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CHAPTER 7

Better understanding and control of new coronavirus infection

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1. How to better understand the 2019 coronavirus disease

We have been continuously deepening our understanding of 2019 coronavirus disease (COVID-19)—an emerging disease. Further knowledge on varying clinical manifestations, phenotypes, clinical course, acute and chronic conditions, susceptibility, as well as research to improve our ability in identification of susceptible populations and tracking the direction of evolution of the virus, are urgently needed.

COVID-19 has a wide spectrum of clinical manifestations, which are not limited to common respiratory tract symptoms, but also include various systemic reactions, such as fatigue and diarrhea. The reason why the World Health Organization named it 2019 coronavirus disease and not some kind of pneumonia or respiratory syndrome is that, in addition to the pulmonary involvement, this novel coronavirus also causes damage to multiple organs. Our accumulated experience on managing this emerging infectious disease is still far from sufficient.
The clinical manifestations, clinical course, prognosis, severity, and treatment response of the disease vary from individual to individual. Moreover, the virus itself has not yet entered a stable state. After being transferred to a human host, the virus will strive to adapt to this new host by evolution and mutation. How the interaction between the virus and the human body determines disease severity and acute and chronic processes, including persistent infection, requires further investigation. For now, many puzzles still exist regarding the disease in clinical practice. For example, whether different populations, interventions, or blocking methods will affect the adaptation, mutation, and evolution of this novel virus, and why hosts with different genetic characteristics have different responses to it, remain unclear. Therefore, we need to pay attention to some detailed and in-depth information on the disease at the early stage.

The coronavirus itself has a lot of complexity. It is unknown how this kind of pathogen will evolve or mutate next. Considering that the new coronavirus has an 80% nucleotide sequence similarity with SARS coronavirus, the International Committee on Taxonomy of Viruses officially named it SARS-CoV-2. From a biological perspective, although two pathogens have a homologous relationship, their phenotypes and biological natures are quite different when there is a 20% difference in nucleotide sequence. A huge knowledge gap remains on the immunogenicity of SARS-CoV-2 and its relationship with its host. SARS-CoV-2 is transferred from a natural host to the human body through a certain route to cause infection. Afterwards, the virus is prone to mutate or evolve for adaptation to the new host, which is the so-called "host adaptation" in biology.

Perhaps the virus’ ideal state is showing persistence or enhancement of transmissibility, but with relatively attenuated pathogenicity. If so, it can exist in the host for a relatively long period of time. The change of the pathogen itself is not only a dependent variable that modifies as the environment changes, but also an independent variable that affects disease conditions of the host. The interactions between the pathogen and the host contribute to different manifestation of the novel disease, which calls for special attention and improved understanding. It remains unclear in which direction the pathogen will evolve. Viruses of different origins have varied survival environments and survival opportunities. For example, all kinds of treatments, intervention measures, and hosts will make a virus change differently.

To sum up, we must fully recognize that after the new pathogen enters the new host of mankind, both pathogen and the host will change in an interactive manner, which is an important feature of this emerging disease.
The understanding of the occurrence and development of this novel disease in terms of viremia, ARDS, SOP-like change, hypercoagulability/fibrinolysis and VTE, myocardial injury and its related markers, AKI, and so on has been mentioned before.

In short, as COVID-19 is a newly occurring disease, clinical and scientific data are still limited, driving further exploration. It is necessary to master some basic knowledge on diagnosis and scientific laws of this disease. For example, nucleic acid detection should be carried out in multiple specimens from different body sites or body fluids simultaneously, including pharynx, saliva, lower respiratory tract secretions, blood, and anus; for antibody detection, IgM serves as an acute phase antibody, and IgG is used as a convalescent antibody.

2. Improving clinical management of respiratory tract virus infection and future research agenda

First, it is necessary to recognize the high frequency and threats of respiratory tract viruses; second, we need to establish a clinical-oriented detection platform; third, we must pay attention to the rational selection and application of antiviral drugs; fourth, we should conduct clinical and basic researches on respiratory tract viruses.

2.1 Detection of respiratory tract viruses: Etiological diagnosis of lung infection and emerging infectious diseases

First of all, identification of etiology could help guide medical treatment decisions. Second, ensuring early diagnosis and treatment of viral infection improves prognosis compared to initiating treatment later. The etiological examination is indispensable to achieve early treatment. Respiratory virus tests are necessary for reducing inappropriate use of antibiotics, surveillance of emerging infectious disease, and exploration of new prophylactic measures.

(1) Influenza detection, diagnosis, and treatment process. The whole process will be performed according to the demands of diagnosis and treatment, so it is necessary to determine whether patients manifest symptoms of influenza. For hospitalized patients presenting influenza manifestations, it is recommended to start empiric antiviral treatment and detection of influenza virus simultaneously. Judging whether hospitalization requirements and high risk factors exist helps us to conduct virus testing and prescribe medication.
Experience of respiratory tract virus detection. Currently, the existing rapid antigen detection reagents are not sensitive enough—PCR is still the gold standard diagnostic method. The positive detection rate in throat swabs is lower than that of lower respiratory tract specimens, especially in patients infected with avian influenza virus or SARS-CoV-2. Convalescent antibody is used for further diagnosis. IgM antibodies appear 3–7 days after the onset of COVID-19. Considering that virus isolation has a low positive rate, it only serves as an important research tool and should not be used for clinical diagnosis. Virus detection should not be limited to influenza viruses or novel coronavirus due to the possibility of infections caused by other respiratory tract viruses.

2.2 Establish a respiratory tract virus research platform for clinical diagnosis and treatment

Confirmed diagnosis requires clinical-oriented detection methods. Currently, many new molecular biological diagnostic methods are available, owing to the huge support of government to help many research teams carry out multidimensional basic research and explore new detection methods during the epidemic outbreak. For example, multiple PCR microfluidic technology (Film-Array and GeneXpert) could obtain detection results within 1–1.5h. There are also other new diagnostic techniques, such as chip technology (Verigene System and shinychip), matrix-assisted laser ionization resolution time-of-flight mass spectrometry (MALDI-TOF), Fourier transform infrared spectroscopy (FT-IR), second- and third-generation sequencing technology, as well as point-of-care testing. These techniques are expected to achieve "four high" requirements: high throughput, high speed, high sensitivity, and high precision. However, many of them are still in development or the early phase of clinical trials. Although the development of new detection techniques is not the area of expertise of our clinicians, the specificity, sensitivity, and influential factors of these methods in clinical application are the issues that clinicians should take into consideration and have a good command of. Relevant clinical research should be carried out, so that we can correctly interpret the results and guide clinical diagnosis.

We should ensure that the specimens are correctly collected and transported according to the appropriate standards, the laboratory test is conducted promptly, and the result is consistent with actual clinical conditions. The combination of respiratory tract virus detection results with
clinical diagnosis and treatment is essential to improve both detection and clinical diagnosis levels.

It has been gradually realized that multiple sampling at different time periods during the whole clinical course and conforming to a standardized process can improve the positive rate of virus detection. In order to reduce repeat tests, we performed a single testing by mixing throat swabs and nasal swabs together rather than separating the specimens for individual detection tests. It turned out that this method yields a higher positive rate and is more cost-effective. Therefore, detection of multiple specimens at the same time can improve the positive rate.

For influenza, prompt intervention and medication can reduce the risk of developing into severe cases and deaths. Therefore, early diagnosis cannot be emphasized enough due to its critical influence on patients’ prognosis.

2.3 Attach importance to rational selection and application of antiviral drugs

When using antiviral drugs, etiology, medication (drug classes, dosage, duration), and the application in special populations should be taken into account. Ten years ago, only a few antiviral drugs were available for clinical treatment. Currently, some newly developed antiviral drugs have been put into use, but there are still limited classes of drugs. It is estimated that there will be emerging antiviral drugs in the next decade.

2.4 Establish a comprehensive treatment platform for severe cases’ life support

ARDS, sometimes accompanied by multiple organ failure, is the most common reason for the lethality of viral pneumonia. Therefore, it is essential to establish a comprehensive treatment platform providing life support to severe cases, which also helps to control the epidemic.

Respiratory support should be graded according to the severity of the disease: at the early stage of disease, oxygen support or high flow oxygen therapy is recommended; when the disease progresses and dyspnea occurs, switching to noninvasive ventilation is advised; and severe patients may receive tracheal intubation for invasive ventilation.

During the outbreak of SARS, although there were no prospective controlled studies showing what kind of ventilation pattern and mask would be more effective, nasal CPAP masks were extensively used for treatment due to the following considerations. First, the noninvasive ventilation in SARS patients is continuously applied for a few days or even 1–2 weeks, among
which the nasal mask achieves the best patient compliance. Second, CPAP does not require man-machine synchronization, and the nasal CPAP mask is therefore preferred for 24-h continuous use, although there is no recommendation from evidence-based medicine.

Fig. 1 shows an H1N1 influenza patient admitted to the respiratory and critical care medicine department of the Guangzhou Institute of Respiratory Health. The patient was supported by ECMO because ventilation alone no longer helped. Managing such a critically ill patient is very challenging. The patient received ECMO support for 1 month and invasive ventilation for 2 months, and finally was successfully extubated and discharged from hospital.

Critical patients sharing similar clinical presentations with the patient illustrated in Fig. 1 are supposed to have survival opportunity in hospitals with relatively good resources, and the change of those patients’ long-term rehabilitation is usually good. There are many fibrous foci in the lungs on discharge, but patients can recover very well in 6 months to 1 year, and can even exercise and work normally. So for this kind of case, we should give comprehensive life support measures to reduce the mortality rate and ensure better long-term effects.
2.5 Develop clinical and basic research in respiratory tract virology

Carrying out scientific exploration and research on the respiratory tract virus with a combination of basic research and clinical work will provide guidance to improve our performance in clinical diagnosis and treatment. Clinical issues including early diagnosis, prompt intervention, early warning of developing into severe cases, and treatment of critically ill patients are all worth investigating. For example, clinical trials should be conducted to determine the specificity, sensitivity, positive predictive value, and negative predictive value of some newly developed detection methods, to establish a standard screening process, to optimize and explore the effects of early application of antiviral drugs, and to explore predictors of developing into severe cases (e.g., viral load, the dynamic change of inflammatory mediators). Patients at risk of progressing to severe cases are very likely to develop into critical illness that requires mechanical ventilation if they do not receive early treatment. Exploring specific treatments, especially convalescent plasma therapy, is urgently needed to prevent such patients from developing into critical cases. Managing severe cases requires comprehensive life support measures, and rigorous evidence-based clinical researches are awaited to guide the reasonable and appropriate use of respiratory support, including the optimal time period to initiate noninvasive ventilation, endotracheal intubation, and ECMO.

3. The need to conduct clinical research in an orderly way

One of the important hallmarks of medical maturity in China is the capability to perform diagnosis and treatment with rigorous standards based on the accumulated experience from past medical history, and to conduct research with great concentration. Considering the large number of current clinical researches, it is vital to strengthen coordination, and guarantee the quality of the implementation. A large amount of literature review and a preliminary observation of 2019 coronavirus disease are necessary for a good research design.

It is expected that in the future, clinical research can be carried out in a more orderly way. It is hoped that Chinese medical practitioners can stand at the forefront of international medical science in confronting clinical emergencies.
4. The importance of PCCM discipline development to cope with the epidemic situation

There is a general consensus among the firstline respiratory and critical care medicine specialists all over China that the tightly combined development of respiratory disease and critical care medicine, which is called pulmonary and critical care medicine (PCCM), is very important for coping with such an epidemic.

If there is no establishment and development of the discipline of PCCM, pulmonologists' understanding of critical care medicine will be insufficient, and their abilities in management of critically ill patients, treatment of respiratory failure and application of respiratory support will not match current performance. To treat COVID-19 patients with comprehensive therapies represented by antiviral drugs and respiratory support, it is necessary to combine etiological treatment and symptomatic treatment, and to have a deep understanding of the pathological changes of the respiratory system, respiratory physiology, and respiratory tract pathogens. The first group of colleagues who have completed PCCM training have acted with clear-minded determination and professionalism, becoming the most important backbone force among frontline fighters in the battle against the COVID-19 epidemic.

As the lungs are the major targets for SARS-CoV-2, most leading frontline experts are pulmonologists. After years of construction and development of PCCM, pulmonologists have shown professional capabilities in this public health emergency and the discipline of respiratory disease is transforming rapidly from scale enlargement to quality improvement. The COVID-19 epidemic is also a test for the achievements of our discipline construction and fellowship training program.

It is recommended that colleagues on the firstline response to COVID-19 from departments of respiratory and critical care medicine all over the country should have greater exchange of academic ideas and understanding of scientific laws of this disease. At the same time, we should focus on the future and take responsibility for preventing diseases from the perspective of discipline construction and fellowship training.

It remains unknown how long COVID-19 will last and whether it will return in the coming years. It has been the third time that coronavirus has endangered human health since the outbreak of SARS 17 years ago, and there is a significant possibility that other coronaviruses will emerge in the next few decades. Identifying coronavirus and determining its specific
effect on immune function are particularly worthy of our attention. What we have learned from the past and should plan for the future include the development of clinical discipline, the construction of emergency and public health systems, and the improvement of the overall public health system, especially the integration of clinical and preventive medicine.