The Daily COVID-19 Literature Surveillance Summary

August 20, 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

Epidemiology

- A retrospective study of 570 children diagnosed with multi-system inflammatory syndrome (MIS-C), nearly all of whom were confirmed COVID-19 positive by PCR or antibody test, found obesity to be the most common underlying condition, and 86% of cases involved 4+ organ systems, leading to 63.9% being admitted to the ICU with a median 5 day stay. The most common symptoms included abdominal pain and vomiting along with shock, myocarditis, and coronary artery dilatation, suggesting the importance of rapid recognition of the signs and symptoms of MIS-C.

Management

- Neurologists in Spain present 2 cases of serotonin syndrome in COVID-19 positive males admitted with respiratory symptoms who were treated with lopinavir/ritonavir and hydroxychloroquine. They suggest that the combination of lopinavir/ritonavir with lithium and duloxetine in the first patient, and with risperidone and morphine in the second may have triggered the onset of serotonin syndrome, arguing that dose adjustment of antidepressants and antipsychotics should be considered in these patients.

R&D: Diagnosis and Treatment

- Analysis of the performance of three SARS-CoV-2 serological assays (from Abbott, Roche, and DiaSorin) using 1,154 serum samples from pre-COVID-19 patients and 65 serum samples from COVID-19 patients found the specificity of the assays were: 99.2% for Abbott), 99.7% for Roche, and 98.3% for DiaSorin. Assuming a 1% seroprevalence, the positive predictive value of the assays were: 52.3% for Abbott, 77.6% for Roche, 32.6% for DiaSorin.
- A systematic review consisting of 8 randomized control trials and observational studies investigated risks and benefits of short-term NSAID use in acute lower respiratory tract infections. The review discovered a trend toward reduction in mortality but increased pleuro-pulmonary complications though does note the studies exhibited high risks of bias due to lack of adjustment for confounding variables and should be interpreted as poor quality evidence. The authors emphasize the need for additional studies on NSAID use with respiratory infections to adequately assess the implications of use during the pandemic.

Mental Health & Resilience Needs

- A group of psychiatrists relay their correspondence with 14- to 25-year-olds in Europe and Africa to highlight the benefits of involving young people in the co-production of research and peer-led interventions during the current pandemic. They found that young people are highly motivated to support each other during this time by sharing experiences, exchanging fact-based information, and providing emotional support. By involving young people in these areas of civic engagement, the authors suggest a greater chance of building resilience in their communities, not only during the COVID-19 pandemic, but during future crises as well.

TABLE OF CONTENTS

PEDIATRICS

COVID-19-ASSOCIATED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN - UNITED STATES, MARCH-JULY 2020

Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, Roguski K, Wallace B, Prezzato E, Koumans EH, Lee EH, Geevarughese A, Lash MK, Reilly KH, Pulver WP, Thomas D, Feder KA, Hsu KK, Plipat N, Richardson G, Reid H, Lim S, Schmitz A, Pierce T, Hrapcak S, Datta D, Morris SB, Clarke K, Belay E; California MIS-C Response Team.. MMWR Morb Mortal Wkly Rep. 2020 Aug 14;69(32):1074-1080. doi: 10.15585/mmwr.mm6932e2.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort study conducted by a group of American clinicians/healthcare professionals associated with the California MIS-C Response Team studied 570 children diagnosed with multi-system inflammatory syndrome (MIS-C), nearly all of whom were confirmed COVID-19 positive by PCR or antibody test (5 were not tested). Obesity was found to be the most common underlying condition, and 86% of cases involved 4+ organ systems, leading to 63.9% being admitted to the ICU with a median 5 day stay. The most common symptoms included abdominal pain and vomiting with more severe dysfunction of the heart with shock, myocarditis, and coronary artery dilatation (Table 1), suggesting the importance of rapid recognition of the signs and symptoms of MIS-C.

ABSTRACT

In April 2020, during the peak of the coronavirus disease 2019 (COVID-19) pandemic in Europe, a cluster of children with hyperinflammatory shock with features similar to Kawasaki disease and toxic shock syndrome was reported in England* (1). The patients' signs and symptoms were temporally associated with COVID-19 but presumed to have developed 2-4 weeks after acute COVID-19; all children had serologic evidence of infection with SARS-CoV-2, the virus that causes COVID-19 (1). The clinical signs and symptoms present in this first cluster included fever, rash, conjunctivitis, peripheral edema, gastrointestinal symptoms, shock, and elevated markers of inflammation and cardiac damage (1). On May 14, 2020, CDC published an online Health Advisory that summarized the manifestations of reported multisystem inflammatory syndrome in children (MIS-C), outlined a case definition, and asked clinicians to report suspected U.S. cases to local and state health departments. As of July 29, a total of 570 U.S. MIS-C patients who met the case definition had been reported to CDC. A total of 203 (35.6%) of the patients had a clinical course consistent with previously published MIS-C reports, characterized predominantly by shock, cardiac dysfunction, abdominal pain, and markedly elevated inflammatory markers, and almost all had positive SARS-CoV-2 test results. The remaining 367 (64.4%) of MIS-C patients had manifestations that appeared to overlap with acute COVID-19 (2-4), had a less severe clinical course, or had features of Kawasaki disease. Median duration of hospitalization was 6 days; 364 patients (63.9%) required care in an intensive care unit (ICU), and 10 patients (1.8%) died. As the COVID-19 pandemic continues to expand in many jurisdictions, clinicians should be aware of the signs and symptoms of MIS-C and report suspected cases to their state or local health departments; analysis of reported cases can enhance understanding of MIS-C and improve characterization of the illness for early detection and treatment.

FIGURES

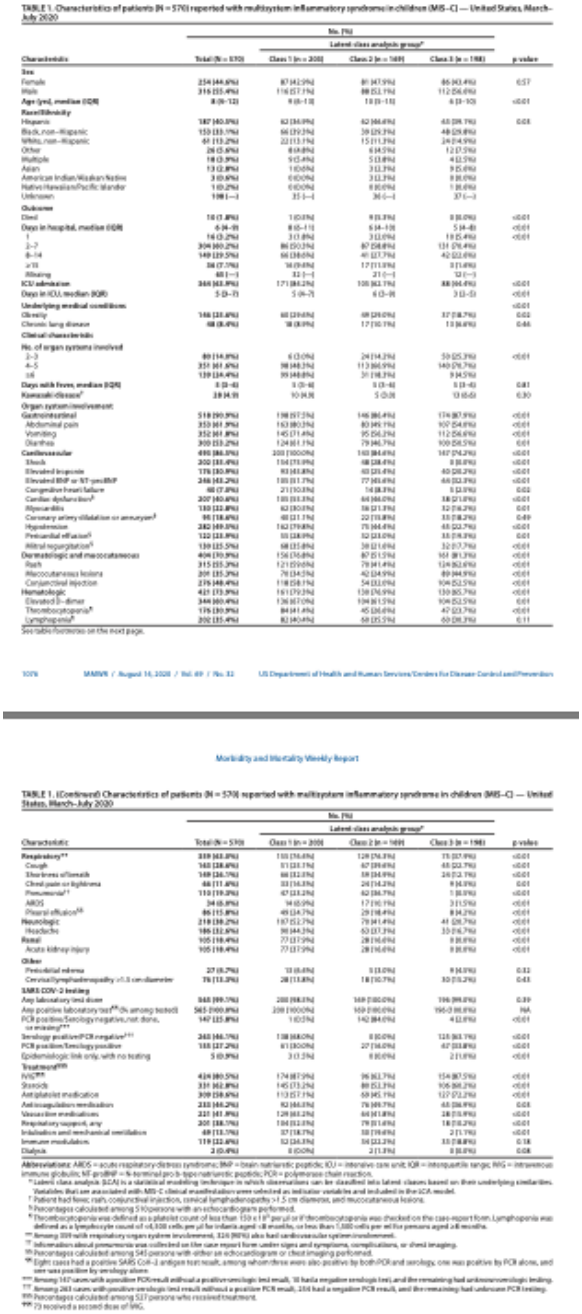


TABLE 1. Characteristics of patients (N = 570) reported with multisystem inflammatory syndrome in children (MIS–C) — United States, March– July 2020

UNDERSTANDING THE PATHOLOGY

HISTOPATHOLOGIC CHANGES AND SARS-COV-2 IMMUNOSTAINING IN THE LUNG OF A PATIENT WITH COVID-19

Zhang H, Wang CY, Zhou P, Yue H, Du R.. Ann Intern Med. 2020 Aug 18;173(4):324. doi: 10.7326/L20-0895.
Level of Evidence: Other - Case Report

BLUF

A case report conducted in China of a 72 year-old male with history of diabetes and hypertension who tested positive for COVID-19, which progressed within 1 week to respiratory failure (see summary below), describes histopathologic lung changes, highlighting diffuse alveolar damage as a result of the disease progression. This case report provides an example of the devastating damage that infection with SARS-CoV-2 can lead to.

SUMMARY

A 72 year-old male with history of hypertension and diabetes presented with initial symptoms of fever and cough. By day 6 of these symptoms, he tested positive for SARS-CoV-2 infection. His symptoms rapidly progressed to respiratory failure, requiring endotracheal intubation and mechanical ventilation after 1 week. Lung CT scan (Figure 1) revealed bilateral patchy ground-glass opacities, and lung biopsy (Figure 2) showed diffuse alveolar damage, type II pneumocyte hyperplasia, inflammatory infiltrates, and loose interstitial fibrosis. The disease progressed rapidly and he died 3 weeks after initial presentation.

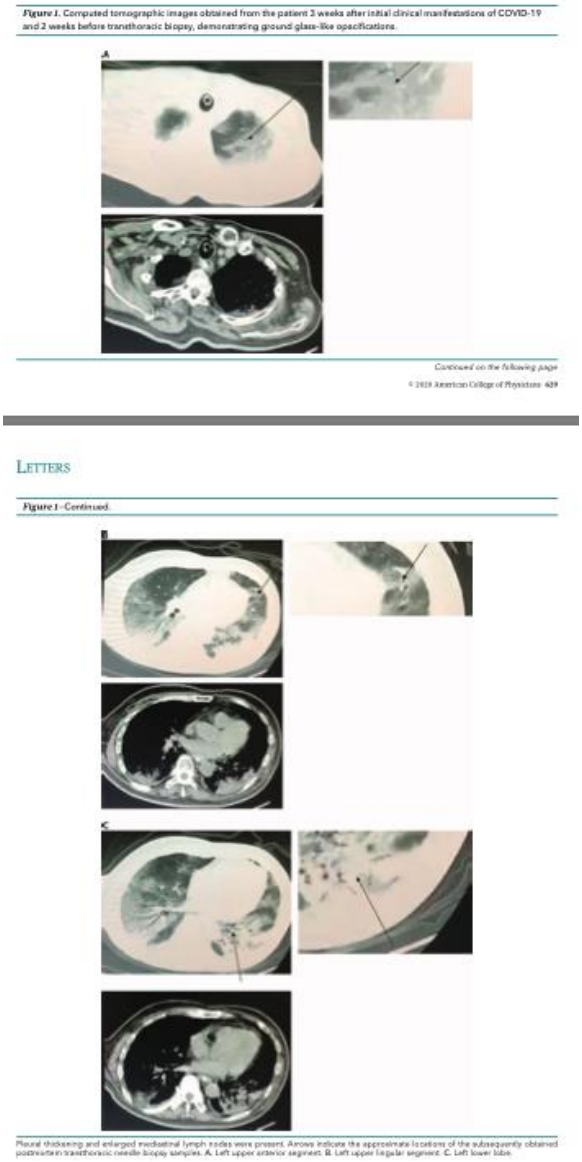
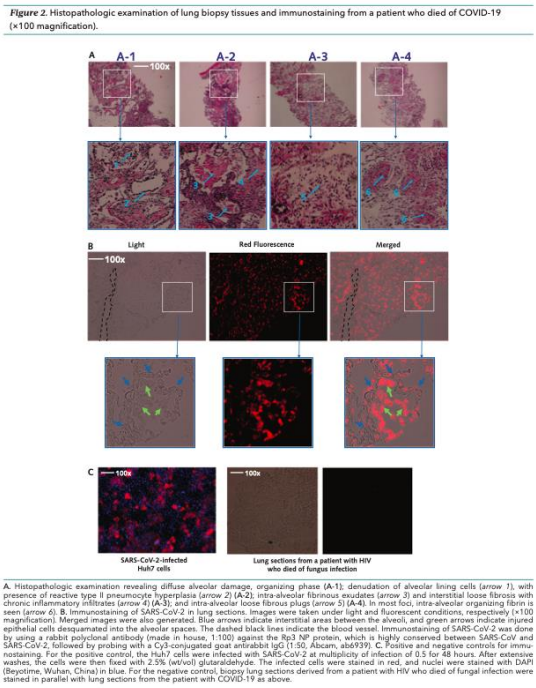


Figure 1. Computed tomographic images obtained from the patient 3 weeks after initial clinical manifestations of COVID-19 and 2 weeks before transthoracic biopsy, demonstrating ground glass–like opacifications. Pleural thickening and enlarged mediastinal lymph nodes were present. Arrows indicate the approximate locations of the subsequently obtained postmortem transthoracic needle biopsy samples. A. Left upper anterior segment. B. Left upper lingular segment. C. Left lower lobe.



A. Histopathologic examination revealing diffuse alveolar damage, organizing phase (A-1); denudation of alveolar lining cells (arrow 1), with presence of reactive type II pneumocyte hyperplasia (arrow 2) (A-2); intra-alveolar fibrinous exudates (arrow 3) and interstitial loose fibrosis with chronic inflammatory infiltrates (arrow 4) (A-3); and intra-alveolar loose fibrous plugs (arrow 5) (A-4). In most foci, intra-alveolar organizing fibrin is seen (arrow 6). B. Immunostaining of SARS-CoV-2 in lung sections. Images were taken under light and fluorescent conditions, respectively (×100 magnification). Merged images were also generated. Blue arrows indicate interstitial areas between the alveoli, and green arrows indicate injured epithelial cells desquamated into the alveolar spaces. The dashed black lines indicate the blood vessel. Immunostaining of SARS-CoV-2 was done by using a rabbit polyclonal antibody (made in house, 1:100) against the Rp3 NP protein, which is highly conserved between SARS-CoV and SARS-CoV-2, followed by probing with a Cy3-conjugated goat antirabbit IgG (1:50, Abcam, ab6939). C. Positive and negative controls for immu- nostaining. For the positive control, the Huh7 cells were infected with SARS-CoV-2 at multiplicity of infection of 0.5 for 48 hours. After extensive washes, the cells were then fixed with 2.5% (wt/vol) glutaraldehyde. The infected cells were stained in red, and nuclei were stained with DAPI (Beyotime, Wuhan, China) in blue. For the negative control, biopsy lung sections derived from a patient with HIV who died of fungal infection were stained in parallel with lung sections from the patient with COVID-19 as above.

MANAGEMENT

ACUTE CARE

CRITICAL CARE

SEROTONIN SYNDROME IN TWO COVID-19 PATIENTS TREATED WITH LOPINAVIR/RITONAVIR

Mas Serrano M, Pérez-Sánchez JR, Portela Sánchez S, De La Casa-Fages B, Mato Jimeno V, Pérez Tamayo I, Grandas F.. J Neurol Sci. 2020 Aug 15;415:116944. doi: 10.1016/j.jns.2020.116944. Epub 2020 May 27.
Level of Evidence: Other - Case Report

BLUF

Neurologists in Madrid, Spain present 2 case reports of serotonin syndrome (SS) in COVID-19 positive males (see summary below) admitted with respiratory symptoms who were treated with lopinavir/ritonavir (LPV/r 400/100mg) and hydroxychloroquine (200mg) BID. They suggest that the combination of LPV/r with lithium and duloxetine in Patient 1, and with risperidone and morphine in Patient 2 may have triggered the onset of SS, arguing that consideration of dose adjustment of antidepressants and antipsychotics when treating with LPV/r is crucial in preventing precipitation of SS in COVID-19 patients.

SUMMARY

Patient 1: A 66-year-old male admitted due to bilateral COVID-19 pneumonia with preexisting hypertension, bipolar disorder, and cervical spinal stenosis was treated with lithium(800mg/day) and duloxetine(120mg/day). He received LPV/r(400/100 mg) and hydroxychloroquine 200mg twice daily. On day 3, he developed acute delirium and was started on haloperidol 1mg BID and subsequently developed obtundation, tachycardia and diaphoresis. Neurological examination revealed multifocal facial, axial, and appendicular myoclonus, in addition to hyperreflexia and ankle clonus. Labs: Elevated CK(767U/L), creatinine(1.47mg/dl), EEG - Diffuse encephalopathy with an insignificant MRI brain. SS was suspected, so drugs were discontinued, cyproheptadine 8mg every 6 hours was administered, and neurological status improved over the next 10 days.

Patient 2: A 78-year-old male admitted due to COVID-19 with mild respiratory symptoms, with prior history of hypertension, diabetic chronic kidney disease, and colorectal carcinoma was treated with LPV/r and hydroxychloroquine. He received Interferon beta-1b (2 doses on days 3 and 4) and tocilizumab (1 dose on day 9) for bilateral pneumonia. On day 10, he developed acute delirium and was given risperidone 1mg twice daily and 1 dose of morphine (3mg) for dyspnea. His level of consciousness decreased and he developed tachycardia and diaphoresis. Neurological examination revealed confusion, multifocal limb myoclonus, ocular clonus, hyperreflexia, and mild rigidity in all 4 limbs. Labs: elevated CK(802U/L), creatinine(1.93mg/dl), EEG - diffuse encephalopathy with insignificant head CT. The drugs were stopped due to SS suspicion and he was treated with clonazepam 0.25mg every 6 hours and the symptoms improved over the next few days.

MEDICAL SUBSPECIALTIES

RHEUMATOLOGY

ACUTE ARTHRITIS FOLLOWING SARS-COV-2 INFECTION

Jovani V, Pascual E, Vela P, Andrés M.. J Med Virol. 2020 Aug 18. doi: 10.1002/jmv.26440. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A commentary of Saricaoglu EM et. al.'s paper (case report of reactive arthritis in a 73 year-old male patient 8 days after finishing COVID-19 treatment) by physicians from Spain highlights how the study did not include a synovial fluid analysis, which is critical in diagnosing acute arthritis. The authors offer examples of diagnosing pseudogout/gout in 4/306 patients

with COVID-19 at their institution in addition to stressing the need for synovial fluid analysis to properly diagnose acute arthritis during the COVID-19 pandemic.

ABSTRACT

We have read with interest the article by Saricaoglu EM et al 1 published in the recent issue of the Journal of Medical Virology. The authors diagnosed reactive arthritis in a 73 year old male patient after debut of polyarthritis in feet eight days after finishing treatment for COVID-19. Although viral-associated arthritis or a reactive arthritis should be considered in differential diagnosis, they do not describe if synovial fluid was analysed.

SIDE BY SIDE COMPARISON OF THREE FULLY AUTOMATED SARS-COV-2 ANTIBODY ASSAYS WITH A FOCUS ON SPECIFICITY

Perkmann T, Perkmann-Nagele N, Breyer MK, Breyer-Kohansal R, Burghuber OC, Hartl S, Aletaha D, Sieghart D, Quehenberger P, Marculescu R, Mucher P, Strassl R, Wagner OF, Binder CJ, Haslacher H.. Clin Chem. 2020 Aug 10:hvaa198. doi: 10.1093/clinchem/hvaa198. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

A nonblinded prospective study by researchers at Medical University of Vienna, Austria analyzed the performance of three SARS-CoV-2 serological assays (Abbott, Roche, DiaSorin) using 1,154 serum samples from pre-COVID-19 patients and 65 serum samples from COVID-19 patients. The specificity (average) of the assays were (Table 2): 99.2% (Abbott), 99.7% (Roche), and 98.3% (DiaSorin), and assuming a 1% seroprevalence, the positive predictive value (average) of the assays were: 52.3% (Abbott), 77.6% (Roche), 32.6% (DiaSorin). The McNemar test revealed significant differences between the DiaSorin and Roche results (Table 6). These findings suggest that while specificities may be similar across different assays, minor differences may have significant effects on positive predictive values at low seroprevalence, which should be considered in the COVID-19 pandemic.

ABSTRACT

BACKGROUND: In the context of the COVID-19 pandemic, numerous new serological test systems for the detection of anti-SARS-CoV-2 antibodies rapidly have become available. However, the clinical performance of many of these is still insufficiently described. Therefore, we compared three commercial, CE-marked, SARS-CoV-2 antibody assays side by side. METHODS: We included a total of 1,154 specimens from pre-COVID-19 times and 65 samples from COVID-19 patients (>=14 days after symptom onset) to evaluate the test performance of SARS-CoV-2 serological assays by Abbott, Roche, and DiaSorin. RESULTS: All three assays presented with high specificities: 99.2% (98.6-99.7) for Abbott, 99.7% (99.2-100.0) for Roche, and 98.3% (97.3-98.9) for DiaSorin. In contrast to the manufacturers' specifications, sensitivities only ranged from 83.1% to 89.2%. Although the three methods were in good agreement (Cohen's Kappa 0.71-0.87), McNemar tests revealed significant differences between results obtained from Roche and DiaSorin. However, at low seroprevalences, the minor differences in specificity resulted in profound discrepancies of positive predictive values at 1% seroprevalence: 52.3% (36.2-67.9), 77.6% (52.8-91.5), and 32.6% (23.6-43.1) for Abbott, Roche, and DiaSorin, respectively. CONCLUSION: We found diagnostically relevant differences in specificities for the anti-SARS-CoV-2 antibody assays by Abbott, Roche, and DiaSorin that have a significant impact on the positive predictive values of these tests.

FIGURES

	COHORT A	COHORT B	COHORT C	TOTAL
	n=494	*n=302*	*n=358*	***n=1,154***
Abbott SARS-CoV-2 IgG	4 (0.8%)	3 (1.0%)	2 (0.6%)[&]	**9** (0.8%)
Roche Elecsys® Anti-SARS-CoV-2	0 (0.0%)*	1 (0.3%)	2 (0.6%)[$]	**3** (0.3%)[%]
DiaSorin LIAISON® SARS-CoV-2 S1/S2 IgG	6 (1.2%)*	5 (1.7%)	9 (2.5%)[$&]	**20** (1.7%)[%]

Table 1. Numbers and percentages of false positive SARS-CoV-2 antibody reactivities in three different specificity cohorts: Cohort A (LEAD-Study), Cohort B (Healthy donor collective), and Cohort C (Rheumatic diseases cohort). χ^2-tests for differences of proportions: *... Roche vs. DiaSorin P=0.015, $... Roche vs. DiaSorin P=0.040, &... Abbott vs. Diasorin P<0.040, %... Roche vs. DiaSorin P<0.001

	Abbott SARS-CoV-2 IgG		Roche Elecsys® Anti-SARS-CoV-2		DiaSorin LIAISON® SARS-CoV-2 S1/S2 IgG	
Statistic	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity	**84.6%**	73.6-92.4	**89.2%**	79.1-95.6	**83.1%**	71.3-91.2
Specificity	**99.2%**	98.6-99.7	**99.7%**	99.2-100	**98.3%**	97.3-98.9
1% Seroprevalence						
PPV	**52.3%**	36.2-67.9	**77.6%**	52.8-91.5	**32.6%**	23.6-43.1
NPV	**99.9%**	99.7-99.9	**99.9%**	99.8-100	**99.8%**	99.7-99.9
5% Seroprevalence						
PPV	**85.1%**	74.7-91.7	**94.8%**	85.3-98.3	**71.6%**	61.7-79.8
NPV	**99.2%**	98.6-99.5	**99.4%**	98.9-99.7	**99.1%**	98.5-99.5
10 % Seroprevalence						
PPV	**92.3%**	86.2-95.9	**97.4%**	92.5-99.2	**84.2%**	77.3-89.3
NPV	**98.3%**	97.0-99.0	**98.8%**	97.6-99.4	**98.1%**	96.8-98.9

Table 2. Values for Specificity, Sensitivity, Positive-Predictive-Value (PPV) and Negative-Predictive-Value (NPV) at 1%, 5% and 10% SARS-CoV-2 seroprevalence (SP) with 95% confidence intervals (95% CI).

	Roche			Difference
Abbott	NEG	POS		**-0.25%**
NEG	1149	6	1155 (94.7%)	95% CI
POS	9	55	64 (5.3%)	-0.87 – 0.38
	1155 (95.0%)	61 (5.0%)	1219	P=0.607

	DiaSorin			Difference
Abbott	NEG	POS		**0.82%**
NEG	1131	24	1155 (94.7%)	95% CI
POS	14	50	64 (5.3%)	-0.17 – 1,81
	1145 (93.9%)	74 (6.1%)	1219	P=0.143

	Roche			Difference
DiaSorin	NEG	POS		**-1.07%**
NEG	1136	9	1158 (95.0%)	95% CI
POS	22	52	61 (5.0%)	-1.96 – -0.17
	1158 (93.9%)	61 (6.1%)	1219	***P=0.029***

Supplemental Table 6. McNemar statistic to test rater disagreement. P<0.05 is statistically significant.

DEVELOPMENTS IN TREATMENTS

THE COVID-19 IBUPROFEN CONTROVERSY; A SYSTEMATIC REVIEW OF NSAIDS IN ADULT ACUTE LOWER RESPIRATORY TRACT INFECTIONS

Vaja R, Chan J, Ferreira P, Harky A, Rogers LJ, Gashaw HH, Kirkby NS, Mitchell JA.. Br J Clin Pharmacol. 2020 Aug 17. doi: 10.1111/bcp.14514. Online ahead of print.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

A systematic review consisting of randomized control trials and observational studies (n=8; Figure 1) investigated risks and benefits of short-term NSAID use in acute lower respiratory tract infections to study all-cause mortality, cardiovascular, renal, and respiratory complications. The SR discovered a trend toward reduction in mortality but increased pleuro-pulmonary complications among the included studies, but does note the studies exhibited high risks of bias due to lack of adjustment for confounding variables (Figure 2) and should be interpreted as poor quality evidence (Table 2). The authors additionally note

that a meta-analysis was not performed due to high heterogeneity, in addition to emphasizing the need for additional studies on NSAID use with respiratory infections to adequately assess the implications of use during the COVID-19 pandemic.

ABSTRACT

AIMS: In light of the recent safety concerns relating to NSAID use in COVID-19, we sought to evaluate cardiovascular and respiratory complications in patients taking NSAIDs during acute lower respiratory tract infections. METHODS: We carried out a systematic review of randomised controlled trials and observational studies. Studies of adult patients with short-term NSAID use during acute lower respiratory tract infections, including bacterial and viral infections, were included. Primary outcome was all-cause mortality. Secondary outcomes were cardiovascular, renal and respiratory complications. RESULTS: In total, eight studies including two randomised controlled trials, three retrospective and three prospective observational studies enrolling 44140 patients were included. Five of the studies were in patients with pneumonia, two in patients with Influenza, and one in patients with acute bronchitis. Meta-analysis was not possible due to significant heterogeneity. There was a trend towards a reduction in mortality and an increase in pleuro-pulmonary complications. However, all studies exhibited high risks of bias, primarily due to lack of adjustment for confounding variables. Cardiovascular outcomes were not reported by any of the included studies. CONCLUSION: In this systematic review of NSAID use during acute lower respiratory tract infections in adults, we found that the existing evidence for mortality, pleuro-pulmonary complications and rates of mechanical ventilation or organ failure is of extremely poor quality, very low certainty and should be interpreted with caution. Mechanistic and clinical studies addressing the captioned subject are urgently needed, especially in relation to COVID-19.

FIGURES

Table 2.
Summary of treatment effects for each outcome measure and GRADE quality of evidence.

Outcome (Number of studies)	Overall treatment effect	GRADE	Reasons for Downgrading
Mortality (5)	Uncertain effect on mortality although there may be a trend towards a reduction.	Very Low	Majority Observational studies Risk of Bias Imprecision Publication bias
Cardiovascular complications (0)	Not Reported in any of the included studies	No Evidence	No Evidence
Pleuro-pulmonary complications (5)	Four of the five included studies reported a significant increase in rates of pleuro-pulmonary complications with NSAID use.	Very Low	All Observational studies Risk of Bias Publication bias
Need for mechanical ventilation (3)	Uncertain effect on the need for mechanical ventilation in all studies	Very Low	Majority Observational studies Risk of Bias Imprecision Publication Bias
Need for Dialysis (2)	Uncertain effects of need for dialysis. Low sample sizes and wide confidence intervals prohibits any meaningful conclusions	Very Low	All Observational studies Risk of Bias Imprecision Publication Bias
Major Organ Failure (2)	Uncertain effects on major organ failure.	Very Low	All Observational studies Risk of Bias Imprecision Publication Bias

Figure 1. A flow diagram demonstrating the number of studies searched, screened, excluded and included inthe final analysis.

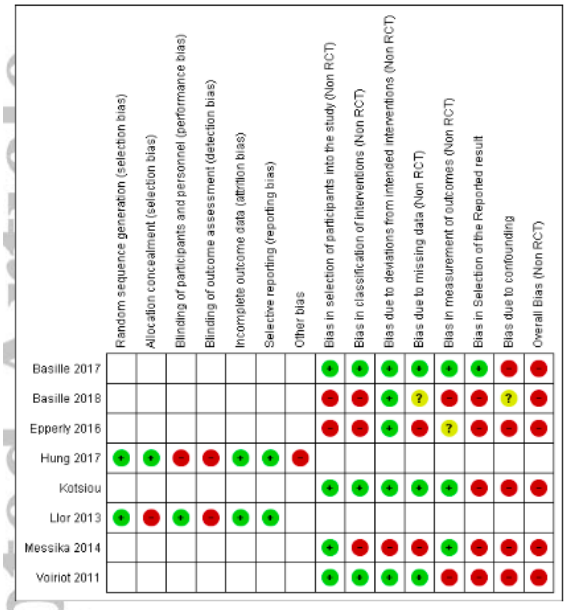


Figure 2. Risk of bias of studies including both Randomised control trials (RCT) and observational studies. (Red: high risk, yellow: unclear risk, green: low risk).

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Need for Dialysis (2)	Uncertain effects of need for dialysis. Low sample sizes and wide confidence intervals prohibits any meaningful conclusions	Very Low	All Observational studies Risk of Bias Imprecision Publication Bias
Major Organ Failure (2)	Uncertain effects on major organ failure.	Very Low	All Observational studies Risk of Bias Imprecision Publication Bias

Table 2: Summary of treatment effects for each outcome measure and GRADE quality of evidence.

HELMINTH COINFECTION AND COVID-19: AN ALTERNATE HYPOTHESIS

Hays R, Pierce D, Giacomin P, Loukas A, Bourke P, McDermott R.. PLoS Negl Trop Dis. 2020 Aug 17;14(8):e0008628. doi: 10.1371/journal.pntd.0008628. eCollection 2020 Aug.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

An opinion piece by Australian scientists from the Australian Institute of Tropical Health and Medicine offer a counterargument that chronic helminth infections may be beneficial in mitigating the inflammatory complications of COVID-19, based on experimental studies and historical epidemiological studies of helminth infections and metabolic disorders. The authors advocate for trials of experimental helminth infections to investigate the potential benefits.

DEBATE: PROMOTING CAPABILITIES FOR YOUNG PEOPLE'S AGENCY IN THE COVID-19 OUTBREAK

Pavarini G, Lyreskog D, Manku K, Musesengwa R, Singh I.. Child Adolesc Ment Health. 2020 Aug 13. doi: 10.1111/camh.12409. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

In this letter to the editor, the authors relay their correspondence with 14- to 25-year-olds in Europe and Africa to highlight the benefits of involving young people in the co-production of research and peer-led interventions during the current COVID-19 pandemic. They found that these populations of young people are highly motivated to support each other during this time by sharing experiences, exchanging fact-based information, and providing emotional support. By involving young people in these areas of civic engagement, the authors suggest a greater chance of building resilience in their communities, not only during the COVID-19 pandemic, but during future crises as well.

ABSTRACT

The COVID-19 pandemic is having a pervasive effect on young people's mental health and well-being, giving rise to feelings of deep uncertainty and lack of control. Inspired by Amartya Sen's capabilities framework, we argue that building capacity and creating opportunities for community and civic engagement during this time will help young people gain agency and well-being. We highlight two key areas for participatory engagement: coproduction of research, and peer-led interventions. Providing capabilities for young people's agency not only builds personal resilience, but also strengthens the quality of our research, interventions and overall response to the global health crisis.

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