Paediatric meningitis

TREATMENT OF BACTERIAL INFECTION

By Paul Baines, MD, FRCA, Nicola Reilly, BSc, MRPharmS, and Andrea Gill, MSc, MRPharmS

Paediatric bacterial meningitis is a serious infection that can result in permanent neurological sequelae or death. Broad-spectrum intravenous antibiotics, started as soon as the condition is suspected, are the mainstay of treatment. Acute resuscitation may also be necessary for patients who are in septic shock. Corticosteroids, careful fluid management and advances in intensive care therapy have improved patient outcomes only modestly.

Antibiotics

There are many bacteria that can cause paediatric meningitis so initial antibiotic choice is made according to the most likely causative organisms; this is determined by the child’s age (see Box 1, p313). Once the causative organism has been identified using cerebrospinal fluid (CSF) microscopy or blood cultures, antibiotic therapy can be changed if necessary — for children under three months of age treatment can be targeted to the specific organism (see Box 2, p313); for children over three months of age, a broad spectrum cephalosporin will most likely cover the organisms and penetrate the CSF well. If the causative organism is not identified, broad spectrum cover should continue. It is vital that antibiotic treatment is started as soon as possible. Treatment delays have been found to correlate with poor outcomes.

According to the Health Protection Agency, most meningococcal infections in England and Wales are susceptible to any one of benzylpenicillin, cefotaxime or ciprofloxacin, and more than 90% are also susceptible to rifampicin. Most pneumococcal infections are susceptible to benzylpenicillin or cefotaxime. Cefotaxime or ceftriaxone are used most frequently as first-line empirical treatment for meningitis in the UK since resistance to them is rare and they are effective against the most common causative organisms. Other antibiotics, including chloramphenicol (alone or in combination with ampicillin

SUMMARY

Paediatric bacterial meningitis can be caused by a variety of different bacteria depending upon the age of the infected child. Pharmacists should ensure that local antibiotic guidelines reflect this, along with local resistance patterns, to ensure initial treatment is appropriate.

Dexamethasone has shown to reduce neurological sequelae so should be used with antibiotic therapies. However, the evidence to guide appropriate fluid management of these patients is currently lacking. Great advances in preventing this disease have been achieved through vaccination campaigns. Future vaccine developments may result in this serious disease being encountered even less frequently.
or benzylpenicillin) or benzylpenicillin alone, may be similarly effective; these are more commonly used in poorer countries for cost reasons. A particular advantage of ceftriaxone is that it distributes into nasal secretions meaning that patients do not need to receive chemotherapy prophylaxis to prevent spread to close contacts (see p316). However, its use has been associated with biliary sludging and bilirubin encephalopathy (especially in premature neonates) since it can displace bilirubin from its albumin binding site. The 2009 BNF for Children recommends using 0.15mg/kg of dexamethasone every six hours for four days. However, some research has shown similar efficacy can be achieved using 0.4mg/kg every 12 hours for two days.

Corticosteroids
Dexamethasone, as adjunctive therapy for meningitis, has been shown to reduce rates of mortality, severe hearing loss and neurological sequelae. One factor affecting the clinical outcome of acute bacterial meningitis is the severity of the patient’s inflammatory response to infection. Meningeal inflammation and cerebral oedema can increase intracranial pressure (ICP), leading to neurological damage and death. Antimicrobial-induced bacterial lysis adds to the inflammatory process through the release of bacterial by-products into the CSF. Passage of antibiotics across the blood-brain barrier is enhanced when the meninges are inflamed. Therefore, the anti-inflammatory effects of dexamethasone could decrease the penetration of antibiotics into the CSF. To achieve clinical improvement and reduce the inflammatory cascade triggered by antibiotic-induced bacterial lysis. Therefore, intravenous dexamethasone should be given before, with or within four hours of the first dose of antibiotics. However, it should not be given to patients displaying clinical signs of septic shock.

Timing of doses
Early initiation of dexamethasone treatment (ie, before the first parenteral dose of antibiotic) has produced better results than late initiation (several hours after starting antibiotics). Presumably, this allows the corticosteroid greater opportunity to reduce the inflammatory cascade triggered by antibiotic-induced bacterial lysis. Therefore, intravenous dexamethasone should be given before, with or within four hours of the first dose of antibiotics. However, it should not be given to patients displaying clinical signs of septic shock.

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Safety
Concern has been raised about the use of corticosteroids in meningitis, especially for infections caused by highly resistant pneumococcal strains. Passage of antibiotics across the blood-brain barrier is enhanced when the meninges are inflamed. Therefore, the anti-inflammatory effects of dexamethasone could decrease the penetration of antibiotics into the CSF. To

### Box 1: Empirical treatment guidelines

<table>
<thead>
<tr>
<th>AGE</th>
<th>LIKELY CAUSATIVE ORGANISM</th>
<th>CHOICE OF THERAPY</th>
<th>DURATION OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – 3 months</td>
<td><em>Group B streptococcus</em>&lt;br&gt;Escherichia coli&lt;br&gt;Neisseria meningitidis&lt;br&gt;Haemophilus influenzae&lt;br&gt;Streptococcus pneumoniae</td>
<td>Cefotaxime + benzylpenicillin</td>
<td>See Box 2</td>
</tr>
<tr>
<td>&gt;3 months</td>
<td>Neisseria meningitidis&lt;br&gt;Haemophilus influenzae&lt;br&gt;Streptococcus pneumoniae</td>
<td>Cefotaxime</td>
<td>7 days&lt;br&gt;10–14 days&lt;br&gt;10–14 days</td>
</tr>
</tbody>
</table>

*Bacteria that cause meningitis among this age group tend to be commensals from the human female genital or gastrointestinal tract, and are transferred to the infants during birth. In most cases, a broad-spectrum cephalosporin is the most appropriate choice to penetrate the cerebrospinal fluid and cover likely organisms.

### Box 2: Targeted treatment for newborns

<table>
<thead>
<tr>
<th>CAUSATIVE ORGANISM</th>
<th>CHOICE OF ANTIBIOTIC</th>
<th>DURATION OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Cefotaxime, Benzylpenicillin</td>
<td>14–21 days depending on severity</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>Benzylpenicillin, Gentamicin</td>
<td>14 days&lt;sup&gt;*&lt;/sup&gt; Until clinical improvement (max 7 days)</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Amoxicillin, Gentamicin</td>
<td>14 days&lt;sup&gt;*&lt;/sup&gt; Until clinical improvement (max 7 days)</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>Cefotaxime, Gentamicin</td>
<td>21 days&lt;sup&gt;†&lt;/sup&gt; 14 days</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Cefotaxime</td>
<td>7 days&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Cefotaxime</td>
<td>10–14 days&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Cefotaxime</td>
<td>10–14 days&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>*</sup>If complicated case, continue antibiotic treatment for 21 days
<sup>†</sup>Longer duration if complicated case

The efficacy of dexamethasone when used for meningitis caused by other bacteria is less certain (for example, there are a few data specific to meningococcal meningitis). A Cochrane review in 2007 concluded that adjunct corticosteroids are beneficial in the treatment of children with acute bacterial meningitis in high-income countries. However, studies in developing countries have not exhibited a significant benefit — possibly because of health and socio-economic factors.
date, however, clinical data suggest that the impact of this effect is insignificant.

Other cautions around the use of dexamethasone include the rare risk of gastrointestinal bleeding and possible long-term cognitive impairment secondary to neuronal apoptosis in the hippocampus.

**Fluid therapy**

Close monitoring of fluid and electrolyte balance is important when treating bacterial meningitis but there is controversy over the best method of management — both over- and under-hydration may be associated with adverse outcomes.

Initial fluid restriction for infected patients has been recommended by some clinicians. Research has shown that serum sodium and urine output often decrease in children with meningitis secondary to the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH). This causes water retention that, in turn, increases cerebral oedema and worsens patient outcomes.

Conversely, other clinicians suggest that fluid maintenance, or maintenance plus fluid replacement, is required. This practice assumes that many patients with meningitis are dehydrated or hypovolaemic. In that case, increased antidiuretic hormone (ADH) secretion is the usual biological response. Fluid restriction in such patients could lead to cerebral ischaemia and poor outcomes. Administering fluid to hypovolaemic patients can normalise concentrations of ADH by providing sufficient sodium and fluid to facilitate the reabsorption of water by the proximal renal tubule — leading ultimately to reduced ADH secretion.

A 2008 Cochrane review on fluid therapy for acute bacterial meningitis drew limited conclusions.

**Other treatments**

Oral glycerol (with or without dexamethasone) might be effective in preventing severe neurological sequelae in children with meningitis. It increases plasma osmolality so is thought to reduce ICP and improve cerebral blood flow.

Although there are no randomised studies on the use of antipyretics or analgesics in childhood meningitis, the use of paracetamol to treat headaches (which can be severe) appears appropriate.

**Vaccination**

Immunisation is the most effective means of preventing bacterial meningitis in children and has reduced its incidence by up to 99% in some countries. The UK childhood immunisation programme vaccinates against pneumococcal, Hib and meningococcal group C (Neisseria meningitidis serogroup C; MenC) infections. In the past, Hib was the most common cause of meningitis in children under five years of age. Since the introduction of the Hib conjugate vaccine in 1992, cases have dropped by over 90%.

**Meningococcal vaccination**

The MenC conjugate vaccine, introduced in 1999, has shown equally impressive results. It induces immunological memory and provides long-term protection; vaccine effectiveness is estimated to be 88–96%. Vaccine failures have been attributed to an inadequate host response or to sub-optimal storage or administration.

For infants under one year old, the primary immunisation schedule includes two doses of MenC at three and four months and a final “booster” at 12 months. Older children and adults up to 25 years should receive one dose.

Previous serogroup C disease is not a contraindication to MenC vaccination because the immune response to natural infection is believed to be less than the response to vaccination, particularly in young children. Patients diagnosed with serogroup C meningitis should receive MenC vaccine, regardless of whether they have been immunised previously.

Several polysaccharide vaccines have been developed against N meningitidis serogroups A, C, Y and W135. Polysaccharide vaccines are made from the outer capsules of inactivated organisms and the protection they offer is not long-lasting. Vaccine-induced immunity lasts three to five years in older children and adults, with a shorter duration noted in younger children. These vaccines are indicated for children travelling to countries where the risk of meningitis is high or for close contacts of those already diagnosed.

In total, 85% of UK cases of meningococcal disease are caused by N meningitidis serogroup B — against which, at present, there is no vaccine. Development of such a vaccine has been problematic because the polysaccharide capsule of group B meningococci is chemically and immunologically different from those of other meningococcal serogroups.
antigenically identical to human brain and fetal antigens. Therefore, immunisation could induce autoimmunity.

Nonetheless, clinical trials are currently being conducted to test the effectiveness of a serogroup B vaccine, which could be commercially available by 2011.

Chemoprophylaxis

The risk of transferring meningitis caused by *N. meningitidis* is low (approximately 0.33% during the first 30 days of infection if no prophylaxis is given); those living in the same household are most at risk. After 30 days the risk reduces to background levels. The risk of transmission is greatest during the 48 hours after the onset of disease in the index case. The Health Protection Agency recommends that, in response to a single case of confirmed or probable meningococcal disease, only those living in the same household as the patient during the seven days before disease onset, or kissing contacts, require antibiotic prophylaxis. Such prophylaxis will eliminate nasal carriage of the causative organism and stop the spread of the infection.

Chemoprophylaxis to prevent *N. meningitidis* or *H. influenzae* transmission should be given as soon as possible (ideally, within 24 hours) after diagnosis of the index case, but can be given up to four weeks after the index case became ill. If a contact is already incubating the bacteria when chemoprophylaxis is given, he or she may still become ill. It is important that all close contacts of infected individuals understand that they are at increased risk of developing meningitis or septicemia. Index cases should receive chemoprophylaxis as soon as they are able to take oral medicines — before discharge from hospital — unless they have been treated with ceftriaxone.

In the BNF for Children, rifampicin, ciprofloxacin and ceftriaxone are all recommended for use in preventing secondary cases of *N. meningitidis* infection (and rifampicin for *H. influenzae*). Ciprofloxacin and ceftriaxone can be given as a single dose. Rifampicin is given twice daily for two days and is the only antibacterial medicine licensed for this purpose (see Box 3, p317).

Healthcare staff only require prophylaxis if their mouths or noses have been splattered with large respiratory-tract secretions from a patient with confirmed or probable meningococcal disease, or if they develop conjunctivitis within 10 days of patient contact.
chemoprophylaxis may lead to harm from drug side effects, the development of antibiotic resistance and the eradication of naturally immunising strains of bacteria from the nasopharynx.

References

Paul Baines is a consultant in paediatric intensive care, Nicola Reilly is lead clinical pharmacist for critical care and Andrea Gill is clinical pharmacy services manager, all at Alder Hey Children’s NHS Foundation Trust, Liverpool. E: nicola.reilly@alderhey.nhs.uk