



Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Review Article

COVID-19: An Update on Therapeutics and Clinical Trials

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ARTICLE INFO

Article history:

Received: 09 June, 2020

Revised: 27 June, 2020

Accepted: 10 July, 2020

Published: 30 July, 2020

Keywords:

Clinical trials, COVID-19,
Therapeutics,
Traditional approaches,
Vaccines.

DOI:

10.25004/IJPSDR.2020.120416

ABSTRACT

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases. A novel coronavirus (nCoV) is a new strain that has not been previously identified in humans. On 30th January 2020, the World Health Organization (WHO) Director-General declared the novel coronavirus (COVID-19) outbreak a public health emergency of international concern. Many fatalities have occurred and continue to happen. Despite staggering research efforts for therapeutics, a complete cure is still a distant dream. The write-up updates the treatment approaches utilized in clinical settings across the globe, and the clinical trials registered in the federal and WHO's register, for drugs and vaccines to combat the pandemic.

INTRODUCTION

Coronaviruses are single-strand RNA viruses that contain the largest known RNA genome that ranges from 27 to 32 kilobases in length.^[1] Morphologically, coronaviruses are spherical, surrounded by a halo of spiky proteins, seen as a crown or the corona of the sun.^[2] Coronaviruses are present in avian and mammalian species due to their similarity in morphology and chemical structure. For example, coronaviruses are antigenically related in the case of human and cattle coronaviruses. Coronaviruses invaded different tissue and became a reason for various diseases in animals, but in the case of humans, they are seen to cause, mainly, mild upper respiratory infection, i.e., common cold.^[3]

Before 2002 and 2003, these were not considered pathogenic to humans until the outbreak of severe acute respiratory syndrome (SARS) in 2002 at Guangdong province, China. SARS-COV primarily infects ciliated

bronchial epithelial cells and type II pneumocytes by acting on angiotensin-converting enzyme 2 (ACE2) receptors. After ten years of SARS, there was an outbreak of another highly pathogenic coronavirus in the Middle Eastern countries, known as MERS-COV. It infects unciliated bronchial epithelial cells by acting on receptor dipeptidyl peptidase 4 (DPP4, also known as CD26). Recently, the new type of coronavirus, COVID-19 has become the reason for many deaths across the globe.^[4] The original animal reservoir hosts of COVID-19 apparently, is Chinese horseshoe bat. Recent reports have traced new hosts, viz., tigris in USA and Indian bats in the state of Kerala.

Despite the denials, on 31st December 2019, clusters of acute respiratory illness cases were reported among people in the city of Wuhan. Within 1-month of reporting of novel coronavirus-associated acute respiratory illness, more than 1,000,000 confirmed cases have been reported, with a reported mortality of around 2 to 3%. The ongoing

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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(COVID-19) outbreak is a Public Health Emergency of International Concern (PHEIC). The temporary name Wuhan virus was changed to “2019-nCoV acute respiratory disease,” in accordance with the WHO naming practices, which further got approval from The International Committee on Taxonomy of Viruses.^[5] The write-up has been undertaken to updating the treatment approaches utilized in clinical settings across the globe, the clinical trials registered in the federal and WHO’s register for drugs and vaccines, and the traditional approach as a preventive measure to combat the pandemic.

SPREAD AND DEMOGRAPHICS STATUS

Firstly, it spread by the direct connection of people of Wuhan to the animals of the wet market, later as a symptom of common cold, it starts spreading from person to person through air-borne particles, surface particles, and close contact with infected individuals. As a precaution, Wuhan was quarantined, but, unfortunately, the coronavirus spread outside the Chinese borders. Globally, as of 10:31 am CEST, 8th June 2020, there have been 6,912,751 confirmed cases of COVID-19, including 400,469 deaths, reported to WHO. The confirmed cases report, country wise, by WHO as on 8th June 2020^[6] is depicted in the bar chart (Fig. 1).

CLINICAL FEATURES

Symptoms

COVID-19 affects different people in different ways. Most infected people will develop mild to moderate illness and recover without hospitalization. The symptoms are very

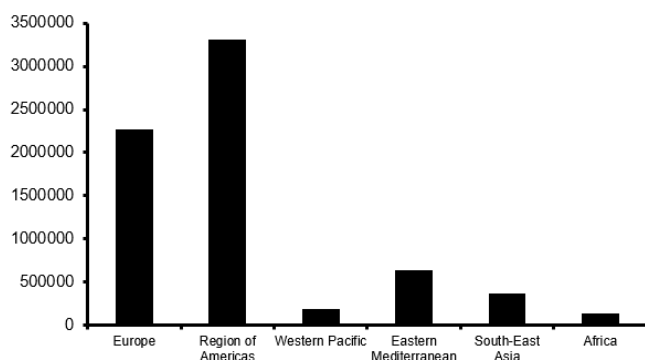


Fig. 1: Situation in numbers, as per WHO dashboard on 8th June 2020

similar to the other viral respiratory infection, and include fever, dry cough, fatigue, phlegm production, shortness of breath, muscle pain, sore throat, and headache. The symptoms can be classified as the most common, less common, and serious symptoms (Table 1).

Any person can have mild to severe symptoms. The symptoms may appear 2 to 14 days after exposure to the virus. Older adults and people who have underlying medical conditions, like diabetes, heart or lung disease, or hypertension, seem to be at higher risk for developing serious complications from COVID-19 illness. The frequency of occurrence of the symptoms is presented in Fig. 2.^[7]

Clinical Classification of COVID-19

Mild Cases

The clinical symptoms are mild, and no pneumonia manifestations can be found in imaging.

Severe Cases

Adults who meet any of the following criteria: respiratory rate ≥ 30 breaths/min; oxygen saturations $\leq 93\%$ at a rest state; arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg. Patients with $> 50\%$ lesions progression within 24 to 48 hours in lung imaging should be treated as severe cases.^[8]

Critical Cases

Meeting any of the following criteria: occurrence of respiratory failure requiring mechanical ventilation; the presence of shock; other organ failures that requires monitoring and treatment in the intensive care unit (ICU), is

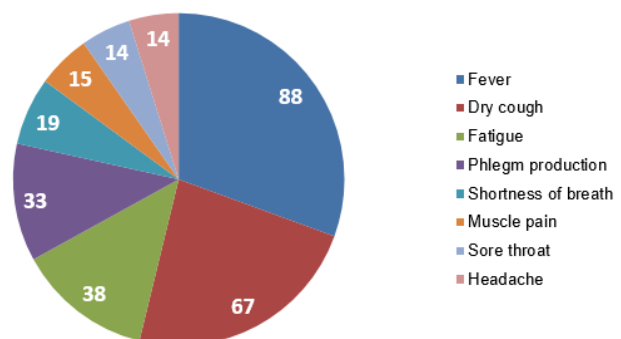


Fig. 2: Frequency of occurrence of symptoms of COVID-19

Table 1: Classification of COVID-19 symptoms

Common symptoms	Less common symptoms	Serious symptoms
Dry cough	Sore throat	Difficulty in breathing or shortness of breath
Tiredness	Headache	Loss of speech or movement
Fever	Conjunctivitis	Chest pain or pressure
	Aches and pains	
	Diarrhea	
	Loss of taste or smell	
	A rash on the skin, or discoloration of fingers or toes	



termed as a critical case. Critical cases are further divided into early, middle, and late stages according to the oxygenation index and compliance of the respiratory system.^[9]

- Early Stage

100 mmHg < oxygenation index $\leq$ 150 mmHg. Compliance of respiratory system $\geq$ 30 mL/cm H₂O. Without organ failure other than the lungs, the patient has a great chance of recovery through active antiviral, anti-cytokine storm, and supportive treatment.

- Middle Stage

60 mmHg < oxygenation index $\leq$ 100 mmHg, 30 mL/cm H₂O > compliance of respiratory system $\geq$ 15 mL/cm H₂O, may be complicated by other mild or moderate dysfunction of other organs.

- Late Stage

Oxygenation index $\leq$ 60 mmHg, compliance of respiratory system < 15 mL/cm H₂O, diffuse consolidation of both lungs that requires the use of extracorporeal membrane oxygenation (ECMO), or failure of other vital organs. The mortality risk is significantly increased.

Stages in COVID-19 Disease

COVID-19 disease has asymptomatic and symptomatic carriers with high transmission capacity by air-borne droplets and fomites. The clinical spectrum of the disease can be typically classified into three categories,^[10] as depicted in Fig. 3.

All three stages are infective. The clinical manifestations of the disease can be categorized into three categories by their severity. Mild illness reported in 80 to 85% of patients is manifested with minor symptoms and self-recovery. Severe illness is characterized by dyspnea, respiratory frequency $\geq$ 30/min, blood oxygen saturation (SpO₂) $\leq$ 93%, PaO₂/FiO₂ ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO₂) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO₂)] < 300, and/or lung infiltrates > 50% within 24 to 48 hours; this occurs in 10 to 15% patients, who require medical support. The critical disease is reported in 5% [respiratory failure, shock, multiple organ dysfunction (MOD)] that may need ICU support. The overall mortality rate is 2.3 to 5%.^[8]

Diagnosis

Multipronged detection approaches may be used depending on the clinical conditions. The first approach includes detection of inflammatory indicators that include (i) detection of SARS-CoV-2 nucleic acid, (ii) virus isolation and culture, (iii) detection of serum antibody, (iv) detecting indicators of an inflammatory response (reactive protein, procalcitonin, ferritin, D-dimer, total and subpopulations

of lymphocytes, IL-4, IL-6, IL-10, TNF- α , INF- γ , and other indicators of inflammation and immune status), and (v) detection of secondary bacterial or fungal infections.^[11]

Secondly, for the diagnosis of COVID-19, monitoring of therapeutic efficacy, and patient discharge assessment, thoracic imaging is done, and the use of high-resolution Computed tomography (CT) is preferred. CT for baseline evaluation of patients with COVID-19 is usually performed on the day of admission, or if ideal therapeutic efficacy is not reached, it can be re-performed after 2 to 3 days. If symptoms are stable or improved after treatment, the chest CT scan can be reviewed after 5 to 7 days.^[12] Lastly, bronchoscopy is also used in the diagnosis and management of COVID-19 patients. Its applications include: a collection of respiratory specimens from the lower respiratory tract (i.e., sputum, endotracheal aspirate, bronchoalveolar lavage) for SARS-CoV-2 or other pathogens guides the selection of appropriate antimicrobials, which may lead to clinical benefits. It can be used for local injection of cold saline, epinephrine, vasopressin, or fibrin, as well as, laser treatment that can be performed via the bronchoscope. Drugs, such as, infusion of α -interferon and N-acetylcysteine can be administered via bronchoscope.^[13]

TREATMENT APPROACHES

Antiviral Treatment

Early antiviral treatment can reduce the incidence of severe and critical cases. Although there is no clinical evidence for effective antiviral drugs, currently, the antiviral strategies based on the characteristics of SARS-CoV-2 are adopted according to Protocols for Diagnosis and Treatment of COVID-19: Prevention, Control, Diagnosis, and Management. At First Affiliated Hospital of Zhejiang University (FAHZU), lopinavir/ ritonavir (2 capsules, p.o., q 12 hours) combined with arbidol (200 mg, p.o., q 12 hours) was used as the basic regimen.^[14] From the treatment experience of 49 patients in the hospital, the average time to achieve a negative viral nucleic acid test for the first time was 12 days [95% credible interval (CI): 8–15 days]. The duration of negative nucleic acid test result (negative for more than two times consecutively with interval < 24 hours) was 13.5 days (95% CI: 9.5–17.5 days). If the basic regimen is not effective, chloroquine phosphate 500 mg, twice a day, for 7 days, for patients between 18 and 56 years of age, who weigh > 50 kg and 500 mg twice a day, for days 1 and 2, and then, 500 mg once a day, for days 3 to 7, for adults who weigh < 50 kg.^[15]

Darunavir/ cobicistat has some degree of antiviral activity in viral suppression test *in vitro*, based on the treatment experience of acquired immunodeficiency syndrome (AIDS) patients, and the adverse events are relatively mild. For patients who are intolerant to lopinavir/ ritonavir, darunavir/ cobicistat (1 tablet qd),

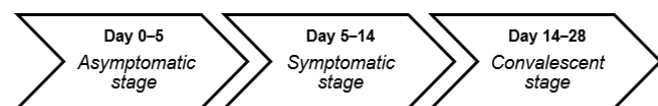


Fig. 3: Stages of COVID-19

or favipiravir (starting dose of 1,600 mg, followed by 600 mg tid) is an alternative option after the ethical review.^[16] Simultaneous use of three or more antiviral drugs is not recommended. Antiviral drugs should be stopped if nucleic acid test results from sputum specimens remain negative for more than three times.

Replication of SARS-CoV-2 depends on the viral RNA-dependent RNA polymerase (RdRp), which is the likely target of the investigational nucleotide analog, remdesivir. Remdesivir shows broad-spectrum antiviral activity against RNA viruses, and previous studies with remdesivir from the Ebola virus and MERS-CoV have revealed that delayed chain termination is remdesivir's possible mechanism of action. Gordon *et al.* expressed and purified active SARS-CoV-2 RdRp, composed on the known structural proteins. Enzyme kinetics indicated that RdRp efficiently incorporates the active triphosphates from remdesivir into RNA that causes termination RNA synthesis.^[17]

Rational Use of Antibiotics to prevent Secondary Infection

COVID-19 is a disease of viral infection, therefore, antibiotics are not recommended to prevent bacterial infection in mild or ordinary patients; it should be used carefully in severe patients based on their conditions. Antibiotics can be used with discretion in patients who have the following conditions: extensive lung lesions; excess bronchial secretions; chronic airway diseases with a history of pathogen colonization in the lower respiratory tract; taking glucocorticoids with a dosage < 20 mg × 7 days (in terms of prednisone).^[18] The options of antibiotics include quinolones, the second or third generation cephalothins, lactamase inhibitor compounds, etc.^[19] The antibiotics should be used for the prevention of bacterial infection in critically severe patients, especially those with invasive mechanical ventilation. The antibiotics, such as, carbapenems, lactamase inhibitor compounds, linezolid, and vancomycin can be used in critically ill patients according to the individual risk factors.^[20]

A group of researchers carried out a pilot observational study on the clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients, with at least a six-day follow-up. All patients improved clinically except one 86-year-old patient, who died, and one 74-year-old patient in intensive care until the study. A rapid fall of nasopharyngeal viral load was noted, with 83% negative on day 7, and 93% on day 8. Virus cultures from patient respiratory samples were negative in 97.5% of patients on day 5. Consequently, patients were able to be rapidly discharged from infectious disease unit (IDU) with a mean length of stay of 5 days. There is urgency to evaluate the effectiveness of this potentially-life saving therapeutic strategy at a larger scale, both to treat and cure patients

at an early stage, before irreversible severe respiratory complications take hold, and to decrease the duration of carriage and avoid the spread of the disease. Furthermore, the cost of treatment is negligible.^[21]

Anti-Fungal Therapy to prevent Fungal Infection

Some COVID-19 patients are at the risk of secondary fungal infections due to weakened cellular immunity caused by viral infections. It is necessary to do respiratory secretions' microbiological detections, such as, smear preparation and cultivation for critically ill patients, and provide timely D-glucose (G-test) and galactomannan (GM-test) of blood or bronchoalveolar lavage fluid for suspected patients.^[22] It is necessary to be vigilant with possible invasive candidiasis infection and anti-fungal therapy. Fluconazole or echinocandin can be used in the following conditions: (i) patients are given broad-spectrum antibiotics for seven days or more; (ii) patients have parenteral nutrition; (iii) patients have invasive examination or treatment; (iv) patients have positive *Candida* culture in the specimen obtained from two body parts or more; (v) patients have significantly increased results of G-test.^[23]

It is necessary to be vigilant with possible invasive pulmonary aspergillosis. Anti-fungal therapy, such as, voriconazole, posaconazole, or echinocandin, is considered to be used in the following conditions: (i) patients are given glucocorticoid for seven days or more; (ii) patients have agranulocytosis; (iii) patients have a chronic obstructive pulmonary disease and *Aspergillus* culture are tested positive in the specimen obtained from the airway; (iv) patients have significantly increased results of GM-test.^[24]

Additionally, many other relevant clinical manipulations are used depending on the clinical settings.

CLINICAL TRIALS

To date, more than 1,982 studies for COVID-19 have been posted on www.clinicaltrials.gov,^[25] ranging from repurposed antiviral drugs to novel diagnostic imaging techniques. Table 2 presents a cross section of clinical trial reports. COVID-19 studies from the WHO database reports 1,416 studies on 8th June 2020.^[26] Antibody- and convalescent plasma-based therapeutic approaches have dominated the news.^[27] Several hospitals have recruited people who had recovered from COVID-19 to do plasma transfers for COVID-19 patients. The Food Drug Administration (FDA) announced the approval of a plasma therapy trial at Johns Hopkins University. The treatment uses the blood sera from recovered COVID-19 patients to treat those who are critically ill, or to boost immunity for those at high risk of contracting the disease.^[28] The strategy of isolating plasma is well established, and with the current advances, it is as safe as a blood transfusion.

Takeda has announced a polyclonal hyperimmune antigen-purified antibody concentrate. The process used



Table 2: A cross-section of clinical trials being conducted globally, posted on www.clinicaltrials.gov^[25]

<i>Study title</i>	<i>Intervention</i>	<i>Status</i>	<i>Location</i>
Application of desferal to treat COVID-19	Deferoxamine	Recruiting	Regenerative Medicine Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
Preventing cardiac complication of COVID-19 disease with early acute coronary syndrome therapy: a randomized controlled trial	Aspirin 75 mg Clopidogrel 75 mg Rivaroxaban 2.5 mg	Recruiting	Charing Cross Hospital London, United Kingdom
Study of open-label losartan in COVID-19	Losartan	Recruiting	University of Kansas Medical Center, Kansas City, Kansas, United States
ALBERTA HOPE COVID-19 for the Prevention of Severe COVID19 Disease	Hydroxychloroquine	Recruiting	University of Calgary/ Foothills Medical Centre Calgary, Alberta, Canada University of Alberta Edmonton, Alberta, Canada
Safety and efficacy of ruxolitinib for COVID-19	Ruxolitinib	Not yet recruiting	University of Colorado, Denver
Treatment of moderate to severe coronavirus disease (COVID-19) in hospitalized patients	Lopinavir/ritonavir Hydroxychloroquine sulfate Baricitinib (Janus kinase inhibitor) Sarilumab (anti-IL-6 receptor)	Not yet recruiting	Nova Scotia Health Authority Halifax, Nova Scotia, Canada
Hydroxychloroquine vs. azithromycin for hospitalized patients, with suspected or confirmed COVID-19	Hydroxychloroquine Azithromycin	Recruiting	Intermountain Medical Center Murray, Utah, United States University of Utah Salt Lake City, Utah, US
An investigation into beneficial effects of interferon beta 1A, compared to interferon beta 1B and the base therapeutic regiment in moderate to severe COVID-19: A randomized clinical trial	Hydroxychloroquine Lopinavir/ ritonavir Interferon beta-1A Interferon beta-1B	Enrolling by invitation	Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences and Health Services Tehran, Iran
Tocilizumab in COVID-19 pneumonia (TOCIVID-19)	Tocilizumab injection	Recruiting	Azienda Ospedaliera "SS. Antonio e Biagio e C. Arrigo" (Dipartimento Internistico SSD Reumatologia) Alessandria, Italy
Treatment of COVID-19 patients with anti-interleukin drugs	Anakinra Siltuximab Tocilizumab	Recruiting	AZ Sint-Jan Brugge Brugge, Belgium University Hospital Saint-Pierre, Brussels, Belgium Erasmus University Hospital Brussels, Belgium
A study of quintuple therapy to treat COVID-19 infection	Drug(s) Hydroxychloroquine Azithromycin	Not yet recruiting	ProgenaBiome Ventura, California, United States
	Dietary supplement(s) Vitamin C Vitamin D Zinc		
Hydroxychloroquine for the treatment of mild COVID-19 disease	Hydroxychloroquine Placebo	Not yet recruiting	Institute for Tropical Medicine, Tübingen, Germany
Treatments for COVID-19: Canadian arm of the SOLIDARITY trial	Lopinavir/ ritonavir	Recruiting	Vancouver General Hospital, Vancouver Coastal Health, University of British Columbia Vancouver, British Columbia, Canada St. Paul's Hospital, Vancouver, British Columbia, Canada The Ottawa Hospital-General Campus Ottawa, Ontario, Canada, and seven more

Critically ill patients with COVID-19 in Hong Kong: a multicentre observational cohort study	Observational study	Completed	Pamela Youde Nethersole Eastern Hospital Hong Kong, Hong Kong Prince of Wales Hospital Hong Kong, Hong Kong Princess Margaret Hospital Hong Kong, Hong Kong
Treatment in patients with suspected or confirmed COVID-19, with early moderate or severe disease	Hydroxychloroquine Azithromycin	Recruiting	University Medical Center New Orleans, New Orleans, Louisiana, United States
Hydroxychloroquine vs. azithromycin for outpatients in Utah, with COVID-19	Hydroxychloroquine Azithromycin	Recruiting	Intermountain Medical Center Murray, Utah, United States University of Utah Salt Lake City, Utah, United States
Gargling and nasal rinses to reduce oro- and naso-pharyngeal viral load in patients with COVID-19	Saline oral/nasal rinse 0.5% povidone/iodine oral/nasal rinse 0.12% chlorhexidine oral/nasal rinse	Recruiting	NYU Langone Health New York, New York, United States
Comparison of lopinavir/ ritonavir or hydroxychloroquine in patients with mild coronavirus disease (COVID-19)	Lopinavir/ ritonavir Hydroxychloroquine sulfate	Recruiting	Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of Korea
Clinical trial of combined use of hydroxychloroquine, azithromycin, and tocilizumab for the treatment of COVID-19	Tocilizumab Hydroxychloroquine Azithromycin	Recruiting	Hospital de la Santa Creu i Sant Pau Barcelona, Spain
Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with severe coronavirus disease (COVID-19)	Remdesivir Standard of Care	Recruiting	Kaiser Permanente Los Angeles Medical Center, 3340 E. La Palma Avenue Anaheim, California, USA Kaiser Permanente Los Angeles Medical Center, 9333 Imperial Highway Downey, California, USA Kaiser Permanente Los Angeles Medical Center, 9961 Sierra Ave Fontana, California, USA (and 149 more)
A randomized placebo-controlled safety and dose-finding study for the use of the IL-6 inhibitor clazakizumab in patients with life-threatening COVID-19 infection	Clazakizumab 12.5 mg Clazakizumab 25 mg Placebo	Recruiting	New York University School of Medicine New York, New York, United States
PVP-I nasal sprays and SARS-CoV-2 nasopharyngeal titers (for COVID-19)	Povidone-iodine 2% Povidone-iodine 0.5% Isotonic saline 0.9%	Not yet recruiting	Stanford Health Care Stanford, California, United States
Convalescent plasma therapy vs. standard of care (SOC) for the treatment of COVID-19 in hospitalized patients	Blood and derivatives Standard of Care	Recruiting	Hospital Clínico Universitario Lozano Blesa Zaragoza, Aragón, Spain Hospital Universitario Severo Ochoa Leganés, Madrid, Spain Hospital Universitario Puerta de Hierro Majadahonda Majadahonda, Madrid, Spain (and six more)
Ivermectin adjuvant to hydroxychloroquine in COVID-19 patients	Ivermectine Hydroxychloroquine sulfate Placebos	Not yet recruiting	Faiq Gorial, University of Baghdad
Evaluation of efficacy of Levamisole and Formoterol + Budesonide in treatment of COVID-19	Levamisole pill + budesonide + formoterol inhaler Drug: Lopinavir/ ritonavir + hydroxychloroquine	Recruiting	Vali-Asr Hospital Fasa, Fars, Iran, Islamic Republic of Iran
Efficacy and safety of siltuximab vs. corticosteroids in hospitalized patients with COVID-19 pneumonia	Siltuximab Drug: Methylprednisolone	Not yet recruiting	Hospital Clínic de Barcelona Barcelona, Spain



Table 3: Vaccines against COVID-19 under trial

<i>Platform</i>	<i>Type of candidate vaccine</i>	<i>Developer</i>	<i>Current stage of clinical evaluation/ regulatory status</i>
Non-replicating viral vector	Adenovirus type V vector	CanSino Biological Inc., Tianjin, China Beijing Institute of Biotechnology, Beijing, China	Phase I
RNA	LNP encapsulated mRNA	Moderna, Inc., Massachusetts, USA NIAID, Maryland, USA	Phase I

Table 4: Reality checks of COVID-19 against the myths

<i>Myth</i>	<i>Reality</i>
Novel coronavirus only affects older people	It is proven that it can affect all groups of people, and as like other viral infection, it easily affects a special group of person that are immunocompromised. Children, seniors, or people with health conditions, such as, diabetes, heart disease, kidney failure, liver disorders, asthma, lung disease, and other respiratory issues are at a higher risk of combating infection.
Family pets can spread the novel coronavirus	Till date, no case has been evidenced of human(s) getting infected because of the pet, so it seems a myth as on date. But, it is advisable to wash hands after touching pets because some bacteria, like <i>Salmonella</i> and <i>E. coli</i> can be transmitted.
You can prevent or treat the novel coronavirus with antibiotics	Antibiotics are used to treat bacterial infection, and the novel coronavirus is a virus. Yes, it is true that antibiotic is given to the coronavirus-positive patient, but to treat the bacterial co-infection. It is possible that the person may have both bacterial infection and viral infection.
You can prevent or treat the novel coronavirus with homeopathic remedies or other specific medications	Till date, no medicine or remedy has been proven to treat the novel coronavirus. The intake of vitamins and other immunity boosters may mount immunity, but this does not mean immunity from the virus.
A surgical mask is enough to protect from exposure to the coronavirus	The use of a surgical mask may prevent air born infection, but multiple uses of disposable masks raises the probability of infection.

to recover antibodies from patients had already been approved for the treatment of other infectious diseases, which the company hopes could lead to fast-track approval. Hyperimmune globulins are plasma derived-therapies that have previously been shown to be effective in the treatment of severe acute viral respiratory infections, and may be a treatment option for COVID-19.^[29] Regeneron has announced it is pursuing a monoclonal antibody strategy, using its humanized mouse antibody screening platform to produce an antibody cocktail, for both therapeutic and prophylactic use. Regeneron has identified hundreds of virus-neutralizing antibodies; plans to initiate large-scale manufacturing by mid-April, with antibody cocktail therapy. It plans to enter human clinical studies by early summer. This program is in addition to the company's separate ongoing clinical program evaluating Kevzara® (sarilumab, an IL-6 receptor antibody) in severe COVID-19 patients.^[30]

Although hopes for antibody-based immunity are high, there is currently little available data on, whether, human populations develop immunity to SARS-CoV-2. The WHO has announced a large-scale effort (named SOLIDARITY II) to aggregate serological data collected from more than half a dozen countries around the globe in different countries, and expects to post results from the initiative within the next few months.^[31]

Several studies have found a correlation between serum levels of interleukin-6 (IL-6) and the severity of COVID-19

symptoms. Additionally, a report, published as a preprint, suggests that treatment of 20 people, diagnosed with severe or critical COVID-19, with the anti-IL-6 receptor drug tocilizumab could have been effective. However, the peer-reviewed version of these results has not yet been published.^[32] Roche announced the launch of a trial of tocilizumab, with a recruiting target of 330 participants diagnosed with severe COVID-19. Participants have to have severe cases of COVID-19, marked by pneumonia, and requiring hospitalization. Initial results are expected in the summer.^[33] Regeneron and Sanofi have expanded the testing in an existing clinical trial of their own anti-IL-6 receptor monoclonal antibody in rheumatoid arthritis, to include severe or critically ill COVID-19 patients. Regeneron is leading the US trials, while Sanofi is leading trials outside the US.^[34] The Table 2 presents a cross-section of clinical trials being conducted globally.

VACCINE STATUS

Vaccines are being developed to try to prevent people from getting the disease in the first place. The WHO is curating a list of vaccine candidates, of which two are currently undergoing clinical evaluation: an adenoviral vector-based approach by CanSino Biological Inc. and the Beijing Institute of Biotechnology, and an RNA product by Moderna Inc. and the National Institute of Allergy and Infectious Diseases. It would take at least 12 to 18 months for a vaccine to become available for wider use (Table 3).

A total of 44 vaccine candidates have been listed on the DRAFT landscape of COVID-19 candidate vaccines, by WHO as of 20th March 2020. As mentioned earlier, two are under clinical trials, and the rest 42 are in the preclinical stage.^[35]

There is no evidence that the Bacille Calmette-Guérin vaccine (BCG) protects people against infection with the COVID-19 virus. Two clinical trials addressing this question are underway, and the WHO will evaluate the evidence, when it is available. In the absence of evidence, the WHO does not recommend BCG vaccination for the prevention of COVID-19.^[36]

MYTHS ABOUT COVID-19

Pandemic in general, triggers various research activities, in an attempt to find a cure, or ways to contain the disease. This research is primarily based on hypothesis and the related literature available. Many of these hypotheses may be myths that need to be resolved, which is an integral part of the dedicated efforts aiming cure. Table 4 highlights the myths associated with COVID-19 and presents the reality checks.

CHALLENGES AND CONCLUSION

The daunting challenges that need aggressive, systematic research approaches, include, understanding the behavior of the virus, working on treatments for people who are already sick, and finding rapid easier ways to test people to see if they are infected. The current treatment of COVID-19 has been limited to general supportive care with the provision of critical care, if required. Many clinical trials are underway to find a definite treatment and a vaccine for prophylaxis of COVID-19. Chloroquine phosphate and hydroxychloroquine have been repositioned as drugs of care for the current pandemic. For definite conclusive therapy, aggressive research efforts are urgently needed to combat COVID-19.

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HOW TO CITE THIS ARTICLE: Pathak K, Pathak D, Yadav R, Kumar R. COVID-19: an update on therapeutics and clinical trials. *Int. J. Pharm. Sci. Drug Res.* 2020;12(4):422-430. **DOI:** 10.25004/IJPSDR.2020.120416