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Editorial

Interpretation of the 7th edition of the "diagnosis and treatment guidelines of coronavirus disease 2019 in China": Progress and challenges

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Since the first patient infected with the novel coronavirus (SARS-CoV-2) was identified in December 2019, the cumulative number of confirmed cases of coronavirus disease 2019 (COVID-19) has exceeded 2,100,000 and has resulted in more than 140,000 deaths globally, as of April 17, 2020. The progression of the epidemic can be divided into two phases. The first phase, which started in December 2019 and ended in February 2020, primarily involved Chinese mainland, which battled the epidemic. The second phase, from February 2020 until now, involves countries other than China that have become the primary battlefields for the virus, whereas the epidemic in Chinese mainland has been largely contained. A review of past experiences and lessons learned suggests that the 1st Trial Edition of the "Novel Coronavirus Pneumonia (COVID-19) Diagnosis and Treatment Guidelines in China", which was released as early as January 23, 2020, largely owing to the Chinese government's prompt response and assemblage of experienced experts from the National Health Commission, played a vital role in regulating diagnoses and treatments across the country. In a little over a month, six more editions of the guidelines have been published, incorporating the latest clinical feedback and research progress, the most recent of which is the 7th edition.[1,2] Compared with the 5th and 6th editions, the 7th edition did not make changes to basic concepts but mainly focused on various revisions and updates regarding transmission routes, clinical manifestations in children, etiological diagnosis, diagnostic criteria, exclusion criteria for suspected cases, and, most importantly, clinical warning signs and treatment of severely and critically ill patients, as well as the refinement of follow-up observations. Furthermore, in addition to the successive publication of several diagnosis and treatment guidelines for severe and critical COVID-19 cases, some military and local units have also issued their own instructions.[3–5] This article reviews and addresses some "hotspots" and key issues pertaining to COVID-19.

Pathological changes in the organs of patients with COVID-19

For the first time, on the basis of the latest research developments, the 7th edition of the guidelines has

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added a description of the pathological changes which occur in the organs of COVID-19 patients, with a particular focus on pulmonary lesions. The guideline states that the lungs of patients with COVID-19 exhibit pulmonary consolidation to different degrees, as well as the presence of intra-alveolar serous fluids, fibromyxoid exudates, and hyaline-membrane formation. The exudates consist mainly of mononuclear macrophages, although multinucleated giant cells are also common. In addition, significant hyperplasia of type II pneumocytes, as well as some desquamation is observed, whereas inclusion bodies are evident inside type II pneumocytes and macrophages. These findings have confirmed that in some critically ill COVID-19 patients, the treatment outcomes of conventional respiratory support have been poor, primarily due to significant deterioration of pulmonary gas-exchange capacity resulting from diffuse alveolar damage in the lung parenchyma. Furthermore, the 7th edition guidelines have emphasized that COVID-19 can affect multiple organs. More specifically, the disease can lead to significantly reduced lymphocyte counts in both the spleen and lymph nodes, as well as a considerable reduction in trilineage hematopoiesis in the bone marrow. These results suggest that SARS-CoV-2 attacks a wide range of organs and is spreading extensively worldwide. In particular, its effects on the immune system are an important risk factor for poor patient prognosis. The presence of a large number of macrophages in various organs−especially the lungs and spleen−indicates that research investigating macrophage-mediated inflammation should be prioritized.[2,6,7] It should be noted that these findings are prevalently obtained from severe cases of COVID-19.

Laboratory examination and pathogen diagnosis

On the basis of the latest research developments, the 7th edition guidelines include two additional sections on laboratory investigations.

Etiological examination

The latest research developments regarding etiological examination includes a recently published article in *Emerging Infectious Diseases*, which reported that an asymptomatic 10-year-old patient was confirmed to be positive for COVID-19 on the basis of viral nucleic acid detection in a stool specimen, while the Guangzhou Research Institute of Respiratory Diseases announced that they successfully isolated SARS-CoV-2 from the stool samples of infected patients.[8,9] Therefore, the 7th edition guidelines recommend adopting the reverse transcriptase-polymerase chain reaction and/or next-generation sequencing technology to detect the presence of SARS-CoV-2 in nasopharyngeal swabs, sputum, and other lower respiratory tract secretions, as well as stool samples. The guidelines also suggest that tests performed using samples from the lower respiratory tract (i.e., sputum or airway suction) are more accurate. These findings indicate that SARS-CoV-2 can be transmitted not only through respiratory secretions but also through feces, making these potential sources of infection for susceptible individuals. In addition, the emphasis on using lower respiratory tract samples rather than nasopharyngeal swabs further supports the limited sensitivity of the latter, which should be given full consideration in clinical practice.[2]

Serological examination

Most SARS-CoV-2-specific immunoglobulin (Ig)M antibodies appeared to test positive 3−5 days after the onset of symptoms, whereas the titer of IgG antibodies was shown to be elevated by $\geq$ 4-fold in the recovery phase compared with the acute phase. In regard to detecting blood-specific SARS-CoV-2 IgM and IgG antibodies, a set of examinations testing peripheral blood levels of IgM and IgG in 173 patients newly diagnosed with COVID-19 revealed positivity rates of 82.7% and 64.7%, respectively. In addition, the examinations revealed that the positivity rate remained <40% within the first 7 days after the onset of symptoms. However, after 15 days, the positivity rate increased substantially, reaching 94.3% for IgM and 79.8% for IgG,[10] indicating an extremely high clinical compliance rate. Currently, there are multiple manufacturers producing clinical detection kits based on various methods, including colloidal gold, chemiluminescence, and enzyme-linked immunosorbent assay. Nevertheless, data regarding the efficacy of such methods for the detection of early SARS-CoV-2 infection are scarce. Therefore, there are still several unanswered questions regarding the use of methods based on the detection peripheral blood IgM and IgG levels as an early screening and diagnostic approach, such as identifying the optimal window for sample detection, how high the positivity rate is, and the reliability of the method. Thus, these methods still require further clinical verification. In addition, because it takes time to generate antibodies after infection, the length of the window in which these antibodies can be detected also needs clarification. Nevertheless, we believe that, as a supplement to

nucleic acid detection, peripheral blood IgM and IgG tests are highly useful for the diagnosis of COVID-19, especially in evaluating the therapeutic effect of plasma therapy and the status of the patient's autoimmune function.

Clinical warning signs of severe and critical illness

The early prediction and evaluation of disease severity are extremely important for patient prognosis. However, because COVID-19 is a novel disease, clinical experience summaries can only be created in-step with the treatment process. Clinical predictive markers used to guide treatment can only be promptly established by reviewing successful treatment outcomes and data accumulated from past experiences. Compared with the previous versions, the 7th edition guidelines have information regarding clinical warning signs for severe and critical cases. For adults, these include the following: progressive reduction of peripheral blood lymphocyte levels, progressive increase in peripheral inflammatory cytokine levels, such as interleukin (IL)-6 and C-reactive protein (CRP), progressive increase in lactate levels, and rapid progression of lung lesions in the short term.[2] Previous studies have reported that 80% of patients diagnosed with COVID-19 experience mild-to-moderate symptoms. However, some patients can suddenly deteriorate and rapidly progress to a severe or critical status, which consequently increases the mortality rate.[11−13] In contrast, the establishment of clinical warning signs enables prompt identification of these patients so that their treatment and care can be prioritized and delivered in a timely manner to reduce mortality. However, whether the implementation of these indicators can play a role as an early indication of disease severity requires further clinical verification.

Glucocorticoid therapy

The role of corticosteroid treatments remains controversial. Although no changes associated with this topic were made in the 7th edition guidelines, in the "Diagnosis and Treatment Guidelines for Severe and Critical COVID-19 Cases (Trial 2nd Edition)", recommendations regarding glucocorticoid therapy included: "As there is currently no clinical evidence of glucocorticoid therapy improving the prognosis of COVID-19 patients, it is not recommended for routine use. For patients exhibiting progressive deterioration in oxygenation, rapid radiological progression, and high levels of cytokine storms, short-term administration of methylprednisolone at a dose of 40 mg every 12 h for a total of 5 days can be considered. And before administration, contraindications to glucocorticoid therapy should be confirmed".

In addition, the Chinese military and local government units have published consensus statements or instructions that have cautiously recommended short-term administration of a certain dose of glucocorticoids in patients with early-stage COVID-19 whose condition is rapidly deteriorating.[3−5] This is further supported by our data from COVID-19 patients in Beijing, China, who received glucocorticoids, which found that glucocorticoid administration was an independent risk factor associated with the development of acid-base disorder. We believe that, despite having immunosuppressive effects, glucocorticoids can inhibit the "cytokine storm". It can also induce other problems, such as susceptibility to secondary infections, disturbance of homeostasis, and prolonged virus shedding. Therefore, it is essential to individualize the administration of glucocorticoids. Based on these data, we recommend that glucocorticoid therapy can be implemented if the disease is in its early stage (within 10 days of onset), progressing rapidly (rapid disease deterioration within 24 h as well as a substantial increase in exudative pulmonary lesions), accompanied by a severe cytokine storm (IL-6/CRP values > 10 times the normal value), and the patient does not exhibit any obvious cellular immunosuppression (absolute lymphocyte count of $\geq 0.6 \times 10^9$/L). The drug should be administered at an appropriate dosage (medium dose of 40−160 mg/day) for a short-term course (usually 5 days and no more than 7−10 days).

Treatment of severe and critical cases

Due to the accumulation of clinical experience, treatment recommendations for severely and critically ill patients have been significantly improved and refined in the 7th edition guidelines, providing supplementary information for all treatment sections. These include emphasizing the importance of lung-protective ventilation, defining indications of extracorporeal membrane oxygenation and continuous renal replacement therapy in detail, as well as close monitoring of hemodynamic data. In terms of new treatment methods, in addition to the provision and refinement of specific indications for convalescent plasma and tocilizumab therapy, the 7th edition guidelines also include relevant recommendations and suggestions regarding the treatment of children and pregnant women.[2]

Comorbidities and rehabilitation

Existing clinical studies indicate that the mortality risk in elderly patients with COVID-19 is significantly higher than that in other age groups and that hypertension and diabetes may both be independent risk factors for poor prognosis in this patient population. Therefore, it is necessary to devote special attention to elderly patients, especially those with chronic underlying diseases, whose treatment course should consider both the primary infection and COVID-19.[12,13] Alternatively, the rehabilitation of COVID-19 patients, which includes both physiological and psychological components, is extremely important during the treatment course. The "COVID-19 Respiratory Rehabilitation Guidelines (2nd Edition)", issued by the Respiratory Rehabilitation Committee of the Chinese Association of Rehabilitation Medicine, is instructive and helpful in guiding the rehabilitation of patients with COVID-19.[14]

In conclusion, as a highly infectious disease, COVID-19 has become a global threat to public health. Therefore, it is essential that we study the virus, promptly learn from clinical experience, and establish global collaborations to fight the disease together, in order to achieve victory against COVID-19.

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Conflicts of interest

None.

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