The Daily COVID-19 Literature Surveillance Summary

September 02, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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

EXECUTIVE SUMMARY

Epidemiology

- A study of 47 COVID-19 patients in JiangXi Province, China found that patients whose SARS-CoV-2 oropharyngeal nucleic acid tests turned negative slowly (over more than one week) were significantly more fatigued than patients whose tests turned negative rapidly (within one week), suggesting fatigue may be a clinical sign of persistent active SARS-CoV-2 infection.
- A case series found that out of 3,375 patients with Systemic Lupus Erythematosus (SLE), 3 were infected with COVID-19. All 3 were treated with various immunosuppressive therapies (including hydroxychloroquine) and needed escalating treatment regimens in conjunction with COVID-19 infection treatment. However, the low number of total infections among SLE patients suggests there is not a major burden of COVID-19 infection among the SLE patient population.

Management

- Cardiologists and Infectious Disease physicians analyzed the effect of hydroxychloroquine + moxifloxacin (HCQ + MOX) on corrected QT interval (QTc) in 76 COVID-19 pneumonia patients and found that QTc increased from a mean baseline of 424 ms to 442 ms after 5 days; however, there were no incidences of atrial or ventricular arrhythmia during the short, 5 day study.
- Obstetricians at Johns Hopkins reviewed 20 studies of COVID-19 positive pregnant women in the UK (n=618) and France (n=413) and found that severe COVID-19 is more likely in pregnant women than non-pregnant women and trans-placental infection of SARS-CoV-2 is rare but possible. Overall, however, the effects of fetal SARS-CoV-2 infection are poorly understood at this time and warrant further study.

R&D: Diagnosis & Treatments

- This review conducted by nanophotonic scientists from Spain provides an overview of current COVID-19 diagnostic techniques, while discussing optical biosensors and their potential as new COVID-19 diagnostic tools for intact virus detection, nucleic acid detection, and serological tests. The researchers argue that the application of nanophotonic biosensors for rapid point-of-care diagnosis and large-scale screening could support more efficient patient isolation and control of COVID-19 transmission.
- Italian immunologists conducted an observational longitudinal study of 20 admitted COVID-19-positive patients treated with baricitinib compared to a control group of 56 patients. They found that baricitinib modulates the immune system by inhibiting the over-tuned inflammatory response in COVID-19, including IL-1beta, IL-6, and TNF-alpha. The authors believe this trial of baricitinib exhibits promising results toward dampening the progression of COVID-19 infection to severe disease.

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CURRENT COVID-19 GUIDELINES FOR RESPIRATORY PROTECTION OF HEALTH CARE WORKERS ARE INADEQUATE

MacIntyre CR, Ananda-Rajah M, Nicholls M, Quigley AL.. Med J Aust. 2020 Aug 31. doi: 10.5694/mja2.50752. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

In this perspective article, the authors from numerous medical education centers in Sydney and Melbourne, Australia, call to prioritize nationally regulated occupational health and safety of health workers in Australia, given their high risk of airborne COVID-19 infection. They advocate for transparent reporting of all health worker acquired COVID-19 infection by an independent panel, appoint COVID-19 to the National Notifiable Diseases Surveillance System to flag health care worker status with infections, implement a national protocol of source infection in order to improve and standardized transparency, and apply national guidelines for use of a respirators for health workers caring for patients with COVID- 19.

CLINICAL CHARACTERISTICS AND FACTORS AFFECTING THE DURATION OF POSITIVE NUCLEIC ACID TEST FOR PATIENTS OF COVID-19 IN XINYU, CHINA

Lu J, Yin Q, Li Q, Fu G, Hu X, Huang J, Chen L, Li Q, Guo Z.. J Clin Lab Anal. 2020 Aug 29:e23534. doi: 10.1002/jcla.23534. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective cohort study of 47 COVID-19 patients conducted at XinYu People's Hospital in JiangXi Province, China in February 2020 found patients whose SARS-CoV-2 oropharyngeal nucleic acid tests (NATs) turned negative slowly (more than one week) were significantly more fatigued than patients whose NATs turned negative rapidly within one week (p = 0.03), suggesting fatigue may be a clinical sign of persistent active SARS-CoV-2 infection.

ABSTRACT

BACKGROUND: The outbreak of a new coronavirus, COVID-19, which was earliest reported in Wuhan, China, is now transmitting throughout the world. The aim of this study was to articulate the clinical characteristics of COVID-19 and to reveal possible factors that may affect the persistent time of positive SARS-CoV-2 nucleic acid test, so as to identify which patients may deteriorate or have poor prognoses as early as possible. METHODS: Retrospective cohort study was carried out on 47 patients with confirmed COVID-19 infection admitted to XinYu People's Hospital of JiangXi Province. Epidemiological, demographic, clinical, laboratorial, management, treatment, and outcome data were also collected and analyzed. RESULTS: In this study, patients were divided into two groups based on whether their SARS-CoV-2 nucleic acid tests in respiratory specimens turn negative within (Group Rapid or Group R) or over (Group Slow or Group S) a week. There was no significant difference in age, sex, travel or exposure history, and smoking history between the two groups. Forty-two patients had been observed with comorbidities. Similar clinical manifestations, for instance fever, cough, sputum, and fatigue, have been observed among patients in both groups, except that patients in Group S were obviously more likely to get fatigue than patients in Group R. Both groups had shown decrease in white blood cell or lymphocyte counts. Chest X-ray or computed tomography scan showed unilateral or bilateral infiltrates. High proportion in both groups has used nasal cannula (89.47% vs. 85.71%) to inhale oxygen. 10.53% of Group S have applied high-flow nasal cannula, while Group R used none. The current treatment is mainly antibiotics, antiviral, and traditional Chinese medicine, while a couple of patients has used methylprednisolone. Only 1 patient out of both groups got even worse despite this active treatment. CONCLUSION: Clinical characteristics of COVID-19 include the exposure history and typical systemic symptoms such as fever, cough, fatigue, decreased WBC and lymphocyte counts, and infiltration in both lower lobes on CT imaging. Among them, fatigue appears to be an important factor that affects the duration of positive SARS-CoV-2 nucleic acid test in respiratory specimens.

COVID-19 INFECTION IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: DATA FROM THE ASIA PACIFIC LUPUS COLLABORATION

Cho J, Kandane-Rathnayake R, Louthrenoo W, Hoi A, Golder V, Chen YH, Luo SF, Wu YJ, Hamijoyo L, Lau CS, Navarra S, Zamora L, Tee M, Flora A Jr, Li ZG, An Y, Sockalingam S, Katsumata Y, Harigai M, Hao Y, Zhang Z, Kikuchi J, Takeuchi T, Basnayake D, Goldblatt F, Chan M, Ng KPL, Bae SC, Oon S, O'Neill S, Gibson K, Kumar S, Law AHN, Tugnet N, Tanaka Y, Nikpour M, Morand E, Lateef A.. Int J Rheum Dis. 2020 Aug 25. doi: 10.1111/1756-185X.13937. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A case series was conducted on 3 patients of the Asia Pacific Lupus Collaboration (APLC) patient cohort (n=3375) that were infected with COVID-19 (Table 1). All 3 were treated with various immunosuppressive therapies (including hydroxychloroquine) and needed escalating treatment regimens in conjunction with COVID-19 infection treatment. However, the researchers report only 3 infectious cases out of 3375 SLE patients in the APLC, suggesting there is not a major burden of COVID-19 infection among SLE patient population.

SUMMARY

Case 1: 58 y/o Japanese female with stable SLE maintained with prednisolone monotherapy (5mg) tested positive for COVID-19 despite being asymptomatic. Her labs revealed severe thrombocytopenia and hypocomplementemia, which the authors do not believe to have been caused by the infection since she was asymptomatic. She was treated with hydroxychloroquine and an increased dose of prednisolone (20mg). She was discharged after the thrombocytopenia improved.

Case 2: 32 y/o Filipino female with SLE and history of poor treatment adherence (hydroxychloroquine, mycophenolate mofetil, and prednisolone 30 mg daily), presented with active lupus nephritis. Due to distance from the clinic, she was following up with her rhematologist via phone consultations. She was started on hemodialysis at her local hospital due to deteriorating renal function. Her rheumatologist subsequently received word that she had passed from COVID-19 pneumonia, with limited access to details surrounding her case.

Case 3: 29 y/o Filipino female with HTN, CKD, and SLE maintained with a regimen of hydoxychloroquine, azathioprine, and low-dose prednisolone presented with bilateral COVID-19 pneumonia and peripheral edema, complicated by active lupus nephritis which required an increase in prednisolone to 50 mg. Once her condition improved and stabilized, she was discharged.

FIGURES

TABLE 1 Number of COVID-19 cases and systemic lupus erythematosus (SLE) patients in the Asia Pacific Lupus Collaboration

Center	No. of patients with COVID-19	Total number of SLE patients in cohort	Proportion of anti-malarial users at last visit (%)
Monash Health, Melbourne, Australia	0	310	85.2
Royal Adelaide Hospital and Flinders Medical Centre, Adelaide, Australia	0	60	88.5
St. Vincent's Hospital, Melbourne, Australia	0	48	85.4
Liverpool Hospital, Sydney, Australia	0	40	85.0
Peking University First Hospital, Beijing, China	0	183	82.0
People's Hospital Peking University Health Science Center, Beijing, China	0	98	96.9
Queen Mary Hospital, The University of Hong Kong, Pok Fu Lam, Hong Kong	0	211	64.2
Padjadjaran University/ Hasan Sadikin General Hospital, Bandung, Indonesia	0	269	35.3
Tokyo Women's Medical University, Tokyo, Japan	0	137	23.4
University of Occupational and Environmental Health, Japan	0	13	23.1
Keio University, Tokyo, Japan	1	84	25.0
Hanyang University Hospital for Rheumatic Diseases, Republic of Korea	0	51	86.3
University of Malaya, Kuala Lumpur, Malaysia	0	176	84.1
Greenlane Clinical Centre, Auckland District Health Board, Auckland, New Zealand	0	26	100.0
Middlemore Hospital, Auckland, New Zealand	0	40	90.0
North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand	0	55	81.2
University of Santo Tomas Hospital, Manila, Philippines	1	206	88.8
University of The Philippines, Philippines	1	[a]	[a]
National University Hospital, Singapore	0	273	91.2
Tan Tock Seng Hospital, Singapore	0	58	89.7
Singapore General Hospital, Singapore	0	30	[a]
Teaching Hospital, Kandy, Sri Lanka	0	83	77.1
Chang Gung Memorial Hospital, Taiwan	0	298	66.8
Taichung Veterans General Hospital, Taiwan	0	303	90.4
Chiang Mai University Hospital, Chiang Mai, Thailand	0	323	19.8

[a]New APLC centers, pending full data.

Table 1: Number of COVID-19 cases and systemic lupus erythematous (SLE) patients in the Asia Pacific Lupus Collaboration.

ADIPOSITY IS THE CRUCIAL ENHANCER OF COVID-19

Yanai H.. Cardiol Res. 2020 Oct;11(5):353-354. doi: 10.14740/cr1118. Epub 2020 Aug 1.
Level of Evidence: Other - Review / Literature Review

BLUF

A letter to the editor by Hidekatsu Yanai, an endocrinologist from Japan, suggests adiposity enhances COVID-19 disease severity via increased ACE2 and DPP4 expression in adipose tissue, alveolar epithelial cells, and liver tissue, facilitating SARS-CoV-2 entry via interaction of S1 spike protein and DPP4 in obese populations. Obesity-induced insulin resistance increases endothelial dysfunction, coagulopathy/thrombosis, and cytokine storm (via IL-6, TNF alpha, plasminogen activator inhibitor-1, and VWF), which the author argues are further worsened in COVID-19, leading to increased ICU admissions and assisted ventilation among obese populations (Figure 1).

FIGURES

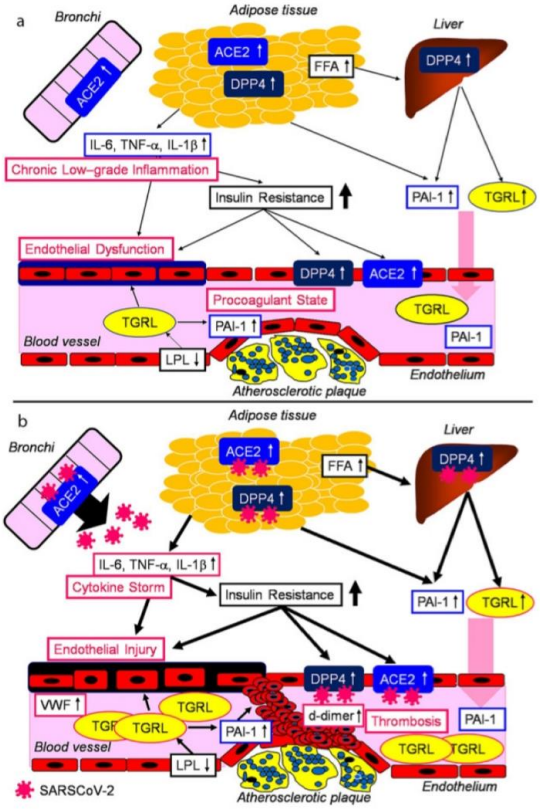

Figure 1: Potential risks for severe COVID-19 in obesity before SARS-CoV-2 infection (a) and the mechanisms for adiposity-mediated exacerbation of COVID-19 (b). COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE: angiotensin-converting enzyme; DPP4: dipeptidyl peptidase 4; FFA: free fatty acids; IL: interleukin; LPL: lipoprotein lipase; PAI-1: plasminogen activator inhibitor-1; TGRL: triglyceride-rich lipoprotein; TNF-α: tumor necrosis factor-alpha; VWF: von Willebrand factor.

CRITICAL CARE

EFFECTS OF SHORT-TERM HYDROXYCHLOROQUINE PLUS MOXIFLOXACIN THERAPY ON CORRECTED QT INTERVAL AND TP-E INTERVAL IN PATIENTS WITH COVID-19

Afsin A, Ecemis K, Asoglu R.. J Clin Med Res. 2020 Sep;12(9):604-611. doi: 10.14740/jocmr4288. Epub 2020 Aug 15.
Level of Evidence: 3 - 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.)

BLUF

Cardiologists and Infectious Disease physicians analyzed the effect of hydroxychloroquine + moxifloxacin (HCQ + MOX) on corrected QT interval (QTc) in 76 COVID-19 pneumonia patients seen at Kahta State Hospital in Adiyaman, Turkey between March and April 2020. Results showed:

- QTc increased from a mean baseline of 424 ms to 442 ms after 5 days (P<0.0001) (Table 3).
- cTp-e interval increased from 72 ms to 75 ms (P<0.0001) (Table 3).
- There were no incidences of atrial or ventricular arrhythmia short-term (5 days) (Table 4).

The authors recommend this HCQ + MOX combination therapy be administered in patients with possible COVID-19 pneumonia patients short-term and with close ECG monitoring in consideration of possible ventricular arrhythmia.

ABSTRACT

Background: Limited data are available regarding hydroxychloroquine (HCQ) and moxifloxacin (MOX) in patients with possible coronavirus disease 2019, (COVID-19). Both drugs may increase risk of malignant ventricular arrhythmias associated with prolongation of QT interval. Methods: A total of 76 subjects with chest tomography findings compatible with COVID-19 pneumonia were enrolled in the study. Standard 12-lead electrocardiogram (ECG) was repeated on days 2 and 5 in patients receiving a combination of HCQ + MOX. Heart rate, QT interval, Tp-e interval, and Tp-e/QT ratio were measured. Results: The mean age of the patients was 61.7 +- 14.8 years and 54% had hypertension. Compared to day 2, ECG on day 5 showed significant increases in QT interval (370.8 +- 32.5 vs. 381.0 +- 29.3, respectively, P = 0.001), corrected QT (QTc) interval (424 (403 - 436) vs. 442 (420 - 468), respectively, P < 0.001), Tp-e interval (60 (55 - 70) vs. 65 (57 - 75), respectively, P < 0.001), cTp-e interval (72.2 +- 12.9 vs. 75.4 +- 12.7, respectively, P < 0.001). Moreover, a slight decrease in Tp-e/QT ratio was observed (0.17 +- 0.03 vs. 0.17 +- 0.02, P = 0.030). QTc was > 500 ms in 5% of the patients, and 8% of patients had an increase in QTc interval > 60 ms. Tp-e/QT ratio was > 0.23 in 4% of patients. Five patients died due to pulmonary failure without evidence of ventricular arrhythmia. No ventricular arrhythmia events, including torsades de pointes (TdP), were observed. Conclusions: HCQ + MOX combination therapy led to increases in QTc interval, Tp-e interval, and cTp-e interval. However, this therapy did not cause ventricular arrhythmia in the short-term observation.

Table 3

Electrocardiographic Parameters of the Study Group (N = 76)

	2nd day	5th day	P
Heart rate (beats/min)	78 (72 - 90)	80 (73 - 90)	0.127
QT interval (ms)	370.8 ± 32.5	381.0 ± 29.3	0.001
QTc interval (ms)	424 (403 - 436)	442 (420 - 468)	< 0.001
Tp-e interval (ms)	60 (55 - 70)	65 (57 - 75)	< 0.001
cTp-e interval (ms)	72.2 ± 12.9	75.4 ± 12.7	< 0.001
Tp-e/QT ratio	0.17 ± 0.03	0.17 ± 0.02	0.03
Tp-e/QTc ratio	0.17 ± 0.03	0.17 ± 0.03	0.228

QTc: corrected QT; Tp-e: transmural dispersion of repolarization; cTp-e: corrected transmural dispersion of repolarization.

Table 3 presents the ECG parameters of the study group. There was no statistically significant change in heart rate during follow-up. ECG showed statistically significant increases in QT interval (370.8 ± 32.5 vs. 381.0 ± 29.3, respectively, P = 0.001), QTc interval (424 (403 - 436) vs. 442 (420 - 468), respectively, P < 0.001), Tp-e interval (60 (55 - 70) vs. 65 (57 - 75), respectively, P < 0.001), and cTp-e interval (72.2 ± 12.9 vs. 75.4 ± 12.7, respectively, P < 0.001) on day 5 compared to day 2. Furthermore, the ratio of Tp-e/QT (0.17 ± 0.03 vs. 0.17 ± 0.02, respectively, P = 0.030) was decreased significantly from day 2 to day 5.

Table 4

Increased Ventricular Arrhythmia Risk and Adverse Events in Study Population (N = 76)

	N	%	Mean ± SD
5th day with QTc interval > 500 ms	4	5	516.3 ± 13.2
Increase in the QTc interval of > 60 ms	10	8	70.4 ± 12.4
Tp-e interval ≥ 110 ms	0	0	-
cTp-e interval ≥ 110 ms	0	0	-
Tp-e/QT ratio > 0.23	3	4	0.24 ± 0.07
Tp-e/QTc ratio > 0.23	0	0	-
Atrial arrhythmia	0	0	-
Torsades de pointes	0	0	-
Nonsustained ventricular tachycardia	0	0	-
Sustained ventricular tachycardia	0	0	-

QTc: corrected QT; Tp-e: transmural dispersion of repolarization; cTp-e: corrected transmural dispersion of repolarization; SD: standard deviation.

In clinical follow-up, four (5%) patients had QTc > 500 ms, while 10 (8%) had an increase in QTc interval > 60 ms. Three (4%) patients had Tp-e/QT ratio > 0.23. No atrial arrhythmia and ventricular arrhythmia events, including TdP, were observed in any patient (Table 4).

SEVERITY OF COVID-19 IN PREGNANCY: A REVIEW OF CURRENT EVIDENCE

Kucirka LM, Norton A, Sheffield J.. Am J Reprod Immunol. 2020 Aug 31:e13332. doi: 10.1111/aji.13332. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

In May 2020, physicians at the Department of Gynecology and Obstetrics at Johns Hopkins School of Medicine reviewed 20 studies, including two large national studies of COVID-19 positive pregnant women in the UK (n=618) and France (n=413), and found that severe COVID-19 is more likely in pregnant women than non-pregnant women. This suggests that pregnancy is a risk factor for severe COVID-19 requiring hospitalization, and pre-term delivery may be indicated in severe cases. Trans-placental infection of SARS-CoV-2 is rare but possible; the effects of fetal SARS-CoV-2 infection are poorly understood at this time and warrant further study.

ABSTRACT

Coronavirus disease 19 (COVID-19), has recently emerged as a major threat to human health. Infections range from asymptomatic to severe (increased respiratory rate, hypoxia, significant lung involvement on imaging) or critical (multi-organ failure or dysfunction or respiratory failure requiring mechanical ventilation or high flow nasal canula). Current evidence suggests that pregnancy women are at increased risk of severe disease, specifically the need for hospitalization, ICU admission and mechanical ventilation, and the already complex management of infection with an emerging pathogen may be further complicated by pregnancy. The goal of this review is to provide an overview of what is known about the clinical course of COVID-19 in pregnancy, drawing on 1) experience with other coronaviruses such as SARS and MERS, 2) knowledge of immunologic and physiologic changes in pregnancy and how these might impact infection with SARS-CoV-2 and 3) the current literature reporting outcomes in pregnant women with SARS-CoV-2. We also briefly summarize considerations in management of severe COVID-19 in pregnancy.

COVID-19 COAGULOPATHY IN PREGNANCY: CRITICAL REVIEW, PRELIMINARY RECOMMENDATIONS AND ISTH REGISTRY - COMMUNICATION FROM THE ISTH SSC FOR WOMEN'S HEALTH

Kadir RA, Kobayashi T, Iba T, Erez O, Thachil J, Kazi S, Malinowski AK, Othman M.. J Thromb Haemost. 2020 Aug 26. doi: 10.1111/jth.15072. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

A review by international experts in obstetrics/gynecology and hematology affiliated with the International Society on Thrombosis and Hemostasis (ISTH) Subcommittee for Women's Health Issues examined hemostatic parameters for COVID-19 coagulopathy in non-pregnant patients (Table 2) and outcomes of COVID-19 during pregnancy as a basis to develop recommendations for management of COVID-19 coagulopathy in pregnancy (Table 3), while also establishing an international registry for data collection on COVID-19-affected pregnancies. Authors suggest these developments could provide clinical guidance to assist in patient care of COVID-19-affected pregnant women with coagulopathy or thrombotic complications and contribute to advancing knowledge in this area.

ABSTRACT

BACKGROUND: Novel coronavirus (SARS-CoV-2), which causes COVID-19, has thus far affected over 15 million individuals, resulting in over 600,000 deaths worldwide, and the number continues to rise. In a large systematic review and meta-analysis of the literature including 2,567 pregnant women, 7% required intensive care admission, with a maternal mortality ~1% and perinatal mortality below 1%. There has been a rapid increase in publications on COVID-19 associated coagulopathy, including disseminated intravascular coagulopathy (DIC) and VTE, in the non-pregnant population, but very few reports of COVID-19 coagulopathy during pregnancy; leaving us with no guidance for care of this specific population. METHODS: This is a collaborative effort conducted by a group of experts which was reviewed, critiqued and approved by the ISTH Subcommittee for Women's Health Issues in Thrombosis and Hemostasis. A structured literature search was conducted, and the quality of current and emerging evidence was evaluated. Based on the published studies in the non-pregnant and pregnant population with a moderate to high risk of bias as assessed by Newcastle-Ottawa scale and acknowledging the absence of data from

randomized clinical trials for management of pregnant women infected with SARS-CoV-2, a consensus in support of a guidance document for COVID-19 coagulopathy in pregnancy was identified. RESULTS AND CONCLUSIONS: Specific haemostatic issues during pregnancy were highlighted, preliminary recommendations to assist in the care of COVID-19-affected pregnant women with coagulopathy or thrombotic complications were developed. An international registry to gather data to support the management of COVID-19 and associated coagulopathy in pregnancy was established.

FIGURES

	Normal Values	Pathological alterations in COVID-19		ISTH Interim Guidance and Expert Opinion[24,25,26]
PT	9.9- 13.1 Sec.	Prolonged in 50% of non-survivors but only 7% of survivors (p< 0.0001)[30]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy • Admit if PT is prolonged • Monitor PT at least twice daily in all hospital admitted patients • In bleeding patients (rare in COVID-19), maintain PT ratio <1.5
APTT	24-36 Sec.	No significant changes at admission but significant prolongation of PT and not APTT at day 4[67]		
D-Dimer	0-0.5 µg/mL	>0.5 µg/mL is associated with severe disease compared[86] significantly elevated in critically ill patients compared to non[87]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy • Admit if markedly raised • Monitor at least twice daily in all hospital admitted patients
Platelet	150-450 x 10^9/l	<100x109/l is associated with severe disease or in critically ill[30,87,88] Increased platelet counts in severe cases due to cytokine storm[43,89]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy • Admit if count <100x • Monitor at least twice daily in all hospital admitted patients • In bleeding patients (rare in COVID-19), maintain count >50 x 10^9 /L
Fibrinogen	2-4 g/L	Increased > 4 upon admission with significant difference between survivors and non survivors[30,67]		• Measure in all patients with COVID-19 to identify and monitor coagulopathy and admit if >2 g/L • Monitor at least twice daily in all hospital admitted patients • In bleeding patients (rare in COVID-19), maintain >2.0 g/L
FDPs		Increased[30,90]		
Lupus Anticoagulant		Positive[71]		
VTE risk		Number of patients admitted to ICU	Number (percentage) of patient developed VTE	• Prophylactic LMWH in all patients (including non-critically ill) who require hospital admission, in the absence of contraindications (active bleeding and platelet count less than 25 x 109 /L). Abnormal PT or APTT not a contraindication. • Consider VTE in the setting of rapid respiratory deterioration and/or high D-dimer • Consider CT angiography or ultrasound of the venous system of the lower extremities to evaluate • Presence/absence of VTE
		184[64,91]	28 (27%)	
		75[65,66]	35 (47%)	
		150[71]	64 (42%)	
		48[75]	8 (16.7%)	

Table 2. Haemostatic parameters in COVID-19 coagulopathies in non-pregnant patients. A summary of published studies, ISTH guidance, and expert opinion for recognition and management in hospitalized patients.

Laboratory parameter	Normal Values				Possible alterations in pregnancy with COVID-19	Potential prognostic markers	*Levels reported in severe COVID-19 outside pregnancy
	Third trimester of Pregnancy			Non-pregnant women			
PT	8.5-11.0 Sec.			9.4-16.0 Sec.	↑ - COVID coagulopathy or DIC - PPH	Yes	• 3 sec extension • >6 in 47.6% of non-survivors with DIC compared to 3 in survivors
APTT	25.5 - 42.5 Sec.			27.0 - 37.0 Sec.	↑ - COVID coagulopathy or DIC - PPH - Consumption events ↓ - FVII release	Yes	5 sec extension
D-dimer	0.16 - 1.7 µg/mL				↑ - COVID coagulopathy or DIC - Acute phase reactant - VTE - Trauma - Liver/renal disease	Yes (severe disease and in hospital mortality Cut off: 2.0 µg/mL)	• 2.12 in non survivors Vs 0.61 in survivors • >3 in 86% non-survivors with DIC
Platelet count Mean (range)	Third trimester	Delivery	PP		↓ - COVID coagulopathy or DIC - PPH ↑ - Cytokines induced	Yes Thrombo-cytopenia (severe disease + mortality)	• <100 in 33% of non-survivors • <50 in 24% non-survivors with DIC
	225 (57-505) X 10^9 /L	217 (63-552) X 10^9 /L	264 (91-575) X 10^9/L	273 (111–999) X 10 ^{9}/L			
Fib.	2.48 - 5.06 g/L			2.5 - 4.0 g/L	↓ - COVID coagulopathy or DIC - PPH ↑ - Acute phase reactant - Inflammation	Yes	• 5.16 in non survivors vs 4.5 in survivors (non signifcant difference) • <1 in 29% non-survivors with DIC
FDPs	<15 µg/mL			3.09 ± 1.96 µg/mL	↑ - COVID coagulopathy or DIC - Acute phase reactant		• 7.6 in non survivors vs 4.0 in survivors

Table 3: Coagulation parameters in normal pregnancy (third trimester) and possible alterations in COVID-19 in association with pregnancy. Please note this table is a guide. Age and Ethnic variations exist and need to be considered. PT: prothrombin time. APTT: activated partial thromboplastin time. Fib: Fibrinogen. FDPs: Fibrin degradation products. VTE: venous thromboembolism. DIC: disseminated intravascular coagulopathy. PP: postpartum.

HOW NANOPHOTONIC LABEL-FREE BIOSENSORS CAN CONTRIBUTE TO RAPID AND MASSIVE DIAGNOSTICS OF RESPIRATORY VIRUS INFECTIONS: COVID-19 CASE

Soler M, Estevez MC, Cardenosa-Rubio M, Astua A, Lechuga LM.. ACS Sens. 2020 Aug 24. doi: 10.1021/acssensors.0c01180. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

This review conducted by nanophotonic scientists from Spain provides an overview of current COVID-19 diagnostic techniques, while discussing optical biosensors and their potential as new COVID-19 diagnostic tools (see summary). Authors argue that application of nanophotonic biosensors for rapid point-of-care (POC) diagnosis and large-scale screening could support more efficient patient isolation and control of COVID-19 transmission.

SUMMARY

Summary of current diagnostics and optical biosensors:
1. Nucleic acid amplification tests (NAATs; i.e. polymerase chain reaction [PCR])
• Benefits: high levels of accuracy and sensitivity
• Limitations: considerably longer sample-to-results time (i.e. from 4 hours to a few days)
2. Rapid antigen diagnostic tests (RADTs):
• Benefits: rapid POC diagnosis and ability for large scale testing
• Limitations: poor positive predictive value (PPV) and very limited sensitivity, especially for adults
3. Lateral flow assays (LFAs):
• Benefits: inexpensive and rapid POC testing
• Limitations: only provide qualitative information (i.e. presence or absence of antibodies), and lack sensitivity and reproducibility.
4. Optical biosensors: viral diagnosis (Table 1), respiratory virus diagnosis (Table 2), and genomic assay (Figure 3)
• Benefits: excellent sensitivity, robustness, quantitative measure, and immunity to electromagnetic interferences, while also allowing for rapid POC diagnosis. Possess potential to combine rapid viral genomic analysis, serology assays, and direct virus detection/identification in one integrated platform.
The authors report key factors that must be addressed for successful implementation of nanophotonic biosensors in COVID-19 diagnostics: (1) appropriate and high-quality bioreceptors to ensure high sensitivity and selectivity, and (2) appropriate biofunctionalization strategy on the sensor surface.

ABSTRACT

The global sanitary crisis caused by the emergence of the respiratory virus SARS-CoV-2 and COVID-19 outbreak has revealed the urgent need for rapid, accurate, and affordable diagnostic tests to broadly and massively monitor the population in order to properly manage and control the spread of the pandemic. Current diagnostic techniques essentially rely on polymerase chain reaction (PCR) tests, which provide the required sensitivity and specificity. However, its relatively long time-to-result, including sample transport to a specialized laboratory, delays overly the massive detection. Rapid lateral flow tests (both antigen and serological tests) are a remarkable alternative for rapid point-of-care diagnostics, but they exhibit critical limitations as they do not always achieve the required sensitivity for reliable diagnostics and surveillance. Next-generation diagnostic tools capable to overcome all the above limitations are in demand, and optical biosensors are an excellent option to surpass such critical issues. Label-free nanophotonic biosensors offer high sensitivity and operational robustness with an enormous potential for integration in compact autonomous devices to be delivered out-of-the-lab at the point of care (POC). Taking the current COVID-19 pandemic as a critical case scenario, we provide an overview of the diagnostic techniques for respiratory viruses and analyze how nanophotonic biosensors can contribute to improving such diagnostics. We review the ongoing published work using this biosensor technology for intact virus detection, nucleic acid detection or serological tests, and the key factors for bringing nanophotonic POC biosensors to the accurate and effective COVID-19 diagnosis in a short term.

genomic detection		
receptor	advantages	limitations
DNA probes	Stability and specificity	Not sensitive enough in some scenarios
	Easy to produce and attach to the surface	
Tagged stem-loop probes	Lower limits of detection	Need for labels, chemical modifications
		Additional steps
Amplification + DNA probes	Lower limits of detection	Additional steps
		Cost of the enzyme, reagents
intact virus detection		
receptor	advantages	limitations
Antibodies	Robust and well established	Animal requirement
	Wide range of ligands	High production costs
	High binding affinities and selectivity	Activity decrease in long-term storage
		Low reusability
Recombinant antibody fragments	No animal requirement in the production	Need to know the sequence, or find binding regions through phage display
	Less costly to produce than the whole antibodies (microorganism bioreactors)	Storage and reusability
Aptamers	Possibility of engineering	SELEX procedure is long and complex
	Less costly than antibodies	
	Stability and long-term storage	
	Reusability	
Glycans	Less cost in production	Limited to a few viruses
	Increase selectivity in combination with other receptors	Need of prior studies of glycan affinities to viruses
serological assay		
receptor	advantages	limitations
Viral lysates	Easy to produce	Not homogeneous receptor layers
	No need to know the viral antigens or genome sequence	Cross-reactivity due to incorporation of host proteins in virions
Recombinant viral antigens	Homogeneous receptor layer	Need to identify the gene sequence
	Relatively easy to produce	Cross-reactivity with strains of the same family
Antigenic domains of viral proteins	Less cross-reactivity with viruses of the same family	Need to know sequence, structure, and identify the domain

Table 1. Bioreceptors Applied for Virus Diagnosis

genomic detection						
biosensor technique	virus	receptor	target	sample	sensitivity	ref
LSPR	SARS-CoV-2	DNA probe	RNA	Buffer	0.2 pM	98
Microring Resonators	Influenza A and B, hCoV-OC43/229E, RSV A and B	DNA probe	RNA	Nasopharyngeal samples	25 copies/reaction	99
SPR	Influenza A and B, H1N1, RSV, parainfluenza, adenovirus, and SARS-CoV	DNA probe	RNA	Buffer	1–5 nM	100
SERS	High-pathogenic avian influenza (HPAI)	Raman-tag hairpin DNA probe	RNA	Buffer	2–3 aM	62
intact virus detection						
biosensor technique	virus	receptor	target	sample	sensitivity	ref
SPR	Avian influenza H6N1	Antibodies	H6N1 virion	Buffer	5×10^6 EID_{50}/mL	103
SPR	Avian influenza H7N9	Antibodies	HA protein	Buffer	200 copies/mL	104
SPR	Enterovirus 71	Antibodies	VP1 protein	Culture media	67 virus particles/mL	105
SPR	Avian influenza H5N1	Aptamer	HA protein	Poultry swab samples	0.128 HAU/mL	70
SPR	Avian influenza H5Nx	Aptamer	HA protein	Buffer	200 EID_{50}/mL	69
Waveguide interferometer	High-pathogenic avian influenza (HPAI)	Antibodies	HA protein	Buffer	0.0005 HAU/mL	106
Silica Inverse Opal	Avian influenza H1N1	Antibodies	HA protein	Buffer	10^5 PFU/mL	107
Photonic Crystal	Avian influenza H1N1	Antibodies	HA protein	Saliva samples	1 ng/mL	108
Mach–Zehnder	Avian influenza H1N1	Antibodies	HA protein	Buffer	10^{10} virus particles	109

Table 2. Nanophotonic Biosensors Applied for Respiratory Virus Diagnosis

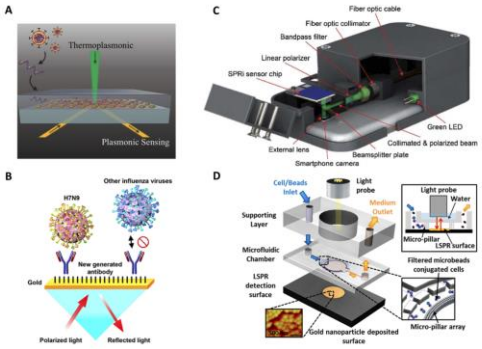

Figure 3. (A) Example of nanophotonic biosensor applied for COVID-19 diagnosis via genomic detection of SARS-CoV-2. Reprinted (adapted) with permission from ref 98. Copyright (2020) American Chemical Society. (B) Example of nanophotonic biosensor applied for direct detection of intact viruses (influenza). Reprinted (adapted) with permission from ref 104. Copyright (2018) American Chemical Society. (C) Example of smartphone- integrated optical biosensor. Reprinted (adapted) with permission from ref 130. Copyright (2017) Elsevier. (D) Example of microfluidics-integrated optical biosensor. Reprinted (adapted) with permission from ref 134. Copyright (2014). American Chemical Society. Please refer to original articles for reprint.

DEVELOPMENTS IN TREATMENTS

BARICITINIB RESTRAINS THE IMMUNE DYSREGULATION IN SEVERE COVID-19 PATIENTS

Bronte V, Ugel S, Tinazzi E, Vella A, De Sanctis F, Canè S, Batani V, Trovato R, Fiore A, Petrova V, Hofer F, Barouni RM, Musiu C, Caligola S, Pinton L, Torroni L, Polati E, Donadello K, Friso S, Pizzolo F, Iezzi M, Facciotti F, Pelicci PG, Righetti D, Bazzoni P, Rampudda M, Comel AC, Mosaner W, Lunardi C, Olivieri O.. J Clin Invest. 2020 Aug 18:141772. doi: 10.1172/JCI141772. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

Italian clinicians, mainly from the immunology department at the University and Hospital Trust of Verona, conducted an observational longitudinal study from March 18 - April 18, 2020 of admitted COVID-19 positive patients treated with baricitinib (n=20) compared to a control group (n=56) (Table 1). They found that baricitinib modulates the immune system by inhibiting the over-tuned inflammatory response in COVID-19, including IL-1beta, IL-6, and TNF-alpha (details in summary) (Figures 1, 2). The authors believe this trial of baricitinib exhibits promising results toward dampening the progression of COVID-19 infection to severe disease.

SUMMARY

An observational longitudinal study to analyze the effect of baricitinib, a reversible JAK1/JAK2 inhibitor and immune regulator in COVID-19 patients was studied. Initially, 88 COVID-19 positive patients were enrolled and 12 were excluded due to malignancies. Out of 76 remaining patients, 20 were trialed on baricitinib, and 56 were used as controls. The treatment group received baricitinib 4mg twice daily for 2 days followed by once daily for 7 days. Major findings include:
- Baricitinib significantly inhibited pSTAT3 in T lymphocytes, NK cells, monocytes, and neutrophils.
- T-distributed stochastic neighbor embedded analysis (t-NSE) revealed increases in naïve CD4+ T-cells (11.2% to 13.8%), central memory (11.9% to 16.7%), and B lymphocytes (11.8 % to 15.7%).
- T-distributed stochastic neighbor embedded analysis (t-NSE) revealed a decrease in senescent (7.3 % to 3.3 %) with a concomitant increase in both naïve (4.3 % to 5.3 %) and memory (3.4 % to 4.8 %) CD8+ T lymphocytes.
- A significant increase in IgG against the SARS-CoV-2 spike protein were observed in the treatment group in comparison to the control group, but no barcitinib-related differences in IgA were observed. Only 1/20 patients in the treatment group never presented virus-specific IgG and died.
- Among the treatment group, there was a significant reduction in the plasma levels of pSTAT3 in immune cells, IL-6, IL-1beta, TNF-alpha, CRP ($p<0.001$).
- Mortality - 1/20 in baricitinib-treated group and 25/56 in non-baricitinib group ($p<0.001$).

ABSTRACT

BACKGROUND: COVID-19 patients develop pneumonia generally associated to lymphopenia and severe inflammatory response due to uncontrolled cytokine release. These mediators are transcriptionally regulated by the JAK-STAT signaling pathways, which can be disabled by small molecules. METHODS: A group of subjects (n = 20) was treated with baricitinib according to an off-label use of the drug. The study was designed as an observational longitudinal trial and approved by the local ethical committee. The patients were treated with baricitinib 4 mg twice daily for 2 days, followed by 4 mg per day for the remaining 7 days. Changes in the immune phenotype and expression of pSTAT3 in blood cells were evaluated and correlated with serum-derived cytokine levels and antibodies anti-SARS-CoV-2. In a single treated patient, we evaluated also the alteration of myeloid cell functional activity. RESULTS: We provided evidences that baricitinib-treated patients have a marked reduction in serum levels of interleukin (IL)-6, IL-1beta and tumor necrosis factor (TNF)-alpha, a rapid recovery in circulating T and B cell frequencies, and increased antibody production against SARS-CoV-2 spike protein, which were clinically associated with a reduction in oxygen flow need and progressive increase in the P/F. CONCLUSION: Baricitinib prevented the progression towards a severe/extreme form of the viral disease by modulating the patients' immune landscape and these changes were associated with a safer and favorable clinical outcome of patients with COVID-19 pneumonia. TRIAL REGISTRATION: The ClinicalTrials.gov identifier of this project is protocol NCT04438629. FUNDING: This work was supported by Fondazione Cariverona (ENACT Project) and Fondazione TIM.

FIGURES

Table 1. Clinical Characteristics of Enrolled Patients During Treatment

Characteristic	BARICITINIB					NO BARICITINIB					P VALUE
Clinical, laboratory, respiratory parameters during treatment	Baseline (t0)	Day 4 (t4)	Day 7 (t7)	P value t0 vs t4	P value t0 vs t7	Baseline (t0)	Day 4 (t4)	Day 7 (t7)	P value t0 vs t4	P value t0 vs t7	P value t0 Baricitinib vs t0 no Baricitinib
Enrolled patients (alive)	n=20	n=20	n=20			n= 56	n= 35	n=29			
Respiratory rate (n/min), median (IQR)	19 (16.25-24)	17.5 (15-19)	16 (15-18)	0.04	0.02	22 (20-30)	22 (20-28)	20 (18-30)	0.64	0.30	0.01
P/F, median (IQR)	241 (200-295.8)	290 (248-319)	331 (287.5-367.3)	0.08	0.02	220 (128.5-319)	141 (86.25-215.3)	225 (150-281.0)	0.02	0.3	0.57
FiO2 required (%), median (IQR)	29.5 (25-34.25)	28 (24-40)	22.5 (21-28)	0.59	<0.001	31 (21-50)	36 (28-60)	28(21-70)	<0,001	0.08	0.70
C-reactive protein, (mg/L), median (IQR)	53.15 (43.08-77.63)	13.9 (7.83-22.75)	9.7 (4.33-14.23)	<0.001	<0.001	64.5 (37-130.3)	70.5 (43.75)	38 (12-63.25)	0.87	0.12	0.16
Fever °C, median (IQR)	36.9 (36.25-38)	36.2 (36.2-36.7)	36.4 (36.05-36.6)	0.003	0.010	37.2 (36.48-38)	36 (36-36.93)	36 (36-36.48)	0.006	0.007	0.57
Primary outcomes	**BARICITINIB**					**NO BARICITINIB**					**P VALUE**
Deaths, n (%)	1 (5)					25 (45)					<0.001
Incidence of acute respiratory distress syndrome, n (%)	3 (15)					15 (27)					0.37
Duration of the hospitalization, days, median (min - max)	12 (5-24) n=19					11 (3-46) n=31					0.28
Logistic Regression Analysis of Mortality											
Indipendent Variable	**ODDS RATIO**					**95 % CI**					**P VALUE**
Baricitinib treatment	0.001					2.44e$^{-0.41}$					0.024
Gender (Female vs Male)	0.022					0.0005-0.95					0.047
Age	1.35					1.06-1.74					0.017
D-dimer	1.00					0.99-1.00					0.665
Comorbidities (Hypertension)	27.6					0.48-1586.4					0.108

* IQR denotes interquartile range, P/F PaO2/FiO2, PaO2 oxygen partial pressure, FiO2 fraction of inspired oxygen

Table 1: Clinical characteristics of enrolled patients during treatment.

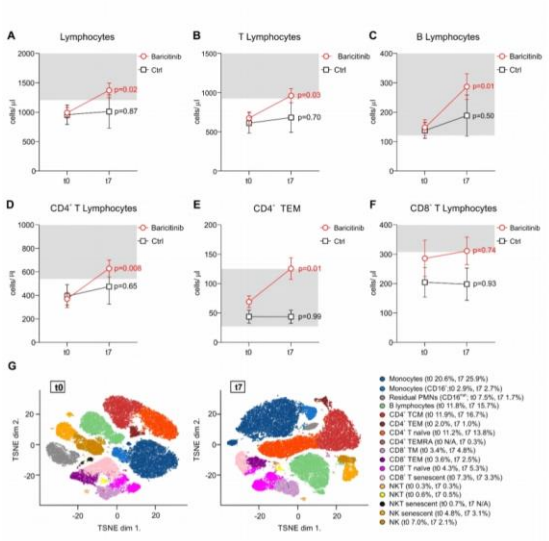

Figure 1: Baricitinib treatment restores normal lymphocyte counts in the blood. Peripheral blood of COVID-19 patients enrolled in either baricitinib (n=12) or basic treatment (n=8,Ctrl) arms was analyzed at t0

(baseline), and t7 (7 days following treatment) by flow cytometry. Number of cells/µl was reported for lymphocytes (A), T lymphocytes (B), B lymphocytes (C), CD4+ T lymphocytes (D), CD4+ T effector-memory (E), CD8+ T lymphocytes (F). The normal reference range is shown in light gray boxes. Data are reported as mean ± SEM. Statistic performed by One-way RM ANOVA. (G) t-SNE analysis of peripheral blood from 12 patients at t0 (left) and t7(right) of baricitinib treatment. The identified clusters are reported in different colors as follow: monocytes, monocytes (CD16+), residual PMNs (CD16high), B lymphocytes (CD19+CD45RA+), CD4+ T central memory (TCM, CD3+CD4+CD27+CD45RA-), CD4+ T effector memory (TEM, CD3+CD4+CD57+CD27-CD45RA), CD4+ T naïve (CD3+CD4+CD27+CD45RA+), CD4+ T effector memory re-expressing CD45RA (TEMRA, CD3+CD4+CD45RA+CD57+), CD8+ T memory (TM, CD3+CD8+CD27+CD45RA-), CD8+ T effector memory (TEM, CD3+CD8+CD45RA- CD57+), CD8+ T naïve (CD3+CD8+CD27+CD45RA+), CD8+ T senescent (CD3+CD8+CD57+CD45RA+),NKT (CD3+CD16+CD56+CD45RA+), senescent NKT (CD3+CD16+CD56+CD45RA+CD57+), NK CD16+ CD56+CD45RA+) and senescent NK (CD16+CD56+CD45RA+ CD57+).

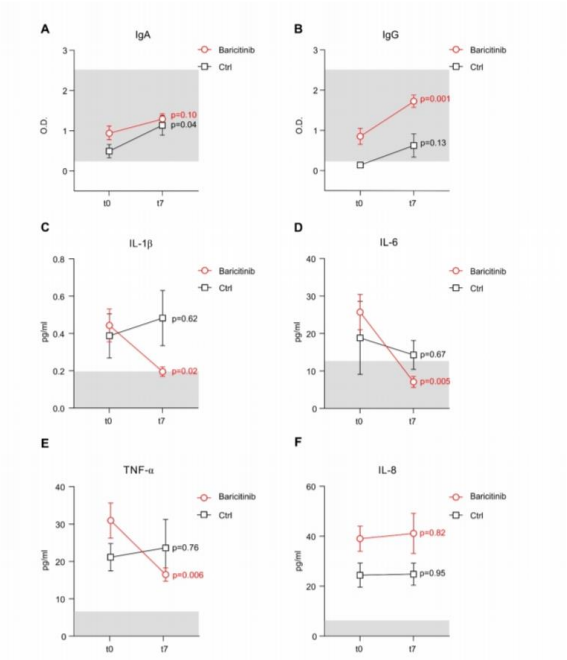

Figure 2: Baricitinib treatment affects IgG levels and production of inflammatory cytokines that contribute to the cytokine storm. Plasma of COVID-19 patients enrolled in either baricitinib (n=20) or basic treatment (n=8, Ctrl) arms was analyzed at t0 (baseline), and t7 (7 days following treatment) to evaluate the concentration of IgA (A), IgG (B), IL-1β (C), IL-6 (D), TNFα (E), and IL-8 (F). For serological data, the light gray boxes identify the range of Ab detection. Normal median value of cytokines is shown by light gray boxes. Data are reported as mean ± SEM. Statistic performed by One-way RM ANOVA.

CONCERNS ABOUT THE SPECIAL ARTICLE ON HYDROXYCHLOROQUINE AND AZITHROMYCIN IN HIGH RISK OUTPATIENTS WITH COVID-19 BY DR. HARVEY RISCH

Fox MP, D'Agostino McGowan L, James BD, Lessler J, Mehta SH, Murray EJ.. Am J Epidemiol. 2020 Aug 29:kwaa189. doi: 10.1093/aje/kwaa189. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Editors of the American Journal of Epidemiology respond to the opinion piece by Risch (2020) on the use of hydroxychloroquine (HCQ) plus azithromycin (AZ) as early treatment of symptomatic COVID-19. The editors believe they did not offer due diligence in documenting errors in the original article and felt it necessary to bring them to light, which include:

- Dr. Risch noted a 50-fold benefit in this treatment which was never reported in the original study.
- Dr. Risch noted the effects of the treatment could not be ascribed to confounding, when evidence pointed otherwise.
- Dr. Risch cited five studies in his publication, however only 2 of these studies contained control groups.

The editors suggest these inaccuracies make the evidence moot in Dr. Risch's opinion piece, thus undermining the initial claim of benefit from HCQ+AZ as early treatment for COVID-19.

ABSTRACT

In May, this journal published an opinion piece by one of the members of the Editorial Board, Dr. Harvey Risch, that reviewed several papers and argued that using hydroxychloroquine (HCQ) + azithromycin (AZ) early to treat symptomatic COVID-19 cases in high-risk patients should be broadly applied. As members of the journal's editorial board, we are strongly supportive of open debate in science, which is essential even on highly contentious issues. However, we must also be thorough in our examination of the facts and open to changing our minds when new information arises. In this commentary, we document several important errors in the manuscript by Dr. Risch, review the literature he presented and demonstrate why it is not of sufficient quality to support scale up of HCQ+AZ, and then discuss the literature that has been generated since his publication, which also does not support use of this therapy. Unfortunately, the current scientific evidence does not support HCQ+AZ as an effective treatment for COVID-19, if it ever did; and even suggests many risks. Continuing to push the view that it is an essential treatment in the face of this evidence is irresponsible and harmful to the many people already suffering from infection.

PERCEIVED FEAR OF COVID-19 INFECTION ACCORDING TO SEX, AGE AND OCCUPATIONAL RISK USING THE BRAZILIAN VERSION OF THE FEAR OF COVID-19 SCALE

Andrade EF, Pereira LJ, Oliveira APL, Orlando DR, Alves DAG, Guilarducci JS, Castelo PM.. Death Stud. 2020 Aug 26:1-10. doi: 10.1080/07481187.2020.1809786. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A survey study of 1,743 Brazilians (aged 18-74 years) from May 12 to May 24, 2020 by researchers affiliated with veterinary medicine and health sciences assessed participants via State-Trait Anxiety Inventory and “Fear of COVID-19 Scale” and found women had overall higher anxiety and fear of COVID-19 infection, while fear was lower among older participants and men with occupational risk of disease had lower fear than men not at risk. Authors suggest these findings could inform government agencies for development of public health interventions, particularly those addressing mental health.

ABSTRACT

We investigated the fear of COVID-19 infection after proper translation and cultural adaptation of the "Fear of COVID-19 Scale" to the Brazilian Portuguese language. A sample of 1,743 Brazilian participants were included. The scale showed excellent psychometric characteristics. Women showed higher anxiety levels. Fear of COVID-19 scores were lower in males with occupational risk of contamination. On the other hand, women and younger individuals showed higher fear of COVID-19 infection scores. The Brazilian Fear of COVID-19 Scale proved to be a reliable tool with excellent psychometric properties for identifying fear of COVID-19 infection in the Brazilian population.

ACKNOWLEDGEMENTS

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