Clinical and economic implications of antimicrobial resistance for the management of community-acquired respiratory tract infections

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Lower respiratory tract infections (RTIs), particularly community-acquired pneumonia (CAP), account for over 50 million deaths annually worldwide. They place an extensive clinical and financial burden on healthcare authorities. Upper RTIs, usually mild and non-life threatening, also incur significant healthcare costs. The rising prevalence of resistance of the major causative agents of CAP (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) to β-lactam antimicrobials and newer macrolides has necessitated new strategies for appropriate antimicrobial usage. A successful clinical outcome will depend on the patient, choice of drug, and the epidemiology and resistance of the pathogen. Treatment failure will result in increased costs, particularly if hospitalization is required. Pharmacokinetic and pharmacodynamic parameters are being used increasingly to predict maximally effective therapy and optimal bacterial eradication, thus limiting the development of resistance. Antimicrobial susceptibility criteria by MIC should be dictated by the type and location of the infection. Modifying the current MIC breakpoints for penicillin so that more pneumococcal pneumonia isolates are reported appropriately as being susceptible may lead to a decrease in the use of broad-spectrum antimicrobial therapy and its associated increased costs, in favour of more narrow-spectrum therapy. Targeting the pathogen with the most effective antimicrobial in an appropriately selected patient should optimize clinical and microbiological success and, consequently, maximize response rates and economic outcomes. In addition, research efforts need to concentrate on developing new agents with low propensity to select for or induce resistance.

Introduction

Respiratory tract infections (RTIs) are among the most widespread and serious infections, accounting for over 50 million deaths globally each year. RTIs also represent the most common reason for physician visits and prescription of antibiotics. Infections of the lower respiratory tract include community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB), which are associated with significant rates of mortality and are among the top 10 causes of death in the developed world. In developing countries, infants under 4 years of age are at greatest risk of mortality from lower RTIs, whereas in developed countries the severity of infection and rate of mortality are greatest in the elderly.

Community-acquired pneumonia, which is caused by a range of bacterial pathogens including Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis, is common and is the sixth leading cause of death in the USA. Chronic bronchitis is also very common, and in 1994 it was estimated that more than 14 million Americans were affected, representing ~5.4% of the adult population of the USA. The prevalence of lower RTIs places an extensive clinical and financial burden on healthcare authorities.

Infections of the upper respiratory tract, such as sinusitis, pharyngitis and acute otitis media (AOM), occur within the population at a higher frequency than lower RTIs, but are usually mild and non-life-threatening. However, upper RTIs may also incur significant healthcare costs and can lead to serious complications if not treated effectively. For example, AOM is the most commonly diagnosed bacterial infection in children, and ~75% of children will have had three or more ear infections by the age of 7. Furthermore, AOM is the most common reason for antibiotic prescribing in young children and infants, and the number of physician visits for AOM has risen steadily in recent times, reaching almost 30 million visits in 1996.
Current antimicrobial therapy for community-acquired RTIs (CARTIs) is typically empirical and is influenced by local differences in aetiology and bacterial susceptibility. Rising prevalence of resistance among *S. pneumoniae* to the β-lactam antibiotics and the newer macrolide antimicrobials, together with cross-resistance between the macrolides, has been reported. In response to these trends, the fluoroquinolones are now being more widely prescribed. More recently, a low, but increasing incidence of fluoroquinolone resistance among *S. pneumoniae* has been observed. Furthermore, there are clear differences in the *in vitro* activity of different fluoroquinolones against this pathogen. Resistance to β-lactams is also rising at an alarming rate in some countries among strains of *H. influenzae* and is already particularly high globally in *M. catarrhalis*. Data from PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) show rates of β-lactamase production among isolates of *H. influenzae* that range from 3.3 to 64.7% (overall 16.6%); for *M. catarrhalis* the range is 84.2–100% (overall 94.7%).

Overall, these issues threaten the effectiveness of empirical treatment strategies in patients with CARTIs, and may result in poor clinical outcome and an extensive financial and clinical burden. This burden is likely to increase further as life expectancy increases in developed countries and levels of antimicrobial resistance rise. Consequently, new emphasis is being placed on strategies for appropriate antimicrobial usage, and research efforts are concentrating on developing new agents with low propensity to select for or induce resistance. This paper discusses some of the issues relating to the clinical and economic impact of antimicrobial resistance on the management of patients with CARTIs, with a particular emphasis on *S. pneumoniae* resistance in CAP.

**Evaluation of outcome in patients with CAP**

In the management of infectious diseases, including those affecting the respiratory tract, maximizing the probability of a good clinical outcome is one of the key aims of antimicrobial treatment. The host, issues relating to drugs and drug selection, and the changing epidemiology and resistance in specific pathogens, all affect the probability of a successful clinical outcome and have the potential to impact on the cost-effectiveness of treatment. Commonly used outcome evaluations in clinical trials involving patients with CARTIs include both clinical and microbiological endpoints, which are frequently assessed at the end of therapy and/or at the end of the study period. Specific clinical evaluations include cure or failure rates following treatment, or assessment of changes in symptoms of infection. Microbiological evaluations include determination of whether the causative pathogen persists or has been eradicated by antimicrobial therapy. Many of these outcomes are of both conventional and historical value, and are used routinely for registration purposes, but do not necessarily provide sufficient predictive information concerning the effects of antimicrobial intervention.

Specific additional measures that would add valuable insight into the outcome of antimicrobial chemotherapeutic intervention include: the duration of effect, measured by the patient’s disease-free interval, for example in patients with AECB; the correlation between clinical response and microbiological eradication; and the economic consequences of treatment, which invariably focuses on the utilization of healthcare resources. Targeting the causative pathogen with the most effective antimicrobial agent in an appropriately selected patient would be expected to optimize clinical and microbiological success and, consequently, maximize rates of response and economic outcomes.

**Evolving resistance in common RTI pathogens**

One of the key issues concerning the selection of the most appropriate antimicrobial agent is the development of resistance among the most common bacterial RTI pathogens. Increasing prevalence of resistant isolates may impede pathogen eradication in lower RTIs, potentially exacerbating the spread of resistant clones. This can lead to recolonization of the mucosal membranes with such clones and has implications for host-to-host transmission and global spread of resistant clones.

Penicillin susceptibility criteria by MIC have been defined by the NCCLS based on *S. pneumoniae* infections in cerebrospinal fluid (CSF): susceptible, MIC ≤ 0.06 mg/L; intermediate, MIC 0.12–1.0 mg/L; or resistant, MIC ≥ 2 mg/L. However, it is important to note that MIC breakpoints have different meanings depending on the type and location of the infection being treated. The effect of antimicrobial resistance in *S. pneumoniae*, the major bacterial cause of RTIs, is most evident at sites of infection where antibiotic penetration is restricted, for example in patients with closed-space infections such as meningitis or otitis media. The reason for this is that much higher levels of penicillin are achieved in the blood and the alveoli compared with the CSF. Consequently, intermediate susceptibility to penicillin, as defined by the current NCCLS criteria, is unlikely to be clinically relevant in patients with pneumonia treated with generally accepted doses of penicillins. However, high-level resistance (MIC ≥ 4 mg/L) may impede clinical response.

**Penicillin and macrolide resistance in pneumococcal pneumonia**

PROTEKT is a global surveillance study of the prevalence of resistance among bacterial pathogens causing CARTIs. Data from the PROTEKT surveillance study (www.protek.org) have shown that up to 22% of *S. pneumoniae* isolates are...
resistant to penicillin, with combined intermediate and resistant strains accounting for over 36% of isolates examined worldwide. A similarly high proportion of isolates (31%) is resistant to the macrolides. These recent findings support those from two previous major antimicrobial surveillance studies, namely the Alexander Project\textsuperscript{16,26} and the SENTRY study,\textsuperscript{17} which also indicated that resistance to β-lactams and macrolide antimicrobials is widespread.

In terms of penicillin breakpoints specific for CAP, evidence published by the Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group\textsuperscript{27} suggests that strains of this pathogen should be considered susceptible if the penicillin MIC is $\leq 1$ mg/L. Strains for which the penicillin MICs are 2 and 4 mg/L should be considered to be of intermediate susceptibility. Some evidence indicates that there is no increase in the number of pneumonia treatment failures when penicillin-intermediate strains are implicated, whereas other evidence suggests that there is an increased risk of mortality or complications in patients with infection due to strains of intermediate susceptibility. Whilst too few patients with pneumonia due to pneumococcal isolates with penicillin MICs of $\geq 4$ mg/L have been studied to draw appropriate conclusions, pharmacodynamic considerations indicate theoretical reasons for concern.\textsuperscript{27}

These observations suggest that higher susceptibility testing breakpoints for penicillin are appropriate for non-central nervous system infections, and revised breakpoints should be considered based on the site of infection as well as pharmacokinetic/pharmacodynamic considerations.\textsuperscript{25} Modifying the MIC breakpoints so that more pneumococcal pneumonia isolates are reported appropriately as being susceptible, may lead to a decrease in the use of broad-spectrum antimicrobial therapy in favour of more narrow-spectrum therapy.\textsuperscript{27}

The effectiveness of the macrolides in the management of CARTIs has been affected by the emergence of macrolide-resistant pneumococci in the late 1990s; prevalence rates exceeding 30% are not uncommon.\textsuperscript{13–17} However, in the year 2000, reports of fewer than 10 macrolide treatment failures have been published,\textsuperscript{26,29} which is a low frequency considering the high number of prescriptions for this class of antimicrobial agent.

Why have there not been more reports of macrolide failure? Consideration should be given to the fact that the majority of macrolide prescriptions are written as part of empirical therapy for outpatients where no microbiological or antibiotic susceptibility testing data exist. In addition, sputum cultures are rarely taken, even in patients who have failed previous courses of antimicrobial therapy.\textsuperscript{28} Furthermore, most community infections are of mild to moderate severity and some resolve spontaneously without treatment. The need to repeat a treatment course may be due to resistance but this is rarely proven. In addition, data from clinical trials are not always informative in this respect because patients who are at greatest risk are often excluded.

In a recent study, three patients who received azithromycin 500 mg for 3–5 days presented with bacteraemic community-acquired lower RTI caused by drug-resistant S. pneumoniae.\textsuperscript{28} These patients were subsequently successfully treated with the fluoroquinolone levofloxacin (500 mg/day), with complete resolution of symptoms and chest roentgenogram abnormalities after 14 days of therapy. Molecular characterization of azithromycin resistance revealed that one of the S. pneumoniae isolates contained a mef determinant, which encodes for a macrolide efflux pump,\textsuperscript{30} whilst another contained an erm(B) determinant, which confers resistance to the macrolide–lincosamide–streptogramin-B (MLS\textsubscript{B}) antimicrobials via methylation of the binding site of these agents at the ribosomal level (23S rRNA).\textsuperscript{31}

In a retrospective study conducted in Spain and the USA during 1986–1999, Garau et al.\textsuperscript{32} identified 57 macrolide-resistant pneumococcal blood isolates. A total of 12 patients, 11 of whom had pneumonia, developed bacteraemia while receiving treatment with macrolides (erythromycin, clarithromycin, azithromycin or josamycin) for 2–8 days. Of these, all nine isolates from Spain contained the erm determinant, and one of three isolates from the USA contained the mef determinant. Two of the isolates had high-level penicillin resistance (MIC 2 mg/L), six had intermediate resistance and three were fully susceptible to penicillin. Subsequently, all of the patients were treated successfully with a β-lactam antibiotic. In another study, four outpatient receiving macrolides developed bacteraemia due to resistant S. pneumoniae.\textsuperscript{39} All of the strains were resistant to erythromycin but susceptible to clindamycin. While the mechanisms of resistance were not assessed, their susceptibility to clindamycin suggests that they contained the mef determinant responsible for the efflux mechanism of resistance, which is supported by the MICs (8–16 mg/L) associated with the low-level resistance often observed with this efflux system.

**Genotypic prevalence of S. pneumoniae macrolide resistance**

Azithromycin and clarithromycin have different pharmacokinetic profiles both at the peripheral site (plasma) and at the site of infection (epithelial lining fluid, ELF).\textsuperscript{33} Additionally the in vitro potency of these two agents is markedly different for S. pneumoniae as is evident from the MIC distribution analysis from a recent US surveillance study.\textsuperscript{34} These surveillance data also reveal the trimodal MIC distribution pattern of this organism, since ~75% of pneumococci are susceptible to macrolides, 18% are efflux mutants (mef, MIC 1–32 mg/L), and 7% are high-level (erm, MIC $\geq 64$ mg/L) resistant strains (Figure 1).
Overlaying ELF clarithromycin concentrations upon the MIC distribution of the same compound reveals that drug concentrations at the site of infection exceed the MIC of susceptible isolates and many of those pneumococci exhibiting the efflux resistance mechanism. As a result of this pharmacodynamic profile at the infection site the currently used MIC breakpoints may be inaccurate, i.e. the effective resistance rate is ~10–12% compared with the reported surveillance resistance rates of 25–30%. In comparison, the concentrations of azithromycin in the ELF are ~2 mg/L, which does not exceed the compound’s MICs for pneumococci with either mef- or erm-mediated resistance. Consequently, the MIC breakpoint for azithromycin appears to be correct, i.e. the reported resistance rate is probably similar to the effective resistance rate. These findings indicate that strains of S. pneumoniae with MIC ≤ 0.5 mg/L are susceptible to azithromycin, whereas those exceeding this value should be considered resistant (Figure 2). It is important, therefore, to consider not only microbiological potency, but also to take into account drug concentrations at the site when assessing the clinical utility of the macrolides (i.e. microbiologically determined breakpoints versus those achieved by means of pharmacodynamic analysis).

The prevalence of the erm and mef determinants amongst macrolide-resistant pneumococci varies according to the geographical region. A number of studies conducted in the USA, Canada, Europe and Japan have examined the genotype of S. pneumoniae macrolide resistance. Efflux (mef) resistance is more prevalent in the USA and Canada (56–71%), while high-level (erm) resistance is more prevalent in Europe (97%) (Table 1). In Japan, the overall macrolide resistance exceeds 70% and the prevalence of erm and mef genotypes is similar (40% and 43%, respectively), while dual genotypes have been noted in most of the remaining macrolide-resistant pneumococci. Confirmatory results from PROTEKT are presented elsewhere.

Resistance of RTI pathogens implicated in acute exacerbations of chronic bronchitis and acute otitis media

Resistance of bacteria commonly implicated in AECB and AOM, namely S. pneumoniae, H. influenzae and M. catarrhalis, has been reported in a number of prospective surveillance studies. Indeed, data from 845 S. pneumoniae isolates analysed as part of the SENTRY surveillance study showed that, although resistance rates varied widely, 28% of isolates demonstrated intermediate resistance to penicillin and 16% had high-level resistance. Alexander Project data from 1992–1997 indicate that the prevalence of β-lactamase production among isolates of H. influenzae appears to have reached a steady state in some countries, such as France and the USA, but may be as high as 35% in some areas. A number of studies have illustrated the effect of β-lactamase production on the efficacy of amoxicillin in patients with AOM, revealing that eradication rates for β-lactamase-positive isolates were similar to spontaneous eradication rates observed for H. influenzae. Although the use of a vaccine against the most virulent serotype of H. influenzae (serotype b) may decrease the importance of this strain, resistant, non-typeable strains remain clinically significant CARTI pathogens.

β-Lactam resistance is almost invariably higher in M. catarrhalis than in H. influenzae. Most (50–80%) isolates of M. catarrhalis collected as part of the Alexander Project during 1992 produced β-lactamase. However, the rate of β-lactamase production had increased to 90–100% in the participating centres in this study by 1997. Resistance to other (non-β-lactam) antibiotic classes was stable in both M. catarrhalis and H. influenzae.
Antimicrobial resistance in community-acquired RTIs

Table 1. *S. pneumoniae* macrolide resistance: genotypic prevalence

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<td>-</td>
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<td>-</td>
<td>6</td>
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Clinical impact of antimicrobial resistance in RTIs

**Pneumococcal pneumonia**

Little published data are available on the impact of antimicrobial resistance on the rate of response in non-susceptible pneumococcal pneumonia. However, one study has been conducted to determine the usefulness of procaine penicillin in the treatment of suspected pneumococcal pneumonia of mild to moderate severity in an area with a high prevalence of penicillin resistance. Of 49 patients receiving procaine penicillin (1.2 million units given intramuscularly every 12 h), 40 (82%) were cured and no deaths due to infection were reported. Seventeen patients had documented *S. pneumoniae* infection, five of whom had penicillin-resistant isolates (MICs 0.25–4 mg/L). Although 15 of the patients infected with *S. pneumoniae* were cured (one patient had an allergic reaction and the other failed treatment), the duration of the following symptoms was longer in patients infected with penicillin-resistant isolates compared with those from whom penicillin-susceptible pneumococci were isolated: fever (3.6 versus 1.9 days), cough and sputum production (6.0 versus 2.7 days), and pleuritic pain (3.6 versus 2.1 days). Even though the number of cases in this study was too small to perform a rigorous statistical analysis, these results suggest that penicillin susceptibility may have an impact on symptom resolution in patients with pneumococcal infection.

**Acute exacerbations of chronic bronchitis**

Although the in vitro data indicate significant levels of resistance, few data are available on the clinical impact of antimicrobial resistance in patients with AECB. Most studies do not demonstrate any difference in outcome between patients infected with penicillin-resistant isolates and those infected with susceptible strains. However, a review of 12 studies of patients with AECB demonstrated a strong correlation ($r = 0.91$) between eradication failure rates and clinical failure rates following treatment with macrolides, fluoroquinolones, penicillins, cephalosporins, or co-trimoxazole (Figure 3).

These data support the premise that bacteriological eradication is an important determinant of clinical outcome in this setting and suggest that high MICs are associated with increased rates of clinical failure.

**Acute otitis media**

Elevated MICs have been associated with lower rates of eradication of pathogens from the middle ear, correlating with high rates of clinical failure in patients with AOM. The effect of bacteriological failure on clinical failure has been investigated in 206 children with AOM using the double-tympanocentesis method. Of 123 children culture-positive before treatment, 57 (46%) were culture-positive on day 4–5 of antibiotic therapy and 66 (54%) showed bacteriological eradication. Among the 57 children who were culture-positive at day 4–5, there were 21 clinical failures (37%) at day 10 of the study. In contrast, of the 66 children that were culture-negative on day 4–5, only two (3%) were clinical failures at day 10. While clinical success was clearly maximized (97%) through bacterial eradication, 63% of bacteriological failures at day 4–5 were clinically cured by day 10.

Figure 3. Relationship between eradication failure rates and clinical failure rates in patients with AECB. (Reproduced with permission from the *Journal of Antimicrobial Chemotherapy*)
Economic impact of resistance on the management of RTIs

Current antimicrobial therapy for CARTIs is empirical and influenced by local differences in aetiology and bacterial susceptibility. Consequently, the reported rise in antimicrobial resistance has the potential to increase direct healthcare resources and costs in patients with upper and lower RTIs. Furthermore, the reliance on empirical strategies in recent times may have reduced the costs associated with laboratory culture and susceptibility testing, but unfortunately appears to have increased associated drug costs due to the widespread use of broad-spectrum antimicrobials and increasing numbers of clinical failures.

A number of factors associated with the rise in treatment failures among bacterial infections have an impact on the use of healthcare resources and costs, including the need for reconsultation, additional antibiotic prescriptions, and longer stays in hospital. The combination of these factors results in the high cost of treating patients with lower RTIs, particularly those who require hospitalization. Resistance among RTI pathogens also has the potential to increase indirect costs to society, including lost productivity and income, absenteeism from work or school, and reduction in patients’ quality of life.

Community-acquired pneumonia

CAP is the sixth leading cause of death in the USA, where 3–6 million cases are reported per year, accounting for approximately 10 million physician visits, 500000–800000 hospitalizations (of which ~125000 are pneumococcal in origin) and 45000 deaths. Pneumococcal infections are a major cause of morbidity and mortality and are estimated to cause 500000 cases of pneumonia, 550000 cases of bacteraemia and 6000 cases of meningitis annually in the USA. Whilst few data on the economic impact of pneumococcal disease in outpatients have been reported in the literature, inpatient care accounts for over 90% of the total cost of managing CAP. Furthermore, if antibiotic resistance causes higher rates of outpatient treatment failure, higher rates of hospitalization are likely to result. Consequently, continued efforts are being made to manage CAP patients more effectively in the outpatient setting.

In a retrospective, observational cohort study of all patients admitted to the University of Iowa Hospital and Clinics in the USA between 1995 and 1998, blood or respiratory sources were tested for positive S. pneumoniae cultures. Patients infected with S. pneumoniae were hospitalized for ≥2 days after their first positive culture and received ≥2 days of antimicrobial therapy directed against the pathogen. A total of 235 cases were identified, of which 144 (61%) were penicillin susceptible and 91 (39%) were non-susceptible to penicillin. Healthcare expenditures peaked on day 0 (10% of total) and declined to pre-day 0 levels by day 14. Of the total charge, 50%, 12%, 1% and 8% were attributable to room/nursing, pharmacy, antibiotics and laboratory utilization, respectively. Median total charges over the infection window (days ~2 to 14) were $19372.21 and $27958.70 for susceptible and non-susceptible strains, respectively (P < 0.05), meaning that the penicillin non-susceptible strains resulted in excess charges of $8582 (95% CI $402; $16762) over this period of time. Charges were also greater in the non-susceptible group [$2575 (95% CI $21.67; $5129)] compared with the susceptible group during the intervention window (days ~1 to 7). Regardless of the window used, significant differences in resource utilization between the two groups were observed in terms of total charges, hospital room charges, nursing care and pharmacy charges.

A second case control study involving 72 patients infected with either penicillin-susceptible (n = 36) or -non-susceptible (n = 36) strains of pneumococci revealed that 29% of the patients infected with susceptible strains had bacteraemia compared with 8% of those who were infected with non-susceptible strains (P = 0.09). The proportion of patients surviving at 30 days was similar, however, in the susceptible and non-susceptible groups (94% versus 89%, P = NS). Importantly, the average duration of hospitalization was significantly longer in the patients harbouring penicillin-non-susceptible pneumococci than those infected with penicillin-susceptible strains (26.8 versus 11.5 days, P = 0.001). Average pharmacy (antibiotic) costs were also much higher in the non-susceptible group compared with the penicillin-susceptible group ($736 versus $213, P = 0.0001). These results indicate that, while the initial clinical presentation of patients with penicillin-non-susceptible S. pneumoniae seems milder, patients tend to require a longer stay in hospital and the use of more expensive antibiotics.

A recent mathematical model study estimated the impact of resistance and cross-resistance on the rate of initial treatment failure, hospitalization rates and treatment costs for the whole episode of care in the outpatient treatment of adult CAP in the USA. Outcomes were calculated for three scenarios, namely actual resistance and cross-resistance rates, assuming an absence of cross-resistance, and assuming no resistance. Two representative treatment strategies were chosen: oral amoxicillin (500 mg three times a day) followed by oral clarithromycin (500 mg twice a day); or oral clarithromycin (500 mg twice a day) followed by oral levofloxacin (500 mg once a day). Susceptibility and cross-resistance data were taken from the 1997 Alexander Project surveillance data (www.alexander-network.com). The estimates suggested that antibiotic resistance is having a major impact on hospitalization and cost (Table 2). For example, almost 40% of the hospitalizations and costs associated with amoxicillin plus clarithromycin treatment may be attributable to resistance. Furthermore, for S. pneumoniae, cross-resistance had a significant impact on
the effectiveness of treatment with amoxicillin plus clarithromycin.

Acute exacerbations of chronic bronchitis

Niederman et al. reported that the total cost of treating patients with AECB was $1.2 billion/year for patients over 65 years of age and $419 million for those less than 65 years old (1994 charges inflated to 1995 prices). Hospital costs accounted for a large proportion of the total cost in the two age groups ($1.1 billion and $408 million), while outpatient visits contributed $24.9 million and $15.1 million, respectively. In addition, analysis of the average total costs for the management of ambulatory sinusitis and bronchitis patients revealed that 85% of the costs are related to medical expenditure, including laboratory costs, X-rays, initial visits, follow-up visits, etc., followed by only 8% for prescription antibiotics, and 7% for other prescription drugs.

Consequently, as in CAP, it is important that initial therapy is successful because treatment failure can result in marked increases in costs, particularly if hospitalization is required. This was illustrated by an evaluation of the efficacy of four treatment options in the management of patients with AECB, during which Backhouse et al. calculated the direct cost for each successfully-treated patient. The cost of treatment failure was typically much higher than the acquisition costs of first-line antibiotics. In a further study that investigated the primary factors determining the cost-effectiveness of different antibiotic classes in the management of patients with AECB, the costs of treatment were greater for patients with more severe AECB than for patients with mild-to-moderate infection because of the increased need for hospitalization. These findings confirm that the cost of treatment failure as a result of antimicrobial resistance is high and is affected by the efficacy of the antibiotic regimen used as first-line therapy.

Table 2. Impact of resistance on additional duration of hospitalization and additional costs

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<th>Amoxicillin/clarithromycin</th>
<th>Clarithromycin/levofloxacin</th>
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<td>Overall duration</td>
<td>4.4</td>
<td>2.2</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>4.3</td>
<td>4.1</td>
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<td>H. influenzae</td>
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<td>Overall cost ($)</td>
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<td>S. pneumoniae</td>
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<td>H. influenzae</td>
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Acute otitis media

In the USA, the total annual direct medical cost of AOM for children under 5 years of age, including the costs of prescriptions plus office visits, has been estimated at $4 billion. Adding the costs of treating AOM in older children brings the total to more than $5 billion. In addition, the estimated total cost of treating one complicated 3-month episode of AOM is $1331 and treatment costs for recurrent episodes are substantially higher. Furthermore, it has been estimated that 90% of the costs of treating an episode of AOM can be attributed to indirect costs, primarily for parental or caregiver time away from work.

The potential consequences of the increasing prevalence of resistant bacterial strains include treatment failures, the need for additional courses of antibiotics and unresolved respiratory infections. In patients with AOM, inadequate treatment can result in persistence of middle ear effusion, suppurrative complications, the need for surgical implantation of tubes, long-term hearing loss, decreased perception of language, impaired speech development and learning deficiencies. In addition, the obvious disease sequelae caused by chronic infection may be accompanied by a significant drain on healthcare resources.

Conclusions

The increasing prevalence of antimicrobial resistance in S. pneumoniae and other common RTI pathogens, such as H. influenzae and M. catarrhalis, impacts greatly on the usefulness of the currently available antibiotics. When penicillin is considered, the implications of in vitro resistance in the management of RTIs are dependent upon the site of infection, highlighting the need for modification of current MIC breakpoints. The impact of pneumococcal resistance on the clinical and microbiological efficacy of the macrolides has also become apparent in recent times, although effective resistance rates vary according to the macrolide examined. It must be remembered, however, that all currently available 14- and 15-membered ring macrolides are strong inducers of MLSB resistance, and so selection pressure will, therefore, be maintained as they are used.

While the available data on the economic impact of antimicrobial resistance on patients with RTIs are limited, the total cost of care is driven by medical, rather than prescription costs. It is important to note that individual antimicrobial agents differ with respect to the optimization of microbiology, pharmacology and toxicity profiles, the potential for the development of resistance, and their impact on the total cost of care. Consequently, pharmacokinetic and pharmacodynamic parameters are being used increasingly to predict the potential for maximally effective therapy and optimal bacterial eradication, thus limiting the development of resist-
Pharmacokinetic parameters, including absorption, distribution, metabolism and excretion, have an effect on the concentration of the active drug present at the infection site. Along with pharmacodynamic parameters, such as time- or concentration-dependent killing, these factors influence clinical outcome, microbiological outcome and other outcome measures of efficacy such as the rate of response and disease-free interval. Use of these parameters alongside the results from studies of local susceptibility patterns should be employed to facilitate appropriate prescribing of antimicrobials only for indications for which they have proven efficacy.

Optimizing the selection of patients most eligible to receive antibiotics according to stringent clinical criteria is the first step in promoting both good clinical practice and cost effectiveness. The efficacy of antimicrobial therapy rather than medical expenditure, including laboratory costs, X-rays, initial visits, follow-up visits, etc., would then be the major driver of cost, particularly if the need for hospitalization was reduced. Thus, effective first-line antimicrobial therapy with new antibiotics active against emerging resistant pathogens could reduce the overall cost of cure in patients with both upper and lower RTIs. Furthermore, such strategy may significantly impact on the emergence of antimicrobial resistance and if allied with careful selection of antimicrobials to ensure eradication of both susceptible and resistant pathogens, could help to prevent the development and spread of bacterial antimicrobial resistance in the community.

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Clinical and economic implications of antimicrobial resistance for the management of community-acquired respiratory tract infections

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Lower respiratory tract infections (RTIs), particularly community-acquired pneumonia (CAP), account for over 50 million deaths annually worldwide. They place an extensive clinical and financial burden on healthcare authorities. Upper RTIs, usually mild and non-life threatening, also incur significant healthcare costs. The rising prevalence of resistance of the major causative agents of CAP (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) to β-lactam antimicrobials and newer macrolides has necessitated new strategies for appropriate antimicrobial usage. A successful clinical outcome will depend on the patient, choice of drug, and the epidemiology and resistance of the pathogen. Treatment failure will result in increased costs, particularly if hospitalization is required. Pharmacokinetic and pharmacodynamic parameters are being used increasingly to predict maximally effective therapy and optimal bacterial eradication, thus limiting the development of resistance. Antimicrobial susceptibility criteria by MIC should be dictated by the type and location of the infection. Modifying the current MIC breakpoints for penicillin so that more pneumococcal pneumonia isolates are reported appropriately as being susceptible may lead to a decrease in the use of broad-spectrum antimicrobial therapy and its associated increased costs, in favour of more narrow-spectrum therapy. Targeting the pathogen with the most effective antimicrobial in an appropriately selected patient should optimize clinical and microbiological success and, consequently, maximize response rates and economic outcomes. In addition, research efforts need to concentrate on developing new agents with low propensity to select for or induce resistance.

Introduction

Respiratory tract infections (RTIs) are among the most widespread and serious infections, accounting for over 50 million deaths globally each year. RTIs also represent the most common reason for physician visits and prescription of antibiotics. Infections of the lower respiratory tract include community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB), which are associated with significant rates of mortality and are among the top 10 causes of death in the developed world. In developing countries, infants under 4 years of age are at greatest risk of mortality from lower RTIs, whereas in developed countries the severity of infection and rate of mortality are greatest in the elderly. Community-acquired pneumonia, which is caused by a range of bacterial pathogens including Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis, is common and is the sixth leading cause of death in the USA. Chronic bronchitis is also very common, and in 1994 it was estimated that more than 14 million Americans were affected, representing ~5.4% of the adult population of the USA. The prevalence of lower RTIs places an extensive clinical and financial burden on healthcare authorities.

Infections of the upper respiratory tract, such as sinusitis, pharyngitis and acute otitis media (AOM), occur within the population at a higher frequency than lower RTIs, but are usually mild and non-life-threatening. However, upper RTIs may also incur significant healthcare costs and can lead to serious complications if not treated effectively. For example, AOM is the most commonly diagnosed bacterial infection in children, and ~75% of children will have had three or more ear infections by the age of 7. Furthermore, AOM is the most common reason for antibiotic prescribing in young children and infants, and the number of physician visits for AOM has risen steadily in recent times, reaching almost 30 million visits in 1996.
Current antimicrobial therapy for community-acquired RTIs (CARTIs) is typically empirical and is influenced by local differences in aetiology and bacterial susceptibility. Rising prevalence of resistance among S. pneumoniae to the β-lactam antibiotics and the newer macrolide antimicrobials, together with cross-resistance between the macrolides, has been reported. In response to these trends, the fluoroquinolones are now being more widely prescribed. More recently, a low, but increasing incidence of fluoroquinolone resistance among S. pneumoniae has been observed. Furthermore, there are clear differences in the in vitro activity of different fluoroquinolones against this pathogen. Resistance to β-lactams is also rising at an alarming rate in some countries among strains of H. influenzae and is already particularly high globally in M. catarrhalis. Data from PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) show rates of β-lactamase production among isolates of H. influenzae that range from 3.3 to 64.7% (overall 16.6%); for M. catarrhalis the range is 84.2–100% (overall 94.7%).

Overall, these issues threaten the effectiveness of empirical treatment strategies in patients with CARTIs, and may result in poor clinical outcome and an extensive financial and clinical burden. This burden is likely to increase further as life expectancy increases in developed countries and levels of antimicrobial resistance rise. Consequently, new emphasis is being placed on strategies for appropriate antimicrobial usage, and research efforts are concentrating on developing new agents with low propensity to select for or induce resistance. This paper discusses some of the issues relating to the clinical and economic impact of antimicrobial resistance on the management of patients with CARTIs, with a particular emphasis on S. pneumoniae resistance in CAP.

Evaluation of outcome in patients with RTIs

In the management of infectious diseases, including those affecting the respiratory tract, maximizing the probability of a good clinical outcome is one of the key aims of antimicrobial treatment. The host, issues relating to drugs and drug selection, and the changing epidemiology and resistance in specific pathogens, all affect the probability of a successful clinical outcome and have the potential to impact on the cost-effectiveness of treatment. Commonly used outcome evaluations in clinical trials involving patients with CARTIs include both clinical and microbiological endpoints, which are frequently assessed at the end of therapy and/or at the end of the study period. Specific clinical evaluations include cure or failure rates following treatment, or assessment of changes in symptoms of infection. Microbiological evaluations include determination of whether the causative pathogen persists or has been eradicated by antimicrobial therapy. Many of these outcomes are of both conventional and historical value, and are used routinely for registration purposes, but do not necessarily provide sufficient predictive information concerning the effects of antimicrobial intervention.

Specific additional measures that would add valuable insight into the outcome of antimicrobial chemotherapeutic intervention include: the duration of effect, measured by the patient’s disease-free interval, for example in patients with AECB; the correlation between clinical response and microbiological eradication; and the economic consequences of treatment, which invariably focuses on the utilization of healthcare resources. Targeting the causative pathogen with the most effective antimicrobial agent in an appropriately selected patient would be expected to optimize clinical and microbiological success and, consequently, maximize rates of response and economic outcomes.

Evolving resistance in common RTI pathogens

One of the key issues concerning the selection of the most appropriate antimicrobial agent is the development of resistance among the most common bacterial RTI pathogens. Increasing prevalence of resistant isolates may impede pathogen eradication in lower RTIs, potentially exacerbating the spread of resistant clones. This can lead to recolonization of the mucosal membranes with such clones and has implications for host-to-host transmission and global spread of resistant clones.

Penicillin susceptibility criteria by MIC have been defined by the NCCLS based on S. pneumoniae infections in cerebrospinal fluid (CSF): susceptible, MIC ≤ 0.06 mg/L; intermediate, MIC 0.12–1.0 mg/L; or resistant, MIC ≥ 2 mg/L. However, it is important to note that MIC breakpoints have different meanings depending on the type and location of the infection being treated. The effect of antimicrobial resistance in S. pneumoniae, the major bacterial cause of RTIs, is most evident at sites of infection where antibiotic penetration is restricted, for example in patients with closed-space infections such as meningitis or otitis media. The reason for this is that much higher levels of penicillin are achieved in the blood and the alveoli compared with the CSF. Consequently, intermediate susceptibility to penicillin, as defined by the current NCCLS criteria, is unlikely to be clinically relevant in patients with pneumonia treated with generally accepted doses of penicillins. However, high-level resistance (MIC ≥ 4 mg/L) may impede clinical response.

Penicillin and macrolide resistance in pneumococcal pneumonia

PROTEKT is a global surveillance study of the prevalence of resistance among bacterial pathogens causing CARTIs. Data from the PROTEKT surveillance study (www.protekt.org) have shown that up to 22% of S. pneumoniae isolates are
resistant to penicillin, with combined intermediate and resistant strains accounting for over 36% of isolates examined worldwide. A similarly high proportion of isolates (31%) is resistant to the macrolides. These recent findings support those from two previous major antimicrobial surveillance studies, namely the Alexander Project\textsuperscript{16,26} and the SENTRY study,\textsuperscript{17} which also indicated that resistance to \( \beta \)-lactams and macrolide antimicrobials is widespread.

In terms of penicillin breakpoints specific for CAP, evidence published by the Drug-Resistant \textit{Streptococcus pneumoniae} Therapeutic Working Group\textsuperscript{27} suggests that strains of this pathogen should be considered susceptible if the penicillin MIC is \( \leq 1 \) mg/L. Strains for which the penicillin MICs are 2 and 4 mg/L should be considered to be of intermediate susceptibility. Some evidence indicates that there is no increase in the number of pneumonia treatment failures when penicillin- intermediate strains are implicated, whereas other evidence suggests that there is an increased risk of mortality or complications in patients with infection due to strains of intermediate susceptibility. Whilst too few patients with pneumonia due to pneumococcal isolates with penicillin MICs of \( \geq 4 \) mg/L have been studied to draw appropriate conclusions, pharmacodynamic considerations indicate theoretical reasons for concern.\textsuperscript{27}

These observations suggest that higher susceptibility testing breakpoints for penicillin are appropriate for non-central nervous system infections, and revised breakpoints should be considered based on the site of infection as well as pharmacokinetic/pharmacodynamic considerations.\textsuperscript{25}Modifying the MIC breakpoints so that more pneumococcal pneumonia isolates are reported appropriately as being susceptible, may lead to a decrease in the use of broad-spectrum antimicrobial therapy in favour of more narrow-spectrum therapy.\textsuperscript{27}

The effectiveness of the macrolides in the management of CARTIs has been affected by the emergence of macrolide-resistant pneumococci in the late 1990s; prevalence rates exceeding 30% are not uncommon.\textsuperscript{13–17} However, in the year 2000, reports of fewer than 10 macrolide treatment failures have been published,\textsuperscript{28,29} which is a low frequency considering the high number of prescriptions for this class of antimicrobial agent.

Why have there not been more reports of macrolide failure? Consideration should be given to the fact that the majority of macrolide prescriptions are written as part of empirical therapy for outpatients where no microbiological or antibiotic susceptibility testing data exist. In addition, sputum cultures are rarely taken, even in patients who have failed previous courses of antimicrobial therapy.\textsuperscript{28}Furthermore, most community infections are of mild to moderate severity and some resolve spontaneously without treatment. The need to repeat a treatment course may be due to resistance but this is rarely proven. In addition, data from clinical trials are not always informative in this respect because patients who are at greatest risk are often excluded.

In a recent study, three patients who received azithromycin 500 mg for 3–5 days presented with bacteraemic community-acquired lower RTI caused by drug-resistant \textit{S. pneumoniae}.\textsuperscript{28}These patients were subsequently successfully treated with the fluoroquinolone levofloxacin (500 mg/day), with complete resolution of symptoms and chest roentgenogram abnormalities after 14 days of therapy. Molecular characterization of azithromycin resistance revealed that one of the \textit{S. pneumoniae} isolates contained a \textit{erm}(B) determinant, which encodes for a macrolide efflux pump,\textsuperscript{30} whilst another contained an \textit{erm}(E) determinant, which confers resistance to the macrolide–lincomamide–streptogramin-B (MLS\textsubscript{B}) antimicrobials via methylation of the binding site of these agents at the ribosomal level (23S rRNA).\textsuperscript{31}

In a retrospective study conducted in Spain and the USA during 1986–1999, Garau et al.\textsuperscript{32} identified 57 macrolide-resistant pneumococcal blood isolates. A total of 12 patients, 11 of whom had pneumonia, developed bacteremia while receiving treatment with macrolides (erythromycin, clarithromycin, azithromycin or josamycin) for 2–8 days. Of these, all nine isolates from Spain contained the \textit{erm} determinant, and one of three isolates from the USA contained the \textit{erm} determinant. Two of the isolates had high-level penicillin resistance (MIC 2 mg/L), six had intermediate resistance and three were fully susceptible to penicillin. Subsequently, all of the patients were treated successfully with a \( \beta \)-lactam antibiotic. In another study, four outpatients receiving macrolides developed bacteremia due to resistant \textit{S. pneumoniae}.\textsuperscript{39} All of the strains were resistant to erythromycin but susceptible to clindamycin. While the mechanisms of resistance were not assessed, their susceptibility to clindamycin suggests that they contained the \textit{erm} determinant responsible for the efflux mechanism of resistance, which is supported by the MICs (8–16 mg/L) associated with the low-level resistance often observed with this efflux system.

**Genotypic prevalence of \textit{S. pneumoniae} macrolide resistance**

Azithromycin and clarithromycin have different pharmacokinetic profiles both at the peripheral site (plasma) and at the site of infection (epithelial lining fluid, ELF).\textsuperscript{33} Additionally the \textit{in vitro} potency of these two agents is markedly different for \textit{S. pneumoniae} as is evident from the MIC distribution analysis from a recent US surveillance study.\textsuperscript{34} These surveillance data also reveal the trimodal MIC distribution pattern of this organism, since \( \sim75\% \) of pneumococci are susceptible to macrolides, 18% are efflux mutants (\textit{erm}, MIC 1–32 mg/L), and 7% are high-level (\textit{erm}, MIC \( \geq 64 \) mg/L) resistant strains (Figure 1).
Overlaying ELF clarithromycin concentrations upon the MIC distribution of the same compound reveals that drug concentrations at the site of infection exceed the MIC of susceptible isolates and many of those pneumococci exhibiting the efflux resistance mechanism. As a result of this pharmacodynamic profile at the infection site the currently used MIC breakpoints may be inaccurate, i.e. the effective resistance rate is ~10–12% compared with the reported surveillance resistance rates of 25–30%. In comparison, the concentrations of azithromycin in the ELF are ~2 mg/L, which does not exceed the compound’s MICs for pneumococci with either mef- or erm-mediated resistance. Consequently, the MIC breakpoint for azithromycin appears to be correct, i.e. the reported resistance rate is probably similar to the effective resistance rate. These findings indicate that strains of *S. pneumoniae* with MIC ≤0.5 mg/L are susceptible to azithromycin, whereas those exceeding this value should be considered resistant (Figure 2). It is important, therefore, to consider not only microbiological potency, but also to take into account drug concentrations at the site when assessing the clinical utility of the macrolides (i.e. microbiologically determined breakpoints versus those achieved by means of pharmacodynamic analysis).

The prevalence of the *erm* and *mef* determinants amongst macrolide-resistant pneumococci varies according to the geographical region. A number of studies conducted in the USA, Canada, Europe and Japan have examined the genotype of *S. pneumoniae* macrolide resistance. Efflux (*mef*) resistance is more prevalent in the USA and Canada (56–71%), while high-level (*erm*) resistance is more prevalent in Europe (97%) (Table 1). In Japan, the overall macrolide resistance exceeds 70% and the prevalence of *erm* and *mef* genotypes is similar (40% and 43%, respectively), while dual genotypes have been noted in most of the remaining macrolide-resistant pneumococci. Confirmatory results from PROTEKT are presented elsewhere.

Resistance of RTI pathogens implicated in acute exacerbations of chronic bronchitis and acute otitis media

Resistance of bacteria commonly implicated in AECB and AOM, namely *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, has been reported in a number of prospective surveillance studies. Indeed, data from 845 *S. pneumoniae* isolates analysed as part of the SENTRY surveillance study showed that, although resistance rates varied widely, 28% of isolates demonstrated intermediate resistance to penicillin and 16% had high-level resistance.

Alexander Project data from 1992–1997 indicate that the prevalence of β-lactamase production among isolates of *H. influenzae* appears to have reached a steady state in some countries, such as France and the USA, but may be as high as 35% in some areas. A number of studies have illustrated the effect of β-lactamase production on the efficacy of amoxicillin in patients with AOM, revealing that eradication rates for β-lactamase-positive isolates were similar to spontaneous eradication rates observed for *H. influenzae*. Although the use of a vaccine against the most virulent serotype of *H. influenzae* (serotype b) may decrease the importance of this strain, resistant, non-typeable strains remain clinically significant CARTI pathogens.

β-Lactam resistance is almost invariably higher in *M. catarrhalis* than in *H. influenzae*. Most (50–80%) isolates of *M. catarrhalis* collected as part of the Alexander Project during 1992 produced β-lactamase. However, the rate of β-lactamase production had increased to 90–100% in the participating centres in this study by 1997. Resistance to other (non-β-lactam) antibiotic classes was stable in both *M. catarrhalis* and *H. influenzae*. 

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**Figure 1.** Macrolide MIC frequency distribution for *S. pneumoniae* (1999–2000, n = 1531).

**Figure 2.** Azithromycin pharmacodynamics at the site of pulmonary infection: ELF.
Antimicrobial resistance in community-acquired RTIs

Table 1. _S. pneumoniae_ macrolide resistance: genotypic prevalence

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Clinical impact of antimicrobial resistance in RTIs

_Pneumococcal pneumonia_

Little published data are available on the impact of antimicrobial resistance on the rate of response in non-susceptible pneumococcal pneumonia. However, one study has been conducted to determine the usefulness of procaine penicillin in the treatment of suspected pneumococcal pneumonia of mild to moderate severity in an area with a high prevalence of penicillin resistance.45 Of 49 patients receiving procaine penicillin (1.2 million units given intramuscularly every 12 h), 40 (82%) were cured and no deaths due to infection were reported. Seventeen patients had documented _S. pneumoniae_ infection, five of whom had penicillin-resistant isolates (MICs 0.25–4 mg/L). Although 15 of the patients infected with _S. pneumoniae_ were cured (one patient had an allergic reaction and the other failed treatment), the duration of the following symptoms was longer in patients infected with penicillin-resistant isolates compared with those from whom penicillin-susceptible pneumococci were isolated: fever (3.6 versus 1.9 days), cough and sputum production (6.0 versus 2.7 days), and pleuritic pain (3.6 versus 2.1 days). Even though the number of cases in this study was too small to perform a rigorous statistical analysis, these results suggest that penicillin susceptibility may have an impact on symptom resolution in patients with pneumococcal infection.

_Acute exacerbations of chronic bronchitis_

Although the _in vitro_ data indicate significant levels of resistance, few data are available on the clinical impact of antimicrobial resistance in patients with AECB. Most studies do not demonstrate any difference in outcome between patients infected with penicillin-resistant isolates and those infected with susceptible strains.22 However, a review of 12 studies of patients with AECB demonstrated a strong correlation (r = 0.91) between eradication failure rates and clinical failure rates following treatment with macrolides, fluoroquinolones, penicillins, cephalosporins, or co-trimoxazole (Figure 3).46 These data support the premise that bacteriological eradication is an important determinant of clinical outcome in this setting and suggest that high MICs are associated with increased rates of clinical failure.

_Acute otitis media_

Elevated MICs have been associated with lower rates of eradication of pathogens from the middle ear, correlating with high rates of clinical failure in patients with AOM.47,48 The effect of bacteriological failure on clinical failure has been investigated in 206 children with AOM using the double-tympanocentesis method.47 Of 123 children culture-positive before treatment, 57 (46%) were culture-positive on day 4–5 of antibiotic therapy and 66 (54%) showed bacteriological eradication. Among the 57 children who were culture-positive at day 4–5, there were 21 clinical failures (37%) at day 10 of the study. In contrast, of the 66 children that were culture-negative on day 4–5, only two (3%) were clinical failures at day 10. While clinical success was clearly maximized (97%) through bacterial eradication, 63% of bacteriological failures at day 4–5 were clinically cured by day 10.

Figure 3. Relationship between eradication failure rates and clinical failure rates in patients with AECB.41 (Reproduced with permission from the _Journal of Antimicrobial Chemotherapy_)
Economic impact of resistance on the management of RTIs

Current antimicrobial therapy for CARTIs is empirical and influenced by local differences in aetiology and bacterial susceptibility. Consequently, the reported rise in antimicrobial resistance has the potential to increase direct healthcare resources and costs in patients with upper and lower RTIs. Furthermore, the reliance on empirical strategies in recent times may have reduced the costs associated with laboratory culture and susceptibility testing, but unfortunately appears to have increased associated drug costs due to the widespread use of broad-spectrum antimicrobials and increasing numbers of clinical failures.49

A number of factors associated with the rise in treatment failures among bacterial infections have an impact on the use of healthcare resources and costs, including the need for reconsultation, additional antibiotic prescriptions, and longer stays in hospital.22,49,50 The combination of these factors results in the high cost of treating patients with lower RTIs, particularly those who require hospitalization.49 Resistance among RTI pathogens also has the potential to increase indirect costs to society, including lost productivity and income, absenteeism from work or school, and reduction in patients’ quality of life.22,51

Community-acquired pneumonia

CAP is the sixth leading cause of death in the USA, where 3–6 million cases are reported per year, accounting for approximately 10 million physician visits, 500,000–800,000 hospitalizations (of which ~125,000 are pneumococcal in origin) and 45,000 deaths.5,7 Pneumococcal infections are a major cause of morbidity and mortality and are estimated to cause 500,000 cases of pneumonia, 55,000 cases of bacteraemia and 6,000 cases of meningitis annually in the USA.52,53 Whilst few data on the economic impact of pneumococcal disease in outpatients have been reported in the literature, inpatient care accounts for over 90% of the total cost of managing CAP.6,7 Furthermore, if antibiotic resistance causes higher rates of outpatient treatment failure, higher rates of hospitalization are likely to result. Consequently, continued efforts are being made to manage CAP patients more effectively in the outpatient setting.6

In a retrospective, observational cohort study of all patients admitted to the University of Iowa Hospital and Clinics in the USA between 1995 and 1998, blood or respiratory sources were tested for positive S. pneumoniae cultures.50 Patients infected with S. pneumoniae were hospitalized for ≥2 days after their first positive culture and received ≥2 days of antimicrobial therapy directed against the pathogen. A total of 235 cases were identified, of which 144 (61%) were penicillin susceptible and 91 (39%) were non-susceptible to penicillin. Healthcare expenditures peaked on day 0 (10% of total) and declined to pre-day 0 levels by day 14. Of the total charge, 50%, 12%, 1% and 8% were attributable to room/nursing, pharmacy, antibiotics and laboratory utilization, respectively. Median total charges over the infection window (days –2 to 14) were $19,372.21 and $27,958.70 for susceptible and non-susceptible strains, respectively (P < 0.05), meaning that the penicillin non-susceptible strains resulted in excess charges of $8582 (95% CI $402; $16762) over this period of time. Charges were also greater in the non-susceptible group [$2575 (95% CI $21.67; $5129)] compared with the susceptible group during the intervention window (days –1 to 7). Regardless of the window used, significant differences in resource utilization between the two groups were observed in terms of total charges, hospital room charges, nursing care and pharmacy charges.

A second case control study involving 72 patients infected with either penicillin-susceptible (n = 36) or non-susceptible (n = 36) strains of pneumococci revealed that 29% of the patients infected with susceptible strains had bacteraemia compared with 8% of those who were infected with non-susceptible strains (P = 0.09). The proportion of patients surviving at 30 days was similar, however, in the susceptible and non-susceptible groups (94% versus 89%, P = NS).54 Importantly, the average duration of hospitalization was significantly longer in the patients harbouring penicillin-non-susceptible pneumococci than those infected with penicillin-susceptible strains (26.8 versus 11.5 days, P = 0.001). Average pharmacy (antibiotic) costs were also much higher in the non-susceptible group compared with the penicillin-susceptible group ($736 versus $213, P = 0.0001). These results indicate that, while the initial clinical presentation of patients with penicillin-non-susceptible S. pneumoniae seems milder, patients tend to require a longer stay in hospital and the use of more expensive antibiotics.

A recent mathematical model study estimated the impact of resistance and cross-resistance on the rate of initial treatment failure, hospitalization rates and treatment costs for the whole episode of care in the outpatient treatment of adult CAP in the USA.55 Outcomes were calculated for three scenarios, namely actual resistance and cross-resistance rates, assuming an absence of cross-resistance, and assuming no resistance. Two representative treatment strategies were chosen: oral amoxicillin (500 mg three times a day) followed by oral clarithromycin (500 mg twice a day); or oral clarithromycin (500 mg twice a day) followed by oral levofloxacin (500 mg once a day). Susceptibility and cross-resistance data were taken from the 1997 Alexander Project surveillance data (www.alexander-network.com). The estimates suggested that antibiotic resistance is having a major impact on hospitalization and cost (Table 2). For example, almost 40% of the hospitalizations and costs associated with amoxicillin plus clarithromycin treatment may be attributable to resistance. Furthermore, for S. pneumoniae, cross-resistance had a significant impact on
the effectiveness of treatment with amoxicillin plus clarithromycin.

**Acute exacerbations of chronic bronchitis**

Niederman et al.\(^8\) reported that the total cost of treating patients with AECB was $1.2 billion/year for patients over 65 years of age and $419 million for those less than 65 years old (1994 charges inflated to 1995 prices). Hospital costs accounted for a large proportion of the total cost in the two age groups ($1.1 billion and $408 million), while outpatient visits contributed $24.9 million and $15.1 million, respectively. In addition, analysis of the average total costs for the management of ambulatory sinusitis and bronchitis patients revealed that 85% of the costs are related to medical expenditure, including laboratory costs, X-rays, initial visits, follow-up visits, etc., followed by only 8% for prescription antibiotics, and 7% for other prescription drugs.\(^5^6\)

Consequently, as in CAP, it is important that initial therapy is successful because treatment failure can result in marked increases in costs, particularly if hospitalization is required. This was illustrated by an evaluation of the efficacy of four treatment options in the management of patients with AECB, during which Backhouse et al.\(^5^7\) calculated the direct cost for each successfully-treated patient. The cost of treatment failure was typically much higher than the acquisition costs of first-line antibiotics. In a further study that investigated the primary factors determining the cost-effectiveness of different antibiotic classes in the management of patients with AECB, the costs of treatment were greater for patients with more severe AECB than for patients with mild-to-moderate infection because of the increased need for hospitalization.\(^5^8\)

These findings confirm that the cost of treatment failure as a result of antimicrobial resistance is high and is affected by the efficacy of the antibiotic regimen used as first-line therapy.

**Table 2. Impact of resistance on additional duration of hospitalization and additional costs\(^5^5\)**

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<th>Amoxicillin/clarithromycin</th>
<th>Clarithromycin/levofloxacin</th>
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<td>Additional duration of hospitalization (%)</td>
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**Acute otitis media**

In the USA, the total annual direct medical cost of AOM for children under 5 years of age, including the costs of prescriptions plus office visits, has been estimated at $4 billion.\(^5^9\) Adding the costs of treating AOM in older children brings the total to more than $5 billion.\(^2\) In addition, the estimated total cost of treating one complicated 3-month episode of AOM is $1331\(^6^0\) and treatment costs for recurrent episodes are substantially higher. Furthermore, it has been estimated that 90% of the total costs of treating an episode of AOM can be attributed to indirect costs, primarily for parental or caregiver time away from work.\(^6^0\)

The potential consequences of the increasing prevalence of resistant bacterial strains include treatment failures, the need for additional courses of antibiotics and unresolved respiratory infections. In patients with AOM, inadequate treatment can result in persistence of middle ear effusion, suppurrative complications, the need for surgical implantation of tubes, long-term hearing loss, decreased perception of language, impaired speech development and learning deficiencies.\(^2\) In addition, the obvious disease sequelae caused by chronic infection may be accompanied by a significant drain on healthcare resources.

**Conclusions**

The increasing prevalence of antimicrobial resistance in *S. pneumoniae* and other common RTI pathogens, such as *H. influenzae* and *M. catarrhalis*, impacts greatly on the usefulness of the currently available antibiotics. When penicillin is considered, the implications of *in vitro* resistance in the management of RTIs are dependent upon the site of infection, highlighting the need for modification of current MIC breakpoints. The impact of pneumococcal resistance on the clinical and microbiological efficacy of the macrolides has also become apparent in recent times, although effective resistance rates vary according to the macrolide examined. It must be remembered, however, that all currently available 14- and 15-membered ring macrolides are strong inducers of MLS\(_B\) resistance, and so selection pressure will, therefore, be maintained as they are used.

While the available data on the economic impact of antimicrobial resistance on patients with RTIs are limited, the total cost of care is driven by medical, rather than prescription costs. It is important to note that individual antimicrobial agents differ with respect to the optimization of microbiology, pharmacology and toxicity profiles, the potential for the development of resistance, and their impact on the total cost of care. Consequently, pharmacokinetic and pharmacodynamic parameters are being used increasingly to predict the potential for maximally effective therapy and optimal bacterial eradication, thus limiting the development of resist-
Pharmacokinetic parameters, including absorption, distribution, metabolism and excretion, have an effect on the concentration of the active drug present at the infection site. Along with pharmacodynamic parameters, such as time- or concentration-dependent killing, these factors influence clinical outcome, microbiological outcome and other outcome measures of efficacy such as the rate of response and disease-free interval. Use of these parameters alongside the results from studies of local susceptibility patterns should be employed to facilitate appropriate prescribing of antimicrobials only for indications for which they have proven efficacy.

Optimizing the selection of patients most eligible to receive antibiotics according to stringent clinical criteria is the first step in promoting both good clinical practice and cost effectiveness. The efficacy of antimicrobial therapy rather than medical expenditure, including laboratory costs, X-rays, initial visits, follow-up visits, etc., would then be the major driver of cost, particularly if the need for hospitalization was reduced. Thus, effective first-line antimicrobial therapy with new antibiotics active against emerging resistant pathogens could reduce the overall cost of cure in patients with both upper and lower RTIs. Furthermore, such strategy may significantly impact on the emergence of antimicrobial resistance and if allied with careful selection of antimicrobials to ensure eradication of both susceptible and resistant pathogens, could help to prevent the development and spread of bacterial antimicrobial resistance in the community.

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Clinical and economic implications of antimicrobial resistance for the management of community-acquired respiratory tract infections

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Lower respiratory tract infections (RTIs), particularly community-acquired pneumonia (CAP), account for over 50 million deaths annually worldwide. They place an extensive clinical and financial burden on healthcare authorities. Upper RTIs, usually mild and non-life threatening, also incur significant healthcare costs. The rising prevalence of resistance of the major causative agents of CAP (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) to β-lactam antimicrobials and newer macrolides has necessitated new strategies for appropriate antimicrobial usage. A successful clinical outcome will depend on the patient, choice of drug, and the epidemiology and resistance of the pathogen. Treatment failure will result in increased costs, particularly if hospitalization is required. Pharmacokinetic and pharmacodynamic parameters are being used increasingly to predict maximally effective therapy and optimal bacterial eradication, thus limiting the development of resistance. Antimicrobial susceptibility criteria by MIC should be dictated by the type and location of the infection. Modifying the current MIC breakpoints for penicillin so that more pneumococcal pneumonia isolates are reported appropriately as being susceptible may lead to a decrease in the use of broad-spectrum antimicrobial therapy and its associated increased costs, in favour of more narrow-spectrum therapy. Targeting the pathogen with the most effective antimicrobial in an appropriately selected patient should optimize clinical and microbiological success and, consequently, maximize response rates and economic outcomes. In addition, research efforts need to concentrate on developing new agents with low propensity to select for or induce resistance.

Introduction

Respiratory tract infections (RTIs) are among the most widespread and serious infections, accounting for over 50 million deaths globally each year. RTIs also represent the most common reason for physician visits and prescription of antibiotics. Infections of the lower respiratory tract include community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB), which are associated with significant rates of mortality and are among the top 10 causes of death in the developed world. In developing countries, infants under 4 years of age are at greatest risk of mortality from lower RTIs, whereas in developed countries the severity of infection and rate of mortality are greatest in the elderly.

Community-acquired pneumonia, which is caused by a range of bacterial pathogens including Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis, is common and is the sixth leading cause of death in the USA. Chronic bronchitis is also very common, and in 1994 it was estimated that more than 14 million Americans were affected, representing ~5.4% of the adult population of the USA. The prevalence of lower RTIs places an extensive clinical and financial burden on healthcare authorities.

Infections of the upper respiratory tract, such as sinusitis, pharyngitis and acute otitis media (AOM), occur within the population at a higher frequency than lower RTIs, but are usually mild and non-life-threatening. However, upper RTIs may also incur significant healthcare costs and can lead to serious complications if not treated effectively. For example, AOM is the most commonly diagnosed bacterial infection in children, and ~75% of children will have had three or more ear infections by the age of 7. Furthermore, AOM is the most common reason for antibiotic prescribing in young children and infants, and the number of physician visits for AOM has risen steadily in recent times, reaching almost 30 million visits in 1996.
Current antimicrobial therapy for community-acquired RTIs (CARTIs) is typically empirical and is influenced by local differences in aetiology and bacterial susceptibility. Rising prevalence of resistance among *S. pneumoniae* to the β-lactam antibiotics and the newer macrolide antimicrobials, together with cross-resistance between the macrolides, has been reported. In response to these trends, the fluoroquinolones are now being more widely prescribed. More recently, a low, but increasing incidence of fluoroquinolone resistance among *S. pneumoniae* has been observed. Furthermore, there are clear differences in the *in vitro* activity of different fluoroquinolones against this pathogen. Resistance to β-lactams is also rising at an alarming rate in some countries among strains of *H. influenzae* and is already particularly high globally in *M. catarrhalis*. Data from PROTEKT (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin) show rates of β-lactamase production among isolates of *H. influenzae* that range from 3.3 to 64.7% (overall 16.6%); for *M. catarrhalis* the range is 84.2–100% (overall 94.7%).

Overall, these issues threaten the effectiveness of empirical treatment strategies in patients with CARTIs, and may result in poor clinical outcome and an extensive financial and clinical burden. This burden is likely to increase further as life expectancy increases in developed countries and levels of antimicrobial resistance rise. Consequently, new emphasis is being placed on strategies for appropriate antimicrobial usage, and research efforts are concentrating on developing new agents with low propensity to select for or induce resistance. This paper discusses some of the issues relating to the clinical and economic impact of antimicrobial resistance on the management of patients with CARTIs, with a particular emphasis on *S. pneumoniae* resistance in CAP.

**Evaluation of outcome in patients with RTIs**

In the management of infectious diseases, including those affecting the respiratory tract, maximizing the probability of a good clinical outcome is one of the key aims of antimicrobial treatment. The host, issues relating to drugs and drug selection, and the changing epidemiology and resistance in specific pathogens, all affect the probability of a successful clinical outcome and have the potential to impact on the cost-effectiveness of treatment. Commonly used outcome evaluations in clinical trials involving patients with CARTIs include both clinical and microbiological endpoints, which are frequently assessed at the end of therapy and/or at the end of the study period. Specific clinical evaluations include cure or failure rates following treatment, or assessment of changes in symptoms of infection. Microbiological evaluations include determination of whether the causative pathogen persists or has been eradicated by antimicrobial therapy. Many of these outcomes are of both conventional and historical value, and are used routinely for registration purposes, but do not necessarily provide sufficient predictive information concerning the effects of antimicrobial intervention.

Specific additional measures that would add valuable insight into the outcome of antimicrobial chemotherapeutic intervention include: the duration of effect, measured by the patient’s disease-free interval, for example in patients with AECB; the correlation between clinical response and microbiological eradication; and the economic consequences of treatment, which invariably focuses on the utilization of healthcare resources. Targeting the causative pathogen with the most effective antimicrobial agent in an appropriately selected patient would be expected to optimize clinical and microbiological success and, consequently, maximize rates of response and economic outcomes.

**Evolving resistance in common RTI pathogens**

One of the key issues concerning the selection of the most appropriate antimicrobial agent is the development of resistance among the most common bacterial RTI pathogens. Increasing prevalence of resistant isolates may impede pathogen eradication in lower RTIs, potentially exacerbating the spread of resistant clones. This can lead to recolonization of the mucosal membranes with such clones and has implications for host-to-host transmission and global spread of resistant clones.

Penicillin susceptibility criteria by MIC have been defined by the NCCLS based on *S. pneumoniae* infections in cerebrospinal fluid (CSF): susceptible, MIC ≤ 0.06 mg/L; intermediate, MIC 0.12–1.0 mg/L; or resistant, MIC ≥ 2 mg/L. However, it is important to note that MIC breakpoints have different meanings depending on the type and location of the infection being treated. The effect of antimicrobial resistance in *S. pneumoniae*, the major bacterial cause of RTIs, is most evident at sites of infection where antibiotic penetration is restricted, for example in patients with closed-space infections such as meningitis or otitis media. The reason for this is that much higher levels of penicillin are achieved in the blood and the alveoli compared with the CSF. Consequently, intermediate susceptibility to penicillin, as defined by the current NCCLS criteria, is unlikely to be clinically relevant in patients with pneumonia treated with generally accepted doses of penicillins. However, high-level resistance (MIC ≥ 4 mg/L) may impede clinical response.

**Penicillin and macrolide resistance in pneumococcal pneumonia**

PROTEKT is a global surveillance study of the prevalence of resistance among bacterial pathogens causing CARTIs. Data from the PROTEKT surveillance study (www.protekt.org) have shown that up to 22% of *S. pneumoniae* isolates are
Antimicrobial resistance in community-acquired RTIs

resistant to penicillin, with combined intermediate and resistant strains accounting for over 36% of isolates examined worldwide. A similarly high proportion of isolates (31%) is resistant to the macrolides. These recent findings support those from two previous major antimicrobial surveillance studies, namely the Alexander Project\textsuperscript{16,26} and the SENTRY study,\textsuperscript{17} which also indicated that resistance to \(\beta\)-lactams and macrolide antimicrobials is widespread.

In terms of penicillin breakpoints specific for CAP, evidence published by the Drug-Resistant \textit{Streptococcus pneumoniae} Therapeutic Working Group\textsuperscript{27} suggests that strains of this pathogen should be considered susceptible if the penicillin MIC is \(\leq 1\) mg/L. Strains for which the penicillin MICs are 2 and 4 mg/L should be considered to be of intermediate susceptibility. Some evidence indicates that there is no increase in the number of pneumonia treatment failures when penicillin-intermediate strains are implicated, whereas other evidence suggests that there is an increased risk of mortality or complications in patients with infection due to strains of intermediate susceptibility. Whilst too few patients with pneumonia due to pneumococcal isolates with penicillin MICs of \(\geq 4\) mg/L have been studied to draw appropriate conclusions, pharmacodynamic considerations indicate theoretical reasons for concern.\textsuperscript{27}

These observations suggest that higher susceptibility testing breakpoints for penicillin are appropriate for non-central nervous system infections, and revised breakpoints should be considered based on the site of infection as well as pharmacokinetic/pharmacodynamic considerations.\textsuperscript{25} Modifying the MIC breakpoints so that more pneumococcal pneumonia isolates are reported appropriately as being susceptible, may lead to a decrease in the use of broad-spectrum antimicrobial therapy in favour of more narrow-spectrum therapy.\textsuperscript{27}

The effectiveness of the macrolides in the management of CARTIs has been affected by the emergence of macrolide-resistant pneumococci in the late 1990s; prevalence rates exceeding 30% are not uncommon.\textsuperscript{13–17} However, in the year 2000, reports of fewer than 10 macrolide treatment failures have been published,\textsuperscript{28,29} which is a low frequency considering the high number of prescriptions for this class of antimicrobial agent.

Why have there not been more reports of macrolide failure? Consideration should be given to the fact that the majority of macrolide prescriptions are written as part of empirical therapy for outpatients where no microbiological or antibiotic susceptibility testing data exist. In addition, sputum cultures are rarely taken, even in patients who have failed previous courses of antimicrobial therapy.\textsuperscript{28} Furthermore, most community infections are of mild to moderate severity and some resolve spontaneously without treatment. The need to repeat a treatment course may be due to resistance but this is rarely proven. In addition, data from clinical trials are not always informative in this respect because patients who are at greatest risk are often excluded.

In a recent study, three patients who received azithromycin 500 mg for 3–5 days presented with bacteraemic community-acquired lower RTI caused by drug-resistant \textit{S. pneumoniae}.\textsuperscript{28} These patients were subsequently successfully treated with the fluoroquinolone levofloxacin (500 mg/day), with complete resolution of symptoms and chest roentgenogram abnormalities after 14 days of therapy. Molecular characterization of azithromycin resistance revealed that one of the \textit{S. pneumoniae} isolates contained a \textit{mef} determinant, which encodes for a macrolide efflux pump,\textsuperscript{30} whilst another contained an \textit{erm(B)} determinant, which confers resistance to the macrolide–lincomamide–streptogramin-B (MLS\textsubscript{B}) antimicrobials via methylation of the binding site of these agents at the ribosomal level (23S rRNA).\textsuperscript{31}

In a retrospective study conducted in Spain and the USA during 1986–1999, Garau \textit{et al.}\textsuperscript{32} identified 57 macrolide-resistant pneumococcal blood isolates. A total of 12 patients, 11 of whom had pneumonia, developed bacteraemia while receiving treatment with macrolides (erythromycin, clarithromycin, azithromycin or josamycin) for 2–8 days. Of these, all nine isolates from Spain contained the \textit{erm} determinant, and one of three isolates from the USA contained the \textit{mef} determinant. Two of the isolates had high-level penicillin resistance (MIC \(2\) mg/L), six had intermediate resistance and three were fully susceptible to penicillin. Subsequently, all of the patients were treated successfully with a \(\beta\)-lactam antibiotic. In another study, four outpatients receiving macrolides developed bacteraemia due to resistant \textit{S. pneumoniae}.\textsuperscript{39} All of the strains were resistant to erythromycin but susceptible to clindamycin. While the mechanisms of resistance were not assessed, their susceptibility to clindamycin suggests that they contained the \textit{mef} determinant responsible for the efflux mechanism of resistance, which is supported by the MICs (8–16 mg/L) associated with the low-level resistance often observed with this efflux system.

Genotypic prevalence of \textit{S. pneumoniae} macrolide resistance

Azithromycin and clarithromycin have different pharmacokinetic profiles both at the peripheral site (plasma) and at the site of infection (epithelial lining fluid, ELF).\textsuperscript{33} Additionally the \textit{in vitro} potency of these two agents is markedly different for \textit{S. pneumoniae} as is evident from the MIC distribution analysis from a recent US surveillance study.\textsuperscript{34} These surveillance data also reveal the trimodal MIC distribution pattern of this organism, since \(\sim 75\%\) of pneumococci are susceptible to macrolides, 18% are efflux mutants (\textit{mef}, MIC 1–32 mg/L), and 7% are high-level (\textit{erm}, MIC \(\geq 64\) mg/L) resistant strains (Figure 1).
Overlaying ELF clarithromycin concentrations upon the MIC distribution of the same compound reveals that drug concentrations at the site of infection exceed the MIC of susceptible isolates and many of those pneumococci exhibiting the efflux resistance mechanism. As a result of this pharmacodynamic profile at the infection site the currently used MIC breakpoints may be inaccurate, i.e. the effective resistance rate is ~10–12% compared with the reported surveillance resistance rates of 25–30%. In comparison, the concentrations of azithromycin in the ELF are ~2 mg/L, which does not exceed the compound’s MICs for pneumococci with either mef- or erm-mediated resistance. Consequently, the MIC breakpoint for azithromycin appears to be correct, i.e. the reported resistance rate is probably similar to the effective resistance rate. These findings indicate that strains of S. pneumoniae with MIC ≤ 0.5 mg/L are susceptible to azithromycin, whereas those exceeding this value should be considered resistant (Figure 2). It is important, therefore, to consider not only microbiological potency, but also to take into account drug concentrations at the site when assessing the clinical utility of the macrolides (i.e. microbiologically determined breakpoints versus those achieved by means of pharmacodynamic analysis).

The prevalence of the erm and mef determinants amongst macrolide-resistant pneumococci varies according to the geographical region. A number of studies conducted in the USA, Canada, Europe and Japan have examined the genotype of S. pneumoniae macrolide resistance. Efflux (mef) resistance is more prevalent in the USA and Canada (56–71%), while high-level (erm) resistance is more prevalent in Europe (97%) (Table 1). In Japan, the overall macrolide resistance exceeds 70% and the prevalence of erm and mef genotypes is similar (40% and 43%, respectively), while dual genotypes have been noted in most of the remaining macrolide-resistant pneumococci. Confirmatory results from PROTEKT are presented elsewhere.

Resistance of RTI pathogens implicated in acute exacerbations of chronic bronchitis and acute otitis media

Resistance of bacteria commonly implicated in AECB and AOM, namely S. pneumoniae, H. influenzae and M. catarrhalis, has been reported in a number of prospective surveillance studies. Indeed, data from 845 S. pneumoniae isolates analysed as part of the SENTRY surveillance study showed that, although resistance rates varied widely, 28% of isolates demonstrated intermediate resistance to penicillin and 16% had high-level resistance. Alexander Project data from 1992–1997 indicate that the prevalence of β-lactamase production among isolates of H. influenzae appears to have reached a steady state in some countries, such as France and the USA, but may be as high as 35% in some areas. A number of studies have illustrated the effect of β-lactamase production on the efficacy of amoxicillin in patients with AOM, revealing that eradication rates for β-lactamase-positive isolates were similar to spontaneous eradication rates observed for H. influenzae. Although the use of a vaccine against the most virulent serotype of H. influenzae (serotype b) may decrease the importance of this strain, resistant, non-typeable strains remain clinically significant CARTI pathogens.

β-Lactam resistance is almost invariably higher in M. catarrhalis than in H. influenzae. Most (50–80%) isolates of M. catarrhalis collected as part of the Alexander Project during 1992 produced β-lactamase. However, the rate of β-lactamase production had increased to 90–100% in the participating centres in this study by 1997. Resistance to other (non-β-lactam) antibiotic classes was stable in both M. catarrhalis and H. influenzae.
Clinical impact of antimicrobial resistance in RTIs

Pneumococcal pneumonia

Little published data are available on the impact of antimicrobial resistance on the rate of response in non-susceptible pneumococcal pneumonia. However, one study has been conducted to determine the usefulness of procaine penicillin in the treatment of suspected pneumococcal pneumonia of mild to moderate severity in an area with a high prevalence of penicillin resistance.45 Of 49 patients receiving procaine penicillin (1.2 million units given intramuscularly every 12 h), 40 (82%) were cured and no deaths due to infection were reported. Seventeen patients had documented S. pneumoniae infection, five of whom had penicillin-resistant isolates (MICs 0.25–4 mg/L). Although 15 of the patients infected with S. pneumoniae were cured (one patient had an allergic reaction and the other failed treatment), the duration of the following symptoms was longer in patients infected with penicillin-resistant isolates compared with those from whom penicillin-susceptible pneumococci were isolated: fever (3.6 versus 1.9 days), cough and sputum production (6.0 versus 2.7 days), and pleuritic pain (3.6 versus 2.1 days). Even though the number of cases in this study was too small to perform a rigorous statistical analysis, these results suggest that penicillin susceptibility may have an impact on symptom resolution in patients with pneumococcal infection.

Acute exacerbations of chronic bronchitis

Although the in vitro data indicate significant levels of resistance, few data are available on the clinical impact of antimicrobial resistance in patients with AECB. Most studies do not demonstrate any difference in outcome between patients infected with penicillin-resistant isolates and those infected with susceptible strains.22 However, a review of 12 studies of patients with AECB demonstrated a strong correlation (r = 0.91) between eradication failure rates and clinical failure rates following treatment with macrolides, fluoroquinolones, penicillins, cephalosporins, or co-trimoxazole (Figure 3).46 These data support the premise that bacteriological eradication is an important determinant of clinical outcome in this setting and suggest that high MICs are associated with increased rates of clinical failure.

Acute otitis media

Elevated MICs have been associated with lower rates of eradication of pathogens from the middle ear, correlating with high rates of clinical failure in patients with AOM.47,48 The effect of bacteriological failure on clinical failure has been investigated in 206 children with AOM using the double-tympanocentesis method.47 Of 123 children culture-positive before treatment, 57 (46%) were culture-positive on day 4–5 of antibiotic therapy and 66 (54%) showed bacteriological eradication. Among the 57 children who were culture-positive at day 4–5, there were 21 clinical failures (37%) at day 10 of the study. In contrast, of the 66 children that were culture-negative on day 4–5, only two (3%) were clinical failures at day 10. While clinical success was clearly maximized (97%) through bacterial eradication, 63% of bacteriological failures at day 4–5 were clinically cured by day 10.

![Figure 3. Relationship between eradication failure rates and clinical failure rates in patients with AECB.](Reproduced with permission from the Journal of Antimicrobial Chemotherapy)
Economic impact of resistance on the management of RTIs

Current antimicrobial therapy for CARTIs is empirical and influenced by local differences in aetiology and bacterial susceptibility. Consequently, the reported rise in antimicrobial resistance has the potential to increase direct healthcare resources and costs in patients with upper and lower RTIs. Furthermore, the reliance on empirical strategies in recent times may have reduced the costs associated with laboratory culture and susceptibility testing, but unfortunately appears to have increased associated drug costs due to the widespread use of broad-spectrum antimicrobials and increasing numbers of clinical failures.49

A number of factors associated with the rise in treatment failures among bacterial infections have an impact on the use of healthcare resources and costs, including the need for reconsultation, additional antibiotic prescriptions, and longer stays in hospital.22,49,50 The combination of these factors results in the high cost of treating patients with lower RTIs, particularly those who require hospitalization.49 Resistance among RTI pathogens also has the potential to increase indirect costs to society, including lost productivity and income, absenteeism from work or school, and reduction in patients’ quality of life.22,51

Community-acquired pneumonia

CAP is the sixth leading cause of death in the USA, where 3–6 million cases are reported per year, accounting for approximately 10 million physician visits, 500,000–800,000 hospitalizations (of which ~125,000 are pneumococcal in origin) and 45,000 deaths.5,7 Pneumococcal infections are a major cause of morbidity and mortality and are estimated to cause 500,000 cases of pneumonia, 55,000 cases of bacteraemia and 6000 cases of meningitis annually in the USA.52,53 Whilst few data on the economic impact of pneumococcal disease in outpatients have been reported in the literature, inpatient care accounts for over 90% of the total cost of managing CAP.5,7 Furthermore, if antibiotic resistance causes higher rates of outpatient treatment failure, higher rates of hospitalization are likely to result. Consequently, continued efforts are being made to manage CAP patients more effectively in the outpatient setting.6

In a retrospective, observational cohort study of all patients admitted to the University of Iowa Hospital and Clinics in the USA between 1995 and 1998, blood or respiratory sources were tested for positive S. pneumoniae cultures.50 Patients infected with S. pneumoniae were hospitalized for ≥2 days after their first positive culture and received ≥2 days of antimicrobial therapy directed against the pathogen. A total of 235 cases were identified, of which 144 (61%) were penicillin susceptible and 91 (39%) were non-susceptible to penicillin. Healthcare expenditures peaked on day 0 (10% of total) and declined to pre-day 0 levels by day 14. Of the total charge, 50%, 12%, 1% and 8% were attributable to room/nursing, pharmacy, antibiotics and laboratory utilization, respectively. Median total charges over the infection window (days –2 to 14) were $19,372.21 and $27,958.70 for susceptible and non-susceptible strains, respectively (P < 0.05), meaning that the penicillin non-susceptible strains resulted in excess charges of $8582 (95% CI $402; $16,762) over this period of time. Charges were also greater in the non-susceptible group [$2575 (95% CI $21.67; $5129)] compared with the susceptible group during the intervention window (days –1 to 7). Regardless of the window used, significant differences in resource utilization between the two groups were observed in terms of total charges, hospital room charges, nursing care and pharmacy charges.

A second case control study involving 72 patients infected with either penicillin-susceptible (n = 36) or non-susceptible (n = 36) strains of pneumococci revealed that 29% of the patients infected with susceptible strains had bacteraemia compared with 8% of those who were infected with non-susceptible strains (P = 0.09). The proportion of patients surviving at 30 days was similar, however, in the susceptible and non-susceptible groups (94% versus 89%, P = NS).54 Importantly, the average duration of hospitalization was significantly longer in the patients harbouring penicillin non-susceptible pneumococci than those infected with penicillin-susceptible strains (26.8 versus 11.5 days, P = 0.001). Average pharmacy (antibiotic) costs were also much higher in the non-susceptible group compared with the penicillin-susceptible group ($736 versus $213, P = 0.0001). These results indicate that, while the initial clinical presentation of patients with penicillin non-susceptible S. pneumoniae seems milder, patients tend to require a longer stay in hospital and the use of more expensive antibiotics.

A recent mathematical model study estimated the impact of resistance and cross-resistance on the rate of initial treatment failure, hospitalization rates and treatment costs for the whole episode of care in the outpatient treatment of adult CAP in the USA.55 Outcomes were calculated for three scenarios, namely actual resistance and cross-resistance rates, assuming an absence of cross-resistance, and assuming no resistance. Two representative treatment strategies were chosen: oral amoxicillin (500 mg three times a day) followed by oral clarithromycin (500 mg twice a day); or oral clarithromycin (500 mg twice a day) followed by oral levofloxacin (500 mg once a day). Susceptibility and cross-resistance data were taken from the 1997 Alexander Project surveillance data (www.alexander-network.com). The estimates suggested that antibiotic resistance is having a major impact on hospitalization and cost (Table 2). For example, almost 40% of the hospitalizations and costs associated with amoxicillin plus clarithromycin treatment may be attributable to resistance. Furthermore, for S. pneumoniae, cross-resistance had a significant impact on
the effectiveness of treatment with amoxicillin plus clarithromycin.

**Acute exacerbations of chronic bronchitis**

Niederman *et al.*\(^8\) reported that the total cost of treating patients with AECB was $1.2 billion/year for patients over 65 years of age and $419 million for those less than 65 years old (1994 charges inflated to 1995 prices). Hospital costs accounted for a large proportion of the total cost in the two age groups ($1.1 billion and $408 million), while outpatient visits contributed $24.9 million and $15.1 million, respectively. In addition, analysis of the average total costs for the management of ambulatory sinusitis and bronchitis patients revealed that 85% of the costs are related to medical expenditure, including laboratory costs, X-rays, initial visits, follow-up visits, etc., followed by only 8% for prescription antibiotics, and 7% for other prescription drugs.\(^56\)

Consequently, as in CAP, it is important that initial therapy is successful because treatment failure can result in marked increases in costs, particularly if hospitalization is required. This was illustrated by an evaluation of the efficacy of four treatment options in the management of patients with AECB, during which Backhouse *et al.*\(^57\) calculated the direct cost for each successfully-treated patient. The cost of treatment failure was typically much higher than the acquisition costs of first-line antibiotics. In a further study that investigated the primary factors determining the cost-effectiveness of different antibiotic classes in the management of patients with AECB, the costs of treatment were greater for patients with more severe AECB than for patients with mild-to-moderate infection because of the increased need for hospitalization.\(^58\)

These findings confirm that the cost of treatment failure as a result of antimicrobial resistance is high and is affected by the efficacy of the antibiotic regimen used as first-line therapy.

**Table 2.** Impact of resistance on additional duration of hospitalization and additional costs\(^55\)

<table>
<thead>
<tr>
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<th>Amoxicillin/clarithromycin</th>
<th>Clarithromycin/levofloxacin</th>
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<tbody>
<tr>
<td>Additional duration of hospitalization (%)</td>
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<td></td>
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<tr>
<td>overall</td>
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<td>2.2</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
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<td>4.1</td>
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<tr>
<td><em>H. influenzae</em></td>
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</tr>
<tr>
<td>Additional cost ($)</td>
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<td>209</td>
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<td>380</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>1379</td>
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</tr>
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</table>

**Acute otitis media**

In the USA, the total annual direct medical cost of AOM for children under 5 years of age, including the costs of prescriptions plus office visits, has been estimated at $4 billion.\(^59\) Adding the costs of treating AOM in older children brings the total to more than $5 billion.\(^2\) In addition, the estimated total cost of treating one complicated 3-month episode of AOM is $1331\(^60\) and treatment costs for recurrent episodes are substantially higher. Furthermore, it has been estimated that 90% of the total costs of treating an episode of AOM can be attributed to indirect costs, primarily for parental or caregiver time away from work.\(^60\)

The potential consequences of the increasing prevalence of resistant bacterial strains include treatment failures, the need for additional courses of antibiotics and unresolved respiratory infections. In patients with AOM, inadequate treatment can result in persistence of middle ear effusion, suppurative complications, the need for surgical implantation of tubes, long-term hearing loss, decreased perception of language, impaired speech development and learning deficiencies.\(^2\) In addition, the obvious disease sequelae caused by chronic infection may be accompanied by a significant drain on healthcare resources.

**Conclusions**

The increasing prevalence of antimicrobial resistance in *S. pneumoniae* and other common RTI pathogens, such as *H. influenzae* and *M. catarrhalis*, impacts greatly on the usefulness of the currently available antibiotics. When penicillin is considered, the implications of *in vitro* resistance in the management of RTIs are dependent upon the site of infection, highlighting the need for modification of current MIC breakpoints. The impact of pneumococcal resistance on the clinical and microbiological efficacy of the macrolides has also become apparent in recent times, although effective resistance rates vary according to the macrolide examined. It must be remembered, however, that all currently available 14- and 15-membered ring macrolides are strong inducers of MLS\(_B\) resistance, and so selection pressure will, therefore, be maintained as they are used.

While the available data on the economic impact of antimicrobial resistance on patients with RTIs are limited, the total cost of care is driven by medical, rather than prescription costs. It is important to note that individual antimicrobial agents differ with respect to the optimization of microbiology, pharmacology and toxicity profiles, the potential for the development of resistance, and their impact on the total cost of care. Consequently, pharmacokinetic and pharmacodynamic parameters are being used increasingly to predict the potential for maximally effective therapy and optimal bacterial eradication, thus limiting the development of resist-
Pharmacokinetic parameters, including absorption, distribution, metabolism and excretion, have an effect on the concentration of the active drug present at the infection site. Along with pharmacodynamic parameters, such as time- or concentration-dependent killing, these factors influence clinical outcome, microbiological outcome and other outcome measures of efficacy such as the rate of response and disease-free interval. Use of these parameters alongside the results from studies of local susceptibility patterns should be employed to facilitate appropriate prescribing of antimicrobials only for indications for which they have proven efficacy.11

Optimizing the selection of patients most eligible to receive antibiotics according to stringent clinical criteria is the first step in promoting both good clinical practice and cost effectiveness.61 The efficacy of antimicrobial therapy rather than medical expenditure, including laboratory costs, X-rays, initial visits, follow-up visits, etc., would then be the major driver of cost, particularly if the need for hospitalization was reduced. Thus, effective first-line antimicrobial therapy with new antibiotics active against emerging resistant pathogens could reduce the overall cost of care in patients with both upper and lower RTIs. Furthermore, such strategy may significantly impact on the emergence of antimicrobial resistance and if allied with careful selection of antimicrobials to ensure eradication of both susceptible and resistant pathogens, could help to prevent the development and spread of bacterial antimicrobial resistance in the community.

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