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Inhaled antibiotics and airway bacterial decolonization for patients with chronic obstructive pulmonary disease: The rationale and future

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According to the Global Burden of Disease (GBD) study, chronic obstructive pulmonary disease (COPD) has become the third leading cause of death all over the world. The high prevalence, years lived with disability (YLDs), and disability-adjusted life-years (DALYs) of COPD make it a significant challenge for health-care system.[1] More importantly, it has been proved that severe exacerbations of COPD are associated with the worse survival outcome and the mortality can even increase with the frequency of severe exacerbations.[2] Therefore, the prevention of acute exacerbations of COPD (AECOPD) is urgently needed.

Currently, the Global Initiative for COPD (GOLD) report (2021) suggested that the prevention measures of AECOPD include the use of bronchodilators, inhaled corticosteroids (ICS), phosphodiesterase-4 inhibitors and mucolytic drugs, and non-drug therapies, such as smoking cessation, vaccinations, and pulmonary rehabilitation. Long-term use of intermittent low-dose macrolides, which may act as a modulator of inflammation rather than an antimicrobial agent, is also a kind of new effective prevention measure, but the balance of benefits and risks needs to be considered.[3]

It has been well recognized that bacteria play an important role in the disease course of COPD. Bacterial infection is a major etiology of AECOPD, which accounts for 25%–81% of the events. The main pathogenic bacteria isolated during AECOPD are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and so on.[4, 5] About 74% of those COPD patients in stable stage have lower respiratory tract (LRT) colonization of potential pathogens, including *H.influenzae*, *Moraxella pneumoniae*, *S. pneumoniae*, *P. aeruginosa*, and so on, among which Gram-negative bacteria (GNB) occupy the majority.[6-8] More importantly, studies have shown that bacterial colonization could enhance bronchial inflammation.[9] In recent years, thanks to the technical improvements, progress has been made on the relationship of altered airway microbiome and COPD. Studies showed that colonized *H.influenzae* were associated with a high level of inerleukin-6 trans-signaling, which could be an important disease-driving factor of COPD.[10, 11] That is to say, the airway microbiome in COPD patients may cause abnormally elevated airway inflammation. Since chronic inflammation of airway is the basis for COPD,[12] colonized bacteria may contribute to the progression of COPD. Vice versa, the airway inflammation of COPD can further disrupt lung defense mechanisms and make it more susceptible to bacterial colonization or infection.[13] The use of antibiotics for COPD patients with repeated exacerbations, as a measure to decolonize, may stop the vicious cycle of bacterial colonization and inflammation and directly reduce airway bacteria load or inflammation. All these reasons provide an opportunity for antibiotics to prevent AECOPD.

The research on the application of antibiotics in COPD was first started in the 1950s. Staykova *et al.* analyzed nine of these

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studies and found a small reduction of exacerbations per patient per year (odds ratio [OR] = 0.91, 95% confidence interval [CI] 0.84, 0.99).[14] In addition, an increased risk of bacterial resistance was observed. These trials have consistent limitations in study design, including small sample size, deficiencies in efficacy assessment, and use of narrow-spectrum antibiotics. Studies in the last decade have been better designed, but the results are also less encouraging, suggesting that long-term antibiotics not only fail to provide significant benefits, but may also cause bacterial resistance and side effects. It is probably because the study drugs, mainly quinolones (moxifloxacin) and tetracyclines (roxithromycin and doxycycline), are poorly effective against GNB such as *P. aeruginosa*.[15-18] However, GNB have been found to be the most common bacteria that colonize in the LRT of patients with stable COPD.[7] In addition, the antibiotics were administered orally in these studies. Orally given antibiotics tend to distribute throughout the body and only a small part of them reaches the lung, which leads to low concentration of the drugs in the lung.[19] The difficulty in achieving minimum inhibitory concentration (MIC) of antibiotics in the lung increases the growth of drug-resistant bacteria.[20] On the other hand, drugs presented elsewhere in the body may cause unwanted systemic side effects. Therefore, systemic delivery may lead to unavoidable side effects of the long-term antibiotics and increase of bacterial resistance. With the subsequent development of bronchodilators and ICS, which were found to be more effective in controlling COPD, there has been a decline in the interest in use of antibiotics for preventing exacerbations.

However, despite the appropriate use of available measures including long-acting bronchodilators and ICS, over 60% of patients with moderate or severe COPD had at least one exacerbation annually,[21] and Contoli *et al.* found that ICS may increase sputum bacterial load.[22] Patients with moderate-to-severe COPD were particularly more prone to LTR bacterial colonization, which may lead to frequent exacerbations of COPD.[23] Meanwhile, recent studies have found an increase of GNB colonization in the LRT of moderate-to-severe COPD.[6,7] Severe airflow limitation and a history of repeated exacerbations serve as risk factors for *P. aeruginosa* colonization. Repeated exacerbations and related use of antibiotics lead to increased colonization with drug-resistant pathogens. Compared with the last century, the development of new antibiotics, such as inhaled tobramycin and colistin, makes it possible for effective airway decolonization, thereby preventing AECOPD. Aminoglycosides and polymyxins conserve good susceptibility to GNBs, but the systemic administration of these agents has high frequency of side effects including kidney injury, which limit their clinical use for years. Poor pulmonary penetration is another weakness for LRT infection. The inhaled antibiotics can directly deliver drugs to the lung, thereby reducing administration dosage and systemic exposure.[19] Inhaled antibiotics can theoretically compensate for the shortcomings of systemic delivery and are particularly suitable for lung infections or colonization, thus having a great potential for LRT decolonization in COPD.

At present, studies on inhaled antibiotics are mainly focused on ventilator-associated pneumonia (VAP), cystic fibrosis (CF), bronchiectasis, and nontuberculous mycobacterial (NTM) lung diseases. The efficacy and safety of inhaled antibiotics in these diseases have already been confirmed.[24-27] Since COPD has similar conditions to CF, such as chronic airway inflammation, LRT bacterial colonization, and exacerbations caused by bacteria, the success of long-term inhaled antibiotics in CF suggests the feasibility in COPD. De la Rosa Carrillo *et al.* conducted a retrospective study on long-term inhaled antibiotics in COPD and found a decline in the number of exacerbations, hospital admissions, and hospitalization days.[28] However, only one published perspective study was found to be relevant to stable COPD (Table 1). Long-term inhaled colistin was used in 36 COPD patients with bronchial colonization by *P. aeruginosa*. One million international units of colistin in 1 mL 0.45% saline was delivered twice a day and at least for 3 months. The study showed a reduction in hospitalizations (2.0 *vs.* 0.9 per individual year, $P = 0.0007$) and length of hospital stay (23.3 *vs.* 10.9 days, $P = 0.00005$), but no difference in the number of AECOPD cases not requiring admission.[29] Despite the small sample size and inadequate design of outcome measures, the results of this study initially confirmed the efficacy of inhaled colistin. A pilot multicentric randomized controlled trial (RCT) is ongoing to evaluate the efficacy and safety of long-term intermittent inhaled amikacin in patients with moderate-to-very severe COPD (NCT03449459) (Table 1).[30] The primary outcome of the study is time to the first moderate-to-severe exacerbation. Lung function, COPD assessment test (CAT) scores, modified Medical Research Council (mMRC) scale, LRT bacterial load, and adverse events are also planned to be assessed.

LRT decolonization by inhaled antibiotics is a promising treatment strategy for COPD, but sufficient evidence is lacking for its clinical application. Subsequent clinical trials with large samples and long follow-up period are necessary. To maximize the therapeutic effect and reduce the overuse of antibiotics, it would be helpful to choose the appropriate patients for treatment. The targeted patients who might benefit from inhaled antibiotics are supposed to have the following features: (1) patients with severe airflow limitation and frequent exacerbations despite undergoing adequate therapy with bronchodilators and (2) patients with

Table 1: Clinical studies on inhaled antibiotics in COPD

Study	Enrollment	Study design	Country	Medications	Main findings
NCT00739648 Results first posted: March 2012*	322	Randomized, double blind, placebo controlled	USA	MP-376 (levofloxacin inhalation solution) 240 mg, aerosol inhalation, b.i.d., 5 days within a 28-day treatment cycle for up to 12 cycles	No change in exacerbation rate
Bruguera-Avila *et al*. (2017)[29]	36	Perspective	Spain	Colistin, 1 × 10^6 IU + 1 mL 0.45% saline, aerosol inhalation, b.i.d., at least 3 months	Decrease in hospitalizations and the length of hospital stay in COPD patients with bronchial colonization by *Pseudomonas aeruginosa*
De la Rosa Carrillo *et al*. (2021)[28]	693	Retrospective	Spain	≥1 dose of inhaled antibiotics (not specific) in the last 5 years	Decrease in the number of exacerbations, hospital admissions, and hospitalization days
NCT03449459 Completed: 2021[30]	144 (est.)	Randomized controlled	China	Amikacin sulfate injection 0.4 g + 5 mL 0.9% saline, aerosol inhalation, b.i.d., 5–7 days per month for 3 months	To be announced

COPD: chronic obstructive pulmonary disease; b.i.d.: twice a day; est.: estimated. *There is not an agreement between principal investigators (PIs) and the sponsor (or its agents), which restricts the PIs' rights to discuss or publish trial results after the trial is completed.

microbiological evidence of a high load of LRT bacteria, particularly GNB. Additionally, sensitive antibiotics should be selected as interventions in the future studies.

In conclusion, inhaled antibiotics have the potential for controlling COPD and preventing exacerbation by airway bacterial decolonization. Prior to the clinical application, well-designed studies on clinical efficacy, drug safety, and dose finding may contribute to a better understanding of inhaled antibiotics in COPD. Ultimately, this insight may lead to a generally accepted new treatment in stable COPD.

Conflict of Interest

Authors state no conflict of interest.

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