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CHAPTER 4

Diagnosis of COVID-19

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1. Diagnosis

The diagnosis of COVID-19 is based on epidemiological history, clinical manifestations, and pathogenic confirmation.

1.1 Definition of suspected case

Patients who meet any one of the epidemiological criteria and any two of the clinical manifestations are suspected to have COVID-19. If there is no clear epidemiological history, three of the clinical manifestations should be met.

Since the first edition of the pneumonia diagnosis and treatment plan for novel coronavirus infection (trial) issued by the National Health Commission, it has been updated to the seventh edition, most of which was revised from late January to mid-February (second edition on January 18, third edition on January 22, fourth edition on January 27, fifth edition on February 4, revised on February 8, and sixth edition on February 18). The consecutive update of guidelines suggests that diagnosis should be constantly revised based on up-to-date clinical experience. The change of the definition of epidemiology is a good example. The current epidemiological history is as...
follows: (1) history of residence in or travel to Wuhan and surrounding areas or other communities with positive case reports within 14 days before onset; (2) history of contact with SARS-CoV-2-infected persons (with positive nucleic acid test) within 14 days before onset; (3) history of contact with patients from Wuhan and surrounding areas, or patients with fever or respiratory symptoms from a case-reporting community within 14 days before the onset of illness; or (4) clustered cases. Compared with the original diagnosis and treatment plan, the main change in the history of epidemiology is the update of travel history or residential history to Wuhan and surrounding areas, or other case-reporting communities. The first reason is that other areas have also found community cases, and second, the "exposure to fever and respiratory symptoms" has become increasingly blurred. It has also been emphasized that there is a history of contact with SARS-CoV-2 infected persons, and SARS-CoV-2 infection refers to those with positive detects of pathogenic nucleic acids, no matter where they come from.

At the same time, the definition of clinical performance has also been revised because of a better understanding of the disease. On the other hand, a contemporary revision fulfills the needs of different regions. For example, the primary update in clinical performance in the fifth version is to distinguish Hubei from other provinces. The diagnostic criteria for suspected cases in Hubei were greatly extended. In the diagnostic criteria of suspected cases (Hubei), the clinical manifestations were: fever and/or respiratory symptoms; the total leukocytes count in the early stage was normal or decreased; or reduced lymphocyte count. Compared with the previous clinical manifestations, it added "and/or respiratory symptoms" and did not require pneumonia. Patients with no definite history of epidemiology and those who met two of the clinical symptoms simultaneously were diagnosed as suspected cases. In the definition of suspected cases in other provinces except Hubei, the clinical manifestations were: fever and/or respiratory symptoms; imaging features of pneumonia; normal or decreased white blood cells at the early stage of onset; or decreased lymphocyte count. In accordance with any two of the clinical manifestations, regarding "without pneumonia" patients from outside of Hubei, pneumonia manifestations are not required in order to avoid missed diagnosis. Any of the three clinical manifestations are required with no specific epidemiological history. Starting from the sixth version, a difference in origin is no longer included in the definition of clinical manifestation, unified as follows: (1) fever and/or respiratory symptoms; (2) consistent with the imaging of COVID-19; or (3) normal or decreased total count of white blood cells in the early stage of the disease and normal or decreased lymphocyte count.
1.2 Definition of confirmed case

If any one of the following pathogenic or serological tests is positive, the patient is confirmed as COVID-19: (1) positive RT-PCR results for SARS-CoV-2 nucleic acid; (2) viral gene sequencing highly homologous to the known SARS-CoV-2; or (3) serum samples positive for SARS-CoV-2-specific IgM and IgG antibodies. The SARS-CoV-2-specific IgG antibody is required to change from negative to positive or the titers in the recovery period are required to be four times or higher than those in the acute phase.

In the fifth version of the plan, blood samples were added to the specimens except for respiratory tract specimens. Blood samples were collected from patients from whom it was difficult to obtain respiratory secretions. The sixth version was further revised, and nucleic acid tests no longer emphasized the detection of samples. As long as the SARS-CoV-2 was positive, it could be counted as a confirmed case.

1.3 Clinical diagnosis

The fifth edition of the program was specially designed for Hubei to establish the diagnostic criteria of "clinical diagnosis cases," which include clinical compliance with the characteristics of viral pneumonia, such as corresponding clinical symptoms and imaging CT findings, especially the multiple lobes exudative ground-glass shadow and intermittent consolidation, normal or decreased total count of white blood cells in laboratory examination, and reduced lymphocyte count. Even if there is a lack of nucleic acid test results, it can also be applied for clinical diagnosis. For patients who meet the clinical diagnostic criteria of COVID-19, they should be treated within a restricted space.

The reason for these criteria is that Hubei and Wuhan city have gathered a large number of suspected patients waiting for nucleic acid testing. According to the nucleic acid detection capability of Hubei province, it is difficult to complete all tests in a short time. Based on the intention of early diagnosis and treatment, such a clinical standard should be applied in Hubei in order to ensure that all patients receive timely treatment without developing into a severe or critical condition, in line with clinical practical needs. Meanwhile, patients with a clinical diagnosis should be isolated in time to reduce the risk of infection transmission. This is not applicable nationwide because cases throughout the country are sporadic, so we have adequate time for diagnosis and etiological examination. It is possible to give priority to frontline
isolation treatment. Therefore, the relevant provisions of the fifth edition are applicable only to Hubei province. Subsequently, this province has rapidly admitted suspected cases within a short period of time, and its nucleic acid detection capability has become able to meet the clinical needs. There is no requirement to distinguish between inside and outside Hubei province. In this context, when the sixth version of the plan was introduced, the clinical diagnosis criteria were unified in and out of Hubei province.

2. Etiological test

2.1 Respiratory tract virus detection

Novel coronavirus pneumonia is actually a form of community-acquired pneumonia (CAP). Pathogens causing CAP include bacteria, viruses, and atypical pathogens. In terms of when and what specimens should be collected for laboratory tests among CAP patients, the guidelines for diagnosis and treatment of adult community-acquired pneumonia in China (2016 edition) clearly recommend that under normal circumstances, outpatients do not have to receive an etiological examination. However, laboratory tests should be carried out under certain circumstances and for hospitalized patients. Etiological examinations are highly recommended in specific clinical situations with CAP. Five situations require respiratory virus screening: cluster outbreak, initial empiric treatment failure, severe cases, multiple lobe lesions, and immunodeficiency.

In cases where viral pneumonia is strongly suspected, the relevant virological examination should be considered. Currently, there are four recommended assays, including virus isolation and culture, serum-specific antibody detection, virus antigen detection, and nucleic acid detection. Since virus isolation and culture are very challenging, they are only used for laboratory research instead of as diagnostic criteria. Serum-specific antibody tests include IgM and IgG. IgM presents only within a shorter time, while IgG is only found in convalescent serum, which limits its value for diagnosis. Therefore, in practical clinical diagnosis, there are two main indicators of viral pneumonia. One is viral antigen detection, which includes direct immunofluorescence assay (DFA) and the colloidal gold method. The colloidal gold method is more widely used; however, although it has good specificity, its sensitivity is not high. The other indicator is nucleic acid detection. In the diagnosis of influenza A, for instance, the main methods of clinical application are virus antigen detection (such as colloidal gold detection) and nucleic acid detection. Therefore, nucleic acid detection is critical.
2.2 Nucleic acid detection for SARS-CoV-2

In the detection of SARS-CoV-2, nucleic acid detection is used as the laboratory diagnostic standard of confirmed cases. Positive means that novel coronavirus nucleic acids can be detected in specimens of nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, or feces. In the sixth edition, the source of samples is no longer required. As long as nucleic acid detection is positive, it can be diagnosed. The methods are: (1) real-time fluorescence RT-PCR detection of SARS-CoV-2 nucleic acid positive and (2) viral gene sequencing, highly homologous with the known novel coronavirus.

Nucleic acid detection is an irreplaceable diagnostic method: it is critical for optimized use of limited medical resources and timely treatment of patients. First, the detection of pathogen antibodies has a window period, and antibodies present at the late phase, usually later than nucleic acid detection. Second, the sensitivity of nucleic acid detection is much higher than other laboratory detection methods, as mentioned above. Third, nucleic acid detection is possible earlier than detection through changes in chest CT images, which has allowed us to identify asymptomatic COVID-19 patients. Fourth, quantitative nucleic acid detection can enable us to monitor dynamically the level of virus infection and observe the therapeutic effect.

PCR detection is a method to detect the change of amplification product from each PCR cycle by measuring fluorescence intensity, which is a quantitative analysis method for the initial template. Many clinical real-time quantitative PCR detection kits are available for clinical use. Although PCR tests are very sensitive, the detection rate can only reach 30%–50%. It requires clinicians to go carefully over the epidemiology, clinical imaging, and dynamic changes, and not simply rule out infection due to a negative result of an upper respiratory tract examination. Dynamic follow-ups and repeated examinations can help improve the accuracy of diagnosis.

The wide application of the next generation of gene sequencing technology (NGS) has given us a better understanding of the sequencing of the pathogenic genes. NGS is designed to sequence the gene of the specimen. If the gene is highly homologous with the known SARS-CoV-2 gene, then it can be determined. The method is accurate and effective, which can be used in final confirmation for a controversial sample, monitoring of virus mutation, and origin tracing, but the cost is relatively high. The process is complex, requiring sequencing and professional bioinformatics analysis.
Gene sequencing offers various advantages. First, the virus cannot be detected by PCR when mutation happens during the transmission process. However, high depth metagenomic sequencing (the total reads number of sequencing is no less than the 80 M DNA sequence) can compensate for the shortcomings of RT-PCR and monitor the potential variation. Second, viral load in some samples is too low to be detected by RT-PCR. Metagenomic sequencing assay can effectively improve the detection rate when the human origin background is low. Third, for suspected cases with negative detection of SARS-CoV-2, metagenomic sequencing can provide effective information on other possible pathogens. Fourth, metagenomic sequencing can also provide related pathogen information on multiple or secondary infection.

The PCR assay is easy to operate and fast with low cost, making it more suitable for processing large numbers of patients, whereas NGS is expensive and time consuming, which is difficult for mass inspection. Therefore, PCR is more applicable for census. In cases where a patient happens to have a positive result followed by a negative one, a gene-sequencing test should be used. If a patient has typical clinical symptoms but provides a negative result, we recommend the use of NGS because existing PCR kits may fail in detection due to gene mutation. Moreover, in critically ill patients who are suspected of mixed viral and bacterial infections besides SARS-CoV-2, or with immunocompromised status such as diabetes or receiving immunosuppressive agents, NGS is also strongly recommended. We have to make use of NGS because it has more advantages than PCR assay.

A combination of RT-PCR and metagenomic detection is highly recommended to detect SARS-CoV-2 comprehensively and effectively, as well as to monitor the potential viral mutation during the transmission process.

2.3 Problems and troubleshooting in PCR testing

At present, the problems encountered in virus nucleic acid detection may come from the following:

(1) Timing and location malfunction of specimen collection. The organs impacted by the virus change over time. The virus affects the upper respiratory tract at the onset of the disease. This then clears, while the viral load in the lower respiratory tract increases. Therefore, it would be better to collect specimens from the lower respiratory tract (deep sputum, BALF). BALF is optimal but it is difficult to obtain
and time consuming, with a high risk of transmission. Not all patients require this or are suitable. Among critically ill patients, deep sputum is also not easy to obtain, but it would be more useful, even if it is “saliva sputum,” than specimens of nasopharyngeal swabs. Although nasopharyngeal swabs are most commonly used, their optimal collection time remains unknown. According to the characteristic of influenza A, it reaches a peak at 24–72 h and then drops rapidly. It is possible that SARS-CoV-2 may have a similar rate of change to influenza and become undetectable from nasopharyngeal swabs at the late stage. In addition, limitation of accuracy may also be related to human factors. The firstline officials undergo enormous risk of infection, which may lead to incomplete and malfunctional sampling. The standards of procedure as well as the quality of swab product are also crucial.

(2) Sample shipping limitation. The preservation and transportation of samples have influence on the results. Unlike DNA virus, RNA virus is much more likely to mutate and degrade. During the collection process, the nucleic acid of RNA virus is one of the most difficult biological molecules to maintain in a stable condition due to self-degradation and enzyme-mediated degradation. Samples containing viral RNA should be stored in a dedicated virus preservation solution, and must be stored in refrigerated conditions (i.e., 4°C or colder) and delivered for inspection as soon as possible. Whether a laboratory has the capability to conduct a professional test is also one of the key factors.

(3) Reagent kit issue. Several commercial PCR kits were introduced after the nucleic acid detection standard was announced. The national FDA initially screened 7 of 53 capable companies, and 4 of them eventually passed the expedited process on January 26. They were the detection kit for SARS-CoV-2 from Beijing Genomics Institution (BGI), DNBSEQ-T7 sequencing system, SARS-CoV-2 nucleic acid detection kit from Shanghai Jienuo (RT-PCR), and SARS-CoV-2 nucleic acid detection kit from Shanghai ZJ Bio-Tech (RT-PCR), followed by another three companies. However, such a rush launch inevitably brought much negative feedback regarding product quality and over-promising in advertisements, such as “quick response in only ten minutes,” and “100% sensitivity and specificity.” In addition, more clinical evidence is still required as a reference upon laws for registration renewal as well as subsequently clinical application.

(4) The absence of large sample studies and clinical evidence. It needs to be determined whether these detection kits detect completely and
accurately in clinical application. Most of the novel coronavirus reagents are targeted at specific areas of SARS-CoV-2. The \textit{ORF1ab} gene and \textit{N} gene are measured with fluorescence intensity by RT-PCR. The current reagent can only design primers based on existing data, which limits comprehensive understanding in the real world. In addition, the research on SARS-CoV-2 has just started; several questions need to be answered, such as the frequency of variation of viral gene, mutation hotspots, or conservative regions of evolution. Whether any false negatives exist due to the mutation in the amplification area requires further observation.

Future strategies and development directions for nucleic acid detection are as follows:

1. Standardize the protocol of specimen collection. Try to collect lower respiratory tract specimens, especially BALF or deep phlegm, to improve the positive rate. Master timing of collection: nasopharyngeal swabs for the early phase and BALF for the late phase. However, this does not mean that nasopharyngeal swabs are useless at the late stage. For instance, two patients with confirmed COVID-19 were hospitalized for almost 20 days. During hospitalization, nucleic acid testing was conducted intermittently and the results remained positive until day 20. Standard operation procedures of nasopharyngeal and throat swabs include appropriate personal protective equipment (medical N95 masks, goggles, gloves, protective masks, protective suits, etc.), authorized nasopharyngeal and throat swab products for collection, and standard laboratory operating procedures. Unlike ordinary cotton swabs, well-designed swabs are expensive. Samples can be collected through the pharynx as well as the nasal cavity. If we only collect in the area of the nostrils, the positive rate will be low. Therefore, the method of collecting nasopharyngeal swabs is critical.

Regarding the sampling sites, nucleic acid can be collected from five places: (1) nasopharyngeal swabs; (2) saliva under the tongue when getting up next morning, where the virus accumulates easily; (3) deep respiratory secretions, including phlegm, aspiration, or bronchoalveolar lavage fluid; (4) blood, in which the viral load is relatively high during viremia; and (5) anal swabs, preferring rectal mucosa swabs. Based on experience from some institutions, the anal swab can still be positive when the throat swab becomes negative. Faced with this novel disease, we have to avoid deducing the whole picture of its pathogenesis only from partial experience. We have to think of the whole procedure from sampling to detection, and take into account collection sites as well as distribution of the virus \textit{in vivo}.  

(2) Improve the delivery of specimens. Collect and ship specimens in time; reduce the degradation of RNA virus nucleic acid; store in a dedicated viral preservation solution and refrigerator (i.e., 4°C or lower); and expedite the transportation process and save waiting time for detection.

(3) Improve approval process of kit production. To expedite the verification and approval process of reliable reagent manufacturers, the National Health Commission has verified seven companies that can produce reliable commercial detection kits for clinical application. Meanwhile, we have to promote the construction of a P2 laboratory (Physical Containment Level 2) in the designated hospital, to give access to more hospitals. More attention needs to be paid to the biosafety issues in laboratories. In order to ensure the quality of test reagents, all manufacturers need to complete all the clinical verifications in accordance with the requirements of laws and regulations so that they can be registered for routine clinical diagnosis.

The performance from different manufacturers is not equal. The reasons are as follows: ① The specificity and efficiency of primer probe systems require good reference sequences, bioinformatics analysis ability, and suitable target areas. ② The stability of the process system requires extensive development of *in vitro* diagnostic reagents and the establishment of a stable and efficient production process system. We hope to select reliable kits with higher sensitivity to improve the positive rate and reliability. We should select the reagents with stable performance that are validated by clinical positive samples and subsequently obtain NMPA registration certificates. In this way, the quality of products can be guaranteed.

(4) Improve the detection technology. A standard virus-specific detection area is required. SARS-CoV-2 is a linear single-stranded RNA (ssRNA) virus with a total length of 29,903 nucleotides, containing 10 genes. After analyzing the complete genome sequence of SARS-CoV-2, three genetic regions (ORF1ab, E, N) of the virus were recommended by the National Health Committee, which can be used as target sequences for the design of primer probes. Coronavirus is a large class of viruses, including SARS, MERS, and other coronaviruses causing the common cold. The E and N genes are relatively conserved in the coronavirus, especially within coronavirus 229E/OC43/HKU-1, which can infect human beings but has poor transmission capability. The virus above exists within the natural environment cycle; therefore, target sequence detection may lead to cross positive responses from other species of coronavirus. To avoid cross contamination, a good reference sequence and powerful bioinformatics analysis capability are required to design the specific region of novel coronavirus
for suitable primer probes. Recent studies showed that the specific region mainly concentrates on the *ORF1ab* gene and *S* gene. For the detection genes, fewer are better. In fact, the primer probes will interfere with each other, leading to the decrease of sensitivity. The double domain will be weaker than the single one, and triple will be still weaker. For example, in HIV detection kits, the target sequence includes *gag* and *env* genes, and only one of them is detected, which has already achieved high sensitivity and accuracy.

(5) Comprehensive assessment (back to bedside). Finally, we have to emphasize that results of nucleic acid tests should be interpreted back to clinical practice. We should speed up the production of kits of good quality, improve construction of laboratories, and standardize clinical practice, especially in primary hospitals and healthcare centers. We should standardize the process of collecting clinical specimens and laboratory testing to ensure the reliable interpretation of experimental results. Based on the clinical manifestations and epidemiological history, it would be better to make a comprehensive evaluation and to avoid making a decision only on numerical results.

In conclusion, the optimal detection methods need selection from the baseline. First of all is quality control of the sampling process, including whether the swab and the transport medium used for sampling, sampling manipulation, and storage and shipping temperature are appropriate. Second, a reliable detection kit is required. Finally, a reasonable judgment and interpretation of the results are also required. Since various pathogens can share similar signs and symptoms of respiratory infection, we should not ignore the possibility of other respiratory tract pathogens.

### 2.4 Antibody detection assay for SARS-CoV-2

To date, there are few antigen detection reagents for clinical use. The detection of coronavirus antigen is prone to cross reactions. It is difficult to select antigen recognition sites and the key point is to find the specific designed binding domain for antibodies. For example, the antigen detection reagent developed by the Institute of Pathogen Biology of the Chinese Academy of Medical Sciences/Beijing Union Medical College is facing a challenge in how to select more sensitive antibodies by ensuring the level of specificity. The current reagents need to solve the cross contamination issue with known pathogens, and need to be refined constantly. Antigen test assay is characterized by rapid and specific diagnosis—for instance, that used in influenza viruses detection. We hope that the method of antigen detection assay can be applied to COVID-19 detection in the near future.
Antibody detection assay has become a relatively reliable method in clinical use. There are many kinds of antibodies, such as viral-specific antibodies, IgM at the early phase, and IgG at the convalescent phase, which is a major component of neutralizing antibodies. We should also pay attention to IgA at the early phase, which presents at the same time as IgM or even earlier. However, the role of airway-secreted IgA requires further investigation.

In addition, the evaluation of neutralizing antibodies determines the real antiviral effect; however, to date, it has not become feasible to evaluate neutralizing antibodies. The RBD antibody detection assay seems to have only a weak prediction value on neutralizing antibodies, but more assays are needed. Currently, specific IgG and IgM are mainly used for disease diagnosis. If we plan to use convalescent plasma as a therapeutic strategy, we have to preevaluate the level of antibodies in the donators, at least the level of IgG. The evidence suggested that the plasma level of specific IgG at the recovery stage corresponds to the level of the neutralizing antibody. In a recent study from Wuhan Tongji Hospital, two critically ill patients received convalescent plasma and the level of neutralizing antibody reached up to 1:640. In short, antibody detection is not only for pathogen diagnosis but also for the overall situation of the disease.

3. Severity evaluation

COVID-19 can be classified as mild, moderate, severe, and critical, as follows:

(i) **Mild:** Clinical symptoms are few, with no pneumonia manifestation on lung imaging. (ii) **Moderate:** Fever and respiratory symptoms with pneumonia manifestation on imaging; without dyspnea or other complications. (iii) **Severe:** Patients meet any of the following criteria: shortness of breath, respiratory rate (RR) ≥30 beats/min; resting state, oxygen saturation ≤93%; partial pressure of arterial oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) ≤300 mmHg (1 mmHg = 0.133 kPa). At higher altitudes (>1000 m), PaO₂/FiO₂ should be corrected according to the following formula: PaO₂/FiO₂ × [atmospheric pressure (mmHg)/760]; pulmonary imaging shows that the lesions have developed by >50% within 24–48 h. (iv) **Critical:** Patients with one of the following criteria: respiratory failure requiring mechanical ventilation; shock; and multiorgan failure requiring ICU monitoring and treatment.

We list the following risk factors of severe COVID-19: (i) elderly patient (age >65 years); (ii) comorbidities, such as hypertension, diabetes, and coronary
heart disease; (iii) progressive decrease in peripheral blood lymphocytes, CD4+ T lymphocyte count < 250/µL; (iv) progressive increase in serum level of inflammatory factors, such as interleukin (IL)-6 and C-reactive protein; (v) progressive increase in lactic acid and lactic dehydrogenase (LDH) > 2 times over the upper limit of normal value; (vi) intrapulmonary lesions significantly progressed by > 50% within 2–3 days; (vii) metabolic alkalosis; (viii) high sequential organ failure assessment scores; and (ix) D-dimer levels > 1 mg/L at admission.

4. Differential diagnosis

In the differential diagnosis of COVID-19, we need to clarify several issues during winter and spring seasons.

First, diagnosis of pneumonia, in general, must have imaging changes. However, the WHO defines novel coronavirus pneumonia as “COVID-19” mainly because it includes mild infections, like influenza. Similar to coronavirus, we find that that many patients with influenza will not develop pneumonia, just a mild infection with upper respiratory tract or systemic symptoms. Therefore, in the sixth edition of the diagnosis and treatment plan, we proposed a differential diagnosis according to the mild infection and novel coronavirus pneumonia.

Second, mild COVID-19 should be distinguished from the common cold and influenza. The common cold primarily presents with low fever and catarrhal symptoms without seasonality. Although the entire population is vulnerable, it is typically self-limiting. Influenza can cause more systemic symptoms, such as headache and myalgia, with the most prevalent period from late November to the end of the following February. We should not ignore mild infection of SARS-CoV-2 by only focusing on other common upper respiratory tract infection viruses.

Third, for moderate, severe, and critical cases with different levels of pulmonary infiltration, epidemiological and medical history, laboratory examination, and imaging findings should be incorporated to distinguish from other types of pneumonia caused by viral (such as influenza virus, parainfluenza virus, adenovirus, respiratory syncytial virus, rhinovirus, metapneumovirus, other coronaviruses, and other known viruses) or atypical (such as Mycoplasma pneumoniae and Chlamydia pneumoniae pneumonia) pathogens. Before the breakout of novel SARS-CoV-2, during the annual winter and spring seasons, those viruses causing pneumonia were very common,
and a main cause of mortality. Therefore, especially out of Wuhan and Hubei, most cases of COVID-19 are mostly imported. The confirmation of pneumonia caused by SARS-CoV-2 should be particularly cautious. For example, after the announcement of a top-level alert in Shanghai, we received dozens and hundreds of fever cases in clinics at different hospitals. However, there were only a few COVID-19 cases in Shanghai. Most febrile patients actually had a common upper respiratory tract infection such as influenza or adenovirus pneumonia. Therefore, we have to make a comprehensive differentiating diagnosis, especially in places outside Hubei and Wuhan, and recognize the possibility of noninfectious diseases such as vasculitis, dermatomyositis, and organic pneumonia.

Fourth, special emphasis should be placed on the detection of suspected respiratory tract pathogens by means of rapid antigen detection and multiplex PCR nucleic acid detection.

Due to the lack of specificity in clinical manifestations, it is difficult to identify influenza, COVID-19, or other pneumonia only by clinical manifestations. In Fig. 4.1, the left panel shows influenza viral pneumonia and the right panel shows RSV viral pneumonia. It is difficult to identify pathogens just from CT imaging. Although the imaging features of different viral pneumonia have their own characteristics, the specificity is low. We have to establish a set of virological detection methods for clinical needs, which help us better guide clinical diagnosis and identification as well as improve the efficacy of treatment.

Fifth, clear diagnosis, isolation of patients in time, infection prevention, and avoiding excessive consumption of medical resources are vital.

Fig. 4.1 Imaging findings of influenza virus pneumonia (left) and RSV virus pneumonia (right).
5. Cases reporting procedure

Since COVID-19 has been classified as a secondary-level infectious disease, but management is as primary level, medical workers at all levels of medical institutions should start an isolation process as soon as suspected cases are defined. After consultation with the designated senior experts, suspected cases have to be reported to the network within 2h. A SARS-CoV-2 nucleic acid test for respiratory tract or blood specimens should be conducted and the patients should be transferred to the designated hospital at the same time. Those intimate contactors who had an epidemiological correlation with the suspected case must also receive an etiological test, even if the common respiratory pathogen tests were positive.

While waiting for the response of the nucleic acid test, the patient should be transferred to a designated hospital by ambulance. It should be emphasized that the patient’s condition and severity should be judged and safety is the priority. Moreover, since it is flu season, a SARS-CoV–2 nucleic acid test should also be carried out with a history of COVID-19 contact, even if the influenza test is positive. Evidence suggests that about 10% of cases suffer mixed infections at the same time. Be aware of those patients with positive influenza tests, because they may infect family on returning home, or lead to a hospital outbreak when admitted to a general ward.

6. Exclusion of cases

Two consecutive negative respiratory tract nucleic acid detection results (sampling interval of at least 1 day) can exclude the diagnosis of COVID-19. However, different points of view suggest that the period of two detections of nucleic acid at the onset of the disease could be less than 6 days, and all the nucleic acid results could be false negative. Therefore, during the onset of illness, it is recommended to have a CT scan 3 days before admission. Patients with typical imaging changes should not be allowed to return home even if two nucleic acid tests are negative.