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**History, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical features, diagnosis, and treatment of COVID-19: A review**

Mokhria RK *et al*. An update on COVID-19 disease

Rajesh Kumar Mokhria, Jitender Kumar Bhardwaj, Ashwani Kumar Sanghi

**Rajesh Kumar Mokhria,** Department of School Education, Government Model Sanskriti Senior Secondary School, **Chulkana, Panipat,** 132101, Haryana, India

**Jitender Kumar Bhardwaj,** Reproductive Physiology Laboratory, Department of Zoology, Kurukshetra University, Kurukshetra 136119, Haryana, India

**Ashwani Kumar Sanghi,** School of Allied and Health Sciences, MVN University, Palwal 121102, Haryana, India

**Author contributions:** Mokhria RK, Bhardwaj JK and Sanghi AK designed the outline, collected the data, wrote the manuscript, and proofread the paper.

**Corresponding author: Rajesh Kumar Mokhria, PhD, Lecturer,** Government Model Sanskriti Senior Secondary School, Chulkana, Panipat, 132101, Haryana, India. mokhria79@gmail.com

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**Abstract**

In December, 2019, pneumonia triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surfaced in Wuhan, China. An acute respiratory illness named coronavirus disease 2019 (COVID-19) is caused by a new coronavirus designated as SARS-CoV-2. COVID-19 has surfaced as a major pandemic in the 21st century as yet. The entire world has been affected by this virus. World Health Organization proclaimed COVID-19 pandemic as a public health emergency of international concern on January 30, 2020. SARS-CoV-2 shares the same genome as coronavirus seen in bats. Therefore, bats might be its natural host of this virus. It primarily disseminates by means of the respiratory passage. Evidence revealed human-to-human transmission. Fever, cough, tiredness, and gastrointestinal illness are the manifestations in COVID-19-infected persons. Senior citizens are more vulnerable to infections which can lead to dangerous consequences. Various treatment strategies including antiviral therapies are accessible for the handling of this disease. In this review, we organized the most recent findings on COVID-19 history, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical features, diagnosis, and treatment strategies.

**Key Words:** COVID-19; SARS-CoV-2; Severe acute respiratory syndrome; World Health Organization; Pathogenesis

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**Core Tip:** An acute respiratory illness (COVID-19) is caused by a new coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to β-coronaviruses, and it shares the same genome as coronavirus seen in bats. It primarily disseminates by means of the respiratory passage. Much evidence revealed human-to-human transmission. Fever, cough, tiredness, and gastrointestinal illness are the manifestations in COVID-19-infected persons. Various antiviral therapies are accessible for the handling of COVID-19 disease.

**INTRODUCTION**

In December 2019, in Wuhan (China) an outbreak of pneumonia symptomatized by fever, dry cough, fatigue, and occasional gastrointestinal symptoms was revealed. Most of these pneumonia patients were associated with the Huanan Seafood Market, Wuhan, China which deals in fish and various live animal species (poultry, bats, marmots, and snakes)[1].

By using reverse transcription polymerase chain reaction **(RT-PCR)**, researchers determined the reason for the above symptoms and the rapid spread of cases being a novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causative agent of the Coronavirus Disease-2019 (COVID-19)[2-4].

On 30 January 2020, World Health Organization (WHO) stated the novel coronavirus outburst in Wuhan, China, a global crisis[5]. Later on WHO accepted that SARS-CoV-2 has the ability to spread worldwide[6,7]. On 11 March 2020, the WHO announced COVID-19, a pandemic[8]. In successive months, several thousand people in different provinces of China and cities were invaded by the unchecked spread out of this disease[9]. Later, this disease traveled to various countries i.e. Thailand, Japan, Republic of Korea, Vietnam, Germany, United States, Singapore, and India. On comparison COVID-19 cases have overtaken the infected cases and deaths from Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS) at this point of the disease outburst[10]. The early effect of COVID-19 was so dreadful that the various countries had to implement phases of lockdowns. All age groups including children and pregnant women were badly affected due to this infectious disease.

CoVs (Coronaviruses) relates to the order Nidovirales and they have the largest RNA genome[11]. CoVs pertain to Coronaviridae family. They are positive single-stranded RNA-enveloped viruses. Four genera of CoVs are Alpha-, Beta-, Gamma-, and Deltacoronavirus. Seven human coronaviruses (HCoVs) have been revealed till now and they belong to the Alpha- and Betacoronavirus genera. The Alphacoronavirus genus includes HCoVNL63 and HCoV-229E and Betacoronavirus genus includes HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and the novel SARS-CoV-2[12–17]. The alphacoronaviruses (HCoV-NL63 and HCoV-229E) and the betacoronaviruses (HCoV-OC43 and HCoV-HKU1) generally induce common colds, but severe lower respiratory tract infections can also appear, notably in the old age persons and kids[18]. HCoV-NL63 infection causes croup (laryngotracheitis)[19,20], and HCoV-OC43 infection causes severe lower respiratory tract infection among kids[21]. SARS-CoV and MERS-CoV are zoonotic viruses that cause severe respiratory syndrome[11].

This review summarizes the latest findings on the history, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical features, diagnosis, and cure of COVID-19.

**History of the Coronavirus**

Human coronaviruses (229E and OC43) was first diagnosed in late 1960 as a reason for the common cold and were observed safe for human beings[22,23]. In Guangdong province in China in 2002–2003, a disease outbreak resulted in which a new coronavirus (β genera) originated in bats and was crossed to human beings by intermediate host of Himalayan palm civet cats[24]. This virus named SARS-CoV had a fatality rate of 10%[14,25,26]. This virus had been quickly spreading worldwide, particularly in Asia[27].

Almost ten years after SARS in year 2012, another highly pathogenic CoV, MERS-CoV, appeared in Middle East countries[17]. MERS-CoV, was also of bat origin, with dromedary camels as the intermediate host, and intermediate host reservoir species were also observed in goats, sheep, and cows[28]. MERS-CoV affected approximately 2000 people with approximately 34% mortality rate[17].

Recently, in December 2019, the novel Coronavirus 2019 (nCoV) or SARS-CoV-2 surfaced in Huanan Seafood Market, Wuhan (China) which cause pneumonia epidemic of unknown cause[29].

**Epidemiology: origin, reservoirs, and transmission of COVID-19**

COVID-19 was thought to be originated in Wuhan (China). Environment specimens from the Huanan seafood market in Wuhan, China were examined positive, suggesting that the COVID-19 virus originated there[30]. According to several reports, Bat might be the likely pool of SARS-CoV-2[31,32]. Bats are the natural pool of a range of CoVs, including SARS-CoV-like and **MERS-CoV-like** viruses[33–35]. When the genome of COVID-19 and Bat CoV RaTG13 was compared and analyzed by virus genome sequencing and it revealed 96.2% genome sequence similarity with the Bat CoV RaTG13 genome[24]. It revealed that bat CoV and human SARS-CoV-2 might share the same ancestor[36]. It had > 70% resemblance with the SARS-CoV[37]. The SARS-CoV-2 emanated from bats and intermediate animals through which it reaches humans is unknown. Present suspects are pangolins and snakes[37]. Figure 1 shows the transmission cycle of SARS-CoV-2.

It seems that majority of early COVID-19 cases had a contact record with the seafood market, in Wuhan, China[24,38]. There is the possibility of human-to-human (Transmission *via* Aerosols, Nosocomial-Related Infections & Maternal Transmission) spread in people who did not have vulnerable to the seafood market of Wuhan, China[39]. It is also revealed that 31.3% of COVID-19 patients have traveled a short time ago to Wuhan and 72.3% of patients who are nonresidents of Wuhan, have contact with people of Wuhan[40]. Instances of COVID-19 in different provinces of China and in almost all countries of the world were recorded in people who were returning from Wuhan City, China[37]. COVID-19 cases were observed in countries outside China with no travel history to China indicating human-to-human transmission locally[41].

In India during the early period (from March 2020 onwards), there was an alarming rise in COVID-19 patients but now the recovery rate from this disease is much more and the situation is under control now.

**Genome structure of Coronaviruses**

SARS-CoV-2 belongs to beta-coronaviruses. Genome of SARS-CoV-2 is positive-sense single-stranded RNA [(+) ssRNA] with a 5'-cap, 3'-UTR poly(A) tail. The SARS-CoV-2 genome length is < 30 kb, having 14 open reading frames (ORFs) which encode non-structural proteins (NSPs), structural proteins *i.e.* spike (S), envelope (E), membrane/matrix (M) and nucleocapsid (N), and accessory proteins[42,43].

Coronavirus virions have a diameter of about 125 nm and are spherically shaped[44,45]. The genomes of coronaviruses encode five structural proteins: the spike (S), membrane (M), envelope (E) glycoproteins, hemagglutinin esterase (HE), and nucleocapsid (N) protein. All virions have all envelope protein and N protein, but only some beta coronaviruses possess the protein hemagglutinin esterase (HE)[46].

***S glycoproteins***

These proteins are located outside the virion and contribute to its usual shape. The homotrimers of the S proteins create the sun-like appearance that assigns coronaviruses their name[44,47,48]. Through their C-terminal transmembrane domains, S proteins attach to the virion membrane and also join with M proteins[49]. Virion attachment to particular surface receptors present in the host cell's plasma membrane is made possible by the N-terminus of the S proteins[50].

***M glycoproteins***

Three transmembrane domains are present in M glycoproteins. Glycosylation of M proteins occurs in the Golgi body[51-53]. Alteration in M protein is required to enter virion into the cell and for protein to become antigenic[54–56]. The M protein aids to regenerate new virions.

***E glycoproteins***

These are tiny proteins and are made from about 76 to 109 amino acids. The N-terminus of the E proteins typically has 30 amino acids, which facilitates adhesion to the virus membrane[57]. Additionally, Coronavirus E proteins perform an essential part in the assembly and morphogenesis of virions inside the cell.

***N proteins***

They are phosphoproteins in nature. They possess flexible viral genomic RNA and have the ability to bind to helixes. N proteins perform a vital part in coronavirus virion structure, replication, and transcription[58,59].

The complete genome of Wuhan-Hu-1 coronavirus, a strain of SARS-CoV-2 (taken from a COVID-19 pneumonia patient), is of 29.9 kb size[36]. The CoVs genome contains between 6 and 11 ORFs[60]. Two polyproteins named pp1a and pp1ab, encode 16 non-structural proteins, which are translated by approximately 66% of the viral RNA present in the first ORF (ORF1a/b). The remaining ORFs form structural and accessory proteins. Spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein[11] are the four structural proteins encoded by the remaining part of the virus genome. SARS-CoV-2 is found to be more similar to SARS-like bat CoVs when compared with the known SARS-CoV and MERS-CoV genomes. The majority of genome-encoded proteins of SARS-CoV-2 are alike to those of SARS-CoVs. Zhang *et al*[61] observed that SARS-CoV-2 had been mutated in various patients in China. Tang *et al*[62] categorized two strains of SARS-CoV-2, the L type, and the S type. The L-type strains (derived from S-type) are more infectious and dangerous in terms of evolution than the S-type. As a result, virologists and epidemiologists must carefully examine the novel coronavirus and conduct additional research to determine its virulence and pandemic.

**Coronavirus Replication**

Here, we summarise the main steps of the SARS-CoV-2 infection cycle.

***Entrance into the host cell***

The human lower respiratory tract has ACE2, the SARS-CoV receptor[63]. Coronavirus S-glycoprotein may bind to ACE2 receptor present on outer surface of human cells[64]. S glycoprotein comprises of S1 and S2 subunits[65]. S1 subunit specifies the virus-host range and cellular tropism with the help of the RBD domain, whereas S2 subunit helps the fusion of virus with cell membrane with the help of heptad repeats 1 (HR1)[66] and heptad repeats 2 (HR2)[67] domains.

***RNA synthesis and virion assembly***

After fusing with the membrane, genomic RNA of virus is delivered inside the cytoplasm. This RNA forms pp1a and pp1ab polyproteins after translation[68], which further form non-structural proteins, and replication-transcription complex (RTC) in two-layered vesicles[69].RTC replicates repeatedly and forms a set of subgenomic RNAs[70], which further form accessory proteins and structural proteins.Newly generated genomic RNA, nucleocapsids, and envelope glycoproteins unite to form new viral particles in the ER and Golgi apparatus[71].

***Virion release***

At last, virion-containing vesicles combine along with the plasma membrane, and viruses are released outside.

**Epidemiology and Pathogenesis**

This infection can affect people of any age. In humans, it is very contagious, especially in the elders and those who already have illnesses like fever, cold, or cough[72,73]. Large droplets released by symptomatic patients when coughing and sneezing are used to spread the infection; however, this can also happen from asymptomatic individuals prior to the start of symptoms[44]. COVID-19 infection transmits mainly by way of respiratory droplets, respiratory secretions, and direct contact[38]. Further, SARS-CoV-2 was also observed in faeces of severe pneumonia patients. Even after patients have recovered from the sickness, patients with symptoms can still spread infections. The infected droplets can deposit on surfaces and spread infection up to 1-2 meters away. In a suitable atmosphere, the virus can survive on surfaces for days. Disinfectants like hydrogen peroxide and sodium hypochlorite can destroy viruses[74]. Infection can be gained by inhaling infectious droplets or by touching surfaces that have been exposed to the virus and subsequently contacting mouth, nose, and eyes. Further, virus is found in faeces and affects the water reservoirs and then spreads by faeco-oral route or through aerosolization[75]. Transplacental transfer from pregnant women to their foetuses has not yet been documented. Although, post-natal transmission in neonates is reported[76]. The incubation period of this virus ranges from 2 to 14 d[77].

**Clinical Features**

The clinical characteristics of patients with COVID-19 are shown in Figure 2.Asymptomatic state, acute respiratory distress syndrome, and multi-organ failure are all possible clinical manifestations of COVID-19[37]. Fever, coughing, sore throat, headaches, sputum production, sore throat, lethargy, myalgia, shortness of breath, and conjunctivitis are frequent clinical symptoms[37]. Acute respiratory distress syndrome (ARDS), arrhythmia, shock[78], acute renal injury, acute cardiac injury, liver dysfunction, and secondary infection were the disorders related to this infection[40]. This infection can lead to pneumonia, respiratory failure, and even death after the first week. IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα are inflammatory cytokines that have dramatically increased during the advancement of this disease[79]. Recovery from this infection began in the second or third week. Elderly persons are more likely to experience negative effects which can lead to death[37]. Additionally, it has been noted that this disease in neonates, kids, and children is substantially less severe than in adults[37].

**Diagnostic criteria**

An individual having fever, sore throat, and cough who has a traveling record to China or different locations with chronic community transmittance, or has contacted individuals having the same traveling experiences, or who have come into contact with a confirmed COVID-19 infected person is considered a suspected COVID-19 case[72]. A confirmed COVID-19 case is a suspected one having a positive molecular diagnostic test[72].

Until recently, the standard clinical diagnosis approach for COVID-19 is nucleic acid identification in swabs taken from nose, throat, or other parts of the respiratory system by using real-time polymerase chain reaction and furthermore verified by sequencing[80].

**Treatment strategies for COVID-19**

***General precautions***

COVID-19 patients are adequately isolated to stop infection to other persons in contact, patients, and health personnel. Keeping adequate water in the body and a proper diet plan while managing fever and cough are the best ways to treat moderate infection at home. It is advised to provide oxygen to hypoxic patients using nasal prongs, face masks, a high-flow nasal cannula, or non-invasive ventilation[72].

Four classes of medicines have been identified based on how they work: (1) Viral entry and membrane fusion inhibitors; (2) protease inhibitors; and (3) RdRp inhibitors, and (4) immunomodulatory medicines.

Table 1 shows various therapeutic agents used for the treatment of COVID-19.

Umifenovir, camostat mesylate, ACE inhibitors, angiotensin receptor-1 blockers, soluble recombinant human ACE2, chloroquine phosphate, and hydroxychloroquine sulfate are the various medications that were tested to prevent attachment and fusion of the virus to the cell membrane[81]. Due to their increased production capacity and lower danger of antibody-dependent enhancement, MAbs act more efficient than convalescent plasma as medication for COVID-19 patients[82]. A new MAb cocktail called REGN-COV2 binds to the receptor-binding domain of S1 or S2 subunits of the SARS-CoV-2 spike protein to stop the virus from entering the host cell[83]. Three more MAbs (B38, H4, and CR3022), might be potent against SARS-CoV-2 in upcoming studies[84,85].

Another class of medications that have been used for a long time to treat AIDS is protease inhibitors. Under the trade name Kaletra®, lopinavir is commonly compounded with ritonavir (LPV/r). The LPV/r effectiveness has been demonstrated earlier in cell culture as opposed to SARS-CoV-1 andMERS-CoV[86] and in recent times opposed to SARS-CoV-2[87].

RdRp inhibitors, in particular, demonstrated [encouraging](https://www.powerthesaurus.org/encouraging/synonyms) results in COVID-19 patients[88-90]. For instance, Remdesivir (RDV, GS-5734, Gilead) inhibited the spread of SARS-CoV-2 at smaller doses[89]. Another RdRp inhibitor, favipiravir (T-705, Avigan®), has demonstrated efficacy against SARS-CoV-2 in Vero E6 cells at higher concentrations[89]. Another RdRp inhibitors, such as β-D-N4-hydroxycytidine (EIDD-1931), were very effective at stopping SARS-CoV-1, SARS-CoV-2, and MERS-CoV replication in *in vitro* condition[91].

To lessen the intensity and complexities of COVID-19 and escape the inflammatory immune reactions (in serious patients), a variety of therapy is frequently applied[92]. Proinflammatory cytokine-suppressing medications, including MAbs (tocilizumab and sarilumab) and IL receptor inhibitors (anakinra), are now available[93]. In Vero E6 cells, nitazoxanide showed antiviral activity as opposed to SARS-CoV-2[89].

Corticosteroids aid to escape ARDS and acute lung injury by lowering cytokine storm and lung inflammation[94]. Induced pluripotent stem cells, mesenchymal stromal cells, and T cells are various cell therapy techniques that have been researched[95-98].

**Prevention**

Currently, only a few approved medications are available to treat COVID-19 infection. Preventive measures play an important role to prevent this infection. It is advisable to keep confirmed or suspected cases having mild sickness isolated at home. Patients should wear a face mask and follow cough hygiene. Additionally, caregivers need to wash their hands regularly and should wear a surgical mask in the patient ward. Frequent sanitization of the rooms, surfaces, and equipment should be done with sodium hypochlorite. N95 respirators, safety suits, and goggles should be provided to healthcare professionals and workers. Healthcare professionals should also be frequently checked for various signs of COVID-19. Once a patient has been apyretic for at least three days and has two successive negative molecular tests with a sample gap of one day, they could be discharged from isolation. The only requirement for discharge was not the results of negative molecular tests[72].

Community-wide precautions include avoiding crowded places, forbidding large-scale gatherings, and delaying unnecessary travel to locations where transmission is still occurring. People should inculcate habit of good hand hygiene frequently, and exercise good cough hygiene by coughing into their sleeves or tissue paper rather than in their hands[99].

A law of banning the sale and trade of wild animals is also being introduced in China[100].

**CONCLUSION**

In this review, we outline the history, origin, transmission, genome structure, replication, epidemiology, pathogenesis, clinical characteristics, diagnosis, and treatment of COVID-19. The COVID-19 disease propagates rapidly across China and has disseminated to different countries of the world. Due to this viral epidemic, the economic, clinical, and public health frameworks of almost all countries of the world had affected. We wish that the horrible scenario created by this pandemic will not affect our life further.

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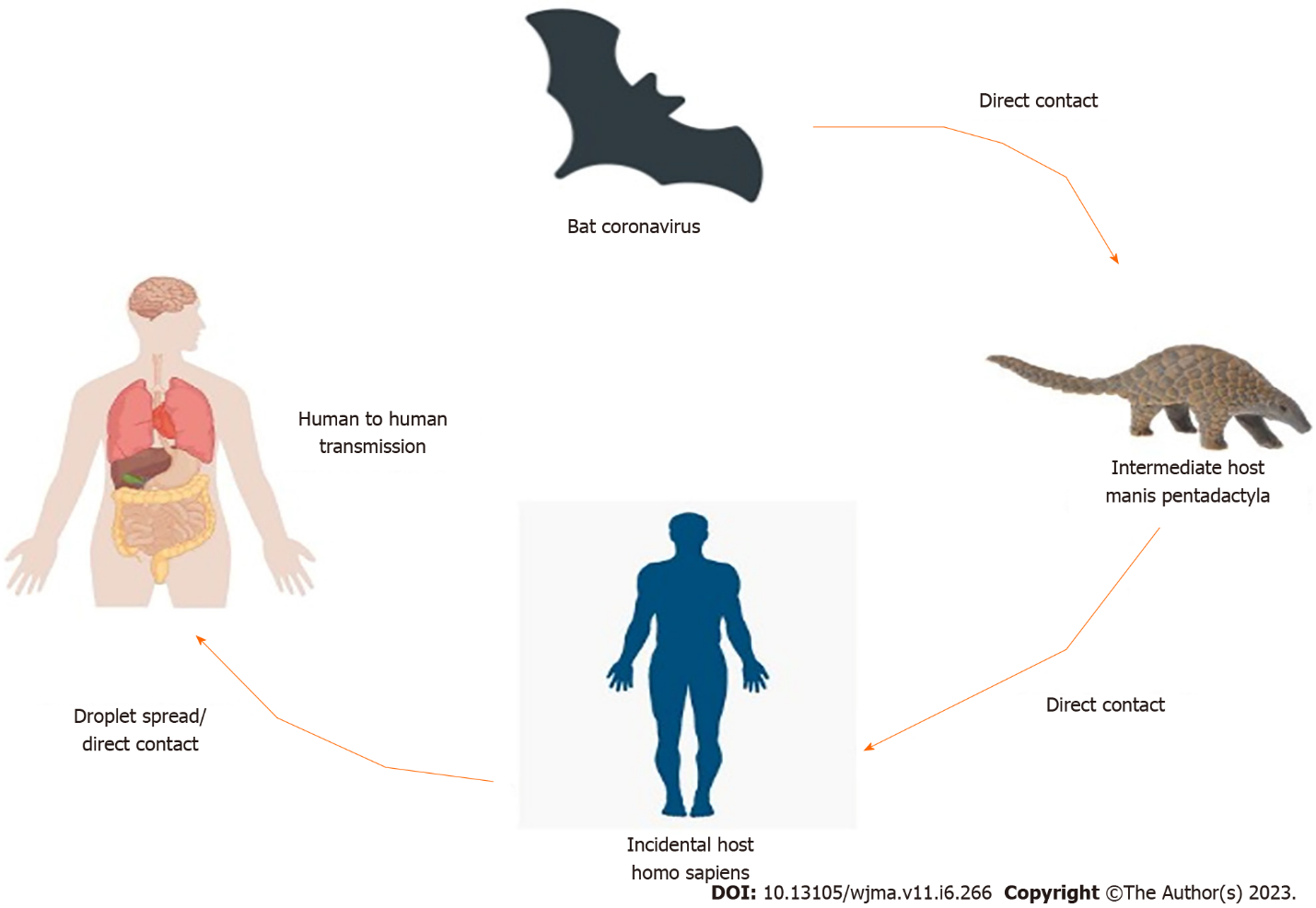
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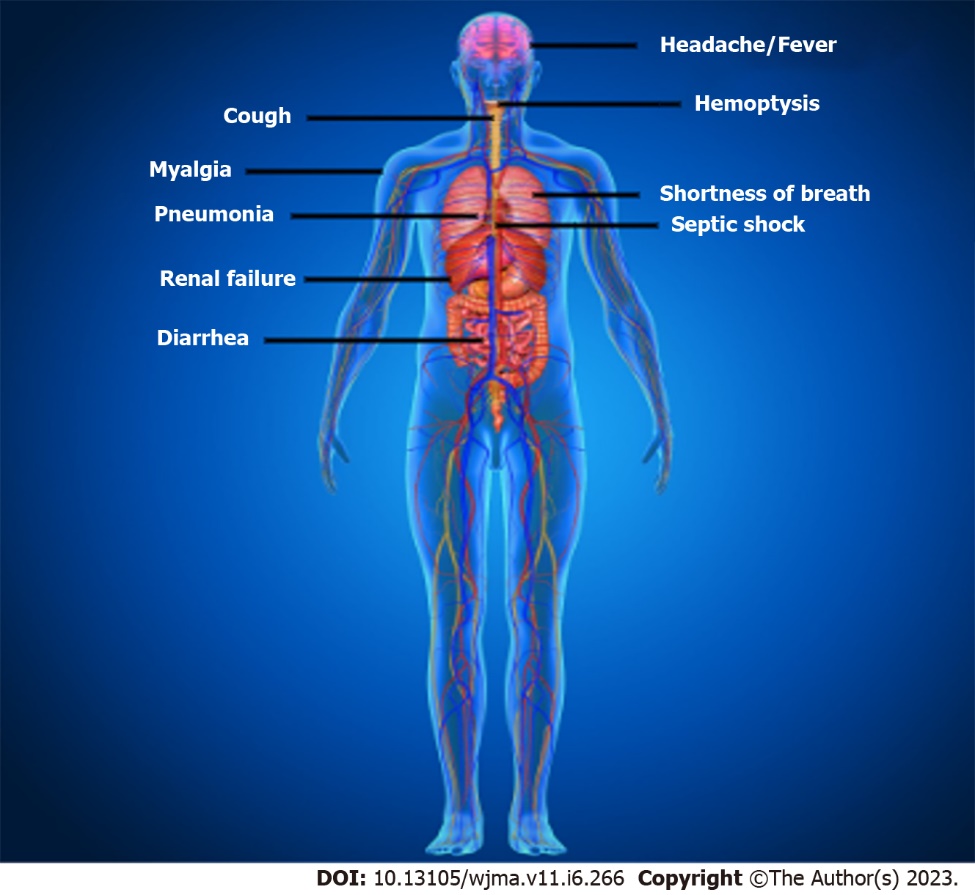
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**Figure Legends**



**Figure 1 Transmission cycle of severe acute respiratory syndrome coronavirus 2.**

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**Figure 2 Clinical Features of patients with coronavirus disease 2019.**

**Table 1 Various therapeutic agents used for the treatment of coronavirus disease 2019**

|  |  |  |
| --- | --- | --- |
| **Sr. No.** | **Therapeutic agents** | **Examples** |
| 1 | Antiviral agents | 1 Remdesivir |
| 2 Favipiravir |
| 3 Ribavirin |
| 4 Interferons |
| 5 Ritonavir/Lopinavir |
| 6 Arbidol |
| 7 Chloroquine/Hydroxychloroquine |
| 8 Recombinant soluble ACE2 |
| 9 Azithromycin |
| 10 Ivermectin |
| 11 Nitazoxanide |
| 12 Camostat mesylate |
| 13 Paxlovid |
| 2 | Biologic agents | 1 Monoclonal antibodies |
| 2 Convalescent plasma |
| 3 Hyperimmune sera |
| 4 Exogenous surfactant delivery |
| 3 | Anti‑inflammatory agents | 1 Corticosteroids |
| 2 Fluvoxamine |
| 3 Anakinra |
| 4 Granulocyte-macrophage colony-stimulating factor inhibitors |
| 5 Intravenous immunoglobulin |
| 6 Janus kinase inhibitors |
| 7 Colchicine |
| 4 | Herbal agents | Various Chinese herbal medicine |
| 5 | Preventive agents | Vaccines |

ACE2: Angiotensin converting enzyme 2.



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