

# Perspectives on Repurposed Drugs Based on Globally Accepted Therapeutic Guidelines to Combat SARS-CoV-2 Infection

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**Abstract:** A beta coronavirus was identified in Wuhan, China, in December 2019 and was named severe acute respiratory syndrome coronavirus-2. It spread globally at a rapid rate and killed innumerable people. The SARS-CoV-2 infection, also called coronavirus disease 2019, was declared a pandemic by WHO on March 11, 2020. The increasing number of SARS-CoV-2 related deaths is due to a number of reasons. A few antiviral, antimicrobial, and immune-based drugs have been repurposed for treatment as well as improvement of patient prognosis. These drugs are currently being studied in clinical trials conducted by the World Health Organization (WHO), National Institutes of Health (NIH), and other global health organizations to identify the agents that produce maximum positive patient outcomes and reduction in mortality rate. The aim of this article is to discuss the safety and efficacy of the repurposed drugs in SARS-CoV-2 infection based on currently available clinical evidence and to emphasize the importance of caution required whilst employing the international therapeutic guidelines. Also highlighted in this article are certain specific comorbid conditions, that either involve treatment with the repurposed drugs or have a direct impact of the virus in patients owing to their vulnerability.

**Keywords:** MERS, SARS-CoV-2, acute respiratory distress syndrome, cytokine storm syndrome, therapeutic guidelines, COVID-19

## Background

Coronaviruses are a large family of viruses that predominantly reside in and circulate amongst animals. They can be categorized into *alpha*, *beta*, *gamma*, and *delta* subtypes, which together belong to the *Coronaviridae* family and *Nidovirales* order. The *alpha* and *beta* coronaviruses have the ability to transfer between animals and humans. These include the ones that induce common cold, along with MERS and SARS coronaviruses that cause Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome, respectively.<sup>1</sup> The coronaviruses are enveloped, containing non-segmented, positive polarized, single stranded RNA. They derive the name “Coronavirus” from a common feature shared by all of these viruses – the Spike (S) protein projecting out of the viral envelope, providing a crown like appearance under the electron microscope.<sup>1</sup> The SARS coronavirus (SARS-CoV) that caused a serious acute viral respiratory infection was first reported from Asia in February 2003. More than 8,000 people contracted the infection with 774 deaths. SARS spread exponentially to 26 countries before it

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was controlled within about 4 months. No SARS cases have been reported since 2004.<sup>2,3</sup> Likewise, the MERS coronavirus (MERS-CoV) that induced a similar respiratory disease was first documented in September 2012 in Saudi Arabia, and has since spread to 27 countries, as per the World Health Organization reports.<sup>2</sup> Those infected with MERS-CoV developed similar symptoms to SARS, which included cough, shortness of breath, and fever.<sup>2,3</sup> The World Health Organization has confirmed 2,519 cases of MERS and 866 deaths since its inception till date.<sup>1-3</sup>

In December 2019, an unexplained etiological pneumonia was identified in Wuhan, China, and was reported to the WHO Country Office. Subsequently, it led to the identification of a novel *beta* coronavirus (SARS-CoV-2) in January 2020 as the cause of the outbreak in Wuhan.<sup>4</sup> The infection later came to be known as coronavirus disease 2019 (COVID-19) and spread globally at a rapid rate. WHO announced it as a global pandemic on March 11, 2020.<sup>4,5</sup> Within the first 3 months of its emergence, nearly 1 million people were afflicted and 50,000 had died.<sup>2,4-7</sup> The SARS-CoV-2 causes respiratory symptoms similar to the SARS and MERS coronaviruses. The majority of the infected patients experienced mild-to-moderate respiratory symptoms such as dry cough, fever, fatigue, and malaise, and they recovered with general symptomatic therapy and did not require intensive care. However, geriatric patients (age >60 years) and those with underlying medical conditions like cardiovascular and renal diseases, diabetes, chronic respiratory disorders, cancer, hepatic syndromes, and the immunocompromised were found to be more vulnerable to developing serious life-threatening symptoms due to their weaker immune systems.<sup>7</sup> As per the latest WHO report dated July 22, 2020, the worldwide number of COVID-19 cases had crossed 14 million, with over 600,000 deaths.<sup>8</sup> The virus has a normal incubation period of 14 days from the time of exposure. However, most patients tend to develop symptoms within 4–5 days following exposure.<sup>9-11</sup> Breathing failure from acute respiratory distress syndrome (ARDS) is the main cause of mortality in patients with COVID-19.<sup>11</sup> Yet, recent evidence suggest that an immune reaction called “Cytokine Storm Syndrome” contributes as a secondary cause of death in a subgroup of patients with severe SARS-CoV-2 infection by inducing multiple organ failure, including fulminant myocarditis, leading to severe myocardial damage and circulatory failure.<sup>11-14</sup> Increased production of rapid response inflammatory cytokines such as Interleukin-6, Interleukin-1 $\beta$ , and Tumor Necrosis Factor

(TNF) leads to the “cytokine storm” which in turn induces vascular hyperpermeability, inflammation of tissues leading to multi-organ failure, and ultimately death. Hence, there is a growing need to suppress the high cytokine concentrations in COVID-19 patients who have other comorbid conditions and have developed an advanced form of the infection.<sup>12,14-16</sup> Moreover, studies have shown that some of the COVID-19 patients with a poor prognosis have had high values in their D-dimer results. The possible reason for this would be the subsidiary activation of the coagulation pathway as a result of the immune response, which leads to the development of microthrombosis and disseminated intravascular coagulation.<sup>15-21</sup>

## Guidelines for Management

The main objective of this article is to bring attention to the currently available therapeutic guidelines for management of COVID-19, with a special focus on treatments involving the drug classes that have been repurposed to treat the infection. Therapeutic guidelines provided by the majority of the international health organizations, including WHO and NIH, shed light on Antithrombotic Therapy, Immune Based Therapy, and specific Antiviral and Anti-Malarial drugs that have been hypothesized to produce promising results in COVID-19 patients.<sup>9,20,22</sup>

## Antithrombotic Therapy

As discussed earlier, there is a strong association between COVID-19 and thrombotic events resulting from inflammation and activation of coagulation pathways. This results in a prothrombotic state, thereby leading to an increase in the concentration of fibrin and fibrin degradation products, fibrinogen, and D-dimers in COVID-19 patients.<sup>15-21</sup> The NIH as well as WHO recommends the use of anticoagulants such as LMWH (enoxaparin) or unfractionated heparin in hospitalized COVID-19 patients as prophylaxis to prevent thromboembolic events, unless contraindicated.<sup>9,20</sup> For cases with contraindications, the use of mechanical prophylaxis such as intermittent pneumatic compression devices is recommended.<sup>20</sup>

## Immune-Based Therapy

Sufficient data is not available concerning the use of immunomodulators such as interleukin-1 (eg, Anakinra) and interleukin-6 (eg, tocilizumab, sarilumab) inhibitors, interferons, blood derived products such as convalescent plasma therapy, mesenchymal stem cells (MSCs), or SARS-CoV-2

specific immunoglobulins.<sup>9,20,22</sup> Interferons ( $\alpha$  and  $\beta$ ), a family of signaling proteins that are produced and released by host cells in response to viral activity, have been suggested as a potential treatment for COVID-19 due to their *in-vivo* and *in-vitro* antiviral characteristics.<sup>9,20,22–24,26,27</sup> However, it was clearly evident from prior studies related to infections caused by other coronaviruses (SARS and MERS) that there were no significant positive outcomes in the patients. Furthermore, the risk of adverse events and toxicity caused by interferons far outweighs its benefit.<sup>20,23–27</sup> Therefore, the WHO as well as NIH recommend against the use of these therapeutic agents for the treatment of SARS-CoV-2 infection.<sup>9,20</sup> Similarly, the use of Janus Kinase Inhibitors such as Baricitinib are also not recommended as per the therapeutic guidelines provided by WHO and NIH due to the enhanced immunosuppressive action of these drugs.<sup>9,20</sup> JAK inhibitors exert their anti-inflammatory effects by inhibiting the JAK signal transducer and activation of the transcription pathway. This helps in ameliorating inflammatory immune responses in autoimmune conditions such as rheumatoid arthritis and interferonopathies.<sup>28,29</sup> However, as there are not any clinical data available on the efficacy of JAK inhibitors in COVID-19 patients, and also due to the fact that extended use of these drugs poses a threat of superinfection as a result of immunosuppression, the use of these is strongly not recommended.<sup>20</sup>

## Other Antimicrobial and Antiviral Therapy

The WHO strongly recommends against the use of Remdesivir – the investigational antiviral drug, as well as others including Lopinavir, ritonavir, Umifenovir, and Favipiravir as treatment or prophylaxis of COVID-19. The same is applicable for the antimalarial drugs: chloroquine and hydroxychloroquine due to the inadequacy of available clinical data on their efficacy against the SARS-CoV-2 virus.<sup>20</sup> As per the remarks on WHO interim clinical management guidelines, the current scientific literature on the above-mentioned drugs is largely observational in nature and there have been very few clinical trials done to study the effectiveness of these agents in COVID-19 patients.<sup>20</sup> Also, the adverse effects induced by these agents outweigh the possibility of benefit.<sup>23–27,30–32</sup> A recent update on the WHO website dated June 17, 2020, stated that the hydroxychloroquine (HCQ) phase of the Solidarity Trial to identify an effective treatment for COVID-19 has been

discontinued based on clinical data from the Solidarity Trial as well as other clinical trials conducted worldwide including the UK's Recovery Trial, France's Discovery Trial, and a Cochrane review of other HCQ related evidence. The data suggested that comparing to standard of care therapy, there was no significant reduction in the mortality rate of hospitalized patients with SARS-CoV-2 infection when treated with HCQ.<sup>33,34</sup> However, the preliminary clinical data from the randomized control trial, called the Adaptive COVID-19 Treatment Trial (ACTT), that was initiated on February 21, 2020 with 1,063 patients and sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), suggested that patients receiving Remdesivir had a 31% faster recovery period than those receiving placebo.<sup>35</sup> Based on this data, the NIH recommends the use of the drug in hospitalized COVID-19 patients with severe disease and extreme lung damage. The drug is currently available under the emergency use authorization of the FDA for specifically hospitalized adults and children with severe COVID-19 infection.<sup>9</sup>

## Considerations in Special Comorbid Conditions

Although there are many comorbidities that could exacerbate the clinical condition of COVID-19 patients, this article focuses primarily on a few specific conditions that either involve treatment with the repurposed drugs discussed above or have a direct impact of the virus in patients owing to their vulnerability. These include hepatic disorders, genetic heart diseases, rheumatic autoimmune diseases, chronic kidney diseases, diabetes, and obesity.

## Hepatic Disorders

The SARS-CoV-2 virus has a 82% resemblance to the genetic sequence of SARS-CoV virus and hepatic impairment has been reported in up to 60% of SARS patients.<sup>37</sup> Moreover, the SARS-CoV-2 virus uses the angiotensin converting enzyme 2 (ACE 2) receptor to bind and get internalized into its target cells. These receptors are abundantly present on the epithelial cells of hepatic and biliary systems. Hence, patients with SARS-CoV-2 infection are at increased risk of developing liver complications, especially those who have preexisting liver problems.<sup>38,39</sup> The latest report from the European Association for the Study of the Liver (EASL) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) provides guidelines on the safety of the above discussed repurposed

investigational drugs on COVID-19 patients with preexisting liver conditions or transplantations.<sup>40</sup> Patients who undergo liver transplantations are most likely to develop severe infection due to the immunosuppressive agents. The same is applicable for patients with liver carcinomas and undergoing radiation/chemotherapy. It is crucial to consider the drug–drug interactions between the COVID-19 investigational medications and those that are already being used to treat the patient's preexisting condition.<sup>36,38,40</sup> The EASL-ESCMID position paper recommends that COVID-19 patients with liver disease and risk factors for development of severe infection must be started on an early antiviral therapy program or enrolled in clinical trials at various COVID-19 specific healthcare centers.<sup>40</sup> This recommendation is based on the fact that early initiation of antiviral treatment has shortened the course of other viral infections such as influenza. Thus, it might be beneficial in patients suffering from SARS-CoV-2 infection as well. Nevertheless, appropriate dose adjustments are required based on the functioning capacity of the liver, identified from the patient's Child-Pugh score. It is also imperative to carefully monitor for adverse events and toxicities.<sup>38,40</sup>

## Genetic Heart Diseases

It is discernible that genetic heart diseases are relatively rare amongst populations and SARS-CoV-2 is a newly discovered virus. Hence, scientific data about the best clinical practice in this area is limited. Nevertheless, the Cardiac Society of Australia and New Zealand (CSANZ) has provided a few recommendations in their recent consensus statement to effectively manage COVID-19 patients with genetic heart diseases. As per this statement, patients with congenital structural cardiac problems are recommended to continue their cardiovascular drugs such as beta blockers, Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), etc.<sup>41</sup> There have been conflicting opinions about the safety of ACEIs and ARBs in SARS-CoV-2 patients due to the binding site of the virus on ACE 2 receptors that are found on the cell membranes of renal tissue as well as the epithelial cells of the GI tract and lungs. A few preclinical studies have demonstrated that prolonged use of ACEIs/ARBs upregulates the expression of ACE 2 receptor, thereby causing healthcare professionals combating the infection and leading research scientists to question the possibility of these drugs posing a threat of exacerbating the SARS-CoV-2

infection.<sup>39,42–47</sup> However, as these concerns are largely theoretical in nature and there are not any relevant clinical trials or other sufficient evidence to substantiate this, international organizations focusing on cardiovascular medicine recommend the continuation of the patients' regular cardiac medications.<sup>41–46</sup> Moreover, a recent cohort study showed that the use of ACEIs/ARBs has been associated with significantly improved survival rates amongst hospitalized hypertensive patients with SARS-CoV-2 infection.<sup>47</sup> It is also imperative to consult a specialist cardiologist in genetic heart diseases prior to initiating atypical-repurposed drugs discussed above or enrolling in clinical trials involving these drugs in patients coinfecting with SARS-CoV-2 infection.<sup>41</sup>

## Rheumatic Autoimmune Diseases

The American College of Rheumatology Guidelines recommend continuing the use of regular antirheumatic drugs in COVID-19 patients suffering from preexisting rheumatic conditions. This includes the use of ACEI/ARB for scleroderma renal crisis or SLE, due to the protective effects of these drugs on the kidneys.<sup>48–51</sup> As for NSAIDs, it was recommended in the guidelines to use them with caution in newly diagnosed rheumatic disorders; nonetheless stop if patients develop severe SARS-CoV-2 infection due to the poor prognosis resulting from the cardiac, kidney, and liver injury that have been associated to COVID-19 as severe manifestations of the infection.<sup>38,40,41,48,49,52</sup> In the case of Glucocorticoid therapy, there has been conflicting evidence in favor of their use in COVID-19 patients. Emerging data indicate that their anti-inflammatory properties could potentially minimize the impact of SARS-CoV-2 infection, especially in its late stages which is characterized by cytokine storm and hyperinflammation.<sup>48,53,54</sup> However, these are very limited data to support the use of glucocorticoids in SARS-CoV-2 infected patients given the risk of glucocorticoid induced immunosuppression, leading to opportunistic infections. Moreover, the plethora of evidence available in support of the detrimental effects of glucocorticoids contradict the limited evidence in support of their beneficial effects. Hence, the guidelines recommend continuing standard of care treatment using the lowest effective doses of glucocorticoids drugs and avoiding sudden termination of therapy in patients with underlying rheumatic disease. However, it was also acknowledged by the guidelines panel that higher doses may be required in cases of serious, life-threatening situations with vital organ damage

even after exposure to SARS-CoV-2.<sup>48</sup> Moreover, an update from the UK's Recovery Trial has demonstrated that Dexamethasone, a synthetic glucocorticoid agent, could save the lives of critically ill patients with SARS-CoV-2 infection. Treatment with the agent showed about one-third reduction in mortality for patients on ventilators whilst for those requiring only oxygen the mortality rate was reduced by about one-fifth.<sup>55</sup>

The panel recommends continuation/initiation of Conventional Synthetic disease-modifying antirheumatic drugs (csDMARDs) when required regardless of whether the patient has been exposed to SARS-CoV-2 infection or not. This recommendation was formed based on the fact that risk of severe infection with these drugs is considerably lower, especially when administered as monotherapy.<sup>48,56,57</sup> Nevertheless, caution must be exercised due to the known adverse effects of these drugs such as diarrhea and other gastrointestinal manifestations, hepatitis, cytopenia, and cardiotoxicity which could be misinterpreted with symptoms of SARS-CoV-2 infection.<sup>48</sup> Likewise, due to lack of sufficient randomized controlled trials data to support sustained use, the panel recommended that all immunomodulators, immunosuppressants, and JAK inhibitors be temporarily withheld or discontinued in the light of reported or suspected SARS-CoV-2 infection.<sup>48</sup>

## Chronic Kidney Diseases

The NICE COVID-19 rapid guideline for CKD recommends the continuation of regular medications including ACEI/ARB, diuretics, and immunosuppressants in patients underlying kidney disease exhibiting symptoms of SARS-CoV-2 infection. Dose reduction and therapeutic dose monitoring have been recommended by the Renal Association Guidance for patients on immunosuppressants, corticosteroids, and anti-cancer drugs such as cyclophosphamide.<sup>58,59</sup> This is particularly applicable for patients on the "Induction" phase. Immunosuppressive medications should be assessed on a case-by-case basis, balancing the risk of insufficient therapy or acute relapse against the risk of SARS-CoV-2 infection affecting a particular patient.<sup>59</sup> Abrupt cessation of corticosteroid maintenance therapy is deemed detrimental to patients with autoimmune kidney disease due to risk of relapses and thereby not recommended. In patients under maintenance regimens with biologics such as LA-Rituximab, delayed time interval between infusions is recommended, if the risk of disease flare is less and the likelihood of severe manifestations of SARS-CoV-2

infection is more.<sup>59</sup> Non-Steroidal Anti-inflammatory Drugs (NSAIDs) are to be avoided in patients with both acute as well as chronic kidney diseases. Patients exhibiting flu symptoms are to be treated with acetaminophen (paracetamol). As for patients preparing for renal transplant, the procedure or immunosuppression must not be initiated unless the SARS-CoV-2 nasopharyngeal swab test result is negative.<sup>60</sup> Lastly, dialysis following transplantation must be done in a COVID-19 secure area after having taken precautionary safety measures.<sup>58-60</sup>

## Diabetes and Obesity

Based on recent evidence, it is known that both diabetes and obesity are related to severe complications in SARS-CoV-2 infection.<sup>61</sup> Epidemiological findings from regions severely affected by SARS-CoV-2, along with CDC reports have shown that the risk of mortality due to COVID-19 is approximately 50% greater in diabetic patients.<sup>61,62</sup> Likewise, hospitalized COVID-19 patients who were overweight or obese with a body mass index (BMI) of greater than 25 kg/m<sup>2</sup> were at increased risk of requiring mechanical ventilation.<sup>63</sup> There is a strong association between insulin resistance and visceral adipose tissue (VAT) that are abundantly present in obese patients. The adipocytes secreted most of the inflammatory and coagulopathic molecules including TNF- $\alpha$  and interleukin-6, relating to the SARS-CoV-2 induced cytokine storm.<sup>63-65</sup> Evidence suggests that Type-2 diabetic patients had increased levels of TNF- $\alpha$ .<sup>63,66</sup> Moreover, individuals with both the comorbidities had lower levels of Interleukin-10 (IL-10), which is a protective anti-inflammatory cytokine.<sup>63,67</sup> Hence, obese patients with Type 2 diabetes mellitus are at a significantly increased risk of developing a severe form of SARS-CoV-2 infection.<sup>63,68,69</sup>

A few retrospective observational studies have suggested the use of Metformin, the first line therapeutic agent for Type-2 diabetes mellitus, to mitigate the impact of SARS-CoV-2 infection in diabetic and obese patients. It was found that metformin decreased the levels of IL-6, TNF- $\alpha$ , and increased the levels of IL-10.<sup>63,70</sup> Over the years, metformin has been used for treatment of various diseases apart from type-2 diabetes. It is used as an off-label medication for weight loss in the USA.<sup>68,71</sup> Furthermore, findings from a retrospective cohort study demonstrated that early administration of metformin is associated with substantially lower mortality in geriatric patients with pneumonia.<sup>68,72</sup> Since elderly patients are at increased risk of mortality due to SARS-CoV-2, it would be appropriate to consider incorporation of metformin as an adjuvant agent

for treatment of the infection.<sup>68,73</sup> Other beneficial effects of metformin in minimizing the impact of SARS-CoV-2 include reduced macrophage cytokine synthesis, increased insulin sensitivity, and activation of AMP-activated protein kinase (AMPK).<sup>63,68,70,71</sup> Lastly, metformin has also been hypothesized to possess a viral inhibitory capability through increasing insulin sensitivity.<sup>68,74</sup> Therefore, it is plausible to consider metformin as an effective therapeutic agent for management of COVID-19 in obese, diabetic, and geriatric patients. However, there is a need for further research into this topic and, due to the lack of sufficient data from clinical trials, the efficacy of Metformin in SARS-CoV-2 remains to be validated.

## Conclusion

At present, limited clinical data is available to substantiate the beneficial effects of repurposed drugs on SARS-CoV-2 patients. The clinical guidelines highlighted above have been made to provide optimal care during the prevailing pandemic situation. Hence, due to the evolving nature of literature as a result of ongoing research to identify the best possible therapeutic agents to combat the infection, frontline health professionals are recommended to keep a close watch for recent updates to the guidelines based on clinical trial results. Furthermore, when patients with serious underlying comorbid conditions contract SARS-CoV-2 infection, it is imperative that the specialist physician involved in the treatment of their underlying condition is also included in the healthcare team treating the infection. This is particularly important for making crucial decisions such as enrolment of patients in clinical trials involving repurposed drugs, initiating the drugs as pre-/post-exposure prophylaxis, and dose alterations as necessitated by standard of care therapeutic guidelines for the patients' underlying disease.

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## References

- Palacios Cruz M, Santos E, Velázquez Cervantes MA, León Juárez M. COVID-19, a worldwide public health emergency. *Rev Clin Esp (Barc)*. 2020. Available from: [www.ncbi.nlm.nih.gov/pmc/articles/PMC7173827/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7173827/). Accessed May 3, 2020.
- National Institute of Allergy and Infectious Diseases (NIAID). COVID-19, MERS & SARS [Internet]. National Institute of Health (NIH); 2020. Available from: [www.niaid.nih.gov/diseases-conditions/covid-19](http://www.niaid.nih.gov/diseases-conditions/covid-19). Accessed May 8, 2020.
- Lehrer S, Rheinstein PH. Human gene sequences in SARS-CoV-2 and other viruses. *In Vivo (Brooklyn)*. 2020;34(3Suppl):1633–1636. doi:10.21873/in vivo.11954
- Coronavirus Disease (COVID-19) - events as they happen [Internet]. World Health Organization (WHO). 2020. Available from: [www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen](http://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). Accessed May 12, 2020.
- Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed*. 2020;91(1):157–160.
- Khan S, Siddique R, Ali A, Xue M, Nabi G. Novel coronavirus, poor quarantine, and the risk of pandemic. *J Hosp Infect*. 2020;104(4):449–450. doi:10.1016/j.jhin.2020.02.002
- Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention (CDC). 2020. Available from: [www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html](http://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html). Accessed May 18, 2020.
- Coronavirus Disease (COVID-19) Situation Reports [Internet]. World Health Organization (WHO). 2020. Available from: [www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports](http://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports). Accessed May 20, 2020.
- COVID-19 Treatment Guidelines Panel. *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines*. National Institutes of Health (NIH); 2020. Available from: [www.covid19treatmentguidelines.nih.gov/](http://www.covid19treatmentguidelines.nih.gov/). Accessed May 21, 2020.
- Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med*. 2020;172(9):577–582. doi:10.7326/M20-0504
- Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720. doi:10.1056/NEJMoa2002032
- Mehta P, McAuley D, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–1034. doi:10.1016/S0140-6736(20)30628-0
- Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846–848.
- Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents*. 2020;55(5):105954. doi:10.1016/j.ijantimicag.2020.105954
- Jose R, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med*. 2020;8(6):e46–e47. doi:10.1016/S2213-2600(20)30216-2
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062. doi:10.1016/S0140-6736(20)30566-3
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844–847. doi:10.1111/jth.14768
- Ingraham NE, Lotfi-Emran S, Thielen BK, et al. Immunomodulation in COVID-19. *Lancet Respir Med*. 2020;8(6):544–546. doi:10.1016/S2213-2600(20)30226-5
- Vincent J, Taccone F. Understanding pathways to death in patients with COVID-19. *Lancet Respir Med*. 2020;8(5):430–432. doi:10.1016/S2213-2600(20)30165-X
- Clinical management of COVID-19: interim guidance [Internet]. World Health Organization (WHO). 2020. Available from: [www.who.int/publications/i/item/clinical-management-of-covid-19](http://www.who.int/publications/i/item/clinical-management-of-covid-19). Accessed June 8, 2020.
- Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145–147. doi:10.1016/j.thromres.2020.04.013

22. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117(20):10970–10975. doi:10.1073/pnas.2005615117
23. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J Infect Dis*. 2014;20:42–46. doi:10.1016/j.ijid.2013.12.003
24. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis*. 2020;70(9):1837–1844.
25. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252–256. doi:10.1136/thorax.2003.012658
26. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090–1095. doi:10.1016/S1473-3099(14)70920-X
27. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN- $\alpha$ 2a or IFN- $\beta$ 1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129–2132. doi:10.1093/jac/dkv085
28. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243–1252. doi:10.1056/NEJMoa1507247
29. Smolen JS, Genovese MC, Takeuchi T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. *J Rheumatol*. 2019;46(1):7–18. doi:10.3899/jrheum.171361
30. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4):e208857. doi:10.1001/jamanetworkopen.2020.8857
31. Chen J, Lui D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. *J Zhejiang Univ*. 2020;49(2):215–219.
32. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an Open-Label Control Study. *Engineering (Beijing)*. 2020. doi:10.1016/j.eng.2020.03.007
33. “Solidarity” clinical trial for COVID-19 treatments [Internet]. World Health Organization (WHO). 2020. Available from: [www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments](http://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments). Accessed July 13, 2020.
34. Institut National de la Santé Et de la Recherche Médicale, France. Trial of treatments for COVID-19 in hospitalized adults (DisCoVeRy). Clinicaltrials.gov. 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT04315948>. Accessed July 13, 2020.
35. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 — final report. *N Engl J Med*. 2020;383(19):1813–1826. doi:10.1056/NEJMoa2007764
36. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol*. 2020;5(5):428–430. doi:10.1016/S2468-1253(20)30057-1
37. Chau TN, Lee KC, Yao H. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology*. 2004;39(2):302–310. doi:10.1002/hep.20111
38. *Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement [Internet]*. Alexandria, Virginia, USA: American Association for the Study of Liver Diseases (AASLD);2020. Available from: [www.aasld.org/sites/default/files/2020-06/AASLD-COVID19-ExpertPanelConsensusStatement-June252020-v2-FINAL.pdf](http://www.aasld.org/sites/default/files/2020-06/AASLD-COVID19-ExpertPanelConsensusStatement-June252020-v2-FINAL.pdf). Accessed June 28, 2020.
39. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426(6965):450–454. doi:10.1038/nature02145
40. Boettler T, Newsome PN, Mondelli MU, et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep*. 2020;2(3):100113. doi:10.1016/j.jhepr.2020.100113
41. *Consensus Statement for Patients with Genetic Heart Disease and COVID-19 [Internet]*. Sydney, New South Wales, Australia: Cardiac Society of Australia and New Zealand (CSANZ);2020. Available from: [www.csanz.edu.au/wp-content/uploads/2020/04/CSANZ-Consensus-statement-for-patients-with-Genetic-Heart-Disease-and-COVID-19-web.pdf](http://www.csanz.edu.au/wp-content/uploads/2020/04/CSANZ-Consensus-statement-for-patients-with-Genetic-Heart-Disease-and-COVID-19-web.pdf). Accessed July 1, 2020.
42. Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. *Curr Cardiol Rep*. 2020;22(5):31. doi:10.1007/s11886-020-01291-4
43. Sommerstein R, Kochen M, Messerli F, Gräni C. Coronavirus disease 2019 (COVID-19): do angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have a biphasic effect? *J Am Heart Assoc*. 2020;9(7). doi:10.1161/JAHA.120.016509
44. South A, Brady T, Flynn J. ACE2 (angiotensin-converting enzyme 2), COVID-19, and ACE inhibitor and Ang II (Angiotensin II) receptor blocker use during the pandemic. *Hypertension*. 2020;76(1):16–22. doi:10.1161/HYPERTENSIONAHA.120.15291
45. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21. doi:10.1016/S2213-2600(20)30116-8
46. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. *Hypertension*. 2020;75(6):1382–1385. doi:10.1161/HYPERTENSIONAHA.120.15082
47. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126(12):1671–1681. doi:10.1161/CIRCRESAHA.120.317134
48. Mikuls T, Johnson S, Fraenkel L, et al. American college of rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 1. *Arthritis Rheumatol*. 2020;72(9):1–11.
49. Bertias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis*. 2012;71:1771–1782. doi:10.1136/annrheumdis-2012-201940
50. Duran-Barragan S, McGwin G Jr, Vila LM, Reveille JD, Alarcon GS. Angiotensin converting enzyme inhibitors delay the occurrence of renal involvement and are associated with a decreased risk of disease activity in patients with systemic lupus erythematosus—results from LUMINA (LIX): a multiethnic US cohort. *Rheumatology (Oxford)*. 2008;47:1093–1096. doi:10.1093/rheumatology/ken208
51. Tselios K, Gladman DD, Su J, Urowitz MB. Does Renin-angiotensin system blockade protect lupus nephritis patients from atherosclerotic cardiovascular events? A Case-Control Study. *Arthritis Care Res (Hoboken)*. 2016;68(10):1497–1504. doi:10.1002/acr.22857
52. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing symptoms (including at the end of life) in the community. 2020. Available from: [www.nice.org.uk/guidance/ng163](http://www.nice.org.uk/guidance/ng163). Accessed July 7, 2020.
53. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934. doi:10.1001/jamainternmed.2020.0994

54. D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transplant*. 2020;26(6):832–834. doi:10.1002/lt.25756
55. RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial and University of Oxford. Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 [Internet]. 2020. Available from: [https://www.recoverytrial.net/files/recovery\\_dexamethasone\\_statement\\_160620\\_v2final.pdf](https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf). Accessed July 9, 2020.
56. Ibrahim A, Ahmed M, Conway R, Carey J. Risk of infection with methotrexate therapy in inflammatory diseases: a systematic review and meta-analysis. *J Clin Med*. 2018;8(1):15. doi:10.3390/jcm8010015
57. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. *Rheumatology*. 2007;46(7):1157–1160. doi:10.1093/rheumatology/kem076
58. COVID-19 Rapid Guideline: Chronic Kidney Disease (CKD) - [NICE Guideline NG176] [Internet]. London, United Kingdom: National Institute for Health and Care Excellence (NICE); May 15, 2020. Available from: <https://www.nice.org.uk/guidance/ng176/resources/covid19-rapid-guideline-chronic-kidney-disease-pdf-66141964574917>. Accessed July 12, 2020.
59. Guidance for Clinicians with Patients Receiving Immunosuppression Treatment for Autoimmune Conditions of Their Native Kidneys During Covid-19 [Internet]. Version 2. Bristol, United Kingdom: The Renal Association; April 1, 2020. Available from: <https://renal.org/wp-content/uploads/2020/04/Treatment-of-patients-with-AI-kidney-disease-during-Covid19-outbreak-010420.pdf>. Accessed July 13, 2020.
60. National Institute for Health and Care Excellence. COVID 19 rapid guideline: renal transplantation. June 19, 2020. Available from: [www.nice.org.uk/guidance/ng178](http://www.nice.org.uk/guidance/ng178). Accessed July 13, 2020.
61. Bornstein S, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol*. 2020;8(6):546–550. doi:10.1016/S2213-8587(20)30152-2
62. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet*. 2020;395(10231):1225–1228. doi:10.1016/S0140-6736(20)30627-9
63. Bramante C, Ingraham N, Murray T, et al. Observational Study of metformin and risk of mortality in patients hospitalized with covid-19. *medRxiv*. 2020;2020.06.19.20135095.
64. Liu L, Feng J, Zhang G, et al. Visceral adipose tissue is more strongly associated with insulin resistance than subcutaneous adipose tissue in Chinese subjects with pre-diabetes. *Curr Med Res Opin*. 2018;34(1):123–129. doi:10.1080/03007995.2017.1364226
65. Luo P, Qiu L, Liu Y, et al. Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. *Am J Trop Med Hyg*. 2020;103(1):69–72. doi:10.4269/ajtmh.20-0375
66. Gupta-Ganguli M, Cox K, Means B, Gerling I, Solomon SS. Does therapy with anti-TNF- $\alpha$  improve glucose tolerance and control in patients with type 2 diabetes? *Diabetes Care*. 2011;34(7):e121. doi:10.2337/dc10-1334
67. Blüher M, Fasshauer M, Tönjes A, Kratzsch J, Schön MR, Paschke R. Association of interleukin-6, C-reactive protein, interleukin-10 and adiponectin plasma concentrations with measures of obesity, insulin sensitivity and glucose metabolism. *Exp Clin Endocrinol Diabetes*. 2005;113(9):534–537. doi:10.1055/s-2005-872851
68. El-Arabey AA, Abdalla M. Metformin and COVID-19: a novel deal of an old drug [published online ahead of print, 2020 Apr 29]. *J Med Virol*. 2020. doi:10.1002/jmv.25958
69. Dietz W, Santos-Burgoa C. Obesity and its Implications for COVID-19 mortality. *Obesity (Silver Spring)*. 2020;28:1005.
70. Cameron AR, Morrison VL, Levin D, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. *Circ Res*. 2016;119(5):652–665. doi:10.1161/CIRCRESAHA.116.308445
71. El-Arabey AA. Update on off label use of metformin for obesity. *Prim Care Diabetes*. 2018;12(3):284–285. doi:10.1016/j.pcd.2018.02.004
72. Eric M, Antonio A. Association of metformin and mortality for patients with diabetes who are hospitalized with pneumonia. *Eur Res J*. 2018;52(Suppl. 62):PA2639.
73. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: a comparison with young and middle-aged patients. *J Infect*. 2020;80(6):e14–e18. doi:10.1016/j.jinf.2020.03.005
74. Chen Y, Gu F, Guan J-L. Metformin might inhibit virus through increasing insulin sensitivity. *Chin Med J (Engl)*. 2018;131(3):376–377. doi:10.4103/0366-6999.223856

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