Brave new world an update on COVID-19 pandemic – A review

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ABSTRACT

Epidemics and pandemics have happened throughout the history of mankind. Before the end of the 20th century, scientific progress successfully eradicated several of the pathogens. While no one has to be afraid of smallpox anymore, there are some new pathogens that have never caused human disease before. Coronaviruses are a family of enveloped RNA viruses. In the 21st century, three of them have caused serious pandemics, including severe acute respiratory syndrome in 2002 and Middle East Respiratory Syndrome in 2012. In 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused the coronavirus disease-19 (COVID-19) pandemic, which has destroyed hundreds of thousands of lives and continues to rage.

KEYWORDS

COVID-19, thrombotic risk, pandemic, antiviral treatment

INTRODUCTION

On March 11th, 2020, the World Health Organization (WHO) officially determined that COVID-19 should be characterized as a pandemic [1]. The first confirmed COVID-19 cases were reported in Wuhan, a city in Hubei Province in central China with 11 million inhabitants. Clinical characteristics were very similar to those of viral pneumonia. Analysis of respiratory samples revealed that the pneumonia was caused by a novel coronavirus [2]. The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and WHO officially named the disease COVID-19.

The outbreak began at seafood and live animal market in Wuhan on December 12, 2019 [3]. It rapidly spread, resulting in an epidemic throughout China, followed by a continuously increasing number of cases in more than 180 countries all over the world. At the time of preparing this manuscript, the World Health Organization had reported 4,990,470 confirmed cases, including 324,990 deaths [4].

Economic, financial, social, psychological, and health aspects of this pandemic hardly can be established yet, but it will definitely have a huge impact on the whole world, and it will be a major challenge to overcome the crisis generated by COVID-19.

Route of the virus

Coronaviruses are single-strand RNA viruses, the majority of which cause diseases in animals. Six were previously known to cause respiratory diseases in humans, and SARS-CoV-2 became the seventh. It belongs to the family Coronavirus a large family of viruses prevalent...
system and protects against organ damage, thereby playing an important role in hypertension, diabetes, and cardiovascular disease.

ACE2 is also involved in SARS-CoV-2 invasion of the human alveolar epithelial cells [12]. COVID-19 patients with severe pneumonia have a typical acute respiratory distress syndrome (ARDS) pathology in the lung. Though ACE2 normally has a protective effect on this type of acute lung injury ARDS is a disease characterized by high mortality [13]. Histologic studies of COVID-19 pneumonia reveal alveolar spaces with the focal hyaline membrane, pneumocyte proliferation, and metaplastic changes. Signs of virus-induced cytopathy, such as multinucleation and nuclear atypia, are also common. Lymphocytes and macrophages constitute the vast majority of inflammatory cells [14].

Host immune response and immunopathology

A marked immunological feature of COVID-19 is lymphocytopenia and the reduction of both T cells and natural killer (NK) cells. The number of NK cells is extremely low in some critically ill patients. As there is no ACE2 expression on lymphocytes, it might be supposed that the disturbed functioning of the immune system is caused by a cytokine storm, not the virus itself.

Endothelium damage is also a typical clinical feature in severe COVID-19 patients. Vasculitis-like manifestations, necrosis of extremities, and thrombosis could be seen in severe COVID-19 patients. Vascular damage may be caused by direct injury of endothelial cells by the virus and may lead to disseminated intravascular coagulation or anti-phospholipid syndrome (APS) [15].

Virus transmission

Transmission of the SARS-CoV-2 virus occurs mainly by virus-containing air droplets but it can also occur by touching the face after touching virus-contaminated surfaces and by the faecal-oral route. Viability of the virus in air droplets and on different surfaces has been studied. There is an exponential decay in virus titer over time. The half-life in droplets is approximately 1.1–1.2 hours, and it is longer on plastic and stainless steel than on copper and cardboard [16].

Basic Reproduction Number (R₀) refers to the average amount of secondary infection that patients may produce in a completely susceptible population without intervention [17]. In the case of SARS-CoV-2, this number is 1.5–3.5. However, there are so-called superspreaders that can give the infection to many more, even to hundreds of people. Super spreading depends on the virulence of the virus, on crowded places, on the hygiene and behaviour of the person, and on co-infection with other pathogens [18].

Diagnosis

Diagnosis is based on clinical findings and demonstration of the virus RNA. Detecting antibodies generated against the virus is also important, but it does not necessarily mean acute disease. Pneumonia can be diagnosed by chest X-ray,
but computed tomography (CT) is much more sensitive. Laboratory tests show an elevated level of inflammatory markers.

**Demonstrating SARS-CoV-2 RNA.** The virus RNA can be demonstrated by real-time reverse-transcriptase polymerase chain reaction (RT-PCR). Throat swab samples or deep nasal cavity swab samples are required for the test. Taking the sample properly is very important; it should be a deep wipe, and the person taking the sample should wear completely protective garments. The positive predictive value of the test is very high. On the other hand, a negative result does not rule out SARS-CoV-2 infection; negativity can be the consequence of bad sampling, or other methodological problems, low virus concentration in the nasal mucosa (mainly in the first few days after infection), or when the virus has already moved into the lower respiratory tract. While a positive is usually considered an indicator of COVID-19 and isolation, a subsequent negative should be followed by discharge or transfer of the patient only with caution. Tests should make such a decision by taking to account several factors [19]. In the stage of viremia, a blood sample is also an appropriate test. SARS-CoV RNA was detected in 50% of the plasma and 78% of serum samples during the first week of illness [20]. The drawback of RT-PCR is time-consuming, requires sophisticated equipment, and it is expensive. The relatively high rate of false-negative results is also a problem. In any case, SARS-CoV-2 RT-PCR plays an essential role in diagnosis and should be strictly standardized.

**Serological tests.** IgM and IgG antibodies produced against SARS-CoV-2 can be demonstrated from the blood. Production of antibodies is a process requiring 7–10 days after infection. First IgM antibodies are produced, then IgG antibodies are produced by B-lymphocytes. It has been demonstrated that high levels of IgM antibodies can be found 5 days after the onset of illness – not only in patients with clinical symptoms but also in asymptomatic patients. Thus, it was proposed that PCR testing should be combined with and IgM ELISA assay for enhanced sensitivity [21]. More evidence is needed to confirm the IgM and IgG kinetics of SARS-CoV-2. The adequate interpretation of results is very important: the presence of antibodies may not mean an acute infection, but rather a recent infection. It may also suggest that the patient has a defense against repeated SARS-CoV-2 infection, but that is still a matter of debate. Though antibody seroconversion provides reliable proof of former infection, serological tests are not suitable for early diagnosis [22]. Among the serological assays, enzyme-linked immunosorbent assay (ELISA) and chemiluminescence assay (CLIA) are suitable for first-line screening because of the large throughput, short processing time, and simple procedure [23].

**Clinical symptoms.** While most patients experience no or very mild symptoms, about 14% of COVID-19 patients with respiratory symptoms require supplemental oxygen, and approximately 5% develop a need for mechanical ventilation [24]. ARDS was observed to develop in 17–29% of hospitalized patients approximately 8 days after symptoms onset [25].

The most frequent symptoms are fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnoea (21.9%) [26]. Minor symptoms include headache or dizziness (12.1%), diarrhoea (4.8%), nausea, and vomiting (3.9%). A special early symptom is the loss of taste and smell [24]. ‘Silent hypoxaemia’ has also been reported [27]. That means the development of respiratory failure without a subjective perception of the difficulty of breathing. Hypocapnia is a characteristic feature of ‘silent hypoxaemia’ because of compensatory hyperventilation. The characteristic symptoms that appear during a viral infection, such as running nose and sore throat, may be present, but less frequently than in influenza.

COVID-19 is more common in men than women: men account for 60 per cent of the cases [26].

The mortality rate of COVID-19 is thought to be around 5% [25]. This rate is much higher (14.8%) in patients over 80 years of age and even higher (49%) among the critically ill requiring mechanical ventilation [28]. It is not easy to determine the exact mortality rate because of the high number of patients with no or mild symptoms, meaning that the total number of SARS-CoV-2 infected people is underestimated. In those countries where few screening tests are performed, the mortality rate would be incorrectly considered high. The mortality rate is much higher in pneumonia patients superinfected with bacteria [29]. Advanced age (>60 years), cancer, ischaemic heart disease, hypertension, diabetes mellitus, chronic lung disease, or major infections also increase the mortality.

Smoking also can be considered a risk factor for more serious symptoms and greater mortality. According to the study of Guan et al., there were higher percentages of smokers among patients that needed ICU support, mechanical ventilation, or who had died [30].

The main causes of mortality are acute respiratory distress syndrome (ARDS), sepsis, acute cardiac injury, acute kidney injury, multi-organ failure, and disseminated intra-vascular coagulopathy. Alkalosis, hyperkalemia, and hypoxic encephalopathy are also more common in deceased than in recovered patients [31].

**Radiography.** A chest CT scan may be useful for the rapid and early diagnosis of COVID-19. The sensitivity of a conventional chest x-ray is 59%, while that of CT is 98% [32]. CT findings may precede laboratory results by as many as 3 days [33]. However, CT findings of COVID-19 may overlap with other viruses, so CT is not suitable to distinguish between virus infections. Because of its high sensitivity, chest CT is very helpful not only for the early diagnosis of COVID-19 pneumonia but also for controlling disease progression and the efficacy of treatment. Common CT features of COVID-19 are ground-glass opacities and consolidation (with or without vascular enlargement), interlobular septal thickening, crazy-paving pattern, and air bronchogram signs [33]. Lesions present on CT images have a peripheral distribution and bilateral...
involvement; they are lower lung predominant and multifocal [34]. The ventral area of the lung is frequently spared, which is why lying face down is favourable for these patients.

CT can also help identify patients in need of emergency care. Architectural distortion, traction bronchiectasis, pleural effusions, and diffuse legions are proportional to the viral load and virulence of COVID-19 and have a higher incidence in emergency patients [34].

CT-revealed abnormalities of COVID-19 pneumonia and the presence of clinical symptoms were evaluated by Wu and his colleagues. They found that COVID-19 clinical symptoms are milder while pulmonary changes revealed by CT are more severe than in other types of pneumonia [35].

Currently, the radiological strategy remains undefined. CT scanning should be reserved for patients with an undefined clinical picture, as well as for some types of differential diagnosis.

Laboratory examinations. Typical laboratory abnormalities are leukocytopenia, lymphocytopenia, increase of C-reactive protein, and lactic dehydrogenase [31]. Serum level of pro-inflammatory cytokines, serum ferritin, and D-Dimer are also characteristic findings [36]. An elevated troponin level may predict fulminant myocarditis. Troponin appears to be a strong prognostic indicator of mortality [37, 38], as well as an elevated plasminogen level and thrombocytopenia [39].

Treatment

Patients with mild COVID-19 symptoms recover on their own, but for others, there are no approved therapeutics or vaccines. There are drugs with a broad antiviral effect, however, that were registered originally for other diseases that appear to be effective against SARS-CoV-2 and are being used off-label. Hydroxychloroquine and chloroquine are effective in vivo against COVID-19. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) may also have some prophylactic effect. There are some promising results with passive immunization with sera of recovered COVID-19 patients. The mainstream treatment is supportive therapy. There are ongoing trials for several COVID-19 treatments. A great number of new compounds are being tested, and some registered drugs are being considered as candidates for repurposing [40]. There are two main classes of drugs: compounds that directly inhibit the replication cycle of the virus, and those that boost innate antiviral immune responses or diminish the cytokine storm induced by the infection [40]. Development of a vaccine capable of active immunization is also under way, but testing for safety and efficacy is a long process.

In the current circumstances, prevention is extremely important. Governments have to fine-tune between restrictive measures and maintaining the economy and ensuring that people have a viable life. The main goal is to keep the number of patients at a manageable level.

Preventive measures

The most important rules to prevent being infected are keeping a social distance of 1.5–2 m, wearing a mask which can screen small particles, and frequent hand washing or disinfection. Using soap is appropriate, as it can remove the lipid-soluble virus. Shaking hands and hugging should be avoided. The elderly and those with chronic diseases should be more careful. They should stay home and ask for help in managing their shopping and business affairs. For healthcare workers, it is compulsory to wear protective clothing during patient care and to submit to frequent screening for SARS-CoV-2 infection. Screening is also important for patients who are admitted to a hospital. The patient should be separated until the result is known. If it is positive, a 14-day quarantine is required. It can be a home quarantine or in the hospital if required by the home circumstances or the symptoms.

Antiviral drugs. The antiviral produgs favipiravir, geldorfir, ribavirin, and remdesivir are nucleoside analogues. Remdesivir was tested against Ebola and Marburg virus infections without success, but it is a promising therapy for COVID-19. As its structure resembles adenosine, it inhibits viral RNA-dependent RNA polymerase by substituting itself for adenosine during RNA synthesis [41]. It is administered intravenously. The first successful remdesivir therapy in a COVID-19 patient was in January 2020 [42]. Since then, remdesivir has been administered on a compassionate use basis to severely ill patients requiring mechanical ventilation. It has significantly reduced mortality [43]. It should be remembered, however, that there are currently no antiviral drugs proven to be effective against COVID-19.

Hydroxychloroquine, chloroquine. The antiviral activity of chloroquine was already identified in the late 1960s [44]. Hydroxychloroquine and chloroquine have recently been reported to have antiviral efficacy against SARS-CoV-2 [45]. Phosphate and sulphate derivatives of chloroquine have been used for decades as an antimalarial agent, while hydroxychloroquine is an immunomodulatory agent widely used for several systemic autoimmune diseases such as systemic lupus erythematoses. The United States Food and Drug Administration (FDA) has provided emergency authorization for the use of chloroquine and hydroxychloroquine for COVID-19 patients [46]. These drugs are frequently combined with the macrolide antibiotic, azithromycin. Being a weak base, hydroxychloroquine accumulates in the acid environment of endolysosomes and other acidic cell organelles and interferes with virus binding [47]. Hydroxychloroquine also has antithrombotic effects, which may favourably interfere with the activated coagulation and microthrombus formation in COVID-19 disease [48]. Chloroquine and hydroxychloroquine have a narrow therapeutic range, meaning that the window between therapeutic and toxic doses is narrow. They, therefore, may easily cause serious toxicity, resulting in a conduction defect (a prolongation of the QTc interval, which may lead to torsade de points, a polymorphic ventricular tachyarrhythmia), ventricular arrhythmias, cardiomyopathy, and retinopathy such as bull’s eye phenomenon, which causes irreversible damage of the macular tissue, visual
deterioration, and severe dyschromatopsia [49]. Because of the high frequency of ventricular arrhythmias, the ECG of patients treated with chloroquine and hydroxychloroquine should be monitored. A synergistic effect of azithromycin and hydroxychloroquine has also been suggested [50]. The real efficacy of hydroxychloroquine has not been established yet, as the largest study to date found no benefit, and increased mortality risk [51].

Role of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). ACEI and ARB are anti-hypertensive drugs given to patients with heart failure and coronary heart disease. For patients with type 2 diabetes mellitus with these indications, they are the drugs of choice. Though at first ACEI and ARB were thought to worsen COVID-19, it has been revealed that they have a beneficial effect [52] by inducing ACE2 receptor blockade and disabling viral entry into the heart and lungs, thereby causing an overall decrease of inflammation. Despite the contradictory hypotheses, cardiology associations strongly advised [61]. Because of the high frequency of ventricular arrhythmias, the ECG of patients treated with chloroquine and hydroxychloroquine should be monitored. A synergistic effect of azithromycin and hydroxychloroquine has also been suggested [50]. The real efficacy of hydroxychloroquine has not been established yet, as the largest study to date found no benefit, and increased mortality risk [51].

Passive immunization. The humoral immune response mediated by antibodies is crucial for preventing viral infections. In active immunization, specific antibodies are generated against viral antigens by B-lymphocytes. Binding of these antibodies to the pathogen antigens antagonizes their interaction with a cell receptor, and they are therefore called neutralizing antibodies. Since vaccines for active immunization have not yet been developed COVID-19 patients may benefit from passive immunization. The plasma of patients who have recovered from COVID-19 contains IgM and IgG immunoglobulins generated against SARS-CoV-2 antigens. These antibodies can be collected as convalescent plasma and transferred by an intravenous injection to a COVID-19 patient, where they can neutralize the pathogen, boost the immunity, and help the patient fight off the disease [54].

Development of a vaccine. Several pharmaceutical companies are developing vaccines, but it is estimated that it will take months to years before they are available for sale. Phase I and II clinical trials are underway with an inactivated vaccine generated from a patient-derived SARS-CoV-2 isolate. The efficacy of the vaccine has been proven on non-human primates. Rhesus macaques were immunized with the vaccine plus alum, then challenged with a virus from a different isolate. Vaccinated macaques had no symptoms and a rapid decrease in viral loads. Yet, there is a long way to find an adequate dose and to prove the vaccine’s safety [55].

Inhibition of inflammation. COVID-19 pneumonia is characterized in a subset of patients by a severe systemic inflammation reaction, called a cytokine storm. An elevated serum level of IL-6 and ferritin is considered a predictor for COVID-19-related mortality, suggesting that hyper inflammation increases the risk of mortality (2). Drugs with an immunomodulatory property may mitigate the virus-induced cytokine storm and limit lung damage in patients with severe disease [58].

Several questions arise concerning the application of anti-inflammatory drugs: when to give them, to whom, and for how long? Which one is the best choice? A drug with a very selective action or a wider one? Some of these drugs, e.g., Janus kinase (JAK) inhibitors, also block interferon-α production, which is important in fighting the virus. Would they do more harm than good? Further studies are needed to answer these questions.

Tocilizumab is a humanized interleukin-6 receptor antagonist that was approved to treat patients with rheumatoid arthritis. Decrease of body temperature and a decrease of oxygen demand were detected in those severe or critical COVID-19 patients who received tocilizumab in a non-randomized Chinese trial [59].

Baricitinib, a JAK inhibitor as well as an AAK1 (AP2-associated protein kinase 1) inhibitor, is also a potential candidate for COVID-19 therapy, considering its relative safety and high affinity. However, it might be a problem that JAK inhibitors can inhibit a variety of inflammatory cytokines, including INF-α, which have a beneficial role in controlling virus activity.

Baricitinib is more effective when used in combination with anti-viral drugs like Remdesivir [60].

Supportive therapy. The mainstay of COVID-19 management is supportive care consisting of symptomatic therapy (antipyretics, antibiotics, parenteral feeding, and fluid replacement) and respiratory support.

Oxygen therapy should be given to patients with hypoxemia. If standard oxygen therapy fails, mechanical ventilation should be applied; high flow nasal catheter oxygen or the bi-level positive airway pressure mode can be used. If there is no improvement, invasive mechanical ventilation should be applied (31). For patients with refractory hypoxemia, extracorporeal membrane oxygenation (ECMO) is advised [61].

Patients with cardiovascular diseases are prone to having more serious COVID-19 symptoms. Supportive treatment of these patients may include anticoagulation, a continuation of renin-angiotensin-aldosterone system inhibitor treatment,
arrhythmia monitoring, and mechanical circulatory support [61].

In the case of concurrent bacterial pneumonia, the application of an antibiotic is recommended. However, the routine use of antibiotics is not advised.

Ophthalmological aspects

As it is known the Coronavirus-19 travels and infects through droplets in the air, sneezing, coughing, or speaking might be the route of infection. It is strongly suspected that the virus can also be transmitted through the eyes. The danger of being infected through the eyes is relatively low compared to breathing the droplets, but eye protection with special plastic goggles is important against infection.

Ophthalmology had an early relevance in December 2019, when ophthalmologist Li Weinlang discovered and reported to his previous classmates the new disease in Wuhan. He found special symptoms among his glaucoma and cataract patients: fatigue, coughing, sneezing, and pneumonia. Later he also got the COVID-19 infection and died in the Intensive Care Unit of Wuhan (Coronavirus kills Chinese whistle blower ophthalmologist BBC, CNN 10th Feb/2020). Later, he became a national hero in China.

In 2003, when the SARS outbreak first happened, it was presumed that the virus entered the body through ACE2 receptors. They are widely found in the body, in the heart, kidney, intestines, and lungs. They can also be found in the retina and in mucous membranes like the conjunctiva. The virus presumably mimics the shape of ACE2 enzyme, so the affected cells allow the virus to enter. Once the virus is in the cell, it replicates until the cell membrane ruptures. In the eye, the virus may cause conjunctivitis, chemosis, and epiphora (tearing). Since COVID-19 positive patients may show ophthalmic symptoms, some precautions are recommended: switching from contact lenses to spectacles to prevent direct contact with the eye, not rubbing the eyes, wearing glasses or sunglasses, washing hands frequently, not touching the face, not shaking hands, wearing a mask in public, and keeping social distance. Although eye symptoms vary between serious COVID-19 patients, the virus can be isolated from the tear; therefore, eye protection is of utmost importance especially for personnel taking care of ophthalmic patients.

Hungarian aspects

In Hungary, the epidemic was successfully curbed owing to the quick and early governmental interventions. At the time this manuscript was submitted, there had been 3713 COVID-19 cases, including 482 deaths and 1,576 patients with the active disease reported. According to a representative survey conducted by the four Hungarian medical universities, with the leadership of the Semmelweis University, the frequency of SARS-CoV-2 positivity among the Hungarian population was 0.02%, and the IgG positivity varied between 0.6 and 0.8%. Passive immunization with sera of convalescent patients was successfully carried out on three severely ill patients. Development of a vaccine has also been started at the University of Debrecen Medical and Health Science Center. It is hoped that small-scale manufacturing will begin in October. Now, as the epidemic is supposed to be in a declining phase, there is a cautious release of restrictive measures throughout the country, but the possible beginning of a second phase of the epidemic is carefully watched for.

Recommendation

We would like to end this review by quoting the opening remarks of the WHO Director-General at the meeting on 11th of March when he announced COVID-19 to be a pandemic:

“This is not just a public health crisis. It is a crisis that will touch every sector – so every sector and every individual must be involved in the fight. ...strategy to prevent infections, save lives, and minimize impact. ...Let me give you some other words that matter much more, and that are much more actionable. Prevention. Preparedness. Public health. Political leadership. And most of all, people. We’re in this together, to do the right things with calm and protect the citizens of the world. It’s doable” [1].

We agree the world will overcome the crisis.

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