Chapter 13
Concurrence of Tuberculosis and Other Major Diseases

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13.1 Concurrence of Tuberculosis and Diabetes

In medical literature, descriptions of concurrence of tuberculosis (TB) with diabetes mellitus can be traced back to Richard Morton's 1694 text, *Phthisiologia*, which suggested that the association between the two diseases could have been observed as early as in Roman times. Nowadays, continuous development of the social economy, which has dramatically changed people's daily diets, has been sharply increasing the incidence of diabetes worldwide (Ottmani et al. 2010). At the same time, the TB epidemic has experienced a resurgence, especially in developing countries in the past two decades, thus resulting in the increased incidence of the combination of these two diseases (Hassani et al. 2005). The two diseases interact to cause additional clinical problems, and this has become a new challenge in TB control (Dooley and Chaisson 2009).

Diabetes is a major risk factor for people infected with TB to develop active disease. Several case–control studies have shown that the relative odds of developing TB in diabetic patients ranges from 2.44 to 8.33 compared with nondiabetic patients (Mboussa et al. 2003; Coker et al. 2006; Jabbar et al. 2006; Shetty et al. 2006). Diabetes is also the most common clinical complication in TB patients. TB patients with diabetes usually have more risk factors for treatment failure, including a higher proportion of smear-positives and large numbers of voids. Patients with concurrence of TB and diabetes also increase the spread of TB infection, thus aggravating the TB epidemic.

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13.1.1 Pathogenesis of TB/Diabetes

Chronic diabetic patients almost always develop clinical symptoms in cardiovascular, nervous, urinary, and immune systems, eventually resulting in dysfunctions of immune system and metabolic disorders. Many studies have shown that abnormalities of some critical cytokine secretions, including IL-1β, TNF-α, and IFN-γ, might be responsible for nonspecific immune deficiency in diabetes patients (Banerjee and Banerjee 2005; Stalenhoef et al. 2008; Al-Attiyah and Mustafa 2009). The onset of TB disease and worsening of TB infections are related to immune deficiency or dysfunction (Stalenhoef et al. 2008).

Diabetes patients' long-term exposure to high blood sugar can also affect their white blood cells' ability for phagocytosis and exocytosis. Electronic microscopy (EM) studies show that white blood cells of diabetics exhibit less protrusion and deformation, reduced phagocytosis and lysosomal functions, and that cytoplasmic organelles are rarely seen. The lower functional ability of alveolar macrophages in diabetics provides more favorable conditions for the replication of TB pathogen, thus increasing TB susceptibility in diabetic patients. In the bronchoalveolar lavage fluid of TB patients with diabetes, alveolar macrophages and their H_2O_2 production are both significantly lower than normal. These factors are negatively correlated to the range of lung lesions and the bacteria quantity in sputum.

Fat metabolism disorders in diabetic patients are often accompanied by hyperlipidemia, which means their levels of triglycerides are higher than normal. One of the triglyceride metabolic products, glycerol, is an important carbon source for *Mycobacterium tuberculosis* growth and reproduction. Deficient protein metabolism may lead to hypoproteinemia and malnutrition which reduces the body's defense capabilities and repair ability.

Many diabetic patients also experience liver dysfunction, reducing the conversion of carotene to vitamin A. As a result, the airway epithelial cells decline in defense. The thickened alveolar epithelium could decrease diffusion capacity and increase glycated hemoglobin, which is not conducive to oxygen release. Tissue with lower oxygen content increases the incidence of TB.

TB has an adverse impact on diabetics as well. Tuberculous fever will increase insulin consumption and the burden on islet cells (Xie 1999). At the same time, chronic consumption of active TB could lead to islet cell malnutrition and decreased function (Dooley and Chaisson 2009). As a result, the risk of people developing diabetes increases, or existing diabetes can be aggravated, and some acute complications such as diabetic ketoacidosis may be induced.

13.1.2 Diagnosis of TB/Diabetes

Patients with both diabetes and pulmonary TB almost always have diabetes first (Feleke et al. 1999). The incidence of TB is higher in diabetic than nondiabetic patients, with the main onset age of 40–69 years (Restrepo et al. 2007). Diabetic

patients may be asymptomatic in the early stage, but once high blood sugar occurs, polydipsia, polyphagia, polyuria, weight loss, and other symptoms will appear, and even diabetic ketoacidosis will occur in severe patients. The WHO officially announced the diabetes diagnostic criteria in 1999: Fasting Plasma Glucose (FPG) level ≥7.0 mmol/L (126 mg/dL); Oral Glucose Tolerance Test (OGTT) glucose levels ≥11.1 mmol/L (200 mg/dL) at the 2 h time point; patient has symptoms of high blood sugar, and his/her plasma glucose is ≥11.1 mmol/L (200 mg/dL) at any time. If there are no symptoms of high blood sugar, then one of these criteria (FPG, OGTT, or non-fasting plasma glucose levels) should be checked again. In 2010, the American Diabetes Association added a glycosylated hemoglobin (HBGA1c) value of ≥6.5 % to the diagnostic criteria above (American Diabetes Association 2010).

Patients with both diabetes and pulmonary TB do not have specific respiratory symptoms. They may have symptoms of TB such as cough, sputum, fever, night sweats, and so on, but the symptoms are often more acute onset, with purulent sputum and hemoptysis. Therefore patients with both diabetes and pulmonary TB are easily misdiagnosed as having acute pneumonia or pulmonary suppuration. Lung wet rale occurs if there are extensive lesions or combined infections. Often, chest X-rays show that saturated, exudated, or cheese-like lesions are most common and they are easily fused, forming cavities and spreading in the bronchus. The lesion sites are not only at the common preferred site of TB but all over the lung lobes as well. The rate of lower lung lobe lesions of TB is higher in TB/diabetic patients than the patients who have TB alone. Cavity formation is more common in TB/diabetic patients, and fluid levels can occur within the hollow region (Pérez-Guzmán et al. 2000, 2001). In addition, the rate of lower lung lobe lesions of TB and cavity formation will increase as the years progress. The sputum smear-positive ratio is higher in TB/diabetic patients than those without diabetes mellitus and there are more drug-resistant (DR) and multidrug-resistant (MDR) patients in the former group (Bashar et al. 2001; Subhash et al. 2003).

In patients with diabetes mellitus, it is important to distinguish between those infected with TB and those with other pulmonary infectious diseases. Diabetics are 32.7–90.5 % more susceptible than the general population to infection with respiratory diseases like pneumonia and acute exacerbation of chronic bronchitis (Marvisi et al. 1996). Characteristics such as cough, sputum, and fever should be noted in the diagnosis. Blood and sputum pathogens should be tested. When performing imaging examination, samples should be taken of tumors/lesions to distinguish between TB and lung or bronchial cancer.

13.1.3 Treatment of TB/Diabetic Patients

For the anti-TB treatment of patients with TB/diabetes, three or four drugs, such as isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (EMB), and/or streptomycin (SM), are usually applied together in the chemotherapy program. Generally speaking, it takes 1–1.5 years to complete a whole course of treatment for

TB, which is longer than for patients with pulmonary TB alone. If drug-resistant TB is confirmed, an even longer course is required with the appropriate drugs according to drug susceptibility testing. Some scholars believe that short-course chemotherapy programs are also appropriate for concurrent treatment of these two diseases. Studies have shown that the sputum conversion rate of new smear-positive patients after 6 months treatment could reach 94 %. Sputum conversion can fail when the patient is older than 45, has a high pretreatment smear grade, and/or has lung field lesions in more than two lung lobes (Banu Rekha et al. 2007). At present, there has not been a randomized controlled study of multicentered large numbers of samples, and there is no standard program indicating the specific time for the course of treatment. It is thought that blood glucose control is the key point for treatment in the patients with both TB and diabetes. If patients' blood glucose control is good to excellent, their sputum conversion rate after both 2 months and after 6 months of treatment will be higher than those whose blood glucose is poorly controlled (Zeng et al. 2006). But there are different views (Balasubramanian et al. 2007). The recurrence rate of pulmonary TB combined with diabetes is higher than that of nondiabetics, especially for the patients with poor glucose control.

Treatment of diabetes is a comprehensive program involving health education, diet, exercise, medication, and blood glucose monitoring. It aims to maintain blood sugar within a standard safety range and to avoid or reduce the incidence of complications. Specific measures could refer to the diabetes-related treatment guidelines. The TB patients' physical status is in chronic consumption, so they require a reasonable calorie intake. High-quality protein should be the main source, which, along with increased intake of both vitamins and dietary fiber, could improve in TB site repairing. Patients with hypoalbuminemia should take special care to increase their protein intake. In addition to the daily calories required (calculated according to patient body weight and activity), appropriate additional energy could be added by increasing carbohydrates to up to 45–60 % of the total calories consumed (Chinese Diabetes Society, China Medicine Doctor Association Nutrition Doctor Specialized Committee 2015). Some studies have shown that the plasma concentration of anti-TB drugs in TB patients with diabetes may be reduced, thus reducing the effectiveness of TB treatment (Nijland et al. 2006; Ruslami et al. 2010). Anti-TB drugs can impact diabetes. INH can interfere with the normal glucose metabolism, increasing sugar in urine and blood and increasing peripheral neuritis as well. RIF is a liver enzyme inducer, which could accelerate the metabolism of sulfonylurea and shorten its half-life, weakening its hypoglycemic effect. Aminoglycosides and fluoroquinolones are harmful to the kidneys. Ethambutol can cause optic neuritis. These drugs should be used with caution in the clinic and patients should be monitored.

As the incidence of diabetes increases worldwide, it becomes increasingly important to control and treat TB effectively in diabetic patients. More prospective studies should be carried out for further improvement to achieve the aim of early detection and early treatment, especially in developing countries.

13.2 Silicosis and TB

Silicosis is due to the long-term inhalation of dust containing free silica, with extensive nodular fibrosis in lung tissues as its main characteristic (Barboza et al. 2008). There are three clinical forms: chronic silicosis, acute silicosis, and accelerating silicosis between the chronic and acute forms. Different clinical manifestations have significant relationships with the exposure of dust concentration levels, silica content, and exposure times. Chronic silicosis is the most common clinical form.

Silicosis and TB are correlated. Studies have shown that pulmonary TB incidence for silicosis patients is 2.8–39 times greater than in the normal population and the incidence of nonpulmonary TB is 3.7 times greater (Barboza et al. 2008). About 61 % of silicosis patients also have pleurisy.

13.2.1 Pathogenesis of Concurrence of Silicosis and TB

We don't know exactly why patients with silicosis can easily suffer TB. TB progression is correlated with macrophages (the effector cells) and T cells (the reactive cells) of the cellular immune system. Silica dust has a cytotoxic effect on lung macrophages, causing metabolic damage to pulmonary macrophages and leading to macrophage necrosis. It was recently found that there is surfactant-associated protein A (SP-A) in silicosis bronchial washing fluid (Lesur et al. 1993). SP-A can activate alveolar macrophages and inhibit the formation of free nitrogen, making patients susceptible to *M. tuberculosis* (Samten et al. 2008). In addition, *M. tuberculosis* may escape from macrophage phagocytosis by going into the silica nodules. Activated macrophages can swallow silica very quickly and then the cell's own lysosomes release and collapse. The cell dies quickly, releasing many materials that could stimulate fibroblasts. As a result, pulmonary capillary beds and the lymphatic system can be seriously damaged, with blood vessel walls thickened and deformed. The lumen can narrow or become occluded, reducing blood circulation to the lungs. The reduced blood supply weakens the lung tissue's resistance to TB bacteria. Pulmonary lymphatic system fibrosis can prevent the lymphatic system from resisting *M. tuberculosis* invasion.

While the pathogenesis of silicon TB is the result of many factors, silica dust deposited in the lung can destroy the cellular immune response to TB. This makes acquired immunity to TB hard to establish in silicosis patients.

13.2.2 Diagnosis and Identification of Silicon TB

Diagnosis of silicon TB includes diagnosis of each disease. The first step is to make a definite diagnosis of silicosis, and then to test whether it is combined with TB. If somebody has close contact with silica dust, clinical manifestation and imaging

features should be analyzed to make a comprehensive diagnosis of silicosis. Sputum smear or bacteria culture is the most reliable method in diagnosis of silicon TB. Generally speaking, the sputum bacteria positive rate of patients with silicon TB is higher due to high cavity incidence. But there are concerns that it is easy to get false negative results for silicosis because of extensive fibrosis and bronchial distortion which complicate the discharge of *M. tuberculosis* (Xie 1999; Chen et al. 2005). Therefore, the bronchial alveolar fluid (BALF) smear or *M. tuberculosis* culture and/or bronchial biopsy can be used for diagnosis if necessary.

Silicosis patients may have TB if their chest X-ray shows the following signs as noted by Calvert et al. (2003):

- There are small pieces of asymmetrical shadows with uneven density in the apex of the lung or sulcus of the subclavian artery.
- The silicon nodules in the upper and middle lung lobes increase significantly in a short period of time, and the nodules' profiles are not discernable, with various ranges in size and density.
- There are sheets of asymmetrical shadows with indistinct profile and uneven density which are connected to lung hila by cable-like shadow of draining bronchus.
- The shadow bulk significantly increases within a short period of time, with no draw back towards the heart, and the lesions spread mainly anterior or around, instead of in a vertical direction into the ribs.
- Big and irregular cavities form in a short period, and lesions disseminate ipsilaterally or contralaterally.
- There are lumpy shadows with unclear outlines, and extensive pleura that are thickened and adhering locally.
- There is pleural effusion (fluid leakage excluded).
- After regular anti-TB treatment for more than 6 months, the abnormal lung shadows are significantly improved.

Silicon TB should be distinguished from other lung diseases because its various X-ray patterns are similar to the imaging of other lung diseases. Silicosis nodes should be distinguished from lung cancer and metastatic lung cancer. Lumpy silicon TB should be distinguished from lung cancer. Lumpy silicon TB should be identified from pure bulk lesions. Distinction should be made between silicosis TB cavity and pure silicosis cavity or pure TB cavity. Silicon TB should be identified with the early phase of silicosis. Identification should be made to distinguish silicon TB from pneumonia (Ehrlich et al. 2006).

13.2.3 Treatment of Silicon TB

Treatment for silicon TB includes two parts: silicosis treatment and TB treatment. Treatment principle for silicosis is to take comprehensive measures and control complications. Its aim is to delay the progression of silicosis, reduce patient suffering, and to prolong and improve the quality of life. There is no effective drug for

silicosis, and the progression of TB is faster than that of silicosis. Active TB can even promote the worsening of silicosis if it is not under control. Therefore, the main program for silicon TB treatment is the same as standard TB control treatment: a three- or four anti-TB drug chemotherapy program is adopted, including INH, RIF, PZA, EMB, SM, and so on, with a 3-month initial phase followed by a 6-month continuation phase (3HRZE(S)/6HR). In cases of MDR-TB, an individualized program of chemotherapy combined with silicosis treatment should be mapped out based on the patient's medication history and TB drug sensitivity results. About 4–5 drugs can be used together with at least 2–3 kinds of sensitive drugs, with the whole course of treatment lasting 18–24 months. The program performs well in the local clinic. Because the treatment course for silicon TB is long, and many types of medication are used, extra attention should be paid to drug toxicity.

13.3 Combined Pulmonary Infection

TB is a chronic lung infection. Clinically, treatment of patients with TB in combination with other infections is straightforward. The clinical characteristics of patients with severe pulmonary TB are a long duration of treatment and repeated deterioration, resulting in bronchial pulmonary structural damage. Lung disease is extensive and always accompanied with cavity, bronchial lesions (bronchial mucosal edema, granulation tissue, and scar stenosis), pulmonary atelectasis, bronchiectasis, and pleural thickening which can induce secondary pulmonary infections. In addition, when diagnosed with other risk factors, the onset age of TB is older. Because of upper respiratory mucous membrane and cellular immune function decline, impaired swallowing reflex can easily lead to the inhalation of pathogens and dysfunctional airway clearance. The elderly can experience serious dysfunction of pulmonary ventilation and/or pulmonary air exchange, which could induce respiratory failure, even leading to death once they get pulmonary infection.

13.3.1 Clinical Types of Combined Pulmonary Infection and Pathogen Distributions

There are different types of TB-related lung infection classifications according to the different pathogens and clinical characteristics involved (Ma et al. 2006).

13.3.1.1 Lung Structural Damage

Lung structural damage caused by TB can include bronchiectasis, pulmonary cavities, and other injury that can leave patients vulnerable to secondary pulmonary infection. Complications include empyema, bronchial fistula, and secondary bacterial infections. Infection of gram-negative bacteria, especially *Pseudomonas*

aeruginosa, Aspergillus, and anaerobic bacteria, is significantly increased. In addition, the number of nontuberculous mycobacterial infections combined with pulmonary TB is increasing (Ma and Wang 2010). The infections above are community-acquired but differ from the general community-acquired pneumonia (CAP) because of the underlying damage to the lung structure.

13.3.1.2 Hospital-Acquired Pneumonia (HAP)

HAP in TB inpatients can be caused by special circumstances in the hospital or by iatrogenic factors. TB patients (especially the ones with severe pulmonary TB) are prone to get HAP due to their prolonged hospitalization, time in the ICU because of respiratory failure, or receiving mechanical ventilation. The incidence of hospital-acquired infections in pulmonary TB patients is higher than that in non-TB patients (Chen et al. 2011). The main infection area is the lung, and the main pathogens are gram-negative bacteria, especially Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia*, *Proteus*, etc.) and G-glucose non-fermenting bacteria (*P. aeruginosa* and other *Pseudomonas*, *Alcaligenes*, *Xanthomonas maltophilia*, and *Acinetobacter* such as nitrate-negative bacilli and *Acinetobacter baumannii*). Such bacteria have high drug resistance and ineffective anti-infective treatment; infection results in high mortality. The detection rate of *Candida* spp. is also high, but the clinical significance of this is controversial (Chen et al. 2012).

13.3.1.3 Immunosuppression

Immunosuppression can lead to the compound infection of TB mixed with other pathogens such as gram-positive cocci, gram-negative bacteria, anaerobic bacteria, fungi, viruses, *Pneumocystis carinii*, and so on.

13.3.1.4 Aspiration pneumonia (AP)

AP refers to a pulmonary syndrome caused by the secretions of mouth, throat, and stomach flowing into the throat and lower respiratory tract. If a small amount of secretions is inhaled, it can lead to bacterial aspirated pneumonia. With a large amount, acute chemical aspirated pneumonia can develop. Aspiration pneumonia is the major risk factor leading to death for elderly people suffering from neurological or cerebrovascular disease. Radionuclide tracer scans demonstrated that about 70 % of the community-acquired pneumonia in the elderly is caused by silent aspirations (Kikuchi et al. 1994). Pathogens of different patients can vary: gram-negative bacilli (including *Haemophilus influenzae*, *P. aeruginosa*, *K. pneumoniae*, *Stenotrophomonas maltophilia*, and *E. coli*) and *Staphylococcus aureus* are common in continuing care facility-acquired aspiration pneumonia (CCFAP) and hospital-acquired aspiration

pneumonia (HAAP) patients. For community-acquired aspiration pneumonia (CAAP) patients, *Streptococcus pneumoniae* can also be isolated from their sputum. In addition, anaerobic bacteria (mainly including *Bacteroides*, *Peptostreptococcus*, and *Fusobacterium*) are also an important kind of pathogen for AP.

13.3.1.5 Pulmonary TB Combined with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

The main symptom of COPD is aggravated shortness of breath, which is always accompanied with wheezing, chest choking, aggravated cough, increased sputum production, increased sputum purulence and/or viscosity changes in sputum, and fever. In addition, symptoms such as whole body malaise, insomnia, drowsiness, fatigue, depression, and mental disorders could also appear. There are many factors that cause AECOPD, 40–60 % of which are due to bacteria (*H. influenzae*, *S. pneumoniae*, *Moraxella catarrhalis*, *P. aeruginosa*, and other gram-positive or gram-negative bacteria), about 30 % due to viruses (influenza, parainfluenza, rhinovirus, coronavirus, adenovirus, and respiratory syncytial virus), and 5–10 % due to atypical pathogens (rare *Chlamydophila pneumoniae* or *Mycoplasma pneumoniae*, but not *Legionella*).

13.3.2 Diagnosis of TB-Combined Pulmonary Infection

Diagnosis of pulmonary infection usually depends on the comprehensive analysis of clinical symptoms, signs, peripheral blood, imaging data, pathogenic microbiology, and serology.

13.3.2.1 Confirmation of TB-Combined Pulmonary Infection

As a special kind of infection, TB is just the same as other pathogen infections in symptoms, signs, peripheral blood, and imaging. Due to interference by mouth and throat bacteria and other factors, the pathogens of the respiratory tract that are detected positive cannot be identified as the real pathogens that infect the lower respiratory tract. Therefore, the diagnosis of TB combined with pulmonary infection is difficult, and the following aspects should be heeded in clinical practice:

1. When symptoms such as cough, increased sputum, purulent sputum, and fever appear, the worsening of TB or hidden lesions of TB must first be excluded.
2. The clinical manifestations in elderly patients with pulmonary infection are often atypical; dyspnea and tachycardia may be the first symptoms indicating a combined infection. Imaging is an effective tool for this diagnosis. Imaging characteristic is valuable in diagnosis of pulmonary TB combined with mycetoma.

3. The following imaging features often suggest additional pulmonary infection in TB patients:
   - The level of emerging liquid from the TB cavity is higher than before, and the infiltrating lesion tends to absorb or the proliferative change around the cavity wall increases.
   - Emerging abscess or cavity lesions.
   - Substantial lesions appear besides the former lesion, or there is infiltrated shadow that does not fit the characteristics of spreading along the bronchial tubes.

   Conditions such as hemoptysis causing blood or blood clots gathering in or blocking the bronchial alveoli, or TB in combination with acute respiratory distress syndrome (ARDS) or pulmonary edema or atelectasis, should be identified.
4. Serological tests are helpful in diagnosis. Antigen and serological examination is mainly used for the diagnosis of atypical pathogens, including *Legionella*, mycoplasma, chlamydia, and viruses. A procalcitonin (PCT) test can help to distinguish bacterial infection. A (1–3)-β-D-glucan Assay (beta-glucan test) can help to diagnose a variety of invasive fungal infections except cryptococcosis or infections caused by zygomycetes such as mucormycosis, phycomycosis, and basidiobolomycosis. Detection of Galactomannan (GM) in the blood contributes to the diagnosis of aspergillosis.

13.3.2.2 Etiological Diagnosis

Etiological diagnosis is very important in guiding the correct and effective antibiotic in the clinic. Before the pathogen is confirmed, some clinical characteristics and imaging figures are helpful to deduce what the pathogen is and offer a guide for treatment.

Sputum

Bacterial pneumonia is often characterized by large amounts of yellow sticky sputum. Sputum from *K. pneumoniae* infection is brick red, jelly-like, and very sticky, similar to strawberry jam. *S. pneumoniae* infection is characterized by rust-like sputum. Sputum of *P. aeruginosa* pneumonia is green. There is a characteristic smell to anaerobic bacteria infecting sputum. Sputum of pulmonary amoebic infection is brown with a stench. *Candida albicans* infection has white and transparent sputum, which is very sticky, hard to cough, and could be pulled into a wire shape (Xu 2005; Johnson et al. 2008).

Imaging

Images of *S. pneumonia* infection have a uniform density distribution in the lobe, segment, or sub-lung segment, but the pulmonary TB patient who is coinfected with other pathogens often has slice or dot-like shadows. *S. aureus* infection shows multiple pulmonary infiltrates or lobar segment inflammatory changes. It begins as flocculent shadows, then its density increases, appearing as translucent honeycomb areas or cavities. Then, one or more pneumatoceles appear around the shadow of the inflammation area which could increase or disappear rapidly in a short time, accompanied by pleural effusion or pneumothorax. For the blood-borne infected patient, mass slice or bulk-like shadow is distributed at both sides, and cavities are easily formed. Early infection of *K. pneumoniae* appears lobularly invasive, then rapidly expands to large-lobe consolidation, with irregular translucent areas. Curved bulging often appears in the fissure of the lobe (lobe bulging sign) because of its thick and heavy exudate. In *H. influenzae* infected cases, 75 % showed changes characteristic of bronchial pneumonia, and the other 25 % appeared lobular or with segmented opaque shadows. The *P. aeruginosa* infected lung has widespread nodular and patchy shadows, mainly in the lower lung, and there are multiple small abscesses, which can merge together with each other to form a large, consolidated shadow. *M. pneumoniae* infection can be found in diverse forms, with a vague, feathery, or uniform shadow. In general, a shadow close to the lung hila is thick, gradually fading along the lung lobes with an obscure edge. The lesions are movable, but a few shadows are patchy and slice-liked. Rickettsial infection has a patchy shadow or an emerging consolidating shadow with uneven density. Its distribution is segmental or lobular, associated with a small amount of pleural effusion. A feature of pulmonary aspergillosis is that aspergillomata can move with a change in body position when performing the chest imaging test.

Etiology Examination

Pathogens that cause lung infection include bacteria, fungi, viruses, and protozoa. The common inspection methods include smear observation through light microscopy, culture identification, histopathology, immunology, and molecular biology techniques. The following points should be attended to in respiratory specimen collection:

1. The specimen should be treated quickly. For example, the rate of isolating *S. pneumoniae*, *S. aureus*, and some gram-negative bacteria will be reduced if the specimen is stored at room temperature for 2–5 h.
2. The role of smear examination cannot be ignored. Smears of some pathogen-caused infections (such as from *S. pneumoniae*, *H. influenzae*, acid-fast bacilli, *Nocardia* and other actinomycetes, *Candida*, *Cryptococcus*, *Aspergillus*, *Mucor*, and *P. carinii*) can provide information for a clear and probable diagnosis or even a definitive one.

3. Sampling should be from the bronchus fiber mirror brush or bronchoalveolar lavage fluid (BALF) in order to reduce contamination from normal flora of the upper respiratory tract.
4. Quantitative culture results are important. If the concentration of bacteria or fungi in quantitative cultures of sputum is $\geq 10^7$ cfu/mL, the pathogen can be considered a lung infection pathogen; if the concentration is $\leq 10^4$ cfu/mL, it should be regarded as contamination. If the concentration is between the above two, reculturing and retesting is recommended. If the concentration is between 10^5 and 10^6 cfu/mL, and the retest shows the same result, the bacteria can be considered an infecting pathogen. If the sample is from bronchoscopy or an artificial airway, a concentration of $\geq 10^5$ cfu/mL indicates an infecting pathogen. If the specimen is from the BALF, a concentration of $\geq 10^4$ cfu/mL indicates an infecting pathogen. If the sample is from a brush used to prevent contamination, or from BALF that employed contamination prevention measures, a quantitative concentration $\geq 10^3$ cfu/mL indicates an infecting pathogen (Woodhead et al. 2011).

13.3.2.3 Evaluation of the Clinical Significance of Pathogen Positive Results

There are many methods that can detect pathogen-induced lung infections, but the positive result should be considered strongly when judging because of the limitations of existing technology and normal flora contamination. The following criteria refer to the standards of the Chinese Society of Respiratory Diseases as noted by the Chinese Thoracic Society (2006).

Confirmation of Pathogen Diagnosis

1. Pathogen has been detected from blood or pleural fluid culture.
2. The pathogen concentration cultured from bronchoscopy or artificial airway specimens is $\geq 10^5$ cfu/mL, or $\geq 10^4$ cfu/mL in BALF samples, or $\geq 10^3$ cfu/mL in BALF specimens collected using contamination prevention measures.
3. Cultured results respiratory tract specimens are positive for *M. pneumoniae*, *C. pneumoniae,* or *Legionella pneumophila*.
4. Serum antibody titers of serum *M. pneumoniae*, *C. pneumoniae*, or *L. pneumophila* change (increase or decrease) four or more times; at the same time, *M. pneumoniae* antibody titers (complement fixation test result) are ≥1:64, pneumonia antibody titers (micro-immunofluorescence test) are ≥l:32, or *L. pneumophila* antibody titers (indirect fluorescent antibody method) are ≥1:128.
5. Urinary antigen test of *L. pneumophila* (enzyme-linked immunosorbent assay) is positive.
6. Antibody titers to serum influenza virus or respiratory syncytial virus change (increase or decrease) four or more times over multiple samples.
7. A urinary antigen test is positive for *S. pneumoniae* (via immunochromatography, except in children).

Prompt Etiological Diagnosis

1. The dominant bacteria cultured from qualified sputum specimen with slow growth ($\geq 10^6$ cfu/mL).
2. There is a small amount of bacteria growing in the sputum specimen, and it is consistent with the smear microscopy examination result (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*).
3. The same bacteria are cultured repeatedly in separate samples within 3 days.
4. The serum *C. pneumoniae* IgG antibody titer is ≥1:512 or the IgM antibody titer is ≥1:16 (micro-immunofluorescence test).
5. The serum *L. pneumophila* antibody titer is ≥1:320 (tube agglutination test) or the IgG antibody titer is ≥1:1024 (indirect fluorescent antibody test).

Diagnosis of Unknown Pathogen

There are a variety of pathogenic bacteria which grow poorly ($<10^6$ cfu/mL) in sputum culture medium. The sputum specimen may be culture positive for normal colonized bacteria of upper respiratory tract (such as *Streptococcus viridans*, *Staphylococcus epidermidis*, nonpathogenic *Neisseria*, and *Corynebacterium diphtheria*). If none of the diagnostic criteria of "Confirmation of Pathogen Diagnosis" section above are met, then a diagnosis of an unknown pathogen may be considered.

13.3.3 Choice of Antibiotic(s) for Treatment of Lung Infection

The choice of treatment is dependent on the nature and severity of the infection.

13.3.3.1 Community-Acquired Pneumonia (CAP)

The choice of antibiotics for TB patients coinfected with CAP is the same as those for CAP patients without TB as long as there is no bronchial pulmonary structural damage. In patients with bronchial pulmonary structural damage or who are undergoing anti-TB treatment, attention should be paid to gram-negative bacterial infections. Antibiotic treatment should begin as soon as possible, as delay in treatment can have severe consequences and prognosis is closely related to the time when treatment is initiated. Taking the first dose of antibiotics within 4 h after the disease onset is optimal. For life-threatening severe pneumonia, it is suggested to use a broad-spectrum antibiotic in the early stage, and pertinent or de-escalation therapy can be applied according to the pathogen examination when the patient is in stable condition. Antibiotic treatments for mild and severe coinfections as recommended by the Chinese Thoracic Society (2006) are detailed below. Note that empirical antiviral treatments are not recommended for patients who are suspected of

influenza virus infection. Combined antiviral therapy is only used for high-risk patients who have typical flu-like symptoms (fever, myalgia, malaise, and respiratory symptoms) with less than 2 days onset and may also be used preventatively in the influenza epidemic period.

TB Patients Coinfected with Mild Pulmonary Infections

For TB patients coinfected with mild pulmonary infections, common pathogens are *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, and *C. pneumoniae*. Suggested antibiotics for treatment include penicillins (penicillin, amoxicillin, etc.), macrolides, doxycycline, and the first or the second generation of cephalosporins.

TB Patients Coinfected with Severe Pulmonary Infections

A diagnosis of severe pneumonia can be given if there are one or more of the following:

- Disturbance of consciousness
- Respiratory rate $\geq$ 30 times/min
- Partial pressure of arterial oxygen (PaO_2) <60 mmHg; partial pressure arterial oxygen and fraction of inspired oxygen ratio (PaO_2/FiO_2) <300; mechanical ventilation treatment is required
- Systolic blood pressure < 90 mmHg
- Concurrent septic shock
- X-ray showing bilateral or multi-lobe involvement, or lesions expanding $\geq$50 % within 48 h of hospitalization
- Oliguria: urine output < 20 mL/h or combined acute renal exhaustion that requires dialysis treatment

Patient treatment depends on the risk factors for infection by *P. aeruginosa*. The risk factors for *P. aeruginosa* infection include:

- Structural lung disease (such as bronchiectasis, pulmonary cysts, and diffuse bronchiolitis)
- Use of glucocorticoids (prednisone > 10 mg/day)
- Over the past 1 month, broad-spectrum antibiotics are used more than 7 days
- Malnutrition
- The number of neutrophils in peripheral blood is less than $1 \times 10^9\ L^{-1}$

If none of these risk factors are present, the main pathogens are *S. pneumoniae*, aerobic gram-negative bacteria, *L. pneumophila*, *M. pneumoniae*, *H. influenzae*, and *S. aureus*. Antimicrobial drug combinations include the third generation of cephalosporins combined with macrolides, β-lactam/β-lactamase inhibitors (such as amoxicillin/clavulanic acid or ampicillin/sulbactam) combined with macrocyclic lactones, and carbapenems combined with macrolides.

If there are risk factors for *P. aeruginosa* infection, the main pathogens are those listed previously plus *P. aeruginosa*. Antimicrobial drugs include β-lactam/β--lactamase inhibitor which have anti-*Pseudomonas* activity, carbapenems, β-lactam antibiotics combined with macrolides (with an aminoglycoside if necessary), and β-lactam antibiotics which have anti-Pseudomonas activity combined with intravenous injection of fluoroquinolones.

Course of Antibiotic Treatment

It is suggested that antibiotic treatment should last at least 5 days and the patient's normal body temperature should be maintained for 48–72 h. There should not be more than one kind of CAP-related clinical condition by the end of the treatment. If the initial treatment is not effective or there is concurrent outer-pulmonary infection, the treatment time should be prolonged. Treatment courses are different due to differences in pathogens and their high degree of variety. The complete absorption of the shadow of the lung cannot be considered as the standard for cessation of antibiotics. For ordinary bacterial infections such as *S. pneumoniae*, medication can stop 72 h after the patient maintains normal temperature. For severe pneumonia, in addition to the completion of the effective, timely, and appropriate anti-infection treatment, nutrition supporting therapy and respiratory secretion drainage are very important.

13.3.3.2 Hospital-Acquired Pneumonia (HAP)

The key point for HAP initial empirical antibiotic therapy is whether the patient has the risk factors for MDR pathogen infection (Chinese Thoracic Society 1999). These factors include the use of antibiotics in the past 90 days and hospitalization for 5 days or longer. The frequency of antibiotic resistance is higher when the patient has been treated in community or other medical institutions. Risk factors for health care-associated pneumonia (HCAP) are hospitalization for more than 2 days due to the exacerbation of infection within 90 days, IV therapy administered at home (including antibiotics), dialysis continuously within 30 days, trauma treatment at home, the presence of family members infected with multidrug-resistant pathogens, and immunosuppressive diseases and/or immunosuppressive therapy.

If the patient has early onset HAP, ventilator-associated pneumonia (VAP), or HCAP with no risk factors for MDR pathogens, the common pathogens include *S. pneumoniae*, *H. influenzae*, *S. aureus*, and Enterobacteriaceae (such as *E. coli*, *K. pneumoniae*, *Proteus*, and *Serratia*). The initial empirical choice of antibiotics includes ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam, or ertapenem.

For the patients with risk factors for MDR pathogens of HAP, VAP, and HCAP, common pathogens include *P. aeruginosa*, *K. pneumoniae* that produce extended-spectrum β-lactamase (ESBL), *Acinetobacter* species, and other bacteria. The initial empirical antibiotic should be anti-*Pseudomonas* cephalosporins (cefepime, ceftazi-

dime), carbapenems (imipenem, meropenem), or β-lactam/β-lactamase inhibition agents (piperacillin/tazobactam). Anti-*Pseudomonas* quinolones (ciprofloxacin or levofloxacin) or aminoglycosides (amikacin, gentamicin, or tobramycin) can be used together. If methicillin-resistant *S. aureus* (MRSA) is suspected, linezolid or vancomycin can be added. If *L. pneumophila* is suspected, macrolides or fluoroquinolones can be added.

Once HAP is suspected in the clinic, and after the specimen is collected for bacterial culture, empirical antibiotic treatment should start as soon as possible (1 h later). Combination therapy must be used for the initial treatment of MDR pathogens to ensure broad-spectrum coverage and reduce the possibility of inappropriate initial empiric antibiotic therapy. Note that if the patient had recently used one kind of antibiotic, the same one should be avoided in empirical treatment to avoid development of antibiotic resistance. All treatments must be based on the local antibiotic resistance situation for choosing the drugs and establishing the appropriate empirical treatment program.

Adequate doses of antibiotics must be used for severe HAP or VAP patients to ensure maximum efficacy (Chronic Obstructive Pulmonary Disease Study Group of the Chinese Thoracic Society 2007). For adult patients with good renal function, the commonly used full doses are as follows: for cefepime and ceftazidime, 2 g every 8 h (q8h); for meropenem, 1 g q8h; for imipenem, 0.5 g q6h or 1 g q8h; for piperacillin/tazobactam, 4.5 g q6h; for ciprofloxacin, 400 mg q8h; for amikacin, 20 mg/kg daily; levofloxacin is 750 mg daily. Patients who haven't changed their antibiotic in the past 72 h can stop antibiotic drug treatment if specimens from their lower respiratory tract are culture negative. Drug adjustment should be made according to the culture results of the specimen of the lower respiratory tract and the clinical effect. For HAP, VAP, or HCAP patients who have received appropriate initial treatment with no evidence of infection by non-fermentative gram-negative bacteria and no complications, a short-course treatment (7–8 days) is recommended if the initial treatment went well. If the patient responds to aminoglycosides present in the combination drugs, this kind of medication should be stopped after 5–7 days.

13.3.3.3 Pneumonia in the Immunocompromised Host

There are numerous pathogens infecting the lung of the immunocompromised host, which increases opportunities for special pathogen infections. As a result, special pathogen infections such as viruses, fungi, and *Pneumocystis jirovecii* should be closely monitored in addition to mycobacteria and bacterial infection.

Bacterial Infections

For the acute onset nidus (3–5 days) with local alveolar infiltration, the main infection pathogen is bacterial. Empirical antibiotic treatment should refer to the CAP and HAP program described above.

P. jirovecii Pneumonia (PCP)

For patients presenting with diffuse pulmonary alveoli and interstitial infiltration accompanied by hypoxemia in occult or subacute onset, *P. jirovecii* may be the causative pathogen. The preferred treatment is sulfamethoxazole (100 mg/kg/day) and trimethoprim (20 mg/kg/day) taken orally or by intravenous drip. The general course of treatment is 14–21 days. Caspofungin will be used if the treatment is ineffective (the first dose is 70 mg, followed by 50 mg daily, by slow intravenous infusion).

Cytomegalovirus Pneumonia

There is no specific clinical feature of Cytomegalovirus (CMV) pneumonia other than the first symptoms of fever, cough with scanty sputum, dyspnea, and hypoxemia. The main imaging manifestation is interstitial pneumonia, which is characterized by the nonconformity between the clinical symptoms and its imaging performance. There is no abnormal image or only thickened blurred lung marking in the early chest X-ray. Then distinct interstitial pneumonia appears in both lungs, and after active antiretroviral therapy, clinical symptoms improve significantly and chest X-ray shows slow absorption of lesions. The best choice is ganciclovir alone or in combination with intravenous immunoglobulin (IVIG), or CMV immunoglobulin. The starting dose of ganciclovir is 5 mg/kg 2 times a day for 14 days, then once a day for an additional 7 days. The course of treatment is usually 21 days.

Invasive Pulmonary Mycosis

Invasive pulmonary mycosis refers to acute or chronic histological damage caused by a direct colonization of the lung or bronchial by fungi. Common pathogens are *Candida*, *Aspergillus*, *Cryptococcus neoformans*, *Zygomycetes*, and *Penicillium marneffei* (mainly seen in Southeast Asia and southern China). Because *Candida* pneumonia is rare, antifungal treatment will generally not be adopted if *Candida* has been cultured from sputum.

The typical progression of invasive pulmonary mycosis is as follows: in the early period (0–5 days) there is inflammation shadow, with mist-like oozing around it (shadow or halo sign caused by bleeding around the lesion). From day 5 to day 10, there is gas chamber consolidation in the inflammatory lesions with visible air bronchogram. From day 10 to day 20, the lesion develops to a half-moon shaped translucent zone (air half sign, caused by coagulation necrosis and pulmonary embolism) and it can deteriorate to complete necrosis cavity, most of which is single onset. The lesion sizes are variable and the distribution has no obvious features. Drugs for treatment could involve voriconazole, itraconazole, caspofungin, or micafungin, and two of them can be combined if necessary. Imaging of pulmonary cryptococcosis often has nodules or mass shadow under pleural in unilateral or bilateral lung

fields, and can be single or multiple onset, with a diameter of l–10 cm and smooth edges or fuzzy or with small burrs. Often, there is a cavity formed, and the wall is relatively smooth with uniform and very neat low-density shadow in the nodular shadow image. It is very important in pulmonary cryptococcosis diagnosis to note the presence of nodules or masses with smooth low-density necrosis areas or cavities, especially in multiple appearances which is usually what happens in patients with healthy immune systems. In contrast, the main progression in the immunocompromised host shows parenchymal infiltration, which is hard to distinguish from pneumonia caused by other pathogens. Amphotericin B and flucytosine can be used together or fluconazole can be used for treatment, with the treatment course lasting from 8 weeks to 6 months. Itraconazole could be used orally for patients who are not coinfected with meningitis. In pulmonary mucormycosis cases, the important symptoms for diagnosis are hemoptysis and chest pain with no other signs. Its early imaging shows bronchial pneumonia, with rapid integration into a large consolidation. This is often seen with a formed cavity and a wedge-shaped shadow which can be seen at the bottom near the pleura (if there is a large pulmonary vessel embolism). This is valuable for diagnosis. Currently, amphotericin B is the most effective medicine in the clinic (the dose is 0.5–1.5 mg/kg/day, with the total amount of 2.5–3.0 g for the course of treatment). It is used in combination with flucytosine.

P. marneffei infection (Penicilliosis) manifests with fever, anemia, skin lesions, cough, hepatosplenomegaly, and generalized lymph node swelling, which is not specific in imaging and is often misdiagnosed as TB. Amphotericin B is used for treatment, with a switch to itraconazole oral therapy 2 weeks later. Immunesuppressed hosts require long-term use of itraconazole.

13.3.3.4 Aspiration Pneumonia

The possibility of aspiration pneumonia should be considered in elderly patients with a history of consciousness disorder or difficulties in swallowing who have respiratory symptoms followed by pulmonary infiltrated shadow. Diagnosing correctly and taking appropriate measures for the swallowing-impaired patient can reduce the incidence of aspiration pneumonia. The following factors are used to evaluate oropharyngeal dysphagia in the clinic: abnormal velopharyngeal reflex (palatal reflex and pharynx reflex), coughing when eating, and a change in sound after swallowing. Treatments are different according to the way the pneumonia is acquired. Treatments for CCFAP, HAP, and CAAP consist of the empirical treatment programs described above. Anaerobic treatment should be considered as well. Penicillin combined with metronidazole, clindamycin, β-lactam/β-lactamase inhibitors, or carbapenems can be used for anaerobic treatment. The general course for treatment is 7–10 days, and the time could be prolonged to 14–21 days or even weeks to months if the patient is coinfected with necrotizing pneumonia or has a lung abscess.

13.3.3.5 Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD)

Once COPD symptoms are exacerbated, especially with the aggravation of cough and purulent sputum, active antibiotic therapy should be adopted. Antibiotic selection should be based on the patient's lung function and common pathogens, and the prevalence of pathogenic bacteria and drug resistance of the area should be taken into account to select sensitive antibiotics. The course of treatment is 3–7 days.

Antibiotics Indications for AECOPD

Antibiotics should be considered in cases of COPD exacerbations with three principal symptoms of increase in sputum volume, increase in sputum purulence, and increase in shortness of breath, or with two principal symptoms when one is an increase in sputum purulence or when the patient requires mechanical ventilation (either noninvasive or invasive).

Risk Factors for *P. aeruginosa* Infection of COPD

Patient risk factors for *P. aeruginosa* include recent hospitalization, frequent antibiotic treatment history (using four courses of antibiotics in the past year), severe COPD deterioration, having isolated *P. aeruginosa* in a previously acute exacerbation period or contracted *P. aeruginosa* clone during a stable period.

Application of Antibiotics

The Chinese Society of Respiratory Disease recommends treatment depending on lung function and the infectious pathogen(s) present (Chronic Obstructive Pulmonary Disease Study Group of the Chinese Thoracic Society 2007).

1. For Grade I (with forced expiratory volume in 1 s, FEV_1, at ≥80 % of the predicted volume) and Grade II (50 % ≤ FEV_1 < 80 % of predicted volume) COPD acute exacerbations, the main pathogens are *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*. Antimicrobial drugs for treatment may include oral penicillin, β-lactam/β-lactamase inhibitor (amoxicillin/clavulanic acid), macrolides (azithromycin, clarithromycin, roxithromycin etc.), the first- and second-generation cephalosporins (cefuroxime, cefaclor), doxycycline, levofloxacin, and so on.
2. For Grade III (30 % ≤ FEV_1 < 50 % predicted volume) and Grade IV (FEV_1 < 30 % predicted volume, or patients with chronic respiratory failure) COPD acute exacerbations with no risk factors for *P. aeruginosa* infection, the main pathogens are *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *K. pneumoniae*, *E. coli*,

and *Enterobacter* spp. Antimicrobial drugs for treatment include intravenous β-lactam/β-lactamase inhibition agents, second-generation cephalosporins (cefuroxime), third-generation cephalosporins (ceftriaxone, cefotaxime, etc.), and respiratory quinolones (levofloxacin, moxifloxacin).

3. In Grade III (30 % ≤ FEV_1 < 50 % predicted volume) and Grade IV (FEV_1 < 30 % predicted volume, or patients with chronic respiratory failure) COPD acute exacerbations with risk factors for *P. aeruginosa* infection, the main pathogens include those in group 2 previously described and *P. aeruginosa* bacteria. Antimicrobial drugs include intravenous injection β-lactam antibiotics (such as ceftazidime, cefepime, piperacillin/tazobactam, cefoperazone/sulbactam, imipenem, and meropenem) with anti-*Pseudomonas* activity. Aminoglycosides and quinolones (ciprofloxacin, etc.) can be combined if it is necessary.

13.3.3.6 MDR Infection

As drug-resistant bacterial infections increase, drug susceptibility results become more and more important in choosing treatment. The most common clinical MDR pathogens are *P. aeruginosa*, *Acinetobacter*, ESBL-producing *Enterobacteriaceae*, and MRSA. Combined therapy, mainly using β-lactam combined with aminoglycosides, is recommended for *P. aeruginosa*. Aminoglycosides can be replaced by fluoroquinolones (mainly ciprofloxacin or levofloxacin). The most effective drugs for *Acinetobacter* treatment include carbapenems, sulbactam, tigecycline, and polymyxins B and E. When isolating ESBL-producing *Enterobacteriaceae*, the third-generation cephalosporin monotherapy should be avoided. For *Enterobacter* bacteria, the most effective drugs are carbapenems. Large-scale, multicenter trials have proved the curative effect of linezolid and vancomycin is equal in MRSA treatment. For patients with renal insufficiency or receiving other nephrotoxic agents, linezolid is recommended. In addition, inhaled antibiotics are valuable as an adjuvant therapy for VAP caused by MDR pathogens. The course of treatment depends on the patient's infection pathogens, severity degree, background diseases, and clinical response to treatment.

13.3.3.7 Treatment Failure

Antibiotic treatment can fail for many reasons. The patient could be misdiagnosed and/or the infectious pathogen(s) misidentified or secondary infection undetected. External sources of infection such as ventilator-related contamination can be persistent. Medication failures can occur due to drug resistance, limitations due to adverse drug reactions, and/or insufficient respiratory drug concentration due to drug or anatomical factors. The pulmonary infection may spread outside the lung. The patient's own immune defense may cause damage, including systemic inflammatory response, leading to acute lung injury or even multiple organ failure.

In cases of treatment failure, the following steps should be adopted: establish a reliable etiological diagnosis, referring to drug sensitivity and/or blood concentration to develop or adjust treatment; eliminate sources of contamination to prevent cross-infection; and prevent, treat, or eliminate other factors that might cause or aggravate lung injury.

13.3.4 Respiratory Failure

Respiratory failure is a physiological and metabolic disorder syndrome that is caused by pulmonary ventilation dysfunction and/or external disease of TB. The direct reason for respiratory failure is that the body cannot maintain effective gas exchange. Respiratory failure is defined when the patient, at rest and breathing air at sea level pressure, has arterial oxygen pressure (PaO_2) lower than 8 kPa (<60 mmHg), with or without carbon dioxide partial pressure ($PaCO_2$) higher than 6.67 kPa (50 mmHg). There is always a process as respiratory failure develops, especially for chronic respiratory failure. Respiratory function may be reduced gradually. If the external respiratory dysfunction causes elevated $PaCO_2$ or decreased PaO_2 and does not reach the standards above, or at rest blood gas values are normal with no obvious clinical symptoms, but PaO_2 decreases apparently or $PaCO_2$ increases only if physical load increases, this state is often called respiratory insufficiency. Once pulmonary TB with concurrent (chronic) respiratory failure is exacerbated acutely by other factors, coma, shock, and life-threatening can occur. As it is reported, 93 % of the patients who died of pulmonary TB with respiratory failure died in transit to the ICU (Lee et al. 2003). The main principles for treatment of TB combined with respiratory failure include keeping the respiratory tract unobstructed, correcting hypoxia and reducing carbon dioxide retention, correcting acid–base imbalances and electrolyte disturbance, initiating/continuing anti-TB therapy, treating inducing factors, preventing complications, and supporting good nutrition.

13.3.4.1 Airway Control

Attention should be paid to posture and basic airway management: head-tilt/chin-lift and jaw-thrust maneuvers should be performed to prevent the tongue from falling back and obstructing the airway.

If the patient loses the function of sputum clearing, clearing the secretions of the mouth, pharynx, larynx, and lower respiratory tract is important. Bronchoscopy can be used for removing the large amount of deep accumulated secretions which are not easy to expel.

The discharge of secretions should be increased. Expectorant can be used if the patient has good mucociliary clearance. Pay attention to the airway humidification and the dilution of sputum (whether sputum is easy to cough or aspirate is the sign

for humidification), and encourage the patient to cough with good posture to promote drainage.

The bronchi should be expanded, and airway inflammation and edema should be reduced. Drugs such as β-receptor stimulants, anticholinergic agents, and methylxanthines may be chosen according to the role of drug and treatment response for patients. It is recommended that aerosols be inhaled into the lung, but if the airway is severely occluded, intravenous injection should be given first.

Artificial airways should be built by nasotracheal intubation or orotracheal intubation if necessary. Nasotracheal intubation is usually more comfortable for the patient, and the airway can be fixed easily, but its disadvantage is that it may cause nasosinusitis or tympanitis. The advantage for orotracheal intubation is that it can be set up easily and requires less equipment. To reduce complications and improve the success rate of recovery, intubation is recommended before patients have irregular breathing, choking, or fall into coma. If the patient requires intubation for more than 3 weeks, tracheotomy is recommended.

13.3.4.2 Oxygen Therapy

High concentrations of oxygen may be given to Grade I respiratory failure patients to increase PaO_2 rapidly. FiO_2 can be adjusted at a beginning reading of 0.4, with the PaO_2 target of 60–80 mmHg.

In Grade II respiratory failure patients, adopt controlling oxygen therapy to prevent respiratory depression. Administer 24–26 % oxygen as long as $PaCO_2$ does not increase by more than 10 mmHg and the patient is conscious. The oxygen concentration may increase, but not more than 30–35 %. For the patient receiving long-term oxygen therapy greater than 15 h daily, the target PaO_2 is 50–60 mmHg with a $PaCO_2$ increase of less than 20 mmHg.

It is important to pay attention to the adverse effects of oxygen therapy. The common adverse reactions include suppressed ventilation (common in chronic Grade II respiratory failure patients) and oxygen toxicity. Oxygen toxicity can affect the lungs (injured epithelial cells of the alveoli cause pulmonary edema) and the central nervous system (manifested as trembling, convulsions, and seizures). It is recommended that patients inhale pure oxygen for less than 24 h, with 70 % oxygen used less than 2 days, and 50 % oxygen used less than 5 days. Note that as the oxygen content of inhaled air is increased and rapidly absorbed by blood exchange, the reduced volume of nitrogen remaining may not be sufficient to keep the lungs inflated and absorption atelectasis can occur.

13.3.4.3 Increasing Ventilation and Reducing Carbon Dioxide Retention

Carbon dioxide retention is one of the principal pathophysiological changes caused by alveolar hypoventilation, and can induce a series of clinical manifestations. Clinically, increasing the amount of alveolar ventilation can effectively reduce CO_2

retention. However, because of the differences in the pathophysiological basis of TB patients combined with respiratory failure, the strategies and measures for increasing ventilation are different. They are summarized below.

Application of a Respiratory Stimulant

Application of a respiratory stimulant is controversial. It may be worth trying for the severe TB cases, especially elderly patients with bronchus and lung structural damage and/or extensive lesions such as cavity and bullae. Mechanical ventilation in these kinds of patients may lead to more complications and higher failure rate.

Conservative therapy can be used for the conscious patient who is hemodynamically stable with $PaCO_2$ < 60 mmHg, oxygenation index between 200 and 300 mmHg, $PaCO_2$ between 50 and 60 mmHg, and blood pH value between 7.30 and 7.35. When using respiratory stimulants, secretion drainage and control of airway spasms should be noticed, and great attention should be paid to patient consciousness and $PaCO_2$ after use. If $PaCO_2$ does not drop or the patient loses consciousness, mechanical ventilation should be used instead.

Mechanical Ventilation

Mechanical ventilation technology is the most important clinical tool for treatment of respiratory failure; however, TB, bullae, and hemoptysis are considered contraindications. Mechanical ventilation may cause the spread of pulmonary TB, making treatment more difficult. Studies have shown that among patients using mechanical ventilation for pulmonary TB combined with respiratory failure, the mortality rate is up to 60 %, which is similar to ARDS and twice that of pneumonia caused by respiratory failure (Lee et al. 2003; Rollas et al. 2015). Therefore, it is necessary to explore a set of effective strategies and programs to guide the application of mechanical ventilation in the treatment of pulmonary TB with respiratory failure. Mechanical ventilation can be either invasive or, if external, noninvasive positive pressure ventilation (NPPV). Many scholars have suggested using a flexible selection scheme: for patients with respiratory failure who have no contraindications for NPPV, NPPV can be implemented and, according to patient response, continued or halted in favor of invasive ventilation. The key point of using this strategy is rationally to master the indications of NPPV and invasive ventilation as well as when to change from NPPV to invasive ventilation. NPPV is widely used clinically because it doesn't require intubation or incision and thus avoids complications of artificial airways. NPPV can also reduce the need for sedatives, as it does not affect normal swallowing, eating, or talking. It can help to preserve the air temperature and humidity of the lungs and minimize coughing. It can also be used intermittently and patients can be taken offline easily. The clinical effectiveness of NPPV should be evaluated 1–2 h after treatment. Signs of clinical improvement include a $PaCO_2$ decrease > 16 %, pH > 7.30, and an oxygenation index > 164 mmHg. There are always a certain percentage

of failures for NPPV treatment. Therefore, for patients with no improvement after NPPV treatment and who have indications of endotracheal intubation, prompt emergency intubation must be considered. Additionally, in the case of irritability or loss of consciousness, inability to clear secretions or tolerate the connection method, hemodynamic instability, oxygenation deterioration, or increase in carbon dioxide retention, intubation should be done as soon as possible.

13.3.4.4 TB Conditions and Ventilation Strategies

There are several common situations for TB patients with respiratory failure; each has their own ventilation strategies (Xie and Liu 2008; Physiology and Intensive Care Medicine Group of the Chinese Thoracic Society 2009).

Severe TB Patients with Bronchial Pulmonary Structural Damage

Severe TB patients with bronchial pulmonary structural damage often have extensive lung lesion cavity, bullae, etc., and may have concurrent infection. These patients easily lose weight, are malnourished, and are prone to respiratory muscle fatigue. Meanwhile, there is often compensatory emphysema in the so-called "healthy" lung tissue. In addition, TB bronchiectasis and pleural thickening are often combined. Most of these patients are elderly and may have TB-associated chronic obstructive pulmonary disease, pulmonary heart disease, and so on. There are several reasons for respiratory failure, not only pump failure, such as thorax, pleural changes, respiratory muscle fatigue, but also lung failure such as airway obstruction, lung tissue lesions, and pulmonary circulation disorders. Mechanisms of respiratory failure include both restrictive hypoventilation and obstructive hypoventilation. There is not only an increase in the functional shunt induced by part of the pulmonary alveoli hypoventilation, but there is also an increase in functional dead space due to the induction of pulmonary alveoli blood hypoperfusion. Both diffusion impairment and anatomic shunt increase. Therefore, such patients usually have both disturbed ventilation and ventilatory disorders, showing type II respiratory failure, chronic respiratory failure, acute exacerbation of chronic respiratory failure, and so on. The preferred strategy is to try to adopt conservative and noninvasive ventilation. Forceful anti-TB treatment, beginning as early as possible, is effective to prevent TB lesions spreading during mechanical ventilation. After the acute phase, patients can receive long-term home NPPV therapy if needed.

Noninvasive ventilation can be used according to the patient's situation as long as the patient is conscious, has stable hemodynamics, can expectorate independently, and following conditions are met: $PaO_2 < 60$ mmHg, oxygenation index between 150 and 200 mmHg, $PaCO_2$ at 50–60 mmHg, and blood pH is between 7.20 and 7.30. Continuous positive airway pressure (CPAP) mode can be used for type I respiratory failure, and bi-level positive airway pressure (BiPAP) mode can be used for type II respiratory failure. Initial inspiratory pressure airway pressure

(IPAP) ranges from 6 to 25 cmH_2O until the patient can no longer tolerate it. The expected tidal volume is 6–8 mL/kg; expiratory pressure airway pressure (EPAP) generally begins from 2 cmH_2O, and the oxygen flow is adjusted to maintain transcutaneous oxygen saturation at more than 90 %. Adjust the IPAP and EPAP at any time according to the patient situation. According to patient tolerance, ventilation time is set to 2 h at a time, three to four times a day, according to patient tolerance, until 24 h with continuous application is reached. Reassess the patient regularly and consider repeat arterial blood gas analysis.

Many conditions suggest that noninvasive ventilation has failed, and a switch to invasive ventilation is required. Main indications of failure include respiratory arrest, loss of consciousness with apnea, severe hemodynamic instability (heart rate < 50 beats/min with unconsciousness, and/or systolic blood pressure < 70 mmHg), and required sedation to control agitation. Secondary failure indications are breathlessness, increasing respiratory rate > 35 breaths/min, PaO_2 < 45 mmHg or oxygenation index < 150 mmHg, $PaCO_2$ increased > 20 % or $PaCO_2$ > 60 mmHg, blood pH value < 7.20, and a change in the state of consciousness.

In invasive mechanical ventilation conditions, lung protective ventilation strategies are adopted such as applying ventilation with lower tidal volumes to maintain the airway platform pressure below 30 cmH_2O and using the mode of pressure control or pressure support to avoid barotrauma. The desired parameters are tidal volume of 6–8 mL/kg, respiratory rate of 15–20 breaths/min, inspiratory flow rate of 40–80 L/min, and an oxygen concentration of 0.6–1 (adjusted according to arterial blood gas analysis results). The expiration time should be extended so the inspiratory-to-expiratory time (I:E) ratio is <1:2. Try to maintain the airway platform pressure at ≤30 cmH_2O; positive end-expiratory pressure (PEEP) should usually be no more than 5 cmH_2O.

Immunosuppression in TB Combined with Secondary Lung Infection

Long-term use of immunosuppressive drugs can cause secondary lung infection and respiratory failure. Most of these patients have more critical illness, more rapid disease progression, and higher mortality rate. It is recommended to use the ICU exclusive NPPV respirator that can precisely adjust the inspired oxygen concentration and choose the oral-nasal mask with a better seal to carry out noninvasive ventilation. Generally, invasive mechanical ventilation mode is not recommended, because it can facilitate the onset of VAP.

Bronchopleural Fistula

A bronchopleural fistula is an opening connecting between the bronchus and the pleural space. TB patients are prone to suffer bronchopleural fistula because of secondary surgery, primary lung structural damage, or pulmonary barotrauma by mechanical ventilation. Mechanical ventilation should be used after taking all kinds

of reasonable measurements to reduce leakage and reduce the possibility of further damage. To implement a permissive hypercapnia strategy, apply lower respiratory rate, lower tidal volumes, and higher inspiratory flow (70–100 L/min) to reduce the inspiratory time and lower PEEP. Patients may be put under deep sedation, and even muscle relaxants can be used to avoid putting the patient in a position that could exacerbate leakage. Use the minimum chest tube attraction to maintain lung expansion, and take strong measures to heal the expiratory flow obstruction caused by bronchial spasms and other reasons. Measurements such as lung ventilation or thoracic drainage catheter plus PEEP can be used if necessary.

TB and AECOPD

NPPV is the preferred treatment for AECOPD patients to support their respiratory system. NPPV is effective for the TB patient with AECOPD and blood pH between 7.25 and 7.35 and $PaCO_2 > 45$ mmHg. For the patient with $PaCO_2 > 45$ mmHg, pH ≥ 7.35, NPPV is suggested for use in the early stage to avoid exacerbating illness. BiPAP mode is recommended. There should be more than 6 cmH_2O D-value between IPAP and EPAP to improve the patient's alveolar ventilation, relieve respiratory muscle fatigue, and correct the hypercapnia. The recommended EPAP level is between 4 and 6 cmH_2O and the maximum should be less than 8 cmH_2O so as not to aggravate lung dynamic hyperinflation (DH). For the patient with severe AECOPD, endotracheal intubation should be actively used for invasive mechanical ventilation treatment in the following cases: pH < 7.25, significant hypoxemia (PaO2 < 45 mmHg) and hypercapnia (PaCO2 > 80 mmHg), unconsciousness, unstable hemodynamics, a large amount of airway secretions, and/or the patient cannot tolerate NPPV treatment or has little or no remission after 2 h of NPPV treatment. The principles for mechanical ventilation are lower tidal volumes (5–7 mL/kg), slower frequency (12–15 times/min), and longer expiration time (I/E < 1:1.5). $PaCO_2$ can be slightly higher than normal, and, in principle, PEEP level should not be too high (70–80 % of the static intrinsic PEEP is allowed). Assisted ventilation (PSV + PEEP, SIMV + PSV + PEEP) mode should be adopted as soon as possible after the patient's condition is stable. Extubation (usually after intubation for 4–6 days) should be executed promptly (based on pulmonary infection control or respiratory physiological parameters) in order to effectively prevent VAP and ventilator-dependence. For COPD patients who are at the stage of rehabilitation, and satisfy the following conditions, NPPV treatment should be applied especially at night: when accompanied with fatigue, shortness of breath, lethargy, and other symptoms; when having abnormal gas exchange ($PaCO_2 \geq 55$ mmHg or is between 50 and 55 mmHg, $SaO_2 < 88$ % in the case of oxygen applied) and the situation continues for more than 10 % of the monitoring time; when having bad effects from bronchodilators and/or hormones, oxygen, and other medical treatment; for patients with moderately severe obstructive sleep apnea who are unresponsive to CPAP treatment.

Bronchial Asthma with Pulmonary TB

Bronchial asthma patients are more prone to TB because of their long-term use of corticosteroids and respiratory failures often related to acute severe attacks of asthma. Routine NPPV treatment is not recommended for severe asthma patients, and when NPPV is used for bronchial asthma, patients should be monitored carefully. Mechanical ventilation is the final effective means for treating severe asthma in TB patients. For some severe asthma patients whose main symptom is solely hypoxemia, application of CPAP can effectively relieve respiratory muscle fatigue and improve oxygenation. Application of BiPAP can relieve respiratory distress rapidly, promote carbon dioxide emissions, and improve respiratory function. Invasive mechanical ventilation should use the strategy of lower tidal volumes (6–8 mL/kg), lower frequency (10–15 times/min), and longer expiration time (I/E < 1:2); sedative drugs are required for patients to coordinate with treatment. PEEP levels should not be too high; generally about 5 cmH_2O is acceptable.

13.3.4.5 Balancing the Acid–Base Ratio and Solving the Electrolyte Turbulence Problem

When suffering from respiratory acidosis, resolution can come by increasing ventilation, and inhaling a small amount of alkali when the pH < 7.20. The main reason for respiratory acidosis with metabolic acidosis is lactic acidosis caused by hypoxia, which can be treated by ventilating, increasing oxygen delivered to tissue, and adding an appropriate amount of alkali. Most cases of respiratory acidosis with metabolic alkalosis are iatrogenic (such as excessive ventilation and diuretics). Symptoms such as low potassium, low chloride, and low sodium are common in electrolyte imbalance, and it is important to remember to replenish electrolytes. Water balance is also important. Excess fluid intake induces or aggravates cardiac insufficiency. Conversely, insufficient fluid is likely to lead to sputum drainage problems which aggravate airway obstruction.

13.3.4.6 Treatment of Predisposing Factors and Basic Diseases

There are many factors that could induce respiratory failure once the respiratory tract is infected. Treatments of pathogens vary according to their different basic diseases, different risk factors, and different pathogenic microorganisms. Moreover, treatment of basic diseases is also very important. For the patient with respiratory failure caused by severe TB who has bronchial pulmonary structural damage, strong anti-TB treatment at an early stage can effectively prevent spread in mechanical ventilation. This could directly impact the prognosis of patients. Goals for the TB patient with COPD are mainly for the treatment of chronic airflow obstruction, reduction of airway inflammation, and increase of secretions from the airway. For the patient with combined bronchial asthma, the key point is asthma control.

13.3.4.7 Preventing Complications

Diuretics and vasodilators could be used appropriately for heart failure, but cardiac glycosides must be used cautiously. Application of β blockers and antiarrhythmic drugs is avoided for arrhythmia. Drugs which could impair liver function are avoided, so as not to affect the normal application of anti-TB drugs. Complications such as gastrointestinal bleeding, shock, and DIC should be treated immediately. A key way to prevent multiple organ failure is to master the right time and method of oxygen therapy and mechanical ventilation to improve ventilation and avoid hypoxia. It is important to determine and treat hypotension promptly to avoid organ hypoperfusion. Also, note that TB is a chronic wasting disease. TB patients with respiratory failure can easily develop anemia, which should be corrected in order to improve blood capacity for oxygen and increasing the oxygen supply.

13.3.4.8 Nutritional Support

The majority of pulmonary TB patients are malnourished, which can make active TB progress and worsen. Protein–energy malnutrition (usually manifested as marasmic kwashiorkor type) affects the structure and function of the respiratory muscle, reduces ventilatory drive capability, and seriously affects the body's immune defenses. This has a negative impact on prognosis; TB is recurrent and hard to heal. In the early stage, nonprotein calories should be low, which may be increased to 30–35 kcal kg^{-1} d^{-1} after the situation is stable. For some patients with severe malnutrition problems who can not be offline, calories should be increased according to the patient tolerance to correct hypoproteinemia and malnutrition. The minimum ratio of glucose and fat calories is 50:50, the ratio of calories and protein should be 100 to 150:1, the protein intake should be 1.5–2.0 g kg^{-1} d^{-1} (Tayek 2002; Kreymann et al. 2009; Chen et al. 2011; Grau Carmona et al. 2011; Elke et al. 2014)

Vitamins and trace elements should be added to balance the electrolytes with special attention to the elements which could affect respiratory muscle function (such as potassium, magnesium, and phosphorus). Because of gastrointestinal disorders and anorexia, TB patients have reduced nutrient intake, resulting in an anabolic reduction. Meanwhile, *M. tuberculosis* will use the body's protein for its metabolism, causing fever, night sweats, weight loss, and other consumable changes, and leading to increased catabolism, decreased fat storage, and loss of lean body mass. When the body temperature increases 1 °C, metabolic rate will increase 13 % (Tan and Li 2000). Nitrogen and amino acids could get lost from sweat. Therefore, TB patients have a relatively higher catabolism rate, and their energy consumption is higher than that of healthy people. The basal metabolic rate (BMR) could increase 50–150 %. In severe stress, the catabolism rate is significantly higher than the anabolism rate, resulting in increased protein loss and muscle tissue loss. This causes skeletal muscle atrophy and negative nitrogen balance, causing hypoproteinemia and decreases immune function, which increases the infection rate and mortality. Glycometabolism is another metabolic disorder when the body is suffering stress.

The symptoms include high blood sugar, decreases in glucose oxidation and utilization rates, insulin resistance, and an increase in gluconeogenesis. Meanwhile, the energy intake reduces and histanoxia can develop, causing increased lactic acid which leads to acidosis. Among the 88.6 % of TB patients with malnutrition, 58.8 % have caloric malnutrition, 25.2 % have mixed malnutrition, and 4.6 % have protein malnutrition (Tan et al. 2005). Weight loss is a main characteristic for TB patients.

Increasing Caloric Intake

TB is a chronic wasting disease. Patients require more energy than healthy people. The general requirement is 30 kcal kg^{-1} of body weight, with the total intake about 2000 kcal each day. For a light manual laborer, 40 kcal kg^{-1} of body weight and about 2400 kcal per day are needed.

Increasing Protein Intake

Patients need more protein not only because of their high consumption, but also due to the benefit of protein for tissue repairing, lesion healing, and body recovery. TB patients need to have an intake of 1.2–1.5 g protein per kilogram of body weight daily, with the total intake of 80–100 g each day, 50 % of which are high-quality proteins such as meat, poultry, seafood, eggs, milk, and soy products.

Increasing Vitamin Intake

Vitamins A, B, C, and D should be supplemented first. Vitamin A can enhance the body's immunity, B vitamins could improve appetite, and vitamin B6 may relieve side effects caused by the use of isoniazid. Vitamin C will help lesions healing and hemoglobin synthesis, and vitamin D can promote calcium absorption. Fresh fruits and vegetables are the main source of vitamins. In addition, milk, eggs, and offal are rich in vitamin A. Yeast, peanuts, beans, and lean meats are rich in vitamin B6.

Calcium and iron should be supplemented in TB patients. Calcium is the raw material for TB calcification. Patient should drink 250–500 g of milk daily, which contains plenty of good calcium. Patients having hemoptysis or hematochezia should add iron, which is an essential raw material for hemoglobin manufacture.

In summary, during the treatment of TB, patients have to be given adequate nutrition, to enhance their immune function and reduce the negative oxygen balance in order to repair the body. Nutritional therapy is mainly focused on energy and protein supplements. In the process of energy supplementation, pay attention to the ratio of sugar and fat so as not to aggravate the liver and lung burden due to excessive sugar. The combined use of fat emulsion and glucose could provide more energy, thereby reducing protein breakdown for energy and improving nitrogen balance. Branched

chain amino acids and other essential amino acids should be supplied to enhance the body's protein levels, reducing albuminolysis, to promote nutritional recovery.

Diabetes mellitus, silicosis, and lung structural damage are the main predisposing factors for pulmonary TB, and recurrent pulmonary infection can weaken the body immunity, inducing pulmonary TB. Given these factors, in the diagnosis and treatment of pulmonary TB with concurrent disease or damage, it is critical to treat the two diseases together. In the course of treatment, we should pay attention to nutritional support and reduce the occurrence of complications.

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