Introduction

It is interesting to apply the evolutionary theme to antimicrobials and see how things have ‘evolved’ or changed since the introduction of these ‘wonder’ drugs and the inception of the ‘age of chemotherapy’. One cannot, however, consider antimicrobials without first considering the target of these drugs, namely the microbes themselves.

Statements by the noted Harvard palaeontologist, Stephen Jay Gould, attest to the fortitude and ingenuity of these microscopic adversaries. ‘This is truly the age of bacteria as it was in the beginning, is now and ever shall be.’ He went on to say that, ‘Bacteria represent the great success story of life’s pathway. They occupy a wider domain of environments and span a broader range of biochemistries than any other group. They are adaptable, indestructible and astounding diverse.’

All of the earliest forms of life, as recorded in the fossil record, were prokaryotes or, essentially, bacteria. They have existed for some 3.8 billion years and today occupy virtually every part of the planet. They are without question the most widespread and abundant life form, a fact that is dramatically illustrated by the finding that one spoonful of high quality soil contains as many as $1 \times 10^{13}$ bacteria. They have been found in oceanic vents and sulphide mounds at temperatures of approximately 250°C and 340°C, respectively, and in oil reservoirs two miles below the sea bed. The total mass of underground bacteria is thought to weigh approximately $2 \times 10^{14}$ tons. In more understandable terms, it is estimated that 10% of our own dry bodyweight is made up of bacteria.

Antibiotic development

The work of pioneering scientists such as Koch, Pasteur and Lister defined the role of microbes in the causation of disease and led the way for the ground-breaking work of Ehrlich and others in the field of antimicrobial chemotherapy. It is a testament to the importance of this field of endeavour that three Nobel prizes have been awarded for work in this area: in 1939 to Gerhard Domagk for work on prontosil, in 1945 to Fleming, Chain and Florey for work on penicillin, and in 1952 to Waksman for the discovery of streptomycin.

A list of selected antibiotics discovered since 1929 is given in Table I. These include a variety of naturally occurring and synthetic compounds and are an indication of the results of the joint efforts of basic and applied scientists in university and pharmaceutical industry laboratories throughout the world.

For many years sulphonamides, tetracyclines, ß-lactams and aminoglycosides have been the principal weapons in our therapeutic arsenal. The past decade has seen a resurgence in the use of macrolides, spearheaded by the two recent additions to this class: azithromycin and clarithromycin. The quinolones also have assumed a very prominent role and have been used to treat a wide variety of infections. This class has progressed rapidly since the discovery of the naphthyridine agent nalidixic acid in the early 1960s, through three generations of quinolones to the present. These drugs were initially used primarily for the treatment of urinary tract infections and shigellosis. As their in vitro activity broadened, their clinical roles were extended to include sexually transmitted diseases, invasive
Gram-negative infections, bone, skin and soft tissue infections. The use of these agents in respiratory tract infections, particularly community-acquired pneumonia (CAP), is a more recent development.

In keeping with the evolutionary theme, let us consider what has evolved over the recent past pertaining to the treatment of respiratory infections. Two specific changes have taken place that have had a direct effect on the treatment of lower respiratory tract infections. These are an appreciation of the importance of the atypical organisms, e.g. Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella spp., and the increased incidence of resistance to commonly used antimicrobial agents among respiratory pathogens.

Recent guidelines published by the Canadian Infectious Disease Society (CIDS), the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) dealing with management of CAP all acknowledge the importance of the atypical pathogens and suggest treatment regimens which provide coverage aimed specifically at them. A study, published recently, of 2776 patients hospitalized with CAP showed that these three atypical pathogens ranked second, third and fourth of all the microorganisms identified as fulfilling the criteria for a ‘definite’ diagnosis. Another study showed that C. pneumoniae can be an important cause of outbreaks of pneumonia in nursing homes and has high attack rates and high mortality rates.

**Resistance**

It is clear that the *in vitro* susceptibility of many common pathogens to various antibiotics has decreased over the past several years. This carries both a literal and figurative price in terms of increased health care costs, increased length of stay in hospital and increased risk of initial use of inappropriate antibiotic therapy or, possibly, less effective alternative therapy.

While the atypical pathogens are certainly significant, the single most common and important bacterial agent in CAP is *Streptococcus pneumoniae*. Of increasing concern, however, has been the slow but steady increase in the frequency of pneumococcal isolates with reduced susceptibility to penicillin. The first such case reported was a hypogammaglobulinaemic patient from Australia in 1967. In North America, the first reported isolates of penicillin-resistant *S. pneumoniae* (PRSP) were in 1974 and 1983 from the USA and Canada, respectively. The NCCLS currently defines strains with MICs of penicillin of ≤0.06 mg/L as sensitive, 0.1–1 mg/L as intermediate and ≥2 mg/L as resistant. PRSP isolates have now been reported from virtually every continent and the USA data show an increased incidence from <5% before 1989 to >35% in 1997. Not only is the decreasing percentage of isolates that are susceptible of concern but there has also been a shift in the ratio of intermediate to high-level resistant isolates from 3 or 4:1 to 2 or 1:1.

Another concern is resistance to other antimicrobials, such as macrolides, fluoroquinolones and, of course, multidrug resistance. So far it appears that pneumococcal resistance to β-lactams is due solely to the presence of low-affinity penicillin-binding proteins (PBPs), resulting in reduced attachment of the β-lactam drug to the target site of action. Macrolide resistance, however, can occur by one of two mechanisms. Either the target site can be modified (erm gene) or an efflux pump mediated by the *mef* gene may be operational. It is estimated that these two mechanisms account for approximately 45% and 55%, respectively, of macrolide-resistant isolates.

Resistance to fluoroquinolones among pneumococcal isolates may occur as a result of changes in one or both target sites (topoisomerase II and IV) resulting from mutations in the *gyrA* and *parC* genes, respectively, or by an efflux pump or both. A recent report highlighted the concern over quinolone misuse and the fact that quinolone resistance is a class phenomenon (as it is with macrolides). The report also noted that two of the 29 pneumococcal isolates studied were resistant not only to ciprofloxacin but also to two potent broad-spectrum quinolones that, at the time the paper was written, had only been used in clinical trials.

The greatest concern, however, is with multidrug-resistant organisms; those pathogens that are resistant to three or more antibiotics having different mechanisms of action. These were first reported in 1977 from South Africa and have now been isolated from a number of countries around the world. It is estimated that in the USA approximately 9% of pneumococcal isolates are multidrug resistant.

The main question regarding PRSP is whether or not β-lactams, in particular penicillin, still have a role to play. A
detailed discussion of this issue is beyond the scope of this paper. This issue is complicated somewhat by the fact that there are data to suggest that infection with PRSP results in prolonged length of hospital stay and increased mortality as well as data implying that \( \beta \)-lactams are still effective.\textsuperscript{22–26}

One way to resolve this controversy is by considering various levels of penicillin susceptibility, i.e. fully susceptible, intermediate and high-level resistance. For the treatment of patients infected with penicillin-susceptible pneumococci (MIC < 0.06 mg/L), any \( \beta \)-lactam, including penicillin G, penicillin V or amoxycillin, would be adequate. For the treatment of infection caused by pneumococcal strains with intermediate resistance (MIC 0.12–1 mg/L), amoxycillin would be appropriate. For highly resistant strains (MIC \( \geq 2 \) mg/L), a fluoroquinolone should be used for oral therapy, or higher doses of penicillin (1.2 g every 6 h) or amoxycillin (1 g every 6 h), or a third-generation cephalosporin such as cefotaxime or ceftriaxone, for in-patient treatment.\textsuperscript{27–29} It is likely that as MICs of penicillin approach 4 mg/L or higher, \( \beta \)-lactams as a class would have to be abandoned for use in patients with pneumococcal pneumonia.

This whole argument, however, is predicated upon the fact that one knows that the pneumococcus is the pathogen. Unfortunately current diagnostic methods do not allow us to determine the aetiologic agent with any degree of certainty and it is for this reason that broader spectrum coverage that includes the pneumococcus, the atypical pathogens and, occasionally, other organisms, must be used.

Case discussions

CAP is a disease that is often underestimated by patients and physicians alike. Many do not appreciate its potential seriousness and the tremendous impact that it has on both individuals and society as a whole. It is estimated that in the USA there are three to four million cases annually resulting in 600,000 admissions to hospital, 640,000 days of restricted activity and approximately 45,000 deaths.\textsuperscript{30,31} Given the impact of the disease, the number of possible pathogens, the possibility of co-pathogens and the limitations of available diagnostic methods, CIDS devised a set of guidelines to deal with initial management of the patient with CAP.\textsuperscript{3} This was followed shortly thereafter by guidelines from the ATS and a few years later by the IDSA.\textsuperscript{4,5} Guidelines have also been published recently in Europe under the auspices of the European Study on Community-acquired Pneumonia Committee.\textsuperscript{32}

Airway infection includes acute tracheobronchitis, chronic bronchitis and acute exacerbation of chronic bronchitis. Together these account for approximately 14 million physician visits per year in the USA. In the UK bronchitis results in 28 million lost working days.\textsuperscript{33} To date, only one set of national guidelines that deals exclusively with the management of chronic bronchitis has been published.\textsuperscript{34} These were published in 1994 as the proceedings of the Canadian Bronchitis Symposium and are currently in the process of being updated.

Three pneumonia cases are outlined in Table II. Cases 1 and 2 are both CAP patients who can be treated as outpatients while Case 3 requires admission to a hospital ward. The first patient has no underlying disease and no obvious risk factors for infection with PRSP. The likely pathogens are \( S. \) pneumoniae, \( M. \) pneumoniae and \( C. \) pneumoniae. A \( \beta \)-lactam such as penicillin or amoxycillin, while potentially effective if the aetiologic agent is \( S. \) pneumoniae, would be inactive against atypical pathogens. A macrolide, however, would cover all likely pathogens in this patient. Despite reports of \textit{in vitro} resistance to macrolides, there are no papers reporting consistent failures with their use. Some, however, feel that macrolides may no longer be appropriate treatment options in areas of high \textit{in vitro} resistance.

The second patient differs from the first in a number of respects. He is older, has structural lung disease and has had a recent course of antibiotics. Although he is certainly at risk of infection by pathogens such as \( S. \) pneumoniae, \( M. \) pneumoniae and \( C. \) pneumoniae, one must also consider \textit{Legionella} spp., \textit{Haemophilus influenzae} and Gram-negative bacilli as well. Neither a \( \beta \)-lactam nor a macrolide as single agents would provide sufficient coverage. A ‘respiratory’ quinolone with its broader spectrum of activity would be far more appropriate.

The third patient requires admission to hospital and, therefore, has a higher risk of dying. According to published guidelines, a macrolide and a second- or third-generation cephalosporin would certainly be appropriate. However, a ‘respiratory’ quinolone would provide the same coverage using a single agent and one could even consider oral therapy as an option. This may be a particularly attractive alternative in elderly patients in whom it is important to maintain mobility as much as possible; something which is more difficult when IV lines must be dealt with.

The acute exacerbation of chronic bronchitis (AECB) case (Case 4) illustrates a number of risk factors that suggest that the patient might fail therapy with drugs such as amoxycillin, a cephalosporin or tetracyclines. These factors include the reduced lung function and the frequent exacerbations; such a patient may well have a better outcome if a quinolone is used.\textsuperscript{33,35}

Summary and conclusions

The past 60 years have been exciting and dramatic times for the practice of medicine and medical research. The antibiotic era was launched and, at times, the fight against infection seemed almost won. We have, however, become
L. Mandell

Table II. CAP and AECB case histories

<table>
<thead>
<tr>
<th>Case</th>
<th>Demography and history</th>
<th>Findings on examination</th>
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<tbody>
<tr>
<td>Case 1</td>
<td>39-year-old male. 5 day history of feeling unwell with a dry, non-productive cough and a mild but persistent headache.</td>
<td>temperature 38.1°C bibasilar crackles</td>
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<tr>
<td>CAP</td>
<td>69-year-old male. known bronchiectasis, recent antibiotics for urinary tract infection, and complaining of a sore throat and non-productive cough for 3 days, and increasing shortness of breath and yellow sputum for 2 days.</td>
<td>temperature 38.3°C rales in right lower lobe respiratory rate 22/min</td>
</tr>
<tr>
<td>Case 2</td>
<td>70-year-old female. COPD³, upper respiratory tract infection for 1 week before admission, increasing cough and shortness of breath and sputum volume for 2 days. allergy to penicillin.</td>
<td>temperature 39.1°C respiratory rate 30/min diffuse rales</td>
</tr>
<tr>
<td>Case 3</td>
<td>58-year-old female. heavy smoker for 40 years, known COPD with frequent AECBs (4/year). FEV1 48% of predicted, increased cough and sputum for 2 days. allergy to penicillin.</td>
<td>temperature 38.2°C diffuse wheezes</td>
</tr>
<tr>
<td>Case 4</td>
<td>58-year-old female. known COPD with frequent AECBs (4/year). FEV1 48% of predicted, increased cough and sputum for 2 days. allergy to penicillin.</td>
<td>temperature 38.2°C diffuse wheezes</td>
</tr>
</tbody>
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CAP, community-acquired pneumonia. COPD, chronic obstructive pulmonary disease. AECB, acute exacerbation of chronic bronchitis.

too complacent and have taken these drugs for granted. The newer agents, particularly the new quinolones, are useful additions to our antibiotic armamentarium and we must guard carefully against their misuse (or we may see the demise of this class of compounds). With considerate use, however, drugs such as gemifloxacin should be useful for many years to come.

Assuming that data from well-designed randomized controlled trials will be forthcoming, the likely roles for newer quinolones such as gemifloxacin in lower respiratory infections might be: AECB with increased dyspnoea, sputum volume and purulence, multiple risk factors and frequent exacerbations; CAP, either in outpatients with structural lung disease or at increased risk of PRSP and/or Gram-negative bacillary infections or inpatients, either in the ward or the ICU.

References


Gemifloxacin: survival of the fittest


