The Daily COVID-19 Literature Surveillance Summary

January 05, 2021

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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

- More transparency is needed for emergency use authorizations (EUA), including drugs and vaccines for COVID-19, according to a journalist writing for the Journal of the American Medical Association reporting on a recent US Government Accountability Office (GAO) report. The report calls on the Food and Drug Administration (FDA) to publicly share safety and efficacy data related to EUAs to improve public confidence during this unprecedented time.

Epidemiology

- Persistence of SARS-CoV-2 in a first trimester placenta may have led to transplacental transmission and fetal demise from an asymptomatic mother. An interdisciplinary group of researchers at Model Hospital in Mumbai, India describe a case of hydrops fetalis detected at 13 weeks gestation in an asymptomatic carrier of the SARS-CoV-2 virus. The patient tested posted for COVID-19 at 7.6 weeks of gestation and then was subsequently found to have detectable SARS-CoV2 in the amniotic fluid and placental cells at 13 weeks gestation. These findings suggest possible transplacental SARS-CoV-2 transmission and viral replication within the placenta. While there was evidence of robust placental inflammation, fetal tissue was unavailable for biopsy and therefore infection of the fetus itself is unable to be determined.

Understanding the Pathology

- Immunometabolism may be useful for inflammaging, immunosenescence, and autoimmunity in COVID-19. In this review, an interdisciplinary group of French researchers propose that inflammaging, which is chronic low-grade inflammation that occurs with aging, may be the common factor predisposing individuals with certain comorbidities to more severe COVID-19. They discuss how the underlying mechanisms of immunosenescence and chronic inflammation seen in diseases such as diabetes, hypertension, metabolic syndrome, systemic lupus erythematosus, and rheumatoid arthritis seem to predispose COVID-19 patients to the immune dysfunction and cytokine storm observed in severe disease. Thus, authors propose an immunometabolism-mediated treatment paradigm that includes metformin, rapamycin, and dimethyl fumarate.

- Muscle biopsy findings in a case sheds light into SARS-CoV-2-associated muscle injury. Researchers at Johns Hopkins and the University of Minnesota describe the muscle biopsy of a patient who died from complications of COVID-19. These findings demonstrate cellular damage within skeletal muscle that is consistent with "primary vascular origin." Since skeletal myocytes have minimal expression of ACE-2 receptors, the authors speculate that damage to skeletal muscles likely results from secondary inflammatory and coagulopathic changes, rather than direct viral damage. They theorize that these findings seen on electron microscopy may correlate with the myalgias and elevated CK enzymes seen in SARS-CoV-2 infection.

Transmission & Prevention

- Intrauterine transmission of SARS-CoV-2 from COVID-19 infected pregnant women is a potential complication according to one review. Members of the Pakistan Health Research Council reviewed 16 articles (498 COVID-19 infected pregnant women) on vertical transmission of SARS-CoV-2 and found vertical transmission occurred in 4.883% of SARs-CoV-2 infected mothers (23/471), and in the 17 cases where outcomes were reported, 4 infants developed COVID-19 pneumonia, 8 required care in the neonatal intensive care unit, 4 received mechanical ventilation, and none died. Authors suggest vertical transmission is possible and that because severe neonatal complications can occur, recommend neonatal screening for infants born to mothers with SARS-CoV-2.

Management

- Do care bundles improve outcomes in patients with COVID-19 or related conditions in intensive care? A systematic review by authors from Ireland and Australia examined the literature on ICU care bundles used in the management of COVID-19 and other acute respiratory pathogens and identified 21 studies encompassing 8 countries, with care bundles most commonly including guidance on ventilator setting, restrictive fluid management, sedation, and prone positioning. The authors ultimately found significant variation in the protocol used for these care bundles, and low-quality evidence to support them. Given that care bundles are a cornerstone of ICU care, there is great need for RCTs in this critical aspect of caring for COVID-19 patients.

- What has been found regarding arterial and venous thrombosis in COVID-19 thus far? A literature review conducted by cardiologists from Harvard Medical School (U.S.) analyzes current data on the incidence and treatment of thrombotic complications in COVID-19 patients. Previous studies have found thrombotic complications in 2.6% of non-critically ill

hospitalized patients and in 35% of critically ill hospitalized patients. Laboratory markers of hypercoagulability are also commonly elevated in these patients, such as D-dimer (100%), Fibrinogen (74%), and Factor VIII (100%). Current guidelines agree that prophylactic anticoagulation with low-molecular-weight-heparin (LMWH) is recommended in critically and non-critically ill hospitalized patients, however there is no consensus on anticoagulation of these patients after discharge. While further research is needed on the ideal management of COVID-19-induced coagulopathy, most societies agree that extended prophylaxis in non-hospitalized patients is not recommended.

Adjusting Practice During COVID-19

- Clarithromycin can be used for adjunct surgical prophylaxis before non-elective cesarean deliveries to adapt to azithromycin shortages in the COVID-19 pandemic. A multicenter prospective cohort study of 240 pregnant patients undergoing non-elective cesarean deliveries, found that use of clarithromycin as surgical prophylaxis resulted in significantly lower rates of of postpartum endometritis compared to the control group (4.5% vs 11.2%, $p = 0.025$). These results are important because there has been pandemic-induced shortages of azithromycin (the macrolide typically used for C-section prophylaxis). Notably, all women were SARS-CoV-2 negative and subgroup analysis revealed a significantly decreased risk for Black women ages 18-29. Therefore, use of clarithromycin for C-section prophylaxis may help improve outcomes in both of these vulnerable populations during the COVID-19 pandemic.

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CLIMATE

MORE TRANSPARENCY NEEDED FOR COVID-19 EMERGENCY AUTHORIZATIONS

Rubin R.. JAMA. 2020 Dec 22;324(24):2475. doi: 10.1001/jama.2020.24201.
Level of Evidence: 5 - Opinion

BLUF

A journalist writing for the Journal of the American Medical Association reports on a recent US Government Accountability Office (GAO) report stating a need for more transparency on Emergency Use Authorizations (EUA) including drugs and vaccines for COVID-19. The report calls on the Food and Drug Administration (FDA) to publicly share safety and efficacy data related to EUAs to improve public confidence during this unprecedented time.

GLOBAL

COVID-19 VACCINE: PROMOTING VACCINE ACCEPTANCE

Laine C, Cotton D, Moyer DV.. Ann Intern Med. 2020 Dec 21. doi: 10.7326/M20-8008. Online ahead of print.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

Editors of the Annals of Internal Medicine discuss methods to address the challenge of vaccine acceptance despite misinformation on social media. The authors suggest battling misinformation by providing accurate information about COVID-19 vaccination, validating any concerns about the vaccine, and emphasizing the goals of vaccination. A link to the recorded video of a Q&A session with the panelists is available in the article.

AFFECTING THE HEALTHCARE WORKFORCE

KNOWLEDGE, PERCEPTIONS, AND PREFERRED INFORMATION SOURCES RELATED TO COVID-19 AMONG HEALTHCARE WORKERS: RESULTS OF A CROSS SECTIONAL SURVEY

Sathianathan S, Van Scoy LJ, Sakya SM, Miller E, Snyder B, Wasserman E, Chinchilli VM, Garman J, Lennon RP.. Am J Health Promot. 2020 Dec 23:890117120982416. doi: 10.1177/0890117120982416. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A medical student and physicians from Penn State College of Medicine in Pennsylvania conducted an online survey from March 25-31, 2020 to compare knowledge, perceptions, and preferred information sources on COVID-19 between clinical decision makers (CDM, n=91), non-CDM (n=850) and non-healthcare workers (non-HCW, n=4951). CDMs reported significantly higher knowledge compared to non-CDM (OR: 1.81, 95%CI: 1.51-2.17) and non-HCW (OR: 1.86, 95%CI: 1.56-2.22), with no significant knowledge difference between non-CDM and non-HCW (OR: 1.03, 95%CI: 0.97-1.09) (Table 1). Government websites were the most commonly reported information source among all groups (Table 2). Authors suggest these findings indicate a need to improve COVID-19 knowledge among non-CDM, such as nurses, who may have significant influence on patients' perceptions and trust.

ABSTRACT

PURPOSE: To compare COVID-19 related knowledge, perceptions, and preferred information sources between healthcare workers and non-healthcare workers. DESIGN: Cross-sectional survey. SETTING: Web-based. SUBJECTS: Convenience sample of Pennsylvanian adults. MEASURES: Primary outcomes were binary responses to 15 COVID-19 knowledge questions weighted by a Likert scale assessing response confidence. ANALYSIS: Generalized linear mixed-effects models to assess comparisons between clinical decision makers (CDM), non-clinical decision makers working in healthcare (non-CDM) and non-healthcare workers (non-HCW). RESULTS: CDMs (n = 91) had higher overall knowledge than non-CDMs (n = 854; OR 1.81

[1.51, 2.17], p < .05). Overall knowledge scores were not significantly different between non-CDMs (n = 854) and non-HCW (n = 4,966; OR 1.03 [0.97, 1.09], p > .05). CONCLUSION: The findings suggest a need for improved education about COVID-19 for healthcare workers who are not clinical decision makers, as they play key roles in patient perceptions and compliance with preventive medicine during primary care visits.

FIGURES

#	Questions and Correct Responses	OR (95% CL)		
		CDM vs. Non-HCW	Non-CDM vs. Non-HCW	CDM vs. Non-CDM
1	Treatments for the symptoms of COVID-19 are available without a prescription = TRUE	**3.33 (2.01, 5.53)**	1.24 (1.03, 1.49)	**2.69 (1.59, 4.57)**
2	Most hospitalized patients with COVID-19 should be treated in an ICU = FALSE	**3.39 (1.63, 7.05)**	1.00 (0.81, 1.23)	**3.39 (1.60, 7.20)**
3	The CDC recommends using corticosteroids for COVID-19 patients with acute respiratory distress syndrome (ARDS) = FALSE	**2.60 (1.32, 5.12)**	0.80 (0.63, 1.02)	**3.25 (1.61, 6.57)**
4	COVID-19 is the first coronavirus to cause disease in humans = FALSE	2.88 (0.62, 13.43)	0.90 (0.62, 1.29)	3.21 (0.67, 15.44)
5	Patients with shortness of breath, fever, and cough should call the emergency room prior to arrival = TRUE	1.17 (0.54, 2.57)	1.21 (0.90, 1.61)	0.97 (0.43, 2.22)
6	Patients whose first (early) symptoms are severe are more likely to die from COVID-19 than those whose first (early) symptoms are less severe = FALSE	0.56 (0.29, 1.05)	**0.70 (0.55, 0.89)**	0.80 (0.41, 1.55)
7	Children ages 5 and under are at higher risk of death from COVID-19 = FALSE	2.14 (0.80, 5.69)	0.93 (0.70, 1.24)	2.29 (0.84, 6.28)
8	In someone who has not received the measles vaccine, measles is more contagious than COVID-19 = TRUE	**2.64 (1.49, 4.66)**	1.05 (0.85, 1.30)	**2.51 (1.38, 4.56)**
9	The incubation period for the coronavirus that causes COVID-19 is up to 21 days = FALSE	0.94 (0.55, 1.62)	1.02 (0.83, 1.24)	0.93 (0.52, 1.64)
10	Healthy people should wear facemasks to help prevent the spread of COVID-19 = FALSE	2.01 (0.85, 4.72)	1.22 (0.94, 1.58)	1.64 (0.68, 3.97)
11	A vaccine for COVID-19 should be available within approximately 3 months = FALSE	3.27 (0.80, 13.42)	0.82 (0.60, 1.13)	3.97 (0.94, 16.68)
12	CDC recommends the use of alcohol-based hand sanitizers with greater than 60% ethanol or 70% isopropanol = TRUE	1.86 (0.53, 6.60)	0.90 (0.63, 1.28)	2.07 (0.57, 7.58)
13	Currently, the CDC recommends that everyone with COVID-19 symptoms should get tested = FALSE	**3.76 (2.01, 7.01)**	**1.47 (1.21, 1.79)**	**2.56 (1.34, 4.87)**
14	Everyone who tests positive for COVID-19 should be treated with hydroxychloroquine (Plaquenil ®) or chloroquine = FALSE	2.36 (0.57, 9.70)	1.06 (0.72, 1.57)	2.23 (0.52, 9.53)
15	COVID-19 testing is not recommended for individuals with no symptoms, even if they were exposed to someone with confirmed COVID-19 within the past 2 weeks = TRUE	**2.84 (1.29, 6.25)**	**1.37 (1.09, 1.72)**	2.07 (0.92, 4.66)
16	Total Score (15-Item)	**1.86 (1.56, 2.22)**	1.03 (0.97, 1.09)	**1.81 (1.51, 2.17)**

Non-HCW = a person not working in healthcare. Non-CDM = a person working in healthcare who is not a clinical decision maker. CDM = a person working in healthcare who is a clinical decision maker (MD, DO, CRNP, PA). OR = Odds Ratio. CL = Confidence Limits. Statistically significant comparisons are **bolded** ($p < .05$).

Table 1: "COVID-19 Knowledge Compared Between Groups".

Information source	Non-HCW (N = 4951)	Non-CDM (N = 850)	CDM (N = 91)
Social Media (Facebook, Instagram, Twitter, etc.)	2%	2%	0%
Government Websites (CDC, NIH, WHO)	41%	54%	66%
Television News channels	29%	17%	7%
Other (Family, Friends, Internet News Websites, Radio, etc.)	28%	27%	27%

Non-HCW = a person not working in healthcare. Non-CDM = a person working in healthcare who is not a clinical decision maker. CDM = a person working in healthcare who is a clinical decision maker (MD, DO, CRNP, PA).

Table 2: ". Current, Single Most Trusted Source for Information About COVID-19 Among Groups".

MESSAGES TO INCREASE COVID-19 KNOWLEDGE IN COMMUNITIES OF COLOR: WHAT MATTERS MOST?

Cooper LA, Stoney CM.. Ann Intern Med. 2020 Dec 21. doi: 10.7326/M20-8057. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A professional opinion piece, written by a physician from Johns Hopkins University and a researcher from the National Institutes of Health (U.S.), discusses the results of a study by Alsan et al., which explored the relationship between aspects of COVID-19 messaging and information-seeking behavior in African American and Latinx groups, as well as general ways to best communicate COVID-19 messages in order to narrow the racial disparities in COVID-19 outcomes in the United States. The Alsan et al. study found that concordance of race with the messenger increased information seeking behavior on the African American group, demonstrating the need to have diverse messaging, though a lack of effect in the Latinx group suggests that other demographic characteristics, such as age, gender, and language, may also be important. The authors of this professional opinion piece also suggest that the well-documented lower level of trust in healthcare professionals among people of color indicates the need for COVID-19 communications to come from trusted members within communities. The authors suggest that these factors be considered in order to increase the effectiveness of COVID-19 communications among all racial groups.

PREGNANT PERSONS

PERSISTENCE OF SARS-COV-2 IN THE FIRST TRIMESTER PLACENTA LEADING TO TRANSPLACENTAL TRANSMISSION AND FETAL DEMISE FROM AN ASYMPTOMATIC MOTHER

Shende P, Gaikwad P, Gandhewar M, Ukey P, Bhide A, Patel V, Bhagat S, Bhor V, Mahale S, Gajbhiye R, Modi D.. Hum Reprod. 2020 Dec 21:deaa367. doi: 10.1093/humrep/deaa367. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

An interdisciplinary group of researchers at Model Hospital in Mumbai, India describe a case of hydrops fetalis detected at 13 weeks gestation in an asymptomatic carrier of the SARS-CoV-2 virus. The patient tested posted for COVID-19 at 7.6 weeks of gestation and then was subsequently found to have detectable SARS-CoV2 in the amniotic fluid and placental cells at 13 weeks gestation. These findings suggest possible transplacental SARS-CoV-2 transmission and viral replication within the placenta. While there was evidence of robust placental inflammation, fetal tissue was unavailable for biopsy and therefore infection of the fetus itself is unable to be determined.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by infection of the respiratory tract by SARS-CoV-2 which survives in the tissues during the clinical course of infection but there is limited evidence on placental infection and vertical transmission of SARS-CoV-2. The impact of COVID-19 in first trimester pregnancy remains poorly understood. Moreover, how long SARS-CoV-2 can survive in placenta is unknown. Herein we report a case of a pregnant woman in the first trimester who tested positive for SARS-CoV-2 at 8 weeks of gestation although her clinical course was asymptomatic. At 13 weeks of gestation, her throat swab tested negative for SARS-CoV-2 but viral RNA was detected in the placenta and the Spike (S) proteins (S1 and S2) were immunolocalized in cytotrophoblast and syncytiotrophoblast cells of the placental villi. Histologically, the villi were generally avascular with peri-villus fibrin deposition and in some areas the syncytiotrophoblast layer appeared lysed. The decidua also had fibrin deposition with extensive leucocyte infiltration suggestive of inflammation. The SARS-CoV-2 crossed the placental barrier, as the viral RNA was detected in the amniotic fluid and the S proteins were detected in the fetal membrane. Ultrasonography revealed extensively subcutaneous edema with pleural effusion suggestive of hydrops fetalis and the absence of cardiac activity indicated fetal demise. This is the first study to provide concrete evidence of persistent placental infection of SARS-CoV-2 and its congenital transmission associated with hydrops fetalis and intrauterine fetal demise in early pregnancy.

IMMUNOMETABOLISM AT THE CORNERSTONE OF INFLAMMAGING, IMMUNOSENESCENCE, AND AUTOIMMUNITY IN COVID-19

Omarjee L, Perrot F, Meilhac O, Mahe G, Bousquet G, Janin A.. Aging (Albany NY). 2020 Dec 27;12. doi: 10.18632/aging.202422. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

In this review, an interdisciplinary group of French researchers propose that inflammaging, which is chronic low-grade inflammation that occurs with aging, may be the common factor predisposing individuals with certain comorbidities to more severe COVID-19 (Figure 1). They discuss how the underlying mechanisms of immunosenescence and chronic inflammation seen in diseases such as diabetes, hypertension, metabolic syndrome, systemic lupus erythematosus, and rheumatoid arthritis seem to predispose COVID-19 patients to the immune dysfunction and cytokine storm observed in severe disease (Figure 2). Thus, authors propose an immunometabolism-mediated treatment paradigm that includes metformin, rapamycin, and dimethyl fumarate (Figure 3).

SUMMARY

Inflammaging, the state of chronic low-grade inflammation, is found to predispose patients to severe forms of COVID-19. Due to it's effects on the levels of inflammaging, the involvement of T-cells in the pathways of inflammation were evaluated due to it's relevance to the pathology of severe autoimmune symptoms. The model of immunosenescence explains how, at several levels, aging, at the cellular level, contributes to both a reduced ability to clear viral infections, and an increased rate of inflammatory-related diseases. Current treatments which target various pathways, including Rapamycin, Metformin, and Dimethyl fumarate hold potential to reduce the autoimmune effects induced by COVID-19 in elderly and pre-disposed patients.

ABSTRACT

Inflammaging constitutes the common factor for comorbidities predisposing to severe COVID-19. Inflammaging leads to T-cell senescence, and immunosenescence is linked to autoimmune manifestations in COVID-19. As in SLE, metabolic dysregulation occurs in T-cells. Targeting this T-cell dysfunction opens the field for new therapeutic strategies to prevent severe COVID-19. Immunometabolism-mediated approaches such as rapamycin, metformin and dimethyl fumarate, may optimize COVID-19 treatment of the elderly and patients at risk for severe disease.

FIGURES

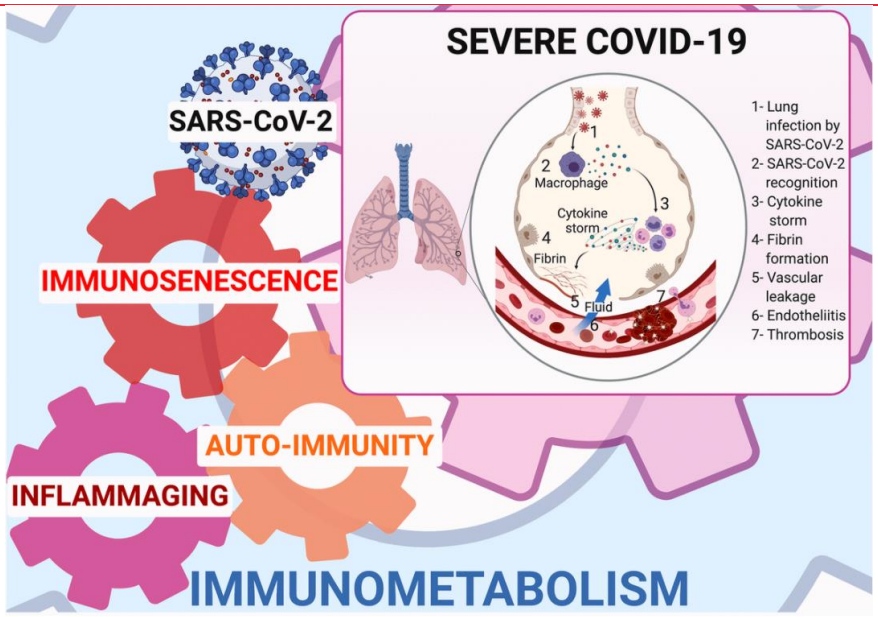


Figure 1. Figure 1. Immunometabolism at cornerstone of inflammaging, immunosenescence, and autoimmunity in COVID-19.

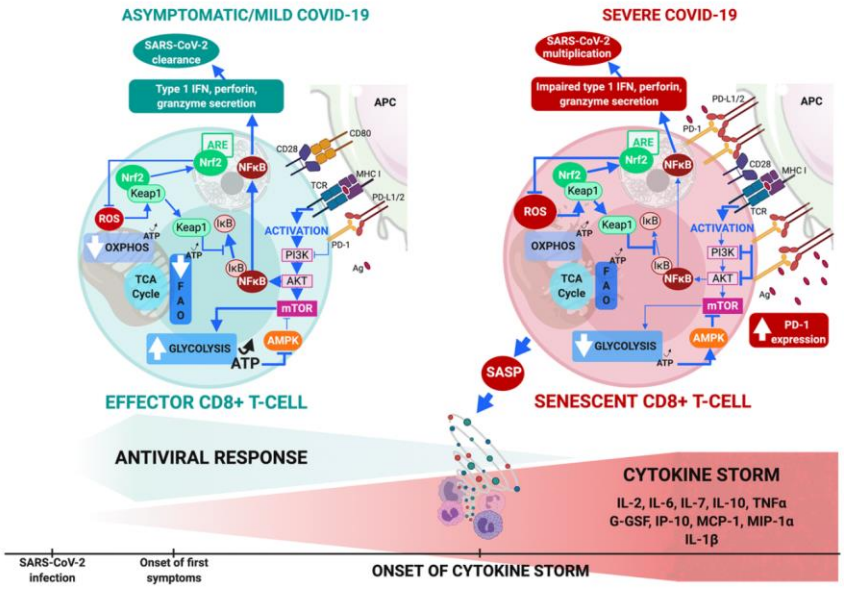


Figure 2. CD8+ T-cell metabolism in COVID-19.
(A) In comorbidity-free patients developing asymptomatic/mild symptomatic forms of COVID-19, cytotoxic immune response mediated by effector CD8+ T-cells results in eradication of virus and patient recovery. Normal antigen levels in antigen-presenting cells and cytokine levels (interleukin IL-2 released by helper CD4+ T-cells) stimulate TCRs and co-receptors such as CD28, thus enhancing mTOR signaling via PI3K and protein kinase B that increases glycolysis. Cells shift from OXPHOS/FAO to glycolytic-based metabolism, whereby anabolic processes activate effector cells to clear infection. This includes production of cytotoxic factors (type 1 Interferon, granzyme, perforin) and enhanced proliferation. Massive increase in glycolysis results in production of ATP (less than OXPHOS but sufficient to inhibit AMPK, preventing mTOR pathway blockade. ROS production activates Nrf2, reducing inflammation and apoptosis by inhibiting NF-κB and pro-inflammatory cytokine production.
(B) Aging and age-related disorders cause CD8+ T-cell senescence in severe COVID-19. Excess antigens upregulate inhibitory receptors (programmed death-1: PD-1) that block TCR activation, thus reducing signaling required for glycolytic metabolic phenotype itself crucial to proper effector functioning. Malfunction is compounded by upregulation of PD-1 expression-enhancing transcription factors, reduction in helper cell survival and proliferation signaling (IL-2), and increase in inhibitory signals. Senescent CD8+ T cells secrete SASP, paracrinely amplifying production of inflammatory cytokines and triggering cytokine storm. Massive decrease in glycolysis causes fall in ATP production and fails to sufficiently inhibit AMPK which then partially inhibits mTOR pathway. Substantial ROS production activates Nrf2 but fails to inhibit NF-κB pathway and pro-inflammatory cytokine production. These events combined make cells malfunction metabolically, inhibit cytotoxic function and exhaust the phenotype.

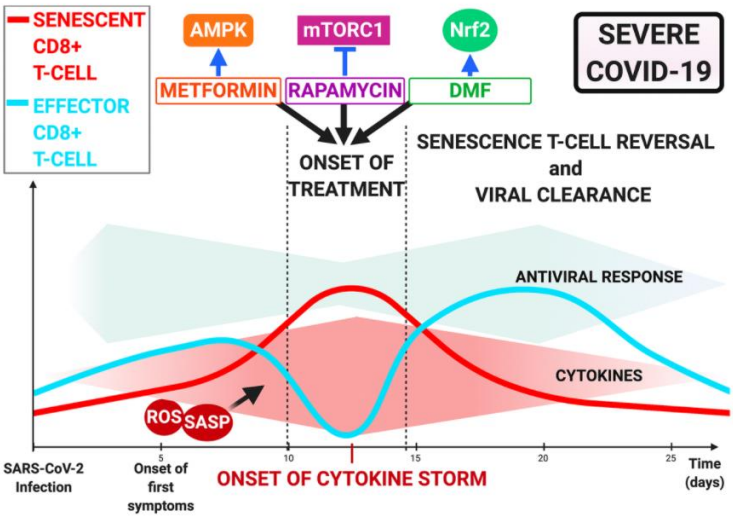


Figure 3. Immunometabolism-Mediated therapies targeting T-cell dysfunction in COVID-19. Onset of cytokine storm as treatment opportunity via rapamycin, metformin, and dimethyl fumarate. Inhibition of mTOR by rapamycin, AMPK by metformin and Nrf2 activation by dimethyl fumarate may restore CD8+ T-cell functionality and improve antiviral response and patient outcome.

MUSCLE BIOPSY FINDINGS IN A CASE OF SARS-COV-2-ASSOCIATED MUSCLE INJURY

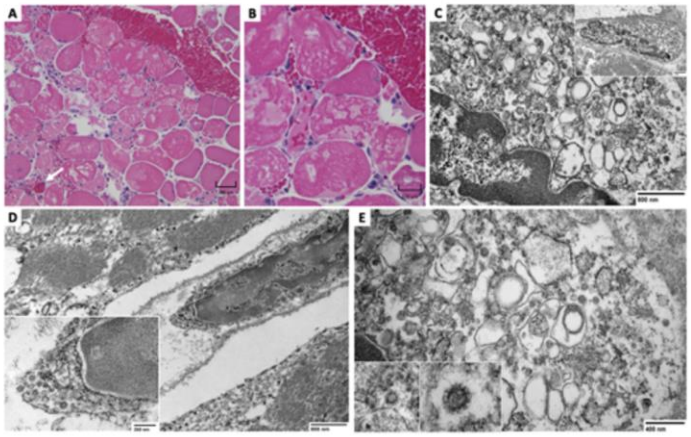
Hooper JE, Uner M, Priemer DS, Rosenberg A, Chen L.. J Neuropathol Exp Neurol. 2020 Dec 22:nlaa155. doi: 10.1093/jnen/nlaa155. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Researchers at Johns Hopkins and the University of Minnesota describe the muscle biopsy of a patient who passed away from complications of COVID-19. These findings (Figure 1) demonstrate cellular damage within skeletal muscle that is consistent with "primary vascular origin." Since skeletal myocytes have minimal expression of ACE-2 receptors, the authors speculate that damage to skeletal muscles likely results from secondary inflammatory and coagulopathic changes, rather than direct viral damage. They theorize that these findings seen on electron microscopy may correlate with the myalgias and elevated CK enzymes seen in SARS-CoV-2 infection.

FIGURES

FIGURE 1.



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(A) Perimysial hemorrhages, vacuolated fibers and one adjacent fibrin microthrombus (arrow) (H&E, ×200). **(B)** Degenerated/atrophic myocyte (H&E, ×400). **(C)** A degenerated cell (inset: direct magnification, ×15 000) with several virus-like particles in cytoplasm (direct magnification, ×25 000). **(D)** Degenerated cell (direct magnification, ×20 000) with a cluster of virus-like particles in the cytoplasm (inset: direct magnification, ×60 000). **(E)** Virus-like particles in close contact with membranes of organelles (direct magnification, ×40 000); cytoplasmic virus-like particles with hairy/spike-like features surrounding the spherical structure (insets: average diameter of 61.47 nm [22 measurements; minimum 49.9–maximum 78.9 nm]).

Figure 1.

VERTICAL TRANSMISSION OF SARS-COV-2 FROM COVID-19 INFECTED PREGNANT WOMEN: A REVIEW ON INTRAUTERINE TRANSMISSION

Naz S, Rahat T, Memon FN.. Fetal Pediatr Pathol. 2020 Dec 27:1-13. doi: 10.1080/15513815.2020.1865491. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Members of the Pakistan Health Research Council reviewed 16 articles (498 COVID-19 infected pregnant women) on vertical transmission of SARS-CoV-2 published between March and October 2020 (Table 1). They found vertical transmission occurred in 4.883% of SARs-CoV-2 infected mothers (23/471), and in the 17 cases where outcomes were reported, 4 infants developed COVID-19 pneumonia, 8 required care in the neonatal intensive care unit, 4 received mechanical ventilation, and none died (Table 2). Authors suggest vertical transmission is possible and that because severe neonatal complications can occur, recommend neonatal screening for infants born to mothers with SARS-CoV-2.

ABSTRACT

BACKGROUND: Fetal safety is a major concern with the global spread of COVID-19, but there is scarce information regarding vertical transmission and how it affects the fetus. OBJECTIVE: To assess and summarize the currently available evidence on vertical transmission (probable/confirmed) of SARS-CoV-2 along with fetal outcomes. METHODS: The current review was carried out from March to October 2020. Relevant databases were searched electronically. Pertinent articles were selected according to eligibility criteria and information was compiled. RESULTS: In 16 selected articles there were total 498 COVID-19 infected pregnant women ranging in age between 15 and 45 years. Gestational age at the onset of COVID-19 symptoms ranged from 25-41 weeks. Vertical transmission (probable and confirmed) rate from series was 4.883% (23/471). Of 17 affected newborns (information available), 08 required NICU admission, 04 developed pneumonia and 04 required mechanical ventilation. CONCLUSION: There is probable intrauterine transmission of SARS-CoV-2. Few adverse fetal outcomes are associated with COVID-19.

FIGURES

Table 1. Characteristics of studies included in the current review.

Author	Study location	Duration	Number of pregnant women	Study design	Maternal age (years) (median)	Vertical transmission	Vertical transmission confirmed by	Test kit used
Liu Y et al [8]	China	December 82,019 to February 25, 2020	13	retrospective study	30 (22-36)	No	SARS-CoV-2 Quantitative RT-PCR	not reported
Chen H et al [9]	Wuhan, China	Jan 20 to Jan 31, 2020	09	retrospective study	28 (26-40)	No	SARS-CoV-2 Quantitative RT-PCR	(COVID-19 Kit (Bio Germ, Shanghai, China)
Cuifang Fan [10]	Wuhan, China	January 2020	02	case series	34 29	No	SARS-CoV-2 Quantitative RT-PCR	(Bioperfectus Technologies, China)
Jie YAN [11]	China	January 20 to March 24, 2020	116	retrospective study	30.8 (24-41)	No	SARS-CoV-2 Quantitative RT-PCR	not reported
Hui Zeng [12]	Wuhan, China	February 16 to March 6, 2020	06	retrospective study	not reported	02/06 (33.3%)	SARS-CoV-2-IgM antibodies	(CLIA assays kit YHLO)
Lan Dong [13]	Wuhan, China	Jan 2020	01	case report	29	Yes	SARS-CoV-2-IgM antibodies	not reported
ZENG et al. [14]	Wuhan, China	January 2020 to February 2020	33	case series	not reported	3/33 (9.0%)	SARS-CoV-2 Quantitative RT-PCR	(Coronavirus PCR Fluorescence Diagnostic Kit [BGI])
Maria Claudia Alzamora [15]	Peru	March 2020	01	case report	41	Yes	SARS-CoV-2 Quantitative RT-PCR	not reported
Marzieh Zamaniyan [16]	Iran	April 2020	01	case report	22	Yes	SARS-CoV-2 Quantitative RT-PCR	SuperScript III Platinum, Invitrogen, USA
Suliman Khan [17]	Hubei China	April 2020	17	case series	24-34	02/17 (11.76%)	SARS-CoV-2 Quantitative RT-PCR	not reported
Julide Sisman [18]	Dallas Texas	September 2020	01	case report	37	Yes	SARS-CoV-2 Quantitative RT-PCR	Xpert Xpress SARS-CoV-2 RT-PCR (Cepheid, Sunnyvale, CA)
Luisa Patane [19]	Bergamo Italy	September 2020	22	case series	not reported	02/22 (9.09%)	SARS-CoV-2 Quantitative RT-PCR	Not reported
Maksim Kirtsman [20]	Ontario, Canada	June 2020	01	Case report	40	Yes	SARS-CoV-2 Quantitative RT-PCR	RT-PCR Allplex 2019-nCoV assay, Seegene
Alexandre J. Vivanti [21]	Paris, France	July 2020	01	Case report	23	Yes	SARS-CoV-2 Quantitative RT-PCR	The RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Altona Diagnostics GmbH, Hamburg, Germany)
Claudio Fenizia [22]	Milan, Italy	October 2020	31	Prospective study	30 (15–45)	2/31 (6.45%)	SARS-CoV-2 Quantitative RT-PCR	Real-Time PCR ELITe InGenius® system and the GeneFinderTM COVID-19 Plus RealAmp Kit assay (ELITechGroup, France)
Marian Knight [23]	UK	May 2020	243	Prospective study	20-35	12/243 (4.93%)	SARS-CoV-2 Quantitative RT-PCR	Not reported

Table 2. Clinical features of SARS-CoV-2 positive newborns.

Author (Study location) [Duration]	Number of SARS-CoV-2 positive newborns	Fever	Dyspnea	Asphyxia	Respiratory distress syndrome	Cyanosis	Pneumonia	Neonatal intensive care unit admission	Mechanical ventilation
Hui Zeng (Wuhan, China) [February 16 to March 6, 2020] [12]	02	not reported	not reported	not reported	not reported	not reported	not reported	not reported	not reported
Lan Dong (Wuhan, China) [Jan 2020] [13]	01	No	No	No	No	No	No	No	No
ZENG et al (Wuhan, China) [January 2020 to February 2020] [14]	03	02/03	01/03	01/03	01/03	01/03	03/03	03/03	01/03
Maria Claudia Alzamora (Peru) [March 2020] [15]	01	No	Yes	No	No	No	No	Yes	Yes
Marzieh Zamaniyan (Iran) [April 2020] [16]	01	Yes	No	No	No	No	No	Yes	No
Suliman Khan (Hubei, China) [April 2020] [17]	02	No	No	No	No	No	Yes	No	No
Julide Sisman (Dallas Texas) [September 2020] [18]	01	Yes	No	No	Yes	No	No	Yes	Yes
Luisa Patane Bergamo Italy September 2020[19]	02	No	No	No	No	No	No	No	No
Maksim Kirtsman (Ontario, Canada) [June 2020] [20]	01	No	No	No	No	No	No	Yes	No
Alexandre J. Vivanti (Paris, France) [July 2020] [21]	01	No	No	No	No	No	No	Yes	Yes
Claudio Fenizia (Milan, Italy) [October 2020] [22]	02	No	No	No	No	No	No	No	No
Marian Knight (UK) [May 2020] [23]	12	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	01	Not reported

PREVENTION IN THE COMMUNITY

SUPPRESSION OF SARS-COV-2 AFTER A SECOND WAVE IN VICTORIA, AUSTRALIA

Giles ML, Wallace EM, Alpren C, Brady N, Crouch S, Romanes F, Sutton B, Cheng A.. Clin Infect Dis. 2020 Dec 23:ciaa1882. doi: 10.1093/cid/ciaa1882. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A report from members of the Department of Health and Human Services in Victoria, Australia details their strategy to combat a second wave of COVID-19 beginning June 2020. Initial interventions included movement limitations in high risk areas, testing/tracing efforts, a stay at home order with limited exceptions, and mandatory masks for all >12-years-old. Restrictions eventually escalated to "stage 4" on August 2, 2020, which included curfew, movement limited to <5km from home, and limiting work to select industries (Figure 1). Because cases subsequently dropped to zero cases for 40 straight days, authors conclude that these measures can successfully suppress community transmission of SARS-CoV-2.

ABSTRACT

Countries around the world are experiencing a second wave of COVID-19 which is proving to be difficult to control. This report describes the combination of physical distancing, mandatory mask wearing, movement restrictions and enhanced test, trace and isolation efforts that can be used to successfully suppress community transmission to zero.

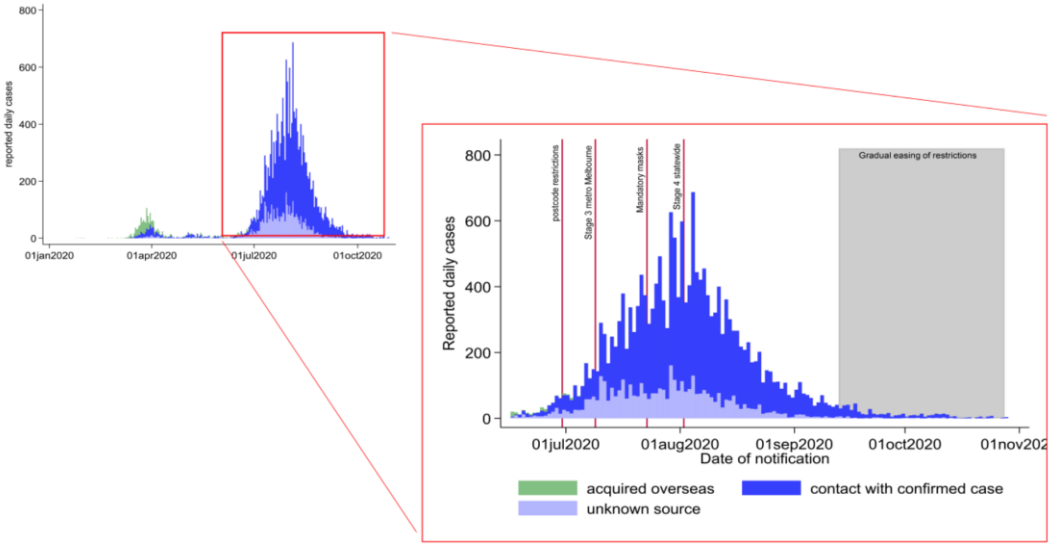


Figure 1: Epidemic curve of COVID-19 in Victoria with restriction levels

CARE BUNDLES FOR IMPROVING OUTCOMES IN PATIENTS WITH COVID-19 OR RELATED CONDITIONS IN INTENSIVE CARE - A RAPID SCOPING REVIEW

Smith V, Devane D, Nichol A, Roche D.. Cochrane Database Syst Rev. 2020 Dec 21;12:CD013819. doi: 10.1002/14651858.CD013819.
Level of Evidence: 2 - Systematic review of randomized trials or n-of-1 trials

BLUF

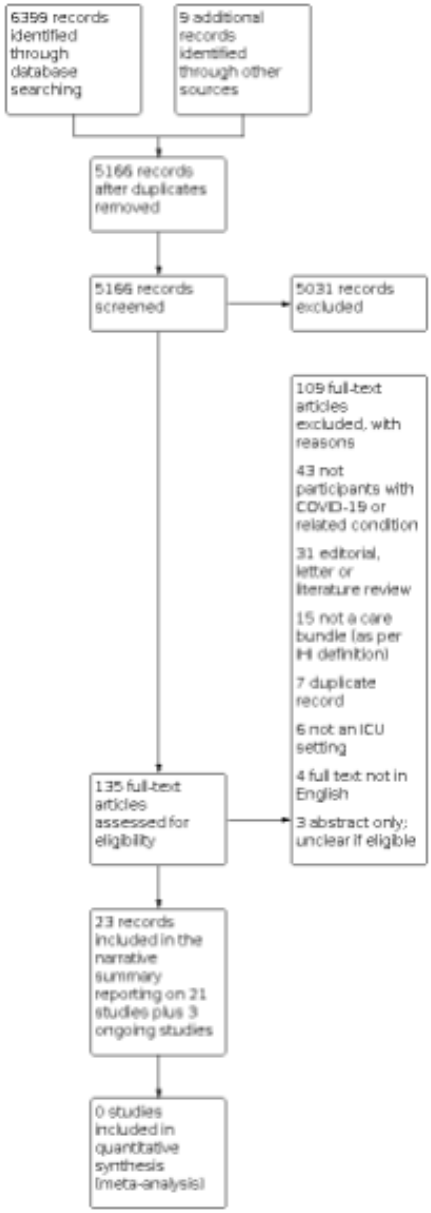
A systematic review by authors from Ireland and Australia examined the literature on ICU care bundles used in the management of COVID-19 and other acute respiratory pathogens. They identified 21 studies encompassing 8 countries (Figure 1), with care bundles most commonly including guidance on ventilator setting, restrictive fluid management, sedation, and prone positioning (summarized in Figures 2-3). The authors ultimately find significant variation in the protocol used for these care bundles, and low quality evidence to support them. Given that care bundles are a cornerstone of ICU care, there is great need for RCTs in this critical aspect of caring for COVID-19 patients.

ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the strain of coronavirus that causes coronavirus disease 2019 (COVID-19) can cause serious illness in some people resulting in admission to intensive care units (ICU) and frequently, ventilatory support for acute respiratory failure. Evaluating ICU care, and what is effective in improving outcomes for these patients is critical. Care bundles, a small set of evidence-based interventions, delivered together consistently, may improve patient outcomes. To identify the extent of the available evidence on the use of care bundles in patients with COVID-19 in the ICU, the World Health Organization (WHO) commissioned a scoping review to inform WHO guideline discussions. This review does not assess the effectiveness of the findings, assess risk of bias, or assess the certainty of the evidence (GRADE). As this review was commissioned to inform guideline discussions, it was done rapidly over a three-week period from 26 October to 18 November 2020. OBJECTIVES: To identify and describe the available evidence on the use of care bundles in the ICU for patients with COVID-19 or related conditions (acute respiratory distress syndrome (ARDS) viral pneumonia or pneumonitis), or both. In carrying out the review the focus was on characterising the evidence base and not evaluating the effectiveness or safety of the care bundles or their component parts. SEARCH METHODS: We searched MEDLINE, Embase, the Cochrane Library (CENTRAL and the Cochrane COVID-19 Study Register) and the WHO International Clinical Trials Registry Platform on 26 October 2020. SELECTION CRITERIA: Studies of all designs that reported on patients who are critically ill with COVID-19, ARDS, viral pneumonia or pneumonitis, in the ICU setting, where a care bundle was implemented in providing care, were eligible for inclusion. One review author (VS) screened all records on title and abstract. A second review author (DR) checked 20% of excluded and included records; agreement was 99.4% and 100% respectively on exclude/include decisions. Two review authors (VS and DR) independently screened all records at full-text level. VS and DR resolved any disagreements through discussion and consensus, or referral to a third review author (AN) as required. DATA COLLECTION AND ANALYSIS: One review author (VS) extracted the data and a second review author (DR) checked 20% of this for accuracy. As the review was not designed to synthesise effectiveness data, assess risk of bias, or characterise the certainty of the evidence (GRADE), we mapped the extracted data and presented them in tabular format based on the patient condition; that is patients with confirmed or suspected COVID-19, patients with ARDS, patients with any influenza or viral pneumonia, patients with severe respiratory failure, and patients with mixed conditions. We have also provided a narrative summary of the findings from the included studies. MAIN RESULTS: We included 21 studies and identified three ongoing studies. The studies were of variable designs and included a systematic review of standardised approaches to caring for critically ill patients in ICU, including but not exclusive to care bundles (1 study), a randomised trial (1 study), prospective and retrospective cohort studies (4 studies), before and after studies (7 studies), observational quality improvement reports (4 studies), case series/case reports (3 studies) and audit (1 study). The studies were conducted in eight countries, most commonly China (5 studies) and the USA (4 studies), were published between 1999 and 2020, and involved over 2000 participants in total. Studies categorised participant conditions patients with confirmed or suspected COVID-19 (7 studies), patients with ARDS (7 studies), patients with another influenza or viral pneumonia (5 studies), patients with severe respiratory failure (1 study), and patients with mixed conditions (1 study). The care bundles described in the studies involved multiple diverse practices. Guidance on ventilator settings (10 studies), restrictive fluid management (8 studies), sedation (7 studies) and prone positioning (7 studies) were identified most frequently, while only one study mentioned chest X-ray. None of the included studies reported the prespecified outcomes ICU-acquired weakness (muscle wasting, weight loss) and users'

experience adapting care bundles. Of the remaining prespecified outcomes, 14 studies reported death in ICU, nine reported days of ventilation (or ventilator-free days), nine reported length of stay in ICU in days, five reported death in hospital, three reported length of stay in hospital in days, and three reported adherence to the bundle. AUTHORS' CONCLUSIONS: This scoping review has identified 21 studies on care bundle use in critically ill patients in ICU with COVID-19, ARDS, viral influenza or pneumonia and severe respiratory failure. The data for patients with COVID-19 specifically are limited, derived mainly from observational quality improvement or clinical experiential accounts. Research is required, urgently, to further assess care bundle use and optimal components of these bundles in this patient cohort. The care bundles described were also varied, with guidance on ventilator settings described in 10 care bundles, while chest X-ray was part mentioned in one care bundle in one study only. None of the studies identified in this scoping review measured users' experience of adapting care bundles. Optimising care bundle implementation requires that the components of the care bundle are collectively and consistently applied. Data on challenges, barriers and facilitators to implementation are needed. A formal synthesis of the outcome data presented in this review and a critical appraisal of the evidence is required by a subsequent effectiveness review. This subsequent review should further explore effect estimates across the included studies.

FIGURES



Study flow diagram. Figure 1 illustrates the searching and selection process.

Studies	Care bundle component	COVID-19 N = 7 studies	ARDS N = 7 studies	Influenza or viral pneumonia N = 5 studies	ARF N = 1 study	Mixed N = 1 study
Balakrishnan 2020; Peng 2020; Mellor 1999; Jung 2012; Luedike 2015; Duggal 2020;	Ventilator settings	O Ca	CP BA BA O	BA BA O	RT	
Mellor 1999; Luedike 2015; Yue 2015; Diaz 2018; Duggal 2020; Cornejo 2011; Wang 2018; Peek 2009	Restrictive fluid management		BA BA BA BA O	BA O	RT	
Balakrishnan 2020; Luedike 2015; Yue 2015; Diaz 2018; Duggal 2020; Cornejo 2011; Wang 2018	Sedation	O BA BA	BA BA BA	O		
Peng 2020; Mellor 1999; Jung 2012; Luedike 2015; Duggal 2020; Cornejo 2011; Peek	Prone positioning	Ca	CP BA BA O	O	RT	
Mellor 1999; Jung 2012; Diaz 2018; Duggal 2020; Georges 2013; Guo 2014; Phua 2016	Vasoactive drugs		CP BA BA O	BA BA		SR
Mellor 1999; Luedike 2015; Diaz 2018; Thomas 2013; Guo 2014; Phua 2016	Antibiotics		BA O BA	BA BA		SR
Balakrishnan 2020; Peng 2020; Janz 2020; Choi 2020	Intubation/respiratory support	CR CR O Ca	BA	BA		
Mellor 1999; Jung 2012; Luedike 2015; Duggal 2020; Cornejo 2011; Peek 2009	ECMO as rescue therapy		CP BA BA O	O	RT	
Singh 2020; Mellor 1999; Luedike 2015; Diaz 2018; Cornejo 2011; Wang 2018	Nutrition	Ca	BA BA O	BA O	RT	
Diaz 2018; Georges 2013; Guo 2014; Phua 2016	IV fluid therapy		BA	BA BA		SR
Albutt 2020; Balakrishnan 2020; Choi 2020	Core team	CR O O				
Luedike 2015; Guo 2014; Thomas 2014	Blood or sputum cultures		BA	BA A		
Balakrishnan 2020; Choi 2020; Wang 2018	Isolation/enhanced PPE/enhanced infection contr	CR O		BA		
Janz 2020; Georges 2013	Extubating	CR		BA		
Singh 2020; Cornejo 2011	Pressure ulcer prevention	Ca		O		
Thomas 2013	Chest X-ray			A		
Georges 2013	Blood transfusion guidance			BA BA		
Georges 2013; Guo 2014	Corticosteroids			BA BA		
Albutt 2020	Arterial lines/ other internal catheters	O				
Cornejo 2011	Mobilisation			O		
Ting 2020	Eye care	Ca				
Choi 2020	Temporary negative pressure ICU	CR				
Choi 2020	Active monitoring for healthcare workers	CR				

ARDS: acute respiratory distress syndrome; **ARF:** acute respiratory failure; **ECMO:** extracorporeal membrane oxygenation; **IV:** intravenous

A: audit
BA: before and after study
Ca: case report
CR/CP: cohort retrospective/cohort prospective
O: observational
RT: randomised controlled trial
SR: systematic review

Figure 2. Care bundle interventions mapped by patient condition and study design

Studies	Pre-specified outcomes	COVID-19 N = 7 studies	ARDS N = 7 studies	Influenza or viral pneumonia N = 5 studies	ARF N = 1 study	Mixed N = 1 study
Peng 2020; Singh 2020; Diaz 2018; Duggal 2020; Jung 2018; Luedike 2015; Mellor 1999; Yang 2014; Yue 2015; Cornejo 2011; Wang 2018; Georges 2013; Thomas 2013; Phua 2016	Death in ICU	Ca Ca	CP CP BA BA BA BA O	BA BA O A		SR
Janz 2020; Peng 2020; Singh 2020; Diaz 2018; Duggal 2020; Yang 2014; Yue 2015; Guo 2014; Georges 2013	Days on ventilation (or ventilator free days)	CR Ca Ca	BA CP BA BA	BA BA		
Peng 2020; Diaz 2018; Duggal 2020; Jung 2019; Yang 2014; Yue 2015; Cornejo 2011; Wang 2018; Georges 2013	Length of stay in ICU	Ca	CP CP BA BA BA	BA O BA		
Janz 2020; Duggal 2020; Mellor 1999; Guo 2014; Peek 2009	Death in hospital	CR	BA O	BA	RT	
Duggal 2020; Cornejo 2011; Wang 2018	Length of stay in hospital		BA	BA O		
Duggal 2020; Luedike 2015; Guo 2014; Thomas 2013	Adherence to the bundle		BA BA	BA A		

Study design key

Systematic review	SR	Randomised controlled trial	RT	Before and after study	BA	Audit	A
Cohort retrospective; Cohort prospective	CR; CP	Observational	O	Case report/case/series	Ca		

ARDS = acute respiratory distress syndrome

ARF = acute respiratory failure

Figure 3. Outcome results mapped by patient condition and study design.

DIAGNOSIS, MANAGEMENT, AND PATHOPHYSIOLOGY OF ARTERIAL AND VENOUS THROMBOSIS IN COVID-19

Piazza G, Morrow DA.. JAMA. 2020 Dec 22;324(24):2548-2549. doi: 10.1001/jama.2020.23422.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

A literature review conducted by cardiologists from Harvard Medical School (U.S.) analyzes current data on the incidence and treatment of thrombotic complications in COVID-19 patients. Previous studies have found thrombotic complications in 2.6% of non-critically ill hospitalized patients and in 35% of critically ill hospitalized patients. Laboratory markers of hypercoagulability are also commonly elevated in these patients, such as D-dimer (100%), Fibrinogen (74%), and Factor VIII (100%). Current guidelines agree that prophylactic anticoagulation with low-molecular-weight-heparin (LMWH) is recommended in critically and non-critically ill hospitalized patients, however there is no consensus on anticoagulation of these patients after discharge (Table 1). While further research is needed on the ideal management of COVID-19-induced coagulopathy, most societies agree that extended prophylaxis in non-hospitalized patients is not recommended.

FIGURES

	Recommendation	
Patient/setting	American College of Chest Physicians	International Society on Thrombosis and Hemostasis
Critically ill	Prophylactic-dose LMWH	Prophylactic-dose LMWH; half-therapeutic-dose LMWH can be considered if patient is high risk
Non-critically ill	Prophylactic-dose LMWH or fondaparinux	Prophylactic-dose LMWH
After discharge	Extended prophylaxis not recommended	LMWH/DOAC for up to 30 d can be considered if high thrombosis risk and low bleeding risk
Nonhospitalized	Routine prophylaxis not recommended	Routine prophylaxis not recommended

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin.

Table. Current Guideline Recommendations for Venous Thromboembolism Prevention in Hospitalized Patients With Coronavirus Disease 2019

MEDICAL SUBSPECIALTIES

HEMATOLOGY AND ONCOLOGY

MORTALITY IN HOSPITALIZED PATIENTS WITH CANCER AND CORONAVIRUS DISEASE 2019: A SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT STUDIES

Desai A, Gupta R, Advani S, Ouellette L, Kuderer NM, Lyman GH, Li A.. Cancer. 2020 Dec 30. doi: 10.1002/cncr.33386. Online ahead of print.
Level of Evidence: 2 - Systematic review of inception cohort studies

BLUF

An interdisciplinary group of American researchers conducted a systematic review and meta analysis of 13 studies on patients with COVID-19 and cancer (See Figure 1) and found a pooled 30-day mortality rate of 30% (95% CI 25-35%) (See Figure 4). After multivariable meta regression, male sex was an independent predictor of higher mortality (See Figure 5), and older age, hematologic malignancy, and active anticancer therapy were also found to be associated with increased mortality. Authors suggest future studies are needed to further investigate how anticancer therapies relate to COVID-19 mortality while accounting for confounding variables such as demographics and comorbidities.

ABSTRACT

BACKGROUND: Heterogeneous evidence exists on the effect of coronavirus disease 2019 (COVID-19) on the clinical outcomes of patients with cancer. METHODS: A systematic review was performed using the Medline, Embase, and CENTRAL databases and the World Health Organization Novel Coronavirus website to identify studies that reported mortality and characteristics of patients with cancer who were diagnosed with COVID-19. The primary study outcome was mortality, defined as all-cause mortality or in-hospital mortality within 30 days of initial COVID-19 diagnosis. The pooled proportion of mortality was estimated using a random-effects model, and study-level moderators of heterogeneity were assessed through subgroup analysis and metaregression. RESULTS: Among 2922 patients from 13 primarily inpatient studies of individuals with COVID-19 and cancer, the pooled 30-day mortality rate was 30% (95% CI, 25%-35%). The overall pooled 30-day mortality rate among 624 patients from 5 studies that included a mixture of inpatient and outpatient populations was 15% (95% CI, 9%-22%). Among the hospitalized studies, the heterogeneity (I2 statistic) of the meta-analysis remained high (I2 , 82%). Cancer subtype (hematologic vs solid), older age, male sex, and recent active cancer therapy each partially explained the heterogeneity of mortality reporting. In multivariable metaregression, male sex, along with an interaction between the median patient age and recent active cancer therapy, explained most of the between-study heterogeneity (R2 , 96%). CONCLUSIONS: Pooled mortality estimates for hospitalized patients with cancer and COVID-19 remain high at 30%, with significant heterogeneity across studies. Dedicated community-based studies are needed in the future to help assess overall COVID-19 mortality among the broader population of patients with cancer.

FIGURES

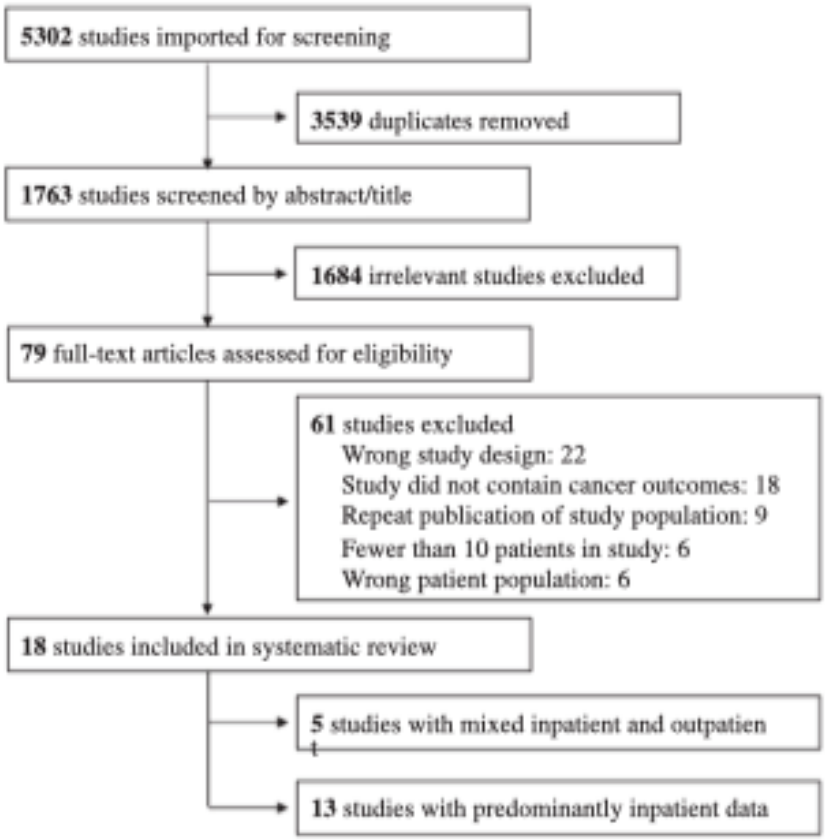


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses study inclusion and exclusion are illustrated.

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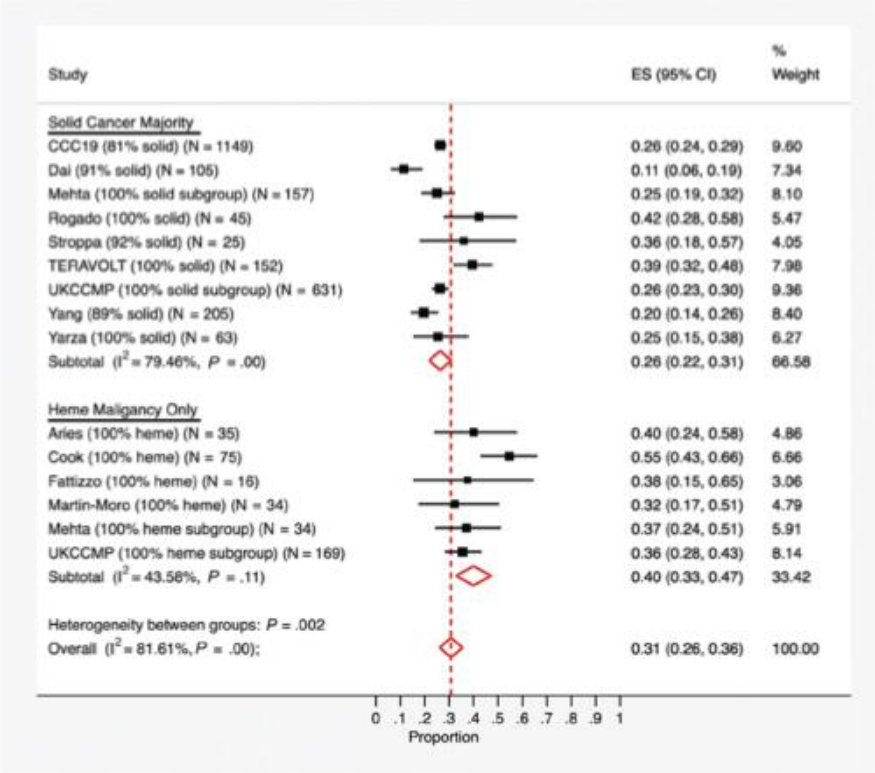
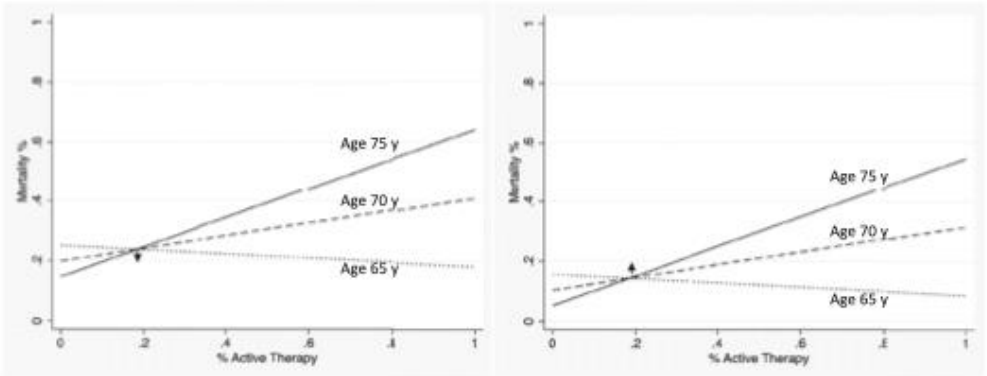


Figure 4. A subgroup analysis of overall mortality among hospitalized patients with cancer and coronavirus disease 2019 (COVID-19) (hospitalized only) is illustrated. CCC19 indicates COVID-19 and Cancer Consortium (Kuderer et al11 and Rivera et al28); ES, effect size; TERAVOLT, Thoracic Cancers International COVID-19 Collaboration (Garassino et al33); UKCCMP, UK Coronavirus Cancer Monitoring Project (Lee et al12). Names on the left are lead author names from the remaining studies that were included in the subgroup analysis.24-27,29-33,34,35



Study-Level Variable	Coefficient	P	Summary Statistics
Median age (1-year increase)	-0.010	.203	R^2 = 96.05% tau2 (current) = 0.000212 tau2 (null) = 0.00538 I^2 residual = 12.45%
Active therapy (1% increase)	-3.719	.002	
Interaction term	0.056	.001	**Interpretation:** older age and male sex are associated with mortality, whereas the effect of active therapy depends on age (significant interaction)
Male (1% increase)	0.473	.024	
Constant term	0.638	.238	

Figure 5. Multivariable meta-regression for mortality among hospitalized patients with cancer and coronavirus disease 2019 (COVID-19) is illustrated.

CLARITHROMYCIN USE FOR ADJUNCT SURGICAL PROPHYLAXIS BEFORE NON-ELECTIVE CESAREAN DELIVERIES TO ADAPT TO AZITHROMYCIN SHORTAGES IN COVID-19 PANDEMIC

Martingano D, Nguyen A, Nkeih C, Singh S, Mitrofanova A.. PLoS One. 2020 Dec 21;15(12):e0244266. doi: 10.1371/journal.pone.0244266. eCollection 2020.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A multicenter prospective cohort study of 240 pregnant patients undergoing non-elective cesarean deliveries from March to June 2020, found that use of clarithromycin as surgical prophylaxis resulted in significantly lower rates of of postpartum endometritis compared to the control group (4.5% vs 11.2%, p = 0.025). These results (Table 2) are important because there has been pandemic-induced shortages of azithromycin (the macrolide typically used for C-section prophylaxis). Notably, all women were SARS-CoV-2 negative and subgroup analysis revealed a significantly decreased risk for Black women ages 18-29. Therefore, use of clarithromycin for C-section prophylaxis may help improve outcomes in both of these vulnerable populations during the COVID-19 pandemic.

ABSTRACT

OBJECTIVE: This study aimed to evaluate safety and effectiveness of clarithromycin as adjunctive antibiotic prophylaxis for patients undergoing non-elective cesarean delivery in comparison with no macrolides, to adapt to azithromycin shortages in COVID-19 pandemic. STUDY DESIGN: We conducted a multi-center, prospective observational cohort study from March 23, 2020 through June 1, 2020. We followed all women receiving either clarithromycin or no macrolide antibiotic for adjunct surgical prophylaxis for non-elective cesarean deliveries. The primary outcome was development of postpartum endometritis. Secondary outcomes included meconium-stained amniotic fluid at time of cesarean delivery, neonatal sepsis, neonatal intensive care unit admission, and neonatal acute respiratory distress syndrome. All patients in this study were tested for SARS-CoV-2 infection and resulted negative. RESULTS: This study included 240 patients, with 133 patients receiving clarithromycin and 107 patients receiving no adjunct macrolide prophylaxis. Patients receiving clarithromycin were noted to have significantly lower rates of postpartum endometritis as compared to those who did not receive adjunct prophylaxis (4.5% versus 11.2%, p = 0.025). In crude (unadjusted) analysis, a significantly lower risk of developing endometritis was noted in the clarithromycin group as compared to the control group (66% decreased risk, 95% CI 0.12 to 0.95, p = 0.040). When adjusted for perceived confounders, a significant difference was again noted (67% decreased risk, 95% CI 0.11 to 0.97, p = 0.034). Stratified analysis of significantly different demographic factors including Black race, BMI, and age was performed. A significantly decreased risk of development of endometritis when taking clarithromycin versus no adjunct macrolide was noted for Black race women in crude and adjusted models (crude: 87% decreased risk, 95% CI 0.08 to 0.83, p = 0.032; adjusted: 91% decreased risk, 95% CI 0.06 to 0.79, p = 0.026). This was also noted for women aged 18-29 years in crude and adjusted models (crude: model, 79% decreased risk, 95% CI 0.06 to 0.80, p = 0.014; adjusted model: 75% decreased risk, 95% CI 0.06 to 0.94, p = 0.028). All other stratified analyses did not yield significant differences in endometritis risk. CONCLUSION: Our study suggests that administration of clarithromycin for adjunctive surgical prophylaxis for non-elective cesarean deliveries may be a safe option that may provide suitable endometritis prophylaxis in cases where azithromycin is unavailable, as was the case during the start of COVID-19 pandemic, most especially for Black race women and women ages 18-29 years.

Table 2. Maternal and neonatal outcomes.

Outcome	Clarithromycin Group n = 133	Control Group n = 107	*p*
Maternal			
Postpartum Endometritis	6 (4.5)	12 (11.2)	0.025[δ]
Meconium Stained Amniotic Fluid (at time of cesarean)	22 (16.5)	14 (13.1)	0.456[δ]
Neonatal			
Intensive Care Unit Admission	10 (7.5)	5 (4.7)	0.365[δ]
ARDS	2 (1.5)	3 (2.8)	0.658[F]
Neonatal Sepsis (Suspected)	3 (2.3)	4 (3.7)	0.703[F]
Neonatal Sepsis (Confirmed)	0 (0)	0 (0)	N/A

Data are presented as mean ± standard deviation (range) or n (%)

[δ] Statistics performed using χ^2 test

[F] Statistics performed using Fischer's Exact Test

*Statistics performed using Welch two-sample two-tailed t-test

Table 2. Maternal and neonatal outcomes.

SUMMARY OF THE DETECTION KITS FOR SARS-COV-2 APPROVED BY THE NATIONAL MEDICAL PRODUCTS ADMINISTRATION OF CHINA AND THEIR APPLICATION FOR DIAGNOSIS OF COVID-19

A R, Wang H, Wang W, Tan W.. Virol Sin. 2020 Dec 22:1-14. doi: 10.1007/s12250-020-00331-1. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

The Chinese Center for Disease Control and Prevention review the 51 approved diagnostic tests for SARS-CoV-2, including nucleic acid, antibody, and antigen methods. Results showed that RT-PCR tests are the most widely approved for COVID-19 (See Figure 1), however emphasis should be placed on utilization of these nucleic acid tests in conjunction with serologic tests to better characterize progression and staging of infection (See Table 3). Authors conclude that increasing the global availability of tests and utilizing a multimodal approach will be critical for ongoing efforts to combat the COVID-19 pandemic.

ABSTRACT

The on-going global pandemic of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been underway for about 11 months. Through November 20, 2020, 51 detection kits for SARS-CoV-2 nucleic acids (24 kits), antibodies (25 kits), or antigens (2 kits) have been approved by the National Medical Products Administration of China (NMPA). Convenient and reliable SARS-CoV-2 detection assays are urgently needed worldwide for strategic control of the pandemic. In this review, the detection kits approved in China are summarised and the three types of tests, namely nucleic acid, serological and antigen detection, which are available for the detection of COVID-19 are discussed in detail. The development of novel detection kits will lay the foundation for the control and prevention of the COVID-19 pandemic globally.

FIGURES

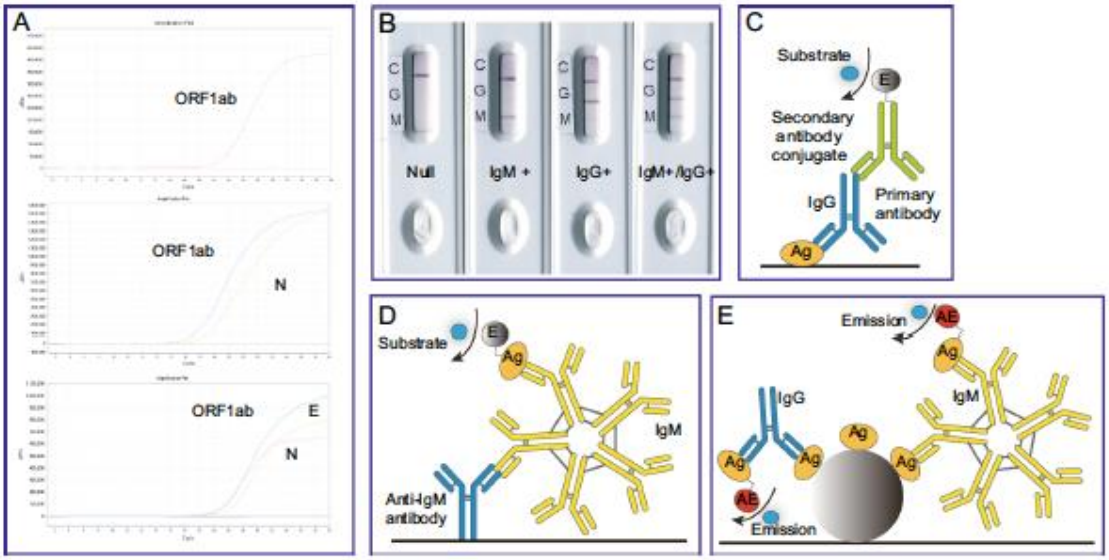


Fig. 1- Representative detection methods developed for SARS-CoV-2. A Representative amplification plots of approved SARS-CoV-2 rRT-PCR kits targeting one (top), two (middle) or three (bottom) regions of the 2019-CoV genome. B Typical results of LFIA approved for 2019-nCoV antibody detection in China. Four lanes show negative, IgM positive, IgG positive, and both IgM and IgG positive results, respectively. C–E Schematic diagram of indirect ELISA for IgG detection; IgM-capture ELISA for IgM detection, and CLIA based on magnetic particle detection for all antibodies, including IgM and IgG.

Table 3 Interpretation of the clinical status of individuals based on nucleic acid and antibody detection results.

No.	Nucleic acid	IgM	IgG	Interpretation	Treatment measures
1	+	–	–	Patients may be during the "window period" of SARS-CoV-2 infection, typically within 2 weeks after infection	Isolation, observation or clinical treatment
2	+	+	–	May be at early infection phage of SARS-CoV-2	
3	+	–	+	May be during the mid and late infection stage or recurrent infection. When the IgG antibody in the recovery period increases by 4 times or more compared with the acute phase, a recurrent infection can be diagnosed	
4	+	+	+	The patient is in the active infection phase, a certain immunity to SARS-CoV-2 has already been developed	
5	–	+	–	One is likely to be in the acute phase of SARS-CoV-2 infection. Nucleic acid testing results should be confirmed first. Other factors such as rheumatoid factors have been found to cause weak IgM positive or positive tests. The result may suggest that one might have been vaccinated recently	Vaccination should be ruled out firstly. Observe, exclude the possibility of false negative of nucleic acid, detect the nucleic acids in different kind of samples once more every 3–5 days, and recheck the antibody level about 7-14 days later to confirm whether elevation appeared. One with both IgM and IgG positive could be diagnosed as a patient. Someone would be isolated according to clinical manifestation and epidemiological history
6	–	–	+	One might have recovered, and the virus has been cleared. The IgG could be detected for a long time in the blood. The result may suggest that one might have been vaccinated previously	
7	–	±	–	One experience the first infection, during an early stage. Thus, the viral load is lower than the lower limit of nucleic acid detection. A small amount of IgM has been produced while IgG has not; a false positive result might be caused by rheumatoid factor. The result may suggest that one might have been vaccinated recently	
8	–	+	+	One might be recently infected with SARS-CoV-2 and is during the recovery period. The virus has been cleared, but the IgM has not been reduced to the lower limit of detection; or the nucleic acid test result might be false negative and the patient is indeed in the active infection stage. The result may suggest that one might have been vaccinated recently	

Note: "+", positive; "-", negative; "±", weak positive

Table 3- Interpretation of the clinical status of individuals based on nucleic acid and antibody detection results.

DRUG DEVELOPMENT POST COVID-19 PANDEMIC: TOWARD A BETTER SYSTEM TO MEET CURRENT AND FUTURE GLOBAL HEALTH CHALLENGES

Aghila Rani KG, Hamad MA, Zaher DM, Sieburth SM, Madani N, Al-Tel TH.. Expert Opin Drug Discov. 2020 Dec 28:1-7. doi: 10.1080/17460441.2021.1854221. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A professional opinion piece by researchers associated with the College of Dental Medicine at the University of Sharjah (UAE) describes challenges that limit the abilities of drug discovery projects as well as potential solutions to these problems. In the wake of rapidly developing diseases (SARS, MERS) and diseases increasing in prevalence (Alzheimer's disease, cancers), the authors suggest that limitations on drug development, such as the substantial cost and risk of drug development, the slow pace of projects, and the lack of data sharing (Figure 2) need to be eliminated if possible. International response to the COVID-19 pandemic demonstrated the possibility of a more streamlined drug discovery process (Figure 1), which the authors believe could be achieved more universally through consortiums of nations, academic institutions, clinicians, pharmaceutical companies, and funders that seek to efficiently tackle the world's major health challenges through drug discovery.

ABSTRACT

Introduction: Despite advances in drug research and development, our knowledge of the underlying molecular mechanisms of many diseases remains inadequate. This have led to limited effective medicines for several diseases. To address these challenges, efficient strategies, novel technologies, and policies are urgently needed. The main obstacles in drug discovery and development are the mounting cost, risk, and time frame needed to develop new medicines. Fair pricing and accessibility is another unmet global challenge. Areas covered: Here, the authors cover the pace, risks, cost, and challenges facing drug development processes. Additionally, they introduce disease-associated data which demand global attention and propose solutions to overcome these challenges. Expert opinion: The massive challenges encountered during drug development urgently call for a serious global rethinking of the way this process is done. A partial solution might be if many consortiums of multi-nations, academic institutions, clinicians, pharma companies, and funding agencies gather at different fronts to crowdsource resources, share knowledge and risks. Such an ecosystem can rapidly generate first-in-class molecules that are safe, effective, and affordable. We think that this article represents a wake-up call for the scientific community to immediately reassess the current drug discovery and development procedures.

FIGURES

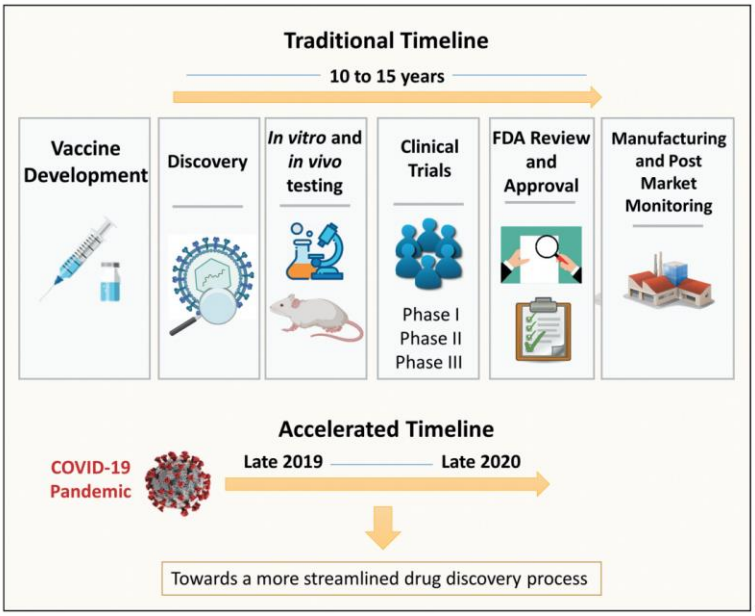


Figure 1. Comparison between the traditional vaccine development timeline and the accelerated development time line in response to the COVID-19 pandemic

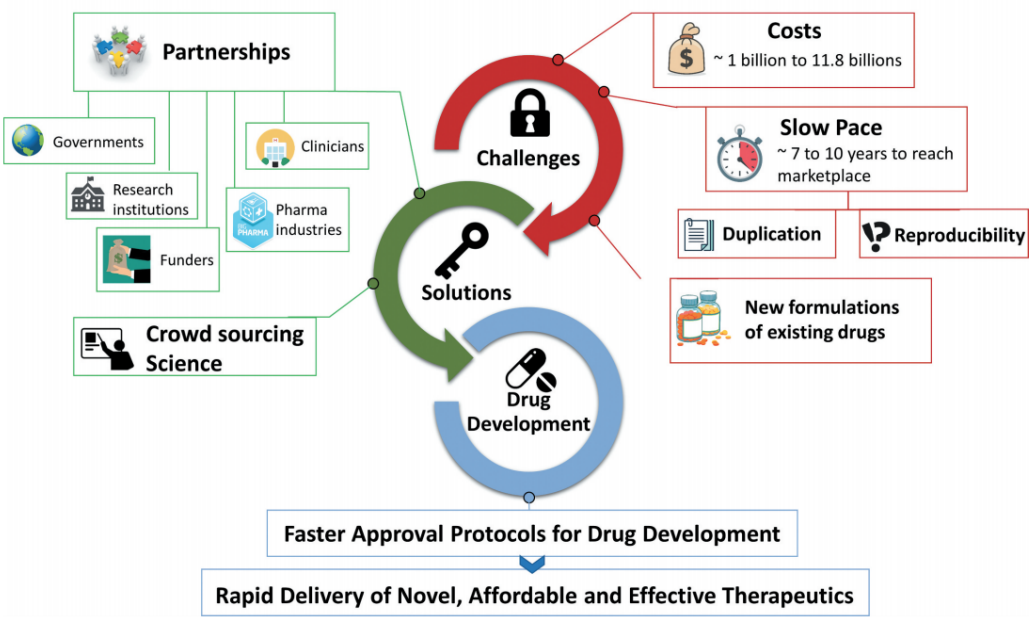


Figure 2. Schematic representation depicting the challenges facing the current drug development process and proposed solutions toward rapid delivery of novel, affordable and effective therapeutics.

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