Antibiotics for Acute and Chronic Respiratory Infection in Patients with Chronic Obstructive Pulmonary Disease

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Prevention and effective treatment of exacerbations are major objectives in the management of patients with chronic obstructive pulmonary disease (COPD). Antibiotics are mainstay treatment for patients with severe COPD with an acute exacerbation that includes increased sputum purulence and worsening shortness of breath. Although such treatment is associated with clinical benefit, treatment failure and relapse rates may be high, particularly in cases of inadequate antibiotic therapy through incomplete resolution of the initial exacerbation and persistent bacterial infection. These aspects have led to recommendations for a stratified approach to antibiotic therapy based on patient characteristics associated with increased risk factors for failure. Patients at greatest risk for poor outcome (i.e., those with severe COPD) are likely to derive greatest benefit from early treatment with antibiotics. Long-term or intermittent antibiotic treatment has been shown to prevent COPD exacerbations and hospitalizations. These effects may be achieved by reducing bacterial load in the airways in stable state and/or bronchial inflammation. Although systemic antibiotics are likely to remain the core treatment for patients with moderate to severe exacerbated COPD, inhaled antibiotics may represent a more optimal approach for the treatment and prevention of COPD exacerbations in the future. Regardless of the route of administration, further studies are required to evaluate the potential long-term adverse events of antibiotics and the development of bacterial resistance.

Keywords: exacerbations of chronic obstructive pulmonary disease; antibiotics; bacteria; prevention; colonization

Approximately 70% of exacerbations in chronic obstructive pulmonary disease (ECOPD) are caused by respiratory infections including bacteria (40–60%), viruses (about 30%), and atypical bacteria (5–10%) (1, 2). For the last 25 years, the clinical criteria described by Anthonisen and colleagues (3) have been incorporated in clinical guidelines to help in selecting patients who require empiric antibiotic therapy (4). More recent studies have identified a change in sputum color or an increase in purulence as a good surrogate marker for the presence of bacterial infection (5–7). Furthermore, only the change in sputum color was rated in clinical guidelines to help in selecting patients who require antibiotic therapy. Persistence of these sputum changes or an increase in sputum purulence and worsening shortness of breath identifies a change in sputum color or an increase in purulence as a good surrogate marker for the presence of bacterial infection. These aspects have led to recommendations for a stratified approach to antibiotic therapy based on patient characteristics associated with increased risk factors for failure. Patients at greatest risk for poor outcome (i.e., those with severe COPD) are likely to derive greatest benefit from early treatment with antibiotics. Long-term or intermittent antibiotic treatment has been shown to prevent COPD exacerbations and hospitalizations. These effects may be achieved by reducing bacterial load in the airways in stable state and/or bronchial inflammation. Although systemic antibiotics are likely to remain the core treatment for patients with moderate to severe exacerbated COPD, inhaled antibiotics may represent a more optimal approach for the treatment and prevention of COPD exacerbations in the future. Regardless of the route of administration, further studies are required to evaluate the potential long-term adverse events of antibiotics and the development of bacterial resistance.

MECHANISMS OF ACTION

Compared with stable COPD, during ECOPD a much larger percentage of patients have PPMs in addition to significantly increased sputum purulence and worsening shortness of breath. Therefore, change in sputum color and increased purulence are the only clinical features that help clinicians to decide whether to use an antibiotic in ambulatory ECOPD.

Understanding of the role of bacteria during stable COPD is still incomplete. In patients with stable COPD, the isolation of potentially pathogenic microorganisms (PPMs) in respiratory samples ranges between 20% and 60% of cases (9–11). Some studies have suggested that these bacteria contribute to chronic airway inflammation leading to COPD progression (9, 10, 12). Therefore, it has been suggested that the term chronic bronchial infection would be more appropriate when addressing the presence of significant concentrations of PPMs in the lower airways of patients with stable COPD (10, 13). Patients with chronic bronchial infection may constitute an infective phenotype (10). Finally, the relevance of the described microbiota in lung health must be established. Molecular culture-independent techniques have identified bacteria previously not amenable to culture. Analysis of the highly conserved 16S ribosomal RNA gene has been used to assign phylogeny and allowed a picture of the complete microbial community in an environment (i.e., upper airway, sinus, bronchial tree, etc.) to be constructed, offering a more comprehensive analysis than classical culture-based techniques (14).

The number of studies examining the lower airway microbiome is limited and there is some overlap between bacteria seen in COPD and healthy individuals (15); however, one study has reported a significantly different bacterial community in patients with very severe COPD compared with nonsmokers, smokers, and patients with cystic fibrosis (16). Studies are clearly needed to understand the role of these microbiomes in healthy individuals and patients with COPD, and furthermore, we need to understand the impact of antibiotics, given for either acute exacerbation or chronic disease, on these bacterial communities.

In chronically infected patients it is possible that reduction of airway bacterial load and/or prevention of new strain acquisition by the use of antibiotics may reduce the frequency and severity of exacerbations. The potential role of long-term antibiotic therapy in the management of COPD was first investigated in trials conducted during the 1950s and 1960s. However, these studies were limited by small patient numbers, use of low doses of narrow-spectrum antibiotics, and inadequate efficacy measurements. Concerns over the potential for developing bacterial resistance further hampered investigation into the value of this treatment (17). Nevertheless, emergence of new antibiotic formulations with improved sensitivities coupled with increased understanding of the pathogenesis of COPD has led to renewed interest in the role of long-term antibiotic use in the management of the condition, although no agents are currently licensed for such therapy in COPD.
that sputum purulence was the most reliable marker of clinical failure in the placebo group (8). Another randomized, placebo-controlled trial investigated the efficacy of doxycycline in addition to systemic corticosteroids in the treatment of hospitalized patients with ECOPD. Doxycycline was equivalent to placebo in the primary end-point clinical success on Day 30; however, it was superior to placebo in other secondary end points such as clinical success and clinical cure on Day 10, microbiological success, use of open label antibiotics, and symptom resolution. The antibiotic was superior in patients with higher plasma levels of C-reactive protein (25). The poor results observed with doxycycline on Day 30 could be explained by the antibiotic bacteriological spectrum and local bacterial resistance patterns.

During an ECOPD, antibiotics can reduce the burden of bacteria in the airway, thus having an impact on the risk of progression to more severe infections, such as pneumonia. A prospective, randomized, double-blind, placebo-controlled trial, evaluating the use of ofloxacin in 90 consecutive patients with ECOPD who required mechanical ventilation showed that the antibiotic-treated group had a significantly lower in-hospital mortality rate (4 vs. 22%; \( P = 0.01 \)) and reduced length of hospital stay (14.9 vs. 24.5 d; \( P = 0.01 \)) compared with the placebo group. In addition, the ofloxacin-treated patients were less likely to develop pneumonia, especially during the first week of mechanical ventilation (19). A summary of the placebo-controlled trials compared with antibiotics in ECOPD is presented in Table E1 in the online supplement.

Antibiotic resistance is a major public health problem worldwide, and international efforts are needed to counteract its emergence. Antibiotic consumption is increasingly being recognized as the main cause of this emerging resistance (26). Therefore, the recognition of clinical characteristics that identify patients with ECOPD that can be safely treated without antibiotics is extremely important. In the case of ambulatory patients with mild to moderate disease, the absence of sputum purulence and low values of C-reactive protein test are associated with high rates of clinical cure without antibiotics (27). Similarly, a small study in admitted patients with ECOPD observed similar short- and long-term outcomes in patients with purulent sputum treated with antibiotics compared with patients with nonpurulent sputum not treated with antibiotics, suggesting that use of antibiotics could be avoided in this last group (28).

After the decision of initiating empirical antibiotic therapy, the choice of antibiotic must be considered. The reported relapse rates for patients with ECOPD range from 17 to 32%, and differ according to the antibiotics prescribed (29, 30). In one study, moxifloxacin treatment was compared with amoxicillin–clavulanate for the primary end point of clinical failure at 8 weeks posttherapy in patients with moderate to severe COPD [mean FEV\(_1\) (%) = 39%] and risk factors for failure. There were no significant differences in the primary end point of the study; however, moxifloxacin resulted in significantly lower clinical failure and higher bacteriological eradication in the subpopulation of patients with bacterial pathogens isolated from sputum at inclusion (31). These results suggest that in confirmed bacterial ECOPD the choice of antibiotic, particularly in patients with severe disease, may result in different outcomes and justifies antibiotic selection based on patterns of antimicrobial resistance and the clinical characteristics of the patients.

**USE OF ANTIBIOTICS TO TREAT COPD EXACERBATIONS**

In 1987 Anthonisen and colleagues (3) reported the results of a large-scale placebo-controlled trial designed to determine the efficacy of antibiotics in ECOPD. In this study, 173 patients with COPD [mean FEV\(_1\) (%), 33%] were monitored for 3.5 years. Patients classified as type 1 ECOPD (with increased shortness of breath, increased sputum production, and change in sputum purulence) and using antibiotics (amoxicillin, trimethoprim–sulfamethoxazole, co-trimoxazole, or doxycycline) showed significant clinical benefits as compared with placebo, whereas there was no significant difference in the success rates between antibiotic and placebo in patients with only one of these symptoms (type 3).

Overall, the antibiotic-treated patients showed more rapid improvement in peak flow and a greater percentage of clinical success. In addition, the length of illness was 2 days shorter for the antibiotic-treated group. The major limitations of this study were the lack of microbiology data and the assumption that all antibiotics were equivalent. We also must take into consideration that this study was done more than 25 years ago, and there has been a significant change in the patterns of bacterial resistance, and in the patient characteristics and patterns of treatment.

In another clinical study, Allegra and colleagues (24) found a significant benefit with the use of amoxicillin–clavulanate therapy compared with placebo in patients with moderate to severe disease. Patients receiving this antibiotic exhibited a higher success rate on Day 5 (86.4 vs. 50.3% in the placebo group; \( P < 0.01 \)) and lower frequency of recurrent exacerbations. A double-blind, placebo-controlled study investigated the efficacy of amoxicillin–clavulanate in patients with exacerbated mild to moderate COPD (FEV\(_1\) > 50% predicted) treated in primary care confirmed these findings. This study demonstrated significant superiority for the antibiotic-treated group in clinical cure rates (74.1 vs. 59.9%; difference, 14.2%; 95% confidence interval, 3.7 to 24.3%). Furthermore, the median time to the next exacerbation was also significantly prolonged in patients receiving antibiotic compared with placebo (233 d compared with 160 d; \( P < 0.05 \)). Interestingly, this study demonstrated higher concentrations of bacteria in the airways (18). Treatment with appropriate antibiotics significantly decreases the bacterial burden (and frequently eradicates the organisms that are sensitive) and reduces clinical failure and the risk of progression to more severe infections, such as pneumonia (19).

Although the increased airway inflammation present during ECOPD is reduced after antibiotic treatment, this resolution has been shown to be dependent on bacterial eradication (20). The incomplete resolution of the initial exacerbation and persistent bacterial infection appear to be important determinants of the risk of relapse and need for rehospitalization.

Among the major goals of COPD treatment in the current guidelines is the prevention of acute exacerbations (21). Clinical studies have shown that long-term continuous or intermittent use of antibiotics has a beneficial effect of reducing exacerbation frequency and extending the time to the next exacerbation (22, 23). The mechanism underlying this improvement is unclear. It is possible that the benefit of long-term antibiotic treatment may be due to eradication of colonizing bacteria and/or a reduction in chronic airway inflammation, although evidence supporting this hypothesis is limited. While macrolides are known to have not only antibacterial, but also antiinflammatory, immunomodulatory, and antiviral effects, in addition to a possible effect against biofilm formation, it is not known which of these actions is responsible for their efficacy when used for the treatment of long-term respiratory conditions.
in these patients. In the last decade, six studies have been published showing the use of continuous long-term antibiotics in patients with COPD (22, 32–35), and one employing intermittent/pulsed treatment has been published (23) (Table E2). In the first open-label, 12-month study, erythromycin therapy was found to have beneficial effects on the prevention of ECOPD (32). The proportion of patients experiencing one or more exacerbations during the treatment period was lower in the erythromycin group (11%) compared with the control group (56%), and significantly more control patients were hospitalized because of exacerbations \(P = 0.0007\). A subsequent trial of erythromycin showed a significant reduction in ECOPD and the median time to exacerbation over a 12-month follow-up with no differences in lung function or inflammatory markers (33). However, other studies showed significant reductions in inflammatory markers and neutrophil counts after 6 months of treatment with azithromycin (36) and erythromycin (35). In a large pivotal study, Albert and colleagues (22) reported the use of 12-month treatment with daily azithromycin in the prevention of ECOPD. In this study, the addition of azithromycin to standard therapy was associated with a 27% decrease in the frequency of exacerbations and an increase in the median time to exacerbation (266 vs. 174 d, respectively; \(P < 0.001\)). In another 12-month retrospective study, azithromycin was also shown to reduce exacerbations, hospitalizations, and length of hospital stay (34). The risk of increasing bacterial resistance with long-term use of macrolides is a concern. In view of the large patient population affected by COPD, widespread use of macrolides, particularly azithromycin, has the potential to substantially influence antimicrobial resistance rates of a range of respiratory microbes (37). In the study by Albert and colleagues (22), the incidence of resistance to macrolides in respiratory pathogens isolated from nasopharyngeal swabs was significantly increased in the group of patients receiving azithromycin compared with the placebo arm.

Intermittent, pulsed fluoroquinolone antibiotic therapy in patients with COPD was reported by Sethi and colleagues (23) in this study, moxifloxacin was given once daily for 5 days, and the treatment was repeated every 8 weeks for a total of six courses. Pulsed therapy with moxifloxacin reduced the odds of an exacerbation by 25% in the primary population for efficacy analysis (per protocol population as prespecified in the protocol) in patients with moderate to severe COPD, whereas in a post hoc analysis, this reduction was 45% in patients with purulent or mucopurulent sputum at baseline. No relevant bacterial resistance was reported in the study with pulsed moxifloxacin treatment (23). However, it cannot be ruled out that more prolonged courses of intermittent treatment with this or other drugs might result in increases in resistance and, therefore, clear stratification of patients is needed before this therapy can be recommended.

**DOSING STRATEGIES FOR ANTIBIOTICS**

The standard duration of antibiotic administration in ECOPD used to be 10 days. However, short-course therapy may reduce the risk of adverse events and the development of bacterial resistance as a result of shorter exposure to antibiotics. A meta-analysis of 7 randomized controlled trials, with a total patient population of 3,083, compared different treatment durations of the same antibiotic regimen. The short-duration treatment proved to be effective and safer than long-duration antimicrobial therapy in patients with ECOPD (38). Short-course therapy was associated with fewer adverse events as compared with standard, longer duration treatment. A second meta-analysis involving 21 double-blind studies and 10,698 patients also found that clinical cure rates, at both early and late follow-up, and bacteriological cure rates observed with short-course therapy were comparable to those achieved with conventional duration therapy in patients with mild to moderate exacerbations (39). Thus, a shorter course of antibiotic treatment may enhance compliance and reduce antibiotic costs.

Clinical studies have demonstrated comparable, and in some cases, superior efficacy for short-course, 5-day fluoroquinolone therapy compared with that of standard therapy in ECOPD, as measured by both clinical and bacteriological outcomes (40). Furthermore, short-course, high-dose fluoroquinolone therapy also demonstrates more rapid symptom resolution and faster recovery rates than traditional therapy using nonfluoroquinolones for standard treatment durations (41).

**COMBINATION OF ANTIBIOTICS AND SYSTEMIC CORTICOSTEROIDS**

It is unclear whether antibiotics have additional benefits when applied in patients with severe exacerbations that have already been treated with systemic corticosteroids. Sachs and colleagues (42) suggested that antibiotics did not provide additional clinical benefit when corticosteroids were given, irrespective of sputum color or bacterial involvement. However, this study had several limitations including a small sample size (\(n = 71\)), a population with mild disease, and enrolled patients with COPD and patients with asthma. In the study by Daniels and colleagues (25), the lack of an effect with doxycycline on top of systemic corticosteroids as the primary end point (clinical success on Day 30) may be related to the scarce antibacterial activity of doxycycline against pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*.

More recent studies suggest that there are different phenotypes of COPD exacerbations, and systemic corticosteroids may be beneficial in those with predominant eosinophilic inflammation (43). The different inflammatory profile of COPD exacerbations will need to be taken into consideration in the design of clinical trials examining the efficacy of antibiotics and/or corticosteroids in this disease.

**MEASURING EFFECTS AND OUTCOMES**

Clinical and microbiological end points in trials of antibiotic treatment of ECOPD are not well defined. Microbiological results depend on the production of a good-quality sputum sample, which results in a positive sputum culture in only 20–50% of the patients. Clinical results are still based on the definition of Chow and colleagues (44): End points are defined as cure (a complete resolution of signs and symptoms associated with the exacerbation) or improvement (a resolution or reduction of the symptoms and signs without new symptoms and signs associated with the exacerbation). Clinical success is considered when either cure or improvement is observed. Failure is defined as incomplete resolution, persistence, or worsening of symptoms that require a new course of antibiotics and/or oral corticosteroids in this disease.
diary cards may allow the quantification of the intensity and duration of patient symptoms and comparison of different treatment outcomes (46–48). More recently, the Exacerbations of Chronic Pulmonary Disease Tool (EXACT), a new patient-reported outcome diary, has been developed (49). The EXACT is a validated instrument for quantifying the frequency, severity, and duration of exacerbations. It consists of 14 items that can be incorporated in the form of an e-diary, with scores ranging from 0 to 100 and higher scores indicating a more severe exacerbation. Some standardized quality of life questionnaires have been demonstrated to be responsive to changes in health status during or after an exacerbation. The Saint George’s Respiratory Questionnaire has been shown to be useful in monitoring recovery from ECOPD (50). The COPD Assessment Test is a short (eight-item) questionnaire that has been demonstrated to provide a reliable score of exacerbation severity (51). The generic European Quality of Life Scale has been demonstrated to be responsive to recovery from ECOPD (52, 53) and is a good predictor of treatment failure (53). The COPD Severity Score is a severity scale developed by Eisein and colleagues (54) that is responsive to recovery from exacerbations and provides better predictive value for clinical success than the usual physiologic and clinical variables (53). However, these quality of life or disease severity questionnaires have not been adequately tested in comparative clinical trials of therapies for ECOPD.

ADVERSE EFFECTS OF ANTIBIOTICS

The adverse effects of antibiotics are variable and depend on the type of drug used and concomitant comorbid conditions. Regarding long-term use, treatment with erythromycin often results in significant gastrointestinal symptoms including nausea, vomiting, abdominal cramps, and diarrhea. This drug also has significant interaction with drugs that are metabolized in the liver via the P-450 enzyme system. The newer generation macrolides are better tolerated, have minimal gastrointestinal symptoms, and fewer drug interactions. However, clarithromycin has a distinctive taste perversion that is less common with the extended release preparation. Macrolides and quinolones have also been associated with a prolonged QTc interval; thus, the U.S. Food and Drug Administration recommends that these antibiotics not be given to patients receiving class IA or class III antiarrhythmic agents or to patients with known prolongation of the QTc interval. Even 5-day treatment with azithromycin has been associated with a small absolute increase in cardiovascular deaths (55).

Long-term azithromycin treatment led to changes in nasal bacteria flora, increasing the prevalence of macrolide-resistant bacteria (22). There are some concerns about the possibility of hearing loss associated with long-term use of macrolides (22). These issues, coupled with concerns of increased antibiotic resistance, indicate that until further well-controlled studies are conducted, such treatment should be reserved for patients with severe COPD who experience frequent exacerbations requiring multiple antibiotic treatments despite optimal bronchodilator and antiinflammatory therapy (56).

In general, quinolones are well tolerated and have an adverse event rate of approximately 4–5%. These adverse effects, which are generally mild and transient, include rash, dizziness, headache, gastrointestinal disturbances (usually nausea, vomiting, dyspepsia, diarrhea, abdominal pain, etc.), and minor hematological abnormalities. The gastrointestinal side effects of quinolones are usually as severe and frequent as those associated with macrolides or with amoxicillin–clavulanate (57). Despite the potential for cardiac side effects, clinical trials have demonstrated the cardiac safety of fluoroquinolones even in elderly hospitalized patients (58). Some of the quinolone preparations can interact with medications that are metabolized by the hepatic cytochrome P-450 system.

CLINICAL GUIDELINES

The current clinical guidelines of antibiotic treatment in ECOPD are based on the Anthonisen criteria (3) and recommend antibiotic treatment when the three key symptoms are present. In addition, antibiotics are also recommended in severe ECOPD or in hospitalized patients with only two of the symptoms when increased purulence of sputum is one of them and/or in patients who require invasive or noninvasive ventilation (4). The Canadian Thoracic Society guidelines were the first to adopt an approach to antibiotic choice based on risk factors for poor outcome and the most likely pathogens involved (Table 1) (59).

In general, COPD guidelines do not recommend the use of long-term antibiotics for the prevention of exacerbations. However, evidence of the efficacy of macrolides and, to a lesser extent, quinolones has been accumulating. More recent guidelines have included, for the first time, a recommendation related to the use of long-term antibiotics in a specific subgroup of patients with severe COPD (56, 60). This treatment must be monitored closely for the possible development of side effects and/or changes in the patterns of bacterial resistance.

FUTURE DEVELOPMENTS OF ANTIBIOTICS FOR COPD

Inhaled antibiotics are likely to have a future role in the long-term management of patients with COPD, because this route of administration has the ability to target drug delivery directly to the respiratory tract, reducing systemic exposure and maximizing pharmacodynamic parameters. Inhaled antibiotics have already been used in the treatment of a number of respiratory tract infections, including cystic fibrosis (61) and bronchiectasis (62, 63).

To date, there has been only one report investigating the use of inhaled antibiotics in patients with COPD. The study, conducted by Dal Negro and colleagues (64), examined the effects of 14-day, twice daily treatment with inhaled tobramycin nebulizer solution (TNS) on clinical outcome and inflammatory markers in bronchial secretions in a small cohort (n = 13) of patients who require invasive or noninvasive ventilation (4). The Canadian Thoracic Society guidelines were the first to adopt an approach to antibiotic choice based on risk factors for poor outcome and the most likely pathogens involved (Table 1) (59).

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TABLE 1. RISK CLASSIFICATION AND MOST FREQUENT MICROORGANISMS

<table>
<thead>
<tr>
<th>Risk Classification</th>
<th>FEV₁ (% Predicted)</th>
<th>Most Frequent Microorganisms</th>
</tr>
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<tbody>
<tr>
<td>Mild to moderate COPD without risk factors</td>
<td>&gt;50%</td>
<td>Haemophilus influenzae, Moraxella catarrhalis</td>
</tr>
<tr>
<td>Mild to moderate COPD with risk factors*</td>
<td>&gt;50%</td>
<td>Haemophilus influenzae, Moraxella catarrhalis, PRSP</td>
</tr>
<tr>
<td>Severe COPD</td>
<td>30–50%</td>
<td>Haemophilus influenzae, Moraxella catarrhalis, PRSP</td>
</tr>
<tr>
<td>Very severe COPD</td>
<td>&lt;30%</td>
<td>Enteric gram negatives, Haemophilus influenzae, Moraxella catarrhalis, PRSP, Enteric gram negatives, P. aeruginosa</td>
</tr>
</tbody>
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*Definition of abbreviations: COPD = chronic obstructive pulmonary disease; PRSP = penicillin-resistant S. pneumoniae.

Data from References 39 and 63.

*Risk factors are as follows: age older than 65, cardiac comorbidity, and frequent exacerbations in the previous year.
multiresistant \textit{P. aeruginosa}–colonized patients with severe COPD. Two-week treatment with TNS resulted in a substantial reduction from baseline of proinflammatory chemotactic mediators and also led to a 42% decrease in the incidence of exacerbations, when compared with the 6-month period before initiating TNS therapy. Ongoing and future trials using inhaled powder formulation of antibiotics (quinolones) will provide information as to whether inhaled antibiotics are a useful therapeutic option in the prevention of ECOPD.

**CONCLUSIONS**

Antibiotics are the mainstay of treatment for patients with moderate to severe COPD with exacerbations that include increased purulence sputum. Antibiotics are associated with clinical benefit, but in high-risk patients treatment failure and relapse rates may be high in cases of inadequate antibiotic efficacy because of incomplete resolution of the initial exacerbation and persistent bacterial infection. Therefore, it is important to identify patients at greatest risk for poor outcomes, because they are the patients who will likely derive the greatest benefits from early treatment with the most potent antibiotic therapy.

Studies conducted over the last decade have indicated that treatment with long-term or intermittent antibiotics may have a beneficial effect by reducing the frequency of exacerbations and hospitalizations or by extending time to next exacerbation. Although systemic antibiotics are likely to remain the core treatment for patients with moderate to severe exacerbated COPD, inhaled antibiotics may represent a more optimal approach for the treatment and prevention of exacerbations in the future. Regardless of the route of administration, further studies are required to estimate the potential risks of antibiotic prophylaxis in terms of long-term adverse events and the development of resistance, and to assess whether the benefits outweigh the potential risks.

**Author disclosures** are available with the text of this article at www.atjournals.org.

**References**


