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Penicillin- and Cephalosporin-Resistant *Streptococcus Pneumoniae*

Emerging Treatment for an Emerging Problem

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Abstract

The global emergence of pneumococci resistant to antimicrobial therapy has led to dilemmas in the management of pneumococcal infections. The principles of pharmacodynamics predict that penicillin and cephalosporin therapy of pneumonia will be successful against pneumococci with minimum inhibitory concentrations of penicillin up to 4 μg/ml. These predictions are supported by the observations of a number of recent clinical studies. Otitis media therapy is influenced by penicillin-resistance and current recommendations are that amoxicillin is the drug of choice for this infection, given at a double dose of 80 to 90 mg/kg/day. For the therapy of meningitis, cefotaxime or ceftriaxone in maximal doses is recommended and vancomycin may be added if cephalosporin-resistant strains are encountered with reasonable frequency in the population. The new fluoroquinolones with excellent antipneumococcal activity may be considered for use in the setting of pneumonia caused by highly resistant pneumococci and are under evaluation for the management of meningitis.

The risk factors that have led to the global pandemic of antibiotic resistance in the pneumococcus were reviewed in the early 1990s.[1,2] At that time there was clear evidence of the failure of penicillin for the therapy of penicillin-resistant pneumococcal meningitis.[1] A number of apparent failures of penicillin, or other β-lactam agents, in the therapy of pneumococcal pneumonia were reported from South Africa[3,4] and from Spain.[5]

As the authors of two of these reports,[3,4] we had a particular responsibility to assure ourselves that the failures of penicillin therapy for bacteraemic pneumococcal pneumonia were caused by the drug resistance and not because the patients had severe underlying disease. Patients continue to have considerable mortality even following prompt therapy when they are infected with penicillin-susceptible strains.[6] A review of all of the available cases of presumed penicillin failure in the management of penicillin-resistant pneumococcal pneumonia, led us to conclude that there was insufficient evidence to suggest that the cause of clinical failure in these patients was the antibiotic resistance of the pneumococcus, as the available data suggest that the levels of penicillin achievable following intravenous management exceed the minimum inhibitory concentrations (MIC) of the resistant isolates.[7,8]

The past 5 years have seen a number of large observational studies which support this conclusion, and our knowledge of the pharmacodynamics of pneumococcal infections have allowed a rational basis to develop the prediction of the success or failure of the management of pneumococcal infections with penicillin and cephalosporins. The double tap methodology of initial plus repeat tympanocentesis has also laid the ground work for rational choices of β-lactams for the management of pneumococcal otitis media.

1. Pneumococcal Meningitis

A large number of anecdotal reports in the 1970s and 1980s described the failure of penicillin in the management of pneumococcal meningitis when the MIC reached the range of intermediate resistance (≥0.1 mg/L).[1] A prospective observational study of the management of pneumococcal meningitis treated with penicillin and chloramphenicol was conducted in South Africa.[9] Although it was known at that time that patients responded poorly to penicillin when they were infected with intermediately penicillin-resistant pneumococci, it was felt that the addition of chloramphenicol would allow the successful treatment of these patients. That study[9] showed that on an intent-to-treat basis, patients who were infected with intermediately penicillin-resistant pneumococci had a 34% increased risk of death or severe neurological outcome of meningitis despite their therapy with penicillin and chloramphenicol. Empiric management of pneumococcal meningitis was therefore switched to cefotaxime and ceftriaxone which had been used with success for many years in the US, because of the threat of β-lactamase–producing *Haemophilus influenzae*.

The report by Bradley and Connor[10] in 1991, of a patient in whom a pneumococcus was cultured from the cerebrospinal fluid (CSF) while the patient was on ceftriaxone therapy, led to a re-evaluation of the break-points of cephalosporin therapy for pneumococcal meningitis. Strains with an MIC of 1 mg/L were considered intermediately resistant and those with an MIC ≥2 mg/L were considered resistant to these agents. Empiric therapy for meningitis was then extended to include the addition of vancomycin,[11] although concern was expressed that the use of dexamethasone may impede the penetration of vancomycin into the CSF of children. A study in humans[12] showed that adequate penetration of the CSF was obtained when using vancomycin in the presence of dexamethasone. That study also showed that the bactericidal activity of the CSF was enhanced in patients who received ceftriaxone plus vancomycin or ceftriaxone plus rifampicin (rifampin).[13] A later study documented that increasing the dose of cefotaxime[13] was not in itself able to achieve reliable concentrations of cefotaxime in the CSF, sufficient to kill cephalosporin-resistant pneumococci.

The current recommendations for the management of penicillin-resistant pneumococcal meningitis therefore remain cefotaxime or ceftriaxone. Vancomycin should be added if cephalosporin-resistant strains are encountered in that country. Alternative drugs for the management of pneumococcal meningitis include meropenem.[14] Further data are required on the efficacy of this agent against cephalosporin-resistant strains. An alternate approach under clinical trial is the use of a fluoroquinolone with Gram-positive activity, for example, trovafloxacin.

2. Pneumonia

A number of prospective observational studies in children have documented that penicillin, ampicillin or cephalosporin therapy of pneumococcal pneumonia is not associated with an adverse outcome. These studies have included data on several hundred children treated in South Africa,[15] South Korea,[16] Uruguay and Argentina.[17] The recent study from Argentina and Uruguay[17] is particularly important as it shows that conventional doses of penicillin or ampicillin are sufficient to cure pneumococcal pneumonia caused by pneumococci that are considered to be fully penicillin-resistant with an MIC between 2 and 4 mg/L.[17] Retrospective studies may be complicated by the perceptions of clinicians who are likely, in the case of pneumo-

coccal infections identified by the laboratory as being resistant, to keep patients longer in hospital and to switch therapy even if there is no evidence of clinical failure.

Despite these limitations, a recent retrospective study in Boston, US[18] of the treatment of children with bacteraemia, showed no difference in mortality or hospital stay of patients with penicillin-resistant isolates largely treated with cephalosporins. When the strains, however, were reported by the laboratory as resistant to cephalosporins, there was no difference in mortality, but more lumbar punctures were performed and there was an increased hospital stay, perhaps reflecting clinicians' concern about identifying antibiotic-resistant isolates in cases of pneumococcal meningitis.[18]

A single case has been reported of the development of meningitis in a patient with pneumococcal pneumonia treated with cefotaxime followed by cefuroxime.[19] Failure of therapy in this single case is difficult to explain, although it is possible that the organisms were protected from the antibiotics within an empyema that was present in that patient.

Prospective studies in adults[5,20] have failed to document any impact of β-lactam resistance on the outcome of pneumococcal pneumonia when the severity of the underlying disease is controlled. Retrospective studies of adults in Omaha in the US have shown no difference in mortality, but a slightly prolonged hospital stay, in patients infected with penicillin-resistant pneumococci.[21] Similar conclusions were reached in a study in Columbus,[22] and a study from Toulouse, France, reported no difference in the mortality of patients with penicillin-susceptible versus penicillin-resistant pneumococcal pneumonia.[23] The reasonably good penetration of cefotaxime or ceftriaxone into pleural fluid[24] suggests that these agents should be effective for the management of strains with MIC up to and including 4 mg/L.

The conclusion from these studies is that intravenous penicillin or ampicillin are adequate therapy for pneumococcal infections with an MIC up to 4 mg/L. Very rarely, strains are encountered with an MIC greater than 4 mg/L and in these cases it may be prudent to add vancomycin to cephalosporin for therapy of pneumonia.

3. Otitis Media

The penetration of oral agents into the middle ear has been correlated in pharmacodynamic models with the MIC of penicillin-resistant pneumococci to predict the outcome of pneumococcal otitis media.[25] These models very closely predict the clinical observations of failure of less active agents against intermediately penicillin-resistant pneumococci.[26] Further, in a series of repeat tympanocenteses, Dagan and his colleagues[27] in Israel have correlated the presence of pneumococci in the middle ear 4 to 5 days after therapy, with clinical failure of treatment of that infection. As most patients with otitis media will have resolution of their signs and symptoms, even without antibiotic therapy, it is essential to document bactericidal activity in the middle ear to predict accurately the activity of new agents against penicillin-resistant pneumococci.

Current oral recommendations for the management of otitis media are high dosage (80 to 90 mg/kg/day) of amoxicillin.[28] This is the most active oral agent, followed by cefuroxime. As macrolide resistance has become increasingly common, the macrolide class of agents are less valuable alternate agents for the management of otitis media.[28]

4. Other Infections

There are insufficient clinical data to make firm recommendations as to the management of other infections caused by penicillin-resistant pneumococci. The available data have recently been summarised in an excellent review by Kaplan and Mason.[29]

5. Conclusions

Penicillin resistance in the pneumococcus has led to the need to treat pneumococcal meningitis with cefotaxime or ceftriaxone. Vancomycin may be added where pneumococcal strains resistant to these agents occur. A growing body of evidence in

both children and adults suggests that the management of pneumococcal bacteraemia and pneumonia can continue with current doses of intravenous penicillin, ampicillin, cefotaxime or ceftriaxone. These data suggest that the break-points for resistance for the management of pneumonia and bacteraemia may be raised, perhaps to a level of 4 mg/L. The oral management of otitis media is problematic and current recommendations are that high doses of amoxicillin represent the best available treatment for penicillin-resistant pneumococcal otitis media.

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