Antibiotics

Chapter 54

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After 60 years of availability of antibiotics, surprisingly little is known about their role in obstructive airway diseases. A review of antibiotic therapy will necessarily involve a discussion of the role of bacterial infection in asthma and chronic obstructive pulmonary disease. This chapter presents an appraisal of the bacterial pathogens causing infective exacerbations, trials of antimicrobial therapy, individual antimicrobial agents and guidelines for their judicious use both in asthma and COPD.

ASTHMA

A causal relationship between respiratory tract infection, especially viral infection and exacerbations of bronchial asthma is well established in the medical literature.[1] In early prospective studies by McIntosh et al.,[2] the relationship between exacerbations of wheezing and infection in hospitalized, previously diagnosed asthmatic children was investigated. A significant fraction (42%) was associated with viral respiratory infections, but not with pathogenic bacteria. Prospective studies on acute exacerbations of asthma in the adult population have suggested that approximately 10–20% of acute exacerbations may be attributable to acute viral infection. Berman and coworkers[3] convincingly failed to show an association between bacterial respiratory infection and asthma. Transtracheal aspirates from 27 adult asthmatic patients with acute exacerbations showed no correlation between bacterial isolates and asthma symptoms. This suggested that overt bacterial infection of the lower respiratory tract does not contribute to the exacerbation of asthma. However, studies of older children and young adults have shown that infection with atypical bacteria e.g. *Mycoplasma* and *Chlamydia* may be responsible for exacerbations. In these studies, rhinovirus was the most important pathogen, followed by influenza A virus, *Mycoplasma* and *Chlamydia*.[4–6] Several other studies have suggested a relationship between respiratory infections in infancy and development of asthma, although this hypothesis awaits more definite proof.

Mycoplasma

Mycoplasma pneumoniae infection is commonly seen in children and young adults, although it may occur in all age groups.[7,8] Seggev et al.[9] showed that 21% of adults hospitalized with asthma exacerbation had evidence of a recent infection with mycoplasma. The illness may start with non-respiratory symptoms such as headache and myalgias, and there is frequently pharyngitis and low-grade fever. A non-productive cough, which tends to be prolonged and severe, is most characteristic. The diagnosis is made based on clinical history and chest radiograph, which shows patchy segmental pulmonary infiltrates. The definitive diagnosis is made by serological studies, particularly a doubling titer in convalescence. Antibiotic therapy is most effective if given within a few days of onset. Erythromycin or tetracycline are equally effective, and treatment is continued for 2–3 weeks. As well as causing exacerbations of asthma, *M. pneumoniae* pneumonia in nonasthmatics may well induce bronchial hyperresponsiveness which may be transient or persistent.[10]

Chlamydia

The TWAR strain of *Chlamydia (Chlamydia pneumoniae)* has been shown to be a common cause of atypical pneumonia and is next in frequency to *Mycoplasma*.[11,12] This is an infection primarily of adolescents and adults. The clinical manifestations are similar to those caused by *M. pneumoniae*. The severity of illness can be quite variable. The diagnosis is difficult to make, as commercial serological tests are generally not available. Chest radiograph shows findings similar to *M. pneumoniae* infection. Several studies have suggested that *C. pneumoniae* infection may precipitate acute bronchospasm and, in addition, may also be a risk factor for the development of chronic bronchospasm. The treatment of *C. pneumoniae* infection requires further study, but erythromycin or tetracycline may be beneficial if given for 10 days or more.

COPD

Although a major cause of COPD is cigarette smoking, infectious organisms play several potential roles:[13,14] (Chapter 30).

- Childhood respiratory infections can predispose to the development of COPD in later life.[15,16]
- Infectious organisms can chronically infect the bronchi and small airways contributing to progressive lung destruction (vicious circle hypothesis).[17,18]
- Acute exacerbations of COPD caused by infection, result in considerable morbidity and are the leading cause of mortality in this disease.

Despite extensive research over the past few decades, our understanding of lower respiratory tract infection in COPD is incomplete. Evidence for the role of bacterial infection in COPD, individual antimicrobial agents and an evidence-based approach to treatment of infection are discussed in the following sections.

Normal microbial flora

Various aerobic and anaerobic bacteria inhabit the mucosal surfaces of the upper respiratory tract. These include

- *Neisseria* sp.,
- *Moraxella catarrhalis*,
- a variety of *Streptococcus* sp.,
- *Streptococcus pneumoniae*,
- *Hemophilus* sp.

A variety of anerobic bacteria are present around the teeth and gums. Enterobacteriaceae and *Pseudomonas* sp. are isolated in about 15% of pharyngeal swab cultures taken from normal subjects.[19,20]

The major bronchi and smaller conducting airways in normal humans are relatively sterile. In a study of 25 normal subjects, samples from multiple sites in the lower respiratory tract were obtained with a protected brush specimen. Most cultures contained bacteria (38 out of 52 specimens, or 73%) similar to those found in the nasopharynx, but the colony counts were often so low (none to five colonies per culture plate) that the cultures probably indicated upper respiratory tract contamination rather than true lower respiratory tract colonization.[21] The nasopharyngeal bacteria may be transiently aerosolized or aspirated into the lower respiratory tract but are removed by mucociliary clearance or cough. Pathogenic aerobic gram-negative rods do not inhabit the upper airways mucosa in normal persons, but may do with alterations in health status such as alcoholism, diabetes, residing in a health-care facility.[22] Subconscious aspiration of oropharyngeal secretions allows these microbes to enter the lower airways and alveoli and become a nidus for subsequent infection.

Airway colonization in chronic bronchitis

Pathogenic bacteria can be cultured from bronchial washings of some 82% of chronic bronchitics compared with normal bronchi which are nearly always sterile.[23] Routine sputum cultures obtained from patients with chronic bronchitis commonly contain nonencapsulated *H. influenzae* and *Strep. pneumoniae*. In most clinical series, one or both of these species have been recovered from approximately 30 to 50% of sputum specimens in patients with chronic bronchitis, and anaerobic bacteria were recovered in 17% of transtracheal aspirate specimens.[24]

Airway colonization with *H. influenzae* and *Strep. pneumoniae* is of uncertain significance. These bacteria tend to be present in sputum during quiescent intervals although the frequency of their recovery is increased during acute infectious episodes. Development of purulent sputum is not specifically correlated with the presence of one or the other of these bacteria in quantitative cultures.

THE DIAGNOSIS OF ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Clinical diagnosis

There is no universally accepted definition of an acute exacerbation of COPD (ACEB). AECB is basically a clinical diagnosis. A descriptive definition could be: "an acute, episodic deterioration superimposed on stable COPD with increased dyspnea, reduced daily performance, with our without changes in sputum volume and color, coughing, or body temperature; and or alterations in mental status".[17,18] The three cardinal symptoms (**Table 54.1**) (Winnipeg Criteria)[25] are

- increased dyspnea,
- increased sputum purulence,
- increased sputum volume.

These features should be present without an objectively documented cause such as pneumonia, congestive heart failure, myocardial ischemia, upper respiratory tract infection, recurrent aspiration, pneumonia and pulmonary embolism. These conditions may resemble an acute exacerbation and need to be excluded.

Laboratory diagnosis of AECB

Microbiological data may play a role in diagnosis and management but must be interpreted with caution. One problem

Table 54.1 Classification of exacerbations

Type	Characteristics
1	Increased dyspnea, sputum volume and sputum purulence (all 3 symptoms present)
2	2 of the above 3 symptoms present
3	1 of the above symptoms present + at least 1 of the following: upper respiratory tract infection in the last 5 days, fever, increased wheezing and increased cough

is that pathogenic bacteria can be cultured from respiratory secretions in as many as 80% of patients with stable chronic bronchitis, therefore, bacterial colonization complicates the laboratory diagnosis of bacterial infection.

Sputum gram stain
The sputum gram stain has been advocated as a means of objectively demonstrating an increase in bacterial flora and bronchial inflammation. In one study, Baigelman et al.[26] compared more than 1000 sputum gram stains from patients with chronic bronchitis during stable states, acute bacterial infections, acute allergic exacerbations, and recovery from acute bacterial exacerbations. The results showed that fewer than two bacteria per oil-immersion field were found in stable patients, while during exacerbations the sputum revealed 12 organisms per oil-immersion field resembling *H. influenzae*, eight organisms resembling *Strep. pneumonia* or 18 organisms resembling *M. catarrhalis*. Over 99% of patients with chronic bronchitis without clinical evidence of infection fell below these thresholds. These findings suggest that an upper limit may be set for the numbers of micro-organisms seen on a gram stain of sputum from patients with COPD in the absence of a bacterial infection. Some clinical trials have incorporated the gram stain as a means of distinguishing bacterial from nonbacterial causes of acute exacerbation. Despite its potential, sputum gram stain does not alter therapy and is not currently recommended as a routine test.

Sputum culture
The routine sputum culture is less useful than the gram stain and is often misleading. Studies examining sputum cultures before, during, and after bacterial exacerbations have correlated poorly with clinical parameters and gram stain results.[26,27] Gram-negative bacilli have often been recovered in sputum culture even when they are absent on gram stain, and clinical recovery has occurred even without specific gram-negative antibiotic therapy. In one study, more than 50% of sputum cultures remained positive long after clinical recovery.[28] The sputum culture may be contributory and should be considered when there is:

- failure of initial antibiotic therapy,
- patients with chronic bronchial sepsis requiring more than four courses of antibiotic therapy per year,
- severe illness or suspected pneumonia.

Viral studies
Viruses apparently do not play an important role in causing acute exacerbations. Therefore, virological stains, cultures and antibody assays are not routinely recommended in the management of chronic bronchitis because of the expense and relatively low yield. Rapid antigen detection has lowered the turnaround time for identifying respiratory viruses, but the value of these tests in AECB has not been established. Recently chemotherapeutic agents for influenza have become available. The guidelines for use of anti-influenza agents recommend early use of these agents based on clinical suspicion and not laboratory confirmation, and COPD patients should probably be treated in the same manner.

Chest radiograph
Chest X-rays are not routinely recommended in mild to moderate exacerbations, as there is usually no change from baseline. Chest radiography should be performed if the patient has high fever, new abnormalities on auscultation, or is severely ill as characterized by worsening hypoxia, hypercapnia or right heart failure.

ROLE OF BACTERIAL INFECTION

COPD is characterized by periodic exacerbations and acute respiratory infection was the most common cause of death in a prospective study of patients with COPD.[29] The role of infection in acute exacerbation of chronic bronchitis is, however, somewhat controversial. Antibiotics are frequently prescribed to these patients but efficacy of this treatment was questioned by Tager and Speizer.[30] Several investigators have found increased numbers of bacteria and neutrophils in the sputum during exacerbations.[31–33] In some studies[34] *M. pneumoniae* has been isolated in 1 to 10% of patients with acute infections. Bacteria may be the primary cause of the exacerbations; alternatively, they may act as secondary invaders after acute viral or mycoplasma infection. However, evaluating the role of bacterial infection in exacerbations has been a difficult task for a variety of reasons. As the upper airways of many patients with COPD are colonized by *H. influenzae, Strep. pneumoniae* and *M. catarrhalis*, the expectorated sputum during exacerbations may be inconclusive.

Serologic studies
A causal relationship between bacterial infection and acute exacerbation can be inferred by the appearance of an acute antibody response in serum to these bacteria. Documenting a serological response to an organism may demonstrate existence of infection with that organism, but these studies have shown conflicting results. Some have shown no difference between patients with chronic bronchitis and control subjects, other studies have revealed higher titers of antibody to *H. influenzae*,[35] in the serum of patients with chronic bronchitis. However, there was no relationship of titers to exacerbations.[36] Such studies generally used the whole organism preparations of unrelated strains as the antigen for serologic studies, and therefore measured a mixture of antibodies to a mixture of antigens. Future studies may utilize antibody response to more specific surface antigens of bacteria to establish the importance of bacterial infection in COPD.

Trials of antibiotic therapy in acute exacerbation
Another approach to assessing the role of bacterial infection in exacerbations of COPD is to consider the effect of antibiotics on the clinical response (**Figs 54.1** and **54.2**). A positive

response to a specific antibiotic prescribed for an exacerbation by a specific organism would provide evidence of a pathogenic role for the bacteria. In a landmark study, Anthonisen and co-workers[25] demonstrated, for the first time, that patients could be stratified according to the symptoms to predict a response to antimicrobial therapy. In patients with at least two of the three cardinal symptoms of acute exacerbation (increased sputum purulence, increased sputum volume and increased dyspnea), broad-spectrum antibiotics (amoxicillin, trimethoprim-sulfamethoxazole, doxycycline) led to improved clinical outcomes, fewer therapeutic failures and a more rapid rate of lung function recovery than did placebo. Overall, the length of illness was 2 days shorter for the antibiotic-treated group as compared with the placebo group. A meta-analysis by Saint et al.[37] showed that there were benefits from antibiotic therapy for exacerbations as compared with placebo (**Fig. 54.3**). In nine prospective randomized trials conducted from 1957 to 1992, the overall effect size (defined as the standard deviation of benefit with therapy versus placebo for the effect measured) favored antibiotics (0.22), and seven of the nine trials showed a benefit for antibiotics. A beneficial effect of antibiotics was demonstrated in studies that included the greatest number of patients and the patients with more severe disease. The demonstration of therapeutic efficacy of antibiotics in exacerbations provides evidence of a pathogenic role for bacteria in exacerbations. Design flaws in the earlier studies, such as small numbers of study patients, unclear selection criteria, uncertain microbiology, nonstandard evaluation criteria and lack of stratification of patients, may account for the discrepancy of outcomes in these studies.[38]

Although antibiotics provide benefit compared with placebo, further studies are required to assess different classes of antibiotics in specific clinical situations. Several studies have suggested that patients with different severities of chronic lung disease have exacerbations with different organisms. Eller et al.[39] found that if patients with better lung function were compared with those with worse lung function (based on FEV_1), the bacteriology shifted from pneumococcus and *H. influenzae* to more complex organisms such as Enterobacteriaceae and Pseudomonas species. Similarly, Miravitlles et al.[40] found that *H. influenzae* and *Pseudomonas aeruginosa* were more common in patients with FEV_1 values of less than 50% of predicted. The patients with worse lung function suffered from more frequent exacerbations and were given repeated antibiotic therapy which likely led to alteration of airway microbial flora.

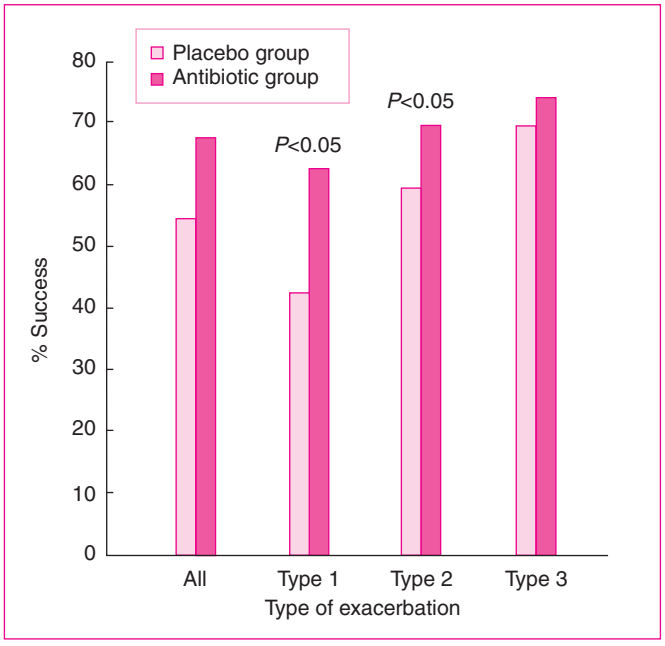

Fig. 54.1. Rate of successful response to antibiotics or placebo in AECB stratified according to the type of exacerbation. Reproduced from Reference 25, with permission.

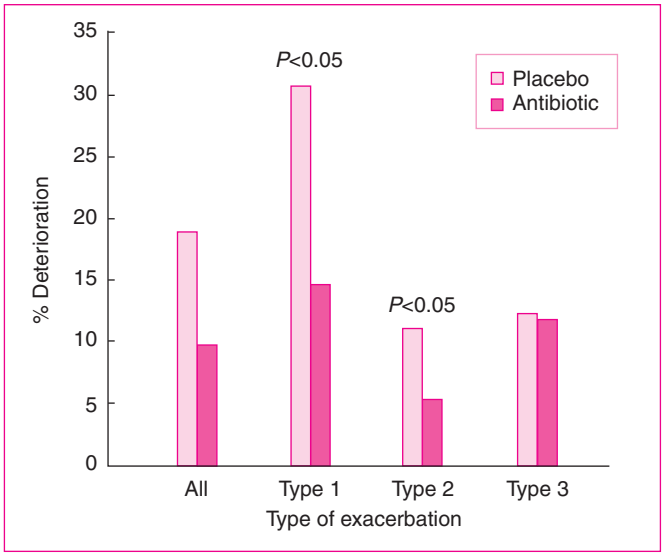

Fig 54.2. Rate of deterioration while on antibiotic or placebo in AECB stratified according to the type of exacerbation. Reproduced from Reference 25, with permission.

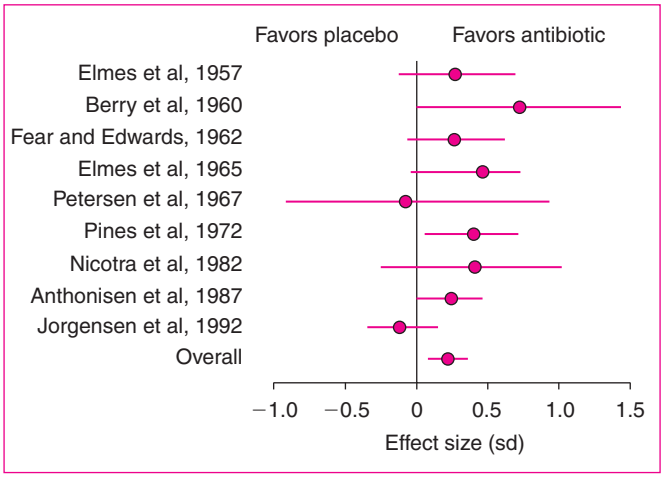

Fig 54.3. Overall benefit of antibiotics in the treatment of acute exacerbation of chronic bronchitis. Reproduced from Reference 37, with permission.

Pathogens

Acute exacerbations of COPD are most often caused by infections although other factors may also cause increased dyspnea. Common infectious etiological organisms will be briefly discussed (**Table 54.2**).

Viruses

Studies of longitudinal cohorts of COPD patients have examined the role of viruses in acute exacerbations with serial serology and viral cultures of upper and lower respiratory tract secretions. A four-fold increase in titer or a positive viral culture was seen in association with one trial of exacerbations.[41,42] The specific viruses and proportion of exacerbations caused by each of these are detailed in Table 54.1. More recently, Soler and associates[43] determined the etiology of 50 exacerbations of COPD that required intensive care admission. Adequate serological samples were available in 38 of these episodes. Viral infection was associated with six (15.8%) exacerbations, influenza virus in five and respiratory syncytial virus in one episode. In three of the five influenza infections, a concomitant bacterial pathogen was present. This study suggests that in severe exacerbations, viral infection is less important and these are often complicated by a bacterial infection.

Atypical bacteria

As these organisms are difficult to culture, serological testing has been used to investigate the role of *Chlamydia* and *Mycoplasma* species in acute exacerbations of COPD. *Mycoplasma* infection has been seen only rarely in this setting. *C. pneumoniae* infection is associated with 5 to 10% of exacerbations. In the study presented by Soler and associates[43] of severe exacerbations requiring intensive care, *C. pneumoniae* infection was present in seven (18%) of 38 cases, although a concomitant bacterial pathogen was present in two of these patients.

Bacteria

Sputum cultures are positive for aerobic bacteria in about half of the exacerbations of COPD.[44] The predominant pathogens and their relative frequency are listed in Table 54.1. Three studies have used bronchoscopic sampling of the lower respiratory tract during exacerbation to avoid oral contamination of the sample. Fagon and colleagues[45] studied 54 patients with COPD requiring mechanical ventilation for respiratory failure due to AECB. Bronchoscopy with a protected specimen brush was performed within 24 hours of intubation, before empiric antibiotic therapy. The findings were similar to that of sputum culture. Of the 44 bacterial species isolated, *H. parainfluenzae* was the most common pathogen (11/44), followed by *Strep. pneumoniae* (7/44), nontypeable by *H. influenzae* (6/44), and *M. catarrhalis* (3/44). A variety of other gram-negative (8/44) and gram-positive (9/44) bacteria were also present as noted in Table 54.1.

Monso and co-workers[46] studied two groups of moderately severe COPD patients with bronchoscopic protected specimen brush (PSB) culture in outpatient settings. Forty

Table 54.2 Pathogens associated with acute exacerbations of COPD

Pathogen class	Frequency of exacerbations (%)	Specific organism	Proportion of pathogen class (%)
Viruses	30–50	Influenza A and B	30–40
		Parainfluenzae 1, 2 and 3	20–30
		Rhinovirus	15–25
		Coronavirus	10–20
		Adenovirus	5–10
		Respriatory syncytial Virus	5–10
Atypical bacteria	5–10	*C. pneumoniae*	90–95
		M. pneumoniae	5–10
Bacteria	50	Nontypeable *H. influenzae*	40–60
		S pneumoniae	15–30
		M.catarrhalis	15–30
		H. parainfluenzae	Isolated frequently but pathogenetic significance unknown
		P. aeruginosa and *Enterobacteriaceae* (*E. coli, Klebsiella*)	Isolated in severe COPD and in recurrent exacerbations

patients had stable COPD, and 29 patients experienced an acute exacerbation. In the stable group, 25% of PSB cultures isolated bacterial pathogens (10^3 CFU/ml) compared with 51.7% of culture-positive samples in the exacerbation group. Nontypeable *H. influenzae* was the most common bacterial pathogen in both groups. A study by Soler et al.[43] demonstrated that 21 of 50 (42%) patients had positive cultures on bronchoscopic samples during an acute exacerbation. In their study, there was a remarkably high incidence of *P. aeruginosa* and other gram-negative bacilli, these were isolated in (14/50) 28% of patients.

Based on the remarkably consistent results of these studies, one can conclude that bacteria are recovered in the distal airways in exacerbations of COPD in 50% of the cases and may be responsible for the clinical symptoms observed.

VICIOUS CIRCLE HYPOTHESIS

A considerable body of evidence in the medical literature highlights the importance of bacterial infection and the usefulness of antimicrobial therapy. This evidence has been used to construct the vicious circle hypothesis (**Fig. 54.4**).[54] According to this hypothesis, initiating factors such as cigarette smoke lead to impaired mucociliary clearance in the airways. This is followed by bacterial colonization and release of bacterial products such as lipooligosaccharides, causing direct damage to airway epithelium and inhibiting mucociliary activity. The neutrophils are attracted by chemotactic bacterial factors released by resident phagocytes, complement components, and directly by chemotactic bacterial products. A destructive, cytokine-mediated inflammatory host response is triggered, which enhances the elastolytic activity in the lung, ultimately causing further airway damage. The changes in the host defense mechanisms predispose to further bacterial infection, thereby establishing the self-perpetuating vicious circle of host and bacterial-mediated respiratory tract damage. Previous studies could not demonstrate a role for respiratory infections in the progression of airways obstruction.[55–57] However, Kanner et al.[58] have recently demonstrated that more rapid decline in lung function occurred with more frequent respiratory tract infections. They found that smokers with mild to moderate COPD suffered from increased numbers of lower respiratory infections as compared with quitters. In addition, one infection per year was associated with an increase in decline of FEV_1 of about 7 mL per year.[59] Recently, Seemungal et al.[60] prospectively followed a cohort of 101 patients with moderate to severe COPD over $2\frac{1}{2}$ year period. In 7.1% exacerbations, recovery of lung function (PEFR) had not occurred in 91 days.[60] Although this model of pathogenesis is popular, more clinical studies and applications of newer techniques are required to study these proposed mechanisms.

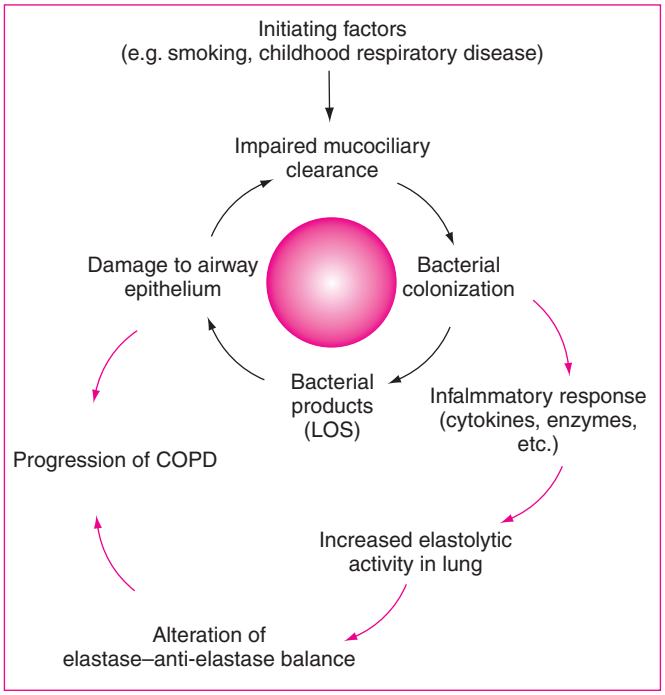

Fig 54.4. "Vicious Circle Hypothesis": The changes in the host defense mechanisms predispose to repeated bacterial infections, thereby establishing the self-perpetuating vicious circle of host and bacterial-mediated respiratory tract damage. Reproduced with permission.

MANAGEMENT OF INFECTIONS IN COPD EXACERBATION

Preventative measures

Vaccines

Annual influenza vaccine reduces morbidity and mortality due to influenza in the elderly by 50%[53] and should be given to patients with COPD. The beneficial effect is thought to be the result of prevention of airway epithelial damage predisposing the patient to subsequent bacterial infection.[61] The beneficial effect of pneumococcal vaccine in patients with chronic bronchitis has not been firmly established. However, the current recommendations are that patients with COPD receive pneumococcal vaccine at least once in their life and should have one repeat at 5 years.[62] It is a prudent policy to follow because of the low cost and few side-effects of the vaccine.

Prophylactic antibiotics

Only a limited number of studies have examined the role of prophylactic antibiotics in COPD.[63,64] In one study of patients with moderate COPD no benefit from prophylactic antibiotics was found with respect to the frequency of exacerbations or to the rate of decline of FEV_1 over 4 or 5 years.[65] In another large study, no benefit from antibiotic prophylaxis during the winter months was observed.[66] The prophylactic use of antibiotics in chronic bronchitis is not supported by clinical trials and is not indicated. Such therapy runs the risk of increasing antimicrobial resistance in the bacterial pathogens responsible for infections.[65,66]

CHEMOTHERAPEUTIC AGENTS USED IN COPD EXACERBATION

There are a large number of antibiotics available to cover the spectrum of bacteria-causing COPD exacerbations. It is useful to classify them as first- and second-line agents. First-line agents are older, cheaper, and available as generics, require multiple doses per day, have a limited spectrum of efficacy and high rates of antimicrobial resistance. Second-line agents are newer, more expensive, require single or twice daily dosing, and have a wider spectrum and lower rates of antimicrobial resistance. They also tend to attain higher levels in bronchial mucosa and sputum, although this has not been established to be a definite advantage.

Antimicrobial resistance

The last two decades have seen an alarming increase in resistance to commonly used first-generation anti-microbial agents among nontypeable *H. influenzae*, *Strep. pneumoniae*, and *M. catarrhalis* (**Table 54.3**). In a North American survey conducted in 1997, 33.5% of nontypeable *H. influenzae* isolates and 92.2% of *M. catarrhalis* isolates produced β-lactamase. In addition, 16.2% of the nontypeable *H. influenzae* isolates were resistant to co-trimoxazole.[67] In a similar North American survey, 43.8% of the *Strep. pneumoniae* isolates were penicillin resistant, with 27.8% displaying intermediate-level and 16% displaying high-level resistance.[68] These resistant *Strep. pneumoniae* isolates demonstrated decreased susceptibility to several other antibiotics including cephalosporins, macrolides, tetracyclines, and trimethoprim–sulfamethoxazole. Resistance rates in Europe vary widely, but in mainland Spain, 31% of *H. influenzae* isolates were resistant to ampicillin, 16.7% to chloramphenicol, 15% to erythromycin (27.9% in France), 17.2% to tetracycline and 41.3% to co-trimoxazole.[69] Most isolates of *M. catarrhalis* produce beta-lactamase (79% of UK isolates). The penicillin resistance among *Strep. pneumoniae* is increasingly worldwide, reaching approximately one-third of all isolates in Spain, 26% in France and 15–20% in the United States.[70–72] A substantial proportion of bacterial exacerbations of COPD may be caused by pathogens resistant to the traditional antibiotics such as amoxicillin, co-trimoxazole, and tetracycline. Therefore, local patterns of antimicrobial resistance should be considered in choosing empiric therapy for this common mucosal infection.

Pharmacokinetic considerations

There are profound differences in the penetration of different antibiotics into the tissues and secretions of the respiratory tract, and the implications of these factors for the treatment of exacerbations of chronic bronchitis deserve consideration. Outcome of antimicrobial therapy may depend to a certain extent on the sputum and bronchial mucosal concentration of these agents.[73] In general, β-lactams attain only 5 to 25% of the serum concentration in sputum and bronchial secretions. Erythromycin and tetracyclines achieve a ratio of 50% or more, while fluoroquinolones produce concentrations in bronchial secretions that are 88 to 200% of serum concentrations.[74,75] Azithromycin is concentrated 50- to 100-fold in sputum as well as bronchial secretions.[76] However, the clinical significance of good penetration into sputum and bronchial tissue has not been demonstrated in AECB.

Antimicrobial agents

Tetracylines

Many of the original trials of antibiotic therapy utilized tetracyclines. Studies performed in the 1960s and 1970s demonstrated that tetracycline therapy was more effective than placebo in milder infections, while derivatives were no more effective than tetracycline itself. Tetracyclines can be used in AECB because they are active against *H. influenzae* and atypical pathogens, but there have been reports of increasing resistance against pneumococci.[77]

Oral penicillins and cephalosporins

Although early placebo-controlled studies did not show a definite advantage for therapy with ampicillin, amoxicillin has been a widely used agent for management of AECB.[78] Oral penicillins and cephalosporins are the drugs of choice

Table 54.3 Important bacterial pathogens in acute exacerbation of chronic COPD

Author Ref. year	Number of isolates	Portion of total isolates		
		H. influenzae	*M. catarrhalis*	*S. pneumoniae*
Davies et al.[47] 1986	127	58.5	15	16.5
Borran et al.[48] 1990	60	43.3	3.3	25
Chodosh[49] 1992	214	37.9	22.4	22.4
Aldons[50] 1991	53	70	13	15
Bachand[51] 1991	8	30	10.7	21.4
Lindsay et al.[52] 1992	398	49.7	19	17
Neu et al.[53] 1993	84	46.4	28.6	25.0

in patients with mild to moderate exacerbations in countries where resistance among *H. influenzae* and pneumococci remains at low levels. Despite their relatively poor activity and suboptimal respiratory pharmacokinetics, cephalexin and cefaclor have been extensively used for the management of AECB. The newer cephalosporins, cefprozil, and cefixime may have some advantages such as activity against resistant pneumococci, but have not been proven to be superior to amoxicillin,[79,80] when organisms were fully sensitive to both agents.

Amoxicillin–clavulanic acid
The addition of clavulanic acid makes the combination resistant to bacterial beta-lactamases, an important concern in patients with AECB. Although most studies of patients with lower respiratory tract infection have shown it to be equivalent to standard comparable agents.[81] An overview of the data from clinical trials demonstrates this to be a valuable agent for infections caused by *H. influenzae* and *M. catarrhalis* even though the degree of penetration of bronchial mucosa is variable.[82] Comparison with cefexime and ciprofloxacin showed greater clinical success but no significant difference in eradication rates.[83]

Trimethoprim–sulfamethoxazole
Although very popular in the 1970s and 1980s trimethoprim–sulfamethoxazole (TMP–SMX) potential for resistance and the increasing availability of safer agents have resulted in the decline of the use of this antibiotic. In older studies, comparisons with oral cephalosporins generally showed equivalent efficacy.[84] Recent studies have shown increased resistance of common respiratory pathogens to TMP-SMX in Europe and the United States, making this antibiotic less useful in the treatment of AECB. Penicillin-resistant pneumococci have an 80 to 90% likelihood of being resistant to TMP-SMX.[85]

Newer macrolides and azalides
Erythromycin has poor activity against *H. influenzae* (MIC 4 to 8 mg/L) and cannot be considered one of the drugs of choice for AECB. Azithromycin and clarithromycin have improved pharmacokinetics and antibacterial activity.[86] A 3-day regimen of azithromycin is clinically and microbiologically equivalent to a 10-day course of co-amoxiclav.[87] The significant advantages of azithromycin are enhanced potency against *H. influenzae,* once daily administration, an abbreviated 4-day course, and perhaps a reduced frequency of relapse during extended follow-up.[88,89] Clarithromycin has only intermediate activity against *H. influenzae* but synergy with a metabolite reduces the overall MIC to around 1 mg/L so thus in the therapeutic range.[90] Clinical studies of clarithromycin involving 7- to 14-day regimens in patients with mild to moderate infections have shown equivalence with ampicillin.[81] A direct comparison with azithromycin and clarithromycin showed no difference in response rates or adverse reactions.[91]

Fluoroquinolones
These agents penetrate well into the respiratory secretions and bronchial mucosa, but clinical relevance is uncertain. Fluoroquinolones are highly active against β-lactamase producing *H. influenzae* and *M. catarrhalis*, and therefore are effective in AECB. Despite a relatively high inhibitory concentration against *Strep. pneumoniae,* ciprofloxacin demonstrated clinical efficacy similar to amoxicillin, clarithromycin, and cefuroxime.[92] A variety of newer fluoroquinolones with longer half-lives has become recently available. The newer agents have enhanced activity against pneumococci compared with ciprofloxacin, thus making them an effective therapy in the management of moderate to severe exacerbations.

An ideal antibiotic
Newer antimicrobial agents have been studied to show equivalence with regimens that have already been approved. Consequently, there are few data showing that one agent is better than the other, because trials have not been designed with this goal in mind. However, there are several theoretical characteristics that would be desirable in selecting an antibiotic:

- activity against the most common and most likely etiological pathogens;
- resistance to destruction by β-lactamase;
- good penetration into the sputum and bronchial mucosa;
- a mechanism of action that does not add to inflammatory events in the airway;
- easy to take, with few side-effects;
- cost effective.

RISK STRATIFICATION AND TREATMENT GUIDELINES

Patients with COPD who have poor ventilatory reserve may develop acute respiratory failure as a consequence of an exacerbation. For this reason, it is prudent to identify this high-risk population for whom an aggressive approach can be applied to prevent deterioration. Mechanical ventilation is required in 20 to 60% of these patients and hospital mortality of 10 to 30% has been reported.[93] Factors reported to be associated with increased hospital mortality include age greater than 65 years, comorbid respiratory and nonrespiratory organ dysfunction, and admission to an intensive care unit.[94] The other factors linked to poor survival are severity of airways obstruction, performance status, and use of oral corticosteriods.[95] Following antibiotic therapy for AECB, factors predicting failure of initial therapy (returning to the physician for more treatment), or the need for hospitalization include co-existent cardiopulmonary disease and the number of previous exacerbations. The presence of cardiovascular comorbidity combined with more than four exacerbations in the previous year has a sensitivity of 70% and specificity of 37% in predicting treatment failure.[96] Therefore, advanced age, significant impairment of lung

function, poor performance status, comorbid conditions, and history of previous frequent exacerbations requiring systemic corticosteroids characterize a high-risk group. Because the cost of failure is high, an aggressive approach to treatment of this high-risk group may improve outcome. Therapy with first-line antibiotics fails in 13% to 25% of exacerbations.[97] Therapeutic failure increases cost of care due to extra physician visits, further diagnostic tests and repeated courses of antibiotics, more hospitalizations, and absence from work. Stratification of patients into risk categories may allow physicians to select appropriate antimicrobial therapy to prevent these consequences in an era of increasing resistance to standard therapy.

Several stratification schemes have been proposed to improve initial microbial selection. In 1991, Lode[98] proposed that patients be divided into three groups:

- first-degree patients have a relatively short duration of chronic bronchitis with a normal lung function and are infected with the usual pathogens *H. influenzae* and *Strep. pneumoniae*. These patients could be treated with oral amoxicillin, doxycycline, co-trimoxazole or a macrolide.
- Second-degree patients have a longer history of COPD, several exacerbations each year and impaired lung function. Use of oral cephalosporins, amoxicillin–clavulanic acid, or quinolones was proposed.
- The third-degree patients were described as hospitalized patients with significant comorbidity, prolonged history of COPD and severe functional impairment. These patients have frequent infections with gram-negative pathogens or resistant *H. influenzae* and *Strep. pneumoniae*. In hospitalized patients, therapy with intravenous cephalosporins or quinolones is suggested, followed by oral therapy with cephalosporins, amoxicillin–clavulanic acid, or quinolones.

In 1994, Balter et al.[99] suggested that patients should be categorized into five groups.

- Group 1: acute simple bronchitis likely viral induced with no previous respiratory problems. Antibiotic therapy was not recommended for this group unless symptoms persisted for more than 1 week.
- Group 2: simple chronic bronchitis with minimal or no impairment of pulmonary function and without any risk factors. Treatment was recommended for patients who have type 1 and type 2 exacerbations (**Table 54.4**). Any antibiotic from the list of first-line agents was suggested as consequences of treatment failure would be few.
- Group 3: moderate to severe chronic bronchitis and other risk factors. Treatment with antibiotics directed towards β-lactamase producing strains of *H. influenzae* and *M. catarrhalis* was suggested.
- Group 4: similar to group 3 but with other significant comorbid illness such as congestive heart failure, diabetes mellitus, chronic renal failure or chronic liver disease, the treatment guidelines were similar to group 3 patients.

Table 54.4 Antibiotics used in the treatment of acute exacerbations of COPD

First-line antibiotics	Second-line antibiotics
Aminopenicillins	2nd generation cephalosporins
Ampicillin	Cefaclor
Amoxicillin	Cefuroxime axetil
Pivampicillin	
Bacampicillin	3rd generation cephalosporins
	Cefixime
Tetracylines	
Tetracycline	Amoxicillin–clavulanic acid
Doxycycline	
Minocycline	Newer macrolides
	Clarithromycin
Trimethoprim–sulfamethoxazole	Azithromycin
	Fluoroquinolones
	Ciprofloxacin
	Levofloxacin
	Moxifloxacin

- Group 5 patients: with bronchiectasis, and sputum cultures were recommended to target therapy to the identified pathogen.

A SIMPLE CLASSIFICATION SCHEME

The authors propose a simpler risk stratification scheme modified from the publications of Wilson,[100] Grossman[101] and others[102] (**Table 54.5**). People with no underlying lung disease are not included in this classification as the etiology of acute bronchitis is likely viral, and the disease is self-limited. If the symptoms are persistent, macrolide or doxycycline could be prescribed to eradicate potential infection with *M. pneumoniae* or *C. pneumoniae*.

- Patients with simple AECB have only mild to moderate impairment of lung function (FEV_1 > 50% predicted), and have less than four exacerbations per year. Common organisms found are *H. influenzae*, *Strep. pneumoniae* and *M. catarrhalis*, although viral infections often precede bacterial superinfection. Treatment with a β-lactam is usually successful, and the prognosis is excellent. Since the consequences of treatment failure are few, any first-line antimicrobial agent (Table 54.3) can be used.
- Patients with complicated AECB have poorer underlying lung function (FEV_1 < 50% predicted) or with concurrent significant medical illness (e.g. diabetes mellitus, congestive heart failure, chronic renal disease, chronic liver disease) and/or experience four or more exacerbations per year. *H. influenzae*, *Strep. pneumoniae* and *M.*

Table 54.5 Risk stratification of patients with acute exacerbations of COPD

Classification	Characteristics
Simple chronic bronchitis	Patients with chronic bronchitis FEV_1 > 50% predicted Experience <4 exacerbations/year No comorbid illness
Complicated chronic bronchitis	Patients with chronic bronchitis FEV_1 < 50% predicted Experience >4 exacerbations/year Comorbid medical illness: congestive heart failure, diabetes mellitus, chronic renal failure, or chronic liver disease
Chronic bronchial sepsis	Complicated chronic bronchitis + frequent hospitalizations and continuous sputum throughout year

catarrhalis continue to be the predominant organisms. However, since initial treatment failure has major implications, treatment with medications directed towards resistant organisms should be used. The second-line agents such as quinolones, amoxicillin–clavulanic acid, second- or third-generation cephalosporins or the second-generation macrolides are recommended.

- Occasional patients with chronic bronchial sepsis are characterized by repeated exacerbations and often require multiple hospitalizations with respiratory failure. They have poor lung function, are at risk for *Pseudomonas* infection, and have a poor prognosis. Therefore an aggressive therapeutic approach can be justified. Empirical therapy using a quinolone with anti-pseudomonal activity and the use of sputum culture in this group of patients to identify possible resistant organisms may be employed.

All the proposed classification systems although not prospectively tested in clinical trials, place emphasis identifying high-risk populations so that they can be treated from onset, with antibiotics targeted to the potential resistant organisms in order to reduce the risk of treatment failure (**Fig. 54.5**).

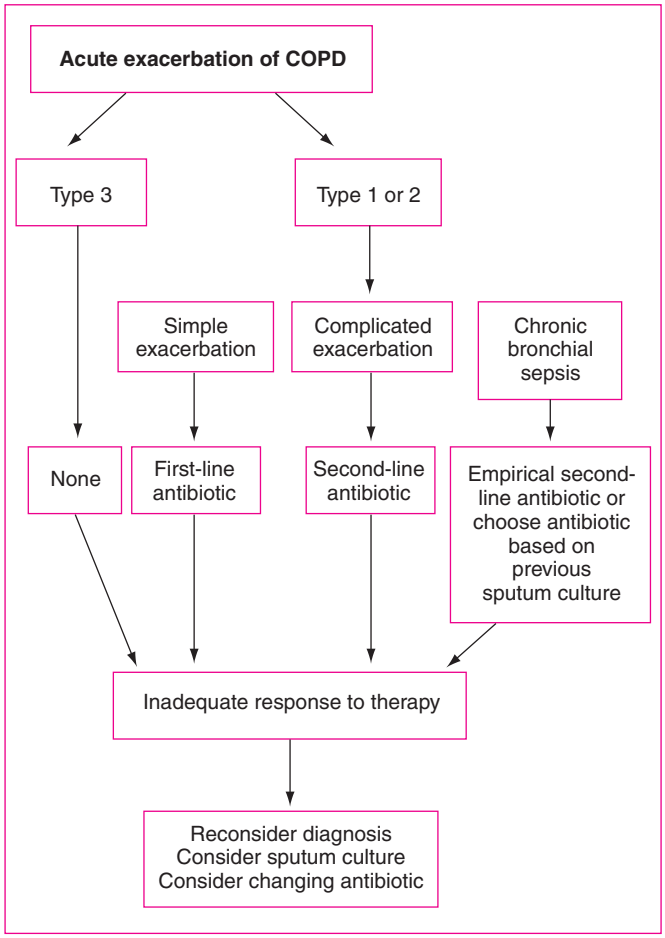

Fig. 54.5 Proposed algorithm for choosing empirical antibiotic therapy in patients with acute exacerbation of COPD. Adapted from Reference 99 and reproduced with permission.

PHARMACO-ECONOMIC CONSIDERATIONS

Cost-effectiveness in the treatment of COPD exacerbations is of utmost significance in the modern-day practice of medicine. Pharmaco-economic analysis involves determining the extra costs required to achieve an additional unit of clinical benefit. In AECB, therapeutic failure is associated with much higher costs, thus identification of subgroups of patients likely to fail low-cost therapy is important. Various techniques including modeling studies, retrospective analysis of data bases, and prospective randomized pharmaco-economic clinical trials have been developed to examine these issues. A retrospective study by Destache and colleagues

showed that the use of newer antibiotics (cephalosporins, macrolides and fluoroquinolones) when compared with first-line agents, reduced overall costs of treating patients despite higher initial acquisition costs.[103] The Canadian Ciprofloxacin Health Economic Study Group[104] randomized patients with more than three exacerbations to receive either ciprofloxacin or any nonquinolone-based therapy. The study measured clinical endpoints (days of illness, hospitalizations, time to next exacerbation) blended with quality of life measurements and total respiratory costs. The use of ciprofloxacin in patients with a history of moderate to severe bronchitis and at least four AECB in the previous year offered substantial clinical and economic benefits. Additional future prospective studies are required to determine if the newer antimicrobial agents offer advantages in terms of costs, quality of life and clinical efficacy.

FUTURE CONSIDERATIONS

Further research is required to find new ways to distinguish between colonization and infective exacerbations of COPD in order to gain a better understanding of the role of infection in the disease. With advances in molecular biology, antigenic structures of bacteria and evaluation of the antibody response to these antigens may become the basis for identifying an AECB. Future therapies may also be directed towards the inflammatory process within the airways that damages the airway mucosa and that leads to greater colonization by pathogenic bacteria. Specific anti-inflammatory mediators directed against various cytokines may interrupt the progressive deterioration of lung function.[105] Most clinical trials of antibiotics were performed for licensing, and patients with pathogens resistant to different antimicrobials were excluded. Further comparative trials showed clinical equivalence and not superiority. Future studies of new antimicrobials should examine clinical efficacy more stringently based on a classification system that would help select patients most likely to benefit from an antibiotic such as those falling in the last two categories in Table 54.5, and should only include patients with Winnipeg type I criteria. These studies should also include well-defined prospective economic analyses and quality of life assessment to ascertain the cost utility of the antibiotic in question.

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