

**REVIEW ARTICLE**

Mysterious Virus: A Review on Behavior and Treatment Approaches of the Novel Coronavirus, 2019-nCoV

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Received for publication April 13, 2020; accepted April 30, 2020 (ARCMED_2020_487).

At the end of the year 2019, the novel coronavirus (2019-nCoV) was spreading in Wuhan, China, and the outbreak process has a high speed. It was recognized as a pandemic by the World Health Organization (WHO) on 11 March 2020. Coronaviruses are enveloped and single-stranded RNA that have several families including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). The pathogenesis mechanism and disease outcomes of SARS and MERS are now clear to some extent, but little information is available for 2019-nCoV. This newly identified corona virus infection represents flu-like symptoms, but usually the first symptoms are fever and dry cough. There has been no specific treatment against 2019-nCoV up to now, and physicians only apply supportive therapy. In the present article, we made an attempt to review the behavior of the virus around the world, epidemiology, a pathway for influx into the host cells, clinical presentation, as well as the treatments currently in use and future approaches; nitazoxanide may be our dream drug. We hope that this review has a positive impact on public knowledge for helping to deal with the 2019-nCoV and move one step forward toward its treatment in the near future. © 2020 IMSS. Published by Elsevier Inc.

Key Words: Novel coronavirus, 2019-nCoV, Treatment approach, Infection, Respiratory problem.

Introduction

In late 2019, the local health authorities in Wuhan, China, declared a high load of individuals that had pneumonia with unknown etiology (1). Subsequently, in early January 2020, numerous medical diagnostic laboratories in China reported that a new coronavirus was the cause of occult pneumonia. The World Health Organization (WHO) named this invasive virus briefly as 2019 novel coronavirus (2019-nCoV) (2). Coronaviruses are enveloped, single stranded RNA, and belong to the subfamily Coronavirinae. It has previously been reported that CoVs which causes human diseases have six types, and is categorized into two

subgroups including gently and extremely pathogenic CoVs. The 229E, HKU1, OC43 and NL63 are gently pathogenic CoVs, leading to 10–30% of upper respiratory tract infections (3,4). Instead, the extremely pathogenic CoVs, containing Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), mostly contaminate lower airways and lead to pneumonia (5). Given that the clinical signs of 2019-nCoV, SARS-CoV, and MERS-CoV have some resemblances, it can range from asymptomatic infections to severe respiratory illnesses (6). The rapid prevalence of the novel type of CoV reminds us that it is a major global health threat. Chen Y, et al. think that severe prevalence of novel CoV in the future is inevitable as climate is changing and human exposure to animals is increasing; therefore, the need for effective treatment modalities and training for CoVs is necessary (2).

In the present article, we attempted to review the behavior of the virus around the world, epidemiology, a

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pathway for influx into the host cells, clinical presentation, as well as the treatments currently in use. We hope that this review could have a positive impact on our knowledge of the new virus and help establish effective ways to combat the novel coronavirus 2019 in near future.

Taxonomy

Coronaviruses (CoVs) form a large and important family of viruses found in nature. CoVs have a positive-sense single-stranded RNA (+ssRNA) with a GC content of 32–43% that belongs to the family *Coronaviridae* and the order *Nidovirales*. They contain the largest genome among the recognized RNA viruses (genome length is about 26–32 kb) (7). Based on the genomic structure and phylogenetic analysis, the family *Coronaviridae* is currently classified into two subfamilies, including *Torovirinae*, and *Coronavirinae*. The *Coronavirinae* includes four genera called *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus* (8). Two genera, *Alphacoronavirus* and *Betacoronavirus*, only cause infection in mammals. They account for respiratory infection in humans and enteritis in animals. The members of the genus *Betacoronavirus* are categorized into five subgenera, in which the two genera *Hibecovirus* and *Nobecovirus* do not infect humans (9,10). The members of the other three genera, *Merbecovirus*, *Sarbecovirus*, and *Embecovirus*, are the cause of the disease in humans. *Merbecovirus* containing MERS-CoV and *Sarbecovirus* containing SARS-CoV are two major zoonotic pathogenic coronaviruses (Table 1). A new pandemic Coronavirus, so called 2019-nCoV, has been recently introduced in Wuhan, China (11). 2019-nCoV is still considered as unclassified *Betacoronavirus*, but according to early phylogenetic studies, this virus is related to SARS and is over 85% matched with the bat SARS-like CoV (9). Accordingly, the International Committee on Taxonomy of Viruses named it severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

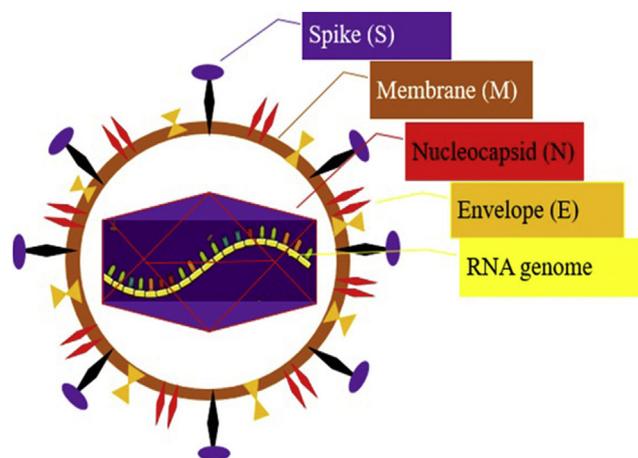


Figure 1. The structure of 2019-CoV.

Morphology and Genome Structure

The 2019-nCoV is an enveloped, spherical, and relatively large (about 120 nm in diameter) particle; the envelope of this virus in electron micrographs emerges as a separated pair of electron-dense shells. The viral envelope contains a lipid bilayer by which the membrane (M), envelope (E) and spike (S) structural proteins are harbored (Figure 1) (12,13). The genome of CoVs is Monopartite, linear, single-stranded positive-sense RNA (+ssRNA) (~30 kb in size), Capped at the 5' end, and poly adenylated at the 3' end with at least six open reading frames (ORFs) and other subsidiary genes (14). The RNA genome includes 29,891 nucleotides (Gene Bank accession number MN908947), encoding 9860 amino acids. The 5' terminal two-thirds of the genome contains two ORFs, ORF1 and ORF2 that encodes ppla and pplab polyproteins, which is further split into 11 and 16 proteins, respectively, which encode non-structural proteins (nsps) (13,15). These proteins are processed into the viral

Table 1. Current taxonomy of the human relevant coronaviruses. According to the NCBI Taxonomy, National Institutes of Health, USA (<https://www.ncbi.nlm.nih.gov/taxonomy>) and ICTV Taxonomy

Family	Subfamily	Genus	Subgenus	Species
Coronaviridae	Torovirinae	Alphacoronavirus	Duvinacovirus	<i>Human coronavirus 229E</i>
			Setracovirus	<i>Human coronavirus NL63</i>
	Coronavirinae	Betacoronavirus	Embecovirus	<i>Betacoronavirus 1</i>
			Hibecovirus	<i>Human coronavirus HKU1</i>
			Nobecovirus	
			Sarbecovirus	<i>SARS-CoV</i>
			Merbecovirus	<i>MERS-CoV</i>
			Unclassified Betacoronavirus	<i>2019-nCoV</i>
			Gammacoronavirus	
			Deltacoronavirus	

2019-nCoV, 2019-novel coronavirus; SARS, Severe Acute Respiratory Syndrome; MERS, Middle East Respiratory Syndrome.

polymerase (RdRp) and other non-structural proteins involved in RNA synthesis (16). The structural proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) are arranged in the order of one-third 3' terminal of the genome (15). One of the most important genes that can help researchers to produce vaccine in the future is S gene because this gene product has an effective role in receptor binding and host specificity (17).

Proposed a Pathway for 2019-nCoV Influx into the Host Cells

Recently reported that between the SARS-CoV genome sequence and the novel coronavirus exist 82% similarity, thus, named 2019-nCoV by WHO (13). This theory may be indicating that 2019-nCoV uses the same SARS-CoV mechanism i.e. through angiotensin-converting enzyme2 (ACE2) receptor and the TMPRSS2 protease to infect the human cells. Coronavirus spike (S) protein facilitates virus entry into target cells. The binding of SARS to the receptor and its entry into the cell depends on a cellular protease (18). Sequence analysis has shown that some of the 2019-nCoV clusters and bat-associated SARS76 CoV viruses (SARSr-CoV) can use the ACE2 receptor to enter the host cell. Analysis of the receptor-binding motif (RBM) and a part of the receptor-binding domain (RBD) that interacts with ACE2, revealed that most of the essential amino acid residues were retained at 2019-nCoV for ACE2 binding, but in the SARSr-CoV S proteins were not observed. It was found that it does not use ACE2 for entry into the cells and need priming the S protein for binding to ACE2 (19). It has been reported that entry of SARS-CoV-2 to host cells may block via a clinical antagonist of the TMPRSS2, a cellular serine protease, that is recruited via SARS-CoV-2 to S protein priming. These new findings have significant implications for our knowledge about the transmission and pathogenesis of SARS-CoV-2 and treatment approaches (20). Shieh W-J, et al., reported that SARS-CoV might goal a full spectrum of similar cells. The SARS-CoV in the respiratory system leads to infect mostly pneumocytes and macrophages (21). In addition to lung, other tissues can expression of ACE2. Thus, SARS-CoV may extent to extrapulmonary organs. While the affinity of SARS-S and SARS-2-S to ACE2 receptor has been comparable, therefore we still expect this for SARS-CoV-2. Previous studies showed that in the upper airways a mild expression of ACE2 (22,23) may be able to reduce SARS-CoV spread, given that the high dispersion ability of SARS91 CoV-2 against SARS-CoV (24). Definitively, it is important to note that the high-level expression of ACE2 can prevent lung damage. However, its downregulated through SARS-S, which lead to stimulate SARS. To enter the virus into host cells and covers S protein cleavage at the S1/S2

and the S2' sites, the need to specific proteases in the host cells for priming of coronavirus S proteins (25). The cutting site of SARS-2-S, several arginine residues (multibasic) that shows high sensitivity for cutting. Actually, into the host cells, SARS-2-S was proficiently cleaved, following by cleaved S protein was incorporated into vesicular stomatitis virus (VSV) particles. Notably, the area in which the incision has occurred can define the zoonotic potential of coronaviruses (26,27); the SARS-CoV100 2 and coronavirus have the most closely associated. SARS-CoV can use endosomal cysteine protease to priming S-protein in TMPRSS2 negative cells. Nevertheless, priming of protein S via TMPRSS2 protease is required for virus entry into target cells, and the spread of the virus in infected host cells (28).

Epidemiology

After the first reports of 2019-nCoV outbreak in Wuhan, Hubei, China, in December 2019, the virus quickly spread throughout China during several weeks, and then on the other Asian countries, the Middle East, Africa, the Americas, Oceania, and Europe. In accordance with the daily information of the WHO, the pandemic of 2019-nCoV till now caused 1,861,672 positive cases and 114,980 deaths in the worldwide by 13th April 2020 (29), that lead to a main global health concern (Table 2) and (Figure 2) (9,30–32). This information is updated daily at the Situation Report site of the WHO (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>). Another source of information is Worldometer (<https://www.worldometers.info/coronavirus/>), which is managed by an international team of researchers, developers, and volunteers with the purpose of providing world statistics available in a thought-provoking and time suitable format to all of the audience around the world.

Table 2. Ten countries with the most reported laboratory-confirmed COVID-19 cases and deaths. Data updated as of 13 April 2020

Country	Cases	Deaths	Death (%)	Recovered
USA	560,433	22,115	3.94	32,634
Spain	169,496	17,489	10.31	64,727
Italy	156,363	19,899	12.72	34,211
France	132,591	14,393	10.85	27,186
Germany	127,854	3,022	2.36	64,300
UK	84,279	10,612	12.59	N/A
China	82,160	3,341	4.06	77,663
Iran	71,686	4,474	6.24	43,894
Turkey	56,956	1,198	2.10	3,446
Belgium	30,589	3,903	12.75	6,707

USA, United States of America; S. Korea, Southern Korea; UK, United Kingdom.

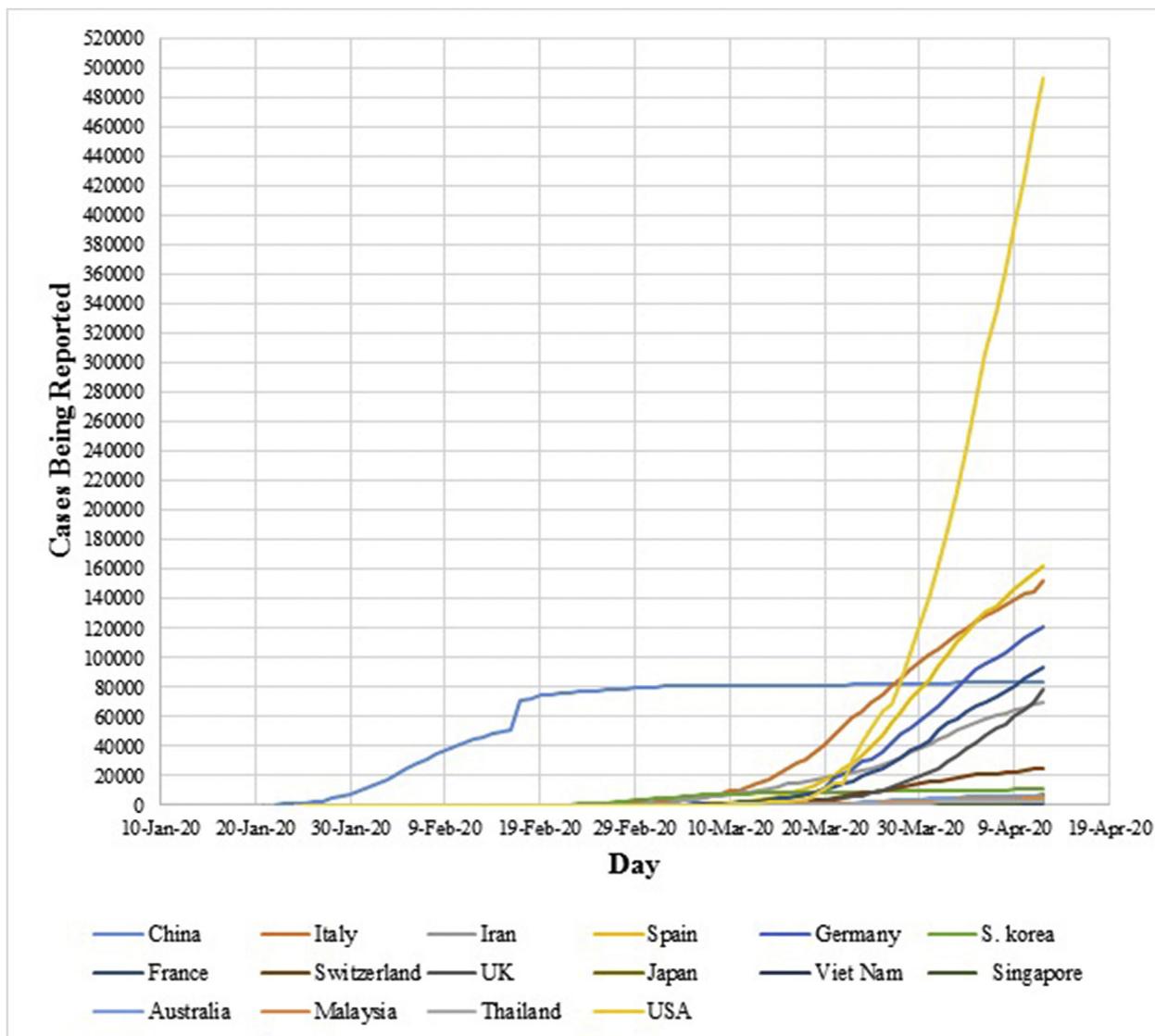


Figure 2. Countries with reported laboratory confirmed COVID-19 cases. Data from January 21st 2020 to April 12th 2020. USA, United States of America; S. Korea, Southern Korea; UK, United Kingdom.

Clinical Features and Transmission

2019-nCoV infections can be hidden for 2–14 d without any symptoms generally, but can display from 3–7 d mostly (33). After the incubation period of the disease, the presentations are mostly fever, exhaustion and cough, which are probably accompanied by nasal congestion, runny nose, expectorant, and rarely diarrhea and headache. Typically, fever can be low to moderate, and even with no fever (34). After a week and with progress of displaying the disease, other signs such as dyspnea, cyanosis, and eventually systemic fatal symptoms appear, including malaise or restlessness, poor feeding, bad appetite, less activity, and

respiratory failure. The late signs that could occur in severe cases may be accompanied by septic shock, metabolic acidosis, irreversible bleeding and coagulation dysfunction (33,35). The clinical presentations and reports from several investigations are summarized in Table 3 (32,36–40). The new virus is diffused through droplets of the respiratory system when patients with infection cough, sneeze, or even during the conversation. Furthermore, other ways for transmission of the virus are embracing and close contact (e.g., contact with the mouth, nose or eyes conjunctiva via polluted hands). It has been not recognized so far that spread can happen by mother to infant or breast feeding (33).

Table 3. Clinical presentations of patients with 2019-nCoV infection

Blood tests		Clinical presentations		CT scan features	
Variables	Changes	Variables	Changes	Variables	Changes
WBC	Normal Or Increase	Mean age (year)	41	Pneumonia (%)	77
Lymphocyte	Decrease Or Intense decrease	Mean incubation time (d)	3	GGO (%)	50
CRP	Normal Or Increase	Fever (%)	88	Bilateral patched shadowing (%)	46
LFT	Intense increase	Fatigue (%)	70	Interlobular septal thickening (%)	73
CK	Increase	Dry cough (%)	68	GGO with consolidation (%)	60
Myoglobin	Increase	Myalgia (%)	35		
D-dimer	Increase	Headache (%)	9		
Serum creatinine	Increase Or Intense decrease	Diarrhea (%)	5		
Blood urea nitrogen	Increase Or Intense decrease				
Total bilirubin	Increase				
Glucose	Increase				

WBC, White Blood Cell; CRP, C-reactive protein; LFT, Liver Function Tests; CK, Creating Kinase; GGO, Ground-glass opacity.

Lung Imaging and Features

2019-nCoV leads to an acute resolved infection, which could be lethal with a mortality rate of about 2%. In the case of severe infection, it might lead to expiration of the patients due to severe alveolar injury and advanced respiratory failure (41,42). However, post-mortem biopsy might be taken from the liver, heart, and lung tissues. In the lung histological studies, bilateral diffuse alveolar damage with cellular fibromyxoid exudate might be seen. Patent desquamation of the pneumocytes and hyaline membrane construction in the right lung has also been seen to demonstrate acute respiratory failure (43). On the other hand, biopsy assay in the left lung exhibited pulmonary oedema with hyaline membrane construction. In the whole lung tissues, interstitial mononuclear inflammatory infiltrates occur mostly by lymphocytes. Furthermore, syncytial cells with abnormal puffy pneumocytes characterized via bulky nuclei, amphophilic granular cytoplasm, and noticeable nucleoli in the intra-alveolar spaces were recognized. These features display viral cytopathic-like variations (44). Pneumonia patients with initial stage lung X-ray analysis demonstrate several small patchy shadows and interstitial variations significant in the lung periphery (6). In patients with severe disease, more progress to bilateral multiple ground-glass opacity, infiltrating shadows, and pulmonary merging, with rare pleural effusion, can be seen. In both lungs of the youngsters with severe disease, multiple lobar lesions may be observed (45). Moreover, biopsy of the liver indicated modest microvascular steatosis and slight lobular activity; nevertheless, there was no definite proof to support 2019-nCoV contamination or drug-induced liver damage as a result. Subsequently, biopsy observations showed that no clear histological variations were seen in the heart tissue, proposing that 2019-nCoV contamination might not directly damage the heart (46). A radiograph of an infected person's chest is shown in Figure 3, as an example.

Treatment Approaches

Presently, there are no FDA-approved treatments or vaccines for 2019-nCoV. The National Institute of Allergy and Infectious Diseases (NIAID) within the National Institutes of Health (NIH) is leading the funding of federal research and response to 2019-nCoV, while certain stakeholders in the US are choosing to supply their own 2019-nCoV research. Internationally, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA) have called for targeted efforts to progress treatments against 2019-nCoV. Some companies are looking to repurpose approved drugs that have worked against similar coronaviruses in the past or are hypothesized to attack or immobilize 2019-nCoV based on the mechanism of action. Plasma and stem cells from patients who have recovered from 2019-nCoV also are being investigated (Table 4). In addition, different companies are working hard for produce vaccine; experts estimate it could take between 12–18 months to develop a vaccine ready for market. Supplementary Table 1 showing the major vaccine candidates in development for prevention of 2019-nCoV. This information is updated weekly at the Situation Report site of the Regulatory Focus™ (<https://www.raps.org/news-and-articles/about-regulatory-focus>). However, some approaches have been suggested to prevent further spread of the infection and controlling 2019-nCoV. In the first step, suspected persons should be isolated and kept separately and the severe and acute patients should be detected as soon as possible. During therapeutic measurements, patients need more attention and their vital symptoms, pO₂, pCO₂, arterial pH, etc. should be regularly checked. Then, the general treatments are started which include resting and supportive therapeutics; adequate calorie and water consumption; keeping water electrolyte balance; and homeostasis. Some treatments are antiviral such as, interferon- α 2b nebulization 100,000–400,00 IU/kg) in addition to lopinavir/

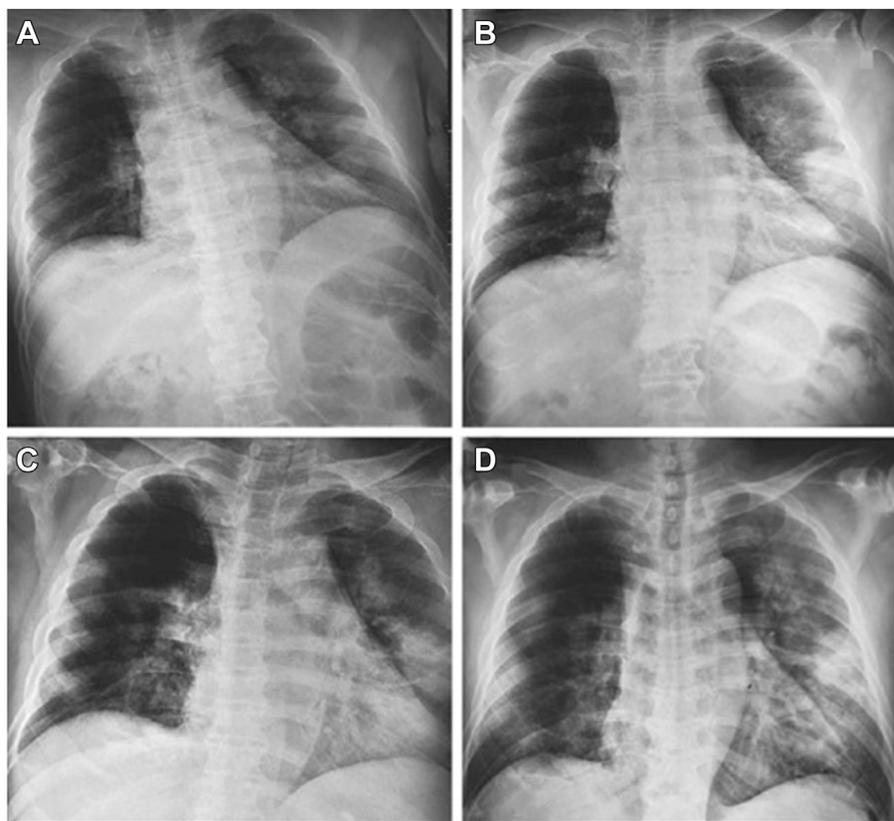


Figure 3. Chest radiographs of the person with CoV-19 infection. - Chest radiographs obtained at admission (A), on day 3 (B), day 5 (C), and day 6 (D) after admission (32).

ritonavir (200 mg/50 mg) (46–48). Furthermore, antibiotics are also used, but illogical usage of antibiotics should be prevented, and rarely the usage of immunomodulation drugs such as corticosteroids should be applied carefully in common types of infection. In certain conditions, rapid lung radiography and confirmation of the incidence of ARDS, observation of clear toxic signs such as encephalitis or encephalopathy, hemophagocytic syndrome and other severe problems, observation of septic shock, and eventually clear wheezing indications are recommended. Certain drugs such as methylprednisolone intravenously (1–2 mg/kg/d) are suggested for 3–5 d, but not for long-term consumption (46,49–52). In severe patients, immunoglobulin can also be recommended intravenously. The suggested dose is 1.0 g/kg/d for 2 d, or 400 mg/kg/d for 5 d (50,53,54). In patients with blood circulation problems, drugs that are vasoactive can be used for recovering microcirculation on the basis of sufficient liquid intake (46). Cases who had acute renal damage should be given kidney tests function. In children, if intracranial hypertension and convulsion happens, there is a need to decrease the intracranial pressure and control convulsion to be suitable (53,54). There is speculation that patients with 2019-nCoV who are receiving ACE inhibitors or angiotensin receptor blockers

(ARBs) may be at increased risk for adverse outcomes (55,56). The ACE2 is a receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and renin-angiotensin aldosterone system inhibitors can increase the ACE2 levels (57). Finally, in the patients who had respiratory complication despite nasal catheter or mask oxygenation, heated humidified high-flow nasal cannula (HHHFNC), non-invasive ventilation such as continuous positive airway pressure (CPAP), or non-invasive high-frequency ventilation can be used. If improvement is not possible, mechanical ventilation with endotracheal intubation and a protective lung ventilation strategy should be adopted (45). It is worth noting that J.-F. Rossignol at 2016 presented nitazoxanide as a broad-spectrum antiviral agent for Flu and other viral respiratory infections; this drug is undergoing clinical progress. *In vitro* studies on nitazoxanide showed its efficient function against MERS-CoV and other coronaviruses by inhibiting expression of the viral N protein. He has also declared that the clinical trials and post-marketing experience approve nitazoxanide as an attractive drug candidate for treatment of MERS-CoV (58). There is a hope that nitazoxanide may be effective for treatment of 2019-nCoV through similar mechanisms.

Table 4. Candidate drugs under testing for 2019-nCoV treatment; updated 10 April 2020

	Drug/Therapy	Medication class	Developer	Original use	Status
Investigational candidates for 2019-nCoV	Remdesivir	Antiviral	Gilead Sciences	Treatment for Ebola and Marburg virus infections	Phase 3 clinical trial; (NCT04252664), (NCT04257656), (NCT04292730), (NCT04292899)
	Mavrilimumab	Monoclonal antibody	Kiniksa Pharmaceuticals	Treatment of rheumatoid arthritis	Phase 2/3 clinical trial
	Convalescent plasma	Immunoglobulin		Treatment for Ebola virus infection	FDA approved
	CD24Fc	Recombinant fusion protein	OncoImmune	Treatment of graft-versus-host disease	Phase 3 clinical trial (NCT04317040)
	Lenzilumab	Anti-human GM-CSF monoclonal antibody	Humanigen	Against cytokine release syndrome	Phase 3 clinical trial
	Leronlimab	Humanized IgG4 monoclonal antibody	CytoDyn	Breast cancer/HIV	
	EIDD-2801	Oral broad-spectrum antiviral	Drug Innovation Ventures at Emory	against infections such as influenza, chikungunya, Ebola and equine encephalitis	launching a clinical trial
Therapeutics Approved for Other Indications	Hydroxychloroquine (Plaquenil) and chloroquine (Aralen)	Quinoline	Sanofi; Mylan, Teva, Novartis, Bayer, Rising Pharmaceuticals	Anti-malaria	Ongoing, (NCT04303507)
	Lopinavir-ritonavir (Kaletra)	HIV protease inhibitor	AbbVie	Treatment of HIV-1	Phase 4 randomized controlled trial, (NCT04255017), (NCT04307693)
	Tocilizumab	IL-6 receptor antagonist	Roche	Treatment of rheumatoid arthritis	Phase 3 randomized controlled trial, (COVACTA)
	Sarilumab	IL-6 receptor antagonist	Sanofi and Regeneron	Treatment of rheumatoid arthritis	Phase 2/3 clinical trial
2019-nCoV Therapeutics Approved Outside the US	Favilavir	Antiviral agent	Fujifilm Toyama Chemical and Zhejiang Hisun Pharmaceutical	Against many RNA viruses	phase 3 clinical trial

FDA, Food and Drug Administration; IL, Interleukin.

Conclusion

The high prevalence of the 2019-nCoV has become a global clinical problem these days. However, we do not know much about precision mechanism and function of this new virus at present. Various pharmaceutical companies around the world are working hard to find effective drug and vaccine against this virus. Until then, we must carefully follow WHO health measures to control infection and prevent further transmission of the virus. On the other hand, it is expected that different countries in this current crisis abandon political disputes, share information, and work unitedly against 2019-nCoV all over the world to combat this life-threatening disease of mankind.

Acknowledgments

The authors gratefully acknowledge Department of Biochemistry and Clinical Laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, and professor Nasser Samadi, DCLS, PhD.

Funding

None.

Competing interests

None declared.

Ethical Approval

Not required.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.arcmed.2020.04.022>.

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