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CHAPTER

Antibiotics

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INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) are a frequent cause for office and emergency room visits as well as hospitalizations. Exacerbations are intermittent episodes of increased respiratory symptoms and worse pulmonary function that may be accompanied by fever and other constitutional symptoms. These episodes contribute significantly to the morbidity associated with COPD, and in advanced disease, they are also the most frequent cause of death [1–3]. The frequency of exacerbations varies widely between patients. Though severity of airflow obstruction is correlated with the frequency of exacerbations, other yet poorly understood factors predispose some patients to have more frequent exacerbations.

Several investigators have reported that exacerbations are important determinants of the decline in health-related quality of life in COPD [4, 5]. Following an exacerbation, acute symptoms usually subside over 2–3 weeks, however, quality of life indices takes several months to return to baseline. Furthermore, recurrent exacerbations are clearly associated with a more rapid decline in quality of life in COPD [6]. Based on studies performed by Fletcher and Peto in the 1960s it was widely believed that exacerbations do not contribute to the decline in lung function (measured as FEV_1). Recent data has disputed these results and shown that the frequency of exacerbations is associated with accelerated long-term decline in lung function, in both mild COPD and more advanced diseases [7, 8].

Undisputedly, exacerbations are a major contributor to the morbidity, costs, and mortality associated with COPD. Substantial progress has been made in understanding their etiology and pathogenesis of exacerbations. In contrast, such richness of data is unfortunately missing in the field of clinical management of exacerbations. Major modalities used to treat exacerbations include bronchodilators, systemic corticosteroids, and antibiotics. Only for systemic corticosteroid use in severe exacerbations requiring emergency room care or hospitalization is the adequate clinical trial data available. Adequately powered, well-designed clinical trials studies for the other modalities used to treat exacerbations are relatively few. Consequently, whether the use of antibiotics for exacerbations is appropriate is still debated and whether antibiotic choice makes a difference is even more controversial [9, 10].

Principles that should guide appropriate use of antibiotics in exacerbations are listed in Table 53.1. The comments in Table 53.1 illustrate the several barriers that currently exist in fully applying these principles in everyday practice. This chapter will describe the optimal approach to antibiotic treatment of exacerbations recognizing these limitations. Such an approach relies upon an accurate diagnosis of an exacerbation, including judicious application of diagnostic tests. This is followed by determining the severity of an exacerbation, the probability that it is bacterial and whether antibiotics are indicated. If antibiotics are indicated, then a risk stratification approach is described to choose an appropriate antibiotic.

DIAGNOSIS OF ACUTE EXACERBATION

Clear, objective, universally accepted definition of a disease or syndrome is a pre-requisite for its accurate diagnosis. Unfortunately, for

TABLE 53.1 Principles of appropriate antibiotic use in exacerbations of COPD.

Principle	Comment
Bacteria cause significant proportion of exacerbations	40–50% of exacerbations are of bacterial origin
Bacterial exacerbations can be reliably distinguished from nonbacterial episodes	Sputum purulence is a useful marker but not always easily assessed or reliable
Placebo-controlled antibiotic trials have shown benefit of antibiotics	This is true for moderate-to-severe exacerbations, but not mild episodes
Antibiotics used are appropriate for the causative pathogen	Sputum cultures are inaccurate and usually not performed, therefore therapy is usually empiric
Antibiotic dose and duration are appropriate	Shorter durations of 3–7 days appear to be as good as 10–14 days
Antibiotic choice makes a difference in outcome	Inadequate study methods have limited their ability to show differences among antibiotics
Risk stratification is useful in choosing antibiotics	Though not prospectively validated, it is widely advocated

exacerbations of COPD, the current definitions are imprecise, variable, and lack objective measures [11]. There are two widely used definitions of exacerbation. In 1987, in a large placebo-controlled trial in exacerbations of COPD, Anthonisen and colleagues defined exacerbations based on the presence of one or more of the three cardinal symptoms, including an increase or new onset of dyspnea, sputum production, and sputum purulence [12]. When only one cardinal symptom is present, then one or more supporting symptoms or signs are required to make the diagnosis, including an upper respiratory tract infection in the past 5 days, wheezing, cough, fever without an obvious source, or a 20% increase in the respiratory rate or heart rate above baseline. Though simple and clinically useful, this definition does have several limitations. It is narrow in its scope, and several important symptoms of exacerbation such as cough, chest congestion, chest tightness, fatigue, and sleep disturbance are not included. It is subjective, however, that limitation applies to all definitions of exacerbations as reliable objective measures of exacerbations are currently unavailable.

A more recent and also commonly used definition came from a consensus panel that defined an exacerbation as an acute sustained worsening of the patients' condition from stable state, beyond day-to-day variability and which requires additional treatment [11]. This definition though more inclusive of symptoms of an exacerbation, is not specific with regard to the nature and duration of symptoms. It lacks objective measures. Longitudinal cohort studies with daily recording of symptoms have revealed that a significant proportion, up to 50%, of episodes of increased symptoms are not reported by patients to their health care providers and therefore are not associated with additional treatment. Such episodes, which likely represent mild exacerbations would not meet this definition of exacerbation.

Missing in both definitions is the clinical exclusion of entities that could lead to increased respiratory symptoms in a manner similar to exacerbation, such as pneumonia, congestive heart failure, upper respiratory infection, noncompliance with medications etc. These clinical entities have distinct etiology, pathogenesis and treatment, and therefore should be in the differential diagnosis of an exacerbation rather than be included under the definition. In our clinical studies, we suspect an exacerbation when a patient with COPD reports a minor increase (or new onset) of two or a major increase (or new onset) of one of the following respiratory symptoms: dyspnea, cough, sputum production, sputum tenacity, sputum purulence [13]. The increase in symptoms should be of at least 24 h duration and should be of greater intensity than their normal day-to-day variability. Furthermore, as described above, clinical evaluation should exclude other clinical entities that could present in a similar manner.

DETERMINATION OF SEVERITY

The decision to treat exacerbations is often based on severity, with antibiotic treatment recommended for moderate to severe exacerbations. However, currently our determination of severity of exacerbations is imprecise, and like the diagnosis, is determined in a variable manner among studies. The severity of an exacerbation is a complicated concept, determined by at least two factors, the severity of the underlying COPD and the acute change induced by the exacerbation. A severe exacerbation may therefore be assessed when a patient with very severe underlying COPD has a relatively small change from his baseline, or when a patient with mild COPD has much larger acute change in his symptoms and lung function. The exacerbation etiology and pathophysiology may differ considerably in these circumstances and may warrant distinct treatment approaches.

Exacerbation severity has been variously defined among studies. Ideally, changes in lung function should be used to define severity of exacerbations. However, spirometry and lung volumes are difficult to measure accurately during exacerbations, especially severe episodes. With simpler

TABLE 53.2 Anthonisen classification of COPD exacerbations based on cardinal symptoms.

Severity of exacerbation	Type of exacerbation	Characteristics
Severe	Type 1	Increased dyspnea, sputum volume, and sputum purulence
Moderate	Type 2	Any two of the above three cardinal symptoms
Mild	Type 3	Any one of the above three cardinal symptoms and one or more of the following minor symptoms or signs – Cough – Wheezing – Fever without an obvious source – Upper respiratory tract infection in the past 5 days – Respiratory rate increase >20% over baseline – Heart rate increase >20% over baseline

Based on data from Ref. [12].

measures, such as peak flow, often the change with an exacerbation is of the same magnitude as its day-to-day variability. Severity has been also measured by site of care, with hospitalized exacerbations regarded as severe, outpatient exacerbations regarded as moderate and self medicated exacerbations as mild [14]. Site of care is unreliable as a measure of exacerbation severity. Though the major factor determining site of care is undoubtedly illness severity, it is also dependent on differences in hospital admission practices among countries and health care systems, patient reporting of exacerbations, physician preferences, etc. The intensity of recommended treatment has also been used as a measure of severity of exacerbations, with treatment with bronchodilators only indicating mild exacerbations, while treatment with antibiotics and steroids in addition to bronchodilators regarded as indicating moderate or severe exacerbations. Such measurement of severity is beset with the same problems of preferences and practice approach as discussed above.

Another widely used determination of severity of exacerbations is the Anthonisen classification [12]. This classification relies on the number of cardinal symptoms and the presence of some supporting symptoms (Table 53.2). Though not developed as a severity classification, it has become so over time. Advantages of this determination of severity are its simplicity and that it correlates with benefit with antibiotics, with such benefit seen only in Type 1 and 2 exacerbations. Limitations include its lack of validation against objective measures of severity and that its ability to predict benefit with antibiotics has not been consistent in other studies. Another limitation is the lack of gradation of severity within each symptom, such that a Type 2 exacerbation with mild changes in two cardinal symptoms would be regarded as the same severity in this classification as an exacerbation with a marked increase in both symptoms.

It is evident that we need a better definition and objective measures of severity of exacerbations. Recent work in the development of patient reported outcomes to measure exacerbations has demonstrated that the experience of an exacerbation from the patient perspective includes not only respiratory symptoms but extra-respiratory manifestations including fatigue, anxiety, sleep disturbance etc. Future definitions of exacerbation should therefore include such symptoms. An expectation in the future is that a properly developed patient reported outcome measure would become universally applied to define exacerbations, where a certain change from baseline in this measure would constitute an exacerbation. Furthermore, the degree of change in such a measure from baseline would represent an objective measurement of severity.

Biomarkers in exacerbations are being vigorously explored, as they hold the promise of being objective measures to define an exacerbation and determine its severity. A recent study explored 36 plasma biomarkers in 90 patients with exacerbations and found that none of them alone or in combination were adequate to define an exacerbation [15]. In another study of multiple serum biomarkers in 20 hospitalized patients with exacerbation, reduction in interleukin-6 (IL-6) and interleukin-8 (IL-8) correlated with decrease in dyspnea during recovery from exacerbation, while decreases in IL-6 and tumor necrosis factor (TNF-α) were proportional to recovery in FEV_1 [16]. Changes from baseline in sputum IL-8 and TNF-α as well as sputum neutrophil elastase (NE) and serum C-reactive protein (CRP) correlate with clinical severity of an exacerbation as assessed by a clinical score based on symptoms and signs [17, 18]. It appears unlikely that a single biomarker will be capable of defining an exacerbation, because of the heterogeneity of these episodes. However, biomarkers do hold promise in objectively determining severity of exacerbations and defining etiology to guide appropriate treatment.

PATHOGENESIS OF EXACERBATIONS

An increase in airway inflammation from the baseline level in a patient appears central to the pathogenesis of most acute exacerbations [19, 20]. Airway inflammation measured in induced or expectorated sputum, bronchoalveolar lavage or bronchial biopsy has revealed that increased inflammation accompanies exacerbations and resolves with treatment [21–25]. Both neutrophilic and eosinophilic inflammations have been described. This acute increase in airway inflammation leads to increased bronchial tone, edema in the bronchial wall and mucus production. In a diseased lung, these processes worsen ventilation-perfusion mismatch and expiratory flow limitation. Clinically, these pathophysiologic changes present as an increase in or new onset of dyspnea, cough, sputum production, tenacity and purulence along with worsening gas exchange, which are the cardinal manifestations of an exacerbation. Inflammation in exacerbations extends beyond the lung, and increased plasma fibrinogen, interleukin 6 (IL-6) and CRP have been described during exacerbations [18, 26, 27]. These and other mediators likely

cause the systemic manifestations of exacerbations, including fatigue and in some instances fever.

The etiology of exacerbations appears to determine the nature and degree of inflammation in exacerbations. Neutrophilic inflammation is characteristic of bacterial exacerbations, while both neutrophilic and eosinophilic inflammations have been described with viral infection [28]. The intensity of neutrophilic inflammation, when measured as associated cytokines/chemokines (IL-8, TNF-α) and products of neutrophil degranulation (NE and myeloperoxidase), is much greater in well-characterized bacterial exacerbations than exacerbations of nonbacterial etiology [18]. Systemic inflammation, measured as serum CRP is also more intense in bacterial exacerbations [18]. These findings have important implications. They can form the basis for biomarkers to distinguish etiology of exacerbations in a reliable and rapid manner, facilitating appropriate therapy. The heightened airway and systemic inflammation with bacterial exacerbations can be potentially damaging to the lungs. Effective antibiotic therapy to eradicate the bacteria responsible for exacerbations and reduce the inflammation to baseline levels becomes desirable and could have potential long-term benefits in COPD.

A variety of noninfectious and infectious stimuli can induce an acute increase in airway inflammation in COPD, thereby causing an exacerbation. Increased respiratory symptoms and respiratory mortality among patients with COPD during periods of increased air pollution have been described [29–31]. Environmental pollutants, both particulate matter, such as PM-10 and diesel exhaust particles, and nonparticulate gases, such as ozone, nitrogen dioxide, sulfur dioxide, are capable of inducing inflammation *in vitro* and *in vivo* [32–34]. Infectious agents, including bacteria, viruses, and atypical pathogens are implicated as causes of up to 80% of acute exacerbations [35].

MICROBIAL PATHOGENS IN COPD EXACERBATIONS

Potential pathogens in COPD exacerbations includes typical respiratory bacterial pathogens, respiratory viruses, and atypical bacteria (Table 53.3). *Pneumocystis jiroveci*, a fungus, appears to cause chronic infection in COPD. Whether it induces exacerbations is being investigated. Among the typical bacteria, Nontypeable *Haemophilus influenzae* (NTHI) is the most common pathogen in COPD and is the best understood [36]. Among the viruses, *Rhinovirus* and *Respiratory syncytial virus* (RSV) have received considerable attention in recent years and their importance in COPD is now better appreciated [37, 38].

The predilection of these pathogens for causing infections in COPD may be related to certain shared characteristics. NTHI, *Streptococcus pneumoniae* and *Moraxella catarrhalis*

TABLE 53.3 Microbial pathogens in exacerbations of COPD.

Proportion of exacerbations (%)	Specific species	Proportion of class of pathogens (%)
Bacteria		
40–50	Nontypeable *Haemophilus influenzae*	30–50
	Streptococcus pneumoniae	15–20
	Moraxella catarrhalis	15–20
	Pseudomonas spp. and *Enterobacteriaceae*	Isolated in very severe COPD, concomitant bronchiectasis, and recurrent exacerbations
	Haemophilus parainfluenzae	Isolated frequently, pathogenic significance undefined
	Haemophilus hemolyticus	Isolated frequently, pathogenic significance undefined
	Staphylococcus aureus	Isolated infrequently, pathogenic significance undefined
Viruses		
30–40	*Rhinovirus*	40–50
	Parainfluenzae	10–20
	Influenza	10–20
	RSV	10–20
	Coronavirus	10–20
	Adenovirus	5–10
Atypical bacteria		
5–10	*Chlamydia pneumoniae*	90–95
	Mycoplasma pneumoniae	5–10

are the predominant bacterial causes of two other common respiratory mucosal infections, acute otitis media in children and acute sinusitis in children and adults. *Pseudomonas aeruginosa* is the dominant mucosal pathogen in cystic fibrosis and noncystic fibrosis bronchiectasis [39]. These mucosal infections have been related to anatomical abnormalities with impaired drainage of secretions, antecedent viral infections and defects in innate and adaptive immunity. All these predisposing factors likely exist in COPD. NTHI, *S. pneumoniae* and *M. catarrhalis* are exclusively human pathogens. Their usual environmental niche in healthy humans is confined to the upper airway which they usually colonize without any clinical manifestations. Acquisition of these pathogens in COPD, because of compromised lung defense, allows establishment of infection in the upper as well as the lower respiratory tract (below the vocal cords). Infection of the lower respiratory tract in COPD can be with or without overt clinical manifestations, the former being addressed as exacerbation while the latter as colonization.

Respiratory viruses implicated in COPD cause acute tracheobronchial infections in healthy hosts, clinically referred to as acute bronchitis. In the setting of COPD, with diminished respiratory reserve, this acute bronchitis has more profound manifestations and serious clinical consequences.

PATHOGENESIS OF INFECTIOUS EXACERBATIONS

Significant progress has been made in our understanding of acute exacerbation pathogenesis, especially in relation to bacterial infection over the last few years. The current model of bacterial exacerbation pathogenesis involves both host and pathogen factors (Fig. 53.1). Acquisition of strains of bacterial pathogens that are new to the host from the environment is the primary event that puts the patient with COPD at risk for an exacerbation [13]. Variation among strains of a species in the surface antigenic structure, as is seen with NTHI, *S. pneumoniae*, *M. catarrhalis*, and *P. aeruginosa*, is crucial to the development of recurrent exacerbations with these pathogens. This variation allows these newly acquired strains to escape the pre-existing host immune response that had developed following prior exposure to other strains of the same species. These newly acquired strains can therefore proliferate in the lower airways and induce acute inflammation. The virulence of the strain and as yet unidentified host factors may determine if the acute inflammatory response to the pathogen reaches the threshold to cause symptoms that present as an exacerbation [40]. In the majority of instances, mucosal and systemic antibodies develop to the pathogen [41, 42]. This immune response, in combination with appropriate antibiotics, eliminates or controls proliferation of the infecting bacteria. However, because of antigenic variability among strains of these bacterial species, these antibodies directed at the infecting strain are usually strain-specific, and do not protect the host from antigenically distinct strains of the same species. This allows recurrent bacterial infection and exacerbations in these patients.

The pathogenesis of acute viral exacerbations is less well understood, but may be similar to bacterial infections. A common cause of exacerbations, the rhinovirus, demonstrates considerable antigenic variation among its more than 100 serotypes, allowing for recurrent infections. The influenza virus demonstrates drift in the antigenic makeup of its major surface proteins, thereby leading to recurrent

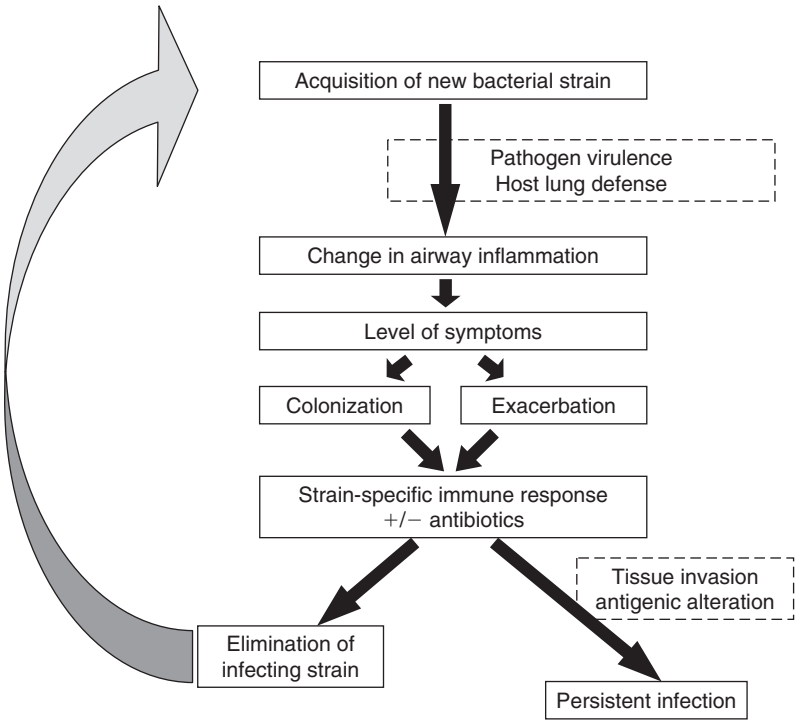

FIG. 53.1 Proposed model of bacterial exacerbation pathogenesis in COPD. Reproduced with permission from Ref. [43].

infections. *In vitro*, viruses can damage airway epithelium, stimulate muscarinic receptors, and induce eosinophil and neutrophil influx [44]. Whether these pro-inflammatory actions are enhanced in epithelial cells from patients with COPD is not known. Bronchial epithelial cells obtained from patients with asthma have diminished production of interferons and increased ICAM-1 expression, changes which could result in increased inflammation, cell lysis, and viral replication on viral infection. Increased ICAM-1 expression in COPD bronchial epithelium has been seen, however the other changes have not been described.

GOALS OF TREATMENT OF EXACERBATIONS

The traditional aims of treatment of an exacerbation are improvement in clinical status and the prevention of complications. Though undoubtedly important, several new observations question the adequacy of these goals. These include the importance of exacerbations in the course of COPD, the role of infection in exacerbations, the high rates of relapse with an adequate initial clinical response, and the potential damaging effects of chronic colonization in COPD. To draw an analogy, confining our goal in the treatment of COPD exacerbations to short-term resolution of symptoms would be the equivalent of treating acute myocardial infarction with the only aim being resolution of chest pain. Several other goals of treatment, both clinical and biological, should therefore be considered (Table 53.4).

A good example of an inadequate goal in the treatment of exacerbations is "clinical success," which is defined as resolution or improvement of symptoms to a degree that no further treatment is required in the opinion of the treating physician. Recent observations have shown that symptoms of an exacerbation are correlated with exaggerated airway and systemic inflammation. Hence, acceptance of clinical improvement as adequate rather than clinical resolution to baseline has important implications. Clinical improvement likely reflects inadequate treatment, permitting the inflammatory process accompanying the exacerbation to persist for prolonged periods of time, causing progressive airway damage [45]. Therefore, clinical resolution of symptoms to baseline is a more appropriate goal of treatment of exacerbations.

Additional important clinical goals of treatment include delaying the next exacerbation, prevention of early relapse and more rapid resolution of symptoms [46–48]. Lengthening the inter-exacerbation interval and prevention of early relapse ultimately translate to a decrease in the frequency of exacerbations, which is now a major focus of COPD treatment. Though most patients and physicians would accept faster recovery to baseline as a desirable goal of treatment, development of this parameter has been hampered by lack of well-validated instruments to reliably measure exacerbation resolution. Patient reported outcomes in development will address this need in the near future.

Biological goals of treatment are either still in their infancy or, in the case of bacteriologic eradication, inadequately assessed in clinical studies to satisfy regulatory requirements for approval of new antibiotics. Most exacerbations are inflammatory events, therefore it is logical that resolution of inflammation to baseline should be an important goal of treatment. Similarly, exacerbations are in many instances induced by infection, therefore eradication of the offending infectious pathogen should be a goal of treatment. Practical application of these biological goals of treatment of exacerbations awaits the development of biomarkers that provide simple, rapid and reliable measurements of inflammation and infection.

A multi-modality approach to treatment of exacerbations is common, that utilizes several modalities simultaneously, to relieve symptoms, to treat the underlying cause or to provide support till recovery occurs [14, 49]. These therapies include bronchodilators, corticosteroids, antimicrobials,

TABLE 53.4 Goals of treatment of COPD exacerbation.

Goals	Comments
Clinical	
Faster resolution of symptoms	Needs validated symptom assessment tools
Clinical resolution to baseline	Needs baseline assessment prior to exacerbation onset for comparison
Prevention of relapse	Relapse within 30 days is quite frequent
Increasing exacerbation-free interval	Needs long-term follow-up after treatment
Preservation of health-related quality of life	Sustained decrements seen after exacerbations
Biological	
Bacterial eradication	Often presumed in usual antibiotic comparison studies
Resolution of airway inflammation	Shown to be incomplete if bacteria persist
Resolution of systemic inflammation	Persistence of systemic inflammation predicts early relapse
Restoration of lung function to baseline	Incomplete recovery is seen in significant proportion
Preservation of lung function	Needs long-term studies

mucolytics and expectorants and, in the more severe cases, oxygen supplementation and mechanical ventilation for acute respiratory failure.

ANTIBIOTICS IN THE TREATMENT OF EXACERBATIONS

The role of antibiotics in the treatment of COPD exacerbations has been a matter of controversy. Even more contentious has been the issue whether antibiotic choice is relevant to clinical outcome of exacerbations. Recommendations for antibiotic use among published guidelines are inconsistent [14, 50–52]. There is a paucity of well-designed, large randomized controlled trials with adequate goals of treatment comparing antibiotics to placebo or among antibiotic classes. This paucity of evidence upon which to base solid recommendations has undoubtedly contributed to the controversy and inconsistency of recommendations regarding antibiotic use [53].

Recently, a few well-designed placebo controlled and antibiotic comparison trials have been reported. Furthermore, epidemiologic studies have consistently identified certain "clinical risk factors," which in the setting of an exacerbation are predictive for failure of treatment or early relapse. The clinical outcomes of exacerbation in observational real-life studies are clearly sub-optimal, with as many as 25–33% of patients experiencing treatment failure or early relapse. Considering the heterogeneity of COPD and of exacerbations, it is clear that the "one size fits all" approach of using the same antibiotic in all episodes is sub-optimal. It is likely that a proportion of treatment failures in exacerbations are related to ineffective antibiotics. Patients "at risk" for poor outcome are the logical candidates for aggressive initial antibiotic treatment, with the expectation that such an approach would improve overall exacerbation outcomes. This "risk stratification" approach has also been advocated for other community-acquired infections such as pneumonia and acute sinusitis [23, 54]. Though improved outcomes with such risk stratification has not yet been demonstrated in prospective controlled trials, this approach takes into account concerns of disease heterogeneity, antibiotic resistance and judicious antibiotic use.

Placebo-controlled antibiotic trials

Exacerbations of COPD result in significant antibiotic consumption, however, there are only a handful of placebo controlled trials in this disease. Two meta-analyses of placebo controlled trials in exacerbations have been published. The first such analysis published in 1995 included nine trials and found a small but significant beneficial effect of antibiotics over placebo [55]. In the second analysis published in 2006, 11 trials were included, and a much larger beneficial effect on mortality and prevention of clinical failure was demonstrated, especially in moderate to severe exacerbations [56]. In this analysis, the number needed to treat in severe exacerbations in hospitalized patients to prevent one death was only three patients and the number needed to treat to prevent one clinical failure was six patients. Diarrhea was the most frequently related adverse effect, with one episode per seven patients treated. Antibiotic treatment was also beneficial in resolving sputum purulence. A benefit on lung function and gas exchange was not observed, however, the data examining this end point was scanty.

The reason that the two meta-analyses came up with different results is in large part inclusion in the later analysis of a study performed by Nouira *et al.* published in 2003. In this randomized double blind study, 93 patients with exacerbations of severe underlying COPD requiring ventilator support in an intensive care unit were randomly assigned to receive a fluoroquinolone antibiotic, ofloxacin, or placebo [57]. No systemic corticosteroids were administered. Bacterial pathogens were isolated in tracheobronchial aspirates in 61% of patients. Ofloxacin administration was associated with dramatic benefits compared to placebo, reducing mortality (4% versus 22%) and the need for additional antibiotics (6% versus 35%) by 17.5-fold and 28.4-fold, respectively.

Another important study, which for some reason has not been included in either meta-analysis, was performed in Italy by Allegra *et al.* and published in 1991. In this double blind randomized trial, amoxicillin/clavulanate was compared with placebo in 414 exacerbations in 369 patients with varying severity of underlying COPD [58]. A unique feature of this study was the measurement of primary outcome at 5 days after the start of treatment, instead of the traditional 2–3 weeks. This earlier timing is clinically of greater relevance than the usual later one, as in clinical practice if patients are not improved within 3–5 days, they are reassessed and their therapy altered. Clinical success (including resolution and improvement) was significantly better with the antibiotic, seen in 86.4% of patients, compared with 50.6% in the placebo arm. In addition, with increasing severity of underlying COPD, the benefit with antibiotics as compared to placebo was larger.

Results of the meta-analyses, the Allegra study, and of the previous classic large placebo-controlled trial conducted by Anthonisen *et al.*, clearly demonstrate that antibiotics are beneficial in the treatment of moderate to severe exacerbations [12, 56–58]. Furthermore, the benefit with antibiotics is more marked early in the course of the exacerbation, suggesting that antibiotics hasten resolution of symptoms [58, 59]. The benefit with antibiotics is also greater as the severity of underlying airflow obstruction increases. This could be related to more frequent bacterial infections and/or a decreased ability of the host in dealing with infections, therefore requiring "help" with antibiotics to resolve them.

Important questions regarding the role of antibiotics in exacerbations still remain. The benefit of antibiotics in mild exacerbations in the context of mild underlying COPD is unproven and warrants a placebo controlled trial. The effect of concomitant treatment with systemic corticosteroids on the benefits of antibiotic therapy in exacerbations is not known. Placebo controlled trials of antibiotics have not systematically regulated concomitant therapy, and all the placebo controlled trials of steroids had antibiotics administered to all patients. Because inflammation and infection are linked, it is likely that there would be additive

benefits when both treatments are used over either treatment alone [56, 60].

Antibiotic comparison trials

Antibiotics are clearly useful in moderate to severe exacerbations of COPD. However, there remains considerable controversy as to antibiotic choice, especially for initial empiric therapy of exacerbations [14, 50–52, 61]. Most exacerbations nowadays are treated without obtaining sputum bacteriology and with the trend to short course antibiotic therapy, this initial empiric choice often becomes the only choice made of antibiotics in exacerbations. Results of antibiotic comparison trials should guide the recommendations for appropriate empiric antibiotics in exacerbations. However, though the literature is replete with such trials, in the vast majority, antibiotic choice does not apparently affect the clinical outcome. However, differences in bacteriological eradication rates among antibiotics are seen, with a dissociation between clinical and bacteriological outcomes [62]. These results are contrary to expectations that antibiotics with better *in vitro* and *in vivo* antimicrobial efficacy and better pharmacodynamic and pharmacokinetic characteristics should show superior clinical outcomes. A closer examination of the trial design of these studies reveals several shortcomings that offer potential explanations for this paradox (Table 53.5) [53]. Many of these deficiencies are related to the fact that these trials are performed for regulatory approval of the drugs, therefore are designed for demonstrating noninferiority rather than differences between the two antibiotics. In the face of this large body of data showing clinical equivalence, it is not surprising that several guidelines do not differentiate between antibiotics for therapy of exacerbations.

Most antibiotic comparison trials are underpowered to detect differences among antibiotics. However, because of regulatory requirements, these studies are conducted in a very similar manner and in similar patient populations. This makes these trials very amenable to a meta-analytic approach. Dimopoulos *et al.* used such an approach to determine whether there was any difference in clinical outcomes among first-line antibiotics (amoxicillin, ampicillin, pivampicillin, trimethoprim/sulfamethoxazole, and doxycycline) and second-line antibiotics (amoxicillin/clavulanate, macrolides, second-generation or third-generation cephalosporins, and fluoroquinolones) in the treatment of exacerbations of chronic bronchitis [63]. They identified 12 randomized controlled trials that had enrolled 2261 patients, 10 of these trials included the penicillins as the first-line antibiotic. Only a single trial each with trimethoprim/sulfamethoxazole and doxycycline was included. In the clinically evaluable patients, first-line antibiotics were only half as effective as second-line antibiotics with an odds ratio for clinical treatment success of 0.51 (95% CI, 0.34–0.75). This result was consistent in several sensitivity analyses, with the exception of trials published before 1991, where the difference between first line and second line antibiotics was not seen. There was no difference between the first-line and second-line antibiotics in adverse effects.

This meta-analysis provides additional evidence that antibiotic choice does make a difference in the treatment of exacerbations. Similar treatment success for first line and second line antibiotics in trials before 1991 but not after 1991, suggests that resistance emergence in causative bacterial pathogens (*H. influenzae, M. catarrhalis, S. pneumoniae*) is responsible for the findings of this meta-analysis. Because of the limited number of studies in which the first line antibiotics were not penicillins, the results of this meta-analysis mainly applies to the penicillins. Based on this meta-analysis, recommendations to use amoxicillin and ampicillin in the treatment of exacerbations cannot be supported.

These investigators also performed a similar meta-analysis where they compared second-line antibiotics,

TABLE 53.5 Limitations of published placebo-controlled antibiotic trials in acute exacerbations of COPD.

Limitation of study design	Potential consequences
Small number of subjects	Type 2 error
Subjects with mild or no underlying COPD included	Diminished overall perceived efficacy of antibiotics
Nonbacterial exacerbations included	Type 2 error
Endpoints compared at 3 weeks after onset	– Spontaneous resolution mitigates differences between arms – Clinically irrelevant as most decisions about antibiotic efficacy are made earlier
Speed of resolution not measured	Clinically relevant endpoint not assessed
Lack of long-term follow-up	Time to next exacerbation not assessed
Antibiotic resistance to agents with limited *in vitro* antimicrobial efficacy	Diminished overall perceived efficacy of antibiotics
Poor penetration of antibiotics used in to respiratory tissues	Diminished overall perceived efficacy of antibiotics
Concurrent therapy not controlled	Undetected bias in use of concurrent therapy

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the macrolides, the fluoroquinolones and amoxicillin/clavulanate in a similar manner [64]. In this analysis of 19 randomized controlled trials that had enrolled 7405 patients, no differences were found among these agents in clinical treatment success defined in the conventional manner.

In addition to these meta-analyses, welcome additions to the literature on antibiotic treatment of exacerbations are two recent antibiotic comparison trials that were designed as superiority studies. They also measured some unconventional but clinically relevant end-points. The GLOBE (Gemifloxacin and Long term Outcome of Bronchitis Exacerbations) trial, a double blind, randomized trial, compared a fluoroquinolone, gemifloxacin, with a macrolide, clarithromycin [65]. End of therapy and long-term outcome assessments were made at the conventional 10–14 day and 28-day time intervals. These assessments, in line with most antibiotic comparison trials, did not demonstrate statistically significant differences in the two arms, with clinical success rates of 85.4% and 84.6% for gemifloxacin and clarithromycin respectively. Also in line with similar studies, bacteriological success, measured as eradication and presumed eradication, was significantly higher with gemifloxacin (86.7%) compared to clarithromycin (73.1%).

Patients with a successful clinical outcome at 28 days were enrolled in a follow-up period for a total of 26 weeks of observation. In this time period, the primary outcomes were the rate of repeat exacerbations, hospitalizations for respiratory disease and health-related quality of life measures. A significantly lower rate of repeat exacerbations was observed with gemifloxacin, with 71% of the patients remaining exacerbation free at 26 weeks compared to 58.5% in the clarithromycin arm. The relative risk reduction for recurrence of exacerbation was 30%. The rate of hospitalization for respiratory tract illness in the 26 weeks was also lower in the gemifloxacin treated than in the clarithromycin treated patients (2.3% versus 6.3%, $p = 0.059$) [65]. Patients who remained free of recurrence in the 26-week period regained more of their health-related quality of life than those who had a recurrent exacerbation [6]. This trial clearly demonstrates that conventional medium-term clinical outcomes are unsuitable for measuring differences among antibiotics in exacerbations. If the 26-week follow-up period had not been included in the GLOBE study, significant differences in the two treatment arms in clinically relevant outcomes of recurrence of exacerbations and respiratory related hospitalization would have been missed.

The MOSAIC trial is another recent landmark antibiotic comparison trial in exacerbations of COPD. Patients in this study were randomized to a fluoroquinolone, moxifloxacin or to standard therapy (which could be one of the following: amoxicillin, cefuroxime or clarithromycin) [66]. Several unique design features of this trial are noteworthy, which relate to observations made in this study and set the standard for future antibiotic comparison trials in this disease. The number of patients enrolled was much larger than previous studies, in order to provide adequate power to demonstrate superiority. Patients were enrolled when stable to establish a baseline as a comparison to reliably distinguish between clinical improvement (enough improvement that no additional antibiotic treatment is required) from clinical cure (improvement of symptoms to baseline) following treatment. A substantial proportion of the patients enrolled had one or more risk factors that would predispose to a poor outcome as discussed below. Patients were followed up to 9 months after randomization to provide an estimate of recurrence of exacerbation.

In line with usual antibiotic comparison trials, moxifloxacin and standard therapy were equivalent (88% versus 83%) for clinical success (resolution and improvement) at 7–10 days after the end of therapy. However, moxifloxacin therapy was associated with a superior clinical cure rate (defined as resolution of symptoms to baseline, rather than simply improvement) than standard therapy (71% versus 63%), as well as with superior bacteriologic response (91.5% versus 81%). Several other *a priori* unconventional end-points were examined. Moxifloxacin treatment resulted in significantly fewer courses of additional antibiotic therapy (8% versus 14%) and an extended time to the next exacerbation (131 versus 104 days) [66]. A composite end-point of clinical failure, requirement of additional antibiotics and recurrence of exacerbation demonstrated a clear difference between the two arms, with moxifloxacin being statistically superior to standard therapy for up to 5 months of follow-up. As with the GLOBE trial, if conventional clinical success would have been measured solely in this study, all the other significant differences in the two arms would have not been discovered.

The GLOBE and MOSAIC trials demonstrate that *in vitro* microbiological superiority as well as the enhanced pharmacokinetic/pharmacodynamic properties in the respiratory tract of the fluoroquinolones does translate to greater *in vivo* effectiveness in the treatment of exacerbation. Antibiotics for exacerbation have very similar results for the standard regulatory end-point of clinical success at 7–14 days after the end of therapy. This standard end-point not only lacks discriminatory power, it also has little clinical relevance. Most decisions about antibiotic benefit in the clinical setting are made within the 1st week of therapy. Differences among antibiotics are perceptible when clinically relevant end-points such as speed of resolution, clinical cure, need for additional antimicrobials and time to next exacerbation are considered [65, 66].

RISK STRATIFICATION OF PATIENTS

Fluoroquinolones are excellent antimicrobials for exacerbations, and based on the MOSAIC and GLOBE studies, it is tempting to prescribe them for all moderate to severe exacerbations. Such a strategy, though likely to be successful in the short-term, would foster antimicrobial resistance to these valuable antibiotics in the long term. Therefore, it would be judicious to make an effort to identify those patients and exacerbations that are most likely to benefit from these antibiotics and use them in those circumstances.

Observational real life studies of the outcome of exacerbations in the community have clearly demonstrated that our current treatment approach is sub-optimal. In these studies, treatment failure rates, either defined as failure to improve or relapse within 30 days of 25–33% are seen

[67, 68]. These studies have also demonstrated that certain patient characteristics that antedate the onset of the exacerbation impact the outcome of the exacerbation [48, 67–71]. Interestingly, several of these characteristics, such as co-morbid cardiac disease and frequent exacerbations, were found to be relevant to outcome in more than one study. These risk factors for poor outcome should be considered in the decision regarding choice of empiric antibiotics when treating exacerbations. In theory, patients at risk for poor outcome would have the greatest benefit from early aggressive antibiotic therapy, such as with the fluoroquinolones. These are the patients in whom the consequences of treatment with an antibiotic ineffective against the pathogen causing the exacerbation are likely to be significant, with clinical failures, hospitalizations and early recurrences likely. These at risk patients contribute substantially to the overall poor clinical outcomes of exacerbations. Therefore, targeting these patients with potentially more effective treatment is likely to have a significant impact on the overall outcomes of exacerbations.

Risk factors for poor outcome identified in various studies are increasing age, severity of underlying airway obstruction, presence of co-morbid illnesses (especially cardiac disease), a history of recurrent exacerbations, use of home oxygen, use of chronic steroids, hypercapnia and acute bronchodilator use [48, 67–71]. It is likely that home oxygen use, hypercapnia and chronic steroid use mainly reflect increasing severity of underlying COPD. Acute bronchodilator use could either be related to the severity of underlying COPD or reflect the wheezy phenotype of exacerbation that would be less responsive to antibiotic treatment. Many of these risk factors are continuous in severity, however, certain thresholds have been defined in studies that are clinically useful and predictive of poor outcome and easier to use clinically. These include an age of more than 65 years, forced expiratory volume in 1 s (FEV_1) <50%, and >3 exacerbations in the previous 12 months.

Another important consideration in choosing antibiotics for exacerbation is recent antibiotic use, especially within the past 3 months. Because of the recurrent nature of exacerbation and the high prevalence of co-morbid conditions in COPD, such antibiotic exposure is likely to be prevalent in COPD patients. In other respiratory infections such as pneumonia, recent antibiotic use leads to increased risk for harboring antibiotic resistant pathogens and therefore having a poor outcome following treatment. This phenomenon has been best described for *S. pneumoniae* among patients with community acquired pneumococcal pneumonia and recently also described for this pathogen among patients with COPD [72, 73]. Whether such selection for antibiotic resistant strains occurs among NTHI and *M. catarrhalis* after antibiotic exposure is not known, but is possible.

RISK STRATIFICATION APPROACH TO ANTIBIOTIC THERAPY IN ACUTE EXACERBATION

A risk stratification approach has been advocated by several experts for the initial empiric antibiotic treatment of exacerbations based on the risk factors discussed above as well as the *in vitro* and *in vivo* efficacy of antibiotics. Our current treatment algorithm is shown in Fig. 53.2 [14, 51, 61]. Once an exacerbation is diagnosed, the initial step in the algorithm is determination of the severity of the exacerbation. We use the Anthonisen criteria by defining single cardinal symptom exacerbations as mild, while the presence of two or all three of the cardinal symptoms defines moderate and severe exacerbations.

Mild exacerbations are initially managed with symptomatic treatment, including bronchodilators, antitussives and expectorants and antibiotics are with held. However, patients are counseled regarding the cardinal symptoms and if additional symptoms appear, then antibiotics are prescribed. If a moderate to severe exacerbation is diagnosed, the next important step is the differentiation of "uncomplicated" patients from the "complicated" patients. Uncomplicated patients do not have any of the risk factors for poor outcome. Complicated patients have one or more of the following risk factors for poor outcome: Age >65 years, FEV_1 < 50%, co-morbid cardiac disease and three or more exacerbations in the previous 12 months [14, 51, 61]. A threshold of four or more exacerbations in the previous 12 months has been used to define frequent exacerbations in previous studies and guidelines. However, current therapy of COPD with long acting bronchodilators and inhaled steroids has reduced overall frequency of exacerbations in this disease by about 25%. Therefore, we use a threshold of three or more exacerbations to define the complicated patient on contemporary COPD treatment.

In uncomplicated patients, antibiotic choices include an advanced macrolide (azithromycin, clarithromycin), a cephalosporin (cefuroxime, cefpodoxime, or cefdinir), doxycycline or trimethoprim/sulfamethoxazole. Amoxicillin (or ampicillin) is not an appropriate choice because of prevalent antibiotic resistance and the results of the meta-analysis discussed above. In complicated patients, our usual antibiotic choice is a respiratory fluoroquinolone (moxifloxacin, gemifloxacin, levofloxacin) with amoxicillin/clavulanate as an alternative.

Other important considerations in choosing antibiotics include exposure to antibiotics within the past 3 months. This exposure history should be elicited not only for respiratory infections, but includes antibiotics prescribed for any indication. The antibiotic chosen to treat the exacerbation should be from a different class of agents from the one prescribed within the past 3 months. For example, exposure to a macrolide in the past 3 months should lead to use of a cephalosporin in an uncomplicated patient. Similarly, prior use of a fluoroquinolone in a complicated patient should lead to use of amoxicillin/clavulanate.

Another important consideration in the complicated patients is a sub-group of these patients who are at risk for infection by *P. aeruginosa* and *Enterobacteriaceae* or have a documented infection by these pathogens [74]. These patients usually have very severe underlying COPD (FEV_1 < 35%), have developed bronchiectasis, are hospitalized (often requiring intensive care), or have been recently hospitalized or have received multiple courses of antibiotics. In such patients, empiric treatment with ciprofloxacin is appropriate. However, resistance among *P. aeruginosa* and

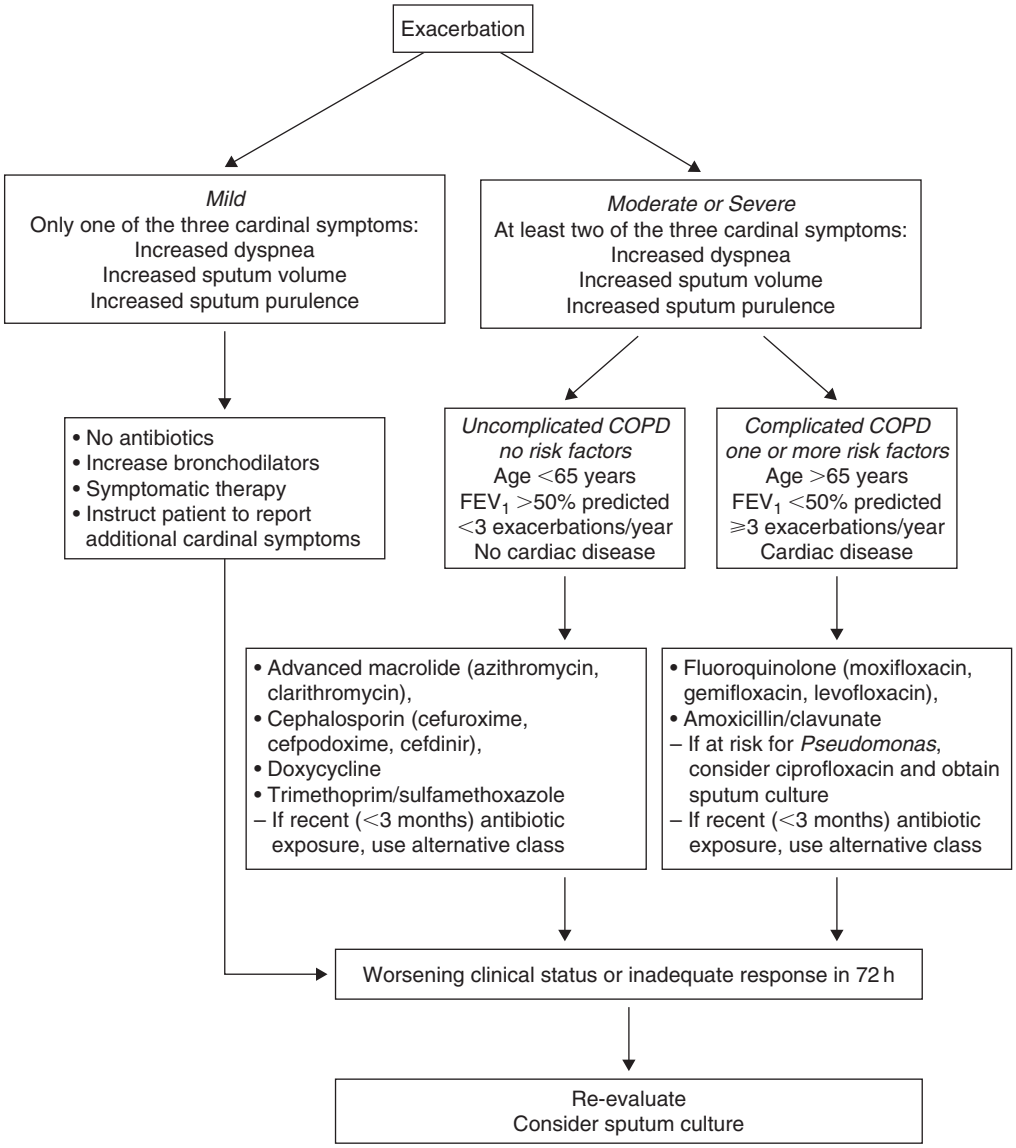

FIG. 53.2 Algorithm for antibiotic treatment of acute exacerbations of COPD.

the *Enterobacteriaceae* to the fluoroquinolones may compromise their efficacy. Therefore, in this sub-group of patients, we obtain a sputum (or tracheobronchial aspirate if intubated) culture to allow adjustment of antibiotics based on the *in vitro* susceptibility of pathogens isolated. Unless dictated by poor clinical response and *in vitro* antimicrobial susceptibility, we do not use combination or parenteral antibiotic therapy for *P. aeruginosa* as this approach has never been systematically examined and is of unproven benefit in exacerbations.

We instruct our patients to report to us any deterioration or lack of improvement at 48–72 h, because in this time frame clinical improvement should be apparent. In these patients who are failing initial empiric antimicrobial therapy, we re-examine the patient to confirm the diagnosis, consider sputum studies to ascertain for resistant or difficult to treat pathogens and treat with an alternative agent with better *in vitro* microbiological efficacy.

ALTERNATIVE APPROACHES TO ANTIBIOTIC THERAPY IN ACUTE EXACERBATION

Patients with COPD exacerbation often experience a change in the color of sputum from white or gray (mucoid) to yellow, green or brown (purulent). Purulence of sputum is related to the presence of myeloperoxidase, a product of neutrophil degranulation. Neutrophil degranulation is associated with bacterial infection, therefore sputum purulence

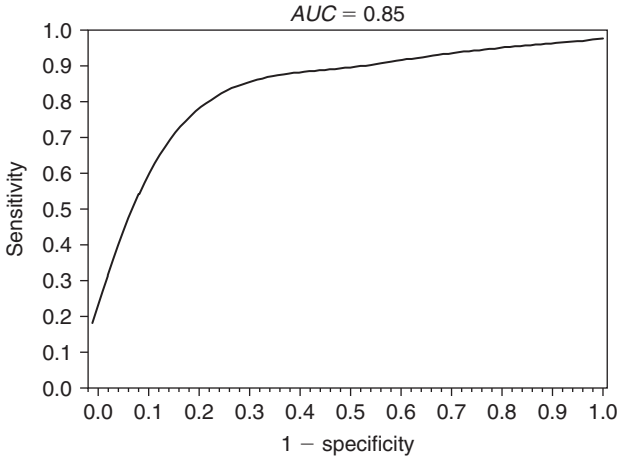

FIG. 53.3 Receiver operating characteristic (ROC) curve for distinguishing new bacterial strain exacerbations from exacerbations without new strains with levels of sputum TNF-α, sputum NE, and serum CRP at exacerbation included in the prediction model. The predictive values for each of the mediators in this model were sputum TNF-α: 0.32 ng/ml; sputum NE: 0.76nM; and serum CRP: 2.37 mg/l. AUC: Area under the ROC. Reproduced with permission from Ref. [18].

at exacerbation is a marker of bacterial infection, defined by quantitative cultures of sputum and bronchoscopic protected brush specimens [75, 76]. Presence of sputum purulence has been advocated as the sole determinant for antibiotic treatment of exacerbations. However, its accuracy and reproducibility as an indicator of bacterial infection is limited, and is likely to be even more so in clinical practice than in research studies [75, 76]. Often, patients have purulent sputum production even when stable, have intermittent purulent sputum production during exacerbation, or have not have observed the sputum color. Sputum purulence is one of the cardinal Anthonisen criteria, and we recommend it should be used in conjunction with other symptoms and other measures of risk stratification in antibiotic treatment of exacerbations (Fig 53.2).

Utilization of biomarkers to rapidly identify bacterial exacerbations and to guide antibiotic use is another potential approach in exacerbations. Several potential biomarkers have been identified in sputum and serum. The best studied biomarker of bacterial infection is serum procalcitonin level. In a recent study in patients hospitalized for exacerbations, antibiotic treatment was only recommended if the procalcitonin level was above a certain threshold. There was no difference in outcomes in spite of reduction in antibiotic use from 72% to 40% with procalcitonin guidance [77]. However, this approach needs to be validated in multi-center trials with varied populations before widespread application [78]. Furthermore, it needs to be tested in outpatients which represent the majority of exacerbations treated, where patients are not as closely supervised and other supportive care is less rigorous. Only a minority of patients received a fluoroquinolone in this study, which should have been the antibiotics of choice in these complicated patients. Therefore, the lack of effect of withholding antibiotics could have been related to their relative inefficacy in the first place. In this study, short-term goals as well as biologic goals of bacterial eradication and inflammation reduction as discussed above were also not recorded.

Other biomarkers that have been explored in COPD exacerbations include sputum TNF-α and NE and CRP (Fig. 53.3). Though individually they do not appear to discriminate between exacerbations, a combination of these parameters reliably distinguishes well-characterized bacterial exacerbations from others [18]. Additional studies are required to confirm and extend these observations.

Other important considerations in antibiotic prescribing are safety and tolerability of the agent, drug interactions and cost of treatment. It is important that cost of the antibiotic not be considered in isolation. Miravittles *et al.* have shown that exacerbations in which initial empiric treatment fails cost 10 times more than clinical successes [79]. The investigators estimated that the overall cost of care could be reduced by half with reduction in clinical failure rates by a third. Though not shown as yet in properly designed studies, it is likely that an appropriate and logical approach to antibiotic choice, as discussed above, would reduce clinical failure rates in exacerbations.

References

1. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease. A prospective study of 200 patients. *N Engl J Med* 280(8): 397–404, 1969.
2. Calverley PM *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 356(8): 775–89, 2007.
3. Soler-Cataluna JJ *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 60(11): 925–31, 2005.
4. Seemungal TAR *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 157: 1418–22, 1998.
5. Spencer S *et al.* Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 163: 122–28, 2001.
6. Spencer S, Jones PW. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax* 58(7): 589–93, 2003.
7. Kanner R *et al.* Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: Results from the lung health study. *Am J Respir Crit Care Med* 164(3): 358–64, 2001.
8. Donaldson GC *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 57(10): 847–52, 2002.
9. Hirschmann JV. Do bacteria cause exacerbations of COPD? *Chest* 118: 193–203, 2000.
10. Murphy TF, Sethi S, Niederman MS. The role of bacteria in exacerbations of COPD. A constructive view. *Chest* 118(1): 204–9, 2000.
11. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 117(5 Suppl 2): 398S–401S, 2000.
12. Anthonisen NR *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 106: 196–204, 1987.
13. Sethi S *et al.* Acquisition of a new bacterial strain and occurrence of exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 347(7): 465–71, 2002.
14. Global Initiative for Obstructive Lung Disease; Available from: www.goldcopd.com [cited].

15. Hurst JR *et al*. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 174(8): 867–74, 2006.
16. Pinto-Plata VM *et al*. Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. *Chest* 131(1): 37–43, 2007.
17. Sethi S *et al*. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 118(6): 1557–65, 2000.
18. Sethi S *et al*. Inflammatory profile of new bacterial strain exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 177(5): 491-7 (2008).
19. White AJ, Gompertz S, Stockley RA. Chronic obstructive pulmonary disease. 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* 58(1): 73–80, 2003.
20. Sethi S. New developments in the pathogenesis of acute exacerbations of chronic obstructive pulmonary disease. *Curr Opin Infect Dis* 17(2): 113–19, 2004.
21. Heckerling PS. The need for chest roentgenograms in adults with acute respiratory illness. *Arch Intern Med* 146: 1321–24, 1986.
22. Bhushan R *et al*. Antigenic characterization and analysis of the human immune response to outer membrane protein E of *Branhamella catarrhalis*. *Infect Immun* 65(7): 2668–75, 1997.
23. Mandell LA *et al*. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 37(11): 1405–33, 2003.
24. Kjaergard LL *et al*. Basophil-bound IgE and serum IgE directed against *Haemophilus influenzae* and *Streptococcus pneumoniae* in patients with chronic bronchitis during acute exacerbations. *APMIS* 104: 61–67, 1996.
25. Hiltke TJ, Sethi S, Murphy TF. Sequence stability of the gene encoding outer membrane protein P2 of nontypeable *Haemophilus influenzae* in the human respiratory tract. *J Infect Dis* 185(5): 627–31, 2002.
26. Wedzicha JA *et al*. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 84(2): 210–15, 2000.
27. Dev D *et al*. Value of C-reactive protein measurements in exacerbations of chronic obstructive pulmonary disease. *Respir Med* 92(4): 664–67, 1998.
28. Papi A *et al*. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 173(10): 1114–21, 2006.
29. Garcia-Aymerich J *et al*. Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: A time series analysis. *J Epidemiol Community Health* 54(1): 73–74, 2000.
30. Sunyer J *et al*. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: A 5-year study. *Am J Epidemiol* 137(7): 701–5, 1993.
31. Sunyer J *et al*. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: A case-crossover analysis. *Am J Epidemiol* 151(1): 50–56, 2000.
32. Ohtoshi T *et al*. Diesel exhaust particles stimulate human airway epithelial cells to produce cytokines relevant to airway inflammation *in vitro*. *J Allergy Clin Immunol* 101(6 Pt 1): 778–85, 1998.
33. Devalia JL *et al*. Effect of nitrogen dioxide and sulphur dioxide on airway response of mild asthmatic patients to allergen inhalation. *Lancet* 344(8938): 1668–71, 1994.
34. Rudell B *et al*. Bronchoalveolar inflammation after exposure to diesel exhaust: Comparison between unfiltered and particle trap filtered exhaust. *Occup Environ Med* 56: 527–34, 1999.
35. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest* 117: 380S–85S, 2000.
36. Eldika N, Sethi S. Role of Nontypeable *Haemophilus influenzae* in exacerbations and progression of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 12(2): 118–24, 2006.
37. Seemungal T *et al*. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 164(9): 1618–23, 2001.
38. Falsey AR *et al*. *Respiratory syncytial virus* infection in elderly and high-risk adults. *N Engl J Med*. 352(17): 1749–59 (2005).
39. Aaron SD *et al*. Adult cystic fibrosis exacerbations and new strains of *Pseudomonas aeruginosa*. *Am J Respir Crit Care Med* 169(7): 811–15, 2004.
40. Chin CL *et al*. *Haemophilus influenzae* from patients with chronic obstructive pulmonary disease exacerbation induce more inflammation than colonizers. *Am J Respir Crit Care Med* 172(1): 85–91, 2005.
41. Sethi S *et al*. Strain specific immune response to *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 169: 448–53, 2004.
42. Murphy TF *et al*. *Moraxella catarrhalis* in chronic obstructive pulmonary disease: Burden of disease and immune response. *Am J Respir Crit Care Med* 172(2): 195–99, 2005.
43. Veeramachaneni SB, Sethi S. Pathogenesis of bacterial exacerbations of COPD. *COPD: J Chronic Obstructive Pul Dis* 3: 109–15, 2006.
44. Johnston SL *et al*. Low grade rhinovirus infection induces a prolonged release of IL-8 in pulmonary epithelium. *J Immunol* 160(12): 6172–81, 1998.
45. White AJ *et al*. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 58(8): 680–85, 2003.
46. Aaron SD *et al*. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 348(26): 2618–25, 2003.
47. Anzueto A, Rizzo JA, Grossman RF. The infection-free interval: Its use in evaluating antimicrobial treatment of acute exacerbation of chronic bronchitis. *Clin Infect Dis* 28(6): 1344–45, 1999.
48. Miravitlles M, Murio C, Guerrero T. Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. DAFNE Study Group. *Eur Respir J* 17(5): 928–33, 2001.
49. Sethi S. Acute exacerbations of COPD: A "multipronged" approach. *J Respir Dis* 23(4): 217–55, 2002.
50. Bach PB *et al*. Management of acute exacerbations of chronic obstructive pulmonary disease: A summary and appraisal of published evidence. *Ann Intern Med* 134(7): 600–20, 2001.
51. Balter MS *et al*. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. *Can Respir J* 10(Suppl B): 3B–32B, 2003.
52. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. *Eur Respir J* 23(6): 932–46, 2004.
53. Sethi S. Bacteria in exacerbations of chronic obstructive pulmonary disease. Phenomenon or epiphenomenon?. *Proc Am Thorac Soc* 1: 109–14, 2004.
54. Sinus A, Allergy Health P. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis 2004. *Otolaryngol Head Neck Surg* 130(1): 1–45, 2004.
55. Saint S *et al*. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. *JAMA* 273(12): 957–96, 1995.
56. Ram FS *et al*. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*(2), 2006. , CD004403
57. Nouira S *et al*. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: A randomised placebo-controlled trial. *Lancet* 358(9298): 2020–25, 2001.
58. Allegra L *et al*. Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: A re-evaluation of previously published data of a placebo-controlled randomized study. *Pulm Pharmacol Ther* 14(2): 149–55, 2001.
59. Miravitlles M *et al*. The efficacy of moxifloxacin in acute exacerbations of chronic bronchitis: A Spanish physician and patient experience. *Int J Clin Pract* 55(7): 437–41, 2001.
60. Wood-Baker RR *et al*. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* (1), 2005, CD001288.
61. Sethi S, Murphy TF. Acute exacerbations of chronic bronchitis: new developments concerning microbiology and pathophysiology – impact

on approaches to risk stratification and therapy. *Infect Dis Clin North Am* 18(4): 861–82, 2004, ix.
62. Obaji A, Sethi S. Acute exacerbations of chronic bronchitis. What role for the new fluoroquinolones?. *Drugs Aging* 18(1): 1–11, 2001.
63. Dimopoulos G *et al*. Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: A meta-analysis of randomized controlled trials. *Chest* 132(2): 447–55, 2007.
64. Siempos II *et al*. Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: A meta-analysis. *Eur Respir J* 29(6): 1127–37, 2007.
65. Wilson R *et al*. A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin Ther* 24(4): 639–52, 2002.
66. Wilson R *et al*. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest* 125(3): 953–64, 2004.
67. Adams SG *et al*. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest* 117: 1345–52, 2000.
68. Dewan NA *et al*. Acute exacerbation of COPD: Factors associated with poor treatment outcome. *Chest* 117(3): 662–71, 2000.
69. Wilson R *et al*. Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. *Thorax* 61(4): 337–42, 2006.
70. Ball P *et al*. Acute infective exacerbations of chronic bronchitis. *Q J Med* 88: 61–68, 1995.
71. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 124(2): 459–67, 2003.
72. Vanderkooi OG *et al*. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis* 40(9): 1288–97, 2005.
73. Sethi S *et al*. Antibiotic exposure in COPD and the development of penicillin and erythromycin resistance in *Streptococcus pneumoniae*. San Francisco, CA: ICAAC, 2006.
74. Soler N *et al*. Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 157: 1498–505, 1998.
75. Stockley RA *et al*. Relationship of sputum color to nature and outpatient managment of acute exacerbations of COPD. *Chest* 117: 1638–45, 2000.
76. Soler N *et al*. Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax* 62(1): 29–35, 2007.
77. Stolz D *et al*. Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 131(1): 9–19, 2007.
78. Martinez FJ, Curtis JL. Procalcitonin-guided antibiotic therapy in COPD exacerbations: Closer but not quite there. *Chest* 131(1): 1–2, 2007.
79. Miravitlles M *et al*. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest* 121(5): 1449–55, 2002.