Meningitis Secondary to Multiply Resistant Streptococcus Pneumoniae

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Streptococcus pneumoniae resistant to penicillin G, chloramphenicol, and tetracycline have been reported with increasing frequency since 1977. A patient with meningitis secondary to multiply resistant S pneumoniae was treated with short courses of ampicillin, penicillin G, and then seven days of chloramphenicol and recovered uneventfully. Review of the literature reveals that after minimum inhibitory concentrations are known, ampicillin, increased doses of penicillin, chloramphenicol, or addition of rifampin may be appropriate therapeutic choices for resistant S pneumoniae infections.

Recently the Centers for Disease Control (Atlanta) reported the first US case of Streptococcus pneumoniae resistant to penicillin G, chloramphenicol, and tetracycline.[1] In 1977 a similar resistance profile had appeared in South Africa in five patients who had received penicillin or chloramphenicol for long periods before or during hospital admission.[2] Clinicians worldwide now may encounter S pneumoniae organisms that are both relatively resistant to penicillin G and multiply resistant to other antibiotics usually effective in gram-positive infections. Since S pneumoniae is among the most common causes of meningitis in the pediatric age group, a clear rationale for therapy is important for the clinician who encounters a multiply resistant organism. This report presents a case of multiply resistant S pneumoniae meningitis, discusses problems in therapy, and provides an approach to antibiotic choice based on a review of the recent literature.

Case Report

The patient is a ten-month-old male infant who presented with fever, lethargy, vomiting, and a stiff neck of one day's duration. He had a history of frequent episodes of otitis media treated with amoxicillin in the previous four months. He had been seen by his pediatrician three days prior to this admission and was begun on trimethoprim-sulfamethoxazole for a suspected otitis media. The patient had spent the two days prior to admission in his usual day care center where most of the children were under three years of age. On admission, the temperature was 38°C; pulse, 80 beats/min; and blood pressure, 104/80 mmHg. Physical examination revealed nuchal rigidity and a right otitis media. The initial white blood cell count was 39,900/mm^3 with 14 percent band forms and 76 percent segmented neutrophils. The cerebral spinal fluid (CSF) showed a white blood cell count of 5,550/mm^3 with 81 percent segmented neutrophils; glucose of 10 mg/100 mL; and protein 112 mg/100 mL. CSF Gram stain revealed gram-positive cocci. Initial serum sodium was 127 percent, and carbon dioxide 15 mg/100 mL. The patient was begun on intravenous ampicillin, 300 mg/kg/d every four hours, and chloramphenicol, 100 mg/kg/d every six hours. Two days after admission the CSF and blood cultures were interpreted as growing S pneumoniae, and the drug regimen was changed to penicillin G, 300,000 U/kg/d every four hours. The patient had shown rapid clinical improvement from the onset of therapy with no evidence of immediate neurologic complications. On the fourth hospital day the microbiology laboratory reported that the S pneumoniae organism showed a relative resistance to penicillin by oxa-

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cillin disc zone of less than 20 mm. At this time, repeat lumbar puncture revealed a CSF white blood cell count of 100/mm^3 with 70 percent lymphocytes and 26 percent segmented neutrophils, glucose of 61 mg/100 mL, and protein of 57 mg/100 mL. There were no bacteria on Gram stain. The patient had been afebrile for 24 hours and was essentially normal in behavior and activity. Because of the risk of penicillin resistance and decreasing permeability of the blood-brain barrier, the patient's therapy was changed to chloramphenicol 100 mg/kg/d. The S pneumoniae organism was submitted for minimum inhibitory concentration (MIC) testing; however, results were not available until the 10th and final hospital day. The patient was completely asymptomatic at that time and was discharged on no medications. Final evaluation of the S pneumoniae organism showed a penicillin G MIC of 0.12 μg/mL, chloramphenicol MIC of 16 μg/mL, tetracycline MIC greater than 16 μg/mL, and vancomycin MIC less than 2 μg/mL. Further testing at the Centers for Disease Control showed ampicillin MIC of less than 0.25 μg/mL, erythromycin less than 0.06 μg/mL, and rifampin less than 0.6 μg/mL. The child has done well since discharge from the hospital.

Discussion

This was the third multiply resistant strain of S pneumoniae (MRP) reported to the Centers for Disease Control in 1981. In the other reported case of MRP meningitis, the resistance was similar to that of this patient.[1] The organism reported here is considered to be relatively resistant to penicillin (MIC 0.1 to 1.0 μg/mL) by Thornsberry's classification.[3] The actual mechanism for resistance remains unknown. A number of studies have suggested that high penicillin use and possibly isolation of a given population of carriers are factors in development of resistant S pneumoniae.[4,5] However, a case control study by Saah and associates[6] implied that no definite relationship exists between finding relatively resistant pneumococcus and prior penicillin administration. Resistance can be produced in the laboratory by steadily increasing the concentration of penicillin exposed to S pneumoniae organisms.[7] These organisms do not lose their resistance after being transferred to an antibiotic-free medium.[7] The patient described here was at risk of exposure to MRP because of his therapy with amoxicillin on several occasions prior to the episode of meningitis and his enrollment in a day care center with children three years old or less. In the other US case of MRP meningitis, the child had attended a day care center in which 4 of 14 children (29 percent) under the age of two years had throat cultures positive for MRP. In day care contacts of that patient, a history of antibiotic use in the prior two months was significantly associated with the presence of MRP in throat cultures.[1] Similar studies of the household and day care contacts of the infant described here have not been performed. In previous studies elimination of MRP from carriers has proven to be very difficult because of rapid emergence of higher levels of resistance, intolerance to multiple drug regimens, and high cost.[5]

This is the first reported case of a favorable outcome of MRP meningitis treated with short courses of ampicillin and penicillin G followed by extended therapy with chloramphenicol. Indeed, after final evaluation of the sensitivity of this organism to chloramphenicol (MIC 16 μg/mL) compared with the peak concentration of chloramphenicol attainable in the CSF, it is likely that this child was effectively treated for S pneumoniae meningitis with just four days of antibiotic therapy. Fortunately, this organism showed a relatively low resistance to penicillin G (MIC .12 μg/mL). In other reported cases of relatively penicillin-resistant S pneumoniae meningitis, effective therapy has required either higher doses of penicillin, conversion to ampicillin, or conversion to chloramphenicol as the primary therapeutic agent (Table 1). In the only other case of MRP meningitis, the patient recovered after treatment with ampicillin, chloramphenicol, and rifampin.[1]

The rationale for using higher doses of penicillin is based on the finding of peak CSF penicillin levels of only 1 μg/mL, even on the first day of therapy.[13] Previous reports of higher CSF to serum ratios of ampicillin as compared with penicillin G have prompted clinicians to use ampicillin in purulent meningitis secondary to MRP.[14] The improved CSF-serum ratio of ampicillin existed whether the CSF showed high or low cell counts.[14] Probenecid has been shown to inhibit the active transport of penicillin from the CSF.[15] It has not been used in cases of resistant S pneumoniae infection but may prove to be a useful adjunct in the future. In both reported cases of MRP, rifampin has shown a low MIC[1]; however, rapid emergence of resistance to

Table 1. Previous Reported Cases of Meningitis Secondary to Relatively Resistant Pneumococcus

Author	MIC to Penicillin G (μg/mL)	Initial Antibiotics	Final Antibiotics
Naraqui et al[8]	.25	Penicillin G 500,000 U/kg/day	Penicillin G 1,000,000 U/kg/day
Howes et al[9]	.19	Penicillin G	Ampicillin
Mace et al[10]	.39	Penicillin G 500,000 U/kg/day	Penicillin G 1,000,000 U/kg/day; chloramphenicol 100 mg/kg/day
Appelbaum et al[2]	—	Penicillin, chloramphenicol, kanamycin, sulfadiazine	Fatal
		Penicillin, chloramphenicol, ampicillin, sulfadiazine	Fatal
		Penicillin, chloramphenicol, cloxacillin, neomycin	Fatal
Iyer et al[11]	.15	Penicillin G 400,000 U/kg/day	Ampicillin 400 mg/kg/day
Paredes et al[12]	.20	Penicillin G 600,000 U/kg/day	Chloramphenicol
Centers for Disease Control[1]	1.0	Penicillin G	Penicillin G, chloramphenicol, rifampin

this drug prevents its use as a single agent in therapy.[5]

Several serotypes have been found to show relative resistance to penicillin or multiple antibiotic resistance, including 4, 6A, 6B, 14, 19A, and 23.[1,4,5] Pneumococcal vaccine licensed for use in the United States contains capsular polysaccharides of types 4, 6A, 14, 19F, and 23.[16] Even if modification of the vaccine to include the antigens of all the antibiotic resistant types can be accomplished, there are no data about the degree of protection for children under two years old. The potential use of pneumococcal vaccine in high-risk populations has been discussed in other reports.[1,5,6]

Conclusions

Recent reports have made it clear that S pneumoniae can no longer be assumed to be sensitive to standard doses of penicillin G, tetracycline, or chloramphenicol. Screening for relatively resistant organisms, as well as MIC studies to determine multiply resistant bacteria, is essential to the appropriate care of S pneumoniae meningitis. The choice of antibiotics should be based on (1) sensitivity of the organism, (2) clinical response, and (3) repeat CSF analysis. It has been shown that repeat CSF findings alone have a poor specificity in predicting relapse of meningitis, and clinical response seems to be a more accurate indicator of treatment effectiveness.[17] The clinical response is particularly important when treating a multiply resistant pneumococcus because of the expected delay in MIC results. When the MIC values are known, continuation of ampicillin, increasing doses of penicillin, conversion to chloramphenicol, or addition of rifampin are the appropriate therapeutic choices (Figure 1).

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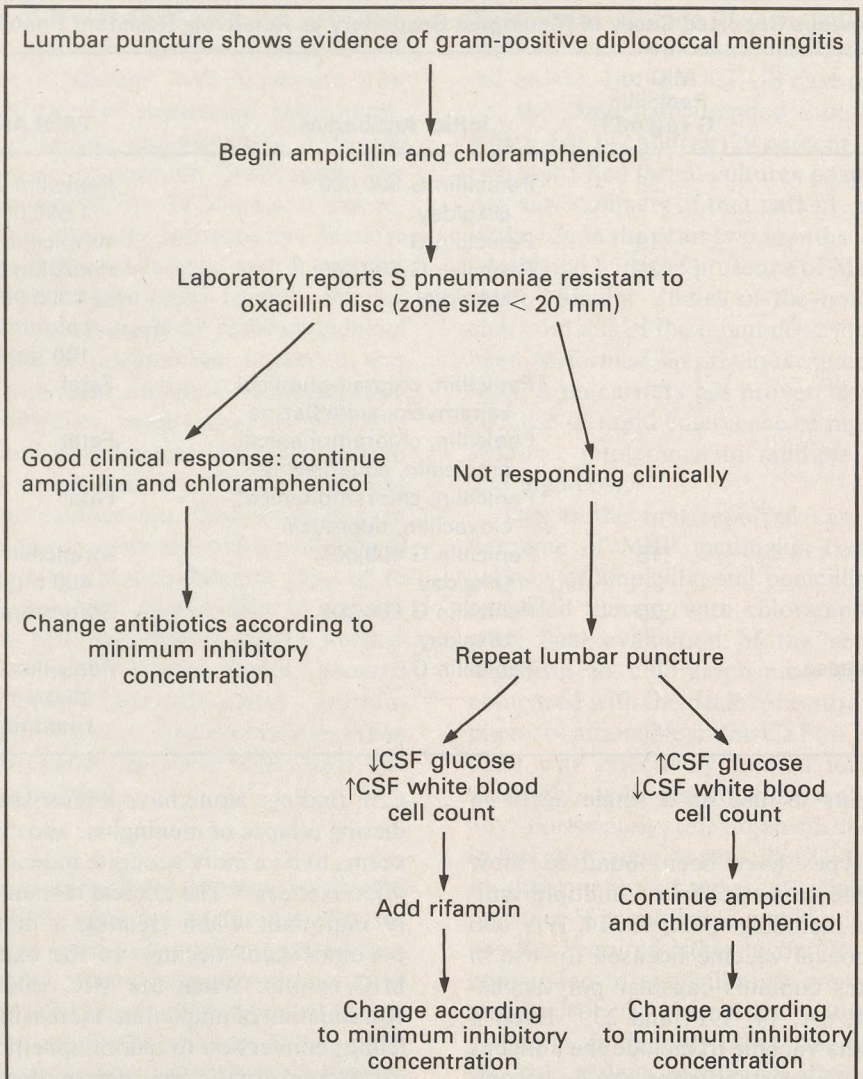

Figure 1. Decision tree for multiply resistant S pneumoniae meningitis

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