



Review Article

The Clinical and Treatment Challenges Posed by COVID-19

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ABSTRACT

Medical profession was unprepared to face the corona virus pandemic and the pharmaceutical armamentarium is currently not robust enough to combat with SARS-CoV-2. Drugs that are used for other medical conditions are also on trial to treat COVID-19. The pandemic is bound to pose psychological and economical sufferings. Testing, treatments and vaccine are the three tools to combat with COVID-19. It is feared that this viral infection would lead to an amplification of existing mental health issues and result in a surge of cases of PTSD and depression. Senior citizens and people with compromised immunity becomes more vulnerable to this toxic pathogen. A sound knowledge of all aspects of COVID-19 becomes essential to deal with the aftermaths of this unprecedented pandemic and mental health professionals will have to refresh their knowledge of virology and immunology. All the medical specialities will have to work together to defeat the novel virus.

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Introduction

The novel Coronavirus disease is now dubbed COVID-19. SARS-CoV-2 is the virus that causes the disease COVID-19, like HIV is the virus and AIDS is the disease. This respiratory infection has been unidentified in humans before and is supposed to have originated in a seafood wholesale market in the city of Wuhan, China [1]. COVID-19 triggered the largest public health emergency the world had ever witnessed, and it has traversed entire continents. The COVID-19 outbreak has been declared a pandemic on 11th March 2020 by the World Health Organization. Since the SARS outbreak in 2003, there have been several other outbreaks of infections. MERS, H1N1 Chikungunya, Zika and Ebola outbreaks were brought under control because of better global coordinating response. While most coronavirus strains only cause mild flu-like symptoms during infection, a few others such as Severe Acute Respiratory Syndrome (SARS) can morph into a pandemic.

Under a microscope, the coronavirus appears to be spherically shaped with numerous spikes covering its surface. Those spikes are surface proteins and the spikes aid them to invade the host cells. Coronaviruses belong to a large family of viruses that can infect nose, sinuses, and

upper respiratory tract. SARS-CoV-2 belongs to the Sarbecovirus subgenus of the Coronaviridae family and the virus is like SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV [2]. They are classified as zoonotic, meaning they are transmitted between animals and humans. Pangolins have been indicated as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses [3]. It is not yet known exactly what caused coronavirus to develop, but viruses mutate all the time. Viruses invade a cell and take over its molecular machinery, causing it to make new progenies through mutation. Morens D.M., *et al.* recognise alarming similarities between the influenza epidemic of 1918 and the COVID-19 [4].

They notice that the flu epidemic started as slow with mostly mild cases and then it suddenly exploded in urban centres almost everywhere at once, making a dramatic entrance after a long, stealthy approach; we are in a similar initial stage with COVID-19. But vaccine technology was not as advanced in the early part of the 20th century as it is now. The virus is impervious to heat and cold, but it is questionable whether ultraviolet rays of sunlight could subdue the virus. As of the end of June

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2020, the virus has killed at least 454,000 people and infected more than 8.5 million since the outbreak began in China late 2019.

Clinical Presentation

Initial symptoms of COVID-19 infection are persistent dry cough, sore throat, fever which may progress to breathlessness and pneumonia, fatigue, headache, aches and pains. Some sufferers experience olfactory and gustatory dysfunctions. Anosmia and loss of taste (ageusia) were considered as unusual symptoms of COVID-19, but recent studies suggest that they are not as uncommon as they were thought to be. A Tehran study showed that anosmia as an isolated symptom without any other clinical symptoms can also occur. The coronavirus is thought to infect olfactory nerve endings. A small number of patients have experienced confusion, low blood oxygen levels and even loss of consciousness suggesting that the virus may be having access to the central nervous system through their olfactory nerve endings right away. Conjunctivitis has also been reported in isolated cases. The fact that the virus has been found in the mucus membrane that covers the eye in a small number of patients may imply that the eye could serve as an entry for the virus. This would justify the practice of using face shields and goggles for protection.

In a recent study, Colavita *et al.* observed that ocular fluids from SARS-CoV-2-infected patients may contain infectious virus and hence may be a potential source of the pathogen [5]. Obviously, ocular mucosa may be a site of virus entrance and a source of contagion. Such a finding highlights the importance of control measures to prevent self-delivery of the virus by touching the nose, mouth, and eyes by frequent hand washing. It also alerts the ophthalmologists to use appropriate personal protective equipment during clinical examination. The virus also is having a clear impact on the gastrointestinal tract, causing diarrhoea, vomiting and other symptoms. The respiratory symptoms have been overemphasised while ignoring the nonclassical symptoms [6]. Reports also indicate that the virus can cause acute viral hepatitis.

Studies also demonstrate that the virus can cause venous thrombosis leading to pulmonary embolism [7]. Different types of dermatological lesions have been revealed in a Spanish study. Such non-classical symptoms that make this infection more than a respiratory disease were missed in earlier studies. There is growing evidence that the virus causes a far greater array of symptoms than was previously understood and its effects can be agonisingly prolonged. Like the psychological symptoms of Flu virus resulting due its antibodies, COVID-19 sufferers have complained of mood symptoms indicating antibody production. The mortality of critically ill patients with SARS-CoV-2 pneumonia is considerable. The survival time of the non-survivors is likely to be within 1-2 weeks after ICU admission and older patients (>65 years) with comorbidities and acute respiratory distress syndrome are at increased risk of death [8]. According to WHO statistics, about 14% of COVID-19 patients will develop symptoms severe enough to need oxygen and 5% will need ventilator support. The recovery process for patients who have been on a ventilator is the most difficult.

In the US, older patients (aged above 65 years) accounted for 31% of all cases, 45% of hospitalisations, 53% of intensive care unit admissions and 80% of deaths, with the highest incidence of severe outcomes in

patients aged above 85 years [9]. The symptoms are reported to linger on for many weeks in some patients. This may be the case with patients who had only mild initial symptoms. The overwhelming consensus appears to be that, as the virus is new, we do not yet know what its trajectory will be. In the nutshell, COVID-19 is more than a common cold [10].

Transmission

SARS-CoV-2 spreads through respiratory droplets produced when an infected person coughs, sneezes, speaks or exhales droplets. Like other respiratory viruses, it is mainly transmitted through inhalation. Tiny droplets of the virus released in the air when an infected person sneezes or coughs can survive in the air for some time which is normally attracted to the ground through gravitational pull of the earth. The virus enters the body when someone breaths through the mouth or nose. Transmission through the eyes, nose, or mouth when contaminated hands contact the face is also possible. Thus, droplets from the already infected patients can be picked up from objects or surfaces, when people touch their eyes, nose, or mouth or if the droplets are breathed in. Transmission occurring through contact with contaminated surfaces followed by such self-delivery is much commoner route of transmission. The contribution of small respirable particles, sometimes called aerosols or droplet nuclei, to close proximity transmission is presently ambiguous. However, airborne transmission from person-to-person over long distances is unlikely. WHO has established that there have been no reports of airborne transmission [11].

There is also evidence that the virus may be transmitted in faeces [12]. The suspected patients with COVID-19 with GI symptoms, such as nausea, vomiting and diarrhoea, should be seriously considered, since accumulated evidence supports SARS-CoV-2 transmission through faeces and tears [13]. Its ability to bind to ACE2 (angiotensin-converting enzyme 2) of the GI tract has been identified [14, 15]. SARS CoV-2, colonise the upper nasal tract, often blocking out the olfactory sense, before moving down into the pharyngeal region. The cells of the nasal tract are rich in ACE2. They enable the “spike proteins” on the surface of the virus to latch on and replicate at pace. At this point patients are highly infectious but may not yet be suffering any symptoms. In any profound way, the virus does not appear to be airborne. Closed environment like households carry a higher risk of transmission rather than outdoor environment. The inhaled virus-ridden particles may come in contact with the cells lining the pharynx and larynx.

These cells have large numbers of ACE-2 receptors on their surfaces. These receptor proteins are also found in some major organs in the body such as the heart, lungs, and kidney. The viral spike proteins bind to the receptors to form complexes. They use these receptors to gain entrance into the bodily cells. In the next stage, proteolysis of the virus-receptor complex by the protease TMPRSS2 takes place. The viral spike protein is split in two by the protease. As a result, the virus invades and releases its RNA into the host cell after fusing with it. RNA replication occurs in the virus. The infection can spread to other areas when these viruses burst out of the destroyed cells. Since the cells of the lungs contain large numbers of ACE-2 receptors, severe symptoms may occur if the infection reaches the lungs and they get infected. Congestion of the lungs results as more and more cells get destroyed. Inflammation results in some cases, where the immune system, by overreacting, causes the lungs

to become flooded with cells in order to attack the virus. This process can run out of control leading to cytokine storm with potentially fatal consequences.

According to WHO, the preliminary reproduction number of SARS CoV-2 estimate is 1.4 to 2.5. That meant every person infected could infect between 1.4 to 2.5 others. MRC Centre researches show that each person may infect 2.6 others [16]. Nosocomial transmission in healthcare workers and patients has been reported in one study in Wuhan [17]. In this single-centre case series of 138 hospitalised patients with confirmed coronavirus-infected pneumonia in Wuhan, presumed hospital-related transmission of COVID-19 was suspected in 41% of patients, 26% of patients received ICU care and mortality was 4.3%. Pervasive spread has been registered in long-term care facilities and on cruise ships [18, 19]. Because of closed environment and contact between international travellers, cruise ship journey has been found to carry a higher risk of contagion of COVID-19 [20].

The reports coming from China suggest that asymptomatic cases are much larger in number than originally thought and even four fifths of cases are asymptomatic [21]. This finding is in par with a large-scale Stanford university study revealing that the asymptomatic silent cases of COVID-19 are many times higher than previously thought, making the infection less deadly on a percentage level and opening the possibility of a quicker herd immunity if it imparts immunity. In that case, this virus has been circulating widely prior to the outbreak in Wuhan, but the “genie came out of the bottle” in December 2019. The infectivity during the incubation period makes it challenging to control the spread of this viral condition [22]. Different people react differently to the invasion of this virus. There have been unconfirmed reports that the virus may spread before symptoms manifest and such cases have been reported in China and Singapore [23-26].

Pathogenesis

COVID-19-infected patients show the following: respiratory abnormalities, higher numbers of white blood cells, and increased levels of pro-inflammatory cytokines in the plasma [27]. Severe pneumonia, RNAemia, the incidence of ground-glass opacities as well as acute cardiac injury constitute the main pathogenesis of COVID-19 infection [28]. COVID-19 patients were found to have high levels of chemokines and cytokines in the blood in considerable amounts including IL1- β , IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFN γ , IP10, MCP1, MIP1 α , MIP1 β , PDGFB, TNF α and VEGFA. Also, increased levels of pro-inflammatory cytokines like IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1 α and TNF α that increase the severity of disease were observed in some cases that were admitted to the ICU [28]. The pathogenesis of COVID-19 occurs in different domains as follows:

I Respiratory System

The fight against COVID-19 infection, for most people that are afflicted, takes place in the lungs. Cough and fever are developed immediately the infection reaches and irritates the respiratory airways. The pulmonary cells that produce surfactant, mucous as well as the cilia covered cells are invaded by the coronavirus a few days after infection. Cilia are utilised by the lungs for mucus dispersal and cleaning. Surfactant, a fluid

that lubricates the lungs, is produced by specialised cells in the lungs called pneumocytes. It facilitates the oxygenation of blood in the lungs. COVID-19, after entering the lungs by binding to ACE2 receptors, disables the type-2-pneumocytes that produce surfactant thereby making the lungs more vulnerable. Pneumonia and shortness of breath are common in many COVID patients when the virus finds its way deep inside the lungs.

Cytokine storm results from an overreaction of the immune system when the virus gets to the lower parts of the lungs. These result in worsening of pneumonia. When lung dysfunction persists or increases, respiratory failure may occur, resulting in the death of some patients. The pulmonary system of survivors may be damaged permanently by an overreaction of the immune system [29]. The presence of holes or lesions (ground-glass opacity) in the lungs of some patients was reported in Wuhan. The viral infection can make the lungs traumatised, rigid, and unable to provide adequate oxygen for breathing, and the patient may then need a ventilator for breathing.

II Cardiovascular

The cells lining the inner surface of blood vessels have ACE receptors. The heart and circulatory system can also be affected by COVID-19. Some patients have been reported to have developed ischaemia and hypotension. In a cytokine storm, the whole circulatory or vascular system suffers. People with a pre-existing cardiovascular condition are at higher risk of developing severe complications. COVID-19 can also cause renal damage (Link) and renal pathogenesis requires further clarification. Clinicians are noticing evidence that suggests the virus also may be causing heart inflammation, acute renal disease, neurological malfunction, blood clots, intestinal damage, and hepatic problems. Small scale studies and case studies are emerging about the incidence of blood clots in asymptomatic patients and it is unclear whether the virus or the immune response that causes these damages. A female health worker reported that her menstrual fluid was full of blood clots and she had only mild symptoms. She proved to be positive for the viral test. Coronavirus destroys lungs, but recent findings suggest that it damages kidneys, hearts and elsewhere. COVID-19 can affect the heart and vascular system directly or indirectly [29]. Some patients develop hypotension, irregular heart rhythm or ischaemia.

In a cytokine storm, the entire vascular system suffers. SARS CoV2 also may be damaging the heart resulting in myocarditis and arrhythmias. This happens to even patients who are doing well with respiratory problems and seems to be out of proportion to their pulmonary status as though it is again a direct effect of the virus. Those who have a premonitory cardiovascular condition are at higher risk of developing severe complications. Autopsies have also shown inflammatory changes in the heart with fine interstitial mononuclear inflammatory infiltrates, but no viral inclusions in the heart. Cytokine storm alone fails to explain the prevalence of these effects. Other potential mechanisms for the cardiac damage are hypoxia-induced myocardial injury, cardiac microvascular damage, and systemic inflammatory response syndrome. Because of massive cardiovascular involvements, there are suggestions to consider COVID-19 as a cardiovascular disease rather than a respiratory disease. The pathological features of COVID-19 are found to be like those seen

in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection [29, 30].

III Renal Pathology

Almost half the people hospitalized because of COVID-19 have blood or protein in their urine, indicating early damage to their kidneys. The huge number of such patients suggest the possibility that the virus attaches to the renal cells and invade them. With the pandemic still raging, we have to admit that these speculations are done with much less data than is normally needed to reach solid clinical conclusions. At least a part of the acute renal damage must be due to direct viral involvement of the kidney, which is distinct from what was seen in the SARS outbreak in 2002. According to US data, having advanced kidney disease was by far the biggest risk factor. People whose kidneys have stopped working to the point where they cannot live without dialysis or a transplant had a hospitalization rate of 1,341 per 100,000. This study may reflect the fact that people with advanced kidney disease generally also suffer from other medical problems that worsen COVID-19 outcomes, such as diabetes. The renal pathogenesis requires further clarification.

IV Gastrointestinal

The novel virus enters the cells of people who are infected by latching onto the ACE2 receptor on cell surfaces. It unquestionably attacks the cells in the respiratory tract, but there is increasing suspicion that it is using the same doorway to enter other cells. The gastrointestinal tract, for instance, contains 100 times more of these receptors than other parts of the body, and its surface area is enormous. It is arguable that such a scenario puts the G.I. system under risk and in isolated cases G.I. symptoms herald the onset of COVID-19. The invasion of this pathogen is more expansive than originally estimated. The liver biopsy specimens of the patient with COVID-19 presented moderate micro-vesicular steatosis and mild lobular and portal activity, indicating the injury could have been caused by SARS-CoV-2 infection [31].

Table 1: COVID Pathogenesis.

<p>Lungs: Clogs and inflames alveoli (air sacs), hampering breathing; pulmonary embolism from breakaway blood clots and micro-clots.</p> <p>Hypercoagulation state:</p> <p>Heart: Weakens heart muscle; causes dangerous arrhythmias and heart attacks due to small clots, myocarditis.</p> <p>Kidneys: Damage to the renal structures that filter metabolic waste from blood; patients often require dialysis.</p> <p>Brain: Strokes from blood clots, neurological issues, encephalitis, Gillian barre syndrome.</p> <p>Eyes: Pinkeye.</p> <p>Nose: Anosmia and gustatory dysfunctions.</p> <p>Haematology: Unexpected blood clotting; attacks the lining of blood vessels.</p> <p>Gastrointestinal system: Vomiting and diarrhoea in some people.</p> <p>Dermatology: "Covid toes," or fingers, a purple rash from the attack on blood vessels.</p> <p>Immune system: Cytokine storm- overactive immune response that attacks healthy tissue.</p> <p>Reproductive system: Effects are unclear and uncertain.</p>
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Prevention

Physical distancing is the key factor in blocking person to person transmissions of SARS-CoV-2. Hand washing with soap and water, respiratory hygiene, and surface sanitation are also effective ways of keeping personal and safety of others. Recent experience with outbreaks in nursing homes (Link) indicate that residents with COVID-19 often do

V Nervous System

Once the virus enters the brain, further infection is almost inevitable: there are ACE2 membrane receptors on the surface of the brain cells, through which the virus easily penetrates the tissue, causing inflammation. Strokes, encephalitis, Guillain-Barré syndrome, confusion and disorientation are some of the neurological symptoms reported. Both ischaemic and haemorrhagic strokes have been reported in the COVID-19. In milder cases, encephalitis can cause flu-like symptoms; in more severe cases, it might bring seizures, paralysis, and confusion. It is not clear whether the encephalitis encountered in COVID-19 is due to a direct invasion of the virus into the nervous system or the destruction is due to the overactivity of the immune system, akin to a cytokine storm. Again, the mechanisms of, Guillain-Barré appears to be associated with the normally protective antibodies of immune system, which are thought to occasionally go haywire as well, attacking the nerves and their coating.

'Covid toes,' or fingers, a purple rash from the attack on blood vessels have been reported. Eye symptoms have been reported in approximately one third of patients in Wuhan in a recent study. The ocular manifestations in the Wuhan patients included conjunctivitis, conjunctival hyperaemia, chemosis, epiphora and increased secretions. The long-term effects of SARS-Cov-2 infection on human fertility (male and female), pregnancy outcomes and the growth and development of their offspring are unclear, and more evidence have to be collected to evaluate the reproductive effects of corona diseases [32]. It is well recognised that when mumps develops in boys in adolescent age or an adult male, it sometimes causes testicular inflammation that can affect sperm production and lead to fertility problems. The truth is that we are not able to make a full assumption of the symptoms and pathogenesis of COVID-19 (Table 1). It appears that COVID-19 consists of more than one syndrome.

not inform staff of the typical symptoms such as fever or respiratory symptoms and some may not report any symptoms. Therefore, unrecognized asymptomatic and pre-symptomatic infections may easily spread in these healthcare settings. Source control, which involves having the infected person wear a cloth face covering or facemask to contain their respiratory secretions, might assist to lower the risk of

transmission of the virus from both symptomatic and asymptomatic patients.

Environmental cleaning and disinfection procedures should be followed consistently and correctly. SARS CoV-2 has an incubation period of 2-14 days and can live on hard surfaces up to 72hrs. An analysis of 22 studies reveals that human coronaviruses such as Severe Acute Respiratory Syndrome (SARS) coronavirus, Middle East Respiratory Syndrome (MERS) and coronavirus or endemic human coronaviruses (HCoV) can stay on inanimate surfaces like metal, glass or plastic for up to 9 days [33]. They can be professionally disarmed by surface disinfection measures with 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute [33].

Early containment and prevention of further spread will be vital to halt the ongoing infectious thread. From the evidence so far, the SARS-CoV-2 can be transmitted in all regions of the world, including areas with hot and humid weather. The best way to protect against COVID-19 is by frequently cleaning the hands. By doing this we may eliminate viruses that may be on our hands and avoid infection that could occur by then touching eyes, mouth, and nose. In addition to personal protective measures, testing, tracking and tracing and lockdown measures have been effective to flatten the COVID-19 curve. At this juncture, it is interesting to remember that it was the Hungarian born, Dr Ignaz Semmelweis who introduced hand washing in clinical practice in the 19th century. The southern Indian state of Kerala has been phenomenally successful to achieve flattening the coronavirus curve, setting up an example to the rest of the world [34].

Pediatric Cases

Children who get infected with SARS-CoV-2 are often asymptomatic or present with mild symptoms [35-37]. However, moderate to severe illness has also been related in children [38]. Polypnoea has been described in children with severe illness [39]. When compared to adults, COVID-19 infection in children is reported much less commonly. A systematic review found that children account for only 1-5% of confirmed cases and that would depend on the country where they live [40]. In China, where the coronavirus outbreak began, children made up just 2.4% of reported cases of COVID-19 according to a WHO-China Joint Mission report published in February 2020. So also, COVID-19 affects children more mildly.

Most often, children present with mild symptoms except for children with underlying health problems who may be more severely affected by this infection and each case will have to be reviewed on its own merits. Nevertheless, children can still catch it and transmit it, even if they have no symptoms [41]. There are also indications that the current situation of low number of pediatric cases could change. There are different speculations about the low incidence of COVID-19 among children. One hypothesis is that a child's immune system is still in the developing stage and is thus shielded from an overzealous response that would result in cytokine release syndrome. During the SARS outbreak, two studies found that children produced relatively low levels of cytokines, which may have been what protected their lungs from serious damage. The developed immune system of adults turns out to be a liability, rather than

an asset. The immune system of children also differs from that of adults in another respect.

The adult immune system may already contain antibodies to previous coronaviruses, such as the influenza and cold viruses, but they may be unable to defeat the SARS-CoV-2 virus. The theory is that their unmatched antibodies combined with the newly produced antibodies are doing more harm than good in the sense that the two sets of antibodies fail to recognise the host's own cells. Children are spared from this confused antibody problem. Though the SARS-CoV-2 virus attaches to the receptor in order to penetrate cells, ACE2 also helps regulate blood pressure and inflammation. Another view is that children may be less susceptible to infection with COVID-19 because they have fewer of these receptors.

Immune responses are activated by hyperthermia, febrile reaction to infection is a beneficiary outcome of immune response. A child's body is more metabolically active, which generates heat. The higher temperature among children is thought to be a protective factor from COVID-19, as immunity cells are more active in higher temperatures. There may be additional unknown mitigating factors for this variance. These conjectures are only straws in the wind. The lower number of reported incidences of COVID-19 among children remains a mystery and might provide some clues regarding immune responses, along with the spread and prevention of this infection. However, the SARS-CoV-2 epidemic has been linked with high incidence of a severe form of Kawasaki disease underaged adults in Bergamo among, an epicentre of COVID-19. It is a genetically allied aberrant immune response and could be precipitated by SARS-CoV-2. A similar outbreak of Kawasaki like disease is expected in countries involved in the SARS-CoV-2 epidemic.

Drug Trials

Early diagnosis and effective treatment can halt the spread of the COVID-19 infection. There is no established treatment for the coronavirus, but antiviral drugs and immunomodulators are on trial. New types of antiviral drugs and immunotherapy treatments could be used as off-label medicines to defeat this infection. Such practices are not uncommon in medicine. Drugs already used in clinical practice could be useful in combating COVID-19. There are currently no specific antiviral drugs targeting COVID-19. Broad-spectrum antiviral drugs (i.e., nucleoside analogues) and HIV protease inhibitors are an available option to weaken this viral infection. The course of treatment includes twice a day oral administration of 75mg of oseltamivir, 500mg of lopinavir and 500mg of ritonavir and intravenous administration of 0.25g of ganciclovir for 3-14 days [42].

Remdesivir is a 'viral RNA polymerase inhibitor', which is a drug that interferes with the production of viral genetic material, thus preventing the virus from multiplying. It was originally developed for the treatment of Ebola virus disease and it has shown broad *in-vitro* activity against different RNA viruses, including SARS-CoV-2 [43]. These antiviral compounds have been used in human patients with a safe track record, so these therapeutic agents can be considered to treat COVID-19 infection [44]. Another report showed that antiviral remdesivir and chloroquine are highly effective in the control of COVID-19 *in vitro*.

According to the data of Sheahan study, the timing of antiviral initiation may be crucial, as administration of remdesivir with high viral loads seen after peaking viral tier failed to reduce lung damage despite reducing viral loads [45]. De Wit *et al.* scrutinised the efficacy of prophylactic and therapeutic remdesivir use in a rhesus macaque model of MERS-CoV [46]. Remdesivir prophylaxis initiated 24 hours before inoculation with MERS-CoV resulted significantly lower viral loads than control treatment in the lungs and prevented clinical infection in this model. Remdesivir therapy initiated 12 hours after inoculation significantly reduced MERS-CoV loads in other respiratory tissues, decreased lung disease and strongly attenuated clinical signs of infection compared with control treatment. Unfortunately, one of the recent hospitalised trials with remdesivir did not show promising results and this failed trial has prompted scientific investigators to caution against giving out drugs on compassionate grounds, even though they have been tested for other uses.

Other drugs in the pipeline include the clinical compound EIDD-2801, which has shown great therapeutic potential against seasonal; pandemic influenza virus infections and therefore represents another drug to be considered for potential treatment of the COVID-19 infection [47]. Broad-spectrum antivirals include lopinavir-ritonavir, neuraminidase inhibitors, peptides (EK1) and RNA synthesis inhibitors. Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamid), is an antiviral drug that selectively inhibited the RdRP of influenza virus. It showed specific activity against all three influenza A, B and C and is being tried for COVID-19. Research into specific antiviral agents against COVID-19 should also be considered as an option to combat this infection.

As mentioned earlier, cytokine release syndrome or cytokine storm, which is an important cause of death, occurs in many patients with severe COVID-19. High levels of a pro-inflammatory cytokine called interleukin-6 (IL-6) have been detected in some severely ill COVID-19 patients [48]. To treat cytokine release syndrome, anti-IL-6 drugs, such as tocilizumab, which is approved for cancer patients who develop this condition as a result of immunotherapy, are being tried. IL-6 plays an important role in cytokine release syndrome. As an IL-6 receptor blocker, tocilizumab has been included as an immunotherapeutic agent for severe and critical patients in the Novel Coronavirus Pneumonia Diagnosis and Treatment Protocol [49]. At present, there are several registered clinical trials of tocilizumab for the treatment of patients with COVID-19. Most trials have targeted severe patients and some trials included an increase of inflammatory factors, such as IL-6, CRP, or ferritin, as one of the inclusion criteria.

CD147, a receptor on host cells, is a novel route for SARS-CoV-2 invasion. Thus, drugs that interfere in the spike protein-CD147 interaction or CD147 expression may inhibit viral invasion and dissemination among other cells, including in progenitor/stem cells [50]. Azithromycin induces anti-viral responses in primary human bronchial epithelial infected with rhinovirus by decreasing viral replication and release. The effect of azithromycin in blocking the invasion of SARS-CoV-2 has not yet been evaluated, but clinical trials suggest a beneficial effect of azithromycin on the viral load of hospitalised patients. In addition to the possible effect of thwarting an invasion, it decreases the expression of some metalloproteinases.

It has been claimed that the antimalarial agent chloroquine has some prophylactic benefits against the coronavirus, and it has been positively tested on SARS patients with favourable effects [51]. But neither the World Health Organization nor the CDC have confirmed the guaranteed efficacy of chloroquine. Chloroquine modifies the immune response and this property is taken advantage of when treating rheumatoid arthritis. Hydroxychloroquine, a less-toxic version of chloroquine, is approved by the FDA for the treatment of malaria, lupus erythematosus and rheumatoid arthritis; U.S. President Trump mistakenly stated that the FDA approved use for COVID-19 as well, but this is not the case [52]. Prophylactic parenteral administration of chloroquine is reportedly on trial in India. Professor Jose de Leon opined that there are no published randomized clinical trials that demonstrate that chloroquine and hydroxychloroquine are effective for the prevention or treatment of COVID-19 [53]. In PubMed, only a French open trial can be found [54]. Another finding is that both drugs block the heart's potassium channels, which contributes to QTc prolongations and occasionally to Torsades de pointes (TdP), a potentially lethal arrhythmia [55].

The latest addition to the anti-COVID treatment regime is dexamethasone. Trial results showed dexamethasone, used since the 1960s to treat inflammatory conditions cut death rates by around a third among the most severely ill COVID-19 patients in the hospital care. Although the dexamethasone study's results are in the initial phase, for patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth. HIV medication is already used to treat viruses such as hepatitis B and researchers have begun exploring whether anti-retroviral drugs can also combat COVID-19. For now, however, evidence of their effectiveness remains largely anecdotal. Health professionals in India, Japan and Thailand have treated COVID-19 with a combination of HIV drugs and flu medicine. A study showed positive results for patients treated with lopinavir and ritonavir anti-retroviral drugs. Later studies found that these drugs, when used in combination, showed favourable clinical effects for patients suffering from SARS, an illness also caused by a coronavirus [56]. Unfortunately, there are also studies that disprove the benefits of HIV medication against COVID-19. Because there are no specific antiviral agents targeting the SARS-CoV-2, trying any alternative option is justifiable. There are even studies with IV-infusions of vitamin C, which is a relatively safe medicine to thwart the cytokine storm, but these studies require further evaluation [57].

It is high time to focus on developing more potent antiviral drugs. There are a few drugs proposed by Farag *et al.* for testing and they are the hypercholesterolemia drug Rosuvastatin, the anti-asthma drug Montelukast and the anti-histaminic Fexofenadine, among others. They suggest that these drugs do not confirm or indicate antiviral activity but can rather be used as a starting point for further in vitro and in vivo testing, either individually or in combination [58]. While immunosuppressant drugs invite this novel pathogen, it is worth considering nonclassical drugs in lower doses that could suppress the overreaction of the cytokines which turn out to be the Trojan horse in the battle against SARS-CoV-2.

Plasma Therapy

Plasma therapy involves extracting plasma from the blood of people who have recovered from the COVID-19 virus and giving it to those who are seriously ill. The idea behind convalescent plasma transfusion treatment is that antibodies generated in the body of patients who have had recovered from the COVID-19 will enhance the immune systems of those seriously affected by the disease and assist speed up their recovery. It is reserved for critically ill patients. This treatment has been tried with some success for Ebola, SARS and MERS [59-65]. Historically, convalescent serum transfusion has been tried since its introduction in 1890 by Emil von Behring in Germany and applied for the treatment of infections including mumps, measles, and polio etc. Trials of convalescent serum transfusion for COVID-19 is in the air as a desperate measure to treat COVID-19 and has been tried in different countries [66].

Plasma therapy is already in progress in China, France, Germany, UK and the U.S. Study centres claim that there has not been any shortage of donors. The donor of the plasma must have been previously diagnosed with positive lab test for COVID-19 and subsequently test negative and other respiratory viruses. They are also tested to exclude Hepatitis B virus, Hepatitis C virus, HIV and syphilis at the time of donation. The donors must be expected to be physically fit, with a high level of COVID-19 specific antibodies. Plasma treatment may not be a permanent solution, but an interim solution that is readily available, since many people who are recovering can serve as a valuable source of plasma with the necessary antibodies. There are unanswered questions, like whether COVID-19 ensures short-term or long-term immunity; it has not even been established whether it confers any form of immunity at all. Advances in the medical field will lead to fast-tracked medications and protocols to deal with COVID-19 and the stories of solitary deaths in hospitals are reminiscent of the AIDS era.

Conclusion

It seems that we all will have to brace up and face the COVID-19 virus at some point in the future and survive the assault of this unseen enemy. Tests, novel treatments, and vaccines are the three tools needed to combat COVID-19. Social distancing, handwashing, and other mitigation measures are important to keep the enemy at bay for a while and buy some time to prepare to challenge this viral invader through immunisation, if that proves to be possible and to discover novel treatment strategies. It is important to be psychologically and spiritually prepared to face the challenges with which we all must grapple. Physical distancing should not involve psychological isolation.

Mental health services run the risk of becoming a soft target in the event of economic crisis. So, they need to be highly proactive in these critical times. Clinicians need to support political decision-making to rapidly adapt priorities and pass the relevant information on to patients [67]. While the world economy is contracting, we are saving lives and mitigating sufferings. Medical professionals working in various capacities should stay abreast of the research being conducted in this field. They have the responsibility to educate the public and highlight the importance of adhering to government guidelines. Knowledge of the enemy can give an initial shock, but it liberates us from unhealthy fears and arms us to confidently deal with this crisis. Health professionals

must deliver the difficult message that this disease is dangerous and that everybody needs to abide by the physical distancing rules without creating unnecessary fear and panic.

Eventually, this will help to wind down public fear-levels about this epidemic. Policies ought to be modified as we accrue more knowledge about the virus. We should aim to postpone the enemy's attack, if possible, so the NHS will not be overburdened. People who are infected will receive better care if fewer people develop the illness at the same time. Health professionals should be cognizant of the fact that there could be return of the vicious tsunami of the contagion if we do not control the spread of the virus effectively and this is the time for action. In the absence of efficient and harmless immunisation, the focus should be on successful treatment strategies and curbing the spread of this disease. This is a time to look into novel chemotherapeutic agents and other effective treatment strategies and promote their trial and implementation. Conducting drug trials is a tremendous undertaking in these pandemic conditions and will require significant resources and commitment, and these obstacles can only be solved through international cooperation.

Human history has been marred by epidemics and pandemics, but the current pandemic unfolded much faster than any of the previous pandemics, and the world community was divided and unprepared to fight against this viral invader. This points towards the fragility of the current technological world union without a deeper alliance of some sort being formed. But an infectious disease outbreak anywhere is a risk everywhere and no one is safe until everybody is safe. Nobody can predict the destiny of this virus; it could become endemic in humans. Many viruses become less virulent over time in the process of 'attenuation'. Historically viruses eventually cause less serious illness with passage through humans, we assume through mutation. So, it could mutate in such a way it becomes virulent, more or less transmissible or it could disappear from the microscopic attention.

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Conflicts of Interest

None.

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