Antibiotic choices for meningitis beyond the neonatal period

In the past decade a variety of new antibiotics have become available that are both highly active against the common meningeal pathogens and that also achieve excellent bactericidal concentrations in the cerebrospinal fluid. There is now an extensive literature documenting the effectiveness of these agents in treating bacterial meningitis. The purpose of this review is to consider the evidence in favour of using the newer antibiotics in preference to more conventional treatment regimens.1

In order to select the optimal antibiotics for the initial treatment of bacterial meningitis, consideration must be given to the following factors: the spectrum of pathogens causing meningitis in different age groups, the changing pattern of antimicrobial resistance, the pharmacological properties of the antibiotics available, and the results of therapeutic trials.

The organisms most commonly responsible for causing bacterial meningitis vary significantly with the age of the patient. The optimal antibiotic regimen will therefore be different for neonates, young infants, and older children. In the neonatal period, Escherichia coli and other Gram negative bacilli, group B streptococcus, and Listeria monocytogenes are the important meningeal pathogens. In children older than 3 months nearly all cases of community acquired meningitis are caused by Neisseria meningitidis, Streptococcus pneumoniae, or Haemophilus influenzae, the latter organism predominantly infecting children younger than 6 years. Infants between 1 and 3 months of age may be affected by either the neonatal or the childhood spectrum of pathogens.2

A major determinant of antibiotic choice in the treatment of bacterial meningitis is the continually changing pattern of antibiotic resistance. When ampicillin was first introduced into clinical practice, all strains of H influenzae were fully sensitive to it. Since then, however, there has been a progressive increase in resistance to this antibiotic and currently at least 15% of H influenzae isolates causing invasive disease in the UK are resistant to ampicillin.3 4 It is disturbing that in some countries, such as the USA, resistance is now as high as 30%. In the light of this, ampicillin can no longer be recommended as the sole agent for the initial treatment of meningitis in children less than 6 years of age.5 6 Although most strains of H influenzae remain sensitive to chloramphenicol, resistance is now found in up to 3% of invasive isolates in England and Wales.7 Moreover, many of these strains are now also resistant to ampicillin,3 4 7 and in Spain resistance to both drugs is increasing.8

Though resistance of H influenzae to conventional anti-

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Annotations

β Lactam antibiotics do not penetrate well into the cerebrospinal fluid in healthy individuals, but in the presence of meningeal inflammation adequate cerebrospinal fluid concentrations are achieved to inhibit sensitive strains.
The exceptional safety record of the penicillins, and their high therapeutic to toxic ratio, have made penicillin the drug of choice for treating meningococcal and pneumococcal meningitis, and ampicillin is still an excellent drug for treating sensitive strains of \textit{H influenzae}.

The first generation cephalosporins proved unreliable for the treatment of meningitis. However, cefuroxime, a second generation cephalosporin active against \textit{H influenzae}, \textit{S pneumoniae}, and \textit{N meningitidis}, penetrates well into the cerebrospinal fluid and has proved effective as a single agent for initial treatment of childhood meningitis.14 16 Cefuroxime has been used extensively in both Europe and the USA as a single agent for treatment of meningitis. However, several reports have suggested that both sterilisation of the cerebrospinal fluid and clinical outcome may be inferior to that achieved with the newer third generation cephalosporins.18-22

The third generation cephalosporins cefotaxime, ceftazidime, and ceftriaxone have greatly enhanced the armamentarium against both the neonatal and childhood meningeval pathogens.18-22 All three agents are extremely active against \textit{S pneumoniae}, \textit{H influenzae} (including β lactamase producing strains) and \textit{N meningitidis} and achieve cerebrospinal fluid concentrations greatly in excess of their minimum bactericidal concentrations. The third generation cephalosporins are also extremely safe and monitoring of serum concentrations is not required. Side effects are rare and are similar to those of the penicillins, including skin reactions, gastrointestinal upset, and neutropenia. Ceftriaxone is the most potent of the new cephalosporins. It has a long plasma half life, and can therefore be administered on a once daily basis.23 24 However gastrointestinal side effects are more common with ceftriaxone, and bile sludging detected by ultrasound is frequently observed, but is probably not clinically significant.18 21

The paediatric and infectious disease literature published over the past few years contains a number of reports of open and comparative trials assessing the use of the new cephalosporins and conventional antibiotic regimens in meningitis. For those hoping that the newer drugs would provide the 'magic bullet' which would reduce the mortality and long term morbidity from meningitis, these trials are disappointing. Cefuroxime, ceftazidime, cefotaxime, and ceftriaxone have all proved effective in treating meningitis, but despite reports that they achieve sterilisation of the cerebrospinal fluid more rapidly than ampicillin and chloramphenicol,24 mortality rates and neurological sequelae have not been significantly improved. From the studies published to date it can be concluded that single drug treatment with cefuroxime or the third generation cephalosporins is as effective but not necessarily better than the standard combination of ampicillin or penicillin and chloramphenicol.

The apparent lack of evidence that the cephalosporins are superior to ampicillin or chloramphenicol, despite their greater in vitro activity, must be interpreted with caution. In order for comparative trials of these antibiotics to show significant differences in mortality or neurological sequelae, hundreds of patients would need to be included in each arm of a trial. Such trials are always very difficult and costly to undertake. All the published studies have contained relatively small numbers of patients and differences in mortality would not necessarily have been detected.

If the cephalosporins are to be used for initial treatment of meningitis in preference to ampicillin and chloramphenicol it is necessary to consider which of these drugs should be recommended.17 There have been few trials directly comparing all of these antibiotics. In studies published to date, ceftriaxone has resulted in more rapid sterilisation of the cerebrospinal fluid than either cefotaxime or cefuroxime.17 18 22 Furthermore in one study the incidence of deafness was reduced in ceftriaxone treated patients compared with those treated with cefuroxime.18 The evidence is therefore accumulating that the third generation cephalosporins, particularly ceftaxidime, are more effective for the treatment of bacterial meningitis than cefuroxime. Ceftazidime is less active against pneumococci than cefotaxime and should be reserved for pseudomonal infections.

**Recommended antibiotics for initial treatment of meningitis in different age groups**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Drug</th>
<th>Dose/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 1 month to 3 months</td>
<td>Ampicillin and ceftriaxone</td>
<td>200 mg/kg</td>
</tr>
<tr>
<td>Older infants and children</td>
<td>Cefotaxime or ceftazidime</td>
<td>200 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Ampicillin and chloramphenicol*</td>
<td>100 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75-100 mg/kg</td>
</tr>
</tbody>
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*Measurement of therapeutic concentrations of chloramphenicol is necessary.

**Current recommendations**

Our current recommendations for initial antibiotic treatment of bacterial meningitis are shown in the table. In infants between 1 and 3 months of age a combination of ampicillin and cefotaxime is a logical choice as cefotaxime provides cover for both neonatal and infant pathogens and ampicillin is effective against \textit{L monocytogenes}.

For older infants and children we recommend a third generation cephalosporin (cefotaxime or ceftazidime) in preference to the combination of penicillin or ampicillin and chloramphenicol. Although the mortality and long term morbidity of patients treated with the newer antibiotics is similar to those treated with conventional therapy, our decision is based upon (1) the lack of toxicity of the third generation cephalosporins, (2) the emerging resistance of the three major pathogens to conventional treatment, (3) the elimination of the need to monitor serum concentrations, and (4) the convenience and reliability of using a single agent which can be administered on a one to three times daily basis. Although the cephalosporins are more expensive than penicillin or ampicillin and chloramphenicol, then the nursing cost of administering two drugs every six hours are compared with those of giving a single agent one to three times daily, the total costs are fairly similar.

Once the causative organism has been identified, and the antibiotic sensitivities determined, intravenous penicillin can be substituted for treating sensitive meningococcal and pneumococcal infections. In cases of meningitis where the identity or the sensitivity of the causative organism cannot be definitively determined, we would continue to use a third generation cephalosporin.

Traditionally \textit{H influenzae} or \textit{S pneumoniae} meningitis have been treated for 10 to 14 days, and meningococcal meningitis for seven days.25 Several recent studies have indicated that seven days of treatment is probably adequate for all three childhood pathogens, but the numbers of patients treated with the abbreviated course are too small to make definite recommendations.26 We currently recommended seven days treatment for \textit{N meningitidis} and 10 days for \textit{H influenzae} and \textit{S pneumoniae} meningitis.

**Conclusion**

There is now a range of antibiotics that are effective in treating bacterial meningitis. Although the results of trials have not as yet indicated that the mortality and morbidity is improved by the third generation cephalosporins, they offer advantages in terms of ease of administration, safety, and
lack of resistance. With an increasing array of new agents becoming available, paediatricians will have to continually re-evaluate antibiotic policies as patterns of microbial resistance change and new drugs enter clinical use. It is unlikely however that new antibiotics alone will significantly alter the mortality and morbidity associated with bacterial meningitis. The advent of effective vaccines and new therapeutic interventions to modulate the damaging host inflammatory response to invading micro-organisms should ultimately improve the outcome of bacterial meningitis in the future.

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Fibreoptic bronchoscopy in infants

In the past decade endoscopic airway examination has become an important diagnostic tool.1 In neonates and infants the aims of fibreoptic bronchoscopy are nearly the same as in older children: assessment of proximal airway patency and sampling of lavage fluids for microbiological, cytological, or chemical studies. There are a number of special problems in infants: frequency of malformations and malacias, and mechanical complications of assisted ventilation. As the fibreoptic bronchoscopes are obstructive, the smallest infants and those with precarious respiratory status demand well trained operators and well adapted techniques and instruments. These precautions should allow exploration of infants' airways safely and lead to subsequent investigations and the diagnosis.

Techniques

Despite some uncertainty as to the indications for rigid bronchoscopes and fibreoptic bronchoscopes, paediatricians generally prefer fibreoptic bronchoscopes for most procedures.2 The standard paediatric fibreoptic bronchoscopes have an external diameter of 3-5 mm and an operating channel of 1-2 mm (Olympus BF 3C20, FB 10-H Pentax). Most examinations can be performed with sedation and local anaesthesia.3 4 The flexibility of the bronchoscope increases the patient's comfort. The controlled angulation of the distal tip allows more selective manoeuvres and improves the visualisation of the upper lobe bronchi. Fewer medical and nursing personnel are required with fibreoptic bronchoscopy. It can be performed on an outpatient basis and even at the bedside of the infants in intensive care units.

Rigid bronchoscopes are more suitable for the removal of foreign bodies, excision of granulation tissue, and examination of tracheo-oesophageal fistulas.5 Their internal diameters allow the insertion of forceps for bronchial biopsies. Clearly rigid and flexible bronchoscopes neither duplicate nor replace each other, rather they are complementary and should be used when appropriate for the particular problem.

When fibreoptic bronchoscopy is indicated, it must be carried out in a properly equipped and staffed room with facilities for resuscitation. In our practice sedation is achieved with subcutaneous atropine 0-01 mg/kg and rectal midazolam 0-25 mg/kg between 6 months and 1 year and 0-5 mg/kg between 1 and 2 years. Infants younger than 6 months are given atropine and rectal diazepam 0-5 mg/kg.

As the fibreoptic bronchoscope is passed through the nose, careful topical anaesthesia of upper airways and larynx is an important step. For a skilled operator, the duration of fibreoptic bronchoscopy does not exceed 2-3 minutes. Oximetry and electrocardiographic monitoring are mandatory in infants with low weights or borderline respiratory status. Supplemental oxygen through the free nostril is indicated in infants less than 5 kg, in children with diffuse lung disease, and in children with borderline or poor blood gases. The fibreoptic bronchoscope is reinserted several times if necessary.

Anatomical indications

Bronchoscopy is required to diagnose anatomical abnormalities responsible for persistent or recurrent pneumonia,
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