

Diagnosis, treatment, and prevention of lower respiratory tract infections in children

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Lower respiratory tract infections (LRTIs) are among the leading causes of childhood morbidity and mortality worldwide, which are an important contributor to the rising burden globally. It was reported that LRTIs remained the second leading cause of death in children younger than 5 years in 2019, following neonatal disorders.¹ Early-life LRTIs might affect lung development and lung function trajectories, leading to chronic respiratory diseases in adults. Therefore, reducing the morbidity, severity, and mortality of LRTIs in children is of great significance.

Etiological diagnosis plays a crucial role in the identification and treatment of LRTIs, while more than 50% of respiratory tract infectious patients fail to diagnose causative agents.² Although the unavailability of qualified samples, antimicrobial treatment prior to sample collection, wide variety of respiratory

pathogens, and influence of the normal flora in the respiratory tract are issues, the lack or inability to obtain pathogen testing is also an important reason. In recent years, progress in molecular diagnosis, especially the novel approaches such as the multi-pathogen detection technology based on polymerase chain reaction (PCR) techniques, clinical metagenomics, clustered regularly interspaced short palindromic repeats (CRISPR), and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF-MS) have developed rapidly, which greatly improved respiratory infections pathogen detection capability. Taking the GeneXpert detection method based on multiplex PCR technology as an example, it improves the diagnosis of active tuberculosis, and its sensitivity and specificity to rifampicin-resistant pulmonary tuberculosis are 92% and 98%, respectively.² The point-of-

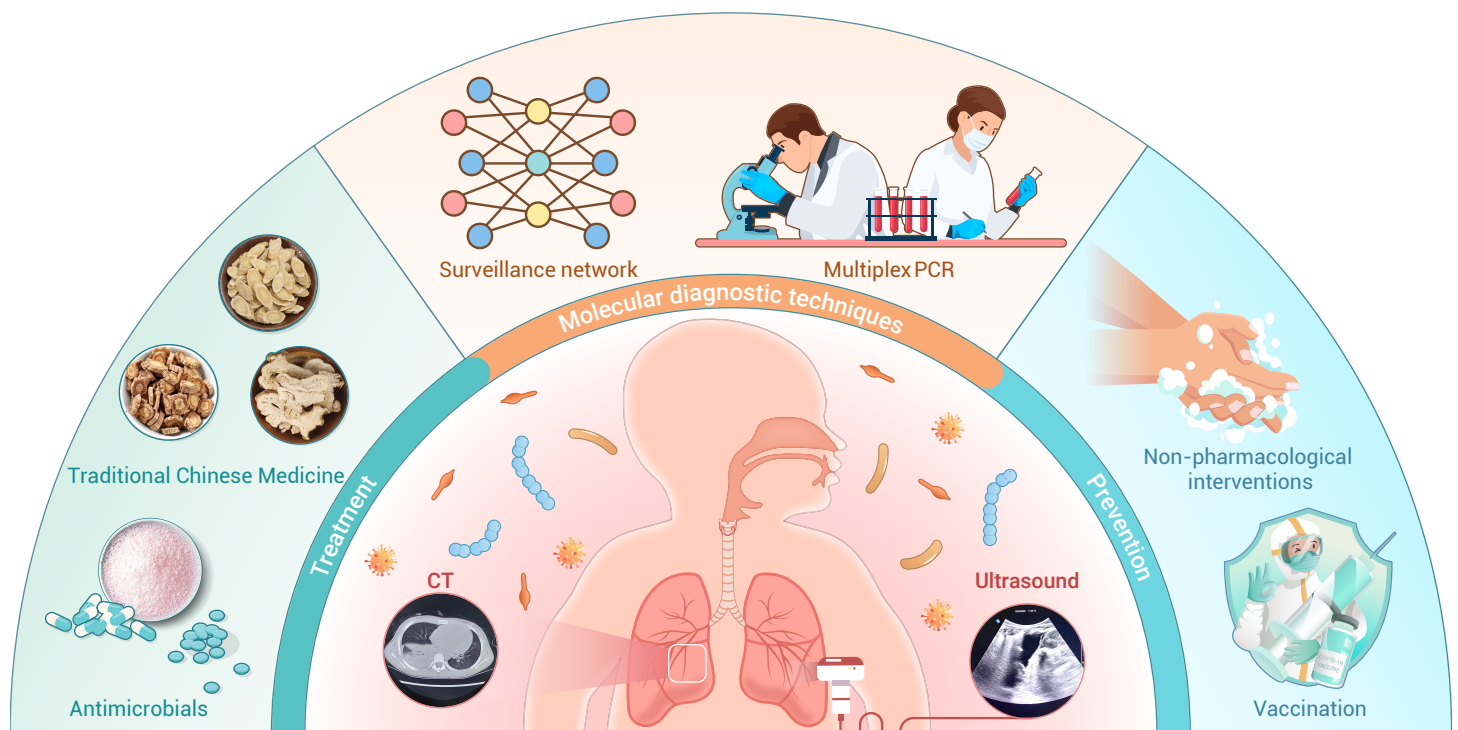


Figure 1. Diagnosis, treatment, and prevention of lower respiratory tract infections in children.

care testing and rapid antigen detection provide faster and more convenient methods enabling patients to receive early diagnosis and precise treatment.

In addition, the diagnosis of lung diseases increasingly relies on computed tomography (CT). Potential ionizing damage caused by accumulated radiation was a concern in the medical and scientific community. A recent large-scale multinational cohort study revealed the risk of hematological malignancies associated with ionizing radiation exposure from CT examination during childhood and young adulthood. The results suggested that for every 10,000 children examined today (mean dose 8 mGy), 1-2 persons are expected to develop a hematological malignancy attributable to radiation exposure in the subsequent 12 years.³ Therefore, there is an urgent need for other imaging diagnostic techniques besides CT scans. Ultrasound, as a low-cost, radiation-free examination technique, is increasingly being used in lung disease diag-

nosis with the improvement of equipment and imaging, especially suitable for patients who require dynamic follow-up and in intensive care units. However, some studies have shown that it has higher consistency with X-ray diagnosis for some certain diseases, while others are lower. Lung ultrasound diagnosis heavily relies on the operator's technical level and machine; therefore, more researches, training, and guidelines are needed to standardize the clinical application of lung ultrasound in pediatric respiratory diseases.

The prominent challenge in the treatment of pediatric respiratory diseases is the lack of drugs or limitations in drug use, such as respiratory syncytial virus (RSV), macrolide-resistant *Mycoplasma pneumoniae* (MRMP) and antibiotic-resistant bacteria. Recently, there has been promising progress in the treatment of RSV, such as AK0529, an RSV fusion protein inhibitor. Phase II clinical trials have confirmed its efficacy and safety, and phase III trial is

underway. Other drugs targeting RSV are also under development. Baloxavir Marboxil, a selective inhibitor of influenza cap-dependent endonuclease, has been officially approved by the National Medical Products Administration of China for use in children aged 5 and above with influenza, providing more drug options for pediatric influenza treatment.

"Prevention is better than treatment". Vaccination has succeeded in the prevention of some communicable respiratory diseases such as *Streptococcus pneumoniae*-associated infections, influenza, etc. Vaccines targeting RSV, the most common cause of acute LRTIs and death in infants younger than 6 months of age, have been researched for decades. Unfortunately, direct infant immunization is not available yet. Nirsevimab, a recombinant human IgG1 kappa monoclonal antibody that locks the RSV fusion protein in the prefusion conformation to block viral entry into the host cell, has been approved for marketing as a preventive measure for RSV in newborns and infants under 24 months of age. A recent study on maternal RSVpreF vaccine administered during pregnancy showed effectiveness against medically attended severe RSV-associated lower respiratory tract illness in infants, with the efficacy of 81.8% and 69.4% in infants within 90 days and 180 days after birth, respectively, without identified safety concerns.⁴ And more new drugs and vaccines will be applied in clinical practice in the near future.

However, most communicable respiratory diseases do not have available vaccines, and non-pharmacological interventions (NPI) play an important role in disease prevention. For example, NPI implemented during the COVID-19 pandemic greatly prevented respiratory infections. Furthermore, nutrition, pollution, and smoking have a significant impact on children's respiratory system, so it is important to improve the strategies for avoidable risk factors.

Respiratory tract infections remain a significant concern for children. In addition, the emergence of new infectious diseases and bacterial resistance poses ongoing challenges. Therefore, monitoring respiratory pathogens is crucial for understanding disease trends, identifying new pathogens, and developing prevention and control strategies. In China, the Chinese Pathogen Identification Net (China PIN), the China Antimicrobial Resistance Surveillance System (CARSS), and the China National Influenza Surveillance Network play vital roles in tracking bacteria and viruses. However, a comprehensive multi-pathogen monitoring network specifically tailored for children is still needed.

Molecular diagnostic techniques offer precise identification of respiratory pathogens, but challenges remain in their application and interpretation. For instance, next-generation sequencing (NGS) can detect numerous microorganisms, yet discerning the true pathogen remains a challenge for clinicians. There is a pressing need for the development of new diagnostic technologies for respiratory diseases, as well as the creation of specific antimicrobial drugs suitable for children, and vaccines targeting pathogens like RSV, adenovirus, and *Mycoplasma pneumoniae*. Future research will focus on the mechanisms, drug development, and pulmonary rehabilitation strategies for severe lower respiratory complications and sequelae, such as bronchiectasis and post-infectious bronchiolitis obliterans. With advances in genetics, an increasing number of monogenic diseases, such as primary ciliary dyskinesia, cystic fibrosis, and primary immunodeficiency, have been identified behind severe or recurrent respiratory tract infections in children, presenting significant treatment challenges. Addressing these challenges necessitates a

multidisciplinary approach involving pulmonologists, radiologists, laboratory technicians, pharmacists, physical therapists, and geneticists.

Traditional Chinese Medicine (TCM) has been practiced in China for thousands of years, characterized by its multi-targeted approach and complex compositions. It is used to treat various stages of diseases. In recent years, extensive researches have been conducted on the mechanisms, efficacy, and safety of TCM, with many high-quality papers published. One example is Yupingfeng (YPF), a TCM used for centuries to treat children with recurrent respiratory tract infections (RRTI). A multi-center prospective randomized controlled trial⁵ demonstrated that during a one-year follow-up, 73.13% of children in the YPF group returned to normal health levels, which was comparable to the positive control group (67.15%) and superior to the placebo group (38.81%), with high safety. More high-quality RCTs and pharmacological studies on TCM are being conducted, gaining increasing recognition and acceptance in the West.

Respiratory tract infections are prevalent and significant in children. Despite advances in diagnostic techniques, drug treatments, and vaccine prevention, challenges persist. In this era of rapid technological advancement, interdisciplinary collaboration among researchers, clinicians, and policymakers is crucial to enhance precise diagnosis, treatment, prevention, and control in children. Embracing the One Health concept, which emphasizes the interdependence of human, animal, and environmental health, is essential for developing a comprehensive framework to address the complex nature of respiratory tract infections in the future (Figure 1).

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DECLARATION OF INTERESTS

The authors declare no competing interests.