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INVITED REVIEW – OPEN ACCESS

Coronavirus Disease 2019 (COVID-19): Diagnosis and Management

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ABSTRACT

The coronavirus family has significant human and animal pathogens. At the end of December 2019, a novel coronavirus was recognized as the reason for a group of pneumonia cases of unidentified etiology in Wuhan, a city in the Hubei Province of China. The novel coronavirus has rapidly become widespread, resulting in an epidemic throughout China, followed by a pandemia, an increasing number of cases in various countries throughout the world. Coronavirus disease 2019 (COVID-19) is spread through large droplets produced during coughing and sneezing by symptomatic patients, as well as asymptomatic individuals before starting of their symptoms. The incubation period of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is assumed to be 14 days succeeding exposure, mostly around four to five days. Individuals of all ages may acquire SARS-CoV-2 infection, although middle age and older individuals are the majority. The usual clinical characteristics involve fever, dry cough, fatigue, sore throat, rhinorrhea, conjunctivitis headache, myalgia, dyspnea, nausea, vomiting and diarrhea. Hence, there are no unique clinical features that yet dependably differentiate COVID-19 disease from other upper/lower airway viral infections. In a subgroup of cases, by the end of the first week, COVID-19 disease may develop to pneumonia, pulmonary failure and death. The aim is here to discuss the COVID-19 disease beginning from virology, epidemiology and continuing with clinical manifestations, diagnosis, its complications and to finish with available therapeutic options and conclusion.

Keywords: Coronavirus, COVID-19 disease, SARS-CoV-2 infection

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INTRODUCTION

Family of coronavirus has significant human and animal pathogens. At the end of December 2019, a novel coronavirus was recognized as the reason of a group of pneumonia cases of unidentified etiology in Wuhan, Huanan Seafood Wholesale Market, the preliminary site to which cases of coronavirus disease 2019 (COVID-19) were related, a city in the Hubei Province of China (1). The novel coronavirus has quickly become widespread, resulting in an epidemic throughout China, followed by a pandemia, an increasing number of cases in various countries throughout the world (2). Since the first reports of COVID-19, the infection has spread to contain more than 81.552 cases in China and growing cases (>1.400.000) worldwide, prompting the World Health Organization (WHO) to announce a public health emergency in late January 2020 and describe it as a pandemic in March 2020 (3). Currently, as epidemics have developed in different nations, escalating numbers of cases have also been described in other countries from all continents, excluding Antarctica. The velocity of new cases outside of China, including the USA, Italy and Spain, has overcome the rate in China. In February 2020, the WHO named the disease as COVID-19. The virus that causes COVID-19 is nominated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); it was formerly described as 2019-nCoV (the novel coronavirus) (4).

Our aim is here to discuss the COVID-19 disease (SARS-CoV-2 infection) beginning from virology, epidemiology and continuing with clinical manifestations, diagnosis, its complications and to finish with available therapeutic options and conclusion. [The articles in this review have been selected from mainly Pubmed, published in the last six months, through keywords, such as Coronavirus, COVID-19 disease, SARS-CoV-2 infection.]

Clinical and Research Consequences

Virology

Coronavirus belongs to the *Coronaviridae* family, *Nidovirales* order. Coronaviruses are separated into four genera as follows: α-, β-, γ-, and δ- CoV. α- and β- CoVs only infect mammals, but γ- and δ- CoVs mostly infects birds. Human CoVs consists of α- CoVs (229E and NL63), β- CoVs (OC43 and HKU1), the Middle East respiratory syndrome-related coronavirus (MERS-CoV), and SARS-CoV (5). The genomic and phylogenic analysis showed that the CoV causing COVID-19 is a β- CoV in the identical subgenus as the SARS virus, but in a different clade (5). On 7th January, the virus was recognized as a CoV that had >95% homology with the bat CoV and >70%

resemblance with the SARSCoV (6). The International Committee on Taxonomy of Viruses has suggested that this virus be named SARSCoV-2 (7). The constitution of the receptor-binding gene region is very like to that of the SARS-CoV, and the virus has been demonstrated to utilize the same receptor, the angiotensin-converting enzyme 2 (ACE2), for entrance into respiratory cells (8). Recent studies have demonstrated that the SARS-CoV-2 originated from untamed animals, e.g., bats, the intermediary animals (such as pangolins and snakes) through which it crossed over to humans are undecided.

Epidemiology

In the beginning, an association with a seafood market selling live animals in Wuhan, where most of the earlier patients having pneumonia had worked or visited, was recognized. However, as the epidemic disease grew, person-to-person transmission became the principal means of spread. COVID-19 infection is spread using large droplets produced during coughing and sneezing by symptomatic cases but may also happen from asymptomatic individuals before starting of their symptoms (9). These infected droplets can travel 1–2 meters and later put down on surfaces. Droplets normally do not extend more than 2 meters and do not hang on in the air. The virus could stay viable on surfaces for days in desirable environmental conditions but are ruined in less than a minute by regular disinfectants, such as sodium hypochlorite and hydrogen peroxide (10). SARS-CoV-2 is obtained either by breathing of the droplets or touching surface tainted by them and then touching the nose, mouth and eyes. Cases may be contagious for as long as the symptoms continue and even after clinical improvement. Moreover, certain cases may behave as super-spreaders. As said by a joint WHO-China statement, the rate of secondary COVID-19 disease attack varied from 1 to 5% among tens of thousands of close contacts of verified cases in China (11). In the USA, the symptomatic secondary attack rate was 0.45% among 445 close contacts of 10 verified cases (12). SARS-CoV-2 RNA has been demonstrated in sputum, blood and stool samples. However, fecal-oral, as well as materno-fetal vertical transmission, have not been identified as an important element in the spread of infectivity

Clinical Features, Course and Complications of COVID-19 Disease

The incubation period of SARS-CoV-2 infection is assumed to be in 14 days succeeding exposure, with most patients taking place around four to five days (13). Individuals of all ages may acquire SARS-CoV-2 infection, although middle age and older individuals are the majority. In some cohorts of hospitalized cases with confirmed COVID-19 infection, the median age varied from 49 to 56 years (14).

The usual clinical characteristics involve fever, dry cough, fatigue, sore throat, rhinorrhea, conjunctivitis headache, myalgia, dyspnea, nausea, vomiting and diarrhea. Hence, there are no unique clinical features that yet dependably differentiate COVID-19 from other upper/lower airway viral infections. In a subgroup of cases, by the end of the first week, COVID-19 may develop to pneumonia, pulmonary failure and death (15). Pneumonia seems to be the most common severe manifestation of COVID-19, distinguished mainly by fever, dry cough, dyspnea, and bilateral infiltrates on chest imaging. The median time from the beginning of symptoms to dyspnea was five days, hospitalization seven days and acute respiratory distress syndrome (ARDS) eight days. Recovery begins in the 2nd or 3rd week. According to the WHO, recovery time appears to be roughly two weeks for mild and three to six weeks for severe COVID-19 disease (16). The median period of hospitalization in recovered cases was 10 days. Poor outcomes and fatality are more common in the elderly than patients with co-morbidities (50–75% of a fatality).

Even asymptomatic cases may have an objective laboratory rather than clinical abnormalities. In a study enrolling 24 patients with asymptomatic COVID-19 infection, all of whom underwent thorax computed tomography (CT), 50% had typical ground-glass opacities or patchy infiltration, and another 20% had atypical lung imaging pathology. Five out of 24 cases had a low-grade fever, with or without other characteristic symptoms, a few days after diagnosis (17).

The clinical picture of COVID-19 disease, SARS-CoV-2 infection, is mostly not severe as follows:

- Asymptomatic (latent) infection: Cases positively tested for SARS-CoV-2, but lacking clinical symptoms or pathologic lung imaging findings
- Acute upper airway viral infection: Patients with only fever, dry cough, pharyngeal pain, nasal congestion/rhinorrhea, fatigue, headache, or myalgia, and devoid of findings of pneumonia by thorax imaging or sepsis.

The scale of COVID-19 disease is diverse, varying from clinically asymptomatic to ARDS and multiorgan failure. The authors of the Chinese CDC report categorized the clinical symptoms of the COVID-19 disease by the severity:

- Mild disease (e.g., with no/mild pneumonia) was described in 81%.
- Severe disease (e.g., with dyspnea, tachypnea: ≥70 /min (<1 year), ≥50/min (≥1 year), hypoxia (oxygen saturation <92%), or >50% pulmonary involvement on imaging within 24 to 48 hours, disturbance of consciousness and feeding difficulty or food refusal, with signs of dehydration) was observed in 14%.
- Critical disease (e.g., with respiratory collapse, shock, or multiorgan failure) was reported in 5% (18).

In a study involving 138 patients, ARDS developed in 20% after a median of 8 days, and mechanical ventilation was required in 12.3%. Age higher than 65 years, diabetes mellitus and hypertension were each found to be related to ARDS (19). The necessity for intensive care admittance was in 25–30% of affected cases in previous reported series (14). Complications comprised acute lung injury, ARDS, shock and acute kidney injury (20). Others included arrhythmias and acute cardiac injury. In one study, these complications were reported in 16.7% and 7.2%, respectively (15).

The general fatality rate is expected to vary between 2% and 3%; no deaths were observed among noncritical cases. The mortality rate in admitted adult patients varied from 4% to 11% (18, 21). As said by a joint WHO-China fact-finding mission, the case-fatality rate ranged from 5.8% in Wuhan to 0.7% in the rest of China (22). The proportion of fatal infections may vary by location, e.g.,

in Italy, the estimated fatality rate was 5.8% in March (23). On the contrary, the estimated case fatality rate in March in South Korea was 0.9% (24). Older age was also associated with higher fatality, with a fatality rate of 8% and 15% among those aged 70–79 and 80 years or older, respectively. Most of the mortal cases have happened in cases with advanced age or predisposing co-morbidities (such as cardiovascular disease -coronary heart diseases-, diabetes mellitus, chronic lung disease, hypertension and cancer) (25).

Differential Diagnosis

The differential diagnosis consists of all kinds of upper/lower airway viral infectious agents, such as adenovirus, rhinovirus, influenza, parainfluenza, respiratory syncytial virus (RSV), human metapneumovirus, other coronaviruses and other well-known viral respiratory infections, atypical pathogens (chlamydia, mycoplasma) and bacterial microorganisms (26).

Diagnosis

In accordance with China National Health Commission, COVID-19 disease is identified on account of the epidemiological history and clinical manifestations, along with verified SARS-CoV-2 infection via one of the subsequent methods: real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay, high-throughput genome sequencing, and serological evaluation of anti-viral immunoglobulin M (IgM) and G (IgG) antibodies (26, 27).

Diagnosis in Suspected COVID-19 Cases

SARS-CoV-2 infection should be supposed in cases that convene any one of the criteria in the epidemiological history and any two of the criteria in clinical symptoms, below.

Epidemiological history comprising cases with a journey or residence history of nearby areas with constant local transmission within 14 days before their disease onset; cases having a contact history with individuals of fever or respiratory symptoms who have a contact history with patients from the epidemic city/adjacent areas; cases who are related to a group (e.g., family) outbreak or close contact with COVID-19 cases; newborns given birth by definite COVID-19 mothers.

Clinical symptoms: i-) fever (certain cases may have a low-grade fever or normal temperature), dry cough, fatigue; ii-) with lung imaging findings; iii-) with normal or decreased leukocyte count, or decreased lymphocyte number during the early phase of the COVID-19 infection; iv-) no other infectious agents are found, entirely explaining the symptoms (26, 28).

Confirmation of COVID-19 Diagnosis

Suspected patients who have any one of the next criteria: I.) Airway or blood samples tested positive for SARS-CoV-2 using RT-PCR; II.) Genetic sequencing of airway or blood samples is extremely homologous with the identified SARS-CoV-2 genome (26, 29).

Laboratory Evaluation (RT-PCR vs. Serology)

SARS-CoV-2 RNA is identified by RT-PCR. Samples from throat swabs (nasopharyngeal in children), sputum, lower airway secretions, stool and blood could be checked for SARS-CoV-2 ribonucleic acids. Studies have demonstrated higher viral loads in the nasal cavity as compared to the throat with no distinction in viral burden between symptomatic and asymptomatic individuals (30). An oropharyngeal swab can be gathered, but is not crucial; if gathered, it should be put in the same container as the nasopharyngeal swab specimen. Negative RT-PCR results from oropharyngeal swabs, regardless of CT findings indicative of viral pneumonia, have been demonstrated in certain cases that ultimately shown to be positive for SARS-CoV-2. The American CDC suggests a collection of a nasopharyngeal swab to analyze for SARS-CoV-2 (31). Sputum should only be obtained from cases with productive cough; sputum induction is not advised. If preliminary testing is negative, but the doubt for COVID-19 persists, the WHO advises recollection and analyzing from several airway sites. Laboratory testing of the SARS-CoV-2 ribonucleic acid may result in false-negative results, and serological analysis of virus-specific IgG and IgM antibodies should be utilized as an option for diagnosis (32). Typical disease manifestations and radiological lung abnormalities in a case with negative four times RT-PCR tests for SARS-CoV-2 and positive IgG and IgM antibodies against the virus were demonstrated (27). It has been earlier shown that some SARS-CoV-2 infected cases are asymptomatic while RT-PCR tests are verified positive, and some cases that improved from COVID-19 disease may still have positive RT-PCR results during follow-up.

Additional laboratory tests, including CBC and biochemistry, are generally nonspecific. The leukocyte count is frequently normal or low. There might be lymphopenia; a lymphocyte count <1.000 has been related to severe disease. The thrombocyte count is generally normal or slightly low. Most cases show high CRP and ESR, but procalcitonin levels are typically normal. An elevated procalcitonin level may point to a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimer, CPK, LDH, myohemoglobin and ferritin levels might be increased and elevated levels might be related to severe disease (20, 26, 33). On hospitalization, many cases having pneumonia have normal serum procalcitonin levels, but, in cases necessitating intensive care unit (ICU) management, they are more likely to be increased. Elevated D-dimer levels and more severe lymphopenia have been shown to be linked with fatality (14).

The lung X-ray (CXR) generally shows bilateral infiltrations but may be normal in the early phase of the disease. The chest CT is more sensitive and specific. Lung CT scans generally demonstrate infiltrates, ground-glass opacities and subsegmental consolidation. Less common abnormalities contain pleural effusion/thickening, and lymphadenopathy. During the early phase of COVID-19 disease, thorax CT shows multiple small plaques and interstitial alterations, evident in the lung periphery, further worsens to bilateral multiple ground-glass opacity and/or infiltrating shadows. Pulmonary consolidation may happen in severe cases. Pleural effusion is infrequently observed (26, 34). Pathologic lung CT imaging has also been utilized to identify COVID-19 in suspected and/or asymptomatic cases with negative RT-PCR; many of them become to have positive PCR when they are repeated (35).

Treatment

Supportive Therapy

Treatment is basically supportive and symptomatic. The first step is to guarantee sufficient isolation to stop spread for other contacted individuals, cases and healthcare workers. Depend on their medical

situations, suspected cases should be isolated in a single room or self-isolated at home subsequent to the doctors' advice. Confirmed patients can be cohorted in the same ward. Critical patients should be admitted to ICU immediately.

The common strategies involve bed rest and palliative therapy, supplying enough calorie and water consumption, sustaining water-electrolyte balance and homeostasis, scrutinizing vital signs and oxygen saturation, maintaining airway unobstructed and supplementing oxygen when needed (26, 36).

Symptomatic Therapy

The mild disease should be managed at home by advising about dangerous signs. The standard approach is continuing hydration, nutrition and managing fever and cough. If a patient has a high temperature exceeding 38.5°C with noticeable distress, bodily cooling (such as lukewarm water bath, antipyretic patches) or antipyretic medicine therapy would be given. Frequent medications involve: acetaminophen orally, 10–15 mg/kg, 4-6 times/day (ibuprofen is recommended to avoid). Routine use of antibiotics and antivirals, such as oseltamivir, should be kept away from verified patients (26).

In hypoxic individuals, oxygen therapy through nasal prongs, face mask, high flow nasal cannula or non-invasive ventilation may be required. Mechanical ventilation and even extra corporeal membrane oxygen (ECMO) treatment might be considered necessary. Children who go through non-invasive mechanical ventilation for two hours without any progress, or cannot put up with non-invasive ventilation, with augmented airway secretions, severe cough, or hemodynamic unpredictability, should rapidly undergo mechanical ventilation. If required, prone position ventilation, pulmonary recruitment, or ECMO can be utilized (37). Renal replacement treatment may be required in certain cases (26, 37).

Antiviral Therapy

There has not been, currently, yet widely accepted therapeutic option for COVID-19 disease. Antiviral drugs, such as ribavirin, lopinavir-ritonavir, have been tried depend on the anecdotal knowledge with HIV, SARS and MERS infection therapies (26, 27).

Lopinavir-ritonavir: This combined protease inhibitor, which has mainly been utilized for HIV infection. This combination has shown to have an effect on the SARS-CoV infection in vitro and some activity against MERS-CoV in animals (38). In a study, including five cases treated with lopinavir-ritonavir, three cases recovered and two cases worsened; four cases of them had gastrointestinal side effects. Lopinavir/ritonavir combination has been currently tried in the treatment of adult SARS-CoV-2 patients with pneumonia, but its efficacy and safety wait to be defined (39).

Ribavirin: In a past control study in SARS, cases treated with lopinavir-ritonavir with ribavirin had better results when compared to the cases used ribavirin only (40).

Remdesivir: Remdesivir is a new nucleotide analogue that has effects against SARS-CoV-2 in vitro and linked coronaviruses (including SARS and MERS-CoV) both in vitro and in animal studies (41). Many randomized clinical trials are ongoing to assess the supportive use of remdesivir efficacy in modest or severe COVID-19 infection and any clinical effects of remdesivir on COVID-19 stay currently unidentified. There is anecdotal practice with the utilization of remdesivir, a wide spectrum anti-RNA medication previously used for Ebola in COVID-19 treatment (42).

Arbidol, oseltamivir and other antiviral drugs: Arbidol, an antiviral drug available in Russia and China, is used for adult SARS-CoV-2 infection; yet, its efficacy and safety stay uncertain (27, 43). A combination with oseltamivir and other anti-influenza medications may be required for coinfections with Influenza A/B. The other antiviral medications evolving daily but now comprise nitazoxanide, favipiravir, nafamostat, and so on (40).

Chloroquine/hydroxychloroquine: Both chloroquine and hydroxychloroquine hamper SARSCoV-2 replication in vitro, even though hydroxychloroquine seems to have a more powerful antiviral effect (41, 44).

Other Drugs

Suggested drugs for immunotherapy are intravenous immunoglobulin (IVIG), interferons, and convalescent immune plasma of improved cases from COVID-19 disease.

Intravenous immunoglobulin can be utilized in severe COVID-19 disease when required, but its efficacy remains uncertain and needs further studies (26, 27). The efficacy of IVIG could be better if the IgG antibodies were gathered from cases improved from SARSCoV-2 infection, to increase the probability of inactivating the virus. This is called as 'convalescent immune plasma' therapy. More specific IgG antibodies would be more effective against COVID-19 disease by enhancing the immune response in infected cases (37, 45). Consequently, immunotherapy with specific IgG antibodies along with antiviral drugs can be an alternative therapy against COVID-19 disease until better choices, such as a vaccine, are accessible. For the first time that a SARS-CoV-specific human monoclonal antibody, CR3022, has been recently reported to be able to potently attach with SARS-CoV-2 receptor-binding domain. Potent binding of SARSCoV-2 spike protein by a SARS-CoV specific human monoclonal antibody could be an alternative therapeutic approach in the near future (46).

Interferon (IFN)-α can decrease viral load during the early stage of COVID-19 disease, and it can help to improve disease manifestations and curtail the course of infection.

1. IFN-α nebulization: 200.000–400.000 IU/kg or 2–4 μg/kg in 2 ml of sterile water, two times per day for 5–7 days;
2. IFN-α2b inhalation (puff): administered for high-risk individuals with close contact with supposed SARS-CoV-2 infected cases or those in the early phase with only upper airway manifestations. Cases should administer 1–2 puffs into the nasal cavity bilaterally, 8–10 puffs on the oropharynx, and the dose of IFN-α2b for every application is 8.000 IU, per 1–2 hours, 8–10 puffs/day for 5–7 days (26, 27, 47).

Hyper-inflammation, which happened by a cytokine storm that arises from an exaggerated immune response to the presence of the SARS-CoV-2, is considered to characterize one of the most important negative prognostic markers in COVID-19 disease. If there is a cytokine storm, the use of selective cytokine blockade agent (e.g., anakinra or tocilizumab) is thought to be helpful.

Anakinra is one of the interleukin antagonists, and it blocks the effect of interleukin-1, which is highly increased during the cytokine storm (48). Strategies from China's National Health Commission comprise the IL-6 inhibitor tocilizumab for severe COVID-19 cases and high IL-6 levels during the cytokine storm phase of COVID-19 disease, which is being assessed in clinical trials (49).

Antibiotics and/or antifungals are required if co-infections, such as Mycoplasma and Chlamydia, are suspected or proven. Prolonged macrolide therapy, as a modulator of immune function, is being evaluated (27).

Anti-parasitic medication Ivermectin was demonstrated to inhibit the replication of SARS-CoV-2 in vitro. Ivermectin was previously found to have broad- spectrum anti-viral activity in vitro, an inhibitor of the pathogen virus (SARS-CoV-2), in Vero-hSLAM cells 2 hours after SARS-CoV-2 infection. It was capable of reducing ~5000-fold in viral ribonucleic acid replication at 48 hours. Ivermectin seems to require further research on possible benefits in COVID-19 disease (50).

Glucocorticoids: Steroids have been related to a higher risk for fatality in influenza patients and postponed viral clearance in MERS-CoV infected patients. Although glucocorticoids were broadly utilized in the therapy of SARS, there has been no good quality proof for advantage, and there was convincing data of short- and long-term adverse effects. The role of steroids is unverified and might have a partial role while existing international consensus advises against their utilization. The WHO/CDC advises them not to be given in COVID-19 disease with pneumonia except for there are other indications (e.g., exacerbation of the chronic obstructive pulmonary disease and asthma) (26, 27, 51). Chinese guidelines also advocate short term therapy with low-to-moderate dose steroids for ARDS complications of COVID-19 disease (52). The utilization of corticosteroids should depend on the severity of hyperinflammatory response, the extent of dyspnea, with or without ARDS, and the advancement of lung imaging status. Corticosteroids can be administered in a short period of time (3–7 days). The suggested dose of methylprednisolone should not surpass 1–2 mg/kg/day.

CONCLUSION

The COVID-19 disease should be mostly thought in cases with fever and/or airway manifestations that have had contact with a verified/suspected case. Upon suspicion of COVID-19 disease, infection control actions should be executed and public health officials visited (53). Besides testing for other respiratory viral pathogens, a nasopharyngeal swab should be sent for RT-PCR testing. Management basically consists of palliative care. Home care may be likely for cases with a mild disease that can be sufficiently isolated. To decrease the danger of spread in society, people should be advised to wash hands assiduously, carry out respiratory hygiene, and keep away from crowds and close contact with sick individuals. Facemasks are not regularly suggested for asymptomatic cases, but social distancing is advised in every place that has society spread.

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