



AN ATTEMPT TO KNOW THE UNKNOWN : COVID-19

Medical Science

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ABSTRACT

COVID-19, an infectious disease caused by the SARS-CoV-2 virus, was declared a pandemic by the World Health Organisation (WHO) in March 2020. This disease affected entire world and various myths are circulating about its diagnosis, treatment and prevention. Although evidence on the pathophysiology of COVID-19 is rapidly growing, an understanding of the underlying pathological mechanisms which cause some patients to get seriously sick while others experience mild symptoms, remains unexplained. A better understanding of the pathological mechanisms of the clinical features of the disease will increase the efficacy of management strategies and subsequently prevent many fatal outcomes.

KEYWORDS

COVID-19, coronavirus, SARS-CoV-2, novel coronavirus

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and has rapidly spread around the globe, emerging as a significant health concern worldwide (1). The first cases of atypical pneumonia of unidentified aetiology were reported on December 31, 2019, from Wuhan, China. By January 7, 2020, a novel betacoronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV-2) was identified, while the disease has been named COVID-19 by WHO on February 11, 2020. COVID-19 has now been declared a pandemic, affected nearly every country, with over 4 million confirmed cases and >285,000 deaths till 13 May 2020 (Centre for Disease Control and Prevention, World Health Organization). In this review article we provide an update for on the recent developments about virology, diagnostics, clinical presentation, viral shedding, and treatment options for COVID-19 based on current literature.

Virology

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA betacoronavirus. The genomic characterization of SARS-CoV-2 suggested that this virus belongs to the subgenus Sarbecovirus, exhibited 79% and 50% identity to severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV), respectively (2).

SARS-CoV-2 shares most of its gene content with SARS-CoV, including the S glycoprotein, the RNA-dependent RNA polymerase (Nsp12) and two proteases papain-like protease (PLpro) and 3C86 like protease (3CLpro). There is also substantial antigenic cross-reactivity between SARS-CoV-2 and SARS-CoV (3). A recent study confirmed that the angiotensin-converting enzyme 2 (ACE2), expressed in the human respiratory tract epithelium, is the entry receptor for SARS-CoV-2 similar to SARS-CoV and has been shown to cause pneumonia in lab mice only expressing human ACE2 (4). Despite the obvious homology between SARS-CoV and SARS-CoV-2, and cross neutralization has been observed, significant structural differences in the S glycoprotein have been noted (5).

How it spreads

The Chief mode of transmission of novel SARS-CoV-2 virus infection is mainly by micro-droplets ejected during cough, sneeze or ordinary talk of an infected person (6, 7). The viral containing droplets can enter a host through the epithelial cells of the upper respiratory tract and conjunctiva (8). However, the virus containing aerosol may reside for hours in the air in insufficiently ventilated rooms and spaces. So, overcrowded waiting rooms endanger patients through the exposition to increased initial viral load (6).

The novel SARS-CoV-2 virus can survive on a variety of surfaces for a significant length of time, its infectivity from this source remains unclear (6). The most difficult epidemiological aspect in COVID-19 is a period that lasts for several days of presymptomatic replication and shedding of SARS-CoV-2 (9).

Pathogenesis

The novel SARS-CoV-2 enters cells through binding of the viral structural spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor by endosome formation. Viral entry is enabled through the promotion of S1 by hosts transmembrane protease serine 2 (TMPRSS2) and endosomal cysteine proteases cathepsin B and L (5). Expression of the ACE2 gene may differ between populations, thus explaining some geographical differences in COVID-19 severity (10). After gaining entry inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles (11-13).

The novel SARS-CoV-2 itself has a broad capacity to infect various human cell types and induce different pathogenic chains of events that correspond with a variety of clinical pictures of COVID-19 due to the vast representation of the above mentioned receptors in human tissues (14, 15). Viral replication begins in the ciliated epithelium of the nasal cavity with the highest expression of its receptors in the goblet/secretory cells and the highest virus yield found in nasal swabs (8). The next site of replication with critical pathogenic consequences is the lower respiratory tract and pneumocytes (16).

Clinical Presentation

The most common symptoms of COVID-19 at onset of illness are fever, cough, fatigue, and myalgia. In many studies only 50 % of patients are febrile at the time of admission (17).

The estimated mean incubation period is reported as 3-6 days (18). The duration from symptom onset to dyspnoea was 5-6 days. Acute respiratory distress syndrome (ARDS) may develop in initially relatively stable patients. The interval from symptom onset to the 122 development of ARDS is approximately 8-12 days (19). Gastrointestinal symptoms like anorexia, nausea, vomiting and diarrhoea are reported in nearly 40% patients in some study groups (20). COVID-19 has been associated with a hypercoagulable state with increased risk of venous thromboembolism (21). Various studies from Italy and other European countries emphasized the remarkably high incidence of pulmonary embolism and thrombosis in the most severe and fatal cases (22, 23).

The cutaneous manifestations of novel coronavirus are similar to those caused by other common viral infections and includes both urticarial and non urticarial exanthems and present in 20 % of patients (24) .

Neurological manifestations, including headache, dizziness, altered consciousness, ischaemic and haemorrhagic strokes have also been reported (25). Conjunctivitis is most common ocular manifestation in COVID 19 patients (26). **COVID-19 during Pregnancy**

SARS-CoV-2 infection during pregnancy is not associated with an increased risk of spontaneous abortion and spontaneous preterm birth. There is no evidence of vertical transmission of SARS-CoV-2 infection when the infection manifests during the third-trimester of pregnancy (27).

Why are elderly patients more at risk?

In immunocompetent subjects, antigen presenting cells present viral antigens to the lymphocytes to recognize and destroy the virus. Anti-viral specific T cells, mainly CD8+ cytotoxic T cells, eliminate the infected cells. B cells are induced by CD4+ T cells produce specific antibodies that stop the spread of viral particles in body fluids. These mechanisms are important for viral containment and clearance. Aging of the immune system has common features present in all subjects, such as reduced production of T cells due to thymic atrophy, increased number of memory lymphocytes at the periphery and increased levels of serum proinflammatory cytokines (28).

In older adults with immunosenescence, the exaggerated inflammation does not induce a sufficient response of the lymphocytes, and the infection spreads further. Persistent infection and inflammation are responsible for secondary bacterial infections and may progress to multiorgan failure and death .This is probably the case of frail elderly but also younger subjects with similar deficiencies (28,29).

Diagnosis

A suspect case is defined as one with fever, sore throat and cough who has history of travel to China or other areas of persistent local transmission or contact with patients with similar travel history or those with confirmed COVID-19 infection. However, cases may be asymptomatic or even without fever. A confirmed case is a suspect case with a positive molecular test (30).

It is essential to collect the proper respiratory tract specimen at the right time from the right anatomic site for a prompt and accurate molecular diagnosis of COVID-19. The preferred testing method is the real-time reverse transcription-polymerase chain reaction (real- time RT-PCR) test method (31,32). A nasopharyngeal swab (NP) rather than oropharyngeal (OP) swab is recommended for early diagnosis or screening because it provides higher diagnostic yields and is better tolerated by the patient and is safer for the operator. A NP swab can be combined with an OP swab to increase sensitivity (33).

On routine blood examination, leucocytes may be normal or low. There may be lymphopenia; a lymphocyte count <1000 has been associated with severe disease. The platelet count is usually normal or mildly low. The CRP and ESR are generally elevated. The liver enzymes, prothrombin time, creatinine, D-dimer, CPK and LDH may be elevated and high levels are associated with severe disease (30).

The chest X-ray (CXR) usually shows bilateral infiltrates but may be normal in early disease. The computed tomography (CT) of chest is more sensitive and specific than chest xray. CT imaging generally shows infiltrates, ground glass opacities and sub segmental consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. It is also used in suspected cases with negative molecular testing (34).

Therapeutic Options

Isolation remains the most effective measure for containment of COVID-19. No specific anti-viral medication or vaccine is currently available (35). Therefore, the treatment of COVID-19 includes symptomatic care and oxygen therapy. Several agents might be considered as a possible treatment based on the efficacy in SARS and MERS. There is a need to determine which of the antiviral agents that have already been synthesized and tested sufficiently effective to block the virus entry and/or stop or slow down its multiplication. A list of drugs have already been tested, including the combination of chloroquine or hydroxychloroquine with azithromycin, oseltamivir,

lopinavir/ritonavir, darunavir, favipiravir, remdesivir and ivermectin. Till now only chloroquine and remdesivir have gained recommendation as the first-line treatment against COVID-19 (36-41). Hydroxychloroquine and Chloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells (42,43). Both agents ,Chloroquine and hydroxychloroquine can cause rare and serious adverse effects including QTc prolongation, hypoglycemia, neuropsychiatric effects, and retinopathy (44). Baseline electrocardiography is recommended to look for prolonged QTc prior to and following initiation of these medications (45). In its active triphosphate nucleoside form, remdesivir binds to ribonucleic acid (RNA)-dependent RNA polymerase and acts as an RNA-chain terminator. Remdesivir is highly selective for viral structural components and have a few side effects on humans (46) . It has a long half-life that allows for once-daily dosing (47).

Prevention

Patients and the general public must cover coughs and sneezes to help prevent aerosol transmission. Frequent handwashing with soap and water is also required or frequent use of hand sanitizers can also be used. Immunocompromised individuals are advised to avoid public gatherings . Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care (48) . The WHO has advised against close contact with patients, farm animals, and wild animals (35). Healthcare personnel must use personal protective equipment such as N95 masks, FFP3 masks, gowns, eye protection, gloves, and gowns.

CONCLUSION

COVID-19 outbreak has dramatically exposed our weaknesses at every level- the individual, health system, scientific, and organizational levels. On the other hand it has given us a chance to unite globally to fight this pandemic and test how strong we are.

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