MINI-REVIEW

COVID-19: pathophysiology, diagnosis, complications and investigational therapeutics

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Abstract

The novel coronavirus disease 2019 (COVID-19) outbreak started in early December 2019 in the capital city of Wuhan, Hubei province, People's Republic of China, and caused a global pandemic. The number of patients confirmed to have this disease has exceeded 9 million in more than 215 countries, and more than 480 600 have died as of 25 June 2020. Coronaviruses were identified in the 1960s and have recently been identified as the cause of a Middle East respiratory syndrome (MERS-CoV) outbreak in 2012 and a severe acute respiratory syndrome (SARS) outbreak in 2003. The current SARS coronavirus 2 (SARS-CoV-2) is the most recently identified. Patients with COVID-19 may be asymptomatic. Typical symptoms include fever, dry cough and shortness of breath. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhoea have been reported; neurologically related symptoms, particularly anosmia, hyposmia and dysgeusia, have also been reported. Physical examination may find fever in over 44% of patients (and could be documented in over 88% of patients after admission), increased respiratory rate, acute respiratory disease and maybe decreased consciousness, agitation and confusion. This article aims at presenting an up-to-date review on the pathogenesis, diagnosis and complications of COVID-19 infection. Currently no therapeutics have been found to be effective. Investigational therapeutics are briefly discussed.

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Introduction

On 31 December 2019, the Chinese authorities reported to the World Health Organization an emerging novel coronavirus in patients from Wuhan, Hubei province [1]. Currently the virus is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease name is coronavirus disease 2019 (COVID-19). This virus has a higher degree of lethality than other endemic viruses, and it is also more lethal to humans compared to the earlier emerging outbreaks of SARS-CoV-1 in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. Both SARS-CoV-1 and MERS-CoV have common ancestry with viruses found in bats. Both have intermediate hosts for transmission: palm civets for SARS-CoV-1 and dromedary camels for MERS-CoV. However, there is not yet strong evidence for an intermediate host.

The current pandemic is caused by SARS-CoV-2. It shares with the earlier two coronaviruses the features of the *Coronaviridae* family. Coronavirus have large (~30 kb) single-stranded, positive-sense RNA genomes; the genome is roughly 80% identical with other coronaviruses at a nucleotide level. A virus closely related (sharing 90% of nucleotide structure) to SARS-CoV-2 is RaTG13-2013, which was identified in bats [2]. The complete genome of SARS-CoV-2 isolated from Wuhan Hu-1 is available online (https://www.ncbi.nlm.nih.gov/nuccore/NC_045512). Genetic epidemiology of hCoV-19 and submitted data since December 2019 are available from the GISAID database (https://www.gisaid.org/). SARS-CoV-2 is composed of at least 11 open reading frames (ORFs), with a full length of 29 903 bp. Four major structural protein-coding genes have been identified in the coronaviruses: spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein

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(N) [3]. The spike protein of SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) as its cell surface receptor, and utilization influences the tropism of the virus.

COVID-19 infects people of all ages. However, there are two main groups at a higher risk of developing severe disease: older people, and people with underlying comorbidities such as diabetes mellitus, hypertension, cardiorespiratory disorders, chronic liver diseases and renal failure. Patients with cancer and those receiving immunosuppressive medication as well as pregnant people are also thought to be at a higher risk of developing severe disease when infected [4].

Pathophysiology

Transmission of infection

The transmission of infection is mainly person to person through respiratory droplets. Faecal–oral route is possible. The presence of the virus has been confirmed in sputum, pharyngeal swabs and faeces [5]. Vertical transmission of SARS-CoV-2 has been reported [6] and confirmed by positive nasopharyngeal swab for COVID-19. The median incubation period of COVID-19 is 5.2 days; most patients will develop symptoms in 11.5 to 15.5 days. Therefore, it has been recommended to quarantine those exposed to infection for 14 days.

Pathogenesis mechanisms

The SARS-CoV-2 infection enters the host cells through the S spike protein by binding to ACE2 for internalization and aided by TMPRSS2 protease. The high infectivity of the virus is related to mutations in the receptor binding domain and acquisition of a furan cleavage site in the S spike protein. The virus interaction with ACE2 may downregulate the anti-inflammatory function and heighten angiotensin II effects in predisposed patients [7]. With the challenge we face with COVID-19, some have been advocating for the use (or cessation) of Angiotensin II receptor type I (AT1 receptor) blockers and ACE inhibitors during the treatment of COVID-19 in patients with hypertension. Currently the recommendation of the Council on Hypertension of the European Society of Cardiology is that patients should continue their antihypertensive treatment with no changes because we do not have evidence supporting its cessation [8]. However, further research is needed to back these recommendations with more evidence.

The invasion of the virus to the lung cells, myocytes and endothelial cells of the vascular system results in inflammatory changes including oedema, degeneration and necrotic changes. These changes are mainly related to proinflammatory cytokines including interleukin (IL)-6, IL-10 and tumor necrosis factor α, granulocyte colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and increased expression of programmed cell death 1, T-cell immunoglobulin and mucin domain 3 (Tim-3) [9]. These changes contribute to lung injury pathogenesis, hypoxia-related myocyte injury, body immune response, increased damage of myocardial cells, and intestinal and cardiopulmonary changes.

Infection with SARS-CoV-2 has been also shown to cause hypoxaemia. These changes lead to accumulation of oxygen free radicals, changes in intracellular pH, accumulation of lactic acid, electrolyte changes and further cellular damage.

Body systems and organs affected

The respiratory system is the primary system affected in SARS-CoV-2, and multiple infiltrates of both lungs may be present. Real-time PCR (RT-qPCR) amplification of SARS-CoV-2 virus nucleic acid of nasopharyngeal swabs or sputum is needed to confirm the diagnosis. However, the test may be negative in the early days of presentation. The clinical picture, including shortness of breath, increased respiratory rate, decreased oxygen saturation and raised C-reactive protein, is nonspecific. Other tests, such as IgG and IgM antibodies against SARS-CoV-2, $CD4^+$ and $CD8^+$, should be ordered. Both $CD4^+$ and $CD8^+$ are substantially lowered in SARS-CoV-2. The pathology of the lungs shows microscopic bilateral diffuse alveolar damages, cellular fibromyxoid infiltrates and interstitial mononuclear inflammatory infiltrates with lymphocyte domination [10].

The cardiovascular system is usually involved in COVID-19 infection. Biomarkers such as elevated highly sensitive troponin-T, natriuretic peptides and IL-6 are prognostic, and their progressive rise is associated with poor outcomes. The inflammation of the vascular system results in the following changes: diffuse microangiopathic thrombi, inflammation of cardiac muscle (myocarditis), and cardiac arrhythmias, heart failure and acute coronary syndrome. These cardiovascular complications may cause death [11,12]. The lymphocytopenia observed during the infection potentially involves $CD4^+$ and some $CD8^+$ T cells. These changes disturb the innate and acquired immune responses, causing delayed virus clearance and hyperstimulated macrophages and neutrophils. Notch signaling is known to be a major regulator of cardiovascular function, and it is also implicated in several biological processes mediating viral infections. Recently it has been debated whether targeting Notch signaling can prevent SARS-CoV-2 infection and interfere with the progression of COVID-19–associated heart and lung disease pathogenesis [13].

The reported gastrointestinal manifestations of COVID-19 include diarrhoea, nausea, vomiting and abdominal pain. SARS-CoV-2 RNA has been isolated from stool specimens and from swabs that sampled the anus/rectum [14]. ACE2 has been found to be expressed in the epithelial cells of the gastrointestinal tract,

suggesting virus entry through the ACE2 receptors and its replication causing inflammatory changes and the patient's symptoms. SARS-CoV-2 also causes liver injury, which manifests as elevated serum alanine aminotransferase and aspartate aminotransferase levels [15]. Mild elevation of serum bilirubin and γ-glutamyl transferase have also been reported in some patients with COVID-19 infection [16]. In most cases, the liver injury was transient and mild. However, severe liver dysfunction or injury has been reported in patients with severe disease. High levels of alanine aminotransferase of over 7500 U/L has been reported in a Chinese study [17]. Microscopically, microvesicular steatosis of the liver and mild lobular injury has been found in COVID-19–infected patents [16]. It is not clear whether the observed SARS-CoV-2–associated liver injury is caused by direct viral injury or if it is related to hepatoxic drugs, coexisting systemic inflammatory changes, sepsis, respiratory distress syndrome–induced hypoxia or multiple organ failure [18].

There is clinical evidence that the SARS-CoV-2 has potential neuropathic properties. Several neurologic-related symptoms have been reported, including headaches, dizziness, seizure, decreased level of consciousness, acute haemorrhagic necrotizing encephalopathy [19], agitation and confusion.

Patients with comorbidities

In patients with type 2 diabetes mellitus who are infected with COVID-19, it is important to remember that two receptor proteins, ACE2 and dipeptidyl peptidase 4, are established in the pathogenesis of COVID-19 infection. These two receptors are also transducers involved in normal physiological processes, including metabolic signals regulating glucose homeostasis, renal and cardiovascular physiology, and pathways regulating inflammation.

History and physical examination

History and physical examination are extremely important for the diagnosis of COVID-19 infection. Common related symptoms are: fever (in 44% of patients on presentation and up to 88% of admitted patients); dry cough; shortness of breath, which may be severe and progressive, particularly when the patient develops pneumonia; myalgia and tiredness; sore throat; and nausea, vomiting and diarrhoea [20].

Patients may have neurologically related symptoms, including: acute cerebrovascular disease, headaches, dizziness, seizure, decreased level of consciousness, encephalopathy and agitation and confusion [40]. Recently, anosmia, hyposmia and dysgeusia have been reported [21]. Physical signs include raised body temperature, increased respiratory rate, decreased oxygen saturation, auscultation of the lungs may be normal or show crackles and signs of heart failure, cardiac arrhythmias, myocarditis, acute coronary syndrome, shock and death may occur.

Evaluation

In patients with clinical evidence of COVID-19 infection, laboratory tests may reveal lymphocytopenia, thrombocytopenia, elevated liver transaminases, elevated C-reactive protein and erythrocyte sedimentation rate, elevated serum lactate dehydrogenase and decreased or normal serum albumin. Elevated serum troponin-T may be present, indicating myocardial injury. The following tests are used in patients with symptoms suggestive of COVID-19 infection.

Viral testing

Viral testing is performed by the RT-qPCR test, used for qualitative detection of the nucleic acid for SARS-CoV-2. Swabs are usually taken from nasal, nasopharyngeal, oropharyngeal, sputum or lower respiratory tract aspirates or wash. Positive tests indicate the presence of SARS-CoV-2 RNA, and together with the clinical picture support the diagnosis. Negative test results do not preclude SARS-CoV-2 infection, and shall be interpreted in light of the clinical picture and epidemiologic information [22].

Serology

Serology testing for SARS-CoV-2 is now available. The test can assess prior exposure to virus and cannot be used in the diagnosis of current infection. Cross-reactivity with other human coronaviruses may occur. The serology test is particularly useful (i) when the viral test is not available. Using the serology test together with the clinical picture could guide in decision making. (ii) Patients with late disease complications and their physicians need to make immediate decisions (the viral test takes more time to get the results). (iii) In some patients, virus shedding is reduced, making RT-qPCR results falsely negative. The serology test can detect IgM and IgG antibodies against SARS-CoV-2 in serum, plasma and whole blood [23].

Rapid antigen testing

Rapid antigen testing is a monoclonal antibody test against the SARS-CoV-2 nucleocapsid protein (N). This protein is abnormally expressed in infected cells. Monoclonal antibodies are specifically directed against nucleocapsid protein, and by using enzyme-linked immunosorbent assay, it is possible to detect SARS-CoV-2. The test has a reported sensitivity of 84.1% and a specificity of 98.5%. No cross-reaction with human and animal coronaviruses in the assay were reported. There are no reports yet about applying this test to SARS-CoV-2 [24].

TABLE 1. Drugs currently in trials to treat COVID-19

Category	Drug name [Reference]	Route	Mechanism of action	Indications, recommendations	Side effects	Precaution	Comments (Clinical trial no.)
Antimalarials and amebicides	Hydroxychloroquine phosphate [35–37]	Oral	Inhibits autophagy and lysosomal acidification. Prevents virus entry *in vitro*.	Moderate to severe	QT prolongation, headache, nausea, loss of appetite, vomiting, diarrhoea, rash	G6PD deficiency, hearing problems, kidney, liver diseases, diabetes (low blood glucose), porphyria, seizures, psoriasis, cardiomyopathy	FDA EUA approved to treat adults and adolescents for COVID-19 admitted in hospitals. (ChiCTR2000029559)
Antimalarials	Chloroquine [35,37,38]	Oral	Not fully understood. Inhibition of viral fusion. Binds and inhibits glycosylation of virus proteins.	Moderate to severe	QT prolongation, headache, nausea, vomiting	G6PD deficiency, hypersensitivity to chloroquine, retinal and visual changes	Considered as part of investigation protocol for patients with COVID-19 infection. (NCT04333628)
Antibiotic	Azithromycin [39,40]	Oral	Azithromycin acts by binding to 50S ribosomal subunit of susceptible microorganisms.	Moderate to severe	QT prolongation, headache, dizziness, cholestasis, hepatitis, diarrhoea	Azithromycin is CYP3A4 (it interacts with >200 drugs)	Currently being investigated in clinical trials and also available through expanded access and compassionate use mechanisms for certain patients with COVID-19. (IRCT20200415047092N1)
Antiviral agent	Remdesivir [41,42]	Intravenous	Inhibits RdRp of RNA viruses.	Mild to moderate	Elevated liver enzymes, diarrhoea, hypotension, acute kidney injury, atrial fibrillation, deep venous thrombosis	Interacts with clarithromycin and rifampin	Prevents MERS coronavirus disease in monkeys; undergoing clinical trials in China, United States and United Kingdom as potential drug in treating COVID-19. (NCT04365725)
Antiviral agent	Favipiravir [43,44]	Oral	Inhibits RdRp of RNA viruses. It is an inhibitor of viral RNA-dependent RNA polymerase, causing chain termination and preventing RNA elongation.	Early to mild	Nausea, vomiting, liver dysfunction	Drug interaction, pregnancy	Approved for treating influenza in Asia. (NCT04358549)
HIV protease inhibitor	Lopinavir/ritonavir [45] (Ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450)	Oral	Aspartate protease inhibitor. Lopinavir binds to site of HIV-1 protease activity and inhibits cleavage of virus Gag-Pol polyprotein precursors, hence interfering with HIV infection.	Moderate to severe	Anorexia, nausea, abdominal discomfort, diarrhoea, acute gastritis, liver dysfunction, thrombocytopenia, skin eruptions	Drug interactions (it is a CYP3A4 substrate)	No benefit observed with lopinavir/ritonavir treatment beyond standard care. (NCT04307693)
Antiprotozoal agent	Nitazoxanide [46]	Oral	Disturbs metabolism in anaerobic microbes and inhibits viral transcription factor.	Moderate to severe	Nausea, vomiting, abdominal pain, headache, dizziness, skin rash	Hypersensitivity to nitazoxanide	Nitazoxanide/azithromycin has been tried in combination to treat COVID-19; clinical trial with hydroxychloroquine vs. nitazoxanide is currently being investigated. (NCT04361318, NCT04360356, NCT04343248, NCT04351347, NCT04348409, NCT04341493)
Immunomodulator (monoclonal antibody)	Tocilizumab [47]	Intravenous	Monoclonal antibody; blocks IL-6 receptor and inhibit IL-6 pathway.	Severe	Nasopharyngitis, headache, hypertension, elevated alanine aminotransferase, rash, dizziness, leukopenia, liver injury	Thrombocytopenia, neutropenia, acute liver injury, renal failure	Considered as part of an investigation protocol for patients with COVID-19 infection. (NCT04356937)
Immunomodulator (monoclonal antibody)	Sarilumab [43]	Subcutaneous	Monoclonal antibody that blocks IL-6 receptor and inhibit IL-6 pathway.	Moderate to severe	Allergy, thrombocytopenia neutropenia, elevated liver transaminases	Allergy to sarilumab, platelets <15 000/m^3, elevated alanine transaminases >5 times upper normal limit	Clinical trial of patients with COVID-19 complicated by pneumonia requiring ventilatory support. (NCT04359901, NCT04357808)
Immunomodulator (monoclonal antibody)	Siltuximab [48,49]	Intravenous (infusion)	Chimeric monoclonal antibody that binds to and blocks IL-6 effects.	Moderate to severe	Elevation of liver transaminases, thrombocytopenia, skin rash, itching, sweating	Raised liver transaminases and liver dysfunction	Clinical trial of patients with COVID-19 complicated by pneumonia requiring ventilatory support. (NCT04329650)

Plasma, neutralizing antibodies	Convalescent plasma [50]	Intravenous	Convalescent plasma contains specific IgG and IgM anti–SARS-CoV-2 antibodies, which can neutralize virus.	Severe and life-threatening	Anaphylaxis	Donors must be screened for transmittable pathogens	FDA outlined requirements that individuals must meet to donate blood for this research. (NCT04333355, NCT04340050, NCT04353206, NCT04343261, NCT04347681, NCT04356482)

COVID-19, coronavirus disease 2019; CYP3A4, cytochrome P450 family 3 subfamily A member 4; EUA, emergency use authorization; FDA, US Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; IL, interleukin; IL, interleukin; MERS, Middle East respiratory syndrome; RNA-dependent RNA polymerase RdRp; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Ultrasonography

Whole-body point-of-care ultrasonography has been provided to COVID-19 patients. Ultrasonography is considered an essential modality to guide treatment in patients with cardiorespiratory failure. Current recommendations are to extend its use to multisystem and whole-body ultrasonography: thoracic, cardiac, abdomen and deep venous thrombosis [25].

Chest computed tomographic scan

Earlier studies during the outbreak in China suggested that patients with and without SARS-CoV-2 can be differentiated by chest computed tomographic imaging, together with clinical presentation and the presence of pneumonia. The authors proposed that radiologic images and clinical features are excellent diagnostic tools for COVID-19 [26].

Predictors of severe disease may include high virus load, elevated neutrophil-to-lymphocyte ratio, chest changes or changed extent of lesion on computed tomography, patient age and presence of comorbidities [27]. Older age and neutrophil-to-lymphocyte ratio are reported to be independent biomarkers for poor clinical outcomes [28].

Complications

Age and sex have been shown to affect the severity of complications of COVID-19. The rates of hospitalization and death are less than 0.1% in children but increase to 10% or more in older patients. Men are more likely to develop severe complications compared to women as a consequence of SARS-CoV-2 infection [29]. Patients with cancer and solid organ transplant recipients are at increased risk of severe COVID-19 complications because of their immunosuppressed status.

The main complications reported in patients with SARS-CoV-2 may include:

- Coagulopathy, mainly disseminated intravascular coagulation, venous thromboembolism, elevated D-dimer and prolonged prothrombin time.
- Laryngeal oedema and laryngitis in critically ill patients with COVID-19.
- Necrotizing pneumonia due to superinfection caused by Panton-Valentine leukocidin–secreting *Staphylococcus aureus* infection. This superinfection is usually fatal [30].
- Cardiovascular complications, including acute pericarditis, left ventricular dysfunction, acute myocardial injury (associated with increased serum troponin), new or worsening arrhythmias and new or worsening heart failure.

- Acute respiratory failure. Approximately 5% of COVID-19 patients require admittance to an intensive care unit because they develop severe disease complicated by acute respiratory distress syndrome [31].
- Sepsis, septic shock and multiple organ failure.
- Higher risk of death, particularly in male patients with severe disease, presence of heart injury and cardiac complications, hyperglycaemia and patients receiving high doses of corticosteroids [32].
- Ventilation-associated pneumonia in up to 30% of patients requiring intensive mechanical ventilation.
- Massive pulmonary embolism complicated by acute right-sided heart failure [33].

Therapeutics

Currently there is no vaccine or specific antiviral therapy for SARS-CoV-2 infection. Management is based on preventive measures and treatment of the symptoms of infected people. The guidelines of the US Centers for Disease Control and Prevention for clinicians regarding investigational therapeutics for patients with COVID-19 (updated 25 April 2020) indicates that there are no drugs or therapeutics potentially approved by the US Food and Drug Administration to prevent or treat COVID-19. The current recommendations include infection prevention as well as control measures and supportive treatment of COVID-19 complications [34]. Because of the rapid spread of SARS-CoV-2, anti-HIV and anti–hepatitis C virus medications have been tried in patients admitted to the intensive care unit with severe pneumonia. Table 1 summarizes these drugs, including their possible mechanisms of action, adverse effects, precautions and recommendations, and lists ongoing registered clinical trials.

Summary

The COVID-19 pandemic represents the most significant public health crisis humans have faced since the pandemic influenza outbreak of 1918. To date (25 June 2020), over 9 million people have been infected, 480 600 have died and over 5 million recovered. The outbreak originated in China, but more significant numbers of infections and deaths are reported from Europe and the United States. SARS-CoV-2 belongs to the betacoronaviruses, which are highly identical to bat coronavirus. The virus uses the ACE2 receptor for cell entry, causing pathophysiologic changes of the respiratory, cardiovascular, gastrointestinal and nervous systems. Human-to-human transmission is evident, with a reproduction number ranging from 2.24 to 3.58, indicating higher transmission. Clinical symptoms include fever, cough and shortness of breath. Symptoms related to the gastrointestinal, cardiac and nervous system have also been reported. Patients at a higher risk of infection include the elderly, those with comorbidities and those who are immunocompromised. Currently no specific therapeutics have been competent to prevent or treat COVID-19. Several drugs have been tried, including antimalarials, antiviral agents, immunomodulators and plasma-neutralizing antibody transfusion. These therapeutics are currently being investigated in clinical trials.

Conflict of interest

None declared.

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