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Topical Reviews

Infection in acute exacerbations of chronic bronchitis: a clinical perspective

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Acute exacerbations of chronic bronchitis (AECB) is an important cause of death and morbidity in developed countries and also has significant economic impact. The disease is characterized by increased dyspnoea, sputum volume and sputum purulence; the most commonly associated pathogens are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. *H. influenzae* and *S. pneumoniae* express virulence determinants that directly and indirectly impair mucociliary clearance and incite other consequences that are permissive to microbial persistence.

Regarding the use of antibiotics, there is currently a lack of large-scale clinical trials that are sufficiently powerful to provide good evidence-based information. Nonetheless, antimicrobial chemotherapy has repeatedly been shown to confer benefit in patients with moderately severe features of AECB. Simple clinical criteria can be used to identify patients in whom there is a higher likelihood of treatment failure or mortality during AECB. These include significant cardiopulmonary co-morbidity, frequent exacerbations, advanced decline in lung function, malnutrition or other generalized debility, advanced age (>70 years) and concurrent treatment with corticosteroids. In such patients, an aggressive antimicrobial approach to AECB may be warranted in order to prevent clinical failure or re-presentation. From a clinical perspective, appropriate drugs include those that are stable to β -lactamases, are bactericidal against causative pathogens, penetrate diseased lung tissue in high concentrations and have a good safety profile.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow obstruction due to chronic bronchitis or emphysema; this is defined as a ratio of forced expiratory volume in 1 sec: forced vital capacity (FEV₁: FVC) of less than 70%. Patients are subject to acute exacerbations in which there is an acute decline in FEV₁, often in association with increased dyspnoea, and production of increased quantities of sputum which may be purulent. Recent epidemiological data from the U.S.A. show that COPD affects an estimated 50 million individuals and is the fifth most common cause of death (1). Development of respiratory failure during an acute exacerbation of COPD occurs in those whose stable airway function is severely impaired (2). However, respiratory failure is not the only cause of death in this group; as acute exacerbation of COPD can also result in death due to other causes, such as acute myocardial infarction (3).

The role of infection in AECB is a contentious issue. Bacteria and neutrophils are frequently identified in the

sputum of patients with AECB, but it is unclear whether they have a causal relationship with the development of exacerbations, or whether bacterial counts are merely allowed to increase as a result of the acute impairment of mucociliary clearance. Studies with antibiotics have revealed a positive, but small effect compared to placebo, in patients with AECB. In the interests of targeting therapy to those who need it most, there are some data that allow us to identify patients who do not benefit from antimicrobial therapy, and others for whom it is probably a mandatory component of management.

Role of infection in AECB

Within the trachea, bronchi and medium to small airways of the lung, the respiratory mucosa is normally sterile. During the evolution of COPD in an individual patient, there is a gradual increase in mucus production, depressed ciliary function and epithelial cell injury. Bacteria that are not normally present in the airway below the larynx are then able to colonize the diseased epithelium (4). The association of purulent sputum in chronic bronchitis with *Haemophilus influenzae* and *Streptococcus pneumoniae* was convincingly demonstrated by May (5). These pathogens, of course, are common colonizers of the upper respiratory tract and they can be recovered from the lower airways even

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during stable COPD (6). Monso *et al.* (7) performed bronchoscopic sampling by protected specimen brush (PSB) of the lower airways of outpatients with stable COPD and compared this with patients with acute exacerbations of COPD. This showed that the prevalence of lower airway bacterial colonization in outpatients with stable COPD is high (25%), mainly due to *H. influenzae* in *S. pneumoniae*, whilst exacerbated COPD is associated with a higher yield (51.7%) of these pathogens and higher numbers of organisms. In patients with more severe AECB, PSB will retrieve a wider range of bacteria including Gram-negative enteric bacilli, *Pseudomonas* sp. and *Stenotrophomonas* sp. (8). Therefore at the very least, even if infection with bacterial pathogens is not the cause of acute exacerbations, they are clearly flourishing in the lower airways in some of these patients, in association with an inflammatory infiltrate (as evidenced by a yield of neutrophils in sputum). Molecular typing of strains of *H. influenzae* isolated from sputum of patients with COPD has demonstrated that a single strain may persist for many months within the lower respiratory tract mucosa of these patients, and remains present even if there have been acute exacerbations of COPD which have been treated with antibiotics (9). This suggests that *Haemophilus influenzae* exists in a state of equilibrium with the host defences, which is lost during exacerbations. During antimicrobial therapy, the equilibrium is restored though the microbe is not eradicated. During chronic colonization there is likely to be a constant balancing act between the host and its bacterial colonizers. On the one hand, host defences include cough, ciliary beating, mucus containing secreted immunoglobulin and lactoferrin, and alveolar macrophages. On the other hand, microbes have adapted to avoid rapid clearance, gain nutrients and survive in the respiratory tract sufficiently to grow and disseminate to other hosts. In the case of *Haemophilus influenzae*, the factors which enable the organism to achieve these aims include the production of a polysaccharide capsule, pili, lipopolysaccharide, outer membrane proteins, iron-regulated proteins and factors toxic to ciliary activity (reviewed by Read and Finch) (10).

The pathogens associated with exacerbations of COPD have been summarized by Ball (11) (Table 1). Although

TABLE 1. Pathogens associated with exacerbations of chronic bronchitis

Bacteria	Viruses
<i>H. influenzae</i>	Influenza/parainfluenza viruses
<i>S. pneumoniae</i>	Respiratory syncytial virus
<i>M. catarrhalis</i>	Rhinoviruses
	Coronaviruses
<i>Staphylococcus aureus</i>	
<i>Pseudomonas aeruginosa</i>	
Enteric Gram-negative bacilli	
<i>Mycoplasma pneumoniae</i>	

there is clear evidence of an increase in bacterial load in some patients with AECB, this is not always the case. Fagon *et al.* (12) performed bronchoscopy with retrieval of organisms by protected specimen brush on 54 patients receiving mechanical ventilation during AECB with hypercapnic respiratory failure. Bacteria (predominantly *H. influenzae* and *S. pneumoniae*) were present in 50% of patients. In the remaining patients, the PSB samples were sterile. No difference was observed in clinical presentation, severity or mortality between the patients infected with bacteria and those not. In at least 30% of AECB, there is evidence of viral infection either by influenza virus, respiratory syncytial virus (RSV) or rhinovirus, detected either by direct culture or serology (13).

In summary, bacteria are present within the lower airways in most patients with stable COPD. In most cases of AECB, there is evidence of increased inflammation in the lower airways together with an increase in bacterial numbers. Whether the latter is cause or effect has not been elucidated.

Antibiotic therapy in COPD

The corps of studies of antibiotic efficacy in bronchitis have been reviewed by Saint *et al.* (14) and Orr *et al.* (15). The review of Saint *et al.* is summarized in Table 2. The studies assessed in this meta-analysis differed in terms of the main outcomes measured (symptom score, days of illness, etc.) so it was able only to report a crude overall effect size relative to placebo, and the effect on peak expiratory flow (PEF), which was reported in the majority of the studies. Overall, the meta-analysis demonstrated a modest but statistically significant benefit from antibiotic therapy (overall effect size 0.22 compared with placebo, 95% CI: 0.10–0.34). The peak expiratory flow improved by a small amount (10.75 l min⁻¹ compared with placebo). None of the studies assessed included any quality of life outcomes. The largest of the studies assessed, by Anthonisen *et al.* (23), stratified patients according to the severity of their illness and was able to demonstrate the largest effect size in those patients with the most severe exacerbations. Antibiotics gave the greatest benefit in terms of resolution of symptoms and avoidance of deterioration, in those patients who had two or more of the following features, increased dyspnoea, increased sputum volume and increased sputum purulence.

In Europe, the commonest antimicrobials used in AECB include the aminopenicillins (U.K. and France), the macrolides (Spain), tetracyclines (Germany) and third generation cephalosporins (Italy) (25). Both the European Respiratory Society (26) and the American Thoracic Society (27) have produced guidelines for the management of COPD. These endorse the judicious use of simple and inexpensive antimicrobial therapy based on individual clinical assessment by physicians. The British Thoracic Society has recommended antibiotic therapy if any two of worsening dyspnoea, increased sputum volume or increased sputum purulence are present (28).

TABLE 2.

Source, y	Setting	No. of subjects	Antibiotic regimen	Main outcome measure(s) [†]	Effect size [‡]
Elmes <i>et al.</i> (16) 1957	Outpatient	113*	Oxytetracycline	Days of illness	0.30
Berry <i>et al.</i> (17) 1960	Outpatient	33	Oxytetracycline	Overall symptom score	0.71
Fear and Edwards (18) 1962	Outpatient	119*	Oxytetracycline	Overall score by physician	0.31
Elmes <i>et al.</i> (19) 1965	Inpatient	56	Ampicillin	Change in PEFR	0.49
Petersen <i>et al.</i> (20) 1967	Inpatient	19	Chloramphenicol	Change in PEFR	-0.04
Pines <i>et al.</i> (21) 1972	Inpatient	149	Tetracycline	Overall score by physician/change in PEFR	0.39
Nicotra <i>et al.</i> (22) 1982	Inpatient	40	Tetracycline	Final PaO ₂ /change in PEFR	0.23
Anthonisen <i>et al.</i> (23) 1987	Outpatient	310*	Combination of sulfamethosazole and trimethoprim, amoxicillin, or doxycycline	Days of illness/change in PEFR	0.38
Jorgensen <i>et al.</i> (24) 1992	Outpatient	262	Amoxicillin	Overall score by physician/change in PEFR	-0.09

*Studies in which the unit of analysis is number of exacerbations; in other studies, the unit of analysis is the number of patients.

[†]PEFR indicates peak expiratory flow rate; [‡]Effect size is the difference between the mean outcome in the antibiotic and placebo groups divided by the pooled sd.

Table reproduced from (14).

Antimicrobial resistance amongst pathogens implicated in AECB

The major pathogen, *Haemophilus influenzae*, is demonstrating rising resistance to the aminopenicillins which is mainly due to production of β -lactamases. In the U.K., prevalence of resistant *H. influenzae* ranges from 4-24% (29). Both of the major β -lactamases are plasmid-mediated and transferable, and so their prevalence is expected to rise with increased use of aminopenicillins in the community. Erythromycin has virtually no activity against *Haemophilus influenzae*, but clarithromycin has better activity, though this is based on a study which demonstrated that 96% of *H. influenzae* isolates had a MIC of 8 $\mu\text{g ml}^{-1}$ or less (29). Azithromycin has better *in vitro* activity than the other macrolides (20). *Moraxella catarrhalis* demonstrates almost universal production of β -lactamases and is also resistant to trimethoprim (reviewed by Amyes and Gemmell) (31). Resistance to β -lactams amongst *Streptococcus pneumoniae* isolates is due to a stepwise mutation of the penicillin-binding proteins. There is controversy regarding the impact of penicillin resistance of pneumococci on the management of patients with respiratory tract infection. Patients with pneumonia treated with high dose penicillin and subsequently shown to be infected with penicillin-resistant

pneumococci, showed no increase in severity of outcome compared to patients with sensitive strains (32). However, the effect of penicillin resistance amongst pneumococci on outcomes in community-treated AECB, where lower doses of oral agents are generally used, has not been investigated. Pneumococcal resistance is associated with childcare facilities, hospital facilities, antibiotic use and immunocompromise (33). Importantly, long-term treatment with low doses of β -lactam antibiotics has recently been shown to contribute to the selective pressure promoting pharyngeal carriage of penicillin-resistant strains of *S. pneumoniae* (34). The potential implications of this for patients with AECB treated in the community are obvious.

Identifying those patients most likely to benefit from antibiotic therapy

With regard to patients presenting to their general practitioner with cough, it is possible to identify patients for whom no benefit will accrue from the use of antibiotics. These include patients with acute bronchitis and otherwise good respiratory health (15,35). A recent meta-analysis of double-blind placebo-controlled trials of antibiotics in patients presenting with acute cough demonstrated that

neither resolution of cough nor clinical improvement was significantly hastened by antibiotic therapy (36).

Regarding patients with COPD, the trial of Anthonisen *et al.* (23) showed that patients with more than two of (i) increased dyspnoea, (ii) increased sputum volume and (iii) increased sputum purulence can benefit from antibiotic therapy, whilst those patients with only one of these features are unlikely to benefit. With such a heterogeneous population, it is possible that positive benefit from antibiotics in the more severe subgroups has been diluted out in the studies of antibiotic therapy in patients with AECB. The majority of patients presenting to their community physician with AECB do not fulfil these simple clinical criteria and are therefore unlikely to benefit from antimicrobial therapy.

There is a strong case for targeting antibiotic therapy in patients with more severe manifestations of AECB. The major determinants of the survival over the long-term in patients with AECB are age and the degree of airways obstruction ($FEV_1 < 50\%$) (37). Co-existing cardiopulmonary disease such as ischaemic heart disease, and also diabetes, have been linked to poor outcome in COPD patients (38). Use of oral corticosteroids has also been linked to poor outcome (39). Seneff *et al.* (40) demonstrated that amongst patients admitted to intensive care units with AECB, variables associated with hospital mortality included age, severity of respiratory and non-respiratory organ system dysfunction, and hospital length of stay before intensive care unit (ICU) admission. These factors imply a worse prognosis of an infective AECB.

Although each of these factors is associated with a poorer outcome of COPD, their effects are not necessarily mediated through infection. Prescott *et al.* (41) investigated patients who had died from an AECB and determined

whether their death was directly linked to infection on clinical grounds. The only historical risk factor that was associated with an infective 'death' was the presence of chronic mucus hypersecretion. Despite this reservation, a strong argument to target therapy at those patients with manifestations of disease associated with a poor prognosis can be made. Future studies should determine whether use of antimicrobial therapy in these patients affects clinical outcome, quality of life measurements and the likelihood of hospital admission. Of further importance, economically, and in terms of quality of life, is the failure of outpatient management resulting in patients needing to return to their physician. One study has determined that these patients can be identified. Those with co-existing cardiopulmonary disease, or who have a history of recurrent exacerbations (>3 per year) are at greatest risk of failing therapy and needing a return visit (42).

Appropriate antimicrobial therapy in patients with AECB

Table 3 suggests appropriate antimicrobial therapy in patients with AECB. The majority of patients presenting to their general practitioner will not require antibiotic therapy. These are patients with acute bronchitis and simple chronic bronchitis with reasonable lung function and less than two of the three of the 'Anthonisen criteria'. Patients who are ambulant and relatively well with no co-existing illnesses, but who present with two or more 'Anthonisen criteria' can probably be managed by simple therapy with β -lactams, for example an aminopenicillin, which is cheap and likely to be efficacious in this group. However, local

TABLE 3. Rationing of antibiotic therapy in cough and AECB

Antimicrobial use	Clinical presentation	Other considerations
None	Acute bronchitis AECB but <2 of ↑ sputum volume, ↑ sputum purulence of ↑ dyspnoea	
Simple antibiotic therapy (e.g. aminopenicillins)	AECB with ≥ 2 of ↑ sputum volume, ↑ sputum purulence or ↑ dyspnoea	Patients who are relatively young, with infrequent exacerbations and no significant comorbidities
Sophisticated antibiotic therapy (e.g. co-amoxiclav, quinolone, modern macrolides)	AECB with ≥ 2 of ↑ sputum volume, ↑ sputum purulence or ↑ dyspnoea AND severe COPD (FEV_1 FVC < 50%) OR elderly OR comorbid conditions OR concurrent oral corticosteroid use	Especially in facilities or areas with high rates of β -lactamase- secreting <i>H. influenzae</i> or penicillin-resistant pneumococci Patients with frequent exacerbations are theoretically more likely to be infected with resistant organisms

microbiology data may point to a high prevalence of β -lactamase-secreting *H. influenzae*, in which case therapy with antibiotics that are stable to β -lactamase is logical. These include co-amoxiclav, the quinolones and modern macrolides (clarithromycin or azithromycin). In patients with advanced age, or with cardiopulmonary comorbidities or moderately to severely impaired lung function ($FEV_1 < 50\%$), it would seem logical to treat infection with more sophisticated antibiotics in order to ensure microbiological clearance. Particularly in those patients with recurrent exacerbations, infection with a β -lactamase-secreting *H. influenzae* is more likely. In addition, these patients are more likely to be infected with unusual pathogens such as the Gram-negatives such as *Enterobacteriaceae* and *Staphylococcus aureus*. In these patients the use of advanced antimicrobials such as co-amoxiclav, quinolones and modern macrolides would seem logical. This has no current evidence basis, and trials to determine whether they have an effect on clinical outcome should be conducted, though some have argued that this will be difficult (43).

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