COVID-19: the epidemiology and treatment

Abstract

After initially emerging in late 2019, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly to cause a global pandemic. SARS-CoV-2 is a betacoronavirus that is closely related to severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus, all of which can cause severe lung injury, respiratory distress and cytokine storm. While mortality rates associated with SARS-CoV-2 are lower than those associated with severe acute respiratory syndrome coronavirus or Middle East respiratory syndrome coronavirus, it is more contagious and spreads more rapidly than these other viruses. This article summarises the epidemiology and potential options for treating COVID-19 to give a foundation for future studies of the diagnosis, treatment and prevention of this deadly disease.

Key words: Antivirals; COVID-19; Immunomodulators; SARS-CoV-2; Vaccines

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Introduction

Coronaviruses are a family of RNA viruses with a 26–32 kb positive-sense single-stranded RNA genome (Schoeman and Fielding, 2019). These viruses, which belong to the order of Nidovirales, are grouped into alpha-, beta-, gamma-, and delta-coronavirus genera (Halaji et al, 2020). They are capable of infecting humans and other animals, and causing respiratory, cardiovascular, neurological, renal, hepatic and haematological diseases (Weiss and Leibowitz, 2011; Yin and Wunderink, 2018). Seven human coronaviruses have been identified to date: the alphacoronaviruses HCoVs-NL63 and HCoVs-229E and the betacoronaviruses HCoVs-OC43, HCoVs-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Bchetnia et al, 2020). SARS-CoV (Drosten et al, 2003) and MERS-CoV (Zaki et al, 2012) have been extensively studied because of their high lethality and because they have caused previous epidemic outbreaks.

In December 2019, a previously unknown respiratory disease was identified in Wuhan, Hubei Province, China. Sequence analyses revealed this to be a newly discovered betacoronavirus, initially designated as 2019 novel coronavirus (2019-nCoV). The virus was later reclassified as SARS-CoV-2 by the World Health Organization, and the disease associated with SARS-CoV-2 infection was named COVID-19 and classified as a pandemic necessitating urgent interventions (Pagliusi et al, 2020). Much like MERS-CoV and SARS-CoV, SARS-CoV-2 can cause severe respiratory disease in infected patients. SARS-CoV-2 rapidly spread throughout China and globally, resulting in severe damage to the health and economic wellbeing of societies across the world. A coordinated global response is essential to facilitate global recovery from this devastating pandemic.

Epidemiology of COVID-19

Initial animal-to-human transmission

The first known cases of COVID-19 pneumonia were diagnosed in December 2019 and linked via epidemiological methods to the Huanan Seafood Wholesale Market in Wuhan, in the Chinese province of Hubei. Live animals at this market were suspected to be the intermediary hosts responsible for SARS-CoV-2 transmission to humans (Hui et al, 2020), thereby facilitating viral transmission of the disease. Although the origin of SARS-CoV-2 is not definitively known, many reports support the idea that SARS-CoV-2 is transmitted from animals to humans (Baghizadeh Fini, 2020).

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Human-to-human transmission of SARS-CoV-2

Given the genomic and phylogenetic similarities between SARS-CoV-2 and SARS-CoV, both of which exhibit similar receptor-binding domain and spike gene sequences, both viruses can be spread directly from human to human (Uddin et al, 2020). Currently, patients with symptomatic COVID-19 pneumonia are believed to be the primary drivers of human-to-human SARS-CoV-2 spread. In addition, it remains possible that so-called 'super-spreaders' may play an important role in of the rapid spread of this pandemic virus (Kumar et al, 2020).

Possible mode of transmission

It is believed that SARS-CoV-2 spreads primarily through respiratory droplets and close person-to-person contact (Gemicioğlu et al, 2020). However, there is growing evidence that the virus can be spread via aerosols and fomites, and that it may remain infectious on surfaces for a number of days and in aerosols for minutes or hours (van Doremalen et al, 2020).

Susceptible populations

As there is no evidence of pre-existing human SARS-CoV-2 immunity, all people are believed to be susceptible to SARS-CoV-2 infection, especially infants, children, pregnant women and the elderly. Older adults and those with multiple comorbidities including cardiovascular disease, lung disease, cirrhosis, HIV, immunosuppression or diabetes are believed to be at an elevated risk of complications (Gruszecka and Filip, 2020).

Pathogenesis

The pathogenesis of SARS-CoV-2 remains to be fully clarified. Work conducted at the Jin Yin-tan Hospital in Wuhan revealed that patients with COVID-19 had elevated plasma levels of interleukin (IL)-1β, IL-1RA, IL-7, IL-8, IL-9, IL-10, interferon (IFN)-γ, fibroblast growth factor, granulocyte colony-stimulating factor (G-CSF/CSF3), granulocyte/macrophage colony-stimulating factor (GM-CSF/CSF2), interferon gamma-induced protein 10 (IP10/CXCL10), tumour necrosis factor (TNF)-β, monocyte chemoattractant protein 1 (MCP1/CCL2), macrophage inflammatory protein-1 alpha (MIP1A/CCL3), macrophage inflammatory protein-1 beta (MIP1B/CCL4), platelet-derived growth factor and vascular endothelial growth factor relative to healthy individuals. Patients with COVID-19 who were admitted to the intensive care unit also show further increases in serum IL-2, IL-7, IL-10, G-CSF, TNFα, IP10, MCP1 and MIP1A levels relative to patients not requiring intensive care. Elevated levels of IL-1β, IFNγ, IP10 and MCP1 in these patients are likely to drive T helper (Th)1-type CD^{4+} T cell responses, while increased IL-4 and IL-10 production may, in turn, drive enhanced Th2 responses (Huang et al, 2020; Rothan and Byrareddy, 2020).

Drug treatments

Convalescent plasma therapy

Convalescent plasma administration is commonly used to treat patients who are severely ill and suffering from viral diseases such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) or influenza (Ko et al, 2018). There is some evidence that convalescent plasma treatment can significantly improve recovery in patients with COVID-19. Patients are generally able to tolerate infusion of 200 ml of inactivated convalescent patient plasma while maintaining high neutralizing antibody titres, resulting in improved laboratory, clinical and radiological findings within 3 days and an absence of detectable virus within 1 week of infusion (Duan et al, 2020). Given these promising early results, convalescent plasma therapy may be a viable approach to treating severely ill patients with COVID-19 when such plasma is available (Shen et al, 2020).

Immunomodulatory therapy

Interferon

Type I interferons (IFN-α, IFN-β) are broadly antiviral signalling molecules that stimulate key intracellular pathways and thereby impair viral internalization, replication and transmission while simultaneously promoting immune cell activation (Cinatl et al, 2004; Wang and Fish, 2019). While potent, interferon treatment can induce influenza-like symptoms and mood

changes, and as such, it is not suitable for patients suffering from severe autoimmune conditions, poor mental health, seizures or decompensated liver disease (Song et al, 2020).

Corticosteroids

Glucocorticoids interact with cytoplasmic receptors and thereby alter gene transcription and consequent production of inflammatory mediators (Neupane et al, 2020). As they are potent anti-inflammatory agents, corticosteroids are commonly given to patients suffering from MERS or SARS to reduce disease-related inflammation and alveolar damage (Arabi et al, 2017). However, whether corticosteroids are beneficial in patients with COVID-19 remains controversial. Indeed, corticosteroids can suppress immune functionality and pathogen elimination in addition to suppressing pulmonary inflammation (Russell et al, 2020). While use of corticosteroids is associated with a slight reduction in patient mortality, it is also possible that such treatment could prolong viral shedding in the airways of infected patients (Mahalmani et al, 2020). There is the risk that patients treated with systemic corticosteroids can develop osteonecrosis of the femoral head (Zhang and Zhang, 2020), and these drugs are not appropriate for patients with COVID-19 who are suffering from shock or lung injury (Russell et al, 2020).

Tocilizumab

As severely ill patients with COVID-19 commonly have elevated systemic levels of IL-6, inhibitors of IL-6 signalling (including siltuximab, sarilumab and tocilizumab) have been suggested as potential treatments that may suppress systemic inflammation (Hozhabri et al, 2020). Tocilizumab is an IL-6 receptor-specific recombinant humanised monoclonal antibody that has been shown to be effective for treating cytokine release syndrome (Cao et al, 2020a). Some studies have found that tocilizumab can suppress SARS-CoV-2-related inflammation (Fu et al, 2020), but the safety and clinical efficacy of this treatment strategy remains to be established.

Baricitinib

Baricitinib is a Janus kinase (JAK1/JAK2) inhibitor that suppresses a range of pro-inflammatory cytokine-induced signalling pathways. Some have proposed the use of baricitinib as a means of disrupting angiotensin-converting enzyme 2 (ACE2)-mediated SARS-CoV-2 internalisation and associated cytokine storm in patients with COVID-19 (Zhang et al, 2020).

Eculizumab

Eculizumab is a high-affinity human monoclonal antibody specific for complement protein C5 that prevents C5a and C5b cleavage and consequent generation of C5b-9, which is necessary for complement-mediated cell lysis (Jodele et al, 2020). Given that C5a is linked to pathogen-induced acute lung injury, eculizumab may be a viable treatment for patients with severe COVID-19-related pneumonia, lung damage or acute respiratory distress syndrome (Diurno et al, 2020).

Angiotensin-converting enzyme 2

As discussed previously, ACE2 is currently believed to be the primary receptor for SARS-CoV-2 on human cells. Viral S proteins directly interact with cell surface ACE2, thereby facilitating viral internalisation and replication. Disrupting this interaction may be an effective means of treating COVID-19 (Monteil et al, 2020). In humans, ACE2 can be found in the soluble form (which is relatively rare) or the more common form of membrane-bound ACE2. While membrane-bound ACE2 functions as a viral receptor, soluble ACE2 is a competitive inhibitor of interactions between membrane-bound ACE2 and the viral S protein that can disrupt viral infectivity (Imai et al, 2005). Clinically relevant doses of human recombinant soluble ACE2 can disrupt SARS-CoV-2 replication in vitro in Vero cells. It can also disrupt viral infection of human engineered blood vessels and renal organs, delay target cell entry and prevent lung injury in patients. As such, administration of human recombinant soluble ACE2 may be an effective means of blocking early SARS-CoV-2 infection (Monteil et al, 2020).

Antiviral therapy

Most patients with COVID-19 receive antiviral treatments, including ribavirin (Li and De Clercq, 2020), favipiravir (Shiraki and Daikoku, 2020), remdesivir (Grein et al, 2020), lopinavir-ritonavir (Płusa, 2020), chloroquine and hydroxychloroquine (Colson et al, 2020). These antiviral agents have potential value for treating this disease. However, the use of three or more antiviral medications in a single patient is not recommended and their use should be terminated if patients exhibit any intolerable toxicities or side effects.

Ribavirin

Ribavirin is a guanosine analogue that can disrupt polymerase activity, thereby interfering with viral replication. Ribavirin also has broad antiviral activity associated with its ability to inhibit inosine monophosphate dehydrogenase and thereby constrain guanosine production (Khalili et al, 2020). Ribavirin is active against many RNA viruses such as vaccinia virus, herpesvirus, vesicular stomatitis virus, hepatitis C virus, respiratory syncytial virus, SARS-CoV and MERS-CoV (Jordan et al, 2018; Hon et al, 2020). However, treatment solely with ribavirin is of limited efficacy in patients with SARS-CoV and MERS-CoV (Falzarano et al, 2013). Instead, it is generally administered in combination with lopinavir-ritonavir or interferons, resulting in enhanced efficacy and reduced infection duration (Hung et al, 2020). However, ribavirin is a potential teratogen and can cause leukopenia, haemolytic anaemia, gout, fatigue and skin reactions, making it suboptimal as a treatment for patients with COVID-19 (Neupane et al, 2020).

Favipiravir

Favipiravir is an RNA polymerase inhibitor that has been approved in Japan for the treatment of a range of respiratory viruses including respiratory syncytial virus, influenza and rhinoviruses. Favipiravir can also treat other severe viral diseases such as Ebola, Lassa fever, rabies and severe febrile thrombocytopenia syndrome (Shiraki and Daikoku, 2020). As there is evidence that it may support viral clearance and improve chest imaging findings, favipiravir was approved by the National Medical Products Administration of China for the treatment of COVID-19 in March 2020 (Tu et al, 2020).

Remdesivir

Remdesivir is an adenosine analogue prodrug that disrupts SARS-CoV-2 viral replication in vitro by disrupting viral RNA polymerase activity (Grein et al, 2020). Owing to its nucleoside analogue activity, remdesivir (GS-5734) can drive premature viral RNA chain termination. As such, it is believed to be among the most efficacious broad-spectrum antiviral treatments available for patients with COVID-19 (Warren et al, 2016).

The active remdesivir metabolite GS-441524 can interfere with SARS-CoV-2 viral RNA polymerase activity while evading viral exonuclease-mediated proofreading, thus impairing overall viral RNA production. Evidence suggests that GS-441524 is the primary metabolite delivered to the lungs, and this metabolite is generally thought to be superior to remdesivir (GS-5734) for treating COVID-19 owing to its in vivo efficacy and ease of synthesis (Yan and Muller, 2020).

Lopinavir-ritonavir

Lopinavir-ritonavir combination therapy is approved by the Food and Drug Administration for the treatment of acquired immunodeficiency syndrome in patients infected with HIV-1. Lopinavir disrupts SARS-CoV protease activity and associated in vitro viral replication (Wu et al, 2004). As a combination partner, ritonavir inhibits cytochrome P450 and thereby extends the half-life of lopinavir in the patient's circulation. While promising in vitro, combination lopinavir-ritonavir treatment is not effective for treating patients with COVID-19, and is associated with a range of adverse reactions such as QT interval prolongation, pancreatitis and hepatotoxicity, thus limiting the amount of these drugs that can be administered to seriously ill patients (Cao et al, 2020b). Given that this drug combination is no more effective than standard care, administration of lopinavir-ritonavir to critically ill patients with COVID-19 is not currently recommended (Alhazzani et al, 2020), and future study of its potential use is warranted (Cao et al, 2020b).

Chloroquine and hydroxychloroquine

Chloroquine has been used for over 70 years as an antimalarial agent and to treat various autoimmune disorders, but there is evidence that it can function as an antiviral drug in certain contexts (Marmor et al, 2016). By lowering endosomal pH levels and interfering with viral binding to ACE2, chloroquine can also constrain SARS-CoV infection of and transmission between cells. Hydroxychloroquine is a safer chloroquine derivative that more robustly inhibits SARS-CoV-2 infectivity (Yao et al, 2020). One study found that combination treatment with hydroxychloroquine and azithromycin was sufficient to reduce viral load and improve treatment outcomes in patients with COVID-19 (Gautret et al, 2020). However, more recent evidence suggests that treating patients with hydroxychloroquine, chloroquine and/or azithromycin can result in QT interval prolongation without an increase in the incidence of fatal arrhythmias. It is thus essential to assess individual patient risk when considering using these agents (Hsia et al, 2020).

Other drugs

Given that SARS-CoV-2 does not encode any neuraminidase protein, neuraminidase inhibitors such as oseltamivir, zanamivir or lamivir are not thought to be effective for treating patients with COVID-19 (Li et al, 2020). However, some studies have found that drugs including arbidol (Zhu et al, 2020), fusion peptide (EK1) (Xia et al, 2019), ganciclovir (Lai et al, 2020), Abelson (Abl) kinase inhibitor (imatinib) (Bernal-Bello et al, 2020), metronidazole (Gharebaghi et al, 2020), antiprotozoal drugs (nitazoxanide and ivermectin) (Mahmoud et al, 2020; Peña-Silva et al, 2020), and 3CL(Pro) inhibitors (Rathnayake et al, 2020) are efficacious when used to prevent SARS-CoV-2 infections in vitro. However, their safety and efficacy in preventing COVID-19 in humans remains to be determined.

Vaccine development

At present, no preventative SARS-CoV-2 vaccines have received regulatory approval. However, a range of different vaccine types are currently in development, including RNA- and DNA-based vaccines, protein-based vaccines, virus-like particle vaccines, vector-based vaccines, and live-attenuated or inactivated viral vaccines (Thanh et al, 2020). At present, seventeen candidate vaccines from different research and development institutions have entered into phase III clinical trials, including:

- Four non-replicating viral vector vaccines developed jointly by the University of Oxford and AstraZeneca (ISRCTN89951424; NCT04516746; NCT04540393; CTRI/2020/08/027170)
- Two non-replicating viral vector vaccines developed by CanSino Biological Inc./Beijing Institute of Biotechnology (NCT04526990; NCT04540419)
- Two non-replicating viral vector vaccines designed by Gamaleya Research Institute (NCT04530396; NCT04564716)
- A non-replicating viral vector developed by Janssen Pharmaceutical Companies (NCT04505722)
- One protein subunit Novavax vaccine (2020–004123-16)
- Two inactivated Sinovac vaccines (NCT04456595; 669/UN6.KEP/EC/2020)
- An inactivated vaccine designed by the Wuhan Institute of Biological Products/Sinopharm (ChiCTR2000034780)
- Two inactivated vaccine developed by the Beijing Institute of Biological Products/ Sinopharm (ChiCTR2000034780; NCT04560881)
- An RNA vaccine developed by Moderna/NIAID (NCT04470427)
- An RNA vaccine developed by BioNTech/Fosun Pharma/Pfizer (NCT04368728).

In addition, several other vaccine candidates are undergoing preclinical and clinical testing (World Health Organization, 2020).

Conclusions

Global cooperation and efforts are urgently needed to contain the COVID-19 epidemic. At present, infection control measures including quarantine, social distancing and the use

Key points

- All humans are believed to be susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
- The pathogenesis of SARS-CoV-2 infection remains to be fully clarified.
- Infected individuals generally receive symptomatic care.
- Several vaccine candidates are undergoing preclinical and clinical trials.

of masks are essential to prevent the ongoing spread of this virus. In addition to wearing masks in populated areas, it is essential that all persons conduct regular disinfection and hand-washing in order to minimize viral transmission through aerosols or contact with foreign objects. Current treatment approaches are based on those that have been used previously to treat SARS and MERS. There is an urgent need for the development of reliable treatments for this disease and for the formulation of a preventative vaccine. Researchers are racing to develop drugs and vaccines against SARS-CoV-2. Improved understanding of the pathogenesis of COVID-19 will allow the use of more rationally selected and targeted treatments to control viral replication and associated immunopathology, helping to reduce the mortality associated with this severe pandemic disease and prevent its further spread.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Alhazzani W, Møller MH, Arabi YM et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Crit Care Med. 2020;48(6):e440–e469. https://doi.org/10.1097/CCM.0000000000004363

Arabi YM, Balkhy HH, Hayden FG et al. Middle east respiratory syndrome. N Engl J Med. 2017;376(6):584–594. https://doi.org/10.1128/microbiolspec.EI10-0020-2016

Baghizadeh Fini M. What dentists need to know about COVID-19. Oral Oncol. 2020;105:104741. https://doi.org/10.1016/j.oraloncology.2020.104741

Bchetnia M, Girard C, Duchaine C et al. The outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a review of the current global status. J Infect Public Health. 2020;S1876-0341(20)30591-30598. https://doi.org/10.1016/j.jiph.2020.07.011

Bernal-Bello D, Jaenes-Barrios B, Morales-Ortega A et al. Imatinib might constitute a treatment option for lung involvement in COVID-19. Autoimmun Rev. 2020;19(7):102565. https://doi.org/10.1016/j.autrev.2020.102565

Cao W, Liu X, Bai T et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis. 2020a;7(3):ofaa102. https://doi.org/10.1093/ofid/ofaa102

Cao B, Wang Y, Wen D et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020b;382(19):1787–1799. https://doi.org/10.1056/NEJMoa2001282

Cinatl J Jr, Michaelis M, Scholz M et al. Role of interferons in the treatment of severe acute respiratory syndrome. Expert Opin Biol Ther. 2004;4(6):827–836. https://doi.org/10.1517/14712598.4.6.827

Colson P, Rolain JM, Lagier JC et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents. 2020;55(4):105932. https://doi.org/10.1016/j.ijantimicag.2020.105932

Diurno F, Numis FG, Porta G et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. Eur Rev Med Pharmacol Sci. 2020;24(7):4040–4047. https://doi.org/10.26355/eurrev_202004_20875

Drosten C, Günther S, Preiser W et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med. 2003;348(20):1967–1976. https://doi.org/10.1002/ssu.2980050207

Duan K, Liu B, Li C et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci Usa. 2020;117(17):9490–9496. https://doi.org/10.1073/pnas.2004168117

Falzarano D, de Wit E, Martellaro C et al. Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Sci Rep. 2013;3(1):1686. https://doi.org/10.1038/srep01686

Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. 2020;35(3):266–271. https://doi.org/10.1007/s12250-020-00207-4

Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020;56(1):105949. https://doi.org/10.1016/j.ijantimicag.2020.105949

Gemicioğlu B, Borekci S, Görek Dilektasli A et al. Turkish Thoracic Society Experts consensus report: recommendations for pulmonary function tests during and after COVID 19 pandemic. Turk Thorac J. 2020;21(3):193–200. https://doi.org/10.5152/TurkThoracJ.2020.20107

Gharebaghi R, Heidary F, Moradi M et al. Metronidazole; a potential novel addition to the COVID-19 treatment regimen. Arch Acad Emerg Med. 2020;8(1):e40

Grein J, Ohmagari N, Shin D et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. 2020;382(24):2327–2336. https://doi.org/10.1056/NEJMoa2007016

Gruszecka J, Filip R. Preliminary information on prevention of infections caused by SARS-COV-2 virus in endoscopic laboratories. Ann Agric Environ Med. 2020;27(2):171–174. https://doi.org/10.26444/aaem/122137

Halaji M, Farahani A, Ranjbar R et al. Emerging coronaviruses: first SARS, second MERS and third SARS-CoV-2: epidemiological updates of COVID-19. Infez Med. 2020;28(suppl 1):6–17

Hon KL, Leung KKY, Leung AK et al. Coronavirus disease 2019 (COVID-19): latest developments in potential treatments. DIC. 2020;9:1–15. https://doi.org/10.7573/dic.2020-4-15

Hozhabri H, Piceci Sparascio F, Sohrabi H et al. The global emergency of novel coronavirus (SARS-CoV-2): an update of the current status and forecasting. IJERPH. 2020;17(16):5648. https://doi.org/10.3390/ijerph17165648

Hsia BC, Greige N, Quiroz JA et al. QT prolongation in a diverse, urban population of COVID-19 patients treated with hydroxychloroquine, chloroquine, or azithromycin. J Interv Card Electrophysiol. 2020;1–9. https://doi.org/10.1007/s10840-020-00822-x

Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. Lancet. 2020;395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Hui DS, I Azhar E, Madani TA et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health: the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264–266. https://doi.org/10.1016/j.ijid.2020.01.009

Hung IF, Lung KC, Tso EY et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1695–1704. https://doi.org/10.1016/S0140-6736(20)31042-4

Imai Y, Kuba K, Rao S et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436(7047):112–116. https://doi.org/10.1038/nature03712

Jodele S, Medvedovic M, Luebbering N et al. Interferon-complement loop in transplant-associated thrombotic microangiopathy. Blood Adv. 2020;4(6):1166–1177. https://doi.org/10.1182/bloodadvances.2020001515

Jordan PC, Stevens SK, Deval J. Nucleosides for the treatment of respiratory RNA virus infections. Antivir Chem Chemother. 2018;26:204020661876448. https://doi.org/10.1177/2040206618764483

Khalili JS, Zhu H, Mak NSA et al. Novel coronavirus treatment with ribavirin: Groundwork for an evaluation concerning COVID-19. J Med Virol. 2020;92(7):740–746. https://doi.org/10.1002/jmv.25798

Ko JH, Seok H, Cho SY et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther. 2018;23(7):617–622. https://doi.org/10.3851/IMP3243

Kumar S, Jha S, Rai SK. Significance of super spreader events in COVID-19. Indian J Public Health. 2020;64(6):139–S141. https://doi.org/10.4103/ijph.IJPH_495_20

Lai CC, Shih TP, Ko WC et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020;55(3):105924. https://doi.org/10.1016/j.ijantimicag.2020.105924

Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV. Nat Rev Drug Discov. 2020;19(3):149–150. https://doi.org/10.1038/d41573-020-00016-0

Li H, Wang YM, Xu JY et al. Potential antiviral therapeutics for 2019 Novel Coronavirus. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43(3):170–172. https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0002

Mahalmani VM, Mahendru D, Semwal A et al. COVID-19 pandemic: a review based on current evidence. Indian J Pharmacol. 2020;52(2):117–129. https://doi.org/10.4103/ijp.IJP_310_20

Mahmoud DB, Shitu Z, Mostafa A. Drug repurposing of nitazoxanide: can it be an effective therapy for COVID-19? J Genet Eng Biotechnol. 2020;18(1):35. https://doi.org/10.1186/s43141-020-00055-5

Marmor MF, Kellner U, Lai TY et al for the American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386–1394. https://doi.org/10.1016/j.ophtha.2016.01.058

Monteil V, Kwon H, Prado P et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020;181(4):905–913.e7. https://doi.org/10.1016/j.cell.2020.04.004

Neupane K, Ahmed Z, Pervez H et al. Potential treatment options for COVID-19: a comprehensive review of global pharmacological development efforts. Cureus. 2020;12(6):e8845. https://doi.org/10.7759/cureus.8845

Pagliusi S, Jarrett S, Hayman B et al. Emerging manufacturers engagements in the COVID-19 vaccine research, development and supply. Vaccine. 2020;38(34):5418–5423. https://doi.org/10.1016/j.vaccine.2020.06.022

Peña-Silva R, Duffull SB, Steer AC et al. Pharmacokinetic considerations on the repurposing of ivermectin for treatment of COVID-19. Br J Clin Pharmacol. 2020; https://doi.org/10.1111/bcp.14476

Płusa T. Możliwości kontrolowania zakażenia nowym wirusem Corona: 2019-nCoV. [Options for controlling new Corona virus infection - 2019-nCoV]. Pol Merkur Lekarski. 2020;48(284):112–119

Rathnayake AD, Zheng J, Kim Y et al. 3C-like protease inhibitors block coronavirus replication in vitro and improve survival in MERS-CoV-infected mice. Sci Transl Med. 2020;12(557):eabc5332. https://doi.org/10.1126/scitranslmed.abc5332

Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433. https://doi.org/10.1016/j.jaut.2020.102433

Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395(10223):473–475. https://doi.org/10.1016/j.jaut.2020.102433

Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J. 2019;16(1):69. https://doi.org/10.1186/s12985-019-1182-0

Shen C, Wang Z, Zhao F et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020;323(16):1582–1589. https://doi.org/10.1001/jama.2020.4783

Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther. 2020;209:107512. https://doi.org/10.1016/j.pharmthera.2020.107512

Song Y, Zhang M, Yin L et al. COVID-19 treatment: close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agents. 2020;56(2):106080. https://doi.org/10.1016/j.ijantimicag.2020.106080

Thanh Le T, Andreadakis Z, Kumar A et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020;19(5):305–306. https://doi.org/10.1038/d41573-020-00073-5

Tu YF, Chien CS, Yarmishyn AA et al. A review of SARS-CoV-2 and the ongoing clinical trials. IJMS. 2020;21(7):2657. https://doi.org/10.3390/ijms21072657

Uddin M, Mustafa F, Rizvi TA et al. SARS-CoV-2/COVID-19: viral genomics, epidemiology, vaccines, and therapeutic interventions. Viruses. 2020;12(5):526. https://doi.org/10.3390/v12050526

van Doremalen N, Bushmaker T, Morris DH et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564–1567. https://doi.org/10.1056/NEJMc2004973

Wang BX, Fish EN. Global virus outbreaks: Interferons as 1st responders. Semin Immunol. 2019;43:101300. https://doi.org/10.1016/j.smim.2019.101300

Warren TK, Jordan R, Lo MK et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature. 2016;531(7594):381–385. https://doi.org/10.1038/nature17180

Weiss SR, Leibowitz JL. Coronavirus pathogenesis. Adv Virus Res. 2011;81:85–164. https://doi.org/10.1016/B978-0-12-385885-6.00009-2

World Health Organization. DRAFT landscape of COVID-19 candidate vaccines-30 September 2020. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 30 September 2020)

Wu CY, Jan JT, Ma SH et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci USA. 2004;101(27):10012–10017. https://doi.org/10.1073/pnas.0403596101

Xia S, Yan L, Xu W et al. A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. Sci Adv. 2019;5(4):eaav4580. https://doi.org/10.1126/sciadv.aav4580

Yan VC, Muller FL. Advantages of the parent nucleoside GS-441524 over Remdesivir for Covid-19 treatment. ACS Med Chem Lett. 2020;11(7):1361–1366. https://doi.org/10.31219/osf.io/5u38s

Yao X, Ye F, Zhang M et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71(15):732–739. https://doi.org/10.1093/cid/ciaa237

Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology. 2018;23(2):130–137. https://doi.org/10.1111/resp.13196

Zaki AM, van Boheemen S, Bestebroer TM et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814–1820. https://doi.org/10.1056/NEJMoa1211721

Zhang B, Zhang S. Corticosteroid-induced osteonecrosis in COVID-19: a call for caution. J Bone Miner Res. 2020; https://doi.org/10.1002/jbmr.4136

Zhang X, Zhang Y, Qiao W et al. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. Int Immunopharmacol. 2020;86:106749. https://doi.org/10.1016/j.intimp.2020.106749

Zhu Z, Lu Z, Xu T et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020;81(1):e21–e23. https://doi.org/10.1016/j.jinf.2020.03.060