## Guideline Interpretation

# Comparison and evaluation of domestic and international guidelines of anti-infective therapy in acute exacerbation of chronic obstructive pulmonary disease treatment

#### Xin Zhou

Department of Respiratory Disease, Shanghai First People's Hospital, Shanghai Jiao Tong University, Shanghai, China

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an important feature of chronic obstructive pulmonary disease (COPD) progression. Repeated AECOPD causes serious consequences for the patients, showed a progressive decline in lung function and increased mortality. Many researches indicated that infection or viruses are important causes of AECOPD. Taking active treatment in AECOPD patients, who have the indications for the use of antibiotics, can rapidly improve the clinical symptoms, increase the cure rate and reduce mortality. In recent years, COPD treatment guidelines or expert consensus were published or updated at home and abroad, and made a special exposition of the relevant content on anti-infective therapy in AECOPD.<sup>[1-4]</sup> Since the bacterial resistance and antibacterials selection vary in different regions and countries, the contents of COPD treatment guidelines are not entirely consistent at home and abroad. To enable clinicians to better grasp the content of anti-infective therapy in AECOPD, we made a comparison of domestic and international guidelines of anti-infective therapy in AEOCOPD treatment.

## INFECTION, THE MAIN REASON OF ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

There has always been a controversy whether respiratory infections is an important reason of AECOPD or not. The

Address for correspondence: Dr. Xin Zhou, Shanghai First People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai 200080. E-mail: xzhou53@163.com

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inconsistent findings caused by the study do not distinguish between bronchitis and AECOPD, no placebo-controlled design and/or the lack of examinations, such as chest X-ray inspection etc., therefore, cannot determine whether the patient is with pneumonia. Similarly, there have been different views on the need for the use of antibiotics in AECOPD.

Over the past decade, a number of research results showed that respiratory bacteria or viruses were important causes of AECOPD. Domestic and international guidelines have always thought that about half of AECOPD infection caused by bacteria or viruses. Among them, Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis are main pathogens in mild to moderate AECOPD; the proportion of Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae increases in severe AECOPD; when combine mechanical ventilation, the resistant bacteria as Acinetobacter baumannii, Staphylococcus aureus, Maltophilia aeromonas etc., are more common. For AECOPD causes by virus infection, rhinovirus is the most common, but also includes the influenza virus, herpes simplex virus, corona virus, and respiratory syncytial virus, etc. In the past, it believed that AECOPD infections caused by atypical pathogens was rare, now it cannot be ignored that Chlamydia pneumoniae, Mycoplasma pneumoniae infection might a reason to induce AECOPD.

Whether it is a bacterial infection or a viral infection, they all make an increase of bacteria quantity in the airways of AECOPD patients. Inflammatory mediators such as leukotriene B4, interleukin-6, tumor necrosis factor-a, also significantly increase, thus increasing the airway inflammation in patients with COPD.

## **USE OF ANTIBIOTICS**

### **Antibiotic therapy treating indications of acute exacerbation of chronic obstructive pulmonary disease** 2011 Edition of global initiative for COPD,<sup>[1]</sup> 2011 Edition of

2011 Edition of global initiative for COPD,<sup>[1]</sup> 2011 Edition of Lower Respiratory Tract Infection Treatment Guidelines of European Respiratory Society/European Society of Intensive Care Medicine (ERS/ESCMID)<sup>[2]</sup> and 2013 Edition of COPD Treatment Guidelines of China<sup>[4]</sup> have raised the AECOPD crowd needed to receive antibiotic treatment:

- 1. The patients have three main symptoms: Difficulty breathing, increased sputum, coughing purulent sputum;
- 2. The patients have two main symptoms including coughing purulent sputum;
- 3. Severe AECOPD patients need the treatment of noninvasive or invasive mechanical ventilation. GOLD recommend to detect procalcitonin (specific indicators of bacterial infection) may help determine whether it is necessary to use antibiotics.

#### **Selection of antibiotics**

2011 Edition of GOLD<sup>[1]</sup> proposed the selection of antibiotics often need to accord to local circumstances of bacterial resistance. The initial empiric therapy often chooses amoxicillin with or without clavulanate, macrolides or tetracyclines (2011 Edition of GOLD guidelines has not fluoroquinolones). The patients with frequent exacerbations, severe airway obstruction and/or mechanical ventilation need to culture sputum or other parts of lung specimens. These patients infected with Gram-negative bacteria (such as *P. aeruginosa*), or resistant pathogens are not sensitive to antibiotics.

The above proposals do not give specific programs on antibiotic application when treating AECOPD. GOLD recommended initial empiric therapy for treating AECOPD is mainly based on epidemiological investigation level, proposes the antibiotics that are not entirely suitable for China. For little experience of clinical applications of amoxicillin with or without clavulanate treating AECOPD, it may not work well with amoxicillin therapy alone. For high resistance rates of *S. pneumonia* to macrolides, it is rarely used macrolides to treat AECOPD in our country. In tetracyclines, in addition to strong mold is used in special clinical infection, other drugs are rarely used. Therefore, GOLD proposed empirical therapy is difficult to promote in the clinic.

2011 Edition of ERS/ESCMID Respiratory Infection Treatment Guidelines<sup>[3]</sup> proposes to take stratified treatment for AECOPD hospitalized patients. The patients of group A have nonadmission risk factor of *P. aeruginosa* infection, those in group B have admission danger of *P. aeruginosa* infection. When it is provided with at least two risk factors of *P. aeruginosa* infection in the following, we consider the dangerous of *P. aeruginosa* infection:

- 1. Recent hospitalization patients;
- 2. Patient frequently (>4 courses/year) or recently (last 3 months) receive antibiotics;
- Patient's condition is serious (forced expiratory volume in 1 <30%);</li>
- 4. Oral corticosteroids (last 2 weeks >10 mg prednisolone).

For hospitalized AECOPD patients, the initial treatment plan is: Multiple antibiotic treatment options are available

for patients in group A, which should be selected according to increasing degree of the disease, local resistance rates, the cost of treatment and treatment compliance, etc., the proposal is to give amoxicillin/clavulanate, while levofloxacin and moxifloxacin are available as alternative medicine.

For patients in group B, if they can take orally, we choose ciprofloxacin as antibiotic treatment (or levofloxacin 750 mg/day or 500 mg/bid). When need parenteral administration, we apply ciprofloxacin or B-lactam against the activity of *P. aeruginosa*, and based on this, we can use aminoglycosides.

In above proposals, the amount of levofloxacin is significantly higher than usual dose of domestic product specification (200 mg, 2 times/day, or 500 mg, 1 time/day), this regimen is currently not suitable for clinical application in our country.

2013 Edition of COPD Treatment Guidelines in China<sup>[3]</sup> also think the choice of antibiotics should consider whether there are clinical risk factors of *P. aeruginosa* infection. The recommended initial antimicrobial treatment is:

- 1. For patients with no risk factors of *P. aeruginosa* infection, the drugs were chosen primarily on the basis of the severity of acute exacerbations, local drug resistance, costs and potential compliance. Mild cases are recommended to use penicillin, amoxicillin with or without clavulanate, macrolides, fluoroquinolones, first-generation or second-generation cephalosporins, which can be administered orally. Serious patients receive B-lactam drugs/enzyme inhibitors, second-generation cephalosporins, fluoroquinolones and third-generation cephalosporins;
- 2. The patients with the risk factors of *P. aeruginosa* infection can administer orally, may choose ciprofloxacin, when require intravenous medication, may choose ciprofloxacin, anti-*P. aeruginosa* B-lactam drugs, with or without enzyme inhibitors, can added aminoglycosides simultaneously.

Our guidelines recommend the treatment program combines recommended treatment plan of GOLD and ERS/ESCMID Treatment Guidelines, propose to be based on the patient's condition to give a stratified treatment. For mild cases, it increases fluoroquinolones, first- or second-generation cephalosporins. For serious patients may use B-lactam/ inhibitor, second- or third-generation cephalosporins and fluoroquinolones. This allows clinicians to have more choice of antibiotics.

#### Duration and approach of antibacterial treatment

Domestic and international guidelines unanimously recommended course of antibiotics is usually 5-10 days, the antimicrobials application time may be extended

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under special circumstances. Medication approach (oral or intravenous administration) depends on the patient's intake condition and pharmacokinetics characteristics of antibiotics, giving oral treatment is the best. Vein treatment is selectable under serious conditions. Three days after intravenous medication, the patient can be changed to oral therapy in stable condition.

Sequential or convert oral treatment can shorten the patient's hospital stay, and reduce adverse reactions caused by the infusion. With advantages of broad antibiotic, strong antibacterial activity, high bioavailability, long plasma halflife, fluoroquinolones are suitable as sequential or conversion therapy.

## THE USE OF ANTIVIRAL DRUGS

Although the viral infection plays an important role in the pathogenesis of AECOPD, our 2013 Edition of COPD Guidelines<sup>[3]</sup> and the 2011 Edition of ERS/ESCMID Treatment Guidelines<sup>[2]</sup> is not recommended antiviral therapy for AECOPD. Clinical studies showed that in addition to the neuraminidase inhibitors zanamivir, oseltamivir could effectively treat influenza virus; other antiviral drugs were not proven to have clinically therapeutic effect.

2011 Edition of ERS/ESCMID Treatment Guidelines<sup>[3]</sup> consider anti-influenza therapy is only for influenza-like symptoms (fever, muscle aches, weakness and respiratory infections) in <2 days, and in patients at high risk of influenza outbreak period. 2011 Edition of GOLD<sup>[1]</sup> is not mentioned antiviral therapy problems.

#### CONCLUSION

The antibiotic therapy in patients with AECOPD is conducive to disease remission, shorten recovery time, improve lung function, and arterial blood gas. Antimicrobial drug selection principles are:

- 1. The severity degree of patients at acute exacerbation period;
- 2. Combining with prevalence of local pathogens and drug-resistant bacteria;
- 3. Referencing international guidelines recommend treatment plan;
- 4. Selecting the appropriate, safe and effective antibiotics.

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