Executive summary of Chinese expert consensus for topical application of anti-microbial agents for lower respiratory tract infection in adults

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In recent years, with the increased prevalence of multi-drug resistant (MDR) bacterial infection and chronic pulmonary infection, the topical application of anti-microbial agents, mainly inhaled antibiotics, has come back to clinical practice. Several formulations for nebulization and dry powder inhaler (DPI) have been approved for inhaled anti-infective therapy. Meanwhile, evidence and experience have been accumulated in the use of anti-microbial agents delivered via airway. However, the available studies in this field are heterogenous in the study population, drug delivery route and dosages. The efficacy and safety of inhaled anti-infective therapy in various types of lower respiratory tract infections (LRTIs) need to be evaluated. Moreover, due to the lack of formulations developed for inhalation in China, there are problems including topical use of intravenous preparations. To standardize the clinical practice of topical anti-infective treatment of adult LRTIs, the Pulmonary Infection Assembly of Chinese Thoracic Society initiated and organized experts to formulate a consensus document, in which anti-microbials for respiratory topical use and their indications are summarized based on available evidence. As the high-quality evidence is scarce, the levels of recommendation are not stated. This article is the executive summary of the consensus, and the full text was

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The drug delivery routes of topical anti-infective therapy through airway include nebulization, dry powder inhalation and injection via bronchoscope. The potential indications for these treatments are refractory pulmonary infections with poor response to systemic anti-microbial treatment. One or more of the following conditions may exist: (1) chronic infection related to structural lung diseases, such as cystic fibrosis (CF) and non-CF bronchiectasis;[2] (2) chronic infection of tuberculosis, non-tuberculous mycobacteria (NTM), aspergillosis and *Pseudomonas aeruginosa* (PA);[3,4] (3) suboptimal lung drug concentration when used systemically due to abnormal blood supply in diseases such as chronic lung abscess and bronchopulmonary aspergillosis;[3,5] (4) susceptible drugs to be used have poor penetration into lung tissue and potential side effects when administrated intravenously, while achieving high and sustained drug concentration in the lung with low systemic absorption when administrated via airway. One example is aminoglycosides and polymyxins for treating MDR pathogens, especially extensively drug resistant Gram-negative bacilli (GNB) in ventilator-associated pneumonia (VAP).[5] In addition, zanamivir can only be used as DPI, which is used for the prevention and treatment of influenza. Drugs with inhalation indications and those off-label but having supportive clinical evidence are listed in Supplementary Tables 1 and 2, http://links.lww.com/CM9/B349.

The recommendations for topical anti-infective therapy of common refractory LRTIs are as follows: (1) VAP: For VAP caused by MDR GNB, if the responsible pathogens are only sensitive to antibiotics such as aminoglycosides or polymyxins, and the anti-infective effect cannot be ensured by increasing the systemic dosage of these drugs due to dose-related side effect, consider adding inhalation of these drugs on systemic anti-infective treatment. Appropriate nebulization device should be used, and appropriate oxygen concentration and ventilation mode should be set according to the pathophysiological characteristics of patients. Empirical use of nebulized antibiotics for patients with VAP is not recommended. (2) Non-CF bronchiectasis: For moderate to severe non-CF bronchiectasis patients with positive sputum culture of PA, nebulized tobramycin is recommended, and intermittent administration for 28 days is recommended for long-term inhalation therapy. Colistin methane sulfonate can also be inhaled for treatment. Inhalation of quinolones is not recommended for the treatment of non-CF bronchiectasis. (3) Chronic pulmonary aspergillosis (CPA): For CPA patients with poor response to systemic anti-fungal treatment, treatment failure or intolerance, combined intracavitary injection of amphotericin B can be considered. (4) Acute bronchopulmonary aspergillosis: For recipients of solid organs (lung, heart) or hematopoietic stem cell transplantation, and patients with hematological malignancies or neutropenia, amphotericin B can be inhaled to prevent pulmonary mycosis. (5) Tracheobronchial tuberculosis: For patients with active tuberculosis of trachea and bronchus, nebulized anti-tuberculosis drugs can be combined with systemic use in the intensive period of chemotherapy. The drugs can also be delivered by bronchoscope. The commonly used drugs are isoniazid and amikacin. (6) Cavitary or drug-resistant tuberculosis: For cavitary or drug-resistant tuberculosis with poor response to systemic chemotherapy, consider trying intratracheal isoniazid, amikacin, or rifampicin via bronchoscope during interventional therapy. (7) Influenza: Zanamivir DPI is recommended for the treatment of non-severe influenza and the prophylaxis of influenza in unvaccinated individuals at high risk of complicated influenza. (8) Prophylactic treatment of patients receiving lung transplantation: According to the known or possible pathogens in donor and/or recipient and time window, prophylactic inhalation of anti-microbial agents can be used. (9) *Pneumocystis Jirovecii* pneumonia (PJP): Inhalation of pentamidine is recommended for the prevention of PJP in high-risk population who are not tolerable to sulfonamides. It is recommended to inhale bronchodilators and quit smoking before pentamidine inhalation. (10) NTM pulmonary disease: In the treatment of NTM, nebulized inhalation of amikacin can be used for those who have difficulty in systemic administration or need long-term treatment. The goal of treatment is to improve clinical symptoms rather than cure diseases.

Cough, wheezing, hemoptysis, aggravation of underlying lung diseases and even death may occur after tracheobronchial use of anti-microbial drugs, so the risks should be carefully evaluated before use. The dosage can be gradually increased to reduce adverse reactions. During the treatment, respiratory side effect should be closely monitored. In addition, drug absorption through airway mucosa may increase systemic adverse reactions, which should be closely observed.

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Conflicts of interest

None.

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