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REVIEW

Coronavirus disease 2019 (COVID-19): latest developments in potential treatments

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Abstract

Many viral respiratory infections can cause severe acute respiratory symptoms leading to mortality and morbidity. In the spring of 2003, the severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV spread globally. In the summer of 2012, the Middle East respiratory syndrome (MERS) outbreak caused by MERS-CoV occurred in Saudi Arabia. In the winter of 2019, the coronavirus disease 2019 (COVID-19) outbreak caused by a novel coronavirus SARS-CoV-2 occurred in China which rapidly spread worldwide causing a global pandemic. Up until 27 May 2020, there are 5.5 million confirmed cases of COVID-19 and 347,587 COVID-19 related deaths worldwide, and there has also been an unprecedented increase in socioeconomic and psychosocial issues related to COVID-19. This overview aims to review the current developments in preventive treatments and therapies for COVID-19. The development of vaccines for SARS-CoV-2 is ongoing and various clinical trials are currently underway around the world. It is hoped that existing antivirals including remdesivir and lopinavir-ritonavir might have roles in the treatment of COVID-19, but results from trials thus far have not been promising. COVID-19 causes a mild respiratory disease in the majority of cases, but in some cases, cytokine activation causes sepsis and acute respiratory distress syndrome, leading to morbidity and mortality. Immunomodulatory treatments and biologics are also being actively explored as therapeutics for COVID-19. On the other hand, the use of steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) has been discouraged based on concerns about their adverse effects. Over the past two decades, coronaviruses have caused major epidemics and outbreaks worldwide, whilst modern medicine has been playing catch-up all along.

Keywords: coronavirus, COVID-19, review, SARS-CoV-2, therapeutics, vaccines.

Citation

Hon KL, Leung KKY, Leung AKC, Qian SY, Chan VPY, Ip P, Wong ICK. Coronavirus disease 2019 (COVID-19): latest developments in potential treatments. Drugs in Context 2020; 9: 2020-4-15. DOI: 10.7573/dic.2020-4-15

Introduction

Viral respiratory infections such as influenza and measles, which can cause severe acute respiratory symptoms, have been responsible for many epidemics. In the spring of 2003, an outbreak of severe acute respiratory infection (SARI) spread globally.[1,2,3] The World Health Organization (WHO) coined the acronym SARS (severe acute respiratory syndrome) for this SARI and subsequently named the causative coronavirus SARS-CoV. In the summer of 2012, another SARI broke out in Saudi Arabia, which was found to be caused by a new coronavirus. The WHO named this respiratory disease Middle East respiratory syndrome also known by the acronym MERS and called the causative coronavirus MERS-CoV. In the winter of 2019, another SARI outbreak occurred in Wuhan, China, which very quickly spread around the world. The culprit was identified as another novel coronavirus, which the WHO named as SARS-CoV-2 due to similarities to SARS-CoV, and the disease was called coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a newly emergent coronavirus closely related to SARS and MERS.[4] COVID-19 is a respiratory tract infection that causes mild symptoms in the majority of cases, but can also lead to

mortality and morbidity. Current reports suggest that COVID-19 causes milder symptoms in children, including fever and cough, but co-infection has also been observed.[4,5] However, COVID-19 is associated with severe outcomes in the older population, immunocompromised patients, and those with chronic cardiovascular or respiratory conditions.[4]

At present, no pharmaceutical products have been shown to be reliable, safe, and effective for treating COVID-19.[6] In the midst of the current global pandemic, many research groups around the world are actively developing treatments against this disease to reduce morbidities and mortalities. In the long term, the goal is to develop a vaccine to prevent further infections and future outbreaks. However, an effective vaccine may take years to develop and to manufacture on a global scale. Furthermore, it is unknown if newborns and patients already recovered from Covid-19 will need to be vaccinated. It is also uncertain if such a vaccine can protect individuals from this novel coronavirus in the future. In this narrative review, we summarise the latest body of evidence and ongoing research on the development of pharmacological therapies for COVID-19. The aim is also to review the suggested pathophysiology, prophylactic treatments, and therapeutic modalities for COVID-19.

Methods

Articles were retrieved using PubMed Clinical Queries with the search term 'Coronavirus COVID-19' regardless of the date of publication. There were 88 articles under clinical study categories (category: therapy; scope: broad) and 11 systematic reviews. The discussion is based on, but not limited to, these search results.

Overview of the history of treatments for coronavirus outbreaks

SARS 2003

Severe acute respiratory syndrome is a viral respiratory disease of zoonotic origin caused by SARS-CoV. The SARS outbreak between November 2002 and July 2003 resulted in 8098 cases and 774 deaths in 29 countries around the world, giving a case-fatality rate of 9.6%.[7,8] Treatments for SARS during the outbreak were mainly supportive, as there were no known effective antiviral agents. The use of broad-spectrum antibiotics to treat secondary bacterial infections was the main treatment regimen.[9] Ribavirin, a broad-spectrum purine nucleoside analogue, was empirically used as a broad-spectrum antiviral agent.[10] Human immunodeficiency virus (HIV) protease inhibitor lopinavir/ritonavir were also used, as it was found to have weak *in vitro* antiviral activity on the prototype SARS-CoV.[10,11] Other therapies included immunomodulators (e.g. corticosteroid, convalescent plasma, and pentaglobulin), interferons, and traditional Chinese medicine (TCM).[9,12] The development of vaccines was underway by the end of the epidemic, but no effective vaccine has since emerged.

MERS 2012

Middle East respiratory syndrome caused by MERS-CoV may have been transmitted to humans through infected camels. The MERS outbreak between September 2012 and January 2020 was reported to have caused 2519 laboratory-confirmed cases and 858 associated deaths globally, giving a case-fatality rate of 34.4%.[13] As of 2019, there is still no effective vaccine or treatment for this disease, although a number of antiviral medications have been investigated.[14] A 2019 systematic review of therapeutic agents against MERS-CoV showed that there is still no general consensus on the optimal treatment strategy for MERS-CoV infection.[15] The MIRACLE trial (MERS-CoV Infection tReated with A Combination of Lopinavir/ritonavir and intErferon-β1b) was the first randomised controlled trial to assess the feasibility, efficacy, and safety of a combination of lopinavir/ritonavir and interferon-β1b in hospitalised patients with MERS.[16,17] The trial was started in July 2016 and enrolled 194 participants, although results have yet to be published.[16,17] At present, only three potential MERS-CoV vaccine candidates have progressed to phase I clinical trials. It is very likely that no MERS vaccine will be available in the near future.[18]

COVID-19

The recent COVID-19 pandemic caused by SARS-CoV-2[19] is suggested to have originated in bats and transmitted to humans via an unknown intermediate host, possibly pangolins.[20,21] SARS-CoV-2 first emerged in Wuhan, Hubei Province, China in December 2019, after a cluster of pneumonia cases with unknown causes was reported. The COVID-19 outbreak in Wuhan quickly spread around the world within a very short period of time. There are 5.5 million confirmed cases of COVID-19 and 347,587 COVID-19 related deaths worldwide up to 27 May 2020, giving a crude case-fatality rate of approximately 7%.[22] Supportive treatment is the mainstay of management, as no antiviral therapy has been clinically proven to be effective against SARS-CoV-2, and no standard pharmacological treatment guidelines have been recommended by WHO.[4]

Potential treatment strategies for COVID-19

SARS-CoV, MERS, and SARS-CoV-2 are all zoonotic β-coronaviruses that have crossed from animals to humans.[23] The origin of SARS-CoV is still a mystery and remains a controversial topic. SARS-CoV is closely related to civet and bat CoVs, but it is phylogenetically divergent from other coronaviruses associated with human infections, including

OC43, NL63, 229E, and HKU1.[9] The full-length genome sequence of SARS-CoV-2 shows that it is similar to SARS-CoV, sharing 79.6% sequence identity.[24] Both SARS-CoV-2 and SARS-CoV use the same cellular receptor, angiotensin-converting enzyme II (ACE2) receptor, to enter into host cells.[24]

The pathophysiology of COVID-19 has yet to be confirmed, but it is likely to involve inflammatory processes that can trigger a massive cytokine storm. The cytokine profile of critically ill patients revealed increased levels of interleukin (IL)-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α.[25] Histopathological examination of the lungs of patients with COVID-19 revealed immunopathological changes including diffuse alveolar damage, desquamation of pneumocytes, pulmonary oedema, hyaline membrane formation, and interstitial mononuclear inflammatory infiltrates.[26] According to the limited number of reports of biopsy/autopsy results of patients with COVID-19, the pathological features resemble those seen in SARS and MERS virus infections.[26–28]

The similarities between SARS-CoV and SARS-CoV-2 suggest that the development of potential prophylactics and therapeutics for COVID-19 could be based on research on SARS.[3,12,19,29–,32] An important strategy would be to possibly control the viral replication using an effective antiviral agent to minimise the subsequent inflammation and tissue damage due to high viral loads. Immunomodulators could play a rescue therapy role, as pathological findings suggest that there is immunopathological damage.[9,26] Although the SARS-CoV-2 S protein receptor-binding domain has higher affinity than the SARS-CoV S protein receptor-binding domain, development of vaccines against SARS-CoV-2 could still be based on research on SARS-CoV.[33–35]

Therapeutics for COVID-19

The majority of COVID-19 patients, especially children, are either asymptomatic or have mild symptoms, and will likely recover by managing their own symptoms without the need for hospitalisation.[36] According to the Report by the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), out of 55,924 patients in China with laboratory-confirmed COVID-19, only 13.8% had severe symptoms including dyspnoea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO_2 ratio <300, and/or infiltrates >50% of the lung field within 24–48 hours; whereas, 6.1% were critical including respiratory failure, septic shock, and multiple organ dysfunction/failure.[37] At present, there is no proven effective therapy against SARS-CoV-2. However, patients who are severely or critically ill might consider experimental therapies. At the time of writing, there are 1135 registered COVID-19 clinical trials, of which 657 are intervention studies using new therapies, but only about 260 trials are beyond phase I.[38] The WHO has also launched the 'Solidarity' international clinical trial, which is investigating effective treatments and is currently comparing four of the most promising treatment options: remdesivir, lopinavir–ritonavir, lopinavir–ritonavir plus interferon β-1a, and hydroxychloroquine.[39] Over 90 countries have joined the 'Solidarity' international clinical trial.[39] In the following discussion, we summarise the latest evidence and research progress from the literature, with focus on pharmacological therapies (Table 1).

Supportive treatment

Empirical antimicrobials should be started within 1 hour after the detection of sepsis based on clinical diagnosis and local epidemiology.[4] For critically ill COVID-19 patients, intensive care treatment can include oxygen therapy, noninvasive mechanical ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation.[40] In addition to the standard management for acute respiratory distress syndrome, the literature also suggests lower intubation threshold, early prone positioning, and cautious fluid status management, considering that the incidence of myocardial dysfunction in COVID-19 patients is high.[41] Further discussion on the intensive care management of COVID-19 patients is beyond the scope of this review.

Pharmacological therapies targeting the virus

Remdesivir

Remdesivir (GS-5734) is a nucleoside analogue prodrug that inhibits viral RNA polymerases, and was developed by Gilead Science in response to the Ebola outbreak in 2017.[42–44] It is considered to be one of the most promising broad-spectrum antivirals for treating COVID-19. *In vitro* antiviral activities of remdesivir have been demonstrated in SARS-CoV, MERS-CoV, and SARS-CoV-2.[45,46] In early April, a preliminary report describing the clinical outcomes of a cohort of 53 hospitalised COVID-19 patients who received remdesivir, 68% of patients showed improvement of their oxygen-support status, but 60% of patients reported adverse events during follow-up.[42] Subsequently, a double-blinded randomised controlled trial in 237 adult patients with severe COVID-19 showed that remdesivir was not associated with statistically significant clinical benefits whilst adverse events were reported in 66% of patients.[47] Separately, the results of an interim analysis of the Adaptive COVID-19 Treatment Trial involving 1063 patients are more encouraging, as it indicated that patients who received redmesivir had a 31% faster time to recovery than those who received placebo (median time to recovery was 11 *versus* 15 days).[48] More recently, a phase 3 SIMPLE clinical trial demonstrated that patients receiving a 5-day and 10-day treatment course of remdesivir achieved similar improvements in clinical status.[49] Common adverse events

Table 1. Potential treatments for patient with COVID-19.

Therapies	Dosage*	Side effects
Antivirals		
Remdesivir (nucleotide analogue)[50,51,110,111]	Adult: loading dose 200 mg IV on day 1, followed by 100 mg IV once-daily maintenance doses for 9 days	Increased hepatic enzymes Diarrhoea Rash Renal impairment Hypotension
Lopinavir–ritonavir (protease inhibitor)[54,56,59,66,110,112]	Adult: 500 mg orally once to twice daily for 10–14 days	Gastrointestinal intolerance Hepatotoxicity Pancreatitis QT prolongation Lipid elevation
Chloroquine[110]	Adult: 400 mg PO daily for 5 days	QT prolongation Nausea and vomiting Retinopathy Rash Hypoglycaemia
Hydroxychloroquine sulfate[64,113]	Adult: 400 mg PO every 12 hours for 1 day, then 200 mg PO every 12 hours for 4 days.	
Protease inhibitor[76,114–116]	Nelfinavir, camostat mesilate, ritonavir, danoprevir, darunavir, flavopiridol, relacatib PO	Lipodystrophy Metabolic effects
Nucleoside analogue[76,117]	Galidesivir IV	Nephrotoxicity Myopathy Mitochondrial toxicity
Fusion inhibitor[76]	Umifenovir PO	Safety profile not established, ongoing clinical trial
RNA polymerase inhibitor[76,116,118]	Favipiravir PO	Safety profile not established, ongoing clinical trial
Neuraminidase inhibitor[76,119]	Oseltamivir PO	Gastrointestinal side effects Headache
Pharmacological therapies targeting the immune system		
Corticosteroids[66,77,110,120]	Adult: methylprednisolone 40 mg IV every 12 hours for 5 days or 1–2 mg/kg/day IV for 7 days	Osteonecrosis Osteoporosis Psychosis
Convalescent plasma[82,87]	No references	No significant side effects
Tocilizumab (monoclonal antibodies)[66,121]	4–8 mg/kg (max 800 mg/dose) IV Doses may be repeated 12 hours later if the initial dose is not effective	Gastrointestinal perforation Anaemia Hepatitis Infusion reaction Neutropenia

*Suggested dosages are adapted from the proposed dose to treat COVID-19 from ongoing clinical trials; the efficacy and safety have not been verified by authors.

reported in the preliminary studies included elevated hepatic enzymes, diarrhoea, constipation, hypoalbuminaemia, rash, renal impairment, anaemia, thrombocytopenia, and hypotension.[42,47] Potential drug–drug interactions with other medications metabolised through the cytochrome P450 system were also reported. The safety profile of this drug needs to be further evaluated. Randomised controlled trials on remdesivir are still ongoing, and two studies are in phase III of clinical trials to evaluate the safety and efficacy of remdesivir.[50–53]

Lopinavir–ritonavir

Lopinavir–ritonavir is a combination therapy used to treat HIV. Ritonavir is an inhibitor of cytochrome P450 and is used to increase the plasma half-life of lopinavir.[54] Lopinavir is a protease inhibitor that has been demonstrated to have antiviral effects against SARS, MERS-CoV, and SARS-CoV-2 *in vitro*.[54,55] Several trials have been investigating the efficacy of lopinavir–ritonavir compared with other drugs as a treatment for COVID-19.[39,56–58] Nevertheless, the results so far

indicate that lopinavir–ritonavir treatment has little benefit as a standalone therapy against SARS-CoV-2 infection. In a clinical trial involving 199 patients with laboratory-confirmed SARS-CoV-2 infection, lopinavir–ritonavir treatment was not associated with any clinical improvements compared with standard care.[54] Furthermore, lopinavir–ritonavir treatment caused gastrointestinal adverse events, and nearly 14% of the recipients could not complete the full 14-day course of treatment.[54] Other adverse effects included gastrointestinal intolerance, hepatotoxicity, pancreatitis, and QT prolongation. The use of ritonavir can cause severe drug–drug interactions in medications metabolised through the cytochrome system. The tolerance of the side effects might limit the dosage needed, as the concentration necessary to inhibit viral replication is relatively high.[54] Other clinical trials have been testing lopinavir–ritonavir combined with different drugs and different combinations such as ritonavir and interferon 1b.[39,56] Early use of lopinavir–ritonavir as an additional treatment to ritonavir–methylprednisolone for SARS-CoV was associated with a reduction in the overall death rate and intubation rate when compared with a matched cohort.[59] A clinical phase II trial has been investigating the use of lopinavir–ritonavir combined with interferon β-1b as a treatment for MERS since 2016, but the trial is ongoing and results have yet to be published.[60]

Ribavirin

Ribavirin is a guanosine analogue that interferes with the replication of RNA and DNA viruses.[61] *In vitro* antiviral activities of Ribavirin have been demonstrated in SARS-CoV and MERS-CoV.[61,62] From the experiences of SARS-CoV, the use of ribavirin as a monotherapy was limited as it required high concentration to inhibit viral replication, and ribavirin usage was associated with dose-dependent haemolysis and liver toxicity.[63,64] In the treatment of SARS and MERS, ribavirin is used in combination with interferon or lopinavir/ritonavir.[11,65] The use of ribavirin in combination with interferon or lopinavir/ritonavir is recommended in the latest Chinese National Treatment Guidelines for COVID-19.[66] A recent multicentre randomised phase 2 trial showed triple antiviral therapy of lopinavir/ritonavir, ribavirin, and interferon β-1b was superior to lopinavir–ritonavir alone in alleviating symptoms, shortening the duration of viral shedding and hospital stay in patients with mild-to-moderate COVID-19.[67]

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are widely used for the treatment of malaria and certain autoimmune diseases. These drugs have an established safety profile and are readily available at relatively low cost. Hydroxychloroquine sulphate has been demonstrated to be less toxic than chloroquine phosphate in animal studies.[68] Both these drugs have been reported to have antiviral effects against SARS-CoV and SARS-CoV-2 *in vitro*. Their potential mechanisms of action include blocking viral entry into cells by inhibiting glycosylation of host receptors, reducing viral replication, and blocking the export of newly constructed virions.[45,69] A trial in China involving more than 100 patients with Covid-19 showed that chloroquine was better able to inhibit exacerbation of pneumonia and improve lung imaging findings compared to the control treatment.[70] A recent small open-label nonrandomised clinical trial showed patients given daily hydroxychloroquine had significantly reduced viral load measured by nasopharyngeal swab on day 6.[5] However, the results in this study may have been confounded by other factors, as some patients also received azithromycin.[71] The combination of hydroxychloroquine and azithromycin should be used with caution in patients at risk for QT prolongation. The use of chloroquine alone is also a risk factor for QT prolongation. A phase IIb clinical trial assessing the safety and efficacy of high-dose chloroquine was terminated early due to prolonged QTc (>500 ms) and high lethality in the high-dose group compared to the low-dose group.[72] A recent analysis of a multinational registry of 96,032 hospitalised COVID-19 patients revealed that hydroxychloroquine or chloroquine was associated with decreased in-hospital survival (mortality of 11.1 *versus* 9.3%) and increased frequency of ventricular arrhythmia.[73] However, concerns have been raised about the veracity of data and analyses in this study and has led to retraction of the article.[74] Other adverse effects of chloroquine include retinopathy, rash, nausea, glucose fluctuation and diarrhoea, and use of chloroquine is contraindicated in patients with porphyria. Chloroquine or hydroxychloroquine should not be used to treat COVID-19 until they have been tested in clinical trials to determine the optimal dosage to balance efficacy and safety. Chloroquine or hydroxychloroquine has been suggested as candidate prophylactics for COVID-19 in populations at high risk of COVID-19 infections, such as Italy and New York.[75]

Other antiviral treatments

Other antiviral treatments for COVID-19 currently undergoing clinical trials include protease inhibitors (nelfinavir, camostat mesilate, ritonavir, danoprevir, darunavir, flavopiridol, relacatib), nucleoside analogues (galidesivir), fusion inhibitors (umifenovir), RNA polymerase inhibitors (favipiravir), and neuraminidase inhibitors (oseltamivir).[76]

Pharmacological therapies targeting the immune system

Corticosteroids

Corticosteroid therapies such as intravenous methylprednisolone are currently being tested as a treatment for COVID-19.[77] Methylprednisolone has already been used in COVID-19 patients in combination with antibiotics, oseltamivir, and oxygen therapy.[25] Long and colleagues reported that corticosteroid therapy using methylprednisolone, dexamethasone, and hydrocortisone was beneficial in treating

SARS-CoV patients,[78] and significantly prolonged survival time in clinical cases.[78] However, other studies reported the use of corticosteroids in early stages of SARS infection increased the viral load.[79] Furthermore, studies on the use of corticosteroids as an adjuvant therapy against MERS-CoV infection were unable to prove efficacy because all patients died.[80] Based on the recommendation by frontline Chinese physicians and local clinical experience during the SARS epidemic, a short course of corticosteroids at a low-to-moderate dose is probably justifiable for critically ill patients.[66,81] Corticosteroids are effective in treating the autoinflammatory cytokine activation syndrome. Reported side effects such as osteonecrosis are concerning, but data are still conflicting and recent recommendations against the use of corticosteroids are based on circumstantial evidence. Routine use of corticosteroids is not recommended as corticosteroids may prolong or worsen the disease, and were found to prolong viral shedding in MERS and SARS. Based on the current body of evidence, corticosteroids may be justified for certain medical indications (i.e. acute respiratory distress syndrome and sepsis) at the discretion of the physician in charge.

Convalescent plasma

Convalescent plasma might be promising as a postexposure prophylaxis for COVID-19 and as a potential treatment after infection, as it was also used as a salvage therapy in the SARS and MERS epidemics.[82–84] Considering the huge number of people exposed to COVID-19, use of convalescent plasma for post-exposure prophylaxis may not be justifiable, but could still be a treatment option. An observational study during the SARS epidemic showed a lower mortality rate in those receiving convalescent plasma as a treatment for SARS.[82] Studies on the clinical effects and outcomes of critically ill COVID-19 patients treated with convalescent plasma have so far shown encouraging results, although it should be noted that these studies were based on small case series.[85,86] Furthermore, studies on the use of convalescent plasma in SARS patients did not report any significant side effects.[82,87] Randomised trials on convalescent plasma therapy are still needed to eliminate the effects of other treatments and to investigate the safety and efficacy and optimal timing of administration. Highly purified preparations of neutralising antibodies against SARS-CoV-2 would be preferable, as it would be safer and have higher activity, but it might be technically difficult to mass produce.[84] Several pharmaceutical companies are starting to develop hyperimmune immunoglobulins against COVID-19.[88,89]

Monoclonal antibodies

The use of tocilizumab, a monoclonal antibody against IL-6, has recently been suggested as a treatment for COVID-19 patients at risk of cytokine storms.[90] Tocilizumab is an IL-6 inhibitor that may be effective in treating COVID-19.[91] The level of IL-6 was found to be correlated with the severity of COVID-19 and levels of C-reactive protein, lactate dehydrogenase, D-dimer, and T cells.[90] A retrospective study of 20 COVID-19 patients receiving tocilizumab found that 75% of them had decreased oxygen requirement.[92] According to The Diagnosis and Treatment Protocol from the China National Health Commission and State Administration of Traditional Chinese Medicine, tocilizumab can be used in patients with extensive pulmonary lesions and in patients with increased IL-6 levels.[66] Clinical trials on the efficacy of intravenous tocilizumab as a treatment for COVID-19 are ongoing.[93,94] However, serious adverse effects have been reported including gastrointestinal perforation, anaemia, hepatitis, and infusion reaction.

Traditional Chinese medicines and other complementary therapies

TCM employs phytotherapeutic formulations and cultural concepts that originated more than 5000 years ago.[95] The use of TCM as a coadjuvant therapy in the early stage of the SARS infection epidemic was reported to increase oxyhaemoglobin arterial saturation.[95] A Cochrane review found that Chinese herbs combined with Western medicines in SARS patients could improve symptoms, quality of life, and absorption of pulmonary infiltration, as well as decrease the corticosteroid usage.[96] Specific components such as glycyrrhizin, baicalin, and MOL376 were shown to have anti-SARS activities *in vitro*.[97–99]

Over 85% of SARS-CoV-2 patients in China received TCM, which has been reviewed by Yang and colleagues.[100] The use of TCM was included in the Chinese National Treatment Guidelines for COVID-19 patients and was recommended for different stages and severity of disease (Table 2).[66] However, the effectiveness of TCM in treating COVID-19 patients still remains unclear. Well-designed, large-scale, randomised, double-blinded, and placebo-controlled studies are necessary to confirm the efficacy of TCM before making any recommendations on their use in the management of patients with COVID-19.

Other complementary therapies such as high doses of vitamins, acupuncture, and exercise have been suggested to promote health. However, there are no reports of specific targeted effects on coronaviruses, and there are no randomised trials of complementary therapies as treatments for COVID-19.

Combination therapy

Several case series reported that combination therapy could be effective in treating patients with COVID-19 patients.[101] A single-centre case series of 89 hospitalised patients with COVID-19 (54 non-ICU and 35 ICU patients) treated with a combination therapy of moxifloxacin, lopinavir, interferon, and methylprednisolone (given to only ICU patients) showed good treatment effects and the mortality rate was less than 1%.[101,102] In another study of 51 COVID-19 patients, 10 (19.6%) patients treated with a combination of traditional Chinese medicine, interferon-a-1b, lopinavir, ritonavir, and short-term (3–5 days) corticosteroids had good treatment results and only

Table 2. Traditional Chinese medicines recommended by the Chinese National Health Commission & State Administration of Traditional Chinese Medicine.[66]

Stage of COVID-19 disease and symptoms		Recommended formulation
Before diagnosis		
Fatigue and gastrointestinal discomfort		Huoxiang Zhengqi capsules
Fatigue and fever		Jinhua Qinggan granules Lianhua Qingwen capsules/granules Shufeng Jiedu capsules/granules Fangfeng Tongsheng pills/granules
Treatment period (confirmed case)		
Mild	Cold dampness and stagnation lung syndrome	Raw ephedra 6 g, raw gypsum 15 g, almond 9 g, loquat 15 g, gardenia 15 g, Guanzhong 9 g, Dilong 15 g, Xu Changqing 15 g, Huoxiang 15 g, Peilan 9 g, Cangzhu 15 g, Yunling 45 g, Atractylodes 30 g, Jiao Sanxian 9 g each, Magnolia officinalis 15 g, betel coconut 9 g, yarrow fruit 9 g, ginger 15 g.
	Dampness and heat-accumulation lung syndrome	Betel nut 10 g, apple 10 g, Magnolia 10 g, Zhimu 10 g, scutellaria baicalensis 10 g, Bupleurum 10 g, red peony 10 g, forsythia 15 g, artemisia annua 10 g (decocted later), green leaves 10 g, raw licorice 5 g.
Moderate	Dampness and stagnation lung syndrome	Raw ephedra 6 g, bitter almond 15 g, raw gypsum 30 g, raw coix seed 30 g, grass root 10 g, patchouli 15 g, artemisia annua 12 g, Polygonum cuspidatum 20 g, verbena 30 g, dried reed root 30 g, gardenia 15 g, orange red 15 g, raw licorice 10 g.
	Cold dampness lung syndrome	Atractylodes lancea 15 g, Chenpi 10 g, Magnolia 10 g, Aquilegia 10 g, grass fruit 6 g, raw ephedra 6 g, Zhihuo 10 g, ginger 10 g, betel nut 10 g.
Severe	Plague poison and lung-closing syndrome	Raw ephedra 6 g, almond 9 g, raw gypsum 15 g, licorice 3 g, fragrant fragrant 10 g (back), Magnolia 10 g, atractylodes 15 g, grass fruit 10 g, pinellia 9 g, Poria 15 g, raw rhubarb 5 g (back), Mongolian Milkvetch Root 10 g, gardenia 10 g, red peony 10 g.
	Syndrome of flaring heat in qifen and yingfen	Gypsum (fried first) 30–60 g, Zhimu 30 g, raw land 30–60 g, buffalo horn (fried first) 30 g, red sage 30 g, black ginseng 30 g, forsythia 15 g, paeonia 15 g, Chinese Goldthread Rhizome 6 g, peony 12 g, gardenia 15 g, raw licorice 6 g.

Stage of COVID-19 disease and symptoms		
Treatment period		
Critical case	Syndrome of inner blocking causing collapse	Ginseng 15 g, Heishun tablets (decoct first) 10 g, dogwood 15 g, delivered with Suhexiang pill or Angong Niuhuang pill.
	Viral infection or combined mild bacterial infection	Xiyanping injection 100 mg bid
	High fever with disturbance of consciousness	Xingnaojing injection 20 mL bid
	Systemic inflammatory response syndrome or/and multiple organ failure	Xuebijing injection 100 mL
	Immunosuppression	Shenmai injection 100 mL bid
	Shock	Shenfu injection bid

(Continued)

Table 2. (Continued)

Stage of COVID-19 disease and symptoms	
Rehabilitation period	
Lung and spleen qi deficiency syndrome	French Pinellia 9 g, Chenpi 10 g, Codonopsis 15 g, Sunburn Astragalus 30 g, Stir-fried Atractylodes 10 g, Poria 15 g, Huoxiang 10 g, Amomum villosum 6 g, and Licorice 6 g
Qi and Yin deficiency syndrome	North and south radix salviae 10 g, ophiopogonis 15 g, American ginseng 6 g, schisandra 6 g, gypsum 15 g, light bamboo leaves 10 g, mulberry leaves 10 g, reed root 15 g, salviae miltiorrhiza 15 g, raw liquorice 6 g.

*Suggested treatment regimen and dosages are adapted from the seventh version of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia released by the National Health Commission & State Administration of Traditional Chinese Medicine; the efficacy and safety have not been verified by authors.

one patient died.[103] In a case report of a 45-year-old woman with COVID-19 treated with thalidomide (100 mg orally once a day) and methylprednisolone (40 mg intravenously bid for 3 days then reduced to once a day for 5 days), she had overall improved status, increased oxygen index, decreased symptoms of nausea and vomiting, and lower cytokine levels.[101] However, we cannot draw any definitive conclusions from this single case report as there was no control.

Prophylaxis for COVID-19

Although the development of vaccines started towards the end of the 2003 SARS epidemic, as of 2020, there are still no approved vaccines for SARS-CoV. The main obstacle to the development of a vaccine is funding. Many vaccines that show promising results at the preclinical stage require further investments from governments or the private sector to progress to clinical trials. As SARS has largely disappeared since 2004 and MERS is primarily confined to Saudi Arabia and Korea, there is little urgency in developing vaccines for these coronaviruses and it would not be in the best interest of investors.[104] There were 33 candidate vaccines targeting SARS-CoV and 48 candidate vaccines targeting MERS-CoV, but most only reached preclinical stages. So far, only two SARS-CoV and three MERS-CoV vaccines have reached the clinical trial stage.[105] Nevertheless, the previous SARI outbreaks pale in comparison to the current COVID-19 pandemic. If vaccines for these previous coronaviruses had been successfully developed, we could have tested their efficacy and safety for COVID-19. Investments in vaccines for coronaviruses might now seem minuscule compared to the economic and social fallout of the current pandemic. The WHO has launched an international randomised trial of candidate vaccines against COVID-19. At the time of writing, there are 115 COVID-19 vaccine candidates and at least five candidate vaccines have reached phase I clinical trials.[105,106]

Many TCM could be used as alternative preventive treatments for COVID-19 based on previous prevention studies in populations at high risk from SARS and H1N1 influenza.[107] The use of TCM to prevent infectious disease epidemics has also been described in the ancient Chinese medicine text, Huangdi Neijing, which was compiled over 2000 years ago. The main principles of TCM are to tonify qi to protect from external pathogens, disperse wind and discharge heat, and resolve dampness. Prospective studies are needed to verify the efficacy and safety of TCM for the prevention of COVID-19.[107]

Conclusion

All the coronaviruses are similar in nature and have defined clinical presentations. The lower prevalence of coronavirus diseases in children might be accounted for by the lower exposure and relatively mild clinical presentation in the paediatric population. Many of the mild and asymptomatic cases are often overlooked and therefore go undiagnosed. Comparing the immunopathology of SARS-CoV-2 infection between children and adults could reveal the pathology of the disease and might lead to possible treatment strategies for 'recurrent' novel coronavirus infections. There is currently no approved antiviral treatment for patients suspected of or confirmed with COVID-19. Research on the SARS and MERS epidemics and data from *in vitro* studies show that antiviral therapy may be beneficial. Antiviral therapies and adjunctive treatments should, therefore, be considered in COVID-19 patients with the unstable clinical condition or clinical deterioration or in patients with comorbidities. As the COVID-19 situation develops, we will learn more about the safety and efficacy of specific treatments, and treatment recommendations are likely to change to reflect the latest evidence.

At the time of writing, the most urgent issue is to curtail the spread of COVID-19. Vaccines could be the answer to this crisis, but vaccines are likely many months away and will take time to scale-up and manufacture on a global scale. In the meantime, public health officials should be focusing on nonpharmaceutical interventions. Measures such as personal hygiene, wearing masks in the general population, social distancing, surveillance programs for testing suspected cases,

early quarantine, vigilant contact tracing, and preventing healthcare-related transmission are key factors to stopping the COVID-19 pandemic.[108]

Although a safe and effective treatment has yet to be found, the sheer number of clinical trials that have started since the beginning of the epidemic is nothing short of impressive. Combining advanced technologies in the field of genomics and computer science, potential treatments could be identified through machine learning, complex molecular dynamics, and artificial intelligence. With the joint efforts of research communities around the world, we are hopeful that an effective treatment or vaccine for COVID-19 can be developed in the near future.[109] This pandemic should also raise the awareness in governments and pharmaceutical companies on the importance of continued funding for research in this area. At the same time, healthcare systems and infrastructures should be reviewed for suitability and preparedness in dealing with future pandemics.

SARS-CoV-2 is the third re-emergence of a coronavirus in the past two decades and has abruptly put a halt to most social and economic activity around the world, the consequences of which are immeasurable.[122] This pandemic will undoubtedly change our daily habits and social routines and should serve as a huge wake-up call that has shown the vulnerability of the human race. For now, the global battle against COVID-19 continues, and together, we will inevitably defeat the coronavirus. Hard lessons will be learned that will better prepare us for the next pandemic.

Contributions: All authors contributed equally to the preparation of this review. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2020/06/dic.2020-4-15-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/coronavirus-disease-2019-(covid-19):-latest-developments-in-potential-treatments

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Provenance: invited; externally peer reviewed.

Submitted: 20 April 2020; **Peer review comments to author:** 4 May 2020; **Revised manuscript received:** 27 May 2020; **Accepted:** 28 May 2020; **Publication date:** 29 June 2020.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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