Introduction

Despite continued improvements in healthcare worldwide, bacterial infections continue to present a challenge to clinicians; these infections include not only those which lead to rare diseases, but also those which occur commonly in our communities—the lower respiratory tract infections (LRTIs) such as pneumonia and acute bacterial exacerbations of chronic bronchitis (ABECB). Certain key issues continue to fuel the debate about the optimal management of these conditions. The long-term effects of repeated bacterial challenge on respiratory function and the ongoing evolution and epidemiology of bacterial resistance—an inevitable consequence of a dynamic environment—are central to many research programmes.

Community-acquired LRTIs—a major healthcare problem

Worldwide, LRTIs are a major cause of morbidity and mortality and an important public health problem. In the UK alone, chronic bronchitis (occurring as an entity on its own or as a part of chronic obstructive pulmonary disease (COPD), affects more than 1 million individuals and is responsible for around 5% of all deaths.1 In the USA, this condition accounts for up to 25% of respiratory complaints affecting more than 7 million people.2 Reports suggest that acute exacerbations of the condition (widely seen in the elderly and in smokers) are one of the most common illnesses treated by physicians.3

Confusion remains over the use of the terms ‘chronic bronchitis’ and ‘COPD’. Chronic bronchitis is a condition associated with prolonged exposure to non-specific bronchial irritants (e.g. cigarette smoking) and is accompanied by mucus hypersecretion leading to chronic productive cough on most days for a minimum of 3 months of the year for at least two consecutive years. COPD is defined as a disorder characterized by reduced maximum expiratory flow and slow forced emptying of the lungs (features which do not change markedly over several months), and may be regarded as the combination of chronic obstructive bronchitis (in which there is disease of the small airways sufficient to cause clinically significant airway obstruction) and emphysema. So, while chronic productive cough (i.e. chronic bronchitis) may be present in those with COPD, it is not necessarily part of this disease.

ABECB (characterized by an increase in cough and sputum volume, sputum purulence and respiratory distress) may lead to a progressive downward spiral of respiratory function. Ultimately, unless this process can be slowed down or halted, the patient’s quality of life will suffer irretrievably. Bacterial infection is responsible for around 50% of acute exacerbations4 and, though there is no consensus on the appropriateness of antibiotic therapy for all acute exacerbations, studies on ‘true’ episodes of bacterial infection have demonstrated the beneficial effects of antibiotic therapy.5

Community-acquired pneumonia (CAP), defined as development of pneumonia unrelated to hospitalization, has presenting signs and symptoms similar to those of ABECB, i.e. increased cough, dyspnoea, rapid respiratory rate and sputum production. Data regarding the incidence of CAP remain incomplete because it is not a notifiable disease, but prospective studies indicate that, in the UK and the USA, the incidence levels are 3.6/1000/year and 3.3/1000/year, respectively.6,7 Severe CAP is associated with considerable morbidity and mortality; the overall mortality is around 3%, rising to 11% in patients with bacteraemic disease8 and, in the USA, CAP is the sixth leading cause of death.9 More than 600,000 of the 4 million patients diagnosed with CAP each year in the USA are hospitalized, though hospital admission rates vary markedly from one geographical region to the next—perhaps related to clinicians’ uncertainty in assessment of disease severity.9,10 A recent review of strategies for management of CAP discusses a predictive model which allows patients to be stratified into groups according to their risk of mortality and other adverse events. Using this model, physicians can identify low-risk patients (around 40% of patients) who are, thus, candidates for treatment in the community.11

Translated into economic terms, it is clear that community-acquired LRTIs place a great burden on healthcare services at a time when providers are most pressurized to justify their expenditure. Figures suggest that total CAP costs in the USA are $23 billion per year,12 while costs for treatment of LRTIs in the UK are in excess of £47 million per year.13
Common pathogens and problems of resistance

Pathogens commonly associated with LRTIs include H. influenzae, Streptococcus pneumoniae and M. catarrhalis. For CAP the range of pathogens is wide and ever-expanding with atypical pneumonias caused by intracellular pathogens, such as Legionella pneumophila, Mycoplasma pneumoniae and Chlamydia pneumoniae becoming increasingly important. In the UK, atypical pneumonia accounts for almost 20% of cases, though the incidence of atypical pneumonias are cyclical, commonly causing epidemics every 4 years.

The increasing incidence of microbial antibiotic resistance to many routinely used antibiotic agents is of global importance. Over the past two decades, significant resistance has emerged among most pathogens commonly associated with respiratory infection. In the USA, almost 100% of clinical M. catarrhalis isolates produce β-lactamase, while it is estimated that up to 50% of H. influenzae isolates are likely to produce β-lactamase by the year 2000. Penicillin-resistant strains of S. pneumoniae are a particular concern worldwide and, in the UK, the number of laboratories reporting antibiotic-resistant pneumococcal strains rose from 3% in 1989 to 21% in 1992. In Spain, which has a high prevalence of drug-resistant pneumococci, 57% of over 5000 isolates between 1979 and 1990 were resistant to one or more antibiotics.

As prescribing for LRTI in the community is largely empirical, there is ongoing debate about appropriate first- and second-line antibiotics. In view of these increasing patterns of resistance, clinicians are becoming more aware that the efficacy of therapy with β-lactam antibiotics, such as the penicillins (e.g. amoxycillin and ampicillin) may be compromised.

Current approaches to therapy of A B E C B and CAP

The way in which community-acquired LRTIs are managed is generally based on a combination of factors, including the intrinsic properties of the available antibiotics, treatment guidelines and cost issues.

Disease guidelines

Disease management guidelines in infectious diseases are a fairly recent development, particularly within Europe, and are generally developed on a per country basis, essentially in an effort to control costs and to educate primary care physicians. However, those developed and distributed by the most prominent societies (e.g. the CAP guidelines from the American Thoracic Society) have been adopted by smaller groups and countries. Many of the world’s developed countries have some form of treatment guideline and use a review of local epidemiology as a rationale for their antimicrobial recommendations. However, all state that in clinical practice, CAP and A B E C B are treated empirically, at least initially and, therefore, require a broad-spectrum agent.

Cost considerations

The need to reduce costs is increasingly behind treatment strategies for LRTI, particularly in the case of patients who require hospitalization. A variety of innovative programmes have been designed to help control the costs of treating LRTIs, including streamlining from combination therapy to a single agent, early switching from parenteral to oral therapy, initiating treatment with oral agents and administering parenteral antibiotics in the outpatient setting from the outset.

Antibiotic choice

Several key factors affect the choice of first- and second-line antibiotics in the treatment of LRTIs: spectrum of activity against common pathogens; blood and tissue pharmacokinetics; safety profile; dose regimen; availability of iv and oral forms.

Of the wide range of antibiotics available, common first-line therapies for A B E C B include amoxycillin–clavulanic acid (often the standard against which newer antibiotics are compared), cephalosporins (e.g. cefaclor, cefpodoxime proxetil and cefuroxime axetil), and the macrolides (e.g. erythromycin, clarithromycin and roxithromycin). However, the fact that up to 25% of patients return within 1 week of receiving an antibiotic would suggest that efficacy is not optimal.

The successful treatment of CAP very much relies on prompt therapy, with clinical improvement usually occurring within 2–4 days. The possibility for patient stratification based on disease severity and risk factors means that more patients may be able to be managed within the community than has been previously thought—primary care prescribers are encouraged to refer to local guidelines. Empirical treatment with aminopenicillins is recommended because early treatment is crucial—though no currently available agent covers all common pathogens. It has been suggested that penicillin should no longer be prescribed empirically for pneumonia because of resistance due to β-lactam-producing H. influenzae strains and there are increasing recommendations for empirical treatment with erythromycin. Unlike the penicillins, erythromycin and the newer macrolides clarithromycin and azithromycin are active against atypical organisms. A combination of erythromycin plus a second-generation cephalosporin (e.g. cefuroxime axetil) may be indicated in patients requiring broader antibacterial coverage, such as those with underlying co-morbid conditions. Once the causative pathogen(s) has been identified, therapy may be modified to ensure appropriate coverage.
Role of the quinolones in LRTI

Numerous clinical studies have established the efficacy of fluoroquinolones against a wide range of bacterial pathogens, including those commonly present in respiratory tract infections.2425 The pharmacokinetic profile of these agents is well suited for the treatment of respiratory infections: they are absorbed well from the gastrointestinal tract after oral administration, and penetrate rapidly into the bronchial mucosa, the site of infection, at concentrations that exceed serum levels.26 In contrast to the macrolides, they also have the advantage of being bactericidal rather than bacteriostatic. Their spectrum of activity provides excellent Gram-negative cover27 (H. influenzae accounts for around 48% of AECB), and also cover against the ‘atypical’ respiratory pathogens; what is considered to be missing from the earlier agents is good Gram-positive cover.28 Thus, there is ongoing interest and speculation about the role of quinolones in respiratory tract infection and in the development of new fluoroquinolones to improve the spectrum of activity and to include adequate cover of Gram-positive organisms, most notably S. pneumoniae.

Currently available quinolones, such as ciprofloxacin and ofloxacin, do not have an ideal spectrum of activity for use in LRTIs and this is reflected in their positioning in most treatment guidelines as ‘alternative’ or second- or third-line agents for AECB and CA P. A ditionally, there has been concern over the safety profiles of these agents (including drug interactions) though, in general, newer fluoroquinolones have a good record of safety and tolerance, and their adverse reaction profiles were largely anticipated from precursors and animal toxicology studies.29 Individual group members exhibit particular properties related to chemical structure,30 and certain members of the class, including ofloxacin, lomefloxacin, sparfloxacin and ciprofloxacin, have all been reported to induce various degrees of photosensitivity.31

The need to combat resistance, particularly to provide activity against penicillin-resistant strains of S. pneumoniae, has driven the development of new fluoroquinolones with improved spectra of activity. Those which are in advanced development include levofloxacin (an improved version of ofloxacin), trovafloxacin and grepafloxacin.

G repafloxacin— a new extended spectrum fluoroquinolone

Grepafloxacin is an oral fluoroquinolone with enhanced activity against Gram-positive organisms, as well as retaining good cover against Gram-negative and atypical organisms.32 In comparison with older fluoroquinolones, in-vitro studies confirm that grepafloxacin has superior activity against S. pneumoniae, irrespective of the strain’s susceptibility to penicillin, and superior activity to amoxycillin against H. influenzae (including β-lactamase-producing and/or ampicillin-resistant strains) and to M. catarrhalis (including β-lactamase-producing strains).33–35 Pharmacokinetic studies show that serum concentrations of grepafloxacin exceed the MIC₉₀ of S. pneumoniae (Glaxo–Wellcome, data on file) for most, or all, of the once-daily dosing interval. moreover, in bronchial mucosa, the site of infection in AECB, the grepafloxacin concentration has been shown to be 3.5 mg/L at 12-13 h post-dose.36 The efficacy and safety of grepafloxacin is now being extensively tested in CAP and AECB. Clearly this agent has the potential to offer prescribers benefits over current therapies.

References


