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Interpretations of "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)"

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Since the outbreak of coronavirus disease 2019 (COVID-19), the National Health Commission of the People's Republic of China has issued a series of timely updated guidelines. The "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)" was published on March 3, 2020 and was developed from the accumulated clinical experience and a deeper understanding of the disease.[1] Compared to the sixth version, the contents on the transmission routes, pathological features, clinical characteristics, diagnosis, triage, treatment, and discharge standards have been revised in the latest edition. This article presents a brief interpretation of the seventh version for a better understanding of the protocol.

Transmission Routes

The new version has included environmental contamination by urinary and fecal viral shedding from patients with 2019 novel coronavirus (2019-nCoV) as a route of transmission, as the virus can be detected in the excreta. It has been generally accepted that 2019-nCoV can be transmitted through droplets, close contact, and under certain circumstances, aerosols. As previously reported, the virus is detectable in fecal and urine samples of the patients with COVID-19, suggesting that contamination by feces and urine of the infected patients increases the risk of transmission.[2] Thus, practicing frequent hand sanitization and availability of well-ventilated lavatories and unobstructed drains are of great importance, which is in line with the recommendations of the World Health Organization.[3,4] However, the possibility of fecal-oral route of transmission must be investigated further to gain more evidence to substantiate this potential transmission route.

Pathological Features

Provision of information on the pathological changes, based on the autopsy findings and biopsy results, in various organs of the patients with COVID-19 is one of the highlights of the updated protocol. On gross examination, the involved lungs show varying degrees of consolidation with areas of hemorrhage and necrosis. The histological examination revealed alveolar edema, extensive fibrin exudation, and hyaline membrane formation, while some parts of the lungs showed organized exudation and interstitial fibrosis. Another typical pulmonary manifestation is cellular infiltration, mainly by monocytes, macrophages, and multinucleated syncytial cells. However, lymphocytes are not mentioned in reference to cellular infiltration, and this is in concordance with previous articles that reported persistent lymphopenia in non-survivors.[5-8] Type II alveolar epithelial cells show extensive hyperplasia, with some necrosis and desquamation. Moreover, latest research has confirmed the post-mortem persistence of 2019-nCoV in the lung tissue of the patients who experienced diffuse alveolar damage followed by rapidly evolving pulmonary fibrosis and respiratory failure.[9]

Furthermore, the disease not only causes damage to the lungs, but also affects various organs, including the spleen, lymph nodes, bone marrow, heart, blood vessels, liver, kidney, brain, and gastrointestinal system. Consequently, several complications, such as acute cardiac injury, acute kidney injury, abnormal coagulation function, shock, and even multi-organ dysfunction, tend to develop in critically ill patients.[8,10,11] The pathological findings reveal that 2019-nCoV affects the organs of the immune system, such as the spleen and lymph nodes, indicating an important role of impaired immune function in the development of COVID-19. Pathological studies have facilitated better understanding of the etiopathogenetic mechanisms, although the exact mechanisms underlying COVID-19 development remain unclear because of the limited number of autopsies of and scarcity of data from patients in the early and middle disease stages.

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Clinical Characteristics

The details of clinical manifestations in specific populations have been included in the new version. The seventh version indicates that some children and newborns with COVID-19 have atypical symptoms; however, there is currently no difference in the clinical manifestations between the pregnant and non-pregnant women or adults of reproductive age.

The guidelines on laboratory examinations are organized in two sections, namely, general laboratory investigations and pathogen detection. The pathogen detection section clearly describes the methods of pathogen detection (reverse transcription-polymerase chain reaction [RT-PCR] and/or metagenomics next-generation sequencing) and sampling sites. Based on the previous clinical experience, the guidelines recommend collection of lower respiratory tract specimens, which have a higher positivity rate. Another highlight of the seventh version is that the detection of 2019-nCoV-specific immunoglobulin (Ig)M and IgG antibodies can aid in diagnosis. Serological testing, predominantly including the colloidal gold method, chemiluminescence method, and enzyme-linked immunosorbent assay, has been widely used for the diagnosis of various infectious diseases and will definitely enhance the efficiency of diagnosis of COVID-19. However, some questions persist with respect to antibody detection, for example, the reliability of new serological testing kits, duration of the window period, time of sample collection, and so on. Further investigations are needed to address these issues. The sensitivity and specificity of COVID-19-specific antibody detection are reported to be nearly 90%, which indicates that serological testing holds great promise for diagnosis.[12,13] Serological testing not only compensates for the limitations of nucleic acid detection by improving diagnostic accuracy and discharge standards, but also minimizes the potential risk of cross-infection during the collection of pharyngeal swabs. Furthermore, serological testing plays a pivotal role in the evaluation of the patient's immune status and screening for individuals with a high neutralizing-antibody titer; such patients are a valuable source of convalescent plasma for therapy after they recover from COVID-19.

Diagnosis and Triage

The protocol of the seventh version defines clustered onset and highlights the diagnostic value of serological testing. COVID-19 can be confirmed based on one of the following criteria: positive COVID-19-specific IgM and IgG expression, a conversion from negative to positive on testing for specific IgG, and a four-fold increase in the IgG titer during the recovery period compared with the results during the acute phase.

Early indicators of disease worsening and progression are other important updates of the seventh version. The previous clinical experience suggests that some patients with mild and moderate disease would inevitably evolve into critically ill states or may even die during hospitalization. Therefore, the prognostic factors for patients at risk of developing more severe disease are of paramount importance in strengthening surveillance and enabling timely initiation of appropriate treatment. Several retrospective observational studies have compared the data between the critically ill and non-critically ill patients and between the survivors and non-survivors. These studies have concluded that the indicators for the early identification of patients likely to progress to the critically ill status include progressive lymphopenia, gradually increasing levels of pro-inflammatory cytokines and lactate dehydrogenase, and rapid exacerbation of pulmonary injury.[6,8,11,14] These factors are closely associated with the prognosis of patients with COVID-19, which indicates that cytokine storms, immune dysfunction, and imbalanced internal homeostasis are pivotal in the disease process. In addition, the protocol presents a detailed introduction of the indicators for progression in children with COVID-19.

Therapeutic Options

The seventh version of the protocol recommends the use of mixed gases, with 66.6% hydrogen and 33.3% oxygen inhalation. There are no new additions to the list of antiviral agents, whereas the usage of previously suggested agents is seriously restricted, with clear indications for their routes of administration and dosage, side effects, contraindications, and drug interactions. Presently, there is no evidence from randomized controlled trials to support a specific drug treatment against the 2019-nCoV; thus, the recommendations for antiviral therapeutics vary among hospitals, regions, and even according to different guidelines and expert consensus. The recommendation with regard to the use of corticosteroids for COVID-19 remains unchanged in the updated protocol, and steroid use remains controversial. To date, there is no evidence-based indication for the routine use of corticosteroids. In the "Diagnosis and Treatment Plan for Severe and Critical Novel Coronavirus Pneumonia (Trial Version 2)", only patients presenting with ongoing deterioration of the oxygenation index, rapid progression of infiltrates on radiological imaging, or excessive activation of the immune response will be considered eligible for short-term corticosteroid therapy (80 mg/day for <5 days).[15]

A more comprehensive and detailed treatment strategy for severely and critically ill patients is included in the updated protocol. Recent studies have reported that the novel coronavirus may not only target the lungs but also have the potential to affect other organs, which eventually leads to multiple organ dysfunction syndrome in the advanced stages.[3,5,9,11] The key objectives of COVID-19 treatment are improvement of the symptoms and underlying diseases, active prevention and control of the potential complications, and provision of timely measures to support organ function. The lung-protective ventilation strategies are to be adopted in cases requiring invasive mechanical ventilation, and detailed setting of the ventilation parameters is recommended. Extracorporeal life support, including extracorporeal membrane oxygenation, must be considered for patients with hypoxemia refractory to invasive mechanical ventilation; the indications and timing for extracorporeal membrane oxygenation have been specifically refined. Furthermore, the seventh protocol

emphasizes the importance of the monitoring methods for the critically ill patients, including the use of the pulse index continuous cardiac output device, invasive blood pressure monitoring, and critical care ultrasonography. Moreover, continuous renal replacement therapy is recommended for patients with acute kidney injury and severe instability of the internal environment. Plasmapheresis can alleviate cytokine storms. Convalescent plasma therapy is recommended as the last resort to improve the prognosis of severely ill patients with COVID-19.[16] In the seventh version, immunotherapy is described as a therapeutic option for the first time. Recent reports have indicated that the serum levels of inflammatory mediators in severely ill patients were significantly higher than in those with milder disease. Tocilizumab, a humanized antibody for interleukin-6 receptor, has been proposed as a therapeutic agent for patients with extensive lung injury and elevated interleukin-6 levels. Currently, tocilizumab has been widely used for the treatment of autoimmune diseases and is approved by the US Food and Drug Administration for decreasing the events of cytokine-release syndrome due to CD19-specific chimeric antigen receptor T-cell therapy in acute lymphoblastic leukemia.[17]

Discharge Standards

The seventh version stipulates that following discharge from the hospital or discontinuation of quarantine, the patients should be instructed to continue the quarantine protocol under self-supervision for the next 14 days, with a proposed clinical follow-up. A recent study reported that a proportion of the recovered COVID-19 patients continued to be tested positive for 2019-nCoV on RT-PCR.[18] Moreover, the exclusion criteria for the suspected cases have been strictly redefined as follows: two consecutive negative RT-PCR test results and negative results for infection-specific IgM and IgG after 7 days of illness onset. The aforementioned updates will facilitate better control and management of the COVID-19 pandemic.

Conflicts of interest

None.

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