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CHEST Special Features

Respiratory Medicine in China

Progress, Challenges, and Opportunities

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The past century witnessed a rapid development of respiratory medicine in China. The major burden of respiratory disease has shifted from infectious diseases to chronic noninfectious diseases. Great achievements have been made in improving the national standard of clinical management of various respiratory diseases and in smoking control. The specialty of respiratory medicine is expanding into pulmonary and critical care medicine. Nevertheless, respiratory diseases remain a major public health problem, with new challenges such as air pollution and nosocomial infections. This review describes the history, accomplishments, new challenges, and opportunities in respiratory medicine in China. ***CHEST 2013; 143(6):1766–1773***

Abbreviations: CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; NIPPV = noninvasive positive pressure ventilation; PAH = pulmonary arterial hypertension; PIC = pulmonary infection control; PTE = pulmonary thromboembolism; SARS = severe acute respiratory syndrome

Respiratory diseases are among the leading causes of death and major health threats in modern China. The development of modern respiratory medicine in China has undergone three phases, primarily driven by the disease burdens and the corresponding regulation priorities.

The first phase (1920s to 1960s) was a phase of prevention and management of TB. During this period, pulmonary TB was the most common respiratory disease in China. TB was extensively studied, and TB control was one of the top priorities in national public health programs in the 1950s.[1] When effective prevention and treatment became available and TB was brought under control, the focus gradually shifted to other respiratory diseases.

The second phase (1970s to mid-1990s) was that of prevention and management of cor pulmonale. The prevention and treatment of the four respiratory diseases of chronic bronchitis, emphysema, cor pulmonale, and influenza dominated the field. As a result, a specialized department focusing on respiratory medicine was established in most general hospitals, and many participating physicians became respiratory specialists. This period laid a solid foundation for the development of respiratory medicine in China.

The third phase (mid-1990s to present) is that of modern respiratory medicine. Respiratory medicine has developed rapidly in China. Respiratory medicine and critical care medicine have been merged as one department of respiratory and critical care medicine in many leading hospitals, and respiratory/medical ICUs

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have been established. This review focuses on the recent achievements, present challenges, and future directions of respiratory medicine in China.

Progress of Respiratory Medicine in China

Along with the rapid development of science and technology and the enhanced international collaborations, respiratory medicine in China has achieved great progress in various disciplines in recent years. Many guidelines on the management of respiratory diseases have been developed or updated based on both the international guidelines/consensuses and local conditions (eg, the specific physiologic conditions or regional economic situations).

COPD

It is estimated that 8.2% of people older than 40 years, or 43 million people, suffer from COPD in China.[2] COPD imposes a huge economic burden in China.[3] The costs of caring for patients with COPD were equivalent to 110% of the annual income of rural residents and 34% of that of urban residents.[4]

Efforts have been made to identify risk factors and mechanisms of COPD development in China. Smoking, air pollution, biomass fuel use, and occupational dust exposure seem to account for the high COPD prevalence. The male sex and low socioeconomic status are also associated with COPD.[5,6] Several genetic factors, such as polymorphisms in IL-27,[7] tumor necrosis factor-α,[8,9] aquaporin 5,[10] heme oxygenase-1,[11,12] and epoxide hydrolase1[13] have been shown to increase susceptibility to COPD in the Chinese population. A causal relationship between depression and COPD exacerbation has also been proposed.[14] The ongoing hot research topics also include the role of inflammation in COPD and the therapeutic interventions aimed at preventing the destruction of lung tissues.

In clinical management, COPD exacerbations can be reduced by carbocisteine,[15] theophylline,[16] and salmeterol/fluticasone propionate.[17] Community-based interventions, including health education, individualized treatment, and pulmonary rehabilitation, may be effective in the prevention and management of COPD.[18]

Although data in older people are abundant, the prevalence of COPD in younger populations is not known. Younger patients should be particularly targeted, since COPD may start early in life, and early diagnosis and intervention may reduce its progression. To achieve this goal, a nationwide survey of lung function has recently been initiated in China, beginning with people ≥ 18 years of age.

The battle against COPD in China is an arduous task and requires joint efforts from the government and medical communities. In 1997, the first Chinese guideline on COPD management was published by the Chinese Thoracic Society.[19] The Chinese guidelines are generally in line with international guidelines but also accommodate practical issues, such as cost and availability of specific interventions. COPD is now listed as one of the major diseases in a government-initiated national project for prevention and control of noncommunicable chronic diseases. The specific goals of this project include early diagnosis and intervention of COPD, smoking control, improvement of patients' self-management, and physicians' compliance with guidelines.

Asthma

Asthma is a major clinical problem and one of the most common causes of hospitalization for children in China. The prevalence of asthma has increased from 0.91% in 1990 to 1.50% in 2000.[20] The prevalence in adults ranges from 0.94% in southern China to 1.25% in northern China.[21-23]

The prevalence of asthma was found to be higher among workers in chemical factories (1.06%) and large petrochemical factories (2.81%) than in farmers living in rural areas (0.43%), prompting an association of asthma with environment pollution.[24] The pathogenesis of asthma may also be associated with the dysregulation of inflammatory reaction in asthma.[25-27]

Hospital-based asthma education and management programs are effective in improving asthma control and quality of life.[28] The Chinese Thoracic Society updates its asthma guidelines every 5 years to keep up with the Global Initiative for Asthma (GINA) and to incorporate new data from Chinese studies.

Respiratory Infections

Respiratory infections have long posed a major health threat to Chinese people. From the 1950s to 1960s, TB, bacterial pneumonia, and lung abscess were the most prevalent lung infections, which shifted to hospital-acquired pneumonia (HAP) and community-acquired pneumonia (CAP) in the 1980s. The isolation of antimicrobial resistant strains in CAP[29-31] and HAP[32] has raised concerns for the misuse of antibiotics. Chinese guidelines on HAP and CAP have been developed.[33,34]

The outbreak of severe acute respiratory syndrome (SARS) in 2003 triggered extensive research[35] and led to the establishment of an effective system in controlling the emerging respiratory viral diseases.[36-39] Corticosteroids were effective to reduce fatality and hospital stay in critically ill patients with SARS,[40] and a vaccine has been developed for its prevention.[41]

With the experience of dealing with SARS, the Chinese medical community and public health system responded quickly to the later epidemic of avian

influenza in 2009.[42,43] The clinical features, such as incubation period and common symptoms, were reported.[44] The efficacy and safety of oseltamivir and maxingshigan-yinqiaosan, a formula of traditional Chinese medicine, in treating 2009 influenza A(H1N1) were tested.[45] Studies on the effectiveness of traditional Chinese drugs are especially important, because these drugs are widely accepted by Chinese people, and some of them have been applied for thousands of years. The rapid and successful control of the A(H1N1) pandemic in China was highly praised.[46]

After the SARS epidemic was brought under control, the Chinese government implemented a series of measures to strengthen its public health system. This was reinforced by the efforts in TB control.[47] With increased inputs on TB control, China achieved its major goals in the fight against TB from 2001 to 2010.[48] However, TB control in China will remain a long-term public health challenge because of the high rates of multidrug resistance and the emerging TB and HIV coinfection. In the foreseeable future, advances in DNA sequencing and genomic technology will allow the rapid identification of new pathogens and facilitate studies on the gene-gene and gene-environment interactions under specific disease conditions and studies on the interactions of the lung microbiome with microbial populations located in other organs/systems.

Interstitial Lung Diseases and Occupational Lung Diseases

Interstitial lung diseases have been increasingly recognized in China. Sarcoidosis is the most studied interstitial lung disease. The HLA-DR gene may be associated with the susceptibility to sarcoidosis in the Chinese population,[49] and glucocorticoid therapy may improve outcome.[50] Idiopathic pulmonary fibrosis is also a common condition in China, and lung transplantation may be feasible for patients with end-stage idiopathic pulmonary fibrosis.[51]

Occupational lung diseases are characterized by their high morbidity and mortality. A large proportion of Chinese people are at high risk for these diseases. Pneumoconioses are the major occupational lung diseases, accounting for 70% to 80% of the total occupational diseases, and 12,000 to 15,000 new cases were reported annually.[52] Exposure to chrysotile asbestos, arsenic, radon, and cadmium can induce pneumoconiosis.[53] Furthermore, a higher incidence of lung cancer was observed in patients with silicosis,[54,55] and its underlying pathogenesis is under investigation.

Lung Cancer

A substantial proportion of cancer-related deaths in China are attributed to lung cancer. In China, about 300,000 new lung cancer cases (23 out of 100,000) and $>250,000$ deaths from the disease are predicted each year.[56] Similar to the developed countries, most lung cancer cases are inoperable at diagnosis. Although high-quality care has become available for residents in socioeconomically developed areas, treatment of lung cancer remains primitive in many rural areas.

Probably unique in China, respiratory physicians are involved in diagnosis as well as management of lung cancer, including administration of chemotherapy. Although the Chinese guideline is widely available,[57] heterogeneity in the quality of care among centers, especially the disparity between urban and rural areas, has restricted the management of lung cancer in a more consistent way. As elsewhere around the globe, platinum-based doublet chemotherapy remains the most commonly used regimen, and some new epidermal growth factor receptor-targeted therapies have also been investigated in many medical centers.[58]

In recent years, increasingly more regional hospitals are equipped with CT scanners and even PET-CT scanners, facilitating early diagnosis of lung cancer. The multidisciplinary treatment, especially the molecular targeted therapy, will further improve the survival of patients with lung cancer.

Pulmonary Vascular Diseases

Pulmonary thromboembolism (PTE) was significantly underdiagnosed in China for a long time, until the late 1990s, when several clinical studies demonstrated that it was in fact a common disease in the Chinese population.[59,60] In 2001, the first guideline for PTE was published,[61] the first national conference on PTE was held, and a nationwide collaborative group was organized in China. The group conducted a series of multicenter studies on PTE,[62-64] which effectively increased awareness and improved diagnosis and management of PTE, leading to a decrease in PTE fatalities in China.[65]

Genetic polymorphisms associated with PTE among the Chinese were characterized, and several genetic traits in fibrinogen β[66] and plasminogen activator inhibitor-1[67] were linked to an increased risk of PTE in the Chinese population. However, the low incidences of factor V Leiden, prothrombin gene G20210A, and methylenetetrahydrofolate reductase gene C677T mutation suggest that they are not the major genetic risk factors for PTE in the Chinese population.[68-70]

Great efforts have been made to find the optimal regimens for treating PTE. Wang et al[71] demonstrated that a short regimen of 2-h urokinase IV showed similar efficacy and safety as standard 12-h urokinase IV in treating acute pulmonary embolism. The new regimen significantly reduces the cost of the treatment. In another multicenter trial, the same group reported a similar efficacy, but better safety, when the dosing

of recombinant tissue-type plasminogen activator was decreased from 100 mg to 50 mg in treating acute massive PTE.[72] Currently, clinical trials on new anticoagulants for PTE and thrombolytic therapy for submassive pulmonary embolism have been initiated.

With improved diagnosis of PTE, more patients with chronic thromboembolic pulmonary hypertension and associated pulmonary arterial hypertension (PAH) have been identified.[73] More than five medical centers in China can provide pulmonary endarterectomy and lung/heart transplantation. Currently, a registry of PAH and multicenter trials for the evaluation of targeted therapy for PAH in the Chinese population are in progress. Laboratory research in pulmonary hypertension, focusing on the effects of the vanilloid-related ion channel[74] and Ca^{2+} ions[75] on proliferation of human pulmonary arterial smooth muscle cell, is being conducted by Chinese investigators.

Critical Care and Ventilatory Support

In China, clinical application of positive pressure ventilation dates back to the 1970s, and the use of noninvasive positive ventilation started in the 1990s. The Chinese Thoracic Society developed guidelines with recommendations for mechanical ventilation in 2007[76] and for noninvasive positive pressure ventilation (NIPPV) in 2009.[77]

In 2005, the concept of a pulmonary infection control (PIC) window was proposed to facilitate transition from invasive to noninvasive ventilation during COPD exacerbation.[78] The PIC window denotes that, in the management of ventilator support in patients with COPD with acute respiratory failure triggered by pulmonary infection, early extubation followed by noninvasive mechanical ventilation during the time of the PIC window will significantly reduce the risk of ventilator-acquired pneumonia and improve the prognosis. The PIC window was subsequently proven useful in replacing intubation with sequential noninvasive ventilation in a nationwide multicenter prospective randomized controlled trial.[78] Another multicenter randomized controlled trial showed that early use of NIPPV in acute exacerbation of COPD could alleviate respiratory muscle fatigue and prevent worsening of respiratory failure.[79] Application of NIPPV was also shown to be beneficial in severe hypercapnic encephalopathy[80] and for acute lung injury.[81] A multicenter, randomized, controlled clinical trial with a larger sample size is being conducted in China to assess the benefit of NIPPV use in patients with acute lung injury.

Sleep Medicine

The link between sleep apnea and respiratory diseases has been increasingly recognized in China. The prevalence of obstructive sleep apnea syndrome is estimated in the range of 3.5% to 4.8% in the Chinese population >30 years old.[82] A close association between obstructive sleep apnea syndrome and cardiovascular diseases[83,84] has been described. The Sleep Breathing Disorder Assembly of the Chinese Thoracic Society was organized in 2000, and the first guideline for sleep breathing disorders was issued in 2002[85] and updated in 2011.[86] More than 600 sleep laboratories have been established throughout China.[82] Almost all university hospitals and hospitals at the province level have established their sleep laboratories, and some laboratories are operated by other departments (eg, ear, nose, and throat department). Sleep medicine in China is still in its infancy. The awareness of sleep breathing disorders remains to be promoted among primary healthcare providers. Insurance coverage for the diagnosis and treatment of sleep disorders will be the key for a wide public benefit.

Smoking Control and Tobacco Medicine

As the world's largest cigarette consumer and manufacturer, China has >300 million smokers, and >740 million nonsmokers are exposed to second-hand smoking.[87] It is estimated that >1 million Chinese people die because of smoking-related diseases each year. The direct economic burden of tobacco use reaches 42.31 billion yuan (equivalent to 6.09 billion US dollars) in China.[88]

With such a huge impact of tobacco use, smoking control becomes a top priority of the Chinese health authorities. Since the ratification of Framework Convention of Tobacco Control in 2005,[89] smoking prevention and cessation programs have been implemented widely. The 2007 Smoking Control Report of China by the Ministry of Health showed promising results.[90] In May 2012, the Ministry of Health issued the first China Report on the Health Hazards of Smoking, which systemically illustrated the harmful effects of smoking.[87] This event has been considered by the World Health Organization as a milestone for disease prevention and control in China.[91]

Despite the progress, enforcement of smoking-related laws and regulations remains a challenging task. The existing public health policies should be strengthened, and new strategies, including raising taxes on tobacco products, will be explored. Physicians play a leading role in smoking control. Smoking cessation training programs for physicians, especially for male physicians, who are less likely to provide smoking cessation counseling for patients, should be enforced.[92]

The research on smoking hazards and smoking control has gradually become a highly specialized area in medicine, which includes the further elucidation of smoking prevalence and social behavior, harmful ingredients in tobacco, smoking-related diseases and their

mechanisms, tobacco cessation and the management of tobacco dependence, and smoking prevention and control. Just like the emergence and development of occupational medicine in the practice of prevention and management of occupational diseases, a specialized medical discipline, tobacco medicine, is growing in popularity.

Future Directions

Respiratory medicine is facing significant challenges. To overcome this obstacle, we need to continue to improve our understanding of the complex respiratory diseases and to develop more effective therapies to prevent and treat these conditions. Rapid development in science and technology offers new approaches to achieve this goal. Advances in biomedical science enable us to understand lung diseases at the molecular level. Modern medicine has been empowered with the development of multiple approaches of pharmaceutical therapies, cell therapies, and bioengineering devices to treat respiratory diseases.

Pulmonary physicians need to integrate the diverse areas in basic science and clinical research. We should conduct translational research that promotes the information exchange between "bench" and "bedside" and advances knowledge in both basic and clinical sciences. We should encourage ourselves to formulate challenging questions based on bedside observations, elucidating the fundamental molecular and cellular mechanisms of disease processes using current science knowledge and technologies. We should also translate the scientific discoveries from basic research into clinical applications. New and improved therapeutic strategies can be developed based on biologic foundation.

Effective national programs for respiratory disease control are urgently needed. Well-designed nationwide epidemiologic studies on the prevalence and morbidity of many respiratory diseases should be carried out to evaluate present and future disease burdens. Studies on genetic susceptibility to respiratory diseases among the Chinese population should be enforced to improve early diagnosis and intervention. Integration of clinical resources and multicenter research should be pushed forward to improve diagnosis and treatment. Community-based comprehensive intervention should be implemented to ensure the availability of medical resources, such as essential drugs, equipment, and human resources. The priorities and future directions will also include the organization of large-scale clinical trials and the development and update of guidelines on respiratory diseases.

Finally, shortage of respiratory physicians remains a challenging problem. Only a limited number of teaching hospitals can offer effective training on respiratory medicine and critical care medicine, and currently no national standard curricula and certification examinations are available in this field. Reform on medical education and training is urgently needed, and continuous medical educational programs should be carefully designed and provided to meet the rapidly increasing demands.

Conclusions

Respiratory diseases are the leading causes of death and socioeconomic burdens in China. Significant progress has been made in improving the management of various respiratory diseases and in tobacco control. Respiratory diseases remain a major public health problem, whereas respiratory medicine is facing more new challenges. In the battle against respiratory diseases, the Chinese Thoracic Society is taking a leading role in promoting the collaborative efforts to improve the standards of medical practice and patient care, to support research, to train young respiratory physicians, and ultimately to fulfill our mission in saving lives and alleviating suffering for patients with respiratory diseases.

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