

Chronic Obstructive Pulmonary Disease

Role of Bacteria and Guide to Antibacterial Selection in the Older Patient

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common problem in the elderly. The disease is characterised by intermittent worsening of symptoms and these episodes are called acute exacerbations. The best estimate, based on several lines of evidence, is that approximately half of all exacerbations are caused by bacteria. These lines of evidence include studies of lower respiratory tract bacteriology during exacerbations, correlation of airways' inflammation with results of sputum cultures during exacerbations, analysis of immune responses to bacterial pathogens, and the observation in randomised, prospective, placebo-controlled trials that antibacterial therapy is of benefit. The most important bacterial causes of exacerbations of COPD are nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Chlamydia pneumoniae*.

In approaching the elderly patient with an exacerbation, it is useful to consider the severity of the exacerbation based on three cardinal symptoms: increased sputum volume, increased sputum purulence and increased dyspnoea compared with baseline. Patients experiencing moderate (two symptoms) or severe (all three symptoms) exacerbations benefit from antibacterial therapy.

Consideration of underlying host factors allows for a rational choice of antibacterial agent. Patients are considered to have 'simple COPD' or 'complicated COPD' based on: (i) the severity of underlying lung disease; (ii) the frequency of exacerbations; and (iii) the presence of comorbid conditions. It is proposed that patients with simple COPD are treated with doxycycline, a newer macrolide, or an extended-spectrum oral cephalosporin; and patients with complicated COPD are treated with amoxicillin/clavulanate or a fluoroquinolone. The major goals of antibacterial therapy for exacerbations of COPD are acceleration of symptom resolution and prevention of the complications of exacerbation.

Chronic obstructive pulmonary disease (COPD) is defined as the presence of irreversible or partially reversible airways' obstruction associated with chronic bronchitis and/or emphysema.^[1] The course of COPD is characterised by intermittent worsening of symptoms, acute or sub-acute in onset, which often necessitate evaluation by the health-care provider and therapeutic intervention. These episodes are called acute exacerbations, and occur with an average frequency of 1.5 to 2.0 episodes per year among patients with moderate to severe disease. Acute exacerbations account for a substantial proportion of the morbidity and mortality associated with COPD.^[2,3]

COPD is one of the chronic diseases increasing in incidence in the US and globally. In the US, mortality associated with COPD has increased in the last 2 decades. Tobacco smoking is the most common antecedent to COPD. Although the propor-

tion of smokers has declined in the US, it has increased in other parts of the world. It has been estimated that the global burden of COPD will increase substantially in the coming decades. This increasing global burden will be associated with a greater number of acute exacerbations. Therefore, understanding the pathogenesis of acute exacerbations, and determining their optimal treatment, is an important part of the overall management of patients with COPD.

1. Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) in the Elderly: Special Considerations

Elderly patients with exacerbations of COPD present special challenges. There may be difficulties in diagnosis. Many of the elderly may be ex-smokers; however, the normal age-related decline in lung function, superimposed on the accelerated

loss of lung function that individuals experienced while they were smoking, can lead to onset of COPD symptoms late in life. The exacerbation itself may have a greater clinical impact in elderly than in younger patients. Comorbid health conditions are an important predictor of poor outcome of acute exacerbations and the frequency of such conditions increases with age.^[4,5] The elderly are more likely to have obtundation or muscular weakness secondary to neurological disease, which makes them less capable of handling the increased respiratory secretions associated with acute exacerbations. The elderly often have diminished respiratory reserve, secondary to cardiac disease and congestive heart failure; this can amplify the respiratory impairment associated with an acute exacerbation. Elderly patients with long-standing COPD often have poor nutritional status and osteoporosis, factors that can impair both the immune response to organisms causing acute exacerbations and the ability to cough effectively and maintain clear airways.

Treatment of acute exacerbations poses other challenges. The elderly tend to have more comorbid conditions, more often require polypharmacy, and have greater susceptibility to the adverse effects of medications, than younger individuals. Elderly patients from long-term care facilities may be more prone to colonisation with pathogens such as methicillin-resistant *Staphylococcus aureus*, and *Pseudomonas aeruginosa* and other Gram-negative enterobacteria compared to those living at home. Therefore, the spectrum of pathogens causing acute exacerbations in elderly patients from long-term care facilities may encompass more antimicrobial-resistant bacteria than usual, thus creating a therapeutic challenge. An approach to evaluating and treating acute exacerbations in the elderly should consider these challenges.

2. Potential Roles of Bacterial Infection in COPD

There are several potentially important roles of bacterial infection in COPD.^[6] Among the elderly,

these include the role of bacterial infection in acute exacerbations and the role of bacteria in inducing inflammation in the chronic stage of COPD. Whether bacterial infection is an important cause of acute exacerbation continues to be debated.^[7,8] This is not simply of theoretical interest, because if bacterial infection is not a major cause of acute exacerbation, then antibacterial therapy is not indicated for acute exacerbation and the choice of antibacterial agent becomes a moot point. In the past, the major tools used to investigate the role of bacterial infection in acute exacerbation were sputum culture, serology and antibacterial versus placebo trials. Each of these lines of investigation yielded conflicting results, and some authors have interpreted this as implying that bacterial infection does not play a role in acute exacerbation.^[7,9] In the last decade, new investigational approaches to this question have emerged with results that support the role of bacteria in some exacerbations of COPD. Overall, a reasonable estimate with regard to the causes of exacerbations is that approximately 50% are caused by bacteria, approximately 30% by viruses and the remainder by non-infectious factors.

2.1 Lower Airways' Bacteriology in Exacerbations

Four studies have utilised bronchoscopy, with the protected specimen brush to sample airways' secretions for culture, in patients experiencing an acute exacerbation.^[10-13] In all four studies, bacterial pathogens were isolated in quantities consistent with tissue infection. In one study, patients with exacerbations were compared with a control group with stable COPD.^[11] Bacterial pathogens were isolated twice as frequently at a concentration of 10^3 colony forming units (cfu) per ml, and four times as frequently at a concentration of 10^4 cfu/ml, from the exacerbation versus control group. In addition, the spectrum of pathogens isolated from bronchoscopic samples has been similar to sputum, with nontypeable *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* being the predominant isolates.^[11-14] The consistent results of these four studies, the

substantial difference from stable COPD and the success of similar studies in defining infections in pneumonia, make these results a compelling line of evidence that bacterial pathogens are indeed responsible for about half of all exacerbations of COPD.

2.2 Airways' Inflammation in Exacerbations

Techniques for investigating airways' inflammation, beyond a qualitative Gram stain, have contributed tremendously to our understanding of asthma. Only recently have investigators started using these techniques to investigate the inflammatory process in COPD. This approach has redefined COPD from being a destructive, hypersecretory process to being an inflammatory disease.^[14] Inflammation in COPD differs in several important respects from that in asthma and is correlated with the extent of lung function impairment.

Markers of airways' inflammation have been measured in sputum during exacerbations and correlated with sputum culture results and gross sputum appearance.^[15-17] Such studies have demonstrated that: (i) purulent (as compared with non-purulent sputum) is associated with a greater neutrophilic inflammation, presence of bacterial pathogens and concentration of bacterial pathogens during an exacerbation; (ii) when airways' inflammation in pathogen-positive sputum is compared with pathogen-negative sputum, there is substantially greater neutrophilic inflammation in the former; and (iii) treatment of purulent-sputum exacerbations with antibacterials is associated with a substantial decline in markers of neutrophilic inflammation. These data lead to the conclusion that bacterial exacerbations induce a neutrophilic influx into the airways' lumen. Subsequent activation and degranulation of neutrophils in the lumen releases considerable amounts of proteolytic enzymes in the airways. The clinical correlates of this inflammatory process are increased secretions and airways' obstruction, which present as the cardinal symptoms of increased dyspnoea, sputum production and sputum purulence. If bacteria were innocent bystanders in the process of

acute exacerbations, one would not expect to see such an association between the presence of bacteria and neutrophilic inflammation. These investigations into the inflammatory aspect of acute exacerbations represent another important line of evidence that bacteria do indeed induce acute exacerbations.

2.3 Immune Responses Following Exacerbations

Development of a specific immune response to an infecting pathogen suggests the presence of tissue infection by the purported pathogen. Previous serological studies examining immune responses to bacterial pathogens in COPD provided inconsistent results, probably related to the methodology employed.^[18]

Recent studies^[19-21] have utilised assays specific for antibodies to the surface of the bacterial pathogen and have used the homologous infecting strain as the antigen. Human serum immune responses to nontypeable *H. influenzae* following acute exacerbations have been studied in most detail.^[19,20] These observations support the pathogenic role of *H. influenzae* in exacerbations and also provide insight into the mechanism of recurrent exacerbations caused by this pathogen. Human serum antibodies that develop in response to this pathogen following an exacerbation are bactericidal against the strain and protect against reinfection with that strain. However, these antibodies are mainly directed to an outer membrane protein (OMP), OMP P2, which demonstrates considerable variability in its antigenic structure among strains of *H. influenzae*. As a consequence, these antibodies are protective against the infecting strain, with little or no bactericidal activity and therefore protective ability against other strains of *H. influenzae*. Acquisition of strains of *H. influenzae* from other individuals is a common phenomenon and it is just a matter of time before the patient acquires a strain of this pathogen to which protective antibodies are absent. If this strain is virulent enough, airways' infection follows the acquisition, which is associated with increased symp-

toms and an exacerbation. Such a process recurs and the patient experiences recurrent exacerbations.

The immune response to *M. catarrhalis* following acute exacerbations has received increasing attention.^[21-24] Development of bactericidal antibodies, and of antibodies that bind to surface epitopes following an acute exacerbation, has been demonstrated.^[21,24] These antibodies appear to be protective because the patient does not experience re-infection with the same strain once it is cleared from sputum.

The development of specific immune responses to infecting pathogens adds another line of evidence to support the role of bacteria in acute exacerbations. Similar data regarding immune responses to *S. pneumoniae* and other bacterial pathogens isolated from sputum during acute exacerbations are not available and are an important area of study.

These new observations regarding immune responses to bacteria following exacerbations of COPD have important implications in interpreting recent work, which has relied exclusively on serological testing to predict the causes of exacerbations.^[25] Because immune responses to bacteria are predominantly strain-specific, serological assays utilising antigens derived from non-homologous strains will not reliably detect immune responses, and will therefore underestimate the role of bacteria in exacerbations. Furthermore, since mucosal immune responses following bacterial exacerbations occur independently of systemic responses, relying on the development of serum antibodies will further underestimate the role of bacteria in the aetiology of exacerbations.

2.4 Dynamics of Bacterial Colonisation and Exacerbations

One of the major arguments against bacteria playing a role in acute exacerbations is that the isolation rates of potential bacterial pathogens from sputum during stable disease and acute exacerbations are identical in longitudinal cohort studies.^[26-28] The past 2 decades have witnessed an increased understanding of genetic heterogeneity

among strains of a single bacterial species, and the development of molecular tools to study more precisely the epidemiology and pathogenesis of infection. When older cohort studies of COPD are examined with this new knowledge, an obvious limitation becomes apparent. At the time of these studies, it was not possible to differentiate between strains of a particular pathogenic species. Therefore, all strains isolated from sputum over the course of a study were regarded as identical if they belonged to the same species. This approach did not detect strain changes within patients over time. Longitudinal cohort studies, in which strain differentiation is incorporated into the experimental design, are being conducted. The results showed that acquisition of a new bacterial strain was associated with a 2-fold increase in the incidence of an exacerbation compared to clinic visits when no new strain was isolated.^[29] Results of these studies could provide another line of evidence to support the role of bacteria in acute exacerbations and provide insight into the mechanism of exacerbations.

In conclusion, identification of the exact cause of an individual exacerbation is difficult. However, based on studies involving bronchoscopic sampling of the lower airways, immune responses, markers of airways' inflammation and responses to antibacterial therapy, the best estimate is that approximately half of all exacerbations are caused by bacteria.

2.5 Association of *Chlamydia pneumoniae* with COPD

Chlamydia pneumoniae is an obligate intracellular Gram-negative bacterium that causes a variety of upper and lower respiratory tract infections. Chronic infection with *C. pneumoniae* is more common in adults with COPD than in healthy adults.^[30,31] The potential role of chronic *C. pneumoniae* infection in the pathogenesis of COPD warrants further investigation.

Several studies have used serological methods to assess *C. pneumoniae* as a cause of exacerbations.^[31-33] Such studies must be interpreted with caution because of the following: different authors

use different criteria for infection; co-infection with other bacteria is common; approximately half of the adult population worldwide is serologically positive for *C. pneumoniae*. A reasonable estimate is that 5 to 10% of exacerbations of COPD are caused by acute infection with *C. pneumoniae*.^[31-33]

3. Consequences of Chronic Bacterial Infection in COPD

Bacteria are absent from the lower airways distal to the vocal cords in healthy individuals but are intermittently present in almost all patients with COPD. This bacterial presence in the lower airways in the stable phase of COPD has been labelled 'colonisation', with the belief that it is innocuous and of no pathophysiological consequence. The origin of this belief appears to be from studies showing that mucus hypersecretion does not correlate with the development of progressive airways' obstruction in COPD.^[34,35] Because mucus hypersecretion was thought to be closely linked to bacterial 'colonisation', when mucus hypersecretion was discounted as an inconsequential phenomenon, so was bacterial colonisation.

Recently, renewed interest in the role of long-term infection in the development of various chronic diseases has spurred a re-examination of the consequences of bacterial colonisation in COPD. *In vitro* studies of respiratory epithelia with *H. influenzae* have shown that this pathogen, and various components of its outer membrane, are capable of increasing mucus secretion, impairing mucociliary clearance, damaging epithelial cells and inducing a cytokine response that would recruit neutrophils to the airways.^[17,36] A bronchoscopic study in patients with stable COPD has shown that the presence of bacterial pathogens is associated with increased neutrophil counts and levels of pro-inflammatory cytokines in the airways' lining fluid.^[37]

Another significant development in our understanding of infection of airways' tissues with *H. influenzae* is the demonstration that this pathogen is not an exclusively extracellular pathogen. It is capable of invading airways' tissues both *in vitro*

and *in vivo*, and can be found in subepithelial spaces and within macrophages.^[38-41] This tissue invasion could explain how these bacteria can persist in patients with COPD for long periods of time and evade bactericidal antibodies and antibacterial agents. Tissue infection also raises the potential of contributing to airways' inflammation in the stable phase of disease, with consequent airways' and lung parenchymal damage.

Further investigation will determine the clinical relevance of chronic infection with pathogenic bacteria in COPD. If persistent infection is important in the pathogenesis of COPD, then the ability of antibacterials administered for an acute exacerbation to eradicate bacteria from the airways (bacteriological efficacy) will assume increased importance.

4. Efficacy of Antibacterial Agents in Exacerbations

A large number of studies, particularly comparative trials of antibacterials, have been performed to evaluate antibacterials in treating patients with exacerbations of COPD. It is not surprising that conflicting results have been obtained concerning the potential benefits of antibacterials in this clinical setting. Patients with COPD are highly heterogeneous with regard to the relative degree of chronic bronchitis or emphysema as the manifestation of COPD, the extent of impaired lung function, the presence of comorbid illnesses, the frequency of exacerbations, and other factors. The definition of an exacerbation is subjective and varies from study to study. A high degree of variability in the severity of exacerbations is observed between patients, and in the same patient, over time. Many studies do not distinguish between the severity of exacerbations. Some studies include microbiology, while others have evaluated strictly clinical parameters. Finally, different endpoints are measured among various published studies. All of these factors make it difficult to compare studies and interpret the literature.

A few well conducted, placebo-controlled trials to test the efficacy of antibacterials in the treatment

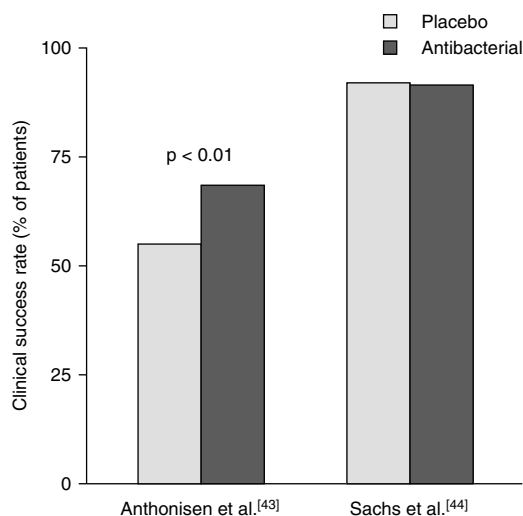


Fig. 1. Results of randomised, prospective, placebo-controlled trials of antibacterial therapy for exacerbations of chronic obstructive pulmonary disease.^[43,44]

of exacerbations have been performed.^[42] The largest and most widely quoted study is that of Anthonisen et al.^[43] An important element of this study is that exacerbations were stratified with regard to severity. The authors focused on three cardinal symptoms of exacerbation: sputum production, sputum purulence (colour), and dyspnoea. These three symptoms were graded compared with baseline symptoms. A mild exacerbation was defined as the presence of one of the three cardinal symptoms; a moderate exacerbation was the presence of two of the three symptoms; and a severe exacerbation was the presence of all three of the symptoms. This grading of symptoms was important because, when exacerbations were stratified in this way, the study showed a statistically significant benefit for antibacterial over placebo in patients with severe exacerbations, but no clear benefit for patients with mild or moderate exacerbations. This observation is useful in identifying patients who are most likely to benefit from antibacterial therapy for exacerbations.

The study by Anthonisen et al.^[43] came to a different conclusion to that of another placebo-controlled trial by Sachs et al.^[44] (figure 1). A comparison of the features of these trials illustrates some of the differences in design that may lead to different conclusions and highlights the importance of careful interpretation of the literature (table I). The Anthonisen et al. study^[43] exclusively included patients with COPD, while the Sachs et al. study^[44] included patients with both COPD and asthma, a significant limitation of the study. The smaller number of patients, the lower severity of lung disease and the inclusion of patients with asthma in the study by Sachs et al.^[44] confound the trial's conclusion that antibacterials are of no benefit in exacerbations of COPD.

Saint et al.^[42] performed a meta-analysis of randomised, placebo-controlled trials of antibacterials in the treatment of exacerbations. Of 230 reports retrieved from MEDLINE and *Index Medicus* searches, the investigators identified nine trials that were randomised and placebo-controlled, and provided sufficient data to calculate an effect size. The nine trials measured various endpoints, including days of illness, symptom scores, clinical scores by physicians, and change in peak expiratory flow rate. Overall, the meta-analysis indicated a small but statistically significant improvement due to antibacterial therapy.

Table I. Comparison of characteristics of two trials of antibacterial therapy for exacerbations of chronic obstructive pulmonary disease

Characteristic	Anthonisen et al. ^[43]	Sachs et al. ^[44]
Number of patients	173	71
Number of exacerbations	362	71
Age (years) [mean \pm SD]	67.3 \pm 9.0	51.7 \pm 16.3
Minimum age (years)	35	18
Smoking (pack years) [mean]	39.9 \pm SD 28.9	16.5 (95% CI 0.15 – 77)
Smokers (%)	93.6	69.1
Patients with asthma	Excluded	Included ^a
FEV ₁ (% predicted) [mean \pm SD]	33.9 \pm 3.7	Not reported
PEFR (L/min) [mean \pm SD]	227.5 \pm 96.1	285.3 \pm 99.2

a Ten patients with asthma were included.

CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; PEFR = peak expiratory flow; SD = standard deviation.

5. Goals of Antibacterial Therapy for Exacerbations

In view of this analysis of the literature, it seems clear that some patients experiencing exacerbations will derive benefit from antibacterial therapy.^[42,43,45,46] The challenge is to identify patients likely to benefit. In this regard, it is useful to consider the goals of antibacterial therapy for exacerbations of COPD. Most patients with exacerbations will eventually recover, even without antibacterial therapy, if exacerbations of all severities are considered. An important goal of therapy is to hasten recovery from the symptoms of an exacerbation. If clinical symptoms are measured too long after initiation of therapy, a hastening in resolution of symptoms may be missed. This factor may explain the lack of benefit for antibacterial over placebo observed in some studies and the lack of differences among antibacterials in some comparative trials. A second goal of antibacterial therapy is to prevent clinical deterioration. This effect is particularly important in patients with the most severe impairment of pulmonary function. Indeed, in a patient with severely impaired lung function, the benefit afforded by antibacterial therapy may prevent the need for hospitalisation or for intubation and mechanical ventilation. A third potential beneficial effect of antibacterial therapy is prolongation of the exacerbation-free interval. Although more studies are needed to evaluate this effect, a small number of studies have suggested that appropriate antibacterial therapy may prolong the time to the next exacerbation.^[47,48]

6. Studies of Antibacterial Therapy

6.1 Comparative Trials

In view of the general agreement among most investigators that antibacterial therapy is beneficial in some exacerbations, few placebo-controlled trials have been performed in the past decade. However, a large number of trials comparing antibacterials with one another have been performed. Most of these trials have been designed to show equivalence for the purpose of generating data for

new product registration and licensing. These studies must be interpreted with caution. Many such trials include patients with poorly defined underlying COPD, and some even combine patients with and without documented lung disease. The inclusion of a substantial proportion of patients with mild or moderate exacerbations is likely to favour the demonstration of equivalence of two antibacterials because, as noted in section 4, patients with severe exacerbations are most likely to derive benefit from antibacterial therapy. Measuring endpoints at later rather than early time points following the exacerbation will miss the potential benefit of accelerated recovery. Suffice it to say that, based on the current literature, it is not possible to make definitive statements regarding the optimal choice of antibacterial for treating exacerbations. However, rational choices can be made based on the current state of knowledge in the area.

6.2 Retrospective Trials

While the comparative trials published to date do not provide definitive guidelines, two retrospective trials provide intriguing preliminary results.^[47,49] Adams et al.^[49] performed a retrospective cohort review of 362 outpatients with exacerbations. Patients treated with antibacterials had a significantly lower relapse rate than patients who did not receive antibacterials. Furthermore, patients treated with amoxicillin had the highest relapse rate, providing objective evidence that the choice of antibacterial is important in the outcome of exacerbations. This study also showed that patients with mild, moderate or severe exacerbations all derived benefit from antibacterial therapy. Destache et al.^[47] performed a retrospective review of 224 patients with exacerbations who were treated with antibacterial therapy. The use of amoxicillin/clavulanate, ciprofloxacin or azithromycin was associated with a significantly reduced failure rate and prolonged time between exacerbations compared with the use of other antibacterials. These two studies provide interesting and potentially important observations with regard to an approach to antibacterial therapy for exacerba-

tions. However, it is appropriate to emphasise that these observations need to be investigated in well designed, prospective studies.

6.3 Bacterial Susceptibility Testing

An important factor in the choice of antibacterial in any clinical setting is the susceptibility profile of the infecting pathogen to antibacterials. Since most exacerbations of COPD are treated empirically, without knowledge of the susceptibility profile of the pathogen, the choice of antibacterial is based on prediction of the likely susceptibility pattern of the infecting pathogen. As discussed previously, the bacterial pathogens that cause exacerbations are nontypeable *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* and *C. pneumoniae*; enteric Gram-negative rods and *P. aeruginosa* may be important in some patients with severe COPD, but the role of these organisms is less well established. Therefore, antibacterial therapy should be chosen with the susceptibility characteristics of *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* and *C. pneumoniae* in mind.

The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor patterns of resistance to antimicrobials, in predominant nosocomial and community-acquired infections, by collecting and studying bacterial isolates from an international network of sentinel hospitals. This ongoing study recently evaluated resistance rates among systemic and respiratory tract isolates in different geographical areas;^[50] results for the major bacterial pathogens implicated in exacerbations are briefly summarised below.

6.3.1 Nontypeable *Haemophilus influenzae*

The rate of β -lactamase-mediated resistance to amoxicillin varied by geographical region from 11.8% (Europe) to 31.5% (US). Several extended-spectrum cephalosporins, including cefixime, cefuroxime, cefpodoxime, cefepime and cefotaxime, were highly active against nontypeable *H. influenzae*. Cefaclor, loracarbef and cefprozil were somewhat less active, particularly in the US and Canada. The rate of resistance to cotrimoxazole (trimethoprim/sulfamethoxazole) varied from 13.9% in

the Asia-Pacific region to 30.8% in Latin America. Tetracycline, the macrolides (except erythromycin) and the fluoroquinolones showed good activity against nontypeable *H. influenzae*.^[50]

6.3.2 *Moraxella catarrhalis*

Essentially, all isolates of *M. catarrhalis* worldwide produce β -lactamase and are resistant to amoxicillin. Most isolates are sensitive to cotrimoxazole, although this agent is somewhat less active than others against *M. catarrhalis*. Macrolides (except erythromycin), extended-spectrum cephalosporins and fluoroquinolones have excellent activity against isolates of *M. catarrhalis*.^[50]

6.3.3 *Streptococcus pneumoniae*

While patterns of antimicrobial resistance for nontypeable *H. influenzae* and *M. catarrhalis* have been relatively stable over the past decade, resistance to several drugs is emerging among pneumococci worldwide.^[50] Changing definitions for susceptibility and resistance of *S. pneumoniae* to penicillin have created some confusion and ambiguity in the literature. When considering bacterial susceptibility to β -lactams in patients with pneumococcal respiratory tract infections, Musher et al.^[51] recommend that an isolate of *S. pneumoniae* should be regarded as susceptible if the minimum inhibitory concentration (MIC) is ≤ 2 $\mu\text{g/ml}$, intermediate if the MIC is >2 and <4 $\mu\text{g/ml}$, and resistant if the MIC is ≥ 4 $\mu\text{g/ml}$. With this new definition, isolates previously described as showing intermediate resistance would now be in the susceptible range.

In the worldwide SENTRY Antimicrobial Surveillance Program,^[50] the rate of resistance to penicillin among pneumococcal isolates varied by region, from 6.8% (Canada) to 17.8% (Asia-Pacific), and may be increasing. Oral cephalosporins had variable activity against pneumococcal isolates. High rates of resistance to macrolides and cotrimoxazole were observed, especially in the Asia-Pacific region. With the exception of ciprofloxacin, the rate of resistance to fluoroquinolones was $<1\%$ overall.

6.3.4 *Chlamydia pneumoniae*

Cell culture techniques are required to isolate *C. pneumoniae*, and these cultures are not performed routinely in clinical microbiology laboratories. Of the antibacterial agents used to treat exacerbations of COPD, doxycycline, the macrolides and fluoroquinolones are active *in vitro* and are effective clinically. *C. pneumoniae* is not susceptible to β -lactams or sulphonamides.

7. Approach to Therapy

In approaching the elderly patient with an exacerbation of COPD, it is useful to consider the severity of the exacerbation in determining which patients are most likely to benefit from antibacterial therapy. Host factors are then used to make a rational choice of antibacterial as outlined in the following subsections and in table II and figure 2.

7.1 Severity of Exacerbations

A useful approach to identifying patients who will benefit from antibacterial therapy is to stratify exacerbations with regard to severity, as described in section 4. The three cardinal symptoms of increased sputum production, increased sputum purulence and increased dyspnoea compared with baseline, are used to classify an exacerbation as mild (one symptom), moderate (two symptoms) or severe (three symptoms). We suggest that patients with moderate and severe exacerbations be treated with antibacterials. This recommendation is based on: (i) the study of Anthonisen et al.,^[43] which showed benefit for antibacterial therapy for severe exacerbations and all exacerbations as a whole; (ii) the meta-analysis of Saint et al.,^[42] which showed a small benefit for antibacterial therapy; and (iii) the retrospective study of Adams et al.,^[49] which showed a benefit for antibacterial therapy for mild, moderate and severe exacerbations.

7.2 Host Factors

Patients with the most advanced underlying COPD and those with comorbid illnesses are the most likely to experience adverse outcomes from exacerbations, including more hospitalisations, ex-

Table II. Host factors to distinguish between 'simple' and 'complicated' chronic obstructive pulmonary disease (COPD)

Simple COPD	Complicated COPD
FEV ₁ >50% predicted	FEV ₁ <50% predicted
<4 exacerbations per year	≥4 exacerbations per year
No significant comorbid illnesses	Comorbid illnesses present
FEV ₁ = forced expiratory volume in 1 second.	

tra physician visits, prolonged absence from work, and repeated courses of antibacterials. Stratifying patients with regard to host factors may allow physicians to identify patients at high risk and select antibacterial therapy in an effort to prevent some of these consequences. Several authors have proposed various such schemes.^[52-54]

7.3 Choice of Antibacterial

On the basis of susceptibility testing of isolates of nontypeable *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, the use of amoxicillin and cotrimoxazole in treating exacerbations of COPD is no longer prudent in our opinion. Appropriate antibacterial therapy for exacerbations includes doxycycline, newer macrolides, extended-spectrum cephalosporins, amoxicillin/clavulanate and fluoroquinolones.

Patients should be stratified as those with 'simple' or 'complicated' COPD based on the three host factors listed in table II. These factors include forced expiratory volume in 1 second (FEV₁), which is a measure of the severity of underlying lung disease, number of exacerbations in the preceding year and the presence of comorbid illnesses. Figure 2 is a simple algorithm outlining an approach to choosing an antibacterial. We propose that patients with simple COPD receive doxycycline, a newer macrolide or an extended-spectrum cephalosporin. Patients with complicated COPD who are experiencing moderate or severe exacerbations should be treated with amoxicillin/clavulanate or a fluoroquinolone.

There is no evidence that the causes of exacerbations differ in patients with simple or complicated COPD. The rationale for recommending dif-

ferent antibacterial agents is that the consequence of administering an agent that is inactive against the causative pathogen is greater in patients with complicated rather than simple COPD, in view of the presence of more severe underlying disease. In other words, there is 'less margin for error' in that initial treatment failure in complicated versus simple COPD has a greater likelihood of resulting in hospitalisation or respiratory failure. Amoxicillin/clavulanate and fluoroquinolones are highly active, broad-spectrum agents that have excellent activity against the likely pathogens. While doxycycline, macrolides and extended-spectrum cephalosporins have activity against most of the pathogens, their activity and pharmacokinetics are less favourable. Furthermore, as noted in section 6, the approach of stratifying patients has not been tested in randomised prospective trials. Until such studies are performed, our view is that the approach outlined in figure 2 is rational.

Recent studies have suggested that enteric Gram-negative rods and *P. aeruginosa* may cause exacerbations in a small number of patients with

advanced COPD, particularly patients requiring management in the intensive care unit.^[6,12] The precise role of these organisms in causing exacerbations is not clear at this time. Although these bacteria may be causative in some patients, current data are also consistent with these bacteria being present as colonisers in patients who have received multiple courses of antibacterials. The patients at highest risk for potential infection with Gram-negative rods and *P. aeruginosa* appear to be those with severe airways' obstruction who experience acute respiratory failure. The administration of fluoroquinolones with broad-spectrum activity against Gram-negative rods may be prudent in the setting of acute respiratory failure due to exacerbation in a patient with complicated COPD. Ciprofloxacin has the best activity of the fluoroquinolones against *P. aeruginosa*.

C. pneumoniae probably causes a small number of exacerbations, an observation based on serological evidence. There do not appear to be any clinically distinguishing features of such exacerbations. Of the agents recommended for treatment of exacerbations, doxycycline, macrolides and fluoroquinolones are active against *C. pneumoniae*.

8. Antibacterials

The various antibacterials appropriate for the treatment of exacerbations of COPD are reviewed briefly, and special considerations regarding administration to older patients are discussed for each agent.

8.1 Doxycycline

The antibacterial spectrums of activity of tetracycline and doxycycline are almost identical. Doxycycline is the preferred agent because it can be given twice a day and is well absorbed. Most isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* are inhibited by the levels of doxycycline achieved in serum. However, the agents discussed in the following subsections have higher activity against these organisms than does doxycycline.^[50] Resistance of pneumococci to doxycycline is associated with resistance to penicillin.^[55]

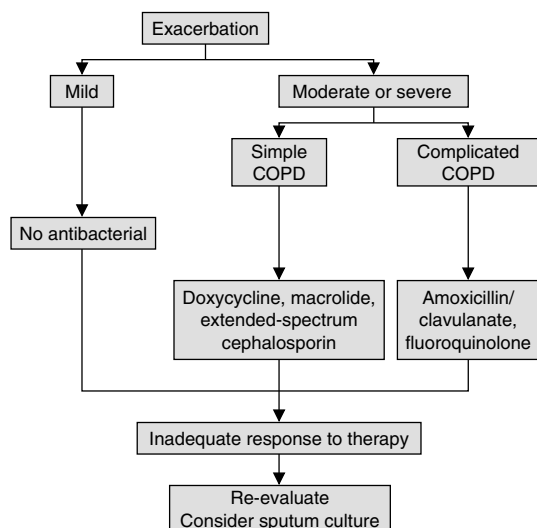


Fig. 2. Algorithm outlining an approach to antibacterial therapy for exacerbations of chronic obstructive pulmonary disease (COPD) in the elderly patient.

Doxycycline diffuses through the porin of Gram-negative bacteria and binds reversibly to the 30S ribosomal subunit, preventing the addition of new amino acids to the growing peptide chain. The drug is absorbed almost completely after oral administration and is distributed widely in tissues. The usual adult dosage is 100mg twice daily. The drug is excreted by the kidney. However, in renal failure, it is excreted in the gastrointestinal tract and no change in doxycycline dosage is required in renal insufficiency.

The most common adverse effect is gastrointestinal upset, which can often be ameliorated by administering doxycycline with food. Other adverse effects include hypersensitivity reactions (e.g. rash), which are uncommon; photosensitivity may occur but is less common than with tetracycline. Doxycycline can also aggravate pre-existing renal failure.

Although doxycycline is generally well absorbed, its absorption is decreased by calcium, magnesium- and aluminium-containing antacids, milk, iron, sucralfate and sodium bicarbonate. Doxycycline may potentiate the effects of oral anticoagulants, so careful monitoring prothrombin time is important.

8.2 Macrolides

The currently licensed macrolides in the US include erythromycin, and the newer agents azithromycin and clarithromycin. The latter two agents share advantages over erythromycin with regard to antimicrobial activity against *H. influenzae*, pharmacokinetics and gastrointestinal adverse effects, and so are preferred to erythromycin for the treatment of exacerbations. Macrolides bind reversibly to the 50S ribosomal subunit and inhibit protein synthesis. An interesting feature of the macrolides is an *in vitro* anti-inflammatory effect; some authors have suggested that this effect contributes to the utility of macrolides in treating exacerbations.^[56-58]

Macrolides are highly active against strains of *H. influenzae*, *M. catarrhalis* and *C. pneumoniae*, with azithromycin showing the best activity against

H. influenzae.^[50] An increasing rate of pneumococcal resistance to macrolides has been observed worldwide. The SENTRY Antimicrobial Surveillance Program,^[50] for example, reported that 10.4 to 38.6% of pneumococcal isolates were resistant to macrolides, with the highest rates of resistance in the Asia-Pacific region. The rate of pneumococcal resistance to macrolides was highest in isolates of *S. pneumoniae* that were intermediately susceptible or highly resistant to penicillin. Since the mechanisms of resistance to penicillin and macrolides are different, this observation probably reflects the pressure of multiple antibacterials on pneumococcal isolates.

We prefer azithromycin as the macrolide for treating exacerbations in view of its superior activity against isolates of *H. influenzae*, once daily administration, short duration of therapy, and low incidence of adverse effects.^[59] The adult dosage is 500mg on day one, followed by 250mg daily for 4 additional days. An equally effective administration schedule is 500mg daily for 3 days. The drug is best administered an hour before or 2 hours after a meal. It should not be taken with magnesium- or aluminium-containing antacids, which decrease the rate of absorption. Azithromycin is widely distributed in tissues, with high concentrations found in lung tissue, alveolar macrophages and neutrophils. Adverse reactions to azithromycin are rare, the most common being gastrointestinal upset.

8.3 Cephalosporins

Second- and third-generation cephalosporins have an antimicrobial spectrum of activity that includes the three major respiratory pathogens, and have shown efficacy in clinical studies of acute exacerbation. Their mode of action is similar to that of the penicillins, with bactericidal activity related to disruption of the bacterial cell membrane. Several of these agents, including cefaclor, cefuroxime, cefpodoxime, loracarbef, ceftriaxone and cefotaxime, have been widely used in respiratory tract infections.^[60-64] Although cephalosporins have been widely used and are well tolerated, their use in acute exacerbations has recently been de-

clining. For some of these agents, the major concerns have been decreasing efficacy against *S. pneumoniae*, long durations of treatment, frequent administration and sub-optimal efficacy against *H. influenzae*. There are no special concerns with the use of these drugs in the elderly. Differential emergence of resistance in *S. pneumoniae* has led several authors to differentiate among the cephalosporins. Cefuroxime, ceftriaxone and cefotaxime are the cephalosporins that have retained the best antimicrobial efficacy against drug-resistant *S. pneumoniae* and have been advocated as the preferred agents. Of these, only cefuroxime is currently available for oral use.

8.4 Amoxicillin/clavulanate

Addition of clavulanate, a β -lactamase inhibitor, to amoxicillin, considerably enhances the spectrum and utility of amoxicillin against *H. influenzae* and *M. catarrhalis*. As a consequence, amoxicillin/clavulanate has been extensively used for the treatment of respiratory mucosal infections for several years and with excellent efficacy.^[65] In recent years, the trend towards an increasing MIC of amoxicillin against *S. pneumoniae* has been a concern; however, less than 10% of strains are resistant using a cutoff of MIC ≥ 4 $\mu\text{g/ml}$.^[50] The usual dosage of amoxicillin/clavulanate is 875mg orally, twice daily.^[66] The major adverse effects are gastrointestinal and β -lactam allergy; however, discontinuation because of adverse effects is uncommon. There are no special concerns in treating elderly patients with amoxicillin/clavulanate.

8.5 Fluoroquinolones

Fluoroquinolones are increasingly being used in the treatment of community-acquired respiratory tract infections.^[67,68] The first-generation drugs ciprofloxacin and ofloxacin have excellent Gram-negative activity, but borderline activity against *S. pneumoniae*. Newer agents have been developed, including levofloxacin, gatifloxacin and moxifloxacin, which have enhanced anti-pneumococcal coverage.^[67,68] However, this anti-pneumococcal activity has come at the expense of

loss of clinically useful activity against *P. aeruginosa*. Therefore, the newer fluoroquinolones have a spectrum of activity that encompasses all the major community-acquired respiratory tract pathogens, including atypical pathogens and penicillin- and macrolide-resistant *S. pneumoniae*.

Fluoroquinolones interrupt bacterial DNA replication and are bactericidal *in vitro*. Adverse effects, including liver toxicity and cardiac arrhythmias, led to the withdrawal or restriction of use of the newer agents trovafloxacin and grepafloxacin. The currently available agents, however, appear to be generally well tolerated in extensive post-marketing surveillance studies. Nevertheless, caution should be exercised in using fluoroquinolones together with other drugs that prolong the QT_c interval, and in critically ill patients with underlying severe heart disease or severe electrolyte abnormalities. Central nervous system adverse effects in the elderly are a concern, but appear to be less of a problem with the newer compounds. Because of their efficacy, convenience of once-daily administration, and short courses of therapy, a concern has become overuse of fluoroquinolones for trivial infections and the subsequent emergence of resistance in *S. pneumoniae*.

9. Conclusions

COPD is a common problem in the elderly. The course of the disease is characterised by intermittent worsening of symptoms; these episodes are called acute exacerbations. Bacterial infections are an important cause of exacerbations of COPD, with the best estimates indicating that approximately half of all exacerbations are caused by bacteria. The role of bacteria in COPD has been the subject of intense investigation: that is, to elucidate the role of infection more precisely and reveal mechanisms of pathogenesis.

The literature provides evidence that antibacterial therapy is of benefit in exacerbations. The primary benefits are acceleration of recovery from exacerbations and prevention of exacerbation complications such as respiratory failure. Although it is difficult to identify the causes of an individual

exacerbation, a rational approach to antibacterial therapy involves consideration of underlying host factors and stratifying exacerbations according to severity.

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