COVID-19 Infection: Structure, Clinical Manifestation, Complications and Management

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Abstract:
Coronavirus was first discovered during the year 1930 and since then, various coronaviruses like HKU1, MERS-CoV , NL63 and SARS-CoV-2 have been found to infect humans. The COVID-19 pandemic caused by SARS-CoV-2 is spreading at an alarming rate, thereby creating a health emergency around the world. SARS-CoV2 is reported to be originated from a wet animal market of Wuhan, China. Since then, the world is searching for effective ways to manage and treat the COVID-19 infection. The infections have already multiplied with several folds compared to the number of persons infected by Middle East Respiratory Syndrome Coronavirus and Severe Acute Respiratory Syndrome. In order to fill the gap of knowledge about this virus, several pieces of evidence are required to control it so more lives could be saved. The present review is based on the publicly available literature in order to explore the knowledge regarding epidemiology, virology, diagnosis, clinical features, pharmacological and therapeutic ways to treat the novel coronavirus. This can be helpful in offering novel insights and potential therapeutics for fighting this disease.

Keywords: COVID-19, respiratory, coronavirus.

Tob Regul Sci. ™ 2023 ;9(1): 6159-6171
DOI: doi.org/10.18001/TRS.9.1.430

Introduction:

The acute respiratory tract infection outbreak that originated in Wuhan, China, in late 2019 that spread throughout the globe is caused by a novel coronavirus. Past outbreaks were also caused by highly pathogenic coronaviruses, including the acute respiratory syndrome coronavirus (SARS-CoV) in 2002, and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 **(1).**

People of any age can catch COVID-19. But it most commonly affects middle-aged and older adults. The risk of developing dangerous symptoms increases with age, with those who are age 85 and older are at the highest risk of serious symptoms. In the U.S., about 81% of deaths from the disease have been in people aged 65 and older. Risks are even higher for older people when they have other health conditions **(2).**

The coronavirus genus is furtherly classified into alpha and beta. Alpha genus includes human coronavirus 229E (HCoV229E) and the HCoV-NL63 while beta includes HCoV-OC43 and HCoV-HKU1. Even if the health authorities pay little attention to these viruses, sometimes they had both morbidity and mortality rates in some countries **(3).**

The 2019 novel CoV, named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) by the International Committee on Taxonomy of Viruses, belongs to the genus beta-CoV. BetaCoV also comprises the Severe Acute Respiratory Syndrome CoV (SARS-CoV), and Middle Eastern Respiratory Syndrome CoV (MERS-CoV). On February 11th, 2020, the World Health Organization (WHO) announced a new name for the disease caused by SARS-CoV-2: CoV disease (COVID-19). On March 11th, 2020, it was declared a pandemic **(4).**

COVID 19 structure

The coronavirus has four structural proteins: envelope (E), membrane (M), nucleocapsid (N), and spike (S) proteins. They enable the virus to gain access to the host cell. The S protein is heavily N-glycosylated which forms large protrusions from the virus surface, giving the appearance of a crown, so the name of coronavirus **(5).**

The N protein is only present in the nucleocapsid, which helps bind the viral genome with the NSP3 protein of the Replication-Transcription Complex (RTC) and packages the RNA species produced during infection into the viral particles. It also serves as an antagonist of interferon (IFN), which appears to be beneficial for viral replication **(Figure.1) (6).**

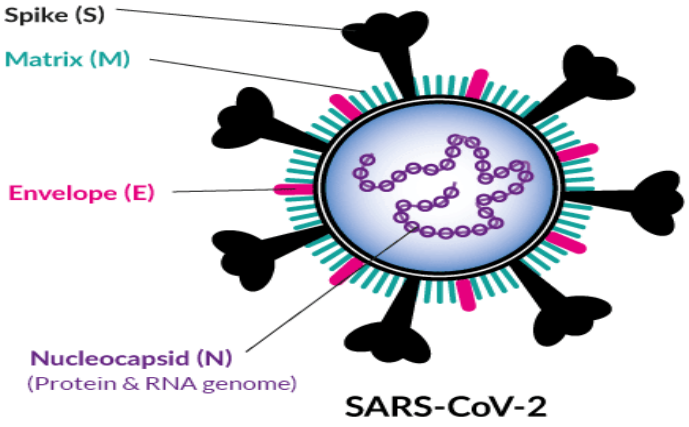

Figure 1: coronavirus structure (7)

SARS-CoV-2 is an enveloped virus containing one positive-strand RNA genome that comprises 29.9 kb. SARS-CoV-2 shares 80% identity with SARS-CoV **(5).**

Coronaviruses are relatively large enveloped, positive-sense, single-stranded RNA (~30 kb) viruses. The SARS-CoV-2 genome encodes four structural proteins and other accessory or non-structural proteins (including the viral pp1a-pp1ab replicase, the 3C-like protease (3CLpro), the papain-like protease (PLpro), and the RNA-dependent RNA-polymerase (RdRp) **(7).**

Virus – host interaction

The virus passes through the mucous membranes, especially nasal and larynx mucosa, then enters the lungs through the respiratory tract. Then the virus attacks the targeting organs that express angiotensin converting enzyme 2 (ACE2), such as the lungs, heart, renal system and gastrointestinal tract **(8).**

SARS-Cov-2 has been shown to use the ACE2 receptor for cell entry. This receptor has also been detected over glial cells and neurons, which make it a potential target for COVID-19. Moreover, SARS-CoV-2 spike protein could interact with ACE2 expressed in the capillary endothelium; the virus may also damage the blood-brain barrier and enter the CNS by attacking the vascular system **(9).**

SARS-Cov-2 binds to ACE2 with a high affinity compared with SARS-CoV. ACE2 is known to be a cardio cerebral vascular protection factor, playing a major role in regulating blood pressure and anti-atherosclerosis mechanisms. Binding to ACE2, the virus causes abnormally elevated blood pressure and increases the risk of cerebral hemorrhage and ischemic stroke. In addition, patients with COVID-19 often suffer from coagulopathy and prolonged prothrombin time, both of which are also contributing factors to secondary cerebral hemorrhage **(10).**

Clinical manifestation and complications

Incubation period

The incubation period for COVID-19 infection is typically 14 days and might extend up to 24 days **(11).**

Clinical Criteria

In the absence of a more likely diagnosis:

Acute onset or worsening of at least two of the following symptoms or signs:

fever (measured or subjective), chills, rigors, myalgia, headache, sore throat, nausea or vomiting, diarrhea, fatigue, congestion or runny nose.

OR

Acute onset or worsening of any one of the following symptoms or signs:

Cough, shortness of breath, difficulty breathing, olfactory disorder, taste disorder, confusion or change in mental status, persistent pain or pressure in the chest, pale, gray, or blue-colored skin, lips, or nail beds, depending on skin tone or inability to wake or stay awake.

OR

Severe respiratory illness with at least one of the following:

Presence of clinical or radiographic evidence of pneumonia or presence of Acute Respiratory Distress Syndrome (ARDS) **(12).**

Complications

- Respiratory manifestations: Pneumonia and Acute respiratory distress syndrome (ARDS)
- Cardiac manifestations: arrhythmias, cardiomyopathy, and acute cardiac injury **(13).**
- Coagulation disorders including thromboembolism and pulmonary emboli, disseminated intravascular coagulation (DIC), hemorrhage, and arterial clot formation
- Renal complications : acute kidney injury
- Thyrotoxicosis and subacute thyroiditis
- Neurologic manifestations such as encephalitis, headache, altered mentality, anosmia. Additionally, myasthenia gravis due to the development of antibodies to acetylcholine receptors and Guillain-Barré syndrome **(14).**
- Septic shock, multiorgan failure and death
- Pediatric multi-system inflammatory syndrome (PMIS or MISC). It has features similar to Kawasaki disease or toxic shock syndrome **(12).**

These complications most commonly occur in certain comorbidities such as hypertension (HT), diabetes and cardiovascular disease **(15).**

Moreover, there have also been reports of an increase in the number of children presenting with a disease termed Multisystem Inflammatory Syndrome in Children (MIS-C), thought to be a result of SARS-CoV-2- induced inflammation **(16).**

Diagnosis

The main methods for diagnosis are:

1- Clinical diagnostic criteria
2- Viral antigens detection
3- Molecular methods

Real-time reverse transcription polymerase chain reaction (RT-PCR) testing of upper and lower respiratory secretions

Nucleic Acid Sequence-Based Amplification (NASBA)

Multiplex real time nucleic acid sequence based amplification (RT-NASBA)

Loop-mediated isothermal amplification (LAMP)

4- Serological methods (antibodies detection)

5- Radiological methods

According to WHO Definitions for **Suspect, Probable, and Confirmed Cases of COVID-19:**

Suspect case:

(a) A patient with acute respiratory illness (fever and at least one sign or symptom of respiratory diseases, such as cough, shortness of breath) AND a history of travel to or residence in a location reporting community transmission of COVID-19 during the 14 days before symptom onset; OR

(b) A patient with any acute respiratory illness AND has been in contact with a confirmed or probable COVID-19 case in the last 14 days before symptom onset; OR

(c) A patient with severe acute respiratory illness (fever and at least one sign or symptom of respiratory diseases, such as cough, shortness of breath; AND who requires hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation

Probable case:

(a) A suspect patient for whom test results reported by the laboratory for the COVID-19 virus are inconclusive; OR

(b) A suspect patient for whom testing could not be performed for any reason

Confirmed case:

A person with confirmed laboratory test results of COVID-19, irrespective of clinical signs and symptoms **(2).**

Viral antigens detection

Direct detection of SARS-CoV-2 viral proteins (antigens) in nasal swabs and other respiratory secretions using lateral flow immunoassays (also known as rapid diagnostic tests, RDTs) offers a faster and less expensive method to test for SARS-CoV-2 than the reference method, nucleic acid amplification tests (NAATs) **(2).**

Lateral flow immunoassays are the handheld portable point of care (POC) platform for the rapid detection of an analyte and are being used in the biomedical, veterinary, agriculture, and food industries. The main advantage of Lateral flow immunoassays is the ease of performing test outside of the clinical laboratory, which makes the assays the superior without burdening the capacity of the laboratories **(17).**

A lateral flow immunoassay (COVID-19 Ag Respi-Strip) is developed for the rapid detection of SARS-CoV-2 antigen from nasopharyngeal specimens. This is the only available POC assay that targets the highly conserved nucleoprotein region of SARS-CoV-2 and is capable of detecting the antigens in 15 min with an overall sensitivity and specificity of 57.6 and 99.5%, respectively **(18).**

Molecular diagnosis

Real-time reverse transcription polymerase chain reaction (RT-PCR) testing of upper and lower respiratory secretions

According to the guidelines for the diagnosis of COVID-19 published by the Chinese government, real-time reverse transcription polymerase chain reaction (RT-PCR) assay is considered the first tool in COVID-19 diagnosis **(19).**

The RT-PCR test can be performed by using nasopharyngeal swabs to obtain nasopharyngeal specimens or by obtaining other upper respiratory tract specimens by using a throat or saliva swab **(20).**

RT-PCR assay was developed targeting different genes such as RNA dependent RNA polymerase (RdRp) gene, nucleocapsid(N) gene, envelope(E) gene, spike(S)gene, and open reading frame 1b (ORF1b) or open reading frame F8 (ORF8) regions of the SARS-CoV-2 genome. The WHO recommends a RT-PCR-based assay targeting the E gene for screening of SARS-CoV-2 followed by a confirmatory test targeting the RdRp gene. Whereas CDC advocated RT-PCR assay was based on two nucleocapsid protein genes (N1, N2) **(21).**

The specificity of most of the RT-PCR test results is theoretically 100% because the primer design is specific to the genome sequence of SARS-CoV-2. However, occasional false positive results may occur owing to technical errors and reagent contamination. Furthermore, it should be realized that a positive RT-PCR test result reflects only the detection of a viral RNA and does not necessarily indicate the presence of viable virus. Another disadvantage of the RT-PCR test is that it takes some time before results are available **(20).**

Several studies found that the initial RT-PCR results for patients with COVID-19 infection were false negatives. These false-negative findings cannot be ignored, especially for those symptomatic people suspected to be infected with COVID-19 **(9).**

Several number of factors can lead to a false negative result, including: poor quality of the specimen, collecting the specimen too early (eg, between exposure to SARS-CoV-2 and symptom onset, which may take up to 1 week) or late in the course of infection (eg, grossly estimated in week 4 after symptom onset and beyond), inappropriate handling and shipping of the specimen and technical reasons inherent in the test **(20).**

Nucleic Acid Sequence-Based Amplification (NASBA)

It is an isothermal amplification technique. Fluorochromes are also added to the reaction in order to make it a real time-based observation (22).

Multiplex real time nucleic acid sequence-based amplification (RT-NASBA)

It can help in the concurrent detection of different viral infections. RT-NASBA has been proven to be 10– 100 times more sensitive than Multiplex RT- PCR, owing to the isothermal conditions where no time is consumed in heating and cooling and production of copies is faster than RT-PCR. This technique can be a choice for the rapid diagnosis of COVID-19 during the current pandemic (22).

Loop-mediated isothermal amplification (LAMP)

It is a PCR- based nucleic acid amplification, which can specifically amplify the target sequence very efficiently, and rapidly under isothermal conditions. The method relies on the use of four-six different primers which recognize specific four or six regions on the target gene and DNA polymerase that elongates the chain at constant temperature by using strand displacement mechanism. Amplification by this method can occur in a conventional water bath/heating block. The amplified product can be visually identified by adding a fluorescent dye. Since SARS-CoV-2 is an RNA virus, are verse transcription step is required (RT-LAMP). After the outbreak, several RT-LAMP assays have been developed and validated for point-of-care diagnosis of COVID-19 (22).

Another approach that combines reverse transcription with LAMP diagnostic technique (RT-LAMP)

This technique was further coupled with a pH indicator, which helped in visual readout of the amplification reaction via color change in the reaction mixture. The challenge related to the LAMP method is the primer optimization and reaction conditions (22).

Serological tests (antibodies detection)

Detecting the antibodies against a virus in infected individuals is one of the most important diagnostic methods in disease surveillance. Though RT-PCR is the most established technique in detecting the SARS-CoV-2 active cases, viral RNA becomes almost undetectable 14 days post-illness. False negative results may also arise due to improper handling of viral samples. These challenges warrant the development of simple test kits based on the detection of human antibodies generated in response to viral infection. The principle behind antibody-based immunodiagnostic is the detection of antibodies developed in response to viral infection (IgG and IgM) and/or, viral antigen through enzyme-linked immunosorbent assay (ELISA). Studies have shown that antigen-specific antibody could be detected in a patient after 3 to 6 days, and IgG could be detected at the later stages of an infection (17).

IgG and IgM-based ELISA kit (EDI™ Novel Coronavirus COVID-19 ELISA Kit) was developed by Epitope Diagnostics Inc for the detection of SARS-CoV-2 infection.

EDI™ Novel Coronavirus COVID-19 IgM ELISA kit utilizes the "IgM capture" method on microtiter plate-based ELISA for the qualitative measurement of the COVID-19 IgM antibody in the patient serum. In this assay, test samples are added to the microtiter plate, which was precoated with anti-human IgM-specific antibodies. Immunocomplex of "Anti-hIgM" antibody and COVID-19 IgM antibody will be detected by HRP labeled recombinant COVID-19 antigen. In the case of EDI™ Novel Coronavirus COVID-19 IgG ELISA Kit, the ELISA plate coated with SARS-CoV-2 recombinant nucleocapsid protein to detect the presence of human IgG against SARS-CoV-2 in the test sample (23).

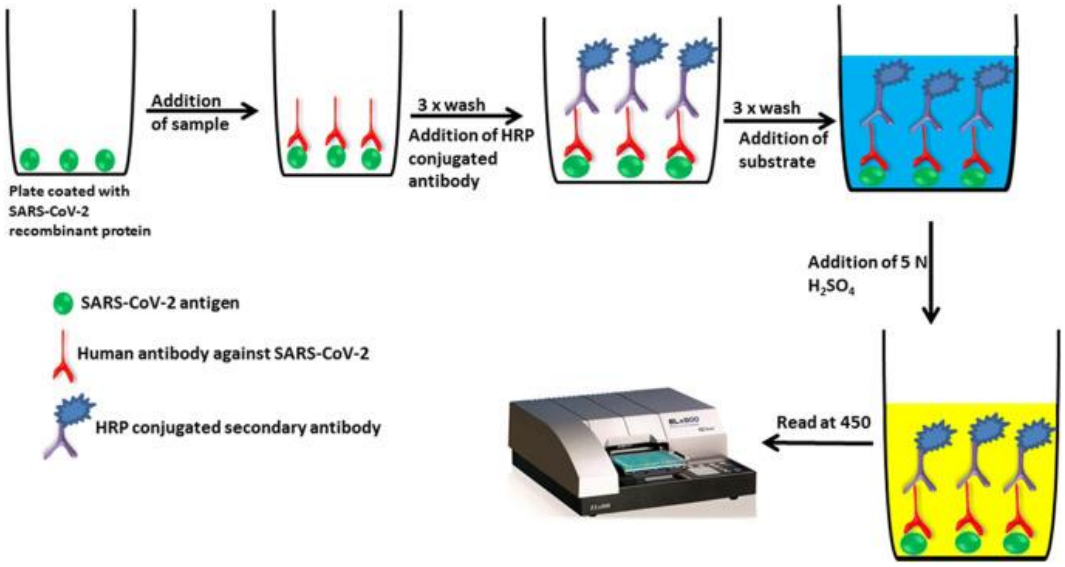

Figure (2): Indirect ELISA for COVID 19 detection (23).

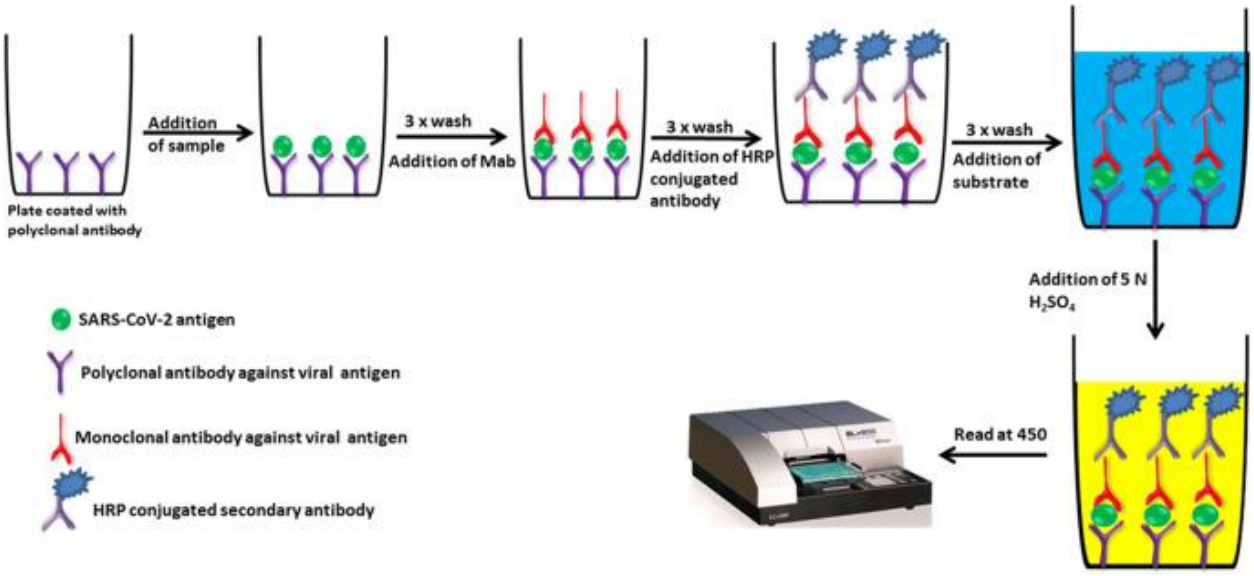

Figure (3): sandwich ELISA for COVID-19 detection (23).

Radiological methods

Diagnostic imaging such as computed tomography (CT) has played an important role in the diagnosis and management of patients with COVID-19. CT of the chest is a routine scanning technique for pneumonia diagnosis. It can be used to follow the extent of lesions and track any changes in those patients whose PCR assays and plain radiographic images were negative **(24).**

Chest CT Appearance of COVID-19

The pulmonary histologic findings of COVID-19, which are characterized by acute and organizing diffuse alveolar damage, resemble those observed in other coronavirus infections (SARS-CoV-1 and MERS-CoV) . The prevalence of chest CT abnormalities in COVID-19 is dependent on the stage and severity of the disease **(25).**

Low viral loads and confinement to the upper respiratory tract are plausible explanations for false-negative chest CT findings for COVID-19 on a patient level. In addition, there are likely host factors that lead to false-negative chest CT findings **(26).**

Several chest CT findings have been reported in more than 70% of RT-PCR test–proven COVID-19 cases, including ground-glass opacities, vascular enlargement, bilateral abnormalities, lower lobe involvement, and posterior predilection. In COVID-19– endemic regions, the observation of these chest CT findings should raise suspicion of possible COVID-19 diagnosis **(Figure 4) (27).**

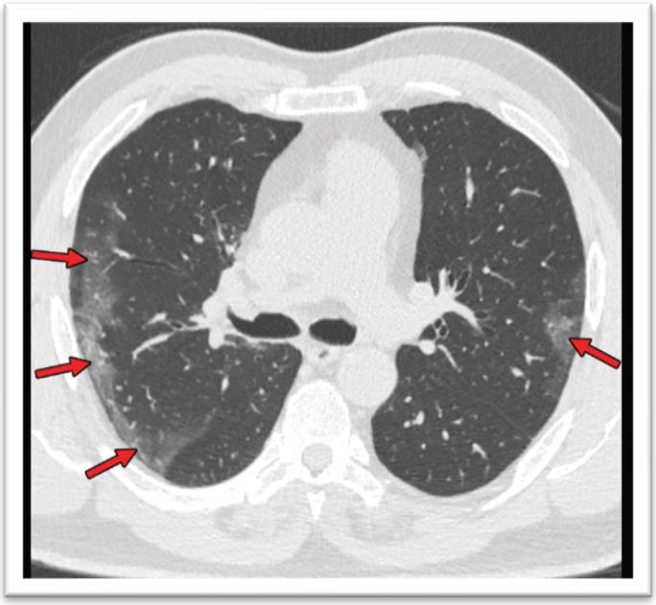

Figure (4): Chest CT Abnormalities with High Incidence (>70%)(27).

Several chest CT findings have been reported to be uncommon in RT-PCR test–proven COVID-19 cases, and these include pleural effusion (5.2%), lymphadenopathy (5.1%), tree-in-bud sign (4.1%), central lesion distribution (3.6%), pericardial effusion (2.7%), and cavitating lung lesions (0.7%). The isolated observation of one or more of these findings is more suggestive of another

diagnosis than of COVID-19, although COVID-19 cannot be completely eliminated from the differential diagnosis. Furthermore, some of these chest CT findings may only occur in some patients later in the course of the disease **(Figure 5) (27).**

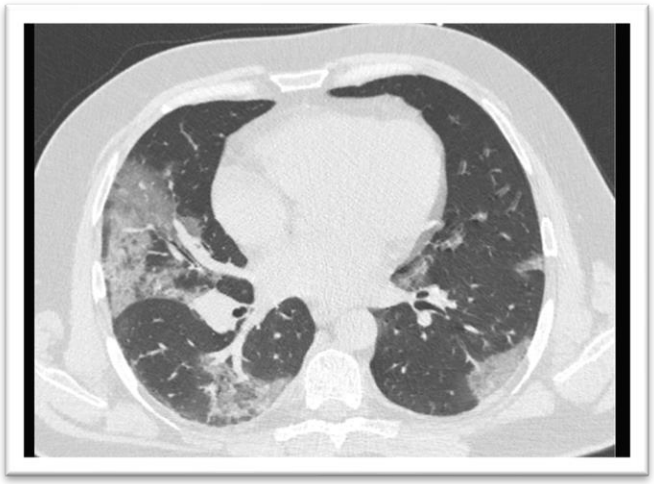

Figure (5): Chest CT Abnormalities with Low Incidence (<10%)(27).

Management of COVID-19 infection

1- Supportive treatment
2- Immune-based therapy
- *Plasma therapy: convalescent plasma(CP)*
- *Immunomodulatory drugs*

A- Anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab)
B- Corticosteroids
C- Interferons (alpha or beta)

3- Antimalarial drugs
4- Antiparasitic drugs
5- Antiviral drugs
6- Adjunctive therapy:
- *Antithrombotic therapy*
- *Antimicrobial therapy*
- *Vitamin C*
- *Vitamin D*
- *Zinc*
- *Others*

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