.1002/oby.22910. Online ahead of print.
Level of Evidence: Other -

BLUF

Researchers affiliated with the Center for Health and Nutrition Research in Mexico's National Institute of Public Health discuss an increase in public relief efforts and tailored marketing by fast food corporations during the COVID-19 pandemic. They express concern that these strategies will worsen obesity rates and predispose more people to chronic inflammation, which may put them at increased risk for severe COVID-19 disease.

ABSTRACT

The consumption of ultra-processed foods is one of the main drivers of the global obesity and non-communicable disease (NCDs) epidemic1 . It is well known that obesity is associated with a low intensity chronic inflammatory state that creates a suboptimal immune response,2 which negatively affects the prognosis of COVID-193 . The epidemic of obesity and COVID-19 can be viewed as a syndemic as they negatively interact with one another to exacerbate the course of disease, leading to greater complications and severe illness. Together, they create a simultaneous and significant burden on the health system4 . Thus, an in-depth analysis on the food industry's role in this pandemic and in our society is necessary.

AFFECTING THE HEALTHCARE WORKFORCE

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

AMID THE COVID-19 PANDEMIC, MEANINGFUL COMMUNICATION BETWEEN FAMILY CAREGIVERS AND RESIDENTS OF LONG-TERM CARE FACILITIES IS IMPERATIVE

Hado E, Friss Feinberg L.. J Aging Soc Policy. 2020 May 22:1-6. doi: 10.1080/08959420.2020.1765684. Online ahead of print.
Level of Evidence: Other -

BLUF

Policy advisors from the American Association of Retired Persons (AARP) highlight the importance of social and emotional connections between care facility residents and their family caregivers, especially as recent federal guidelines have restricted family visitation to limit the spread of COVID-19. The authors suggest increasing communication between care facilities and families to clarify restrictions and allow the continuation of meaningful connections, encouraging families to work together to provide emotional and logistical support to each other, and increasing geriatric social work to mitigate the emotional toll on residents of healthcare facilities.

ABSTRACT

Older adults residing in long-term care facilities are especially vulnerable for severe illness or death from COVID-19. To contain the transmission of the virus in long-term care facilities, federal health officials have issued strict visitation guidelines, restricting most visits between residents and all visitors, including family members. Yet, many older adults rely on family care for social support and to maintain their health, well-being, and safety in long-term care facilities, and therefore need to stay connected to their families. The federal government, state and local leaders, and long-term care facilities should take further actions to enable the relationship between residents of long-term care facilities and families during the COVID-19 pandemic.

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

ARE PATIENTS WITH DOWN SYNDROME VULNERABLE TO LIFE-THREATENING COVID-19?

De Cauwer H, Spaepen A.. Acta Neurol Belg. 2020 May 22. doi: 10.1007/s13760-020-01373-8. Online ahead of print.
Level of Evidence: 4 -

BLUF

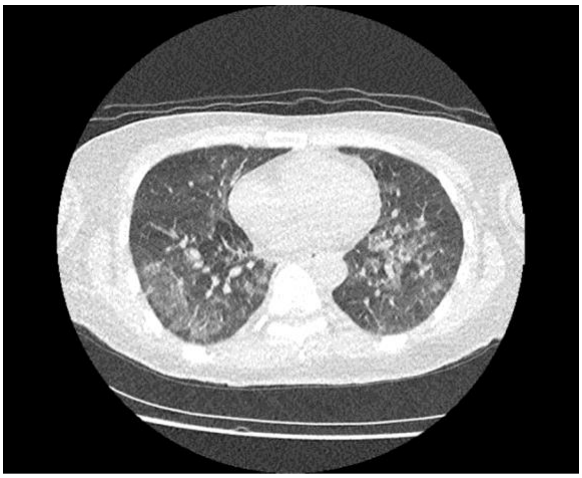
Physicians at a center for intellectual disabilities in Belgium describe a case series of four patients with Down Syndrome (Ages 60, 48, 55 and 62 years-old) who exhibited severe disease during a COVID-19 outbreak. Three required hospitalization and one had a fatal outcome (CT findings in Fig. 1 and 2). They suggest persons with Down Syndrome may be a vulnerable population and further studies are needed to examine COVID-19 outcomes in this group.

ABSTRACT

Patients with Down syndrome are at increased risk of respiratory syncytial virus- and H1N1-related death. Literature on COVID-19 in Down syndrome patients is unavailable thus far. We describe the clinical course of 4 patients with Down syndrome during an outbreak of COVID-19. In all four patients, disease course was severe, warranting hospital care in three patients, with fatal outcome in one patient. Another patient receives supportive care in our institution. Our case series is the first report on probable increased risk of life-threatening disease course of COVID-19 in patients with Down syndrome. Proper surveillance, the adherence of social distancing, and the use of personal protective equipment will be essential in reducing morbidity and mortality in our patients.

FIGURES

Figure. 1 Chest computed tomography scan of patient 2 showing viral pneumonitis in as much as 75% of the lungs



ADULTS

IMPACT OF COVID-19 STAY-AT-HOME ORDERS ON WEIGHT-RELATED BEHAVIORS AMONG PATIENTS WITH OBESITY

Almandoz JP, Xie L, Schellinger JN, Mathew MS, Gazda C, Ofori A, Kukreja S, Messiah SE.. Clin Obes. 2020 Jun 9:e12386. doi: 10.1111/cob.12386. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective medical chart review from an obese medicine clinic and bariatric surgery practice in Texas between 4/15/2020 - 5/31/2020, reviewed 123 patients survey responses about their COVID-19 status and health behaviors when stay-at-home orders were mandated (Table 1). The authors believe this data, although most findings were not statistically significant, see below, can help healthcare providers minimize negative outcomes for patients with obesity during and after the COVID-19 pandemic.
Results from patients with mean BMI of 40.2:
-An increase in stress eating (p=0.590)
-Difficulties achieving weight loss goals (p= 0.266)
-Ethic groups differences in anxiety (p=0.011) but not for depression (p=0.346) (Table 4).

ABSTRACT

OBJECTIVE: How the impact of the COVID-19 stay-at-home orders are influencing physical, mental, and financial health among vulnerable populations, including those with obesity is unknown. The aim of the current study was to explore the health implications of COVID-19 AMong a sample of adults with obesity. METHODS: A retrospective medical chart review identified patients with obesity from an obesity medicine clinic and a bariatric surgery (MBS) practice. Patients completed an online survey from April 15, 2020 to May 31, 2020 to assess COVID-19 status and health behaviors during stay-at-home orders. Logistic regression models examined the impact of these orders on anxiety and depression by ethnic group. RESULTS: A total of 123 patients (87% female, mean age 51.2 years [SD 13.0], mean BMI 40.2 [SD 6.7], 49.2% Non-Hispanic white, 28.7% Non-Hispanic black, 16.4% Hispanic, 7% other ethnicity, 33.1% completed MBS were included. Two patients tested positive for SARS-CoV-2 and 14.6% reported symptoms. 72.8% reported increased anxiety and 83.6% increased depression since stay-at-home orders were initiated. 69.6% reported more difficultly in achieving weight loss goals, less exercise time (47.9%) and intensity (55.8%), increased stockpiling of food (49.6%) and stress eating (61.2%). Hispanics were less likely to report anxiety vs non-Hispanic whites (aOR 0.16; 95% CI, 0.05-0.49; P = 0.009). CONCLUSIONS: Results here showed the COVID-19 pandemic is having a significant impact on patients with obesity regardless of infection status. These results can inform clinicians

and healthcare professionals about effective strategies to minimize COVID-19 negative outcomes for this vulnerable population now and in post-COVID-19 recovery efforts.

NON-FEBRILE COVID-19 PATIENTS WERE COMMON AND OFTEN BECAME CRITICALLY ILL: A RETROSPECTIVE MULTICENTER COHORT STUDY

Li Y, Jiao N, Zhu L, Cheng S, Zhu R, Lan P.. Crit Care. 2020 Jun 8;24(1):314. doi: 10.1186/s13054-020-03037-8.

Level of Evidence: 3 - Local non-random sample

BLUF

The authors' letter to the editor details a retrospective chart review from 15 hospitals in China from January 19 to March 6, 2020 (n=252 patients with COVID-19) to highlight the high proportion of non-febrile patients with COVID-19 (55/252, 21.82%) who became critically ill and required oxygen supplementation (43/55, 78.18%) (Table 1). These findings emphasize that fever alone may not be an adequate measure of COVID-19 presence or progression.

FIGURES

	Total (n = 252)	Febrile (n = 197)	Non-febrile (n = 55)	*P* value
Age, years				
≤ 29	26 (10%)	16 (8%)	10 (18%)	0.121
30–49	106 (42%)	85 (43%)	21 (38%)	
50–69	94 (37%)	73 (37%)	21 (38%)	
≥ 70	26 (10%)	23 (12%)	3 (5%)	
Sex				
Female	110 (44%)	82 (42%)	28 (51%)	0.231
Male	141 (56%)	114 (58%)	27 (49%)	
Temperature, °C				
< 37.3	55 (22%)	0	55 (100%)	**< 0.001**
37.3–38.0	104 (41%)	104 (53%)	0	
38.1–39	80 (32%)	80 (41%)	0	
39.1–41	13 (5%)	13 (7%)	0	
Signs and symptoms				
Cough	177 (70%)	145 (74%)	32 (58%)	**0.027**
Myalgia	42 (17%)	33 (17%)	9 (16%)	0.946
Cephalalgia	22 (9%)	12 (6%)	10 (18%)	**0.005**
Sputum	105 (42%)	92 (47%)	13 (24%)	**0.002**
Hemoptysis	4 (2%)	4 (2%)	0	0.579
Diarrhea	28 (11%)	23 (12%)	5 (9%)	0.590
Dyspnea	35 (14%)	28 (14%)	7 (13%)	0.768
Poor appetite	140 (56%)	117 (59%)	23 (42%)	**0.020**
Comorbidity				
Hypertension	48 (19%)	39 (20%)	9 (16%)	0.566
Diabetes	18 (7%)	14 (7%)	4 (7%)	1.000
Digestive tract disease	4 (2%)	2 (1%)	2 (4%)	0.444
Cardiovascular disease	10 (4%)	8 (4%)	2 (4%)	1.000
Cerebrovascular disease	3 (1%)	3 (2%)	0	1.000
Malignancy	4 (2%)	2 (1%)	2 (4%)	0.444
Liver disease	6 (2%)	3 (2%)	3 (5%)	0.234
Chronic lung disease	8 (3%)	5 (3%)	3 (5%)	0.512
Treatments and outcomes				
Oxygen supplementation	200 (79%)	157 (80%)	43 (78%)	0.806
Mechanical ventilation	10 (4%)	9 (5%)	1 (2%)	0.694
ECMO	4 (2%)	4 (2%)	0	0.579
Critically ill	52 (21%)	40 (20%)	12 (22%)	0.806
ARDS	21 (8%)	17 (9%)	4 (7%)	0.963
ICU admission	43 (17%)	34 (17%)	9 (16%)	0.876
Mortality	6 (2%)	6 (3%)	0	0.344

Table 1. Documentation of Patient Data. Values represent median followed by percentage. P-values were calculated with $\chi 2$ Test, Mann-Whitney U Test, or Fisher's Exact Test when stratifying between febrile and non-febrile patients.

CLINICAL FEATURES OF COVID-19 CONVALESCENT PATIENTS WITH RE-POSITIVE NUCLEIC ACID DETECTION

Zhu H, Fu L, Jin Y, Shao J, Zhang S, Zheng N, Fan L, Yu Z, Ying J, Hu Y, Chen T, Chen Y, Chen M, Chen M, Xiong Z, Kang J, Jin J, Cai T, Ye H.. J Clin Lab Anal. 2020 Jun 7:e23392. doi: 10.1002/jcla.23392. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective study of 98 convalescent patients with COVID-19 conducted in April by researchers in Ningbo, China found that nucleic acids for SARS-CoV-2 were found in sputum or nasopharyngeal samples in 17 of the 98 patients (17.3%) after hospital discharge, despite two negative COVID-19 tests as a requirement for hospital discharge. This may suggest that continuous shedding or relapse of SARS-CoV-2 is possible post-discharge, making it incredibly important for continuous quarantine and follow-up for these patients.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) is a pandemic that has rapidly spread worldwide. Increasingly, confirmed patients being discharged according to the current diagnosis and treatment protocols, follow-up of convalescent patients is important to knowing about the outcome.
METHODS: A retrospective study was performed among 98 convalescent patients with COVID-19 in a single medical center. The clinical features of patients during their hospitalization and 2-week post discharge quarantine were collected.
RESULTS: Among the 98 COVID-19 convalescent patients, 17 (17.3%) were detected positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid during 2-week post discharge quarantine. The median time from discharge to SARS-CoV-2 nucleic acid re-positive was 4 days (IQR, 3-8.5).The median time from symptoms onset to final respiratory SARS-CoV-2 detection of negative result was significantly longer in re-positive group (34 days [IQR, 29.5-42.5]) than in non-re-positive group (19 days [IQR, 16-26]). On the other hand, the levels of CD3-CD56 + NK cells during hospitalization and 2-week postdischarge were higher in re-positive group than in non-re-positive group (repeated measures ANOVA, P = .018). However, only one case in re-positive group showed exudative lesion recurrence in pulmonary computed tomography (CT) with recurred symptoms.
CONCLUSION: It is still possible for convalescent patients to show positive for SARS-CoV-2 nucleic acid detection, but most of the re-positive patients showed no deterioration in pulmonary CT findings. Continuous quarantine and close follow-up for convalescent patients are necessary to prevent possible relapse and spread of the disease to some extent.

CLINICAL FEATURES AND OUTCOMES OF 105 HOSPITALIZED PATIENTS WITH COVID-19 IN SEATTLE, WASHINGTON

Buckner FS, McCulloch DJ, Atluri V, Blain M, McGuffin SA, Nalla AK, Huang ML, Greninger AL, Jerome KR, Cohen SA, Neme S, Green ML, Chu HY, Kim HN.. Clin Infect Dis. 2020 May 22:ciaa632. doi: 10.1093/cid/ciaa632. Online ahead of print.
Level of Evidence: 3 -

BLUF

A retrospective analysis of 105 hospitalized patients with COVID-19 performed at 3 University of Washington affiliated hospitals between March 2 - March 26, 2020 found that elderly patients with comorbidities (eg, hypertension, obesity, cardiovascular disease) were the most impacted by SARS-CoV-2 infection. The authors found a high incidence of severe disease (49%) and mortality (33%) among hospitalized patients, in which 55% had 3 or more comorbidities. These two major findings suggest the need for rapid implementation of preventive measures, especially to protect elderly individuals with co-morbidities who may be the most susceptible to severe disease.

ABSTRACT

BACKGROUND: Washington State served as the initial epicenter of the SARS-CoV-2 pandemic in the United States. An understanding of the risk factors and clinical outcomes of hospitalized patients with COVID-19 may provide guidance for management.
METHODS: All laboratory-confirmed COVID-19 cases in adults admitted to an academic medical center in Seattle, WA between March 2 and March 26, 2020 were included. We evaluated individuals with and without severe disease, defined as admission to the intensive care unit or death.

RESULTS: One-hundred-five COVID-19 patients were hospitalized. Thirty-five percent were admitted from a senior home or skilled nursing facility. The median age was 69 years and half were women. Three or more comorbidities were present in 55% of patients, with hypertension (59%), obesity (47%), cardiovascular disease (38%) and diabetes (33%) being the most prevalent. Most (63%) had symptoms for 5 days or longer prior to admission. Only 39% had fever in the first 24 hours, whereas 41% had hypoxia at admission. Seventy-three percent of patients had lymphopenia. Of 50 samples available for additional testing, no viral coinfections were identified. Severe disease occurred in 49%. Eighteen percent of patients were placed on mechanical ventilation and the overall mortality rate was 33%.
CONCLUSIONS: During the early days of the COVID-19 epidemic in Washington State, the disease had its greatest impact on elderly patients with medical comorbidities. We observed high rates of severe disease and mortality in our hospitalized patients.

FIGURES

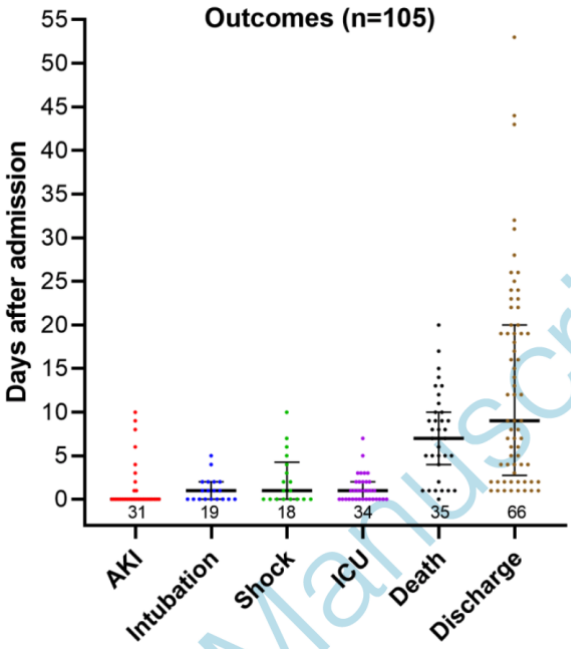


Figure 1: Time to onset of COVID-19 complications. Points represent individual patients; bars represent the median with interquartile ranges; number of observations are noted above the x-axis. Abbreviations: acute kidney injury (AKI) and intensive care unit admission (ICU).

OBESITY IS ASSOCIATED WITH WORSE OUTCOMES IN COVID-19: ANALYSIS OF EARLY DATA FROM NEW YORK CITY

Hajifathalian K, Kumar S, Newberry C, Shah S, Fortune B, Krisko T, Ortiz-Pujols S, Zhou XK, Dannenberg AJ, Kumar R, Sharaiha RZ.. Obesity (Silver Spring). 2020 May 29. doi: 10.1002/oby.22923. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

In this article, authors affiliated with New York-Presbyterian Hospital and Weill Cornell Medical Centre conducted a retrospective descriptive study of 770 COVID-19 patients (mean age 63.5 years, 61% males, and mean BMI 29 kg/m2) from March 4 to April 9, 2020. Results (detailed below) indicated obesity influences clinical presentation, disease severity, ICU admissions, and mortality in COVID-19 patients.

SUMMARY

Compared to underweight (body mass index <18.5) or normal weight (body mass index 18.5-30) cohorts; obese patients were more likely:
- To have preexisting "COPD/asthma (p=0.007) and OSA (p<0.001)" or a preexisting fever (p=0.031).
- To present with the following signs/syptoms; fever (p=0.003), cough (p=0.016), dyspnea (p<0.001), or altered mental status (p<0.001).
- To present with elevated D-dimer (p=0.002) and Troponin (0.004) but not other inflammatory markers such as C-reactive protein, procalcitonin, ferritin, or other abnormalities on the complete blood count.
- To require admission to the ICU (p<0.001), intubation (p=0.002)
Additionally, mortality rates were also higher in the obese cohort with a p value of less than 0.001.

ABSTRACT

OBJECTIVE: The 2019 novel coronavirus disease (COVID-19) has triggered a rapidly-expanding global pandemic in which patients exhibit a wide spectrum of disease severity. Given the high prevalence of obesity in the United States, we hypothesized that the presence of obesity may play a role in the clinical course of COVID-19 patients.
METHODS: This is a retrospective review of adult patients admitted with confirmed SARS-CoV-2. Demographics, clinical characteristics, laboratory data, and clinical outcomes were abstracted. BMI (kg/m2) was analyzed with regard to a composite outcome of ICU admission or death, and intubation rate.
RESULTS: 770 patients were included (61% male, mean age 63.5 yrs). Obese patients were more likely to present with fever, cough and shortness of breath. Obesity was also associated with a significantly higher rate of ICU admission or death (RR = 1.58, p = 0.002) even after adjusting for age, race and troponin level.
CONCLUSIONS: Obese patients had an increased risk of critical illness leading to ICU admission or death compared to normal weight individuals. This study confirms that obesity is a major risk factor for COVID-19 disease severity, significantly impacting disease presentation and critical care requirements.

HYPONATREMIA: A POSSIBLE IMMUNO-NEUROENDOCRINE INTERFACE WITH COVID-19 IN A KIDNEY TRANSPLANT RECIPIENT

Tantisattamo E, Reddy UG, Duong DK, Ferrey AJ, Ichii H, Dafoe DC, Kalantar-Zadeh K.. Transpl Infect Dis. 2020 Jun 8:e13355. doi: 10.1111/tid.13355. Online ahead of print.

Level of Evidence: 5 - Case report

BLUF

Clinicians in California and Michigan present the case of a 55-year-old woman with history of type II diabetes status post kidney transplant who presented with fever, nausea, fatigue, and hyponatremia (serum Na 120 mmol/L), and was diagnosed with COVID-19 on RT-PCR. Her IL-6, a pro-inflammatory marker which has been shown to cause non-osmotic ADH stimulation, became elevated during hospitalization, suggesting hyponatremia may serve as a predictor of poor prognosis. Physicians should be aware of atypical COVID-19 presentation in transplant patients and be vigilant in monitoring symptoms and adjusting immunosuppression when necessary (Table 2).

SUMMARY

This patient's IL-6 level was < 5 pg/mL, which was within normal limits and rose to an unspecified level during hospital stay. She was maintained on triple immunosuppressive therapy of tacrolimus, mycophenolate sodium (MPS), and prednisone after her transplant, but her tacrolimus dose was decreased and MPS was discontinued during her admission. She was treated with hydroxychloroquine and isotonic saline which did not improve her hyponatremia, but her serum Na levels rose to 134 mmol/L after discontinuation of saline which led the authors to suspect her hyponatremia was secondary to syndrome of inappropriate antidiuretic hormone (SIADH). There is currently only one other documented case of hyponatremia in a kidney transplant patient with COVID-19, but that patient had significant underlying immunological risks (asplenia, history of EBV).

ABSTRACT

There is fast-emerging, cumulative clinical data on coronavirus disease 2019 (COVID-19) in kidney transplant recipients. Although respiratory tract symptoms are often the initial presentation among kidney transplant recipients who contract COVID-19, other clinical features which may indicate underlying SARS-CoV-2-related inflammation, such as gastrointestinal symptoms, are not uncommon. Hyponatremia can develop and may reflect underlying inflammation. Interferon-6 is an important pro-inflammatory cytokine involved in the pathogenesis of severe COVID-19 complications and may play a role in the inappropriately higher secretion of antidiuretic hormone leading to hyponatremia. This pathway is the so-called immuno-neuroendocrine interface. Hyponatremia in COVID-19 has been reported in a few case series of non-kidney transplant patients and only one reported kidney transplant recipient. However, the clinical course and prognostic value of hyponatremia in this population is not described in detail. We report a kidney transplant recipient who was infected with COVID-19 and exhibited severe hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion. Hyponatremia is one of the clinical presentations of COVID-19, although less common, and may occur more frequently in kidney transplant recipients. Thus the possible underlying immuno-neuroendocrine relationship related to the inflammatory process of COVID-19 leading to hyponatremia, and its prognostic value, are reviewed.

FIGURES

Patients	➢ Age ➢ Gender (race) ➢ Cause of organ failure	➢ Organ transplant (Donor) ➢ Maintenance immunosuppression (Induction)	➢ Exposure risk for COVID-19 ➢ Duration from transplant until COVID-19 diagnosis	➢ Initial symptoms ➢ Courses ➢ Duration from the symptom onset until admission ➢ Duration from the symptom onset until COVID-19 diagnosis ➢ Diagnosis for SARS-CoV-2	Significant laboratory data	Underlying diseases	Treatment	Outcomes
Guillen et al [3]	- 50 y/o - M - IgAN	- 3rd DDRT - FK, Evaroli-mus, Pred 5 mg daily (Thymo-globulin)	- No history of exposure to COVID-19 - ~3.5 yr	- Fever, vomiting 24 hours. - Five days later, persistent fever and productive cough, left eye conjunctivitis - 1 day - ~ 6 days - NP swab by rRT-PCR	- Lymphopenia - Normal CRP - SNa 129 mmol/L - ↑Procalcitonin - Negative for RSV, influenza A and B - CXR: Medium lobe consolidation on posteroanterior	- ITP s/p splenectomy - EBV-associated PTLD - HTN on losartan	- Empiric ceftriaxone and azithromycin - Lopinavir/Ritonavir, empiric ceftaroline and meropenem - Interferon-β - HQ - Hold FK and evarolimus	- ICU admission. - Intubated - AKI with SCr 2.1 mg/dL and then 3 mg/dL and not discharged at the time of reporting case
Our patient	- 55 y/o - F (Korean) - DM	- 0-A-B-DR mis-matched Ag DDRT (45-y/o M donor) - FK, MPS, and Pred 5 mg daily (Thymo-globulin)	- Family member with positive COVID-19 - 0.68 yr.	- Fatigue - Then, subjective fever, cough, worsening dyspnea, headache, nausea, decreased po intake for 1 week. - 6 days - 6 days - NP swab by rRT-PCR confirmed COVID-19	- SNa 120 mmol/L - Transient lymphopenia - Procalcitonin <0.02 ng/mL - Normal LDH, CRP, IL-6 - Negative for RSV, influenza A & B - CXR: Patchy consolidation in the right middle and lower lung zones	- DM - HTN - HLD - Overweight - GERD - Hashimoto's thyroiditis	- Stop MPS - Lower FK target level - Started Amoxicillin and HQ	- No ICU admission - Serum Na gradually improved to 134 mmol/L - Discharged home on hospital Day 5 - LOS 4 days - Duration from the symptom onset until discharge 10 days

Table 2. A previously published kidney transplant recipients [sic] with confirmed COVID-19 presenting with hyponatremia and our current case

COVID-19 PRESENTING WITH IMMUNE THROMBOCYTOPENIA: A CASE REPORT AND REVIEW OF THE LITERATURE

Murt A, Eskazan AE, Yılmaz U, Ozkan T, Ar MC.. J Med Virol. 2020 Jun 4. doi: 10.1002/jmv.26138. Online ahead of print.

Level of Evidence: 5 - Case report

BLUF

In this article, authors affiliated with Istanbul University - Cerrahpasa present a case of a 41-year-old male with petechiae and nose bleed. He had cough and rhinorrhea 15 days ago which had resolved. He was referred to Istanbul University with diagnosis of ITP after being treated with 4 doses of high dose dexamethasone, which was ineffective. At this time physical examination showed petechia and purpura. Laboratory findings included: thrombocytopenia (9x10^9/L), SARS-CoV-2 positive by RT-PCR, and CT with bilateral ground glass opacities. The diagnosis of "ITP secondary to COVID-19" was made and he was treated with "IVIg [IV immunoglobulin] 2g/kg and Favipiravir in the first two days of admission". After this the platelet count increased to 54x10^9/L. Additionally, the pneumonia resolved within five days of admission. He was followed up for 4 weeks during which the platelet count was 50-100x10^9/L.

SUMMARY

Based on the available literature and the case discussed above, the authors suggest the mechanism of thrombocytopenia in COVID-19 is likely related to cytokine release, direct invasion of bone marrow, consumptive coagulopathy, and/or autoimmune destruction (ITP). They further conclude that IVIG is the preferred treatment for ITP related severe thrombocytopenia ("a poor prognostic factor in COVID-19") as it promotes faster recovery of platelets than steroids. The authors preferred Favipiravir over Hydroxychloroquine as thrombocytopenia may be a rare side effect of hydroxycholoroquine.

ABSTRACT

Novel coronavirus disease (COVID-19) may be associated with thrombocytopenia which might have different mechanisms in different patients and in different phases of the disease. Cytokine release, thrombotic consumption or autoimmune destruction are some leading etiologies of thrombocytopenia in COVID-19. This case report presents a 41-year-old male COVID-19 patient who had petechiae and purpura as the referral symptoms. Laboratory tests revealed isolated thrombocytopenia with no other additional pathologic findings. Most probable diagnosis was COVID-19 induced immune thrombocytopenia (ITP) and high dose intravenous immunoglobulin (IVIg) treatment generated a good response. There were four other recent publications with a total of eight cases in the literature. The presented case was discussed in comparison with those similar cases.

PREGNANT PERSONS

OVARIAN VEIN THROMBOSIS AFTER CORONAVIRUS DISEASE (COVID-19) INFECTION IN A PREGNANT WOMAN: CASE REPORT

Mohammadi S, Abouzaripour M, Hesam Shariati N, Hesam Shariati MB.. J Thromb Thrombolysis. 2020 Jun 8. doi: 10.1007/s11239-020-02177-6. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

Physicians in Sanandaj, Iran present a case study from early May 2020 of a 26-year-old COVID-19 positive female who was 8 weeks pregnant and presented with a 1-week history of abdominal pain, nausea, and vomiting. Upon admission, she was found to have a right ovarian vein thrombosis confirmed by MRI (Figure 2). These findings provide further evidence that venous thrombosis may be a rare but serious side effect of COVID-19 and that assessment and risk classification for DVT are important for the prognosis of patients with COVID-19.

SUMMARY

The authors describe a case of a 26-year-old 8-week pregnant female who presented to the hospital with a 1-week history of abdominal pain, nausea, and vomiting. On May 5th, she tested positive for SARS-CoV-2, confirmed via chest CT (Figure 1). During initial hospitalization, she was afebrile, with an elevated respiratory rate. Laboratory evaluation showed normal kidney function, microcytic anemia, hypocalcemia, and other mild electrolyte abnormalities none of which were discussed further in the case report. Due to her initial abdominal symptoms an ultrasound of her abdomen and pelvis was conducted. During the initial US an incidental finding suggested an ovarian vein thrombosis and an MRI was then conducted confirming this suspicion (Figure 2). In addition to COVID-19, this patient had other comorbidities and thrombotic risk factors including obesity, respiratory failure, and bed-rest. No further information on clinical course or treatment was provided.

ABSTRACT

Corona virus outbreak started in December 2019, and the disease has been defined by the World Health Organization as a public health emergency. Coronavirus is a source of deep venous thrombosis (DVT) due to complications such as over-coagulation, blood stasis, and endothelial damage. In this study, we report a 26-year-old pregnant woman with coronavirus who was hospitalized with a right ovarian vein thrombosis at Besat Hospital in Sanandaj. Risk classification for deep vein thrombosis (DVT) disease is of crucial importance for the forecast of coronavirus.

FIGURES

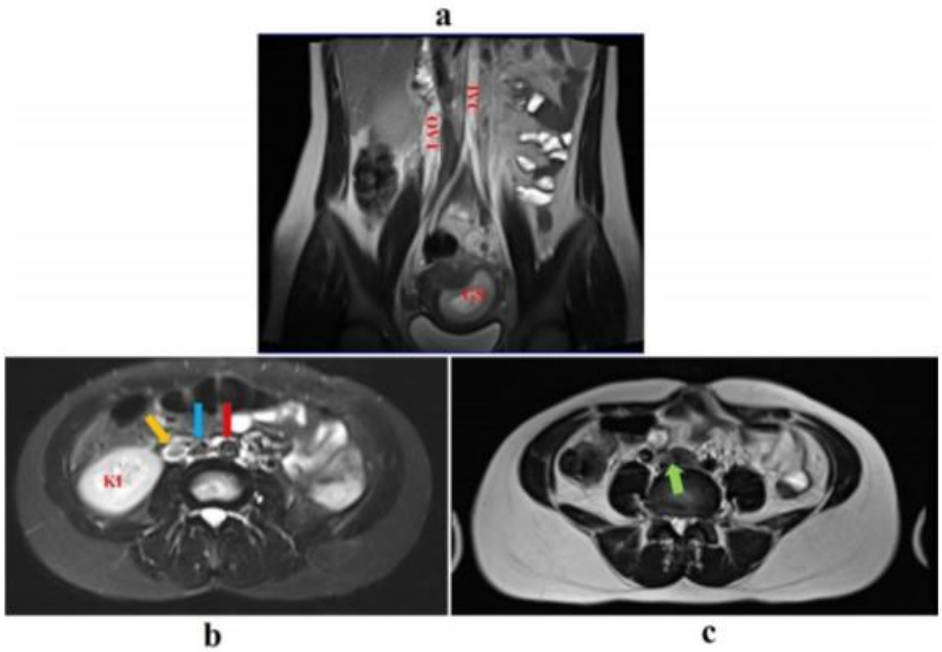


Figure 2. Coronal and axial without contrast-enhanced Magnetic resonance imaging (MRI) image showing a Ovarian vein thrombosis (OVT). yellow arrows show ovarian vein thrombosis, red arrows show aorta artery, blue arrows show inferior vena cava and green arrows show inferior vena cava bifurcation; Ovarian vein thrombosis (OVT), gestational sac (GS), kidney(KI) and inferior vena cava (IVC) in the abdominal and pelvic sections.

Figure 1. Coronal and axial without contrast-enhanced computed tomography (CT) image showing a coronavirus disease (COVID-19) infection

PEDIATRICS

CLINICAL MANIFESTATIONS OF CHILDREN WITH COVID-19: A SYSTEMATIC REVIEW

de Souza TH, Nadal JA, Nogueira RJN, Pereira RM, Brandão MB.. Pediatr Pulmonol. 2020 Jun 3. doi: 10.1002/ppul.24885. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A review of international studies including 1,124 pediatric patients from 1 December 2019 to 6 April 2020 conducted by authors in Brazil at the State University of Campinas pediatric intensive care unit found that although fever (47.5%) and cough (41.5%) were the most common symptoms in children infected with SARS-CoV-2, these should not be considered hallmark symptoms of COVID-19 in children and lack thereof should not exclude infection. In addition, 63% of pediatric patients who underwent CT scan were found to have lung field findings suggestive of infection. The authors overall recommend clinicians have a high clinical suspicion for COVID-19 in this population during the pandemic.

ABSTRACT

BACKGROUND: The coronavirus disease 2019 (COVID-19) outbreak is an unprecedented global public health challenge, leading to thousands of deaths every day worldwide. Despite the epidemiological importance, clinical patterns of children with COVID-19 remain unclear. The aim of this study was to describe the clinical, laboratorial and radiological characteristics of children with COVID-19.
METHODS: The Medline database was searched between December 1st 2019 and April 6th 2020. No language restrictions were applied. Inclusion criteria were: (1) studied patients younger than 18 years old; (2) presented original data from cases of COVID-19 confirmed by reverse-transcription polymerase chain reaction; and (3) contained descriptions of clinical manifestations, laboratory tests or radiological examinations.
RESULTS: A total of 38 studies (1,124 cases) were included. From all the cases, 1,117 had their severity classified: 14.2% were asymptomatic, 36.3% were mild, 46.0% were moderate, 2.1% were severe and 1.2% were critical. The most prevalent symptom was fever (47.5%), followed by cough (41.5%), nasal symptoms (11.2%), diarrhea (8.1%) and nausea/vomiting (7.1%). One hundred forty-five (36.9%) children were diagnosed with pneumonia and 43 (10.9%) upper airway infections were reported. Reduced lymphocyte count were reported in 12.9% of cases. Abnormalities on computed tomography were reported in 63.0% of cases. The most prevalent abnormalities reported were ground glass opacities, patchy shadows and consolidations. Only one death was reported.

CONCLUSIONS: Clinical manifestations of children with COVID-19 differ widely from adults cases. Fever and respiratory symptoms should not be considered a hallmark of COVID-19 in children. This article is protected by copyright. All rights reserved.

FIGURES

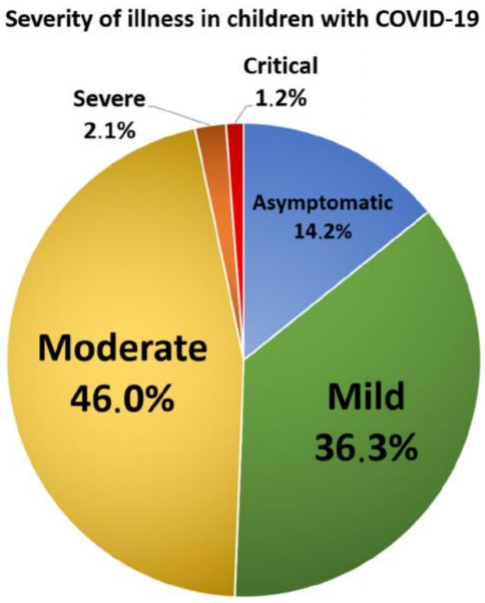


FIGURE 2 Severity of illness of the reported cases. COVID-19, coronavirus disease 2019 [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Distributions of clinical manifestations of children with COVID-19 described in the selected studies

Clinical manifestations	Frequency of occurrence[a]
Fever	187 (47.5%)
Cough	163 (41.5%)
Pneumonia	145 (36.9%)
Pharyngeal erythema	81 (20.6%)
Tachycardia on admission	73 (18.6%)
Tachypnea on admission	53 (13.4%)
Nasal symptoms	44 (11.2%)
Upper airway infections	43 (10.9%)
Diarrhea	32 (8.1%)
Nausea/Vomiting	28 (7.1%)
Fatigue	20 (5.0%)
Respiratory distress	14 (3.5%)
Sore throat	10 (2.5%)
Respiratory failure	7 (1.8%)
Creptations	6 (1.5%)
Sputum	6 (1.5%)
Hypoxemia	5 (1.3%)
Abdominal pain	2 (0.5%)
Sneezing	2 (0.5%)
Cyanosis	2 (0.5%)
Lymphadenopathy	1(0.2%)

Abbreviation: COVID-19, coronavirus disease 2019.
[a]Expressed in absolute number and percentage in relation to the total of cases in which clinical manifestations were described (n = 393).

COVID-19 ASSOCIATED PEDIATRIC MULTI-SYSTEM INFLAMMATORY SYNDROME

Deza Leon MP, Redzepi A, McGrath E, Abdel-Haq N, Shawaqfeh A, Sethuraman U, Tilford B, Chopra T, Arora H, Ang J, Asmar B.. J Pediatric Infect Dis Soc. 2020 May 22:piaa061. doi: 10.1093/jpids/piaa061. Online ahead of print.
Level of Evidence: Other -

BLUF

This case report, released by Children's Hospital of Michigan, discusses a 6-year-old female with COVID-19, diagnosed by PCR of nasopharyngeal swab, who developed incomplete Kawasaki disease (KD)-like illness with fever, signs of cardiogenic shock, and later recovered with ECMO therapy. Noting the absence of reports from China of similar presentations of pediatric COVID-19, the authors urge providers to be more attentive of cardiovascular manifestations of COVID-19 in children with COVID-19.

SUMMARY

This is a case report of a 6-year-old female with COVID-19, who initially presented to the ED with pharyngitis and treated with antibiotics. Upon returning to the ED three days later, the patient developed incomplete KD-like illness with fever, signs of cardiogenic shock, and markedly elevated inflammatory markers (CRP, ESR, ferritin, LDH). After six days of ECMO treatment, the inflammatory markers were reduced, and no signs of end

organ damage were found. Two other pediatric COVID-19 cases were reported in the same hospital with milder KD-like illness, and these patients recovered with IVIG therapy. Pediatric COVID-19 has shown a diverse array of presentations and remaining attentive to cardiovascular complications in febrile children with COVID-19 will help better manage these specific pediatric cases.

ADVANCED AGE

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF 320 DECEASED COVID-19 PATIENTS IN AN ITALIAN PROVINCE: A RETROSPECTIVE OBSERVATIONAL STUDY

Biagi A, Rossi L, Malagoli A, Zanni A, Sticozzi C, Comastri G, Gandolfi S, Villani GQ.. J Med Virol. 2020 Jun 9. doi: 10.1002/jmv.26147. Online ahead of print.
Level of Evidence: 4 - Local non-random sample

BLUF

A retrospective observational study from three hospital in Piacenza Province, Italy between 2/24/2020 - 3/22/2020 reviewed 320 deceased COVID-19 patients, 71.9% were male (median age of 78) with hypertension (most common comorbidity) (Table 4). This data implies most of COVID-19 deceased patients were male over the age of 65 (p=0.01) with several comorbidities (p=0.01) and patient's severe/critical clinical condition in the ER is a reflection of high in-hospital mortality rates (p=0.01) (Table 3).

ABSTRACT

BACKGROUND: Studies have described clinical features of Covid-19 patients. However, limited data concerning the clinical characteristics of the Italian deaths are available. We aim to describe the clinical and epidemiological characteristics of 320 deceased from the Italian experience.
METHODS: We retrospectively collected all consecutive non-survivor patients with laboratory-confirmed Covid-19 infection admitted to the Emergency Rooms (ER) Piacenza Hospital Network during the first month of Covid-19 pandemic in Italy. Clinical history, comorbidities, laboratory findings and treatment were recorded for each patient.
RESULTS: A total of 1050 patients with confirmed Covid-19 pneumonia were admitted to the ERs between 24 February,2020, and 22 March,2020. 320 (30.5%) patients died with a median age of 78.0 years, 205 (64%) non-survivors were above 65 years old, 230 (71.9 %) were male. Non-survivor patients showed frequently several coexisting medical conditions, with hypertension being the most common comorbidity (235 patients, 73.4%). The in-hospital mortality did not change during the progression of the pandemic.
CONCLUSION: In this retrospective Italian study, most of Covid-19 deceased patients were elderly male aged over than 65 years. Hypertension was the most common coexisting disease. In-hospital mortality was high and showed no variation during the first month of the Covid-19 italian epidemic.

FIGURES

		Age<65 (n=32)	Age 65-75 (n=83)	Age>75 (n=205)	
Male (n, %)		28 (87.5)	65 (78.3)	137 (66.8)	p=0.01
Comorbidities	Hypertension (n, %)	16 (50.0)	60 (72.3)	149 (72.7)	p=0.004
	Cardiopathy (n, %)	1 (3.1)	4 (4.8)	34 (16.6)	p=0.002
	Atrial Fibrillation (n, %)	2 (6.2)	12 (14.4)	36 (17.6)	p=0.10
	Dyslipidemia (n, %)	4 (12.5)	32 (38.5)	55 (26.8)	p=0.11
	Diabetes (n, %)	5 (15.6)	26 (31.3)	41 (20.0)	p=0.07
	COPD (n, %)	1 (3.1)	20 (24.1)	35 (17.1)	p=0.02
	CKD (n, %)	3 (9.4)	3 (3.6)	25 (12.2)	0=0.08
	Stroke (n, %)	0	1 (0.1)	11 (5.3)	p=0.12
	Malignancy (n, %)	1 (3.1)	1 (0.1)	7 (3.4)	p=0.58
Patients with 2 or more comorbidities (n, %)		10 (31.2)	50 (60.2)	118 (57.6)	p=0.01
Vital signs at admission	SBP (mmHg)	128.5±19.0	127.1±20.8	127.4±23.4	p=0.788
	RR (breath per minute)	25.3±7.9	24.5±5.2	24.4±7.4	p=0.523
	pO2 (mmHg)	61.8±21.4	56.7±20.4	66.8±30.7	p=0.483
	PAO2/FiO2	181.4±97.3	194.8±93.6	195.5±88.1	p=0.408
	OTI (n, %)	12 (37.5)	19 (22.9)	5 (2.4)	p<0.001
	NIV (n, %)	6 (18.7)	43 (51.8)	44 (21.5)	p<0.001
	IOT time (da ER a iot)	6.1±6.9	6.3±7.9	2.6±3.0	p=0.302
	NIV time	1.8±1.9	2.7±3.5	2.8±2.9	0.433
	IOT duration	6.5±7.5	8.3±14.0	13.8±10.0	0.116
	NIV duration	6.8±6.5	5.8±5.9	3.6±3.1	0.046

Table 3. Age related commodities and vital signs at ER admissions.

		ALL (n=320)	Week 1 (n=33)	Week 2 (n=101)	Week 3 (n=134)	Week 4 (n=52)	
Total ER access (n)		1050	123	306	404	217	
In-hospital death (n, %)		320 (30.5)	33 (26.8)	101 (33.0)	134 (33.1)	52 (23.9)	p=0.15
Age (years)		78.0±10.0	75.6±8.2	79.4±10.4	77.7±10.4	77.4±9.1	p=0.23
Male (n, %)		230 (71.9)	24 (19.5)	67 (21.9)	98 (24.2)	41 (18.9)	p=0.40
Comorbidities	Hypertension (n, %)	235 (73.4)	27 (81.8)	78 (77.2)	88 (65.7)	42 (80.8)	p=0.06
	Cardiopathy (n, %)	39 (12.2)	4 (12.1)	15 (14.9)	12 (9.0)	8 (15.4)	p=0.47
	Atrial Fibrillation (n, %)	50 (15.6)	7 (21.2)	19 (18.8)	18 (13.4)	6 (11.5)	p=0.44
	Dyslipidemia (n, %)	91 (28.4)	13 (39.4)	30 (29.7)	31 (23.1)	17 (32.7)	p=0.23
	Diabetes (n, %)	72 (22.5)	7 (21.2)	22 (21.8)	28 (20.9)	15 (28.8)	p=0.69
	COPD (n, %)	56 (17.5)	7 (21.2)	20 (19.8)	15 (11.2)	14 (26.9)	p=0.06
	CKD (n, %)	31 (9.7)	5 (15.2)	16 (15.8)	8 (6.0)	2 (3.8)	p=0.02
CURB-65	0-1 (n, %)	63 (19.7)	6 (18.2)	18 (17.8)	24 (17.9)	15 (28.8)	
	2 (n, %)	191 (59.7)	24 (72.7)	64 (63.4)	80 (59.7)	23 (44.2)	
	>3 (n, %)	66 (20.6)	3 (9.1)	19 (18.8)	30 (22.4)	14 (26.9)	p=0.15
Covid classification	Moderate (n, %)	7 (2.2)	3 (9.1)	1 (1.0)	1 (0.7)	2 (3.8)	
	Severe (n, %)	248 (77.5)	19 (57.6)	77 (76.2)	112 (83.6)	40 (76.9)	
	Critic (n, %)	65 (20.3)	11 (33.3)	23 (22.8)	21 (15.7)	10 (19.2)	p=0.01
Treatment							
	OTI (n, %)	36 (11.2)	8 (24.2)	15 (14.9)	10 (7.5)	3 (5.8)	p=0.01
	NIV (n, %)	93 (29.0)	12 (36.4)	27 (26.7)	37 (27.6)	17 (32.7)	p=0.66
	OTI time (da ER a OTI)	5.7±7.0	1.2±1.5	6.9±9.5	7.2±5.1	6.7±3.8	p=0.25
	NIV time	2.7±3.1	5.6±6.0	2.6±2.2	2.1±2.4	2.2±1.7	p=0.005
	OTI duration	8.4±11.6	9.2±7.9	9.2±16.1	6.3±7.4	9.6±8.3	p=0.93
	NIV duration	4.8±4.9	6.0±6.3	4,6±4.6	4,8±4.2	4,5±5.7	p=0.85

Table 4. Clinical characteristics of patients during the first 4 weeks of COVID-19.

UNDERSTANDING THE PATHOLOGY

A SINGLE-CELL ATLAS OF THE PERIPHERAL IMMUNE RESPONSE IN PATIENTS WITH SEVERE COVID-19

Wilk AJ, Rustagi A, Zhao NQ, Roque J, Martínez-Colón GJ, McKechnie JL, Ivison GT, Ranganath T, Vergara R, Hollis T, Simpson LJ, Grant P, Subramanian A, Rogers AJ, Blish CA.. Nat Med. 2020 Jun 8. doi: 10.1038/s41591-020-0944-y. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Stanford researchers profiled peripheral blood mononuclear cells (PBMCs) via single-cell RNA sequencing (scRNA-seq) from seven patients hospitalized for COVID-19 (four with acute respiratory distress syndrome, ARDS) versus six healthy controls. Authors describe an immune cell phenotype with heterogeneous interferon-stimulated gene signature, HLA class II downregulation, and a developing neutrophil population that appears closely related to plasmablasts in the ARDS group, highlighting potential targets for immunopathologic study and therapeutic intervention (Figures 1, 2, and 4). Peripheral monocytes and lymphocytes did not produce notable inflammatory cytokines, suggesting they likely do not contribute to the cytokine storm seen in COVID-19.

ABSTRACT

There is an urgent need to better understand the pathophysiology of Coronavirus disease 2019 (COVID-19), the global pandemic caused by SARS-CoV-2, which has infected more than three million people worldwide1. Approximately 20% of patients with COVID-19 develop severe disease and 5% of patients require intensive care2. Severe disease has been associated with changes in peripheral immune activity, including increased levels of pro-inflammatory cytokines3,4 that may be produced by a subset of inflammatory monocytes5,6, lymphopenia7,8 and T cell exhaustion9,10. To elucidate pathways in peripheral immune cells that might lead to immunopathology or protective immunity in severe COVID-19, we applied single-cell RNA sequencing (scRNA-seq) to profile peripheral blood mononuclear cells (PBMCs) from seven patients hospitalized for COVID-19, four of whom had acute respiratory distress syndrome, and six healthy controls. We identify reconfiguration of peripheral immune cell phenotype in COVID-19, including a heterogeneous interferon-stimulated gene signature, HLA class II downregulation and a developing neutrophil population that appears closely related to plasmablasts appearing in patients with acute respiratory failure requiring mechanical ventilation. Importantly, we found that peripheral monocytes and lymphocytes do not express substantial amounts of pro-inflammatory cytokines. Collectively, we provide a cell atlas of the peripheral immune response to severe COVID-19.

FIGURES

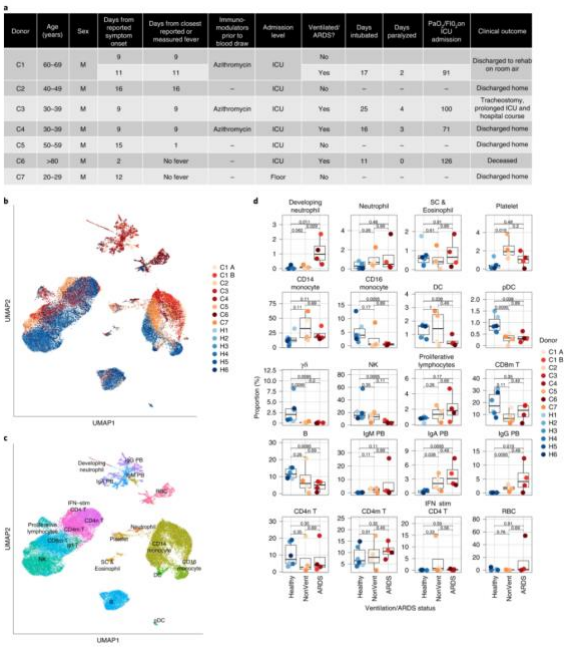


Figure 1: Expansion of plasmablasts and depletion of multiple innate immune cell subsets in the periphery of patients with COVID-19. a, Demographics, sample characteristics and disease course of patients with COVID-19. b, UMAP dimensionality reduction embedding of peripheral blood mononuclear cells (PBMCs) from all profiled samples (n = 44,721 cells) colored by donor of origin. IDs of patients with COVID-19 (n = 7) begin with 'C' and are colored in shades of orange (patients who were not ventilated at the time of draw) or red (patients with ARDS who were ventilated at the time of draw) and those of healthy donors begin with 'H' (n = 6) and are colored in blues. c, UMAP embedding of the entire dataset colored by orthogonally generated clusters labeled by manual cell type annotation. d, Proportions of each cell type in each sample colored by donor of origin. The x axes correspond to the ventilation or ARDS status of each patient. Shown are exact two-sided P values by the Wilcoxon rank-sum test. n = 6, n = 4 and n = 4 biologically independent samples for Healthy, NonVent and ARDS, respectively. Boxplot features: minimum whisker, 25th percentile − 1.5 × inter-quartile range (IQR) or the lowest value within; minimum box, 25th percentile; center, median; maximum box, 75th percentile; maximum whisker, 75th percentile + 1.5 × IQR or greatest value within.

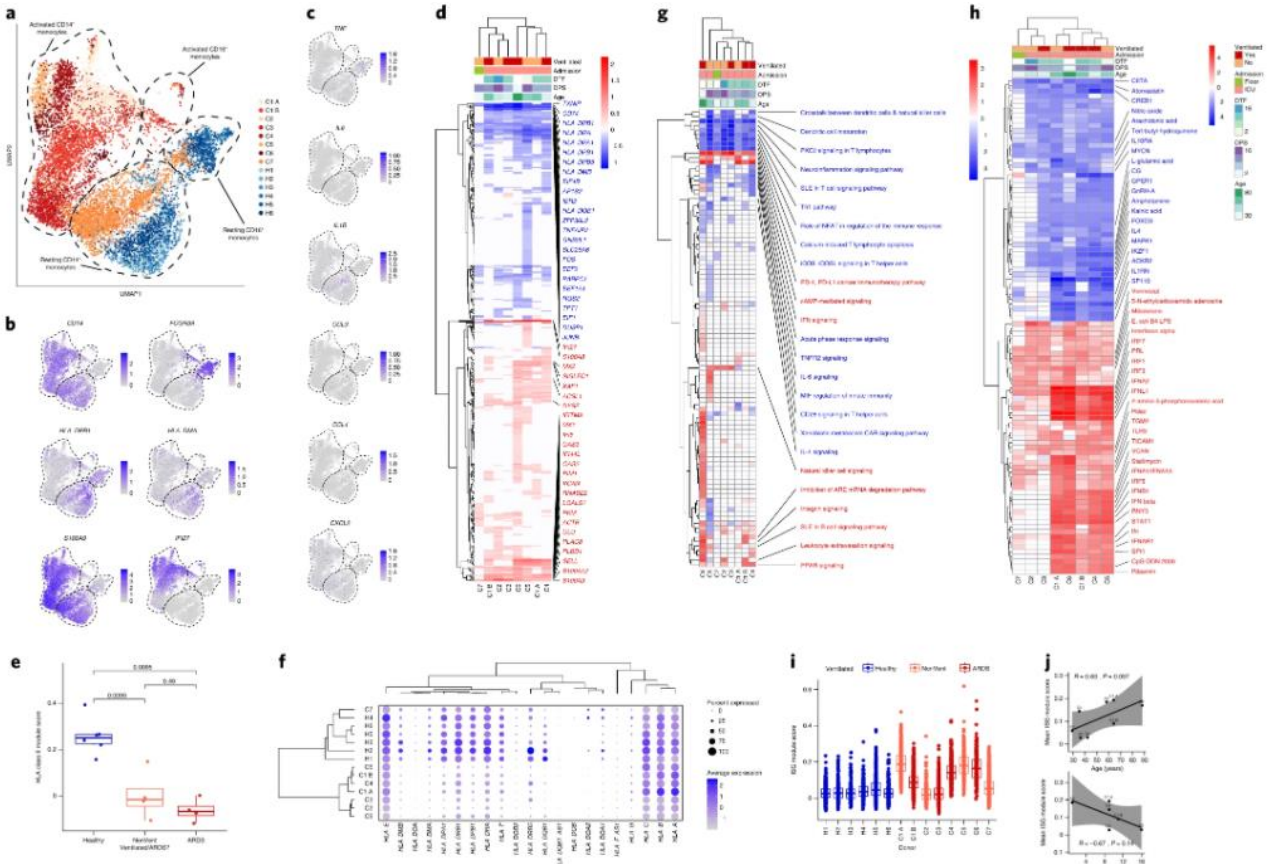


Figure 2: Robust HLA class II downregulation and type I interferon-driven inflammatory signatures in monocytes are characteristics of SARS-CoV-2 infection. a, UMAP embedding of all monocytes colored by sample of origin. n = 10,339 cells are plotted from n = 14 biologically independent samples. b, UMAP embedding of monocytes colored by CD14 and FCGR3A (encoding CD16a, to distinguish between CD14+ and CD16+ monocytes), HLA-DPB1 and HLA-DMA (illustrating HLA class II downregulation in patients with COVID-19) and S100A9 and IFI27 (demonstrating canonical inflammatory signatures in patients with COVID-19). c, UMAP embedding of monocytes colored by genes encoding pro-inflammatory cytokines previously reported to be produced by circulating monocytes in severe COVID-196, namely TNF, IL6, IL1B, CCL3, CCL4 and CXCL2. d,g,h, Heatmaps of DE genes (d), differentially regulated canonical pathways (g) and differentially regulated predicted upstream regulators (h) between CD14+ monocytes of each COVID-19 sample compared to CD14+ monocytes of all healthy controls. The heatmap in d is colored by average log(fold-change), while heatmaps in g and h are colored by z-score. All displayed genes, pathways and regulators are statistically significant at the $P < 0.05$ confidence level by Seurat's implementation of the Wilcoxon rank-sum test (two-sided, adjusted for multiple comparisons using Bonferroni's correction, in d) or Ingenuity Pathway Analysis (IPA) implementation of the Fisher exact test (right-tailed, in g and h). The 50 genes (d), 25 pathways (g) or 50 regulators (h) with the highest absolute average log(fold-change) or z-score across all donors are labeled. Genes with a net positive average log(fold-change) or z-score are labeled in red; genes with a net negative average log(fold-change) or z-score are labeled in blue. DPS, days post-symptom onset; DTF, days from first reported or measured fever. e, Boxplot showing the mean HLA class II module score of CD14+ monocytes from each sample, colored by healthy donors (blue), non-ventilated patients with COVID-19 (orange) or ventilated patients with COVID-19 (red). Shown are exact P values by two-sided Wilcoxon rank-sum test. n = 6, n = 4 and n = 4 biologically independent samples for Healthy, NonVent and ARDS, respectively. f, Dot plot depicting percent expression and average expression of all detected HLA genes in CD14+ monocytes by donor. i, Boxplot showing the IFNA module score of each cell, colored by healthy donors (blue), non-ventilated patients with COVID-19 (orange) or ventilated patients with COVID-19 (red). j, Scatter plots depicting the correlation between the mean ISG module score of CD14+ monocytes in each sample and the patient age (top) and time–distance from first measured or reported fever (bottom). Shown are Pearson's r, exact two-sided P values and the 95% confidence interval. n = 8 (top) and n = 6 (bottom) independent biological samples. Number of cells for

d,f–i: C1 A, 1,561; C1 B, 1,858; C2, 217; C3, 1,102; C4, 713; C5, 462; C6, 277; C7, 2,095; H1, 680; H2, 325; H3, 215; H4, 166; H5, 444; H6, 224. For d,g–h, cells from all healthy controls (n = 2,054 cells) are used to generate comparisons with each COVID-19 sample. For e,i, boxplot features: minimum whisker, 25th percentile − 1.5 × IQR or the lowest value within; minimum box, 25th percentile; center, median; maximum box, 75th percentile; maximum whisker, 75th percentile + 1.5 × IQR or greatest value within.

IMMUNE RESPONSES TO SARS-COV, MERS-COV AND SARS-COV-2

İnandıklıoğlu N, Akkoc T.. Adv Exp Med Biol. 2020 Jun 9. doi: 10.1007/5584_2020_549. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Researchers in Turkey review immune responses to the three coronaviruses responsible for large outbreaks in recent years in order to better inform future vaccine and drug studies. Immunologic studies in severe COVID-19 suggests impaired naïve and memory CD4+ T cell ratio, increased proinflammatory cytokine levels, and increased risk for cytokine storm (Figure 1). Humoral response appears to develop within one week, with elevation of neutralizing IgG antibodies to N protein in 14 days, yet there is currently not enough data to determine length of immunity to SARS-CoV-2 reinfection.

SUMMARY

SARS-CoV causes release of interferon (IFN)-gamma, interleukin (IL)-1beta, IL-6, and IL-12, which may cause release of IL-8 leading to pulmonary inflammation. MERS-CoV infects dendritic cells and T cells, and induces intrinsic and extrinsic apoptotic pathways and an increase in TNF-alpha, IL-6, IFN-gamma, and IL-12. SARS-CoV-2 results in the increase of IL-1, IL-6, TNF-alpha, IL-R2, and IL-18, causing cytokine release syndrome which exacerbates pulmonary symptoms (Figure 1).

ABSTRACT

The world has given an outbreak alarm in the last two decades, with different members of the coronavirus family infecting people at different times. The spread of the SARS-CoV-2 virus, which last appeared in December 2019 in China and spread rapidly to all over the world, has led the scientific world to studies on these viruses. While scientists are trying to develop vaccines or drugs against the virus, the body's immune response to the virus is emerged the biggest guide. In this review, we aimed to provide a good view on immune strategies by comparing immunological responses to SARS-CoV-2 disease among other members of the family, SARS-CoV and MERS-CoV. In the near future, it may contribute to vaccine or drug studies to be developed on immune intervention.

FIGURES

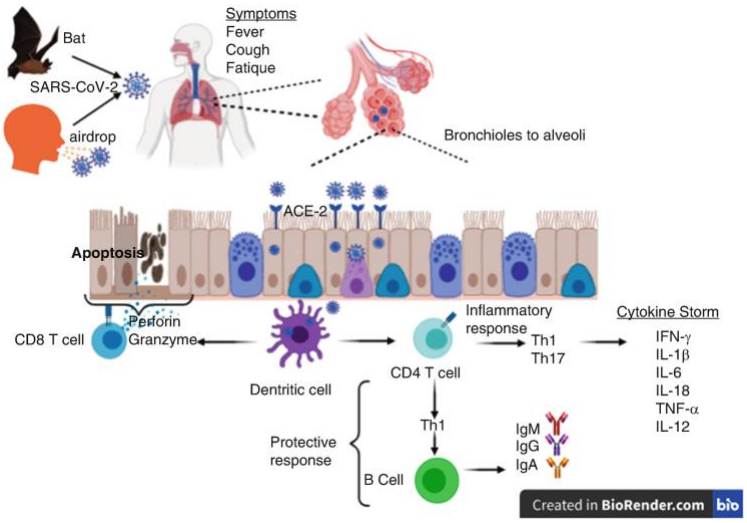


Figure 1: Immune response to SARS-CoV-2 Immune response to SARS-CoV-2. SARS-CoV2 spread out by airway and infect mostly airway bronchioles. Dendritic cells present viral antigen to CD4+T cells and further cytokine storm starts in severe cases. Humoral immune response enhance the production of IgG,IgM and IgA and viral entrance to other cells is prevented. CD8+T cells secrete perforin and granzyme to kill virally infected cells

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.

TRANSMISSION & PREVENTION

MANAGEMENT OF USED PERSONAL PROTECTIVE EQUIPMENT AND WASTES RELATED TO COVID-19 IN SOUTH KOREA

Rhee SW.. Waste Manag Res. 2020 Jun 10:734242X20933343. doi: 10.1177/0734242X20933343. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

The author discusses South Korea's strategies for properly discarding used personal protective equipment and other medical isolation waste generated from the ongoing COVID-19 pandemic. The suggested waste management flow includes four stages: (1) discarded to container for medical waste, (2) storage in designated facility, (3) transportation by vehicle for medical waste, and (4) treatment by incineration (Figure 2). Following proper waste management protocols should reduce the risk of indirect infection from used medical isolation waste.

ABSTRACT

With the rapid spread of coronavirus disease 2019 (COVID-19), the amount of used personal protective equipment (PPE) including face masks and protective clothes has significantly increased. This used PPE in a hospital can lead to the indirect infection by COVID-19. Accordingly, it has been recognized that the management of used PPE is very important to prevent the spread of COVID-19. Through the experience of spreading some infectious diseases such as severe acute respiratory syndrome, Middle East respiratory syndrome and Ebola virus in South Korea (Republic of Korea), a safe management method of waste related to infectious diseases has been developed. In addition, regarding waste related to COVID-19, the Ministry of Environment, SK, proposed special measures to strengthen the management process of waste related to COVID-19 based on principles such as sustainability, transparency and safety.

FIGURES

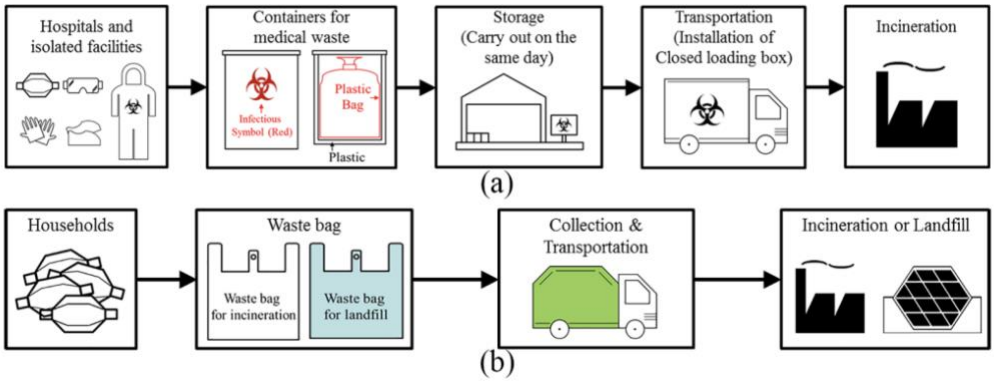


Figure 2. Management flow of used personal protective equipment in South Korea: (a) mask and individual protection from hospitals and isolated facilities; and (b) mask from households.

BREASTFEEDING, HUMAN MILK COLLECTION AND CONTAINERS, AND HUMAN MILK BANKING: HOT TOPICS DURING THE COVID-19 PANDEMIC

Moro GE, Bertino E.. J Hum Lact. 2020 Jun 8:890334420934391. doi: 10.1177/0890334420934391. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Authors in Italy provide guidance on topics related to breastfeeding and sanitation procedures pertaining to milk containers and human milk-banking during the COVID-19 pandemic. Current evidence is lacking in support of vertical transmission of SARs-CoV-2 and reports fail to demonstrate that the virus is transmitted in human milk, but a general consensus is that the health benefits associated with breastfeeding in COVID-19 positive mothers outweighs the risks of not doing so. These recommendations have important implications for health and wellbeing for nursing children and their caretakers, and include the following:

-Authors recommend that mothers wear a surgical mask while breastfeeding or during intimate contact to mitigate infecting infants via respiratory route.
-Authors also emphasize the importance of hand hygiene, disinfecting surfaces as well as thoroughly cleaning plastic and glass milk containers as the virus can remain stable on these materials for several days.
-Human milk donation and milk banking has been negatively impacted by COVID-19, but methods of pasteurization are being investigated.
-Due to milk supply shortages, the authors suggest allocating human milk "to the smallest and most at risk preterm infants (e.g., birth weight <1500 grams or a gestational age <30 weeks) to prevent NEC and other severe illnesses occurring in these extremely fragile infants."

DEVELOPMENTS IN TRANSMISSION & PREVENTION

RISK OF NEUROPSYCHIATRIC DISORDERS IN OFFSPRING OF COVID-19-INFECTED PREGNANT WOMEN AND NUTRITIONAL INTERVENTION

Hashimoto K.. Eur Arch Psychiatry Clin Neurosci. 2020 Jun 2. doi: 10.1007/s00406-020-01148-5. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

This letter raises the potential benefit of dietary intake of sulforaphane and its precursor, glucoraphanin, in reducing the risk of neuropsychiatric disorders in offspring from pregnant persons infected with COVID-19, based on prior evidence of their anti-inflammatory effects.

SUMMARY

From the findings of small epidemiological studies, there remains little evidence to support vertical transmission of COVID-19 in persons who develop COVID-19 pneumonia in the last trimester of pregnancy. There is evidence that maternal immune activation (MIA), such as elevated maternal C-reactive protein, may play a role in the etiology of neuropsychiatric disorders. Thus, there is great interest in studying the potential benefits of anti-inflammatory nutrition during pregnancy to avoid the development of neuropsychiatric disorders. Dietary intake of sulforaphane and its precursor, glucoraphanin, may reduce the risk of neuropsychiatric disorders in offspring due to their anti-inflammatory effects. The consumption of these nutrients warrants investigation as to its effects at reducing these disorders in pregnant persons infected with COVID-19, which raises an inflammatory cascade.

FIGURES

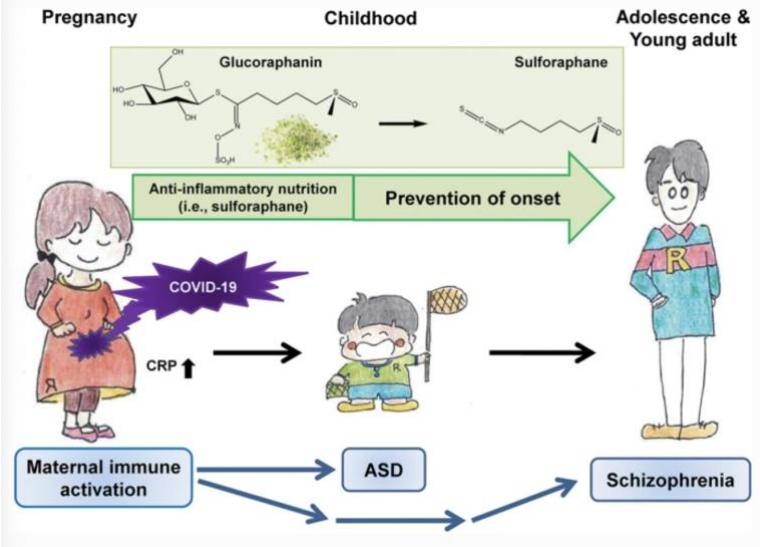


Figure 1. Potential intervention by dietary intake of anti-inflammatory nutrition on the development of neuropsychiatric disorders in offspring after maternal infection of COVID-19. Maternal immune activation (MIA) by COVID-19 infection causes inflammatory events in pregnant women with COVID-19 infection, resulting in higher CRP levels in blood. Given the role of MIA in neuropsychiatric disorders such as ASD and schizophrenia, follow-up investigation of pregnant women infected with COVID-19 and their children is needed. For example, dietary intake of anti-inflammatory nutrition (i.e., sulforaphane and its precursor glucoraphanin) may reduce the risk of neuropsychiatric disorders in offspring after maternal infection of COVID-19.

PREVENTION IN THE HOSPITAL

AIR AND ENVIRONMENTAL SAMPLING FOR SARS-COV-2 AROUND HOSPITALIZED PATIENTS WITH CORONAVIRUS DISEASE 2019 (COVID-19)

Cheng VC, Wong SC, Chan VW, So SY, Chen JH, Yip CC, Chan KH, Chu H, Chung TW, Sridhar S, To KK, Chan JF, Hung IF, Ho PL, Yuen KY.. Infect Control Hosp Epidemiol. 2020 Jun 8:1-32. doi: 10.1017/ice.2020.282. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

Researchers in Hong Kong collected air and environmental samples from two populations during 1/24/2020 - 4/9/2020 inside airborne infection isolation rooms (AIIRs). Their results (detailed below) suggest that COVID-19 is not predominantly transmitted via the airborne route, however, the researchers recommend additional investigation in the cohort ward setting or during aerosol generating procedures.

SUMMARY

Air samples were collected from 10 patients (masked/unmasked patients with COVID-19=6; of these positive control=5, patient 6=positive/negative control) and environmental samples were collected from a second group of 21 patients. The researchers found negative SARS-CoV-2 RNA by RT-PCR in all the air samples, however, these results did not reach statistical significance (p=0.908). The highest environmental contamination was found on mobile phones (7.8%) (Tables 1 and 2) and these results showed statistical significance with positive correlation between viral load and environmental samples (p=0.001). Their results suggest that COVID-19 is not predominantly transmitted via the airborne route, however, the researchers recommend additional investigation in the cohort ward setting or during aerosol generating procedures.

ABSTRACT

BACKGROUND: The role of severe respiratory coronavirus virus 2 (SARS-CoV-2)-laden aerosols in the transmission of coronavirus disease 2019 (COVID-19) remains uncertain. Discordant findings of SARS-CoV-2 RNA in air samples were noted in early reports.
METHODS: Sampling of air close to 6 asymptomatic and symptomatic COVID-19 patients with and without surgical masks was performed with sampling devices using sterile gelatin filters. Frequently-touched environmental surfaces near 21 patients were swabbed before daily environmental disinfection. The correlation of viral load of patients' clinical samples and environmental samples were analyzed.
RESULTS: All the air samples were negative for SARS-CoV-2 RNA in the 6 patients singly isolated inside airborne infection isolation rooms (AIIR) with 12 air change per hour. Nineteen (5.0%) of 377 environmental samples near 21 patients were RT-PCR positive with a median viral load of 9.2x102 copies/ml (range: 1.1x102 to 9.4x104 copies/ml). The contamination rate was highest on patients' mobile phone (7.8%, 6/77), followed by bed rail (5.4%, 4/74) and toilet door handle (5.3%, 4/76). There was a significant correlation between viral load ranges in clinical samples and positivity rate of environmental samples ($p < 0.001$).
CONCLUSION: SARS-CoV-2 RNA was not detectable by air sampler which suggests that airborne route is not the predominant mode of transmission of COVID-19. Wearing of surgical mask, appropriate hand hygiene and thorough environmental disinfection are sufficient infection control measures for COVID-19 patients isolated singly in AIIR. But this may not apply during aerosol generating procedures or in cohort wards with large number of COVID-19 patients nursed together.

FIGURES

Patient	1 [b, c]	2 [c]	3	4	5	6	7	8	9	10
Age/Sex	M/39	F/61	F/34	M/15	M/36	M/62	F/59	F/18	M/53	F/55
Source of infection	Imported (China)	Imported (Japan)	Local [d]	Local [d]	Local	Local [d]	Local [d]	Imported (UK)	Imported (Japan)	Local [d]
Day after symptom onset	D4	Nil	D3	D3	D4	D11	D1	D1	D4	D5
Placement of patient	AIIR (SR)	AIIR (SR)	AIIR (SR)	AIIR (SR)	AIIR (SR)	AIIR (SR) [e]	AIIR (SR)	AIIR (SR)	AIIR (SR)	AIIR (SR)
Therapy at the day of air sample collection:										
Antiviral	Nil	Nil	Nil	Nil	Nil	Yes	Nil	Nil	Nil	Nil
Steroids	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
High flow O_2	Nil	Nil	Nil	Nil	Nil	Yes (100%)	Nil	Nil	Nil	Nil
Covering patients with a shelter during air samples collection: [f]										
	No	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA
Viral load of clinical samples (copies per ml) on the day of air sample collection:										
NPS	3.30 x 10^6 [g]	UD	3.83 x 10^7	6.69 x 10^8 [g]	8.40 x 10^6	7.45 x 10^7	2.97 x 10^8	1.58 x 10^8	1.07 x 10^7	2.14 x 10^8
DTS	5.90 x 10^6	2.07 x 10^{-1}	9.16 x 10^7	NP	2.55 x 10^5	1.98 x 10^7	8.61 x 10^4	4.71 x 10^4	7.93 x 10^7	1.17 x 10^6
Viral load of air samples (copies per ml) while wearing surgical mask: [h]										
	UD	UD	UD	UD	UD	UD	NP	NP	NP	NP
Viral load of air samples (copies per ml) while not wearing surgical mask:										
	UD	UD	UD	UD	UD	UD	NP	NP	NP	NP
Viral load of positive control samples (copies per ml) collected with different maneuvers:										
Sneezing directly to the gelatin filter used by the air sampler:										
	NP	NP	NP	NP	NP	2.54 x 10^4	UD	UD	UD	UD
Spitting of saliva directly onto the gelatin filter used by the air sampler:										
	NP	NP	NP	NP	NP	1.07 x 10^6	2.06 x 10^4	1.94 x 10^4	2.32 x 10^7	1.00 x 10^5

Note. AIIR, airborne infection isolation room with at least 12 air change per hour; D, day; DTS, deep throat saliva collected in early morning before mouth wash; NA, not applicable; ND, not performed; NPS, nasopharyngeal swab; RT-PCR, reverse transcription polymerase chain reaction; SR, single room; TS, throat swab; UD, undetectable; VL, viral load

Table 1. Clinical and epidemiological characteristics of 6 COVID-19 patients (Patient 1 to 6) undergoing air sampling, and 5 patients (Patient 6 to 10) served as positive control by sneezing and spitting

	Number of environmental sample positive for SARS-CoV-2 (%)	Number of environmental sample collected
Patients' mobile phone	6 (7.8%)	77
Bed rail	4 (5.4%)	74
Toilet door handle (outside)	4 (5.3%)	76
Bed table	3 (3.9%)	76
Locker	2 (2.7%)	74

Note. Environmental samples collected before the daily cleaning and disinfection of patients' room.

Table 2. Environmental contamination by SARS-CoV-2 in airborne infection isolation single room caring[sic] COVID-19 patients

FEEDBACK TO PREPARE EMS TEAMS TO MANAGE INFECTED PATIENTS WITH COVID-19: A CASE SERIES

Ghazali DA, Ouersighni A, Gay M, Audebault V, Pavlovsky T, Casalino E.. Prehosp Disaster Med. 2020 Jun 8:1-9. doi: 10.1017/S1049023X20000783. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A case series conducted by the Emergency Department at Assistance Publique-Hôpitaux de Paris (AP-HP) in Paris, France determined that in light of the COVID-19 pandemic universal contact precautions (e.g. surgical masks, hand washing, or application of hydroalcoholic solution) ought to be strictly followed, especially during ventilation or intubation of patients with fever, during transfer, or any other kind of management.

SUMMARY

Case 1: Only the intubating physician was wearing goggles and a facemask during intubation whereas no other person on staff was as protected. Because the patient was a COVID-19 rule out and was determined to be

positive, the other staff at risk and should have had proper PPE.
Case 2: An individual on the ICU care team for a COVID-19 patient was RT-PCR positive for COVID-19 and symptomatic, suggesting the need for improved universal precautions.
Case 3: A team member who performed intubation on a COVID-19 patient became symptomatic and returned a positive RT-PCR for SARS-CoV-2. The patient is currently still in the ICU on mechanical ventilation. "
Case 4: An ED nurse who managed this same patient became COVID-19 positive five days after exposure.

ABSTRACT

Coronavirus Disease 2019 (COVID-19), a new respiratory disease, is spreading globally. In France, Emergency Medical Service (EMS) teams are mobile medicalized resuscitation teams composed of emergency physician, nurse or anesthesiologist nurse, ambulance driver, and resident. Four types of clinical cases are presented here because they have led these EMS teams to change practices in their management of patients suspected of COVID-19 infection: cardiac arrest, hypoxia on an acute pneumonia, acute chronic obstructive pulmonary disease (COPD) exacerbation with respiratory and hemodynamic disorders, and upper function disorders in a patient in a long-term care facility. The last case raised the question of COVID-19 cases with atypical forms in elderly subjects. Providers were contaminated during the management of these patients. These cases highlighted the need to review the way these EMS teams are responding to the COVID-19 pandemic, in view of heightening potential for early identification of suspicious cases, and of reinforcing the application of staff protection equipment to limit risk of contamination.

MANAGEMENT

EFFECTS OF METHYLPREDNISOLONE USE ON VIRAL GENOMIC NUCLEIC ACID NEGATIVE CONVERSION AND CT IMAGING LESION ABSORPTION IN COVID-19 PATIENTS UNDER 50 YEARS OLD

Gong Y, Guan L, Jin Z, Chen S, Xiang G, Gao B.. J Med Virol. 2020 May 22. doi: 10.1002/jmv.26052. Online ahead of print.
Level of Evidence: 3 -

BLUF

A retrospective, non-randomized study conducted at Three Gorges University in Yi Chang, China between January 30, 2020 and February 20, 2020 by First Clinical Medical College of Three Gorges University found that in COVID-19 positive patients under 50 years old, the use of methylprednisolone as a treatment delayed conversion to a negative viral nucleic acid test, but also improved pulmonary findings on CT scan (Figure 2) and oxygen saturation (Figure 3). This suggests methylprednisolone is a promising adjunct therapy for COVID-19, slowing disease progression.

ABSTRACT

The use of corticosteroids has been controversial in viral pneumonia. In most cases, application of methylprednisolone in severe and critical viral pneumonia patients can quickly alleviate the symptoms of dyspnea and prevent disease progression. However, some scholars have confirmed that corticosteroids delayed the body's clearance of the virus. In our retrospective non-randomised study, 34 patients under 50 years old and diagnosed with coronavirus disease 2019 (COVID-19) were included, according to given methylprednisolone treatment (n = 18) or not (n = 16), they were separated into 2 groups. By comparing the clinical data we concluded that corticosteroids therapy can effectively release COVID-19 symptoms such as persistent fever and difficult breathing, improve oxygenation and prevent disease progression. However, it can prolong the negative conversion of nucleic acids.

FIGURES

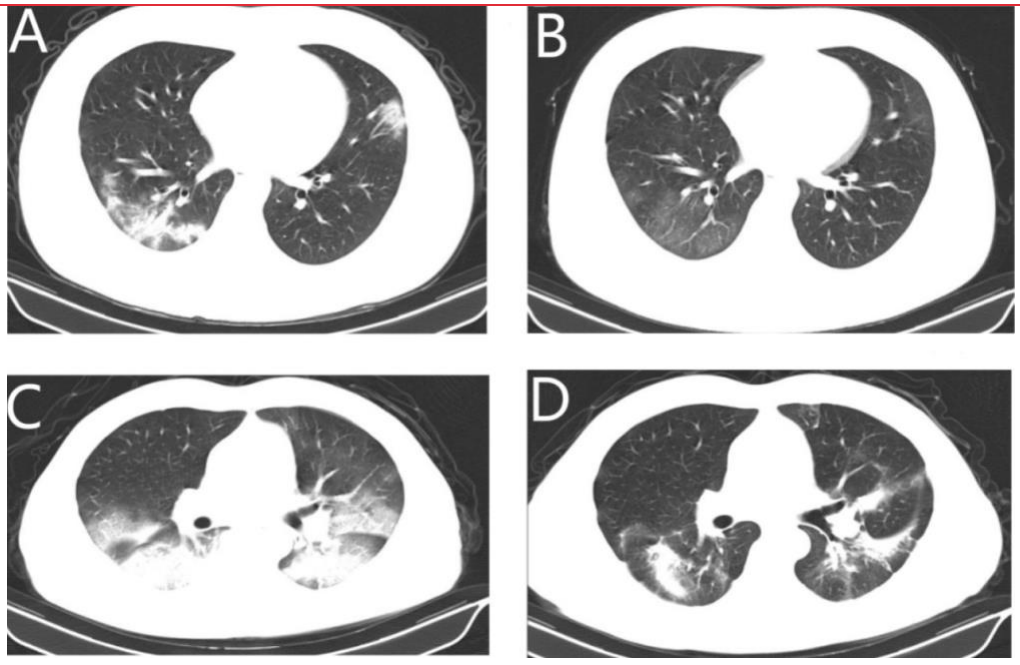
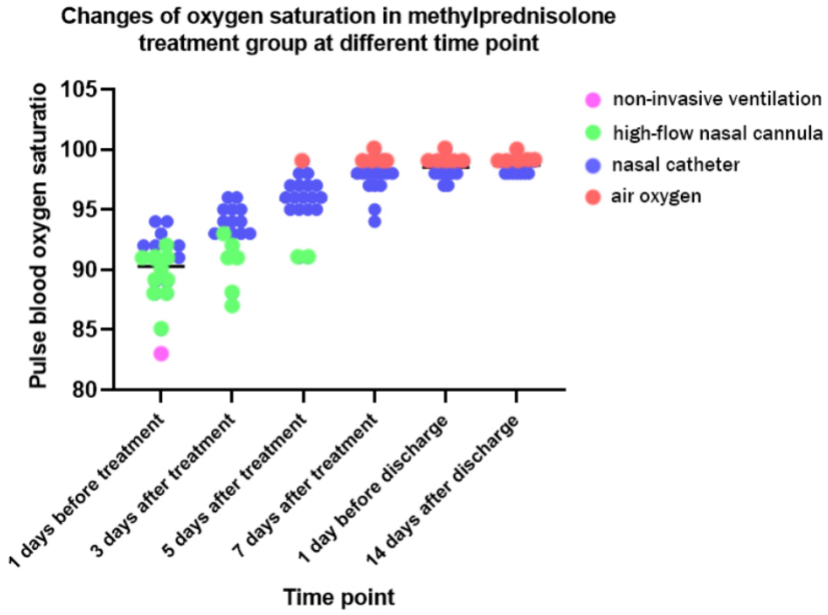


Figure 2: Lung lesion on CT image before and after 20 days of treatment. A: Lung CT image before treatment of non-methylprednisolone treatment group group. B: Lung CT image after 20 days treatment of non-

methylprednisolone treatment group group. C: Lung CT image before treatment of methylprednisolone treatment group. D: Lung CT image after 20 days treatment of methylprednisolone treatment group.



ACUTE CARE

DIAGNOSTIC RADIOLOGY

WHY, WHEN, AND HOW TO USE LUNG ULTRASOUND DURING THE COVID-19 PANDEMIC: ENTHUSIASM AND CAUTION

Gargani L, Soliman-Aboumarie H, Volpicelli G, Corradi F, Pastore MC, Cameli M.. Eur Heart J Cardiovasc Imaging. 2020 Jun 9:jeaa163. doi: 10.1093/ehjci/jeaa163. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A review conducted by various hospitals across Europe proposes a standardized approach (Figure 1) and subsequent interpretation of lung ultrasound (LUS) during the COVID-19 era (Table 2). The authors support the use of LUS for the following reasons:
1. Although sensitivity is low, LUS is quick and readily available in most cases.
2. Chest CT has exceptionally high sensitivity but is "limited by its availability, the need to mobilize the patient, and the long-term risks related to ionizing radiation."
They suggest LUS both to identify typical characteristics of COVID-19 pneumonia and to differentiate from other conditions that may mimic the respiratory findings in COVID-19 patients (Figure 2).

FIGURES

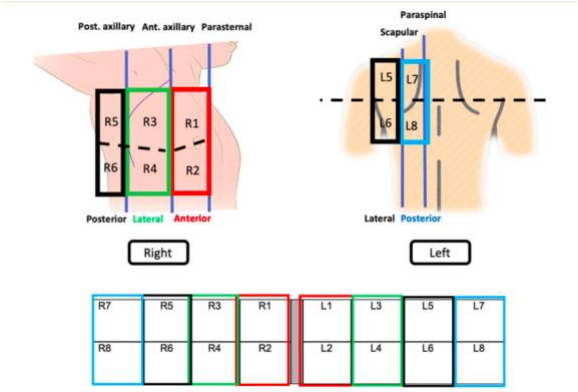


Figure 1. Proposal for lung ultrasound scanning scheme in COVID-19 patients (adapted from Bouhemad et al.)

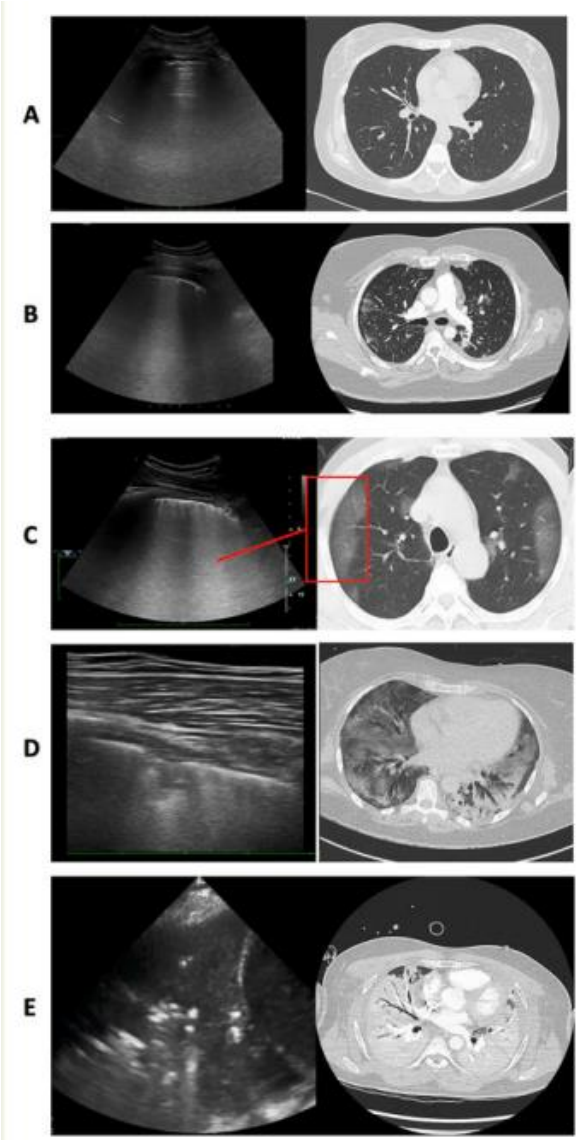


Figure 2. LUS findings correlated to chest CT progressing from normal aeration (A), to progressively more deaerated conditions: coalescent B-lines (B and C), small peripheral consolidation (D),large consolidation (E). The red box in (C) shows an area of groundglass opacification on CT corresponding to confluent B-lines on LUS.

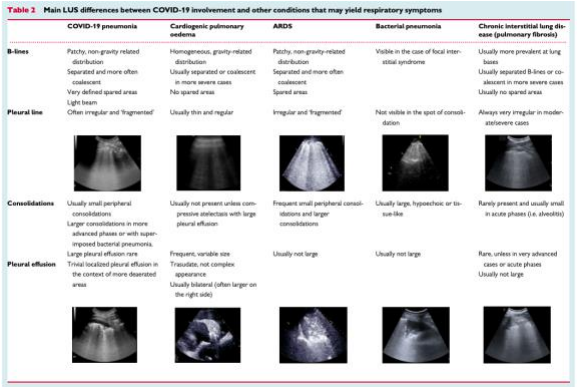


Table 1 Main LUS differences between COVID-19 involvement and other conditions that may yield respiratory symptoms

	COVID-19 pneumonia	Cardiogenic pulmonary oedema	ARDS	Bacterial pneumonia	Chronic interstitial lung disease (pulmonary fibrosis)
B-lines	Patchy, non-gravity related distribution Separated and more often coalescent Very defined spared areas Light beam	Homogeneous, gravity-related distribution Usually separated or coalescent in more severe cases No spared areas	Patchy, non-gravity-related distribution Separated and more often coalescent Spared areas	Visible in the case of focal interstitial syndrome	Usually more prevalent at lung bases Usually separated B-lines or coalescent in more severe cases Usually no spared areas
Pleural line	Often irregular and 'fragmented'	Usually thin and regular	Irregular and 'fragmented'	Not visible in the spot of consolidation	Always very irregular in moderate/severe cases
Consolidations	Usually small peripheral consolidations Larger consolidations in more advanced phases or with superimposed bacterial pneumonia.	Usually not present unless compressive atelectasis with large pleural effusion	Frequent small peripheral consolidations and larger consolidations	Usually large, hypoechoic or tissue-like	Rarely present and usually small in acute phases (i.e. alveolitis)
Pleural effusion	Large pleural effusion rare Trivial localized pleural effusion in the context of more deaerated areas	Frequent, variable size Trasudate, not complex appearance Usually bilateral (often larger on the right side)	Usually not large	Usually not large	Rare, unless in very advanced cases or acute phases Usually not large

Figure 2. LUS findings correlated to chest CT progressing from normal aeration (A), to progressively more deaerated conditions: coalescent B-lines (B and C), small peripheral consolidation (D),large consolidation (E). The red box in (C) shows an area of groundglass opacification on CT corresponding to confluent B-lines on LUS.

CRITICAL CARE

CARDIOPULMONARY RESUSCITATION IN THE PRONE POSITION: A GOOD OPTION FOR PATIENTS WITH COVID-19

Ludwin K, Szarpak L, Ruetzler K, Smereka J, Böttiger BW, Jaguszewski M, Filipiak KJ.. Anesth Analg. 2020 Jun 8. doi: 10.1213/ANE.0000000000005049. Online ahead of print.
Level of Evidence: 1 - Expert Opinion

BLUF

The authors argue that prone positioning improves outcomes in cases of CPR performed on patients who experience cardiac arrest based on the results of two separate studies and cite an additional study that confirmed improved “mortality benefits” in patients with ARDS who were in the prone position. The authors recommend prone positioning in patients with ARDS and COVID-19, as it improves lung function in these patients, and since they are at an increased risk of cardiac arrest.

NEUROLOGY

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

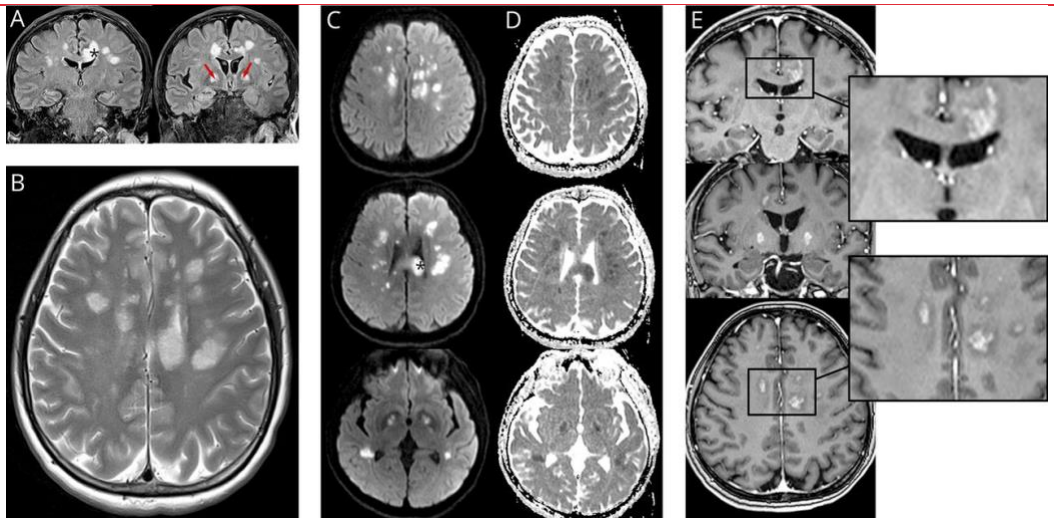


Figure 1. Brain MRI of SARS-CoV-2-related lesions. Multiple supratentorial punctiform and tumefactive lesions involving the white matter bilaterally and showing hypersignal on coronal fluid attenuation and inversion recovery (FLAIR; A), axial T2-weighted images (B), and diffusion-weighted imaging (C) 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

CARDIOLOGY

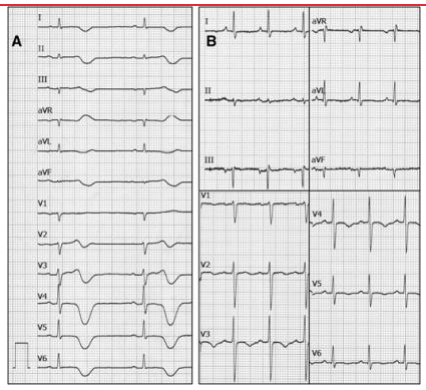
COVID-19 AND QT INTERVAL PROLONGATION: MORE THAN JUST DRUG TOXICITY?

Merino JL, Martínez-Cossiani M, Iniesta A, Escobar C, Rey JR, Castrejón-Castrejón S.. Europace. 2020 May 22:euaa145. doi: 10.1093/europace/euaa145. Online ahead of print.
Level of Evidence: Other -

BLUF

Authors present a case of a 70-year-old man hospitalized in Spain with COVID-19 diagnosed by RT-PCR who was treated with hydroxychloroquine and azithromycin for five days. On hospital day 14 he developed bradycardia, diffuse T-wave inversion, and QT and QTc prolongation (Panel A). His heart rate was restored with isoproterenol, but his ECGs continued to show inverted T waves (Panel B), and he had transient mildly elevated high-sensitive troponin I. Authors note that this collection of findings suggests QT prolongation may be a result of an unknown COVID-19 related mechanism of myocardial inflammation rather than or in conjunction with drug toxicity.

FIGURES



Panel 1: ECG before (A) and after (B) isoproterenol infusion [caption added by COVID-19 LST]

HEMATOLOGY AND ONCOLOGY

HEPARIN RESISTANCE IN COVID-19 PATIENTS IN THE INTENSIVE CARE UNIT

White D, MacDonald S, Bull T, Hayman M, de Monteverde-Robb R, Sapsford D, Lavinio A, Varley J, Johnston A, Besser M, Thomas W.. J Thromb Thrombolysis. 2020 May 22. doi: 10.1007/s11239-020-02145-0. Online ahead of print.
Level of Evidence: 3 -

BLUF

A retrospective study of 15 COVID-19 patients admitted to the intensive care unit (ICU) at Addenbrooke's Hospital from March 1 - April 21, 2020 received either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). The authors found high rates of heparin resistance with intravenous UFH in 80% of patients as well as decreased peak anti-Xa levels with therapeutic LMWH in 100% of patients, which is consistent with observations of thromboprophylaxis failure in COVID-19 patients.

ABSTRACT

Patients with COVID-19 have a coagulopathy and high thrombotic risk. In a cohort of 69 intensive care unit (ICU) patients we investigated for evidence of heparin resistance in those that have received therapeutic

anticoagulation. 15 of the patients have received therapeutic anticoagulation with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH), of which full information was available on 14 patients. Heparin resistance to UFH was documented in 8/10 (80%) patients and sub-optimal peak anti-Xa following therapeutic LMWH in 5/5 (100%) patients where this was measured (some patients received both anticoagulants sequentially). Spiking plasma from 12 COVID-19 ICU patient samples demonstrated decreased in-vitro recovery of anti-Xa compared to normal pooled plasma. In conclusion, we have found evidence of heparin resistance in critically unwell COVID-19 patients. Further studies investigating this are required to determine the optimal thromboprophylaxis in COVID-19 and management of thrombotic episodes.

FIGURES

Number of patients (%)	
Male	11 (73)
Female	4 (27)
Total	15 (100)
Age (%)	
40–49	1 (7)
50–59	5 (33)
60–69	4 (28)
70–79	5 (33)
Weight (%)	
50–99 kg	10 (66)
100–139 kg	3 (20)
> 140–179 kg	2 (13)
Co-morbidities	
Arterial disease[a]	3 (20)
Diabetes mellitus	3 (20)
Chronic respiratory disease	2 (13)
Number of patients receiving haemofiltration (%)	11 (73)
Indications for anticoagulation (%)[b]	
UFH for recurrent haemofiltration circuit clotting	9
UFH for pulmonary embolism	1
LMWH for pulmonary embolism	6
LMWH for line associated thrombosis	1
Number with risk factors for heparin resistance (%)	
Chronic obstructive pulmonary disease	0 (0)
Current or ex-smoker	5 (33)
Median maximum UFH dose/24 h in units (range)	38,400 (22,800–57,600)

LMWH low molecular weight heparin, *UFH* unfractionated heparin

[a]Known atherosclerosis including cerebrovascular disease, peripheral arterial disease or cardiac atheroma

[b]2 patients received therapeutic LMWH for thrombosis followed by UFH for haemofiltration circuit clotting

Table 1. Patient characteristics in the study

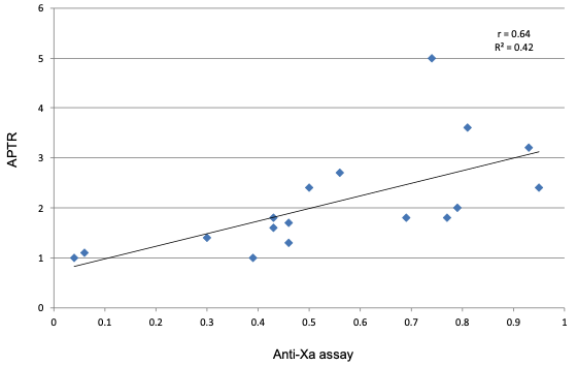


Table 2. Laboratory analysis of the recovery of anti-Xa levels in 12 patients from ICU with COVID-19. In-vitro recovery of 100% was defined as the increase in anti-Xa activity from baseline in the normal pooled plasma after the addition of the low-molecular weight heparin

Patient number	Antithrombin activity (U/dL; reference range ≥ 79U/dL)	Factor VIII:C1 (IU/mL; reference range 0.52–1.43 IU/mL)	Clauss fibrinogen (g/L; reference range 1.46–3.33 g/L)	Baseline anti-Xa (IU/ML)	Anti-X after addition of LMWH (IU/mL)	In-vitro percentage recovery of anti-Xa
Normal pooled plasma	120.0	0.88	2.85	0.05	0.76	100
1	60.8	1.19	3.63	0.00	0.52	73
2	71.2	3.34	7.39	0.56	0.99	61
3	69.6	4.17	8.20	0.11	0.61	70
4	78.3	2.71	5.52	0.36	0.77	58
5	108.0	2.04	6.52	0.11	0.69	82
6	48.6	2.84	4.67	0.19	0.70	72
7	57.9	2.59	4.69	0.09	0.58	69
8	71.5	3.34	5.52	0.16	0.64	68
9	62.2	4.80	6.54	0.21	0.80	83
10	73.7	2.59	6.54	0.35	0.93	82
11	59.5	3.01	8.50	0.42	0.93	72
12	62.9	2.24	4.31	0.05	0.61	79

Table 2. Laboratory analysis of the recovery of anti-Xa levels in 12 patients from ICU with COVID-19. In-vitro recovery of 100% was defined as the increase in anti-Xa activity from baseline in the normal pooled plasma after the addition of the low-molecular weight heparin

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 lymphocytopaenia 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

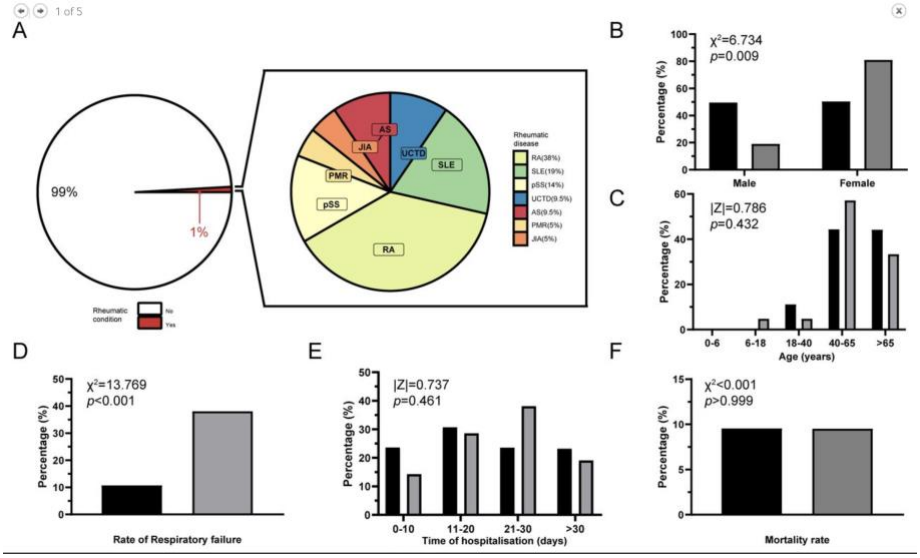
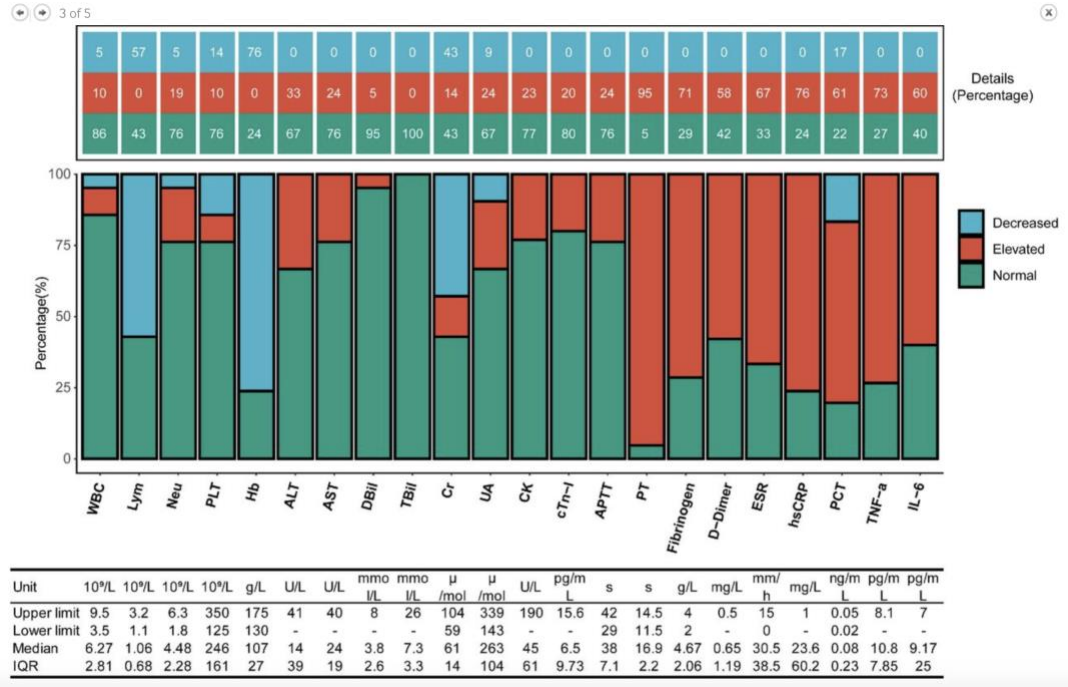


Figure 1: Basic information on rheumatic cases enrolled in this study. Ratio of rheumatic cases to the total number of patients with COVID-19 admitted to Wuhan Tongji Hospital (China), from 13 January 2020 to 15 March 2020 (left). Our series in this study consisted of eight RA cases, four SLE, three 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 $\chi 2$ 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	10⁹/L	10⁹/L	10⁹/L	10⁹/L	g/L	U/L	U/L	mmol/L	mmol/L	μ/mol	μ/mol	U/L	pg/mL	s	s	g/L	mg/L	mm/h	mg/L	ng/mL	pg/mL	pg/mL
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

SURGICAL SUBSPECIALTIES

TRANSPLANT SURGERY

EARLY COVID-19 INFECTION AFTER LUNG TRANSPLANTATION

Keller BC, Le A, Sobhanie M, Colburn N, Burcham P, Rosenheck J, Howsare M, Ganapathi AM, Atyia SA, Haden M, Whitson BA, Mokadam NA, Nunley DR.. Am J Transplant. 2020 May 29. doi: 10.1111/ajt.16097. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

A case study conducted at Ohio State University Wexner Medical Center by a multidisciplinary group of clinicians presented the first known case of reverse transcriptase polymerase chain reaction (RT-PCR) confirmed COVID-19 infection in a lung transplant recipient (68-year-old white female with lung allocation score 31.88) in the acute post-transplant period. The etiology of SARS-CoV-2 infection in this patient was unknown, with either donor-imported infection or nosocomial transmission (2 out of 140 healthcare workers in contact with the patient tested positive for COVID-19) being the most likely pathways. Although the patient's condition required intubation on post-operative day (POD) 2, treatment with chloroquine and azithromycin on POD11, and transfer to the cardiac ICU on POD28, the patient was liberated from mechanical ventilation on POD57 while continuing to improve overall. This case study indicates the importance of COVID-19 testing prior to transplantation in the current pandemic.

ABSTRACT

COVID-19, the clinical syndrome caused by the novel coronavirus, SARS-CoV-2, continues to rapidly spread, leading to significant stressors on global healthcare infrastructure. The manifestations of COVID-19 in solid organ transplant recipients are only beginning to be understood with cases reported to date in transplant recipients on chronic immunosuppression. Herein we report the first case of COVID-19 in a lung transplant recipient in the immediate post-transplant period, and we describe the epidemiologic challenges in identifying the source of infection in this unique situation.

FIGURES

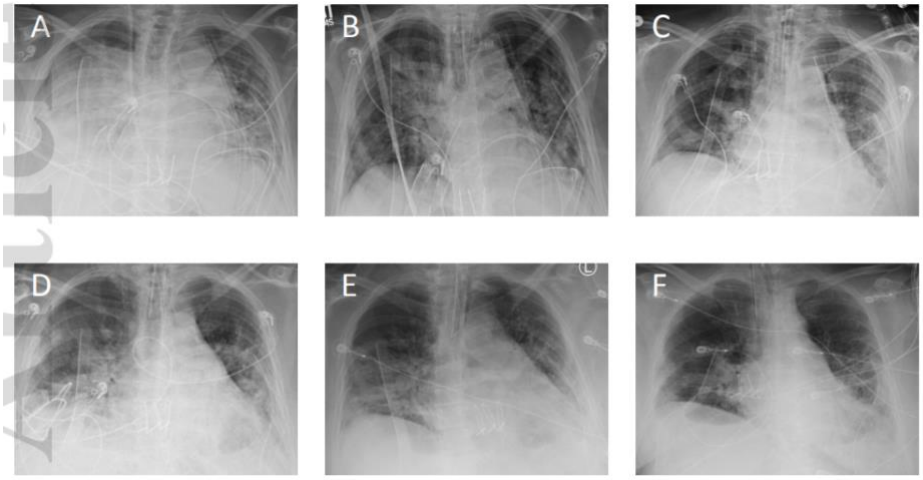


Figure 2: Post-transplant evolution of chest radiographs. Serial post-transplant chest radiographs representing A) PGD on POD1, B) post-intubation for PGD on POD2, C) POD6, D) at time of COVID-19 diagnosis on POD9, E) one day after initiation of chloroquine and azithromycin on POD12, and F) POD17.

	Baseline	COVID-19	Reference range
White blood cell count (K/µL)	7.51	22.51	3.99-11.19
Granulocytes (K/µL)	5.43	21.72	1.64-7.28
Lymphocytes (K/µL)	1.39	0.23	1.16-3.51
Eosinophils (K/µL)	0.48	0.00	0.22-0.87
Lactate (mmol/L)	0.7	1.75	0.5-1.60
Lactate dehydrogenase (U/L)	nd	271	100-190
C-reactive protein (mg/L)	194.15	311.03	<10
Erythrocyte sedimentation rate (mm/h)	nd	50	<30
Ferritin (ng/mL)	nd	593.9	10-291
Fibrinogen (mg/dL)	212	713	220-410
D-dimer (mcg/mL)	nd	2.85	<0.5
Procalcitonin (ng/mL)	nd	1.37	≤0.5
Interleukin-6 (pg/mL)	nd	93.9	<6
Interleukin-2 receptor/soluble CD25 (pg/mL)	nd	2977	≤1033
Quantitative IgG (mg/dL)	nd	283	600-1560
Quantitative IgM (mg/dL)	nd	43	30-360
Quantitative IgA (mg/dL)	nd	111	90-410
Serum creatinine (mg/dL)	0.71	4.62	0.5-1.2
Aspartate transaminase (U/L)	43	34	14-40
Alanine transaminase (U/L)	24	23	9-48

Note: Preoperative laboratory values were within normal limits, but markers of inflammation increased with the onset of fever and diagnosis of COVID-19.

Table 1: Laboratory values obtained at baseline (before transplant or immediately posttransplant) and peak or nadir of values during COVID-19 infection

UROLOGY

SARS-COV-2 AND MALE REPRODUCTIVE HEALTH

Fraietta R, Pasqualotto FF, Roque M, Taitson PF.. JBRA Assist Reprod. 2020 Jun 8. doi: 10.5935/1518-0557.20200047. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Physicians in Sao Paulo, Brazil conducted a review on the relationship between SARS-CoV-2 and male reproductive health. It was found that there might be a possibility of the following:
1. Testicular damage as a result of COVID-19 infection.
2. Infertility following COVID-19 infection.
3. Sexual transmission of SARS-CoV-2.
Based on their findings, the authors suggest that there is currently not enough evidence to support a recommendation for asymptomatic couples to avoid sexual intercourse to prevent viral transmission. However, they do recommend males with COVID-19 should have their reproductive function monitored and assessed.

SUMMARY

The authors present a review of the current literature on SARS-CoV-2 and male reproductive health. Many articles have established that the main path for SARS-CoV-2 entry into cells is via attachment to the ACE2 enzyme, which can be present in the human testes; mainly in Leydig cells and seminiferous tubule cells. Additionally, some hypothesize that SARS-CoV-2 may infect the testicles, causing alterations to the testicular tissues. As of May 15th, 2020, data available from 84 semen samples across three studies found the SARS-CoV-2 virus in six samples (7.1%). Additionally, the authors cite evidence that approximately 18% of men with COVID-19 reported scrotal discomfort. Ultimately, while there is not enough evidence to conclude whether SARS-CoV-2 infects the scrotum, the authors believe it is important to assess and monitor the reproductive functions of men with COVID-19 infections.

ABSTRACT

Critical challenges for the public and private health, research, and medical communities have been posed by the COVID-19 outbreak. Some of these challenges are related to the possible adverse effects of SARS-CoV-2 on male reproductive health, and whether other potential modes of transmission may occur, such as sexual transmission. Moreover, concerns have been raised in terms of whether the COVID-19 outbreak may have an impact on fertility worldwide. In this study, we will discuss the origins of SARS-CoV-2. We will further describe its mechanism of action, diagnosis, symptoms, and potential effects on the male reproductive system.

OBGYN

EFFECTIVENESS AND SAFETY OF AVAILABLE TREATMENTS FOR COVID-19 DURING PREGNANCY: A CRITICAL REVIEW

Favilli A, Mattei Gentili M, Raspa F, Giardina I, Parazzini F, Vitagliano A, Borisova AV, Gerli S.. J Matern Fetal Neonatal Med. 2020 Jun 7:1-14. doi: 10.1080/14767058.2020.1774875. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review of possible treatments for COVID-19 during pregnancy conducted by an international group of researchers found that few drugs have been trialed in pregnant patients due to the safety concerns. Chloroquines, anticoagulants such as low-molecular weight heparin (LMWH), steroids, and various antibiotics have been suggested to provide some benefit to COVID-19 patients and may be used in pregnant patients according to current best practice guidelines (Table 1). More research is needed to elucidate what treatments may be effective for COVID-19 treatment in pregnant patients.

ABSTRACT

Background: COVID-19 is a pandemic disease caused by the SARS-CoV-2 and it spread globally in the last few months. The complete lack of specific treatment forced clinicians to use old drugs, chosen for their efficacy against similar viruses or their in vitro activity. Trials on patients are ongoing but the majority of information comes from small case series and single center reports. We aimed to provide a literature review on the putative effectiveness and safety of available treatments for COVID-19 in pregnant women.
Methods: We reviewed all the available literature concerning the drugs that have been used in the treatment of COVID-19 during pregnancy and whose safe assumption during pregnancy had been demonstrated by clinical studies (i.e. including studies on other infectious diseases). Drugs contra-indicated during pregnancy or with unknown adverse effects were not included in our review.
Results and conclusions: Clinical trials are not often conducted among pregnant patients for safety reasons and this means that drugs that may be effective in general population cannot be used for pregnant women due to the lack of knowledge of side effects in this category of people .The choice to use a specific drug for COVID-19 in pregnancy should take into account benefits and possible adverse events in each single case. In the current

situation of uncertainty and poor knowledge about the management of COVID-19 during pregnancy, this present overview may provide useful information for physicians with practical implications.

FIGURES

Active Principle	Drug Category	Putative Mechanisms of Action	DOSAGE*	Fda Pregnancy Category	References
Lopinavir/Ritonavir	Antiretroviral	*Inhibition of viral replication and release from host cells* -Lopinavir: Inhibition of viral enzyme 3-chymotrypsin-like protease (3CLpro) -Ritonavir: increases the half-life of lopinavir through inhibiting cytochrome P450 3A	400 mg/100 mg tablets, one tablet twice a day for up to 14 days or 200 mg/50 mg tablets, two together every 12 hours with alfa-IFN 5 millions IU in 2 ml of nebulized physiologic solution regardless to meals	Not assigned	Chu et al, 2020. [14] Koss et al, 2014. [19] Berghella, 2020. [20] Roberts et al, 2009. [21] Liang et al, 2020. [22] Dashraat et al, 2020. [32]
Remdesivir	Antiviral	*Inhibition of viral replication* -Viral RNA-dependent RNA polymerase blockage	5 mg/mL vial (reconstituted). Single i.v. 200 mg loading-dose, following by 100 mg daily infusion for 9 days	Not approved	Mulangu et al, 2019. [33]
Hydroxychloroquine	Antimalarial Antiprotozoal Antirheumatic	*Inhibition of viral host cell penetration, viral replication and mitigation of host inflammatory response* -Inhibition of terminal ACE-2 glicosilation -Endosomal pH increase -Inhibition of host TNF-α and IL-6 production	200 mg tablets: 400 mg oral every 12 h for one day, then 200 mg every 12 h for 4 days; or 400 mg daily 5 days; or 200 mg every 8 h for 10 days	Not assigned	Sanders et al, 2020. [16] Berghella,2020. [20] Klumpp, 1965. [44]
Chloroquine	Antimalarial Antiprotozoal Antirheumatic		500 mg or 250 mg tablets: 500 mg oral every 12-24 h for 5-10 days; or 1 g oral for the first day of treatment and than 500 mg daily for 4 to 7 days depending on clinical response	Not formally assigned to a pregnancy category	Sanders et al, 2020. [16] Berghella, 2020. [20] Klumpp, 1965. [44]
Heparin	Anticoagulant	*Inhibition of viral host cell penetration, prevention of endovascular thrombosis* -Factor Xa inhibition	4000 UI s.c. daily, also during post partum if still positive	Not assigned	Berghella, 2020. [20] Di Renzo et al, 2020. [50]
Betamethasone Prednisolone and methylprednisolone	Corticosteroid Corticosteroid	*Mitigation of host inflammatory response* -Inhibition of host IL-1, IL-2, IL-6, IL-12, IFN-γ and TNF-α production	12 mg i.m. two injection 24 h apart as prophylaxis for fetal lung maturation 1–2 mg/kg/day for 3–5 days	Not assigned C/D and C	Poon et al, 2020. [1] Liang et al, 2020. [22] Dashraath et al, 2020. [32] Kakoulidis et al, 2020. [56]
Azithromycin	Antibiotic	*Inhibition of viral host cell penetration, viral replication and bacterial super-infection* -Inhibition of terminal ACE-2 glicosilation -Endosomal pH increase - Binding to the 50S subunit of the bacterial ribosome	500 mg/day for 3–5 days depending on clinical response	B	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/050809s000_Lbl.pdf [61]
Amoxicillin	Antibiotic	- Bactericidal action by inhibiting the synthesis of the bacterial cell wall	1 gr p.os every 8–12 h depending on clinical response	B	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/50-542S017_Amoxil_Prntlbl.pdf [60]
Ceftriaxone	Antibiotic	*- Bactericidal action by interfering with the synthesis of peptidoglycans*	1 gr i.m. or 1–2 gr i.v. daily depending on clinical response	B	https://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/050796s000_PRNTLBL.pdf [62]
Statins	Lipid-lowering agents	*Mitigation of host inflammatory response* -Inhibition of the MYD88 pathway	Lack of data in pregnancy	X	Pollack et al, 2005. [70] Karalis et al, 2016. [71]
Metformin	Oral antidiabetic	*Inhibition of viral host cell penetration* -AMPK activation, leading to ACE2 phosphorylation	500-850 mg day, during or after meals	Not assigned	Gilbert et al, 2006. [67] Li et al, 2015. [68]
Convalescent plasma		*Direct neutralization of the virus, mitigation of host inflammatory response and immunomodulation of a hypercoagulable state* -Virus neutralizing antibodies -Anti-idiotypic antibodies blocking autoreactive recipient antibodies -Saturation of FC receptors	Lack of data in pregnancy	Not assigned	van Griensven et al, 2016. [88]
Tocilizumab	Monoclonal Antibody	*Mitigation of host inflammatory response* -Soluble and membrane-bound IL-6 receptor blockage	400 mg IV or 8 mg/kg IV for 1–2 doses. Second dose after 8–12 h if inadequate response. Infuse in 60 minutes.	Not assigned	Weber-Schoendorfer et al, 2016. [92] Hoeltzenbein et al, 2016. [93] Nakajima et al, 2016. [94]
Pioglitazone	Oral antidiabetic	*Mitigation of host inflammatory response* -Inhibition of host IL-1b, IL-6, and IL-8 and TNF-α production	Lack of data in pregnancy	Not assigned	Yaris et al, 2004. [80] Ota et al, 2008. [81]
Interferon-I	Immunomodulants agents	*Inhibition of viral replication, mitigation of host inflammatory response* -Slowdown of cell metabolism -Inhibition of host IL-1b and TNF-α production	Variable dose, limited data avaible	C	Yazdani et al, 2012. [103] Romero et al, 2015 [104] Hiratsuka et al, 2000. [106] Thiel et al, 2016. [107] Hellwig et al, 2020. [108]

Table 1 (Con't). Inhibition of viral replication, mitigation of host inflammatory response.

ADJUSTING PRACTICE DURING COVID-19

FOR HEALTHCARE PROFESSIONALS

HAND ECZEMA PANDEMIC CAUSED BY SARS-COV-2 HYGIENE MEASURES: THE SETUP OF A HAND ECZEMA HELPLINE FOR HOSPITAL PERSONNEL

Greveling K, Kunkeler ACM.. J Eur Acad Dermatol Venereol. 2020 Jun 2. doi: 10.1111/jdv.16695. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Dermatologists at a hospital in the Netherlands describe the measures they have taken due to the increased incidence of irritant hand dermatitis caused by increased hygiene measures in healthcare professionals. Written educational information was provided including basic skin maintenance measures (moisturizing frequently, limiting duration of glove use when possible, using cotton glove underneath synthetic gloves, using alcohol dispenser over soap when no obvious dirt or contaminant is present). They also set up an electronic consultation service for specific cases within the hospital and established a dedicated reserve of corticosteroid cream for hospital employees to expedite the treatment process (see Table 1 for their 2-week collection of patients who used this consultation service).

ABSTRACT

Hand eczema, also known as hand dermatitis, often results from a combination of causes, including genetics (atopic constitution), irritating substances and contact allergens. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). As current evidence suggests that SARS-CoV-2 can be transmitted through contaminated hands, the World Health Organization recommends frequent handwashing with soap and water, or hand-rubbing with an alcohol based hand rub.

FIGURES

Patient number	Gender (m/f)	Age (y)	Profession	Atopic constitution (e, h, a)	Known contact allergies
1	m	62	Lab assistant	h	none
2	m	44	Technical automation specialist	h	none
3	f	28	Pharmacist	e	none
4	f	35	Medical social worker	e	resin
5	f	32	Neurology resident	e	none
6	f	31	Pharmacy assistant	h,e,a	perfume
7	f	38	Lab assistant	h	none

m, male; f, female; y, year; e, eczema; h, hay fever; a, astma.

Table 1. Patients' characteristics

ACUTE CARE

HIGHER LEVELS OF IL-6 EARLY AFTER TOCILIZUMAB DISTINGUISH SURVIVORS FROM NON-SURVIVORS IN COVID-19 PNEUMONIA: A POSSIBLE INDICATION FOR DEEPER TARGETING IL-6

Quartuccio L, Sonaglia A, Pecori D, Peghin M, Fabris M, Tascini C, De Vita S.. J Med Virol. 2020 Jun 9. doi: 10.1002/jmv.26149. Online ahead of print.

Level of Evidence: 4 - Case-series or casecontrol studies, or poor quality prognostic cohort study

BLUF

Researchers from Italy compared serum interleukin-6 (IL-6) concentrations before and after tocilizumab infusion in 24 patients with COVID-19 pneumonia and found that post-infusion IL-6 levels were significantly higher in non-survivors compared to survivors (2398.5 [430.5-9372] pg/mL vs 290.5 [58.5-1305.5] pg/mL,

p=0.022). Post-infusion IL-6 levels had good predictive value for mortality (AUC 0.815, 95% CI 0.63-0.99, p=0.02; Figure 1), suggesting that post-tocilizumab infusion serum IL-6 concentrations may indicate disease morbidity and help guide further IL-6 treatment options.

ABSTRACT

INTRODUCTION: The most serious COVID-19 deriving from severe acute respiratory syndrome coronavirus 2 causes cytokine release storm and it is associated with worse outcomes. In COVID-19 patients, Interleukin (IL)-6 levels are significantly elevated. Blocking IL-6 preliminary resulted in the improvement of this hyperinflammatory state. It is unknown which patients could require higher doses of tocilizumab to get out of the cytokine storm. MATERIALS AND METHODS: Twenty-four patients affected by COVID-19 pneumonia were included. All the patients underwent tocilizumab 8 mg/kg intravenously and were tested for serum IL-6 24-48 hours before and 12-48 hours after tocilizumab infusion. Comparisons between survivors and non-survivors were performed. RESULTS: Eighteen patients were discharged, while six patients died, with no clinical or laboratory differences between the two groups at baseline. IL-6 was not different at baseline (p=0.41), while 24-48h post-tocilizumab IL-6 serum levels were significantly higher in non-survivors than in survivors [2398.5 (430.5-9372) pg/mL vs 290.5 (58.5-1305.5) pg/mL, p=0.022)]. Serum IL-6 post-tocilizumab showed a good predictive ability to discriminate survivors from non-survivors (AUC 0.815 95%CI 0.63-0.99, p=0.02). CONCLUSION: Repeated measurement of serum level of IL-6 early after tocilizumab may distinguish non-survivors from survivors and support the choice of deeper targeting IL-6 in COVID-19 pneumonia. This article is protected by copyright. All rights reserved.

FIGURES

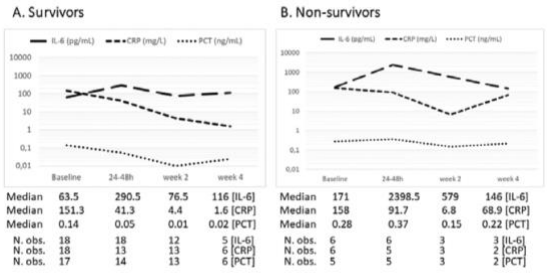


Figure 1: On a logarithmic scale, figure 1 reports the value of Interleukin (IL)-6, C- Reactive Protein (CRP) and procalcitonin (PCT) over time in survivors (panel A) and non-survivors (panel B) as median. Below the graphs, the median and the number of available observations at each time are indicated. For completeness, the interquartile ranges [25%-75% IQR], which have been omitted in the figure, are as follows: for survivors (A), baseline IL-6 (pg/mL) 63.5 [52.2-136], IL-6 24-48h 290.5 [76.7- 1119.7], IL-6 week 2 76.5 [47-198.75], IL-6 week 4 116 [66-124]; baseline CRP (mg/L) 150.6 [66.5-210], CRP 24-48h 41.3 [26.9-63.8], CRP week 2 4.4 [1.5-6.4], CRP week 4 1.6 [0.2-5.1]; baseline PCT (ng/mL) 0.14 [0.08-0.28], PCT 24-48h 0.06 [0.04-0.09], PCT week 2 0 [0-0.04], PCT week 4 0.03 [0-0.04]; for non-survivors (B), baseline IL-6 (pg/mL) 171 [51-523.5], IL-6 24-48h 2398.5 [594-6819.7], IL-6 week 2 579 [338-820], IL-6 week 4 146 [80-212]; baseline CRP (mg/L) 158 [116- 255.5], CRP 24-48h 91.7 [54.5-116.5], CRP week 2 6.8 [3.9-160.6], CRP week 4 68.9 [60.9-77]; baseline PCT (ng/mL) 0.28 [0.09-0.46], PCT 24-48h 0.37 [0.36-1.01], PCT week 2 0.15 [0.09-0.63], PCT week 4 0.22[0.14-0.29].

INTERVENTIONAL RADIOLOGY

REORGANIZING CROSS-SECTIONAL INTERVENTIONAL PROCEDURES PRACTICE DURING THE CORONAVIRUS DISEASE (COVID-19) PANDEMIC

Fananapazir G, Lubner MG, Mendiratta-Lala M, Wildman-Tobriner B, Galgano SJ, Lamba R, Hinshaw JL, Brook OR.. AJR Am J Roentgenol. 2020 May 22:1-5. doi: 10.2214/AJR.20.23227. Online ahead of print.
Level of Evidence: Other -

BLUF

Members of the Society of Abdominal Radiology Cross-Sectional Interventional Radiology Emerging Technology Commission propose recommendations for judicious allotment of personal protective equipment (Table 2) during the COVID-19 pandemic and present guidelines regarding interventional procedures in order to minimize risk of infection among patients and healthcare providers, including:

1. A tiered approach should be considered with target windows for when to perform the procedures (Table 1).
2. Proper PPE to prevent transmission of SARS-CoV-19 from and to health care personnel and patients (Table 2).
3. Hand hygiene is emphasized and techniques for donning and doffing PPE are outlined.
4. All patients, including outpatients, need to be screened for signs and symptoms of COVID-19 before entering the procedure area during the COVID-19 pandemic.
5. Academic institutions should consider limiting personnel in the interventional suite to those who have a direct and essential role in the procedure.
6. Room aeration and equipment cleaning after procedures on patients with known or suspected coronavirus disease.

ABSTRACT

OBJECTIVE. The purpose of this article is to present strategies and guidelines that can be implemented in the performance of cross-sectional interventional procedures during the coronavirus disease (COVID-19) pandemic. CONCLUSION. Radiologists who perform cross-sectional interventional procedures can take several steps to minimize the risks to patients and radiology personnel, including screening referred patients to decide which procedures can be postponed, using appropriate personal protective equipment (PPE), minimizing the number of people involved in procedures, preserving PPE when possible, and applying proper room and equipment cleaning measures.

FIGURES

TABLE 1: Tiered Approach to Cross-Sectional Interventional Procedures

Tier	Time Frame	Example
1	Urgent	Cholecystostomy
		Abscess drainage
		Biopsy for lymphoma
2	Perform within 2 wk	Organ biopsy for suspected fast-growing malignancy
3	Perform within 2 mo	Ablation of fast-growing lesions
4	Can be delayed by 2 mo	Biopsy and ablation of slow-growing lesion
		Liver biopsy for staging of fibrosis
5	Can be delayed by 6 mo	Fine-needle aspiration of thyroid nodule

Note—Examples can vary according to clinical scenario.

Table 1. A tiered approach should be considered with target windows for when to perform the procedures. We propose a five-tier approach: those that are urgent, those that should be performed within 2 weeks, those that should be performed within 2 months, and those that can safely be delayed 2 or 6 months. Discussion with the referring service is critical to ensure adequate triage based on combined available clinical and radiologic data. This tiered approach should be applied to both outpatient and inpatient procedures.

TABLE 2: Current Recommendations for Personal Protective Equipment During Coronavirus Disease (COVID-19) Pandemic

Patient Status	Recommended Personal Protective Equipment
Patient with confirmed or suspected COVID-19 wearing a surgical mask for the duration of the procedure	Surgical mask (N95 respirator after restoration of supplies) Eye protection Surgical cap Gown Gloves
Patient with confirmed or suspected COVID-19 not wearing surgical mask for the duration of the procedure *or* procedure is aerosol producing	N95 respirator Eye protection Surgical cap Gown Gloves
COVID-19 not suspected	Surgical mask Eye protection Surgical cap Gown Gloves

MEDICAL SUBSPECIALTIES

CARDIOLOGY

USE OF RAAS INHIBITORS AND RISK OF CLINICAL DETERIORATION IN COVID-19: RESULTS FROM AN ITALIAN COHORT OF 133 HYPERTENSIVES

Felice C, Nardin C, Di Tanna GL, Grossi U, Bernardi E, Scaldaferri L, Romagnoli M, Tonon L, Cavasin P, Novello S, Scarpa R, Farnia A, De Menis E, Rigoli R, Cinetto F, Pauletto P, Agostini C, Rattazzi M.. Am J Hypertens. 2020 Jun 8:hpaa096. doi: 10.1093/ajh/hpaa096. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

This single-center observational study conducted in Italy on 133 hypertensive patients found that COVID-19 patients with chronic hypertension on renin-angiotensin-aldosterone system inhibitor (RAASi) therapy were less likely to be admitted to semi-intensive/intensive care units compared to the non-RAASi population (Table 2). While these results suggest that chronic use of RAASi does not adversely impact the clinical course of COVID-19, larger studies are needed to investigate the protective effects of RAASi in hypertensive patients with COVID-19.

ABSTRACT

BACKGROUND: The effect of chronic use of renin-angiotensin-aldosterone system (RAAS) inhibitors on the severity of COVID-19 infection is still unclear in patients with hypertension. We aimed to investigate the association between chronic use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and COVID-19 related outcomes in hypertensive patients.
METHODS: A single center study was conducted on 133 consecutive hypertensive subjects presenting to the Emergency Department with acute respiratory symptoms and/or fever who were diagnosed with COVID-19 infection between 9th and 31st March 2020.
RESULTS: All patients were grouped according to their chronic antihypertensive medications (ACEIs, N=40; ARBs, N=42; not on RAAS inhibitors, N=51). There was no statistical difference between ACEIs and ARBs groups in terms of hospital admission rate, oxygen therapy and need for non-invasive ventilation. Patients chronically treated with RAAS inhibitors showed a significantly lower rate of admission to semi-intensive/intensive care units, when compared to the non-RAAS population (odds ratio [OR] 0.25, CI95% 0.09-

0.66 p=0.006). Similarly, the risk of mortality was lower in the former group, although not reaching statistical significance (OR 0.56, CI95% 0.17-1.83, p=0.341).
CONCLUSIONS: Our data suggest that chronic use of RAAS inhibitors does not negatively affect clinical course of COVID-19 in hypertensive patients. Further studies are needed to confirm this finding and determine whether RAAS inhibitors may have a protective effect on COVID 19-related morbidity and mortality.

FIGURES

Table 2. Comparison of main clinical outcomes between hypertensive patients taking or not renin-angiotensin-aldosterone system inhibitors.

	Crude OR	95% CI	*P*	Adj-OR	95% CI	*P*
Hospital admission	0.45	0.09-2.24	0.327	0.39	0.05-2.94	0.365
Oxygen therapy	0.46	0.18-1.18	0.107	0.51	0.15-1.78	0.292
Admission to ICU /sICU	**0.36**	**0.17-0.75**	**0.007**	**0.25**	**0.09-0.66**	**0.006**
NIV	0.70	0.34-1.44	0.336	0.58	0.21-1.60	0.296
Death	0.41	0.18-0.92	0.030	0.56	0.17-1.83	0.341

CI: Confidence Interval; ICU: intensive care unit; sICU: semi-intensive care unit; NIV: non-invasive ventilation; OR: Odds Ratio; Adj-OR: adjusted Odds Ratio. Multi-variable logistic regressions was performed with a pre-defined covariate set, which included age, gender, body mass index, days with symptoms prior to admission, previous cardiovascular events, diabetes and cancer.

CARDIO-ONCOLOGY SERVICES DURING THE COVID-19 PANDEMIC: PRACTICAL CONSIDERATIONS AND CHALLENGES

Farmakis D, Keramida K, Filippatos G.. Eur J Heart Fail. 2020 May 22. doi: 10.1002/ejhf.1898. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

This guideline written by researchers at University of Cyprus and University of Athens Medical Center establishes a set of management recommendations for patients with concomitant cardiovascular (CV) disease and cancer. Briefly, these recommendations include:
- minimizing the exposure of cancer patients to COVID-19.
- risk stratification of CV patients based on cardiotoxicity secondary to oncology treatments, cardiac troponins, and natriuretic peptides.
- CV complications (AMI, HF, myocarditis, arrhythmias) of COVID-19 need to be addressed early.
Additional details on these recommendations can be found in Table 1.

FIGURES

Baseline assessment before cancer therapy	- Omit in patients with low or very low risk of cardiotoxicity including those without: o history of cardiovascular disease o two or more cardiovascular risk factors o history of cardiotoxicity o history of previous cardiotoxic therapy o scheduled anticancer regimens with established cardiotoxicity profile - Maintain in patients with moderate or high cardiotoxicity risk
Follow-up during cancer therapy	- Defer in the absence of symptoms or signs of cardiovascular complications - Consider replacement of cardiac imaging by biomarkers (cardiac troponin, with or without natriuretic peptides) in patients with moderate or high cardiotoxicity risk, including those with: o history of cardiovascular disease o multiple cardiovascular risk factors o history of cardiotoxicity o particularly cardiotoxic anticancer regimens - Establish a tele-consultation system to be used by patients with non-emergent symptoms before arrangement of clinic visit
Routine follow-up of cancer survivors	- Defer in asymptomatic survivors - Establish a tele-consultation system to be used by patients with non-emergent symptoms before arrangement of clinic visit
Diagnostic modalities	- Defer non-crucial cardiac imaging sessions - Consider replacement of imaging by cardiac biomarkers - Consider replacement of conventional echocardiography by focused echocardiography - Apply all relevant protection measures during cardiac imaging
Tele-health and information	- Establish: o a patient tele-consultation system through telephone, web-based applications, mobile applications or other communication means o an emergency telephone number o a telecommunication platform for multidisciplinary physician meetings o a patient information system with regular updates through dedicated webpages or other resources.

Table 1: Proposed adaptations in Cardio-Oncology services during the COVID-19 pandemic

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.

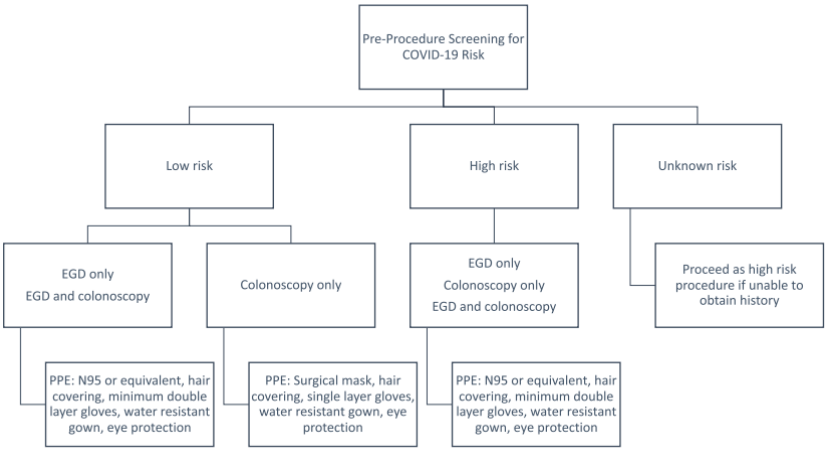


FIGURE 1. Personal protective equipment utilization algorithm for endoscopists.

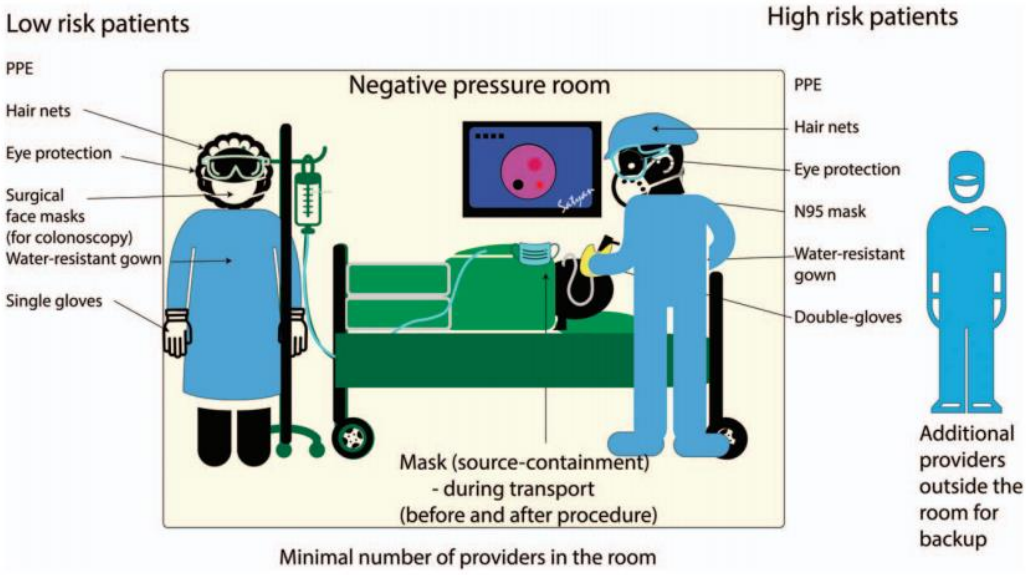


FIGURE 2. Personal protective equipment utilization in the endoscopy suite.

SURGICAL SUBSPECIALTIES

PROCEDURAL SEDATION IN THE COVID-19 ERA

Fawley N, Abdelmalak B.. Cleve Clin J Med. 2020 Jun 8. doi: 10.3949/ccjm.87a.ccc043. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

The authors provide recommendations regarding procedural sedation for pre-procedure testing (Figure 1), management of previously COVID-19 positive patients (Table 3), and reducing the need for supplemental oxygen in sedation (Figure 2). These guidelines are an attempt to allow patients to safely receive their elective procedures while still minimizing risk of COVID-19 transmission within the healthcare system.

ABSTRACT

Resuming procedural sedation services for elective procedures during the COVID-19 pandemic requires unique considerations to ensure safety for patients and providers. Guidelines for resuming these procedures, including timing, screening and testing, use of personal protective equipment, and case planning are discussed. Approaches to procedural sedation can be modified to reduce the risk of droplet or aerosol transmission by decreasing nasal cannula oxygen supplementation flows. Decreasing the need for oxygen supplement can be accomplished by opioid and sedative sparing strategies, including the use of multimodal analgesia and non-pharmacologic analgesic and anxiolytic interventions. Recommendations are made for patients who are COVID-19 positive and require procedural sedation.

FIGURES

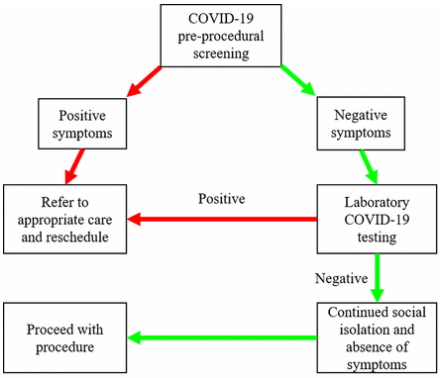


Figure 1. Pre-procedural flowchart for pre-procedural screening and testing patients for COVID-19.

TABLE 3
CDC: Discontinuation of transmission-based precautions for patients previously positive for COVID-19[12]

Symptomatic	Symptom-based strategy	At least 3 days since recovery (resolution of fever without antipyretics, and improvement in respiratory symptoms)
		At least 10 days since symptoms first appeared
	Test-based strategy	Resolution of fever without antipyretics and improvement in respiratory symptoms
		Two consecutive negative COVID-19 tests more than 24 hours apart
Asymptomatic	Time-based strategy	At least 10 days since first positive test without development of symptoms
	Test-based strategy	Two consecutive negative COVID-19 tests more than 24 hours apart

Table 3. CDC: Discontinuation of transmission-based precautions for patients previously positive for COVID-19

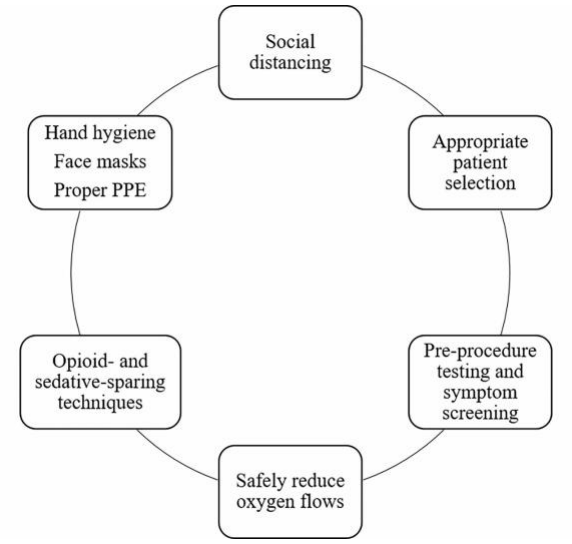


Table 3. CDC: Discontinuation of transmission-based precautions for patients previously positive for COVID-19

OTOLARYNGOLOGY

GUIDANCE FOR OTOLARYNGOLOGY HEALTH CARE WORKERS PERFORMING AEROSOL GENERATING MEDICAL PROCEDURES DURING THE COVID-19 PANDEMIC

Lammers MJW, Lea J, Westerberg BD.. J Otolaryngol Head Neck Surg. 2020 Jun 3;49(1):36. doi: 10.1186/s40463-020-00429-2.
Level of Evidence: Other - Expert Opinion

BLUF

A literature review conducted by Otolaryngologists in Canada recommends that all elective and non-time sensitive Aerosol Generating Medical Procedures should be delayed to mitigate the risk of infection. For procedures that cannot be delayed, one of three levels of PPE should be used depending on the patient's COVID-19 status and if the procedure is considered Aerosol-generating (Table 1).

SUMMARY

Otolaryngologists are at particularly high risk for contracting COVID-19 due to the SARS-CoV-2 virus having a preference for infecting the upper and lower airway mucosa as well as the high number of Aerosol Generated Medical Procedures (AGMP) performed in this specialty. Based on the current literature, it is recommended that all AGMPs be delayed due to the risk of contracting COVID-19. For those procedures that cannot be delayed, there are several levels of PPE that should be followed, depending on the COVID-19 status of the patient and the type of procedure. Level 1 procedures should be used for non-AGMP as well as AGMP procedures where the patient is COVID-19 negative. Level 2 PPE should be used for all AGMP procedures. Level 3 PPE should be used for AGMP procedures where the patient is COVID-19 positive or the test is pending but there is an urgent need to perform the procedure (Table 1). The levels are as follows (Table 2):
- Level 1: Surgical mask, gown, gloves, face shield/goggles, head cover (optional)
- Level 2: N95/FFP2, Water impermeable gown, double gloves, goggles/face shield, head cover, including neck protection
- Level 3: PAPR or N95/FFP2 and surgical mask, coverall, gown and water-impermeable gown, double gloves, goggles and face shield, head cover, including neck protection.

ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for Coronavirus disease 2019 (COVID-19) has a predilection for infecting the mucosa of the upper and lower airways. Otolaryngologists and supporting health care workers (HCWs) are particularly at high risk of becoming infected while treating patients as many in-office procedures and surgeries are Aerosol Generating Medical Procedures (AGMP). Based on a review of the literature and various guidelines, recommendations are made to mitigate the risk to health care workers of becoming infected with SARS-CoV-2 while providing clinical care. RECOMMENDATIONS: During the COVID-19 pandemic all elective and non-time sensitive Otolaryngology procedures should be deferred to mitigate the risk of transmission of infection to HCWs. For non-AGMPs in all patients, even COVID-19 positive patients Level 1 PPE (surgical mask, gown, gloves and face shield or goggles) is sufficient. If local prevalence is favourable and patients are asymptomatic and test negative for SARS-CoV-2, Level 1 PPE can be used during short duration AGMPs, with limited risk of infected aerosol spread. For AGMPs in patients who test positive for SARS-CoV-2 a minimum of Level 2 PPE, with adequate protection of mucosal surfaces, is recommended (N95/FFP2 respirator, gown, double gloves, goggles or face shield and head cover). For long duration AGMPs that are deemed high-risk in COVID-19 positive patients, Level 3 PPE can provide a higher level of protection and be more comfortable during long duration surgeries if surgical hoods or PAPRs are used. It is recommended that these procedures are performed in negative pressure rooms, if available. It is essential to follow strict donning and doffing protocols to minimize the risk of contamination. CONCLUSIONS: By following strict infection prevention recommendations, the risk of HCWs becoming infected with SARS-CoV-2 while treating patients can be minimized. As the COVID-19 pandemic evolves rapidly, these recommendations should serve as guidance and need to be interpreted based on local factors and availability of healthcare resources.

FIGURES

Table 1 Summary of recommendations for minimum Personal Protective Equipment for Health Care Workers during COVID-19 Pandemic

	Level 1 PPE	Level 2 PPE	Level 3 PPE
FOR NON-AGMP PROCEDURES			
Asymptomatic + SARS-CoV-2 negative or unknown	X		
Symptomatic + SARS-CoV-2 negative	X		
Symptomatic + SARS-CoV-2 positive or high risk	X[a]	X[a]	
FOR AGMP PROCEDURES			
Asymptomatic + SARS-CoV-2 negative	X[b]	X[b]	
Asymptomatic + SARS-CoV-2 pending		X	
Symptomatic + SARS-CoV-2 negative		X	
Symptomatic + SARS-CoV-2 pending due to urgency		X[c]	X[c]
Symptomatic + SARS-CoV-2 positive		X[c]	X[c]

[a]This depends on the type and duration of examination and procedure. When there is a prolonged exposure of the HCW within the respiratory cloud of the patient, Level 2 PPE is advised
[b]This depends on the local COVID-19 prevalence, test reliability and type and duration of AGMP. In favourable situations Level 1 PPE is adequate
[c]This depends on the type and duration of AGMP and patient population: for a short duration, low risk AGMP, like intubation, Level 2 PPE is adequate, whereas for procedures with prolonged aerosol formation, like sinonasal surgery using drills, a higher level of protection may be warranted

Table 1. Summary of recommendation for minimum Personal Protective Equipment for Health Care Workers during COVID-19 Pandemic

Table 2 Summary of Personal Protective Equipment levels for Health Care Workers during COVID-19 Pandemic

Level 1 PPE	Level 2 PPE	Level 3 PPE
Surgical mask	**N95/FFP2**	**PAPR or N95/FFP2 + surgical mask**
Gown[b]	**Water impermeable gown**	**Gowns:** **1. coverall +gown[a]** **2. water impermeable gown**
Gloves	**Double gloves**	**Double gloves**
Face shield / goggles[b]	**Goggles / face shield**	**Goggles + (face shield)**
Head cover (optional)	**Head cover, including neck protection**	**Head cover, including neck protection**

[a]Coverall with integrated hood and boots is preferred over gown with separate boot and leg covers and head-neck cover, since it reduces the risk of self-contamination during doffing and will provide optimal protection. A single layer surgical water impermeable gown (AAMI level 4), with a surgical hood or PAPR, and separate boot and leg covers, will provide a similar level of protection. If surgical hoods and PAPRs are not available or cannot be used during the procedure, a surgical gown (AAMI level 4) with properly fitting head and neck cover and goggles will provide adequate protection. Coveralls have to be used in conjunction with a second sterile surgical gown, when used during surgery
[b]Gown and face shield/goggles are recommended when providing direct patient care to COVID-19 patients and optional for in office non-AGMPs in negative or low risk patients, and only advised if there is a risk of fluid spread

Table 2. Summary of Personal Protective Equipment levels for Health Care Workers during COVID-19 Pandemic

PERSONAL PROTECTION AND DELIVERY OF RHINOLOGIC AND ENDOSCOPIC SKULL BASE PROCEDURES DURING THE COVID-19 OUTBREAK

Van Gerven L, Hellings PW, Cox T, Fokkens W, Hopkins C, Hox V, Jorissen M, Schuermans A, Sinonquel P, Speleman K, Vander Poorten V, Van Gool K, Van Zele T, Alobid I.. Rhinology. 2020 May 22. doi: 10.4193/Rhin20.119. Online ahead of print.
Level of Evidence: Other -

BLUF

Rhinologists from Belgium, the Netherlands, the United Kingdom, and Spain review the available anecdotal data to provide safe practice guidelines for outpatient rhinology care and endoscopic endonasal surgery during COVID-19.

SUMMARY

"Summary outpatient rhinology clinic:
• Provide patients with a mask.
• Question patients about COVID-19 contact and symptoms before clinical examination.

• Apply social distancing in the waiting area. Limit the waiting time and number of patients.
• Prepare material before starting the clinical examination.
• Limit the number of manipulations during clinical examination.
• Avoid the use of local anesthetic atomized sprays but use soaked pledgets instead.
• Use an endoscopy tower to avoid close physical contact.
• Allow only essential and experienced staff with proper PPE, work in pairs to optimize the patient flow and to reduce the need of PPE.
• Keep doors shut as much as possible."

"Summary endoscopic endonasal surgery:
• Pre-operative screening of patients for COVID-19 status is strongly recommended.
• In case of unknown or positive COVID-19 status:
  o Consider alternative approaches to treat your patient.
  o Adapt ventilation and pressure in the OR.
  o Check procedure with anesthesiologist for COVID-19 intubation.
  o Provide clear information on the OR doors and keep doors shut as much as possible.
  o Limit the use of powered instruments.
  o Allow only essential staff with proper PPE."

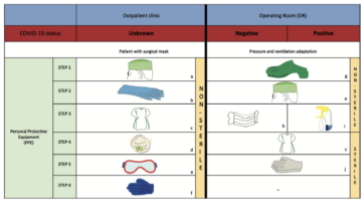
See table 1 and figure 1 for visual schematics.

ABSTRACT

On March 11th 2020, the World Health Organization (WHO) declared COVID-19 pandemic, with subsequent profound impact on the entire health care system. During the COVID-19 outbreak, activities in the rhinology outpatient clinic and operation rooms are limited to emergency care only. Health care practitioners are faced with the need to perform rhinological and skull base emergency procedures in patients with a positive or unknown COVID-19 status. This article aims to provide recommendations and relevant information for rhinologists, based on the limited amount of (anecdotal) data, to guarantee high-quality patient care and adequate levels of infection prevention in the rhinology clinic.

FIGURES

Table 1. Overview of suggested recommendations for PPE during endoscopic endonasal procedures depending on the COVID-19 status of the patient.



(a = surgical cap, b= long gloves, c= impermeable gown, d= FFP2 mask, e= goggles, f= short gloves, g= scrubs , h= surgical mask, i= powered, air-purifying respirator, j= sterile gloves).

Figure 1. (A) Schematic figure of the donning and doffing procedure for personal protective equipment (PPE) in the outpatient rhinology clinic. (B) Illustration of the real-life PPE-procedure.

ORTHOPEDICS

MEDICATIONS IN COVID-19 PATIENTS: SUMMARIZING THE CURRENT LITERATURE FROM AN ORTHOPAEDIC PERSPECTIVE

Tan SHS, Hong CC, Saha S, Murphy D, Hui JH.. Int Orthop. 2020 May 22. doi: 10.1007/s00264-020-04643-5. Online ahead of print.
Level of Evidence: Other -

BLUF

This systematic review summarizes current literature surrounding use of the following medications commonly prescribed by orthopedic clinicians, summarized below:

1. Analgesia and anti-inflammatories: non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are encouraged despite early initial concern over these drugs and COVID-19. Opioids are not recommended due to respiratory and immunity suppression.

2. Steroids: oral steroids should be used when indicated, but risk should be weight against context; for example, spinal metastasis versus a relatively healthy patient who may not benefit greatly. Intra-articular steroid injections per usual are encouraged.

3. Anticoagulants: the use heparin is advised instead of oral vitamin K antagonists due to the instability of that class of drugs in severe COVID-19 infections.

4. Antibiotics: Penicillin and clindamycin are safe to use. When possible, switch to tetracyclines or macrolides for infections due to the possible benefit against COVID-19.

5. Vitamins B, C, D: continued practice is recommended if orthopedic surgeons use these.

ABSTRACT

PURPOSE: The review aims to provide a summary of the current literature regarding common medications prescribed in orthopaedic surgery and their potential implications in COVID-19 patients.
METHODS: A systematic review was performed using the PRISMA guidelines. All clinical studies, reviews, consensus and guidelines related to the above medications and COVID-19 were included.
RESULTS: A total of 18 articles were included. The use of analgesia, anti-inflammatories, steroids, anticoagulants, antibiotics, vitamin B, vitamin C and vitamin D and their potential impact on COVID-19 patients were reported.
CONCLUSION: Eight main recommendations were derived from the review. Firstly, paracetamol remains the first line of analgesia and antipyretic. Secondly, there is no need to avoid NSAIDs for COVID-19 patients. Thirdly, opioids have the potential for immunosuppression in addition to respiratory depression and, therefore, should be prescribed with care in COVID-19 patients. Fourthly, patients with conditions where steroids are proven to be efficacious can continue to receive their steroids; otherwise, systemic steroids are not recommended for COVID-19 patients. Fifthly, orthopaedic surgeons following up on COVID-19 patients who are using steroids should continue to follow them up for possible avascular necrosis. Sixthly, whenever possible, oral anticoagulation should be converted to parental heparin. Seventhly, common orthopaedic antibiotics including penicillin and clindamycin are safe to continue for COVID-19 patients. However, for COVID-19 patients, the antibiotics can potentially be switched to macrolides and tetracyclines if the organisms are sensitive. Lastly, prescription for vitamins B, C and D should continue as per usual clinical practice.

OBGYN

PRACTICAL RECOMMENDATIONS FOR GYNECOLOGIC SURGERY DURING THE COVID-19 PANDEMIC

Chiofalo B, Baiocco E, Mancini E, Vocaturo G, Cutillo G, Vincenzoni C, Bruni S, Bruno V, Mancari R, Vizza E.. Int J Gynaecol Obstet. 2020 May 29. doi: 10.1002/ijgo.13248. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

Authors at the Regina Elena National Cancer Institute in Rome, Italy developed surgical triage categories (Table 1) and recommendations for surgically treating a variety of acute gynecologic conditions in the context of COVID-19 infection. Their recommendations include the following:
- Patients with emergencies should receive immediate surgical intervention with COVID-19 testing and risk assessment.
- Hysteroscopic surgeries are non-aerosolizing and can generally be performed in the outpatient setting as needed.
- Myomas and endometriosis unresponsive to pharmacological therapies may be referred for surgical intervention depending on hospital resources.
- Ovarian lesions determined to have risk of malignancy of ≥5% and patients with endometrial, cervical, and vulvar cancer should be referred to an oncologic surgical center without COVID-19 cases for intervention.
- Proper additional personal protective equipment (PPE) for COVID-19 should be used during surgery for those that cannot be delayed.

Ultimately, the authors argue that intervention should always be considered in the context of COVID-19 exposure risk, resource availability, and overall ratio of patient risks/benefits.

ABSTRACT

Surgery in suspected/confirmed COVID-19 patients is a high-risk venture. In infected patients, COVID-19 is present in the body cavity. During surgery it could be nebulized in the spray generated by surgical instruments and could theoretically infect members of the surgical team. Nevertheless, some surgical gynecologic

pathologies cannot be postponed. We present a list of the most frequent gynecologic diseases and recommendations on their surgical management during the COVID-19 pandemic, based on expert opinion, current available information, and international scientific society recommendations to support the work of gynecologists worldwide. In brief, any kind of surgical treatment should be scrutinized and postponed if possible. Nonoperative conservative treatment including pharmacological therapies for hormone-sensitive pathologies should be implemented. Health risk assessment by patient history and COVID-19 test before elective surgery are pivotal to protect both patients and healthcare providers. In confirmed COVID-19 patients or highly suspected cases, elective surgery should be postponed until full recovery.

FIGURES

Category	Description	Desirable maximum waiting time
1. Urgent	Has the potential to deteriorate quickly to the point where it may become an emergency	Within 30 days
2. Semi-urgent	- Causes pain, dysfunction, or disability - Unlikely to deteriorate quickly - Unlikely to become an emergency	Within 60 days
3. Elective	- Causes pain, dysfunction, or disability - Unlikely to deteriorate quickly - Does not have the potential to become an emergency	Within 365 days

Table 1: Surgical triage categories.

REPRODUCTIVE HEALTH UNDER COVID-19 - CHALLENGES OF RESPONDING IN A GLOBAL CRISIS

Church K, Gassner J, Elliott M.. Sex Reprod Health Matters. 2020 May 22:1-3. doi: 10.1080/26410397.2020.1773163. Online ahead of print.
Level of Evidence: Other -

BLUF

Authors at Marie Stopes International (MSI) discuss impacts of COVID-19 on access and delivery of sexual and reproductive healthcare (SRH) including decreased access due to clinic closures; use of telemedicine for "at-home" abortions; and use of phone, WhatsApp, and Facebook at patient contact centers for patient communication and product guidance. This article indicates the need for innovative SRH care to reduce the rate of unsafe abortions and pregnancy-related deaths during COVID-19.

SUMMARY

This article describes the impact that COVID-19 has had on access to and delivery of sexual and reproductive healthcare (SRH) as observed by the provider Marie Stopes International (MSI), as well as steps that have been taken to preserve access to SRH during the COVID-19 pandemic. Restrictions and lockdown measures have caused MSI clinics to close, challenging SRH access. MSI implemented a model for telemedicine provision of SRH in the UK, and as a result "nearly half of MSI-UK's abortions were delivered 'at home' "(Church et al.).

MSI has taken steps to open patient contact centers that can communicate with patients using phone, WhatsApp, or Facebook and provide guidance regarding self-use SRH products and the appropriate use of PPE. It is vital to implement innovations to providing SRH during the COVID-19 pandemic to reduce the rate of unsafe abortions and pregnancy-related deaths, which are estimated to be as high as 1.2 million and 5,000, respectively.

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, Aloi 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).

WHEN SEPARATION IS NOT THE ANSWER: BREASTFEEDING MOTHERS AND INFANTS AFFECTED BY COVID-19

Tomori C, Gribble K, Palmquist AEL, Ververs MT, Gross MS.. Matern Child Nutr. 2020 May 26:e13033. doi: 10.1111/mcn.13033. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A commentary written by various nursing and public health departments at Johns Hopkins, University of North Carolina, and Western Sydney University argue in favor of keeping breastfeeding as a standard for breastfeeding mothers and infants, even when there is a risk of COVID-19 vertical transmission. Specific arguments discussed below.

SUMMARY

The arguments presented in this article cite the limited evidence of COVID-19 in infants and the cumulative impact of separation on infants:
-Disrupting breastfeeding makes the child more susceptible to infection secondary to lack of antibodies being transferred.
- Separation and discontinuation of breastfeeding does not actually ensure minimized viral transmission.
- Early separation magnifies maternal health consequences of insufficient breastfeeding.
Finally, they authors explain that limiting breastfeeding may disproportionately affect vulnerable infants. They argue that a policy should not be made affecting the standards of mother-baby breastfeeding due to the significant lack of evidence.

ABSTRACT

The World Health Organisation (WHO) has provided detailed guidance on the care of infants of women who are a person under investigation (PUI) or confirmed to have COVID-19, which supports immediate postpartum mother-infant contact and breastfeeding with appropriate respiratory precautions. Although many countries have followed WHO guidance, others have implemented infection prevention and control policies (IPC) that impose varying levels of postpartum separation and discourage or prohibit breastfeeding or provision of expressed breastmilk. These policies aim to protect infants from the potential harm of infection from their mothers, yet they may fail to fully account for the impact of separation. Global COVID-19 data are suggestive of potentially lower susceptibility and a typically milder course of disease among children, although the potential for severe disease in infancy remains. Separation causes cumulative harms, including disrupting breastfeeding and limiting its protection against infectious disease, which has disproportionate impacts on vulnerable infants. Separation also presumes the replaceability of breastfeeding - a risk that is magnified in emergencies. Moreover, separation does not ensure lower viral exposure during hospitalizations and post-discharge, and contributes to the burden on overwhelmed health systems. Finally, separation magnifies maternal health consequences of insufficient breastfeeding and compounds trauma in communities who have experienced long-standing inequities and violence, including family separation. Taken together, separating PUI/confirmed SARS-CoV-2 positive mothers and their infants may lead to excess preventable illnesses and deaths among infants and women around the world. Health services must consider the short-and-long-term impacts of separating mothers and infants in their policies.

GERIATRICS

A HOSPITAL PARTNERSHIP WITH A NURSING HOME EXPERIENCING A COVID-19 OUTBREAK: DESCRIPTION OF A MULTI-PHASE EMERGENCY RESPONSE IN TORONTO, CANADA

Stall NM, Farquharson C, Fan-Lun C, Wiesenfeld L, Loftus CA, Kain D, Johnstone J, McCreight L, Goldman RD, Mahtani R.. J Am Geriatr Soc. 2020 May 22. doi: 10.1111/jgs.16625. Online ahead of print.
Level of Evidence: Other -

BLUF

A partnership between Mount Sinai Hospital and a 126-bed nursing home in Toronto, Canada starting on April 15 2020 found that a multiphasic intervention (Tables 1-3) by an acute care hospital can be effective in stabilizing a nursing home experiencing a COVID-19 outbreak, suggesting that hospital partnerships with nursing homes may be effective in preventing and handling future COVID-19 outbreaks.

SUMMARY

A partnership between Mount Sinai Hospital and a 126-bed nursing home in Toronto, Canada starting on April 15 2020 found that a multiphasic intervention by an acute care hospital can be effective in stabilizing a nursing home experiencing a COVID-19 outbreak, suggesting that hospital partnerships with nursing homes may be effective in preventing and handling future COVID-19 outbreaks. Phases include:
-Phase 1: Engagement, relationship and trust-building
-Phase 2: Environmental scan, team-building and immediate response (first 72 hours; Table 1)
-Phase 3: Early phase response (next 7 days; Table 2)
-Phase 4: Stabilization and Transition Phase (day 10 to present; Table 3)

ABSTRACT

Nursing homes have become "ground zero" for the coronavirus disease 2019 (COVID-19) epidemic in North America, with homes experiencing widespread outbreaks resulting in severe morbidity and mortality among its residents. This manuscript describes a 371-bed acute care hospital's emergency response to a 126-bed nursing home experiencing a COVID-19 outbreak in Toronto, Canada. Like other health care system responses to

COVID-19 outbreaks in nursing homes, this hospital-nursing home partnership can be characterized in several phases: 1) engagement, relationship and trust-building; 2) environmental scan, team-building and immediate response; 3) early phase response; and 4) stabilization and transition period.

FIGURES

1. **An environmental scan of clinical expertise, staffing, supplies and equipment needs**
   - Securing direct access to geriatric medicine, palliative care and IPAC clinicians.
   - Evaluating current and projected nursing home staffing shortages.
   - Determining the PPE stockpile, supply chain and expected burn rate.
   - Assessing shortages and expected needs for medical equipment and medications.

2. **Immediate Infection Prevention and Control assessment**
   - Reviewing the outbreak line list and plotting its epidemiological curve.
   - Risk assessment to understand any gaps in IPAC measures and procedures.

3. **SARS-CoV-2 testing of the remaining residents at the nursing home**
   - Widespread SARS-CoV-2 nasopharyngeal swabbing.

4. **Team building: establishing a clinical and operations team**
   - Members of the hospital team included senior leadership, administrators, nurses and clinicians in geriatrics, palliative care, psychiatry, pharmacy and IPAC. The full list of team members, roles and responsibilities is detailed in *Appendix 1*.

5. **Decanting of 15 nursing home residents to the acute care hospital**
   - The nursing home and hospital agreed to decant 15 residents who were receiving end-of-life care or who would benefit from acute care medical management.

Table 1: Environmental scan, team-building and immediate response (first 72 hours)

1. **Establishing the infrastructure for the provision of virtual care**
   - Telehealth (videoconferencing and remote access to the electronic medical record) was used to reduce staff exposure to SARS-CoV-2 and minimize the PPE burn rate.

2. **Clinical triage of the remaining residents in the home**
   - Medically unwell and end-of-life residents were rapidly identified by chart review and by a screening tool we developed for the nursing home staff (see *Appendix 2*).
   - The clinical team virtually rounded with an on-site registered practice nurse (RPN) on residents, prioritizing those who were potentially medically unwell or end-of-life.

3. **Goals of care discussions for residents determined to be unwell or end-of-life**
   - Goals of care conversations were had with all nursing home residents (and their family members/proxies) identified as being medically unwell or end-of-life.
   - Decisions were made about active vs. medical management, and transfer to the acute care hospital vs. remaining in the nursing home.

4. **Provision of active medical management within the nursing home**
   - STAT and in-home laboratory and imaging services were organized.
   - Hypoxic residents were given low-flow oxygen therapy (maximum of 5L/minute).
   - Volume contracted residents were rehydrated using subcutaneous hypodermoclysis.
   - A geriatrician and palliative care physician were available 24/7 staff to respond to any clinical concerns or emergency situations.

5. **Provision of high-quality palliative care within the nursing home**
   - Residents identified as being end-of-life and wishing to remain within the nursing home for comfort care were assessed on at least a daily basis via virtual care.
   - We helped ensure an adequate supply of comfort care and subcutaneous medications.

6. **IPAC training for frontline staff**
   - Several on-site training sessions focusing on modes of transmission of COVID-19, point of care risk assessment, PPE selection, and donning and doffing procedures.

7. **Ongoing IPAC interventions**
   - Additional SARS-CoV-2 testing.
   - Room changes and terminal cleans.
   - Enhanced environmental cleaning and disinfection.
   - Setting up donning and doffing stations, increasing access to PPE and hand hygiene.

8. **Occupational Heath**
   - The Occupational Health team worked with IPAC, the local Public Health Unit and the nursing home to connect with and support staff away from work for any reason (illness, caregiving responsibilities, or fear) and determine a plan for return to work.

Table 3: Details about the stabilization and transition phase

1. **Deployment of hospital-based nurses to alleviate staffing shortages**
   - The hospital redeployed 1 clinical nurse specialist, 4 registered nurses, and 7 registered practice nurses for a 4-week assignment at the nursing home.

2. **Pharmacist intervention for nursing home residents**
   - Medication administration schedules were consolidated and streamlined to minimize staff exposure and PPE burn rate.
   - Comprehensive medication reviews to optimize medication safety and resident care.

3. **Psychiatric support for nursing home residents**
   - Geriatric psychiatry consultations to residents with new mental health concerns and reassessment and optimization of treatment plans for those with pre-existing mental illness and cognitive impairment.

4. **Psychosocial support for the nursing home staff**
   - The hospital psychiatry group offered one-on-one and group-based counselling.

5. **Stabilizing IPAC interventions within the nursing home**
   - Screening all asymptomatic staff and clearing residents who had recovered from COVID-19 based on symptom onset.
   - Ongoing support around PPE selection, donning and doffing, and environmental cleaning, to ensure a continued safe environment for staff.

6. **Transitioning of medical care back to the nursing home staff and physicians**
   - Coaching and empowering the nursing home staff to monitor and manage geriatric and palliative syndromes as well as pursue goals of care conversations.
   - The nursing home's family physicians started joining virtual rounds, and eventually began rounding independently using the newly established virtual care infrastructure.

Table 3: Details about the stabilization and transition phase

R&D: DIAGNOSIS & TREATMENTS

LOPINAVIR PHARMACOKINETICS IN COVID-19 PATIENTS

Gregoire M, Le Turnier P, Gaborit BJ, Veyrac G, Lecomte R, Boutoille 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

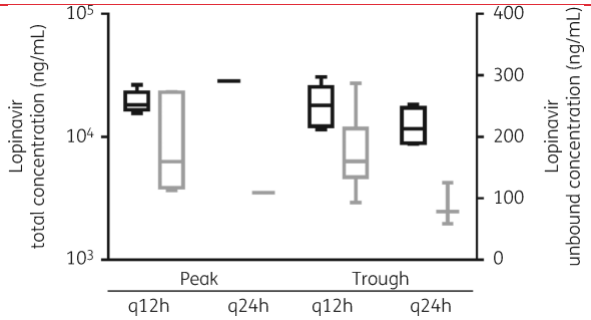


Figure 1. Lopinavir concentrations in SARS-CoV-2-infected patients after ritonavir-boosted lopinavir 400/100 mg once or twice daily. Total (black) and unbound (grey) concentrations are represented by medians, IQRs and ranges at peak (4 ± 1 h after intake) or trough (q12h: at least 10 h after intake;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

TWO LINEAR EPITOPES ON THE SARS-COV-2 SPIKE PROTEIN THAT ELICIT NEUTRALISING ANTIBODIES IN COVID-19 PATIENTS

Poh CM, Carissimo G, Wang B, Amrun SN, Lee CY, Chee RS, Fong SW, Yeo NK, Lee WH, Torres-Ruesta A, Leo YS, Chen MI, Tan SY, Chai LYA, Kalimuddin S, Kheng SSG, Thien SY, Young BE, Lye DC, Hanson BJ, Wang CI, Renia L, Ng LFP.. Nat Commun. 2020 Jun 1;11(1):2806. doi: 10.1038/s41467-020-16638-2.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A multi-center prospective study by researchers in Singapore and the United Kingdom isolated antibodies from the sera of 25 COVID-19 patients and used ELISA and depletion assays to find two linear B-cell epitopes specific to the SARS-CoV-2 virus S protein - S14P5 and S21P2 and these findings were statistically significant (see Figure 2 for additional details and p-values). The authors suggest that antibodies directed at the two epitopes may neutralize SARS-CoV-2 (Figure 3) and that this discovery may have potential in designing more sensitive assays for determining epidemiological trends and vaccine efficiency.

ABSTRACT

Given the ongoing SARS-CoV-2 pandemic, identification of immunogenic targets against the coronavirus spike glycoprotein will provide crucial advances towards the development of sensitive diagnostic tools and potential

vaccine candidate targets. In this study, using pools of overlapping linear B-cell peptides, we report two IgG immunodominant regions on SARS-CoV-2 spike glycoprotein that are recognised by sera from COVID-19 convalescent patients. Notably, one is specific to SARS-CoV-2, which is located in close proximity to the receptor binding domain. The other region, which is localised at the fusion peptide, could potentially function as a pan-SARS target. Functionally, antibody depletion assays demonstrate that antibodies targeting these immunodominant regions significantly alter virus neutralisation capacities. Taken together, identification and validation of these neutralising B-cell epitopes will provide insights towards the design of diagnostics and vaccine candidates against this high priority coronavirus.

CURRENT DIAGNOSTICS

CLINICAL PERFORMANCE OF DIFFERENT SARS-COV-2 IGG ANTIBODY TESTS

Kohmer N, Westhaus S, Rühl C, Ciesek S, Rabenau HF.. J Med Virol. 2020 Jun 8. doi: 10.1002/jmv.26145. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or “poor or non-independent reference standard

BLUF

Authors in Frankfurt, Germany assessed the performance of five assays in detecting IgG antibodies for SARS-CoV-2 in 33 patients with moderate to severe COVID-19 disease. In comparison of 2 ELISA assays,1 lateral flow assay (LFA), and 2 developed assays {immunofluorescence assay (IFA) and plaque reduction neutralization test (PRNT)] they found the following:
- ELISA can be automated and thus used for larger samples.
- Varicell ELISA, IFA, and PRNT demonstrated high sensitivity.
- Antibody testing should be performed 10 days after PCR confirmation as the maximum sensitivity (93.8%-100%) of the assay is noted in the later phase of infection.
- PRNT is the preferred method to detect IgG antibodies.

ABSTRACT

SARS-CoV-2 serological assays are urgently needed for rapid diagnosis, contact tracing and for epidemiological studies. So far, there is limited data on how commercially available tests perform with real patient samples and if positive tested samples show neutralizing abilities. Focusing on IgG antibodies, we demonstrate the performance of two ELISA assays (Euroimmun SARS-CoV-2 IgG and Vircell COVID-19 ELISA IgG) in comparison to one lateral flow assay ((LFA) FaStep COVID-19 IgG/IgM Rapid Test Device) and two in-house developed assays (immunofluorescence assay (IFA) and plaque reduction neutralization test (PRNT)). We tested follow up serum/plasma samples of individuals PCR-diagnosed with COVID-19. Most of the SARS-CoV-2 samples were from individuals with moderate to severe clinical course, who required an in-patient hospital stay. For all examined assays, the sensitivity ranged from 58.8 to 76.5% for the early phase of infection (days 5-9) and from 93.8 to 100% for the later period (days 10-18). With exception of one sample, all positive tested COVID-19 follow up-samples, using the commercially available assays examined (including the in-house developed IFA), demonstrated neutralizing properties in the PRNT. Regarding specificity, some samples of endemic coronavirus (HCoV-OC43, HCoV-229E) and Epstein Barr virus (EBV) infected individuals cross-reacted in the ELISA assays and IFA, in one case generating a false positive result. This article is protected by copyright. All rights reserved.

OCCURRENCE AND TIMING OF SUBSEQUENT SARS-COV-2 RT-PCR POSITIVITY AMONG INITIALLY NEGATIVE PATIENTS

Long DR, Gombar S, Hogan CA, Greninger AL, Shah VO, Bryson-Cahn C, Stevens B, Rustagi A, Jerome KR, Kong CS, Zehnder J, Shah NH, Weiss NS, Pinsky BA, Sunshine J.. Clin Infect Dis. 2020 Jun 7:ciaa722. doi: 10.1093/cid/ciaa722. Online ahead of print.

Level of Evidence: 4 - Case-control studies, or “poor or non-independent reference standard

BLUF

This study conducted by the University of Washington (UW) and Stanford University retested a percentage of 20,912 patients who initially tested negative for SARS-CoV-2 via RT-PCR between March 2nd, 2020 to April 7th, 2020. They were able to retest patients whose symptoms were persistent/worsening (Figure 1) and found that of the 4.1% of the patients from UW and 2.6% from Stanford they retested, 3.5% of these cases (22 patients) returned positive within 7 days, suggesting an initial false negative test that turned positive after a mean of 4 days.

ABSTRACT

Using data for 20,912 patients from two large academic health systems, we analyzed the frequency of SARS-CoV-2 RT-PCR test-discordance among individuals initially testing negative by nasopharyngeal swab who were retested on clinical grounds within 7 days. The frequency of subsequent positivity within this window was 3.5% and similar across institutions.

FIGURES

Figure 1

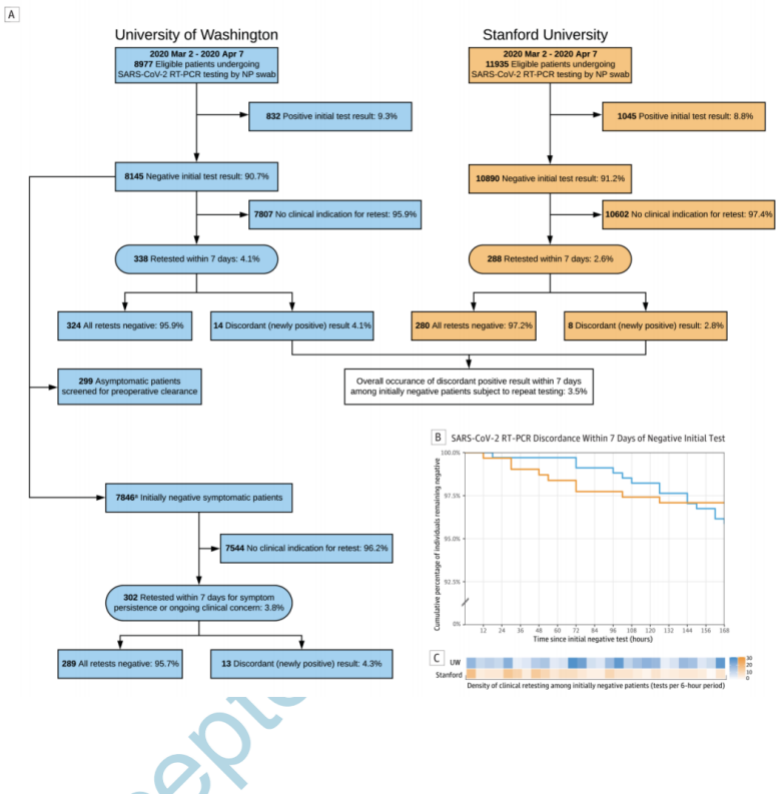


Figure 1. Identification of patients initially testing negative for SARS-CoV-2 and outcomes of repeat testing. A. The primary measure was the occurrence of a discordant (newly positive) result within 7 days. A subgroup analysis excluding asymptomatic patients screened for surgical clearance at the University of Washington yielded similar results. B. Among patients initially testing negative for SARS-CoV-2 by RT-PCR of a nasopharyngeal swab, over 95% of patients at both UW (blue) and Stanford (orange) subjected to retesting

remained negative on subsequent tests performed within 7 days. C. Retesting of initially negative individuals occurred at varied intervals across the 7-day period of observation.

DEVELOPMENTS IN DIAGNOSTICS

A NEW AND RAPID APPROACH FOR DETECTING COVID-19 BASED ON S1 PROTEIN FRAGMENTS

Li H, Liu Z, He Y, Qi Y, Chen J, Ma Y, Liu F, Lai K, Zhang Y, Jiang L, Wang X, Ge J.. Clin Transl Med. 2020 Jun 5. doi: 10.1002/ctm2.90. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or “poor or non-independent reference standard

BLUF

A colloidal gold immunochromatography assay for IgM and IgG antibodies against the receptor-binding domain of SARS-CoV-2 S1 protein is described and evaluated using 214 blood samples, 75 of which were SARS-CoV-2 positive patients from Anhui Provincial Hospital and 139 were healthy control patients from Xuhui Central Hospital spanning from 31 January through 19 February 2020 (Table 1). The assays were tested with IgG and IgM independently as well as together, and it was concluded that a combination of IgM/IgG against the S1 proteins on SARS-CoV-2 had high sensitivity (92.00%), specificity (97.12%), and accuracy (95.33%; Table 2), suggesting the valuable application of this antibody testing kit for diagnosis and epidemic monitoring during the COVID-19 pandemic.

ABSTRACT

The pandemic of novel coronavirus disease 2019 (COVID-19) seriously threatened the public health all over the world. A colloidal gold immunochromatography assay for IgM/IgG antibodies against the receptor-binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S1 protein was established to assess its rapid diagnostic value. We first designed and manufactured all contents of the test cassette of SARS-CoV-2 rapid test kit: the colloidal gold-labeled mouse-antihuman lgM/lgG antibody, the recombinant SARS-CoV-2 antigen, the nitrocellulose membrane control line, and specimen diluents. Furthermore, reverse transcription-polymerase chain reaction (RT-PCR) assay, colloidal gold immunochromatography assay, serological validation of cross reaction with other common viruses, and clinical validation were performed. The kit was finally evaluated by 75 serum/plasma samples of SARS-CoV-2 infection cases and 139 healthy samples as control, with the result of that the sensitivity, specificity, and accuracy for IgM were 90.67%, 97.84%, and 95.33%, whereas for IgG were 69.33%, 99.28%, and 88.79%, respectively; the combination of IgM and IgG could improve the value: 92.00%, 97.12%, and 95.33%, respectively. Therefore, the rapid detection kit has high sensitivity and specificity, especially for IgM&IgG, showing a critical value in clinical application and epidemic control of COVID-19.

FIGURES

Table 1 Basal characteristics of COVID-19 cases and healthy control

	Case group	Control group	Reexamination group
No. of cases	75	139	37
Gender, n (%)			
Male	45 (60.00)	18 (12.95)	21 (56.76)
Female	30 (40.00)	121 (87.05)	16 (43.24)
Age (year), n (%)			
≤16	2 (2.67)	2 (1.44)	1 (2.70)
17-39	24 (32.00)	102 (73.38)	15 (40.54)
40-59	34 (45.33)	27 (19.42)	14 (37.84)
≥60	15 (20.00)	8 (5.76)	7 (18.92)
Median (IQR)	47.5 (20.5)	45.5 (15.5)	60.5 (23)
Sample type, n (%)			
Serum	53 (70.67)	139 (100)	26 (70.27)
Plasma	22 (29.33)	0 (0)	11 (29.73)

Abbreviations: IQR, inter quartile range.

Table 2 Clinical performance of IgM and IgG tested independently or in combination

	COVID-19 IgM/IgG antibody rapid test kit					
	IgM		IgG		IgM and IgG	
Real-time PCR assay	Positive	Negative	Positive	Negative	Positive	Negative
Positive	68	7	52	23	69#	6
Negative	3	136	1	138	4#	135
Subtotal	71	143	53	161	73#	141
Positive percent agreement (sensitivity)	90.67%		69.33%		92.00%	
Negative percent agreement (specificity)	97.84%		99.28%		97.12%	
Positive predictive value (PPV)	95.77%		98.11%		94.52%	
Negative predictive value (NPV)	95.10%		85.71%		95.74%	
False positive rate (FPR)	2.16%		0.72%		2.88%	
False negative rate (FNR)	9.33%		30.67%		8.00%	
Overall agreement (accuracy)	95.33%		88.79%		95.33%	

Note. Positive if any of two markers is positive.

DEVELOPMENTS IN TREATMENTS

DIAGNOSIS AND MANAGEMENT OF THE DRUG HYPERSENSITIVITY REACTIONS IN CORONAVIRUS DISEASE 19

Gelincik A, Brockow K, Çelik GE, Doña I, Mayorga L, Romano A, Soyer Ö, Atanaskovic-Markovic M, Barbaud A, Torres MJ.. Allergy. 2020 Jun 8. doi: 10.1111/all.14439. Online ahead of print.
Level of Evidence: 1 - Review / Literature Review

BLUF

This literature review compiles information regarding hypersensitivity reactions for drugs that are either being investigated in vitro or in clinical trials for the treatment of COVID-19, including antivirals and other agents with the potential for off-label use (Tables 2 and 3). It is vital for providers to differentiate these drug hypersensitivity reactions from the skin manifestations associated with COVID-19 and other viral infections (Table 1) in order to recognize and treat these reactions in a timely manner.

ABSTRACT

Coronavirus disease 2019 (COVID-19), a respiratory tract infection caused by a novel human coronavirus, the severe acute respiratory syndrome coronavirus 2, leads to a wide spectrum of clinical manifestations ranging from asymptomatic cases to patients with mild and severe symptoms, with or without pneumonia. Given the

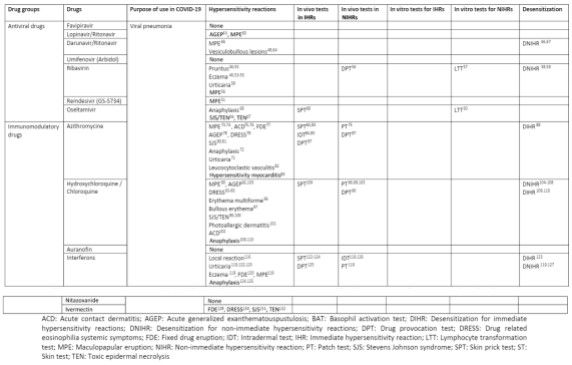
huge influence caused by the overwhelming COVID-19 pandemic affecting over three million people worldwide, a wide spectrum of drugs is considered for the treatment in the concept of repurposing and off-label use. There is no knowledge about the diagnosis and clinical management of the drug hypersensitivity reactions that can potentially occur during the disease. This review brings togetherall the published information about the diagnosis and management of drug hypersensitivity reactions due to current and candidate off-label drugs and highlights relevant recommendations. Furthermore, it gathers all the dermatologic manifestations reported during the disease for guiding the clinicians to establish a better differential diagnosis of drug hypersensitivity reactionsin the course of the disease.

FIGURES

Table 1. Skin manifestations reported associated with COVID-19

Manifestation	Clinical description	Relative frequency*	Similarity to skin rashes of other infections	References
1. Skin manifestations similar to those in other viral infections				
Acute urticaria	Sudden appearance of wheals with a fleeting nature. Continual appearance and disappearance of new lesions is characteristic.	19%	Unspecific for COVID-19; infections are common elicitors for acute urticaria	4,22,23,31
Maculopapular exanthem ("erythematous rash")	Acute erupting, widespread distribution of multiple small, round to oval erythematous macules and/or papules with different degrees of confluence. Mostly trunk, low pruritus.	47%	Unspecific for COVID-19; infections are common elicitors for maculopapular exanthem	4,21,22,24,31,32
Varicella-like exanthem ("chickenpox-like rash")	Monomorphic papulovesicular skin eruption. Erythematous papules and vesicles bilaterally and symmetrically mostly on the trunk.	9%	May be more specific for COVID-19, vesicles are quite uncommon for virus exanthems and more specific for varicella	4,22,25,26
Symmetrical intertriginous exanthem	Flexural erythematous maculopapular exanthem on axillary lesions and trunk +/-antecubal fossae.	Individual case reports	Untypical for infectious exanthems	30
2. Skin manifestations associated with vascular pathologies				
Purpuric exanthem ("purpuric rash")	Skin rash with petechiae.	Individual case reports	Untypical for infectious exanthems,except e.g. Parvovirus B19	22,33
Erythema ab igne ("livedo reticularis")	Transient macular erythema in a broad reticular pattern on thigh unilaterally.	6% together with cutaneous acroischemia	Untypical for infectious exanthems	34
Chilblain-like lesions	Acute-onset, violaceous, infiltrated and painful plaques on the toes and lateral feet. Vesicles and erosions may be present.	19%	Untypical for infectious exanthems	22, 35,36,37
Cutaneous acro-ischemia	Finger and toe cyanosis, purpura, hematoma, skin bulla and dry gangrene.	6% together with Erythema ab igne ("livedo reticularis")	Typical for severely ill patients with sepsis,	38,39

*Relative frequency in percent of this skin manifestations associated with COVID-19 infections according to Ref 26. In cases, where no numbers are given, only individual case reports do exist.



Drug groups	Drugs	Purpose of use in COVID-19	Hypersensitivity reactions	In vivo tests in IHRs	In vivo tests in NIHRs	In vitro tests for IHRs	In vitro tests for NIHRs	Desensitization
Antiviral drugs	Favipiravir	Viral pneumonia	None					
	Lopinavir/Ritonavir		AGEP[7], MPE[10]					
	Darunavir/Ritonavir		MPE[10] Vesiculobullous lesions[40,54]					DNIHR [54,57]
	Umifenovir (Arbidol)		None					
	Ribavirin		Pruritus[46,55] Eczema[46,55,59] Urticaria[59] MPE[54]		DPT[55]		LTT[57]	DNIHR [58,59]
	Remdesivir (GS-5734)		MPE[54]					
	Oseltamivir		Anaphylaxis[60] SJS/TEN[60], TEN[61]		SPT[60]		LTT[61]	
Immunomodulatory drugs	Azithromycine		MPE[54,55], ACD[55,56], FDE[57] AGEP[58], DRESS[59] SJS[60,61] Anaphylaxis[72] Urticaria[74] Leucocytoclastic vasculitis[80] Hypersensitivity myocarditis[81]		SPT[60,61] IDT[60,61] DPT[57]		PT[74] DPT[57]		DNIHR [82]
	Hydroxychloroquine / Chloroquine		MPE[54], AGEP[83,122] DRESS[59,83] Erythema multiforme[84] Bullous erythema[87] SJS/TEN[88,120] Photoallergic dermatitis[89] ACD[120] Anaphylaxis[108,118]		SPT[118]		PT[84,88,120] DPT[88]		DNIHR [84,108] DNIR [88,118]
	Auranofin		None					
	Interferons		Local reactions[110] Urticaria[108,109,110] Eczema[111], FDE[107], MPE[119] Anaphylaxis[104,120]		SPT[102-104] DPT[105]		IDT[105,120] PT[119]		DNIR [121] DNIHR [118,127]
	Nitazoxanide		None					
	Ivermectin		FDE[59], DRESS[59], SJS[59], TEN[59]					

ACD: Acute contact dermatitis; AGEP: Acute generalized exanthematouspustulosis; BAT: Basophil activation test; DIHR: Desensitization for immediate hypersensitivity reactions; DNIHR: Desensitization for non-immediate hypersensitivity reactions; DPT: Drug provocation test; DRESS: Drug related eosinophilia systemic symptoms; FDE: Fixed drug eruption; IDT: Intradermal test; IHR: Immediate hypersensitivity reaction; LTT: Lymphocyte transformation test; MPE: Maculopapular eruption; NIHR: Non-immediate hypersensitivity reaction; PT: Patch test; SJS: Stevens Johnson syndrome; SPT: Skin prick test; ST: Skin test; TEN: Toxic epidermal necrolysis

Table 2: Hypersensitivity reactions due to drugs with antiviral properties investigated for the treatment of COVID-19 in clinical trials or in vitro studies

WEIGHT-BASED DOSING OF PEMBROLIZUMAB EVERY 6 WEEKS IN THE TIME OF COVID-19

Goldstein DA, Ratain MJ, Saltz LB.. JAMA Oncol. 2020 May 27. doi: 10.1001/jamaoncol.2020.2493. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

The authors discuss the benefits in adopting a weight-based dosage of Pembrolizumab in the treatment of COVID-19 based on pharmacokinetics data from the Canadian Agency of Drugs and Technologies in Health.
- Specifically: "a dosage of 4 mg/kg every 6 weeks, with a cap at 400 mg. Given that the fixed dosing every 6 weeks is based on pharmacokinetic data, we similarly propose weight-based dosing based on pharmacokinetic data."
The authors posit that weight-based dosage would decrease patient exposure to SARS-CoV-2, maintain equivalent efficacy, and decrease financial effects for patients because of a more limited, yet specific administration of the drug.

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.
Level of Evidence: 5 -

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

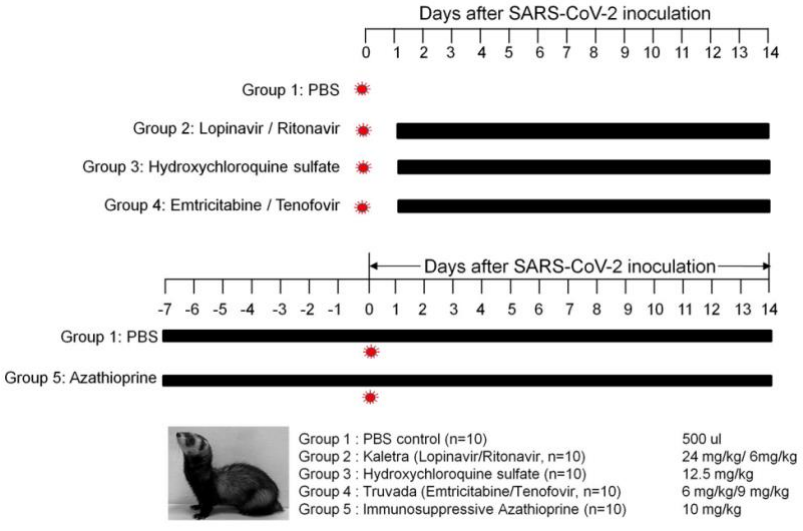


Figure 1. Schedule of drug treatments and SARS-CoV-2 infection in ferrets. To induce the immunosuppression condition, PBS or azathioprine was orally administered to ferrets for the entire experimental period. All groups of ferrets were administered each drug or PBS via oral gavage once, starting at 1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

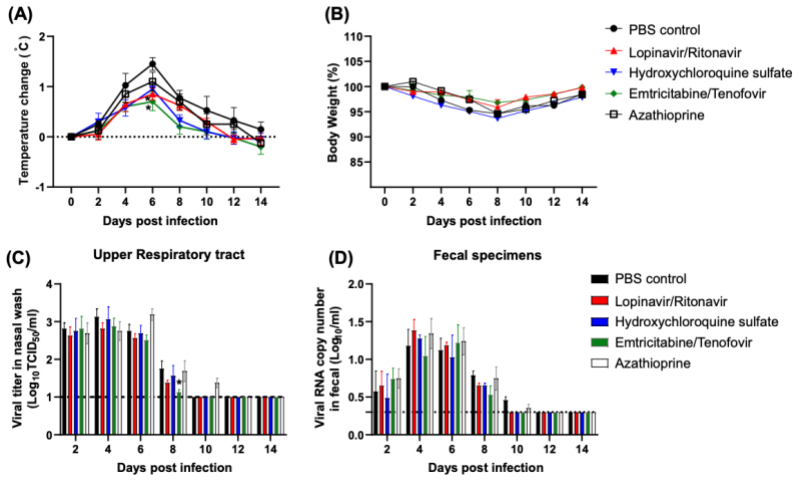
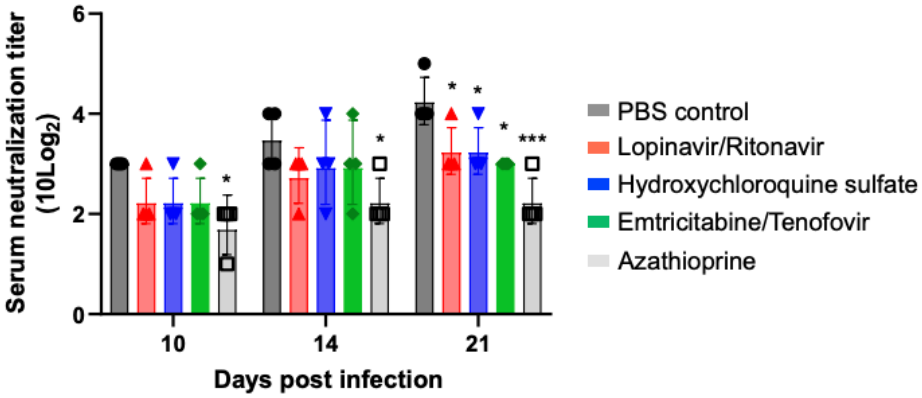


Figure 3. Comparison of serum neutralization antibody titers of drug-treated ferrets. Blood was collected at 10, 14, and 21 dpi from each group of ferrets (n=4), and serum neutralization antibody titers were measured in Vero cells. The serum neutralization titer of each ferret is represented by an individual 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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RESOURCES

COVID-19 AND THE FUTURES OF MACHINE LEARNING

Arga KY.. OMICS. 2020 Jun 8. doi: 10.1089/omi.2020.0093. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

This perspective written by an engineering faculty in Istanbul, Turkey explains that machine learning-driven intelligent algorithms may serve to help develop responses to the COVID-19 pandemic. In brief, the author explains that machine learning can help forecast COVID-19 health outcomes in diverse geographical and health systems settings as well as help reduce diagnostic errors and unnecessary use of diagnostic tools.

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