

Antibiotic resistant *Streptococcus pneumoniae*

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Introductory article

Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain

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Background. Penicillin-resistant strains of *Streptococcus pneumoniae* are now found worldwide, and strains with resistance to cephalosporin are being reported. The appropriate antibiotic for pneumococcal pneumonia due to resistant strains remains controversial. **Methods.** To examine the effect of resistance to penicillin and cephalosporin on mortality, we conducted a 10-year, prospective study in Barcelona of 504 adults with culture-proved pneumococcal pneumonia. **Results.** Among the 504 patients, 145 (29 percent) had penicillin-resistant strains of *S. pneumoniae* (minimal inhibitory concentration [MIC] of penicillin G, 0.12 to 4.0 µg per milliliter), and 31 patients (6 percent) had cephalosporin-resistant strains (MIC of ceftriaxone or cefotaxime, 1.0 to 4.0 µm per milliliter). Mortality was 38 percent in patients with penicillin-resistant strains, as compared with 24 percent in patients with penicillin-sensitive strains ($P=0.001$). However, after the exclusion of patients with polymicrobial pneumonia and adjustment for other predictors of mortality, the odds ratio for mortality in patients with penicillin-resistant strains was 1.0 (95 percent confidence interval, 0.5 to 1.9; $P=0.84$). Among patients treated with penicillin G or ampicillin, the mortality was 25 percent in the 24 with penicillin-resistant strains and 19 percent in the 126 with penicillin-sensitive strains ($P=0.51$). Among patients treated with ceftriaxone or cefotaxime, the mortality was 22 percent in the 59 with penicillin-resistant strains and 25 percent in the 127 with penicillin-sensitive strains ($P=0.64$). The frequency of resistance to cephalosporin increased from 2 percent in 1984–1988 to 9 percent in 1989–1993 ($P=0.002$). Mortality was 26 percent in patients with cephalosporin-resistant *S. pneumoniae* and 28 percent in patients with susceptible organisms ($P=0.89$). Among patients treated with ceftriaxone or cefotaxime, mortality was 22 percent in the 18 with cephalosporin-resistant strains and 24 percent in the 168 with cephalosporin-sensitive organisms ($P=0.64$). **Conclusions.** Current levels of resistance to penicillin and cephalosporin by *S. pneumoniae* are not associated with increased mortality in patients with pneumococcal pneumonia. Hence, these antibiotics remain the therapy of choice for this disease. (N Engl J Med 1995;333:474–80)

For many years penicillin provided very effective treatment for pneumococcal infections. However, the last two decades have seen the emergence of pneumococcal strains with resistance not only to penicillin, but also to other antibiotics.¹ This has contributed to treatment failure, at least in pneumococcal meningitis.² In spite of this, it has been suggested that penicillin may still be an effective treatment for pneumococcal pneumonia as very high tissue concentrations of antibiotic can be achieved.³ In August 1995 Pallares and colleagues, working in Barcelona where the incidence of penicillin resistance in pneumococci is particularly high, published a study comparing mortality from pneumonia due to penicillin sensitive pneumococci with that due to penicillin resistant strains.⁴ Their results suggest that there

may be little difference in mortality between the two groups after correction for an increased incidence of poor prognostic factors amongst those patients with resistant infections.

In this review we will provide a general introduction to the topic of antibiotic resistant pneumococci, discuss the paper by Pallares *et al* in more detail, and finally make our own suggestions on how to deal with the difficult clinical problem of increasing antibiotic resistance in pneumococci.

Pneumococcal infection and the development of antibiotic resistance

PNEUMOCOCCAL PNEUMONIA: THE SIZE OF THE PROBLEM
Pneumococcal infection remains the commonest cause

of community acquired pneumonia in the UK (76% of adult hospital admissions for community acquired pneumonia in Nottingham in 1982⁵). In the USA there are approximately half a million episodes of pneumococcal pneumonia each year with 40 000 deaths.⁶⁷ In developing countries over a million children under the age of five years die annually from pneumonia, most commonly due to *Streptococcus pneumoniae*.⁸ Pneumonia due to pneumococci is commoner in the elderly,⁹ in those with underlying disease particularly immunosuppression such as hyposplenism and HIV disease,^{10 11} and in alcoholics and vagrants.¹² There is a marked seasonal variation with peak incidence in the winter months.^{12 13}

PATHOGENESIS OF PNEUMOCOCCAL PNEUMONIA

Streptococcus pneumoniae is found as normal nasopharyngeal and oropharyngeal flora in approximately 15% of children and 5% of adults.¹⁴ It is thought to be passed from person to person via respiratory secretions and aerosols. Impairment of host defence mechanisms within the bronchial tree such as ciliary movement, cough and secretory immunoglobulin (for example, in chronic lung disease or an acute viral infection) may allow pneumococci to gain access to the lower respiratory tract. The organisms are surrounded by a capsule composed of polysaccharide antigens (used in strain typing) which inhibits phagocytosis. Antibodies to the polysaccharide capsule are protective, suggesting that this is an important virulence factor. Other virulence factors include pneumolysin O, a toxin which causes cell lysis, and a neuraminidase which degrades host cell surface structures. Components of the pneumococcal cell wall are able to interact with C-reactive protein resulting in the activation of host non-specific immune responses.¹⁴

DEVELOPMENT OF TREATMENT FOR PNEUMOCOCCAL INFECTION

At the beginning of this century the mortality from pneumococcal pneumonia approached 75%.¹⁵ Initial treatment was optochin, a drug related to quinine which, although effective, had to be abandoned for clinical use because of ocular toxicity.¹⁶ (It is still used for the identification of pneumococci in the laboratory today.) Pneumococcal antisera and sulphonamides both improved the survival from pneumococcal disease, but the introduction of penicillin reduced the overall mortality rate to approximately 25%,¹⁷ which has remained constant for many years in spite of development of intensive care techniques including positive pressure ventilation.¹⁸

APPEARANCE OF PENICILLIN RESISTANT PNEUMOCOCCI

Not long after the introduction of penicillin in 1940 the first penicillin resistant pneumococcus was produced in vitro,¹⁹ but the first clinical isolate did not appear until 20 years later in Boston, USA.²⁰ In the late 1960s a number of penicillin resistant strains were isolated in Australia and New Guinea, possibly related to a trial of prophylactic oral penicillin in an attempt to reduce the incidence of pneumococcal disease.^{21 22} In the 1970s an epidemic of penicillin and later multidrug resistant pneumococci was seen in paediatric wards in South Africa and in Europe, particularly Spain and Hungary (fig 1).^{1 23-25}



Figure 1 Worldwide prevalence and distribution of penicillin resistance of *Streptococcus pneumoniae*. Data compiled from references 1, 23-25, 33, 36, 53-57.

DIAGNOSIS AND DEFINITION OF PENICILLIN RESISTANT PNEUMOCOCCAL INFECTION

Pneumococci may be identified by Gram staining of specimens such as respiratory secretions, followed by conventional culture techniques, looking for characteristic colonial morphology, α -haemolysis and optochin sensitivity, plus specific reactions with antisera to capsular polysaccharides.¹⁴ Penicillin sensitivity is screened for by disc diffusion techniques. Filter paper discs containing a standardised amount of antibiotic are applied to an agar plate inoculated with the bacterial isolate. After incubation a zone of growth inhibition is present around the disc if the isolate is sensitive to the antibiotic. More sensitive isolates have larger inhibition zones which may be quantified approximately by comparison with a previously characterised strain. In order to quantify accurately the minimum inhibitory concentration of antibiotic (MIC) for a particular isolate, more time consuming microdilution techniques are necessary. A pneumococcal isolate is considered to be sensitive to penicillin if the MIC is $<0.6 \mu\text{g/ml}$. An isolate with intermediate resistance has an MIC of $0.6-1 \mu\text{g/ml}$, while the term "high level resistance" is used to describe isolates with MICs of $\geq 2 \mu\text{g/ml}$. The E-test, a strip of paper impregnated with increasing concentrations of an antibiotic, is a newer less laborious method based on antibiotic diffusion techniques which allows an approximate estimate of the MIC.²⁶

MECHANISMS OF ANTIBIOTIC RESISTANCE

Penicillins work by binding to a number of proteins (usually enzymes) essential for the synthesis of the bacterial cell wall and inhibiting their function. Penicillin resistant pneumococci have been shown to have penicillin binding proteins (PBPs) with much reduced affinity for penicillin, so that the presence of penicillin does not interfere with bacterial wall synthesis (fig 2).²⁷ There are thought to be at least two mechanisms whereby low affinity PBPs are acquired by pneumococci. Other bacteria, particularly viridans streptococci, may transfer genetic material encoding low affinity PBP genes to pneumococci.²⁸ Both types of bacteria may be carried in the oropharynx so that they may come into close proximity. In addition, the presence of penicillin exerts a selective pressure on pneumococci favouring point mutations causing a reduction in PBP affinity and thus an increase in MIC.²⁹ Cephalosporin resistance is also mediated by changes in PBP affinity, but fewer genetic changes are required for resistance to occur.³⁰ The genes for antibiotic resistance may be spread amongst different pneumococcal clones or serotypes by exchange of genetic information.³¹ In addition, a resistant strain can be spread geographically by colonisation of new hosts, as

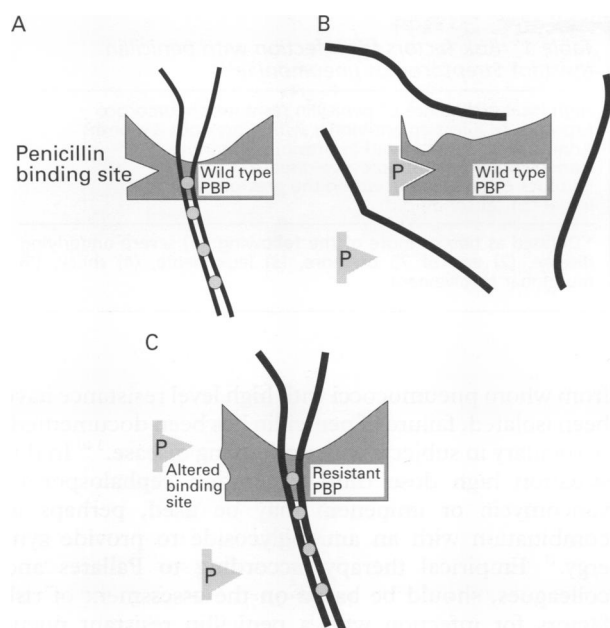


Figure 2 Schematic representation of penicillin resistance due to altered penicillin binding affinity. (A) Penicillin binding protein (PBP) catalyzes cross linking of peptidoglycan chains essential for manufacture of cell wall. (B) Penicillin (P) inhibits cross linking of peptidoglycan chains. (C) Penicillin is unable to interact with altered binding site and therefore cannot inhibit cross linking.

seen in Iceland when penicillin resistant pneumococci were isolated of a type similar to that initially observed in Spain. Presumably the strain was acquired by Icelanders while on holiday in Spain and then transported home.³²

EPIDEMIOLOGY OF ANTIBIOTIC RESISTANT PNEUMOCOCCAL INFECTION

The prevalence of penicillin resistant pneumococci varies throughout the world and is particularly high in South Africa, Spain, Hungary, Israel, and the USA (fig 1).¹ In the UK the level of penicillin resistance is fairly low (1.7% of isolates in 1993).³³ However, the prevalence can vary markedly between districts of one country – for example, in Hungary penicillin resistance in clinical isolates of pneumococci ranges from 3% to over 60% according to region.²⁵ In the USA the rate of penicillin resistance reaches 25% in some areas – for example, Atlanta where 9% of pneumococcal isolates in a recent study were also resistant to extended spectrum cephalosporins.³⁴ This study also noted that, while the overall incidence of invasive pneumococcal disease was more common in blacks than whites, antibiotic resistant *Streptococcus pneumoniae* were more readily isolated from white children living in suburban areas than from black children living in an urban setting. Thus, although lower socioeconomic status may predispose to pneumococcal disease, access to medical care and prior exposure to antibiotics may be a more important predisposing factor for infection with antibiotic resistant pneumococci. Some of the first isolates of penicillin resistant pneumococci were found in a village in New Guinea after prophylactic penicillin had been used in an attempt to reduce the incidence of pneumococcal disease.²² This observation also suggests that exposure to antibiotics increases the likelihood of infection with a resistant rather than a susceptible strain of pneumococci. Resistant pneumococci are again more readily isolated from patients who are already in hospital or who have been in hospital within the previous few months.³ Often

they have serious underlying disease such as cancer or renal insufficiency.³⁵ Such patients are also more likely to have received antibiotics and perhaps to have come into contact with other patients already colonised with resistant bacteria. In South Africa the rate of spread of resistant pneumococcal isolates was found to be related to the degree of overcrowding on paediatric wards, suggesting that the pneumococcus is readily spread by contact with colonised individuals.²³ Penicillin resistance may be found in any of the different pneumococcal serotypes but 80–90% consist of strains covered by the current pneumococcal vaccine Pneumovax II. Just four serotypes (6B, 14, 19A, and 23F) have so far been associated with multidrug resistance.³⁶

Introductory article by Pallares *et al*⁴

STUDY DESIGN

Pallares and colleagues have carried out a large prospective survey over 10 years of patients with definite bacteriological diagnoses of pneumococcal pneumonia based on isolation of pneumococci from blood or lower respiratory tract secretions, together with clinical and radiographic evidence of pneumonia. Patients were admitted under the care of an attending (general) physician who decided on the initial antibiotic regime. Once culture and sensitivity results were available they were reviewed by respiratory or infectious disease physicians who advised on subsequent antibiotic prescribing. The investigators collected data on factors thought likely to influence the outcome, including clinical factors such as age, presence of shock, underlying disease, and whether the infection was acquired in hospital or in the community. Laboratory data collected included white cell counts, multilobar appearance on the chest radiograph, and whether the infection was polymicrobial. The sole outcome examined was mortality with 28 days of diagnosis which was analysed in relation to the antibiotic sensitivity of the pneumococcal isolate and the antibiotic used to treat the infection. Both univariate and multivariate analyses were applied to the data.

TRENDS IN PNEUMOCOCCAL INFECTION OVER THE STUDY PERIOD

The overall incidence of pneumococcal pneumonia increased, probably because of larger numbers of infections seen in HIV patients in the latter part of the study. Such patients have previously been shown to be more susceptible than immunocompetent individuals to bacterial pneumonia, especially pneumococcal infection.^{10,11} The proportion of resistant pneumococcal isolates increased, not only to penicillin but also to cephalosporins, erythromycin, and to second line agents such as imipenem. The number of patients with high level penicillin resistant isolates also increased from 6% to 15%. Cephalosporin resistance was usually found in association with resistance to penicillin. No vancomycin resistance was seen.

MORTALITY

Overall mortality was significantly greater for those patients infected with penicillin resistant pneumococcal strains (38%) than penicillin susceptible strains (24%). However, multivariate analysis revealed a number of independent predictors of poor prognosis including age >70, shock, and multilobar, nosocomial and polymicrobial infections. These factors occurred with greater frequency in the group of patients infected with penicillin

resistant pneumococci. Once such poor prognostic factors were taken into account there was no significant difference in mortality between the penicillin resistant and penicillin susceptible groups. Thus, the isolation of penicillin resistant pneumococci from a patient may be a marker for poor prognosis, as has been observed for vancomycin resistant enterococci.³⁷ No difference in severity of infection at presentation was found between the two groups, which suggests that the presence of penicillin resistance has no effect on pneumococcal virulence. No difference in mortality (uncorrected) was found between patients infected with cephalosporin sensitive in comparison to cephalosporin resistant strains. The patients who were HIV positive had a lower overall mortality, perhaps because these patients were younger than the study group as a whole.

RESPONSE TO ANTIBIOTIC THERAPY

This study was not carried out as a randomised controlled trial, so only limited conclusions can be drawn about the effectiveness of different antibiotic strategies. In addition, the antibiotic treatment of patients was reviewed and sometimes changed in the light of culture results, but this has not been taken into account in the data analysis. In such cases it is not clear whether the data were analysed with regard to initial or final choice of antibiotic. With these caveats, there was no significant difference in mortality rates for patients treated with penicillin or ampicillin regardless of whether they were infected with a penicillin sensitive or resistant pneumococcal strain. This was so for both overall mortality rates, and mortality rates adjusted for the presence of poor prognostic factors. Likewise, penicillin resistance did not appear to have any effect on the outcome of patients treated with ceftriaxone or cefotaxime, or with other antibiotic regimes. The authors point out that eight of nine patients receiving penicillin for isolates with MICs of ≥ 2 $\mu\text{g/ml}$ (high level resistance) recovered. In addition, of eight patients who received cephalosporins for high level penicillin resistant isolates all but one patient survived. However, the numbers of patients with high level penicillin resistance were small so that treatment failures here might not be apparent.

For those patients with cephalosporin resistance the number of patients ($n=5$) treated with cephalosporin was too small to judge whether cephalosporins are effective despite the presence of resistance. Nonetheless, there was little difference in overall mortality for cephalosporin resistant isolates regardless of the antibiotic treatment regimen used.

Approaches to the management of pneumococcal antibiotic resistance

TREATMENT OF ANTIBIOTIC RESISTANT *STREPTOCOCCUS PNEUMONIAE*

Apart from the study by Pallares and colleagues, there is other evidence that β -lactam antibiotics are effective against pneumococci with intermediate penicillin resistance. A study of South African children with pneumococcal pneumonia showed no significant difference in mortality between those with fully sensitive pneumococcal strains (11%) and those with intermediate resistant strains (14%) when both received β -lactam antibiotics.³⁸ Studies in Spain and in Houston similarly failed to show any difference in outcome.^{3,39} Thus, as suggested by Pallares *et al*, high dose penicillin remains the treatment of choice for pneumococcal pneumonia, provided the MIC of the isolate is ≤ 1 $\mu\text{g/ml}$. In patients

Table 1 Risk factors for infection with penicillin resistant *Streptococcus pneumoniae*^{3,35}

High local prevalence of penicillin resistant pneumococci
Exposure to β -lactam antibiotics within previous 3 months
Admission to hospital within previous 3 months
Underlying immunosuppressive disease
Episodes of pneumonia within the previous year
Initial critical condition*

* Defined as two or more of the following: (1) severe underlying disease, (2) age of 75 or more, (3) leukopenia, (4) shock, (5) multilobar involvement.

from whom pneumococci with high level resistance have been isolated, failure of penicillin has been documented, particularly in subjects with underlying disease.^{3,40} In this situation high dose third generation cephalosporins, vancomycin or imipenem may be used, perhaps in combination with an aminoglycoside to provide synergy.⁴¹ Empirical therapy, according to Pallares and colleagues, should be based on the assessment of risk factors for infection with a penicillin resistant pneumococcus – for example, local incidence of penicillin resistance or likelihood of nosocomial infection (table 1). If no risk factors are present, and the probability of death appears low, then these patients can be treated with conventional regimens (benzyl penicillin, ampicillin or amoxicillin). However, if the patient is severely ill or has risk factors of penicillin resistance, they recommend the use of ceftriaxone or cefotaxime with erythromycin if an atypical pathogen cannot be ruled out. If high level cephalosporin resistance is present locally, then alternative regimens such as vancomycin or imipenem should be considered.⁴¹ For pneumococcal disease at other sites, particularly meningitis, it may not be possible to achieve sufficient local penicillin concentrations to treat pneumococci with intermediate resistance with penicillin. Treatment with a third generation cephalosporin such as ceftriaxone or cefotaxime may be necessary in this situation. In areas where cephalosporin resistant pneumococci are present, combination therapy with cefotaxime/ceftriaxone and vancomycin has been recommended.^{36,41}

In the UK and other countries where the prevalence of antibiotic resistant pneumococci is low there is no reason to change the standard treatment for pneumococcal pneumonia at present, although it may be prudent to err on giving higher rather than lower doses of penicillin or amoxicillin to cover possible intermediate resistant strains. However, it is essential to continue careful surveillance of pneumococcal resistance throughout the country in order to detect an increase in prevalence which might necessitate a change in policy. Pneumococcal meningitis should be treated with large doses of cefotaxime (2 g every six hours) or ceftriaxone (4 g per day) until sensitivities are available (table 2).

VACCINES

Because of the many different pneumococcal serotypes it is not possible to protect against all pneumococcal infections with a single vaccine. This problem was partially solved by the development of polyvalent vaccines containing initially 14 and, since 1984, 23 different pneumococcal serotypes (Pneumovax II).⁴² The serotypes contained in the latter preparation cover 80–90% of episodes of pneumococcal infection in most countries. The vaccine also includes most of the serotypes in which pneumococcal resistance is most commonly seen.³⁴ Pneumovax is recommended for individuals with im-

Table 2 Suggested treatment for pneumococcal infections

Site of infection	Type of resistance			
	Fully sensitive	Intermediate penicillin resistance	High level penicillin resistance	High level penicillin and cephalosporin resistance
Pneumonia and/or septicaemia	Benzyl penicillin 1.2 g 6 hourly (ampicillin/amoxycillin)*	High dose benzyl penicillin 2.4 g 4 hourly (ampicillin/amoxycillin)	Cefotaxime 1–2 g 6 hourly	Vancomycin 1 g 12 hourly ± aminoglycoside (imipenem ± aminoglycoside)
Meningitis	Benzyl penicillin 2.4 g 4 hourly	Cefotaxime 2 g 6 hourly (ceftriaxone)	Cefotaxime 2 g 6 hourly (ceftriaxone)	Vancomycin 1 g 12 hourly ± aminoglycoside

* Alternative regimen in parentheses.

munodeficiency states including hyposplenism and HIV infection; chronic lung, cardiac, hepatic and renal disease; and diabetes mellitus. In the USA it is also recommended for all individuals over the age of 65.⁴³ The overall efficacy varies according to the patient group vaccinated and is estimated to be 56% overall, reaching 75% in the immunocompetent population.⁴⁴ It appears to be less effective in patients with chronic renal failure and haematological malignancies. Uptake of the vaccine, at least in the USA, has been a problem with only 28% of the target population receiving it even after an awareness campaign.⁴⁵ Unfortunately the vaccine is not effective in children under two years of age because of immaturity of the immune system. In addition, the capsular polysaccharide antigens do not induce high level, high affinity antibodies or T cell memory as do the peptide-based or protein-based antigens. Thus, new conjugate vaccines are being developed using protein carriers attached to capsular polysaccharide in the hope of improving protection, as has been achieved for the Hib conjugate vaccine. The diversity of the pneumococcal polysaccharides makes this a much more complex task, and initial conjugate vaccines are likely to include only the seven most common serotypes.⁴⁶ We consider the use and development of pneumococcal vaccines as an important means of prevention of resistant pneumococcal disease in at risk groups.

ANTIBIOTIC USAGE

As described above, the occurrence of antibiotic resistant *Streptococcus pneumoniae* is frequently related to antibiotic usage. Antibiotic prescribing has been shown to be inappropriate in many instances – for example, viral

infections where no effect has been shown on either symptom duration or secondary bacterial infection.⁴⁷ As many as 50% of outpatient antibiotic prescriptions were considered unnecessary in one US study.⁴⁸ In the UK antibiotic prescription rates have increased by nearly 50% between 1980 and 1993.⁴⁹ Although the reasons for this increase in antibiotic prescribing have not yet been investigated, it has been suggested that this is due to a gradual increase in the use of antibiotics for respiratory symptoms. In one recent study of 1089 adults who presented to their general practitioner with acute lower respiratory symptoms, three quarters received an antibiotic even though the GP felt antibiotics to be definitely indicated in less than a third of treated cases and not needed in a fifth. Factors such as patient pressure and GP work pressure were found to contribute to the prescribing of unnecessary antibiotics.⁵⁰ In some countries antibiotics can be obtained without prescription which may lead to inappropriate use and the development of resistance. The use of antibiotics in animal food stuffs and in veterinary practice is not well regulated in many countries and may lead to the emergence of resistance genes which may be passed from animal microbial flora to human pathogens.^{51 52} More careful regulation of antibiotic use is necessary to limit the development, not only of antibiotic resistant pneumococci, but other resistant bacteria such as methicillin resistant *Staphylococcus aureus* and vancomycin resistant enterococci. Enterococci are fairly closely related to streptococci and thus the potential exists for transfer of genetic material encoding vancomycin resistance from enterococci to pneumococci. Such an event would leave very few antibiotics effective against pneumococci.

LEARNING POINTS

- * The incidence of penicillin and cephalosporin resistant pneumococci is increasing.
- * High dose penicillin is still effective in intermediate resistant pneumococcal bacteraemia and pneumonia, but probably not in meningitis.
- * Alternative antibiotic regimens are required for pneumococci with high level penicillin resistance; surveillance of local antibiotic resistance is critical for selection of appropriate empirical therapy.
- * Pneumococcal vaccines protect against most pneumococcal serotypes with antibiotic resistance and should be given more frequently, especially in areas where antibiotic resistant pneumococci are common.
- * Antibiotic usage should be more carefully regulated to limit the emergence of antibiotic resistant bacteria.

Conclusion

There is evidence from many different centres throughout the world that the incidence of resistance in pneumococci, not only to penicillin but also to other antibiotics, is increasing rapidly. The evidence presented by Pallares and colleagues is somewhat reassuring in that, for the moment, many of these pneumococcal strains show only intermediate penicillin resistance and, at least in pneumonia, respond to high dose penicillin. However, high level resistance to penicillin and also to cephalosporins is becoming more common, and such strains may require alternative antibiotic regimens. Other strategies which may help to prevent disease due to resistant pneumococci include the increased use of existing pneumococcal vaccines and the development of improved conjugate vaccines. The problem of inappropriate antibiotic use needs to be urgently addressed to control the development, not only of antibiotic resistant *Streptococcus pneumoniae*, but also many other species of resistant bacteria.

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