

# THORAX

## Editorials

### Antibiotic resistance in common acute respiratory pathogens

A consequence of the use of antibiotics is the development of antibiotic resistance amongst pathogens. In respiratory tract infections the emergence of resistant organisms has necessitated changes in antibiotic policy over the past two decades. In the UK the prevalence of antibiotic resistant respiratory pathogens is lower than in other countries. Nevertheless there is concern for the future. The current state of antibiotic resistance in common acute respiratory pathogens is reviewed in this editorial.

#### *Streptococcus pneumoniae*

*S pneumoniae* is the pathogen most commonly implicated in lower respiratory tract infections. It is usually susceptible to penicillins which bind to penicillin binding proteins (PBPs) and inhibit the synthesis of peptidoglycan, a component of the bacterial cell wall. Resistance to penicillins can arise through possession of beta-lactamases, which digest the antibiotic, or alterations in PBPs, the latter being responsible for the resistance of *S pneumoniae* to penicillins. There are several PBPs, each with a different affinity for penicillins. The synthesis of PBPs can be induced and the affinity for penicillins can be altered by mutation. The overall susceptibility to penicillins reflects a complicated mix of the concentration and affinities of the various PBPs.<sup>1</sup> Susceptibility is therefore variable and can be graded. Categories of susceptibility, or resistance, have been defined in terms of in vitro minimum inhibitory concentrations (MICs). For benzylpenicillin susceptible strains have an MIC of <0.1 µg/ml, intermediately resistant strains have an MIC of 0.1-1.0 µg/ml, and highly resistant strains have an MIC of >2.0 µg/ml.

Appelbaum has reviewed the worldwide epidemiology of penicillin resistant pneumococci.<sup>2</sup> The first clinical isolate was reported from Boston in 1965. Over the subsequent decade reports appeared from Australia, Papua New Guinea, and South Africa. Presently resistant pneumococci have been found in all countries in which they have been sought. There is considerable geographical variation in the prevalence of resistant isolates. Prevalence rates exceed 10% in Spain, parts of Eastern Europe, South Africa, Mexico, Alaska and Papua New Guinea. In parts of these countries prevalence rates as high as 40% have been reported.<sup>3</sup> Overall, the prevalence rate in the UK is less than 5%. Initially most isolates had low levels of resistance but with time more highly resistant strains have appeared. This has been a particular problem in South Africa where MICs of 4-8 µg/ml have been reported.<sup>4</sup> Of additional concern has been the occurrence of strains resistant to more than one antibiotic.

The development of resistance reflects the local intensity of penicillin usage. In Spain Baquero *et al* have found a very good temporal correlation between the rising prevalence of resistant isolates and increasing consumption of penicillins.<sup>5</sup> Furthermore, the regional variation in penicillin consumption in Spain is also paralleled by the prevalence rate of resistant isolates. Penicillin resistant strains can also be imported from countries with a high prevalence. In Iceland penicillin resistant pneumococci did not exist before 1988. In the subsequent four years they appeared for the first time and the prevalence rate rose dramatically to 17%. Most of the isolates were of one serotype (6B), had the same pattern of multiple resistance, and genetic analysis suggested that they arose from one clone.<sup>6</sup> They were indistinguishable from a multiresistant, serotype 6B pneumococcal strain prevalent in Spain, a popular holiday destination for Icelanders. It would appear that penicillin resistant pneumococci were introduced into Iceland in the late 1980s by travellers returning from Spain.

Resistant clones are probably selected from pneumococci resident in the nasopharyngeal flora. Resistance can appear in any serotype of pneumococcus but some serotypes predominate over others. These include serotypes 6, 9, 14, 15, 19, and 23<sup>5</sup> which are amongst the serotypes most commonly found in nasopharyngeal carriage.<sup>7</sup> While penicillins successfully clear pneumococcal infection in various tissues, they often fail to eradicate nasopharyngeal carriage and the emergence of penicillin resistant pneumococci in this nasopharyngeal population has been described.<sup>8</sup> Nasopharyngeal spread can then occur readily in overcrowded situations.<sup>9</sup> In an overcrowded paediatric ward in Johannesburg 96% of children, initially negative for penicillin resistant pneumococci in nasopharyngeal specimens, acquired resistant organisms from carriers within three days of admission. On the other hand, in the community only 3% of 134 household contacts acquired resistant pneumococci from 25 carriers after one month. Most nasopharyngeal serotypes are included in the current 23 valent pneumococcal vaccine, but vaccination does not affect acquisition or carriage of pneumococci.<sup>10</sup>

The spectrum of infections caused by penicillin resistant pneumococci is the same as non-resistant strains. The efficacy of benzylpenicillin in treating infections caused by resistant organisms depends on the concentration of antibiotic achieved in tissues and the MIC of the infecting pneumococci. Because benzylpenicillin does not penetrate well into cerebrospinal fluid MICs sufficient to kill intermediate and highly resistant strains are unattainable. Benzylpenicillin should therefore not be used to treat meningitis in areas where such levels of resistance are

prevalent.<sup>11</sup> In contrast, adequate concentrations of benzylpenicillin may be reached in lung. Pallares *et al* reviewed their experience of treating 25 episodes of pneumonia due to penicillin resistant pneumococci<sup>12</sup> and found that, provided patients were not critically ill and MICs did not exceed 4 µg/ml, they responded satisfactorily to high dose intravenous benzylpenicillin. When treatment with benzylpenicillin becomes unreliable a third generation cephalosporin is a valid alternative and is now routinely recommended by the British Thoracic Society for the treatment of severe pneumonias.<sup>13</sup> Macrolides can be used but quinolones do not exhibit much activity against *S pneumoniae*<sup>14</sup> and quinolone resistance does occur.<sup>15</sup>

Like their penicillin relatives the beta-lactam cephalosporins also act by binding to PBPs. Cross resistance between penicillins and cephalosporins is therefore possible although not inevitable. Occasionally isolates are resistant to cephalosporins while remaining sensitive to penicillins. In a study of 431 isolates of *S pneumoniae* 0.9% were resistant to the second generation cephalosporin cefaclor.<sup>16</sup> Pneumococcal resistance to a number of other antibiotics is well described including erythromycin, tetracycline, chloramphenicol, and co-trimoxazole.<sup>17</sup> Resistance rates for these antibiotics have fluctuated with time and reflect changing patterns of antibiotic usage. In the UK erythromycin resistance currently occurs in 6.5% and tetracycline resistance in 8.1% of isolates.<sup>16</sup> Of major concern is the occurrence of multiply resistant pneumococci which limits therapeutic options. In Barcelona 70% of penicillin resistant pneumococci are also resistant to non-beta-lactam antibiotics.<sup>3</sup> This represents a significant proportion of all isolates as the overall prevalence of penicillin resistance in Barcelona is 40%. The most common multiple resistance pattern identified there involves combined resistance to penicillins, tetracycline, chloramphenicol, and co-trimoxazole. In South Africa pneumococcal resistance to two or more antibiotics accounts for about 2% of all pneumococcal isolates. In the UK multiple resistance occurs but is still rare.

### *Haemophilus influenzae*

*H influenzae* accounts for almost half the isolates from sputum samples of patients with exacerbations of chronic obstructive airways disease<sup>18</sup> and about 5% of isolates from patients with community acquired pneumonia. Before the 1970s *H influenzae* was uniformly sensitive to ampicillin, but since this time resistance to ampicillin and other antibiotics has arisen.<sup>19</sup> The major mechanism of resistance to ampicillin is the production of a beta-lactamase, principally TEM-1. However, some isolates are resistant to antibiotics containing a beta-lactamase inhibitor and the mechanism of resistance in these is altered PBP binding. In addition to resistance to ampicillin, resistance to chloramphenicol, co-trimoxazole, tetracycline, erythromycin, and rifampicin has been described. Resistance to chloramphenicol is due to the presence of the inactivating enzyme chloramphenicol acetyl transferase (CAT), and resistance to trimethoprim is due to increased production of dihydrofolate reductase. The genes for beta-lactamase and chloramphenicol resistance are present on plasmids and can therefore be exchanged between bacteria.

Surveys of the prevalence of resistant *H influenzae* have been performed in several countries. In North America about 20% of isolates are beta-lactamase producers.<sup>19</sup> In Europe a survey of 78 laboratories in nine countries revealed an overall rate of beta-lactamase production in 9.1% of isolates.<sup>20</sup> The occurrence of beta-lactamase production was slightly higher in type b (10.5%) than in non-type b (8.6%) isolates. Resistance rates were highest in Spain.

Multiple resistance to three or more antibiotics was found in 1.5% of isolates. In the UK sequential surveys of *H influenzae* resistance have been performed since 1977,<sup>21,22</sup> and have shown a steady rise in the prevalence of strains resistant to antibiotics traditionally used to treat *H influenzae* infection. The latest survey in 1991 showed that beta-lactamase was produced by 21% of type b isolates and 8.3% of non-type b isolates. Non-beta-lactamase ampicillin resistance was present in 5.8%. Overall, of 2212 isolates 14.4% were ampicillin resistant. Trimethoprim resistance was present in 6.8% of isolates. In a separate study resistance to cefaclor was found in 5.2% of 1272 isolates<sup>16</sup>; ampicillin resistance can be associated with cross resistance to cephalosporins. *H influenzae* is generally sensitive to quinolones but there have been case reports of ciprofloxacin resistance.<sup>23</sup> Multiple drug resistance is still rare.

Resistance probably emerges in the same way as penicillin resistance in *S pneumoniae*. *H influenzae* is present in nasopharyngeal flora and is also carried in sputum from chronic sputum producers. Treatment with antibiotics results in the appearance of resistant strains at these sites<sup>24</sup> and spread between close contacts can then occur.<sup>25</sup>

Most *H influenzae* infections can be treated with amoxicillin or co-amoxiclav. If necessary, cephalosporins or a quinolone may be used. Erythromycin is generally not active against this species but other macrolides such as clarithromycin and azithromycin are more effective.

### *Moraxella (Branhamella) catarrhalis*

*M catarrhalis* now has a recognised place in the list of respiratory tract pathogens. In the early 1970s this species was sensitive to all antibiotics used to treat respiratory infections, but antibiotic resistance developed rapidly in the subsequent decade. In the USA beta-lactamase production was present in 75% of isolates by 1980.<sup>26</sup> Two different beta-lactamases are produced, designated BRO-1 and BRO-2. These are encoded on chromosomal DNA but can be transferred between bacteria by conjugation, presumably on transposons. They are clinically significant because treatment failures occur when penicillins are used. However, they are very susceptible to beta-lactamase inhibitors such as clavulanic acid and sulbactam and are therefore sensitive to antibiotics such as co-amoxiclav. *M catarrhalis* retains some susceptibility to cephalosporins but, in addition to penicillins, resistance has been reported to a number of other antibiotics including trimethoprim, tetracycline, erythromycin, and aminoglycosides. Trimethoprim resistance is almost universal amongst isolates and the mechanism of this resistance is not understood. In a survey of resistance patterns in England and Scotland in 1991 90.8% of 413 isolates were beta-lactamase producers and all were resistant to trimethoprim.<sup>27</sup> Apart from this, resistance to other antibiotics was very rare.

### "Atypical" pathogens

In general atypical pathogens are susceptible to macrolides, tetracycline, or quinolones and antibiotic resistance is not a problem. In vitro, *Legionella pneumophila* is most susceptible to rifampicin and ciprofloxacin followed by macrolides. In experimental conditions resistance to erythromycin has been selected<sup>28</sup> but, in a retrospective survey of clinical isolates collected in the USA between 1981 and 1990, no resistance was encountered to various agents.<sup>29</sup> The main limitation to the use of antibiotics in legionellosis is not antibiotic resistance but in vivo efficacy which depends on antibiotics penetrating into the intracellular compartment where *Legionella* reside. Mycoplasmas are susceptible to several antibiotics which

interfere with nucleic acid or protein synthesis and the integrity of the cell membrane. Antibiotics tend to have a static rather than a cidal effect. Resistance to tetracycline has been found in *Mycoplasma hominis* and *Ureaplasma urealyticum* and associated with treatment failures.<sup>30</sup> However, antibiotic resistance has not so far been found in *Mycoplasma pneumoniae*. *Chlamydia pneumoniae* and *Chlamydia psittaci* also remain susceptible to macrolides, tetracycline, and quinolones and resistance is yet to be found.<sup>31</sup>

## Conclusions

In the UK most respiratory pathogens, with the exception of *M catarrhalis*, remain susceptible to first line agents such as an aminopenicillin or a macrolide. There are some situations in which co-amoxiclav, a cephalosporin, or a quinolone have a role.<sup>32</sup> The main lesson to learn from countries experiencing considerable problems with antibiotic resistance is that widespread use of any antibiotic can breed resistance. It is therefore important to limit the indiscriminate prescription of antibiotics, both in hospitals and the community. Unnecessary antibiotic usage should be avoided – for example, in probable viral infections and in broad spectrum combinations when a single agent would suffice. Frequent sequential courses of antibiotics will encourage colonisation with resistant organisms. The detection of resistant organisms, control of their spread, and eradication will be of increasing importance in the activities of infection control teams.

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