Neonatal meningitis

P T Heath, N K Nik Yusoff, C J Baker

Twelve years ago an annotation was published in *Archives of Disease in Childhood* regarding the antibiotic treatment of suspected neonatal meningitis. The authors recommended the use of cephalosporins rather than chloramphenicol and advocated intraventricular aminoglycoside treatment in selected cases. They noted the absence of clinical trials with third generation cephalosporins that showed an improvement in mortality or neurological outcome.

*The purpose of this review is to review progress over the 12 years since the 1990 annotation,* and to make recommendations for the management of neonates with meningitis in the year 2002.

**AETIOLOGY AND EPIDEMIOLOGY**

The age at presentation with meningitis will suggest both the probable organisms and their likely mode of acquisition. Presentation in the first week of life (early onset) and particularly in the first two days of life, reflects vertical transmission, while late onset infection suggests nosocomial or community acquisition. The corresponding organisms are different; early onset meningitis is more likely to be caused by group B streptococcus (GBS), Escherichia coli, and *Listeria monocytogenes*, while late onset meningitis may be caused by other Gram negative organisms as well as staphylococcal species. Unfortunately most case series on neonatal meningitis do not distinguish cases according to their age at onset.

Comparison of data from two studies of neonatal meningitis conducted in England and Wales between 1985–87 and 1996–97 suggests that the bacteria responsible for meningitis have changed very little over this decade. Group B streptococcus remains the leading pathogen (39% of cases, in 1985–87 and 48% in 1996–97), followed by *E coli* (26% and 18%), other Gram negative rods (12% and 8%), *Streptococcus pneumoniae* (6% both periods), and *Listeria monocytogenes* (7% and 5%). The overall incidence of neonatal bacterial meningitis has also changed: 0.22 cases/1000 live births (1985–87) versus 0.21 cases/1000 (1996–97). These data are consistent with other UK studies as well as with data from other industrialised countries. A Canadian review of 101 cases of neonatal meningitis (1979–98) determined that 50% were caused by GBS, 25% *E coli*, 8% other Gram negative rods, 6% *Listeria monocytogenes*, and 3% non-typeable *Haemophilus influenzae*. Other studies have noted an increase in disease caused by *Enterobacter* spp. and *Serratia marcescens*; the majority of these Gram negative organisms were isolated from premature infants with late onset meningitis.

In developing countries, GBS appears to be much less frequent, although this is not universal. Gram negative enteric organisms appear to account for the majority of early onset, and *Streptococcus pneumoniae* for late onset meningitis in developing countries.

**MORTALITY AND MORBIDITY**

A reduction in mortality is evident from the two England and Wales studies (table 1). Data from a more recent (2000–01) national UK and Republic of Ireland surveillance study indicate a mortality of 12.4% (15/121) for GBS meningitis (P Heath, unpublished data). Similar data for GBS meningitis from the United States (2000–01) indicate a mortality of 8.5% (C Baker, unpublished data). A case-control study from the 1985–87 national neonatal meningitis cohort has determined the neurodevelopmental outcome at 5 years of age (table 2). Surprisingly it showed there to be very little difference between GBS and *E coli* regarding disability at 5 years of age (about 50% each) but a dismal outcome following meningitis caused by other Gram negative organisms (78% with disability at 5 years of age). In another study, the neurodevelopmental outcome of very low birth weight infants with meningitis at 20 months corrected age revealed a similar figure; 51% had impairment. Comparison with data from older studies suggests that despite declines in mortality, morbidity has not changed significantly between the 1970s and 1990s.

**MANAGEMENT**

**Lumbar puncture**

Examination of cerebrospinal fluid (CSF) via lumbar puncture (LP) is the only way to confirm meningitis as clinical signs are non-specific and unreliable and blood cultures may be negative in 15–55% of cases.

An LP should be done in all neonates with suspected meningitis, with suspected or proven late onset sepsis, and should be considered in all neonates in whom sepsis is a possibility. The role of LP in neonates who are healthy appearing but have maternal risk factors for sepsis is more controversial; the yield of the LP in these patients will be low.

**Abbreviations:** CoNS, coagulase negative staphylococci; CSF, cerebrospinal fluid; EEG, electroencephalogram; GBS, group B streptococcus; IAP, intrapartum antibiotic prophylaxis; LP, lumbar puncture; MBC, minimum bactericidal concentration
There are few contraindications to performing a LP in a neonate. Cardiorespiratory compromise during the procedure can be minimised using a modified left lateral position (hip flexion at 90° without flexion or extension of the neck). 22 In an unstable neonate the procedure can be deferred until stabilisation is achieved.

**Antibiotic therapy**

Appropriate antibiotic therapy is a critical aspect of management. Antibiotic choice is empirical, based on age at onset, likely pathogens, and antibiotic susceptibility patterns, with a focus on Group B streptococcus (GBS), Group A streptococcus (GAS), Gram negative enteric bacteria, and *Listeria monocytogenes* (box). Antibiotics are modified according to culture and antibiotic susceptibility results. Table 3 details the antibiotic resistance patterns of the common pathogens in England and Wales. However, empirical choice in an individual neonatal unit must consider data regarding pathogens and their susceptibility within that unit. For example, if there is an “outbreak” of multiply antibiotic resistant acinetobacter, empirical antibiotic therapy for neonatal meningitis might include meropenem until the organism is fully characterised. A note of caution should be added. In addition to bacterial causes of meningitis, herpes simplex virus is a rare but important cause of meningoencephalitis, and acyclovir therapy must be started promptly if the outcome is to be favourable. This pathogen should be considered in all cases of meningitis where the initial Gram stain is negative for bacteria.

The goal of antibiotic therapy is to achieve prompt bacteriological cure—that is, sterilisation of CSF. Delayed CSF sterilisation is a particular feature of Gram negative meningitis and may in part account for its higher mortality compared with GBS. CSF sterilisation is dependent on achieving bactericidal antibiotic concentrations within the CSF. This will be influenced by the dose of antibiotic that can be administered safely, the penetration of the antibiotic into the CSF, and the minimum bactericidal concentration (MBC) of the infecting organism. For example, the aminoglycosides have relatively good CSF penetration but the concentration achieved at standard doses may only be minimally above the MBC of Gram negative organisms. A low margin of error between therapeutic and toxic concentrations means that aminoglycoside doses cannot be safely increased to compensate. In contrast, although the CSF penetration of third generation cephalosporins may be modest, the CSF concentrations usually achieved are many fold higher than the MBCs for Gram negative bacteria, and cephalosporin dosage is not limited by toxicity. 23

**Group B streptococcus**

GBS is uniformly susceptible to penicillin, ampicillin, and cephalosporins. It is usually resistant to aminoglycosides. Yet the combination of a penicillin and an aminoglycoside has been the mainstay of GBS treatment for decades. The rationale for this choice is that in vitro and animal studies suggest improved outcome with the combination over a penicillin given alone. 24 There are no clinical trials to support this practice, and none comparing penicillin to ampicillin. It seems prudent to use the narrower spectrum agent, penicillin, in order to minimise any potential impact on antibiotic resistance among other pathogens. Because GBS has an MBC tenfold higher than group A streptococcus, and the inoculum in the CSF of neonates with meningitis is generally much higher than that of older infants and children with meningitis, it is recommended that large doses of antibiotics are administered. For example, the “Red Book” of the American Academy of Pediatrics recommends doses of penicillin up to 450 000 U/kg daily (270 mg/kg/day) divided 8 hourly if <7 days of age and divided 6 hourly if >7 days of age. For ampicillin the recommended dose is up to 300 mg/kg/daily divided 8 hourly if <7 days of age or 4–6 hourly if >7 days of age. 25 Penicillin or ampicillin are initially combined with gentamicin 4 mg/kg/dose daily (32–35 weeks gestation) or 5 mg/kg/dose daily (>35 weeks gestation).

There are no clinical trials comparing a third generation cephalosporin to penicillin or ampicillin, but a narrow spectrum antibiotic—penicillin—is preferred. The recommended doses of cefotaxime are 50 mg/kg/dose 12 hourly (<7 days), 8 hourly (7–21 days), and 6–8 hourly (>21 days). Ceftriaxone could be substituted for cefotaxime for once a day administration, but there is substantially less experience with this drug in neonates, some uncertainty because of its ability to displace bilirubin from plasma protein, and cases of associated cholestasis and gallbladder hydrops have been reported. Meropenem is another alternative for the treatment of GBS meningitis, exhibiting excellent CSF penetration, but there are no clinical trials showing its safety and efficacy, and no specific reasons for its use.

Once GBS has been confirmed as the pathogen, clinical improvement has been documented, and the CSF has been sterilised, there is probably no indication for continuing an aminoglycoside. Penicillin alone can be used to complete therapy.

**Gram negative enteric bacteria**

The bacteria in this group include *E coli*, klebsiella, enterobacter, citrobacter, salmonella, proteus, pseudomonas, and serratia. Table 3 details the antibiotic resistance patterns of isolates from England and Wales. The combination of ampicillin and an aminoglycoside has been used for the treatment of Gram negative meningitis for several decades. However, these Gram negative organisms are frequently resistant to ampicillin, CSF aminoglycoside concentrations are often minimally above their MICs, CSF cultures remain positive longer than with GBS meningitis, and morbidity and mortality from Gram negative meningitis remain high. This led to consideration of other therapeutic strategies such as intrathecal and intravenous administration of antibiotics such as gentamicin.

A multicentre study comparing intrathecal gentamicin (1 mg into the lumbar space) plus ampicillin and gentamicin or ampicillin and gentamicin alone was conducted between 1971
and 1975; 117 cases of Gram negative meningitis were included (70% E. coli). There was no difference between the groups with a mortality of 32% and morbidity of 36%.

Arguing that the problem may lie in the high rate of ventriculitis in Gram negative meningitis and that antibiotics, even administered into the lumbar space did not reach the ventricles, a follow up trial of intraventricular aminoglycoside administration was undertaken. Between 1976 and 1979, 71 cases of Gram negative meningitis were included in a study of ampicillin and gentamicin with or without intraventricular gentamicin (2.5 mg). The study was stopped prematurely when it became apparent that the mortality was higher in the intraventricular gentamicin group (43 v 13%). No further trials have been performed. While certain infants with obstructive ventriculitis complicating Gram negative meningitis may require administration of intraventricular aminoglycoside to assist in sterilisation of the CSF, this therapy is not recommended routinely.

The introduction of cefotaxime has provided an attractive option for therapy of Gram negative meningitis. This is based on the lower MBCs of Gram negative bacteria to cefotaxime compared to penicillins and aminoglycosides and the high CSF concentrations that can be safely achieved. Cefotaxime therapy increases the proportion of infants who will have sterile CSF cultures 48–72 hours into treatment (a correlate of outcome), but mortality and morbidity remain comparable to those of historical studies. There are no randomised controlled clinical trials comparing the safety and efficacy of cefotaxime to ampicillin and aminoglycoside combinations. However, for reasons stated above, cefotaxime (or ceftazidime in the case of Pseudomonas aeruginosa) is recommended for therapy in suspected neonatal Gram negative meningitis in combination with an aminoglycoside, usually gentamicin. Once susceptibility is documented, the combination is continued for at least 14 days after CSF cultures have been sterilised. Thereafter cefotaxime alone is used to complete a minimum total therapy of 21 days. Meropenem has not been sufficiently studied for safety and efficacy in neonates, and is not recommended unless an extended spectrum β lactamase producing organism is identified. In this circumstance, meropenem in combination

| Table 1 | Mortality from neonatal bacterial meningitis in England and Wales, 1985–87 and 1996–97 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Number of cases | Died (24) | Died (12) | Died (10) | Died (10) |
| Group B streptococcus | 112 | 27 | 69 | 8 |
| Escherichia coli | 72 | 18 | 26 | 4 |
| Listeria monocytogenes | 19 | 2 | 7 | 1 |
| Haemophilus influenzae | 9 | 2 | 1 | 0 |
| Neisseria meningitidis | 10 | 0 | 5 | 0 |
| Streptococcus pneumoniae | 18 | 3 | 8 | 0 |
| Other Gram positive bacteria | 14 | 5 | 17 | 0 |
| Other Gram negative bacteria | 26 | 13 | 11 | 0 |
| Total | 280 | 70 | 144 | 14 |

Includes only those cases where bacteria isolated from cerebrospinal fluid. Values in parentheses are percentages.

| Table 2 | Meningitis in the first year of life: number of children by disability and aetiological agent* |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Severe disability | Moderate disability | Mild disability | No disability |
| **Organism** | **Haemophilus influenzae** | **Neisseria meningitidis** | **Streptococcus pneumoniae** | **Escherichia coli** | **Group B streptococcus** | **Other Gram positive bacteria** | **Other Gram negative bacteria** | **Listeria monocytogenes** |
| | 14 (3.4) | 12 (2.9) | 14 (9.7) | 4 (5.7) | 13 (13.3) | 6 (20.6) | 8 (25.0) | 0 |
| | 30 (7.3) | 26 (6.5) | 20 (13.9) | 13 (18.6) | 17 (17.3) | 8 (27.6) | 4 (25.0) | 4 (25.0) |
| | 134 (32.5) | 120 (29.8) | 37 (25.8) | 18 (25.7) | 18 (18.4) | 7 (17.2) | 7 (18.8) | 3 (18.8) |
| | 235 (57.0) | 244 (60.7) | 72 (50.3) | 35 (50.0) | 50 (51.0) | 10 (34.5) | 7 (21.9) | 9 (56.3) |

Values in parentheses are percentages.

| Table 3 | Antimicrobial resistance, % of Gram negative bacteria associated with bacteraemia, England and Wales* |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| % resistant | Ampicillin | Gentamicin | Cefotaxime | Ceftazidime | Meropenem |
| **E. coli** | 55 | 3 | 2 | 2 | – |
| **Klebsiella** | 5 | 6 | 8 | <1 | – |
| **Enterobacter** | 9 | 32 | 32 | 2 | – |
| **Serratia** | 3 | 20 | 4 | <1 | – |
| **Citrobacter** | 3 | 16 | 16 | 1 | – |
| **P. aeruginosa** | 5 | – | 4 | 1 | – |

Source: www.phls.co.uk.

*Data represent all isolates referred to PHLS from bacteraemias of all ages.
†2001; ‡1999–2000.
with an aminoglycoside should be administered for the entire course of therapy.

Listeria monocytogenes

*L. monocytogenes* is not susceptible to cephalosporins. Ampicillin is the mainstay of therapy, and the combination of ampicillin and gentamicin is synergistic in vitro and provides more rapid bacterial clearance in animal models of infection. Thus this combination is favoured for initial therapy, with cessation of the aminoglycoside when the CSF has been sterilised and the patient has improved clinically.

Streptococcus pneumoniae

*S. pneumoniae* in the UK is usually susceptible to penicillin and cefotaxime. While penicillin resistance does occur and may be increasing in incidence, an empirical combination of penicillin or ampicillin and cefotaxime is satisfactory. Once *S. pneumoniae* is identified and susceptibility testing results available, therapy may be completed with either agent alone.

Coagulase negative staphylococci (CoNS)

CoNS rarely invade the CSF except as a complication of CoNS bacteraemia accompanying intraventricular haemorrhage in very low birth weight neonates, in the presence of a foreign body (a ventriculoperitoneal shunt), or after contamination following neurosurgery or direct entry into the ventricular space (following ventricular fluid aspiration). Such infections are late onset. Most CoNS are resistant to penicillin and flucloxacillin, necessitating the use of vancomycin for proven CoNS central nervous system infection. The recommended dosages of vancomycin are 20 mg/kg/dose 18 hourly (<30 weeks), 12 hourly (30–37 weeks), and 8 hourly (>37 weeks).

Duration of antibiotic therapy

There are no controlled clinical trials to guide the recommended duration of antibiotic therapy for neonatal meningitis. Historically, therapy has been continued for 2–3 weeks after sterilisation of CSF cultures. This equates to a minimum of 14 days for GBS and *Listeria monocytogenes* meningitis, and 21 days for Gram negative organisms.

Repeat lumbar punctures

A repeat lumbar puncture 24–48 hours into antibiotic therapy is recommended to document CSF sterilisation. Persistence of infection may indicate a focus, such as obstructive ventriculitis, subdural empyema, or multiple small vessel thrombi. Infants with positive CSF cultures after initiation of appropriate therapy are at risk of these complications as well as a poor outcome. In this situation immediate diagnostic imaging is recommended. The choice and dosage of antibiotics should also be reviewed and (rarely) intraventricular administration considered. Delayed CSF sterilisation and/or abnormalities found on neuroimaging may be an indication for prolonging the total course of therapy (see below).

With regard to LP at the end of treatment, Schaad *et al* reviewed 27 cases of recrudescence and relapse following bacterial meningitis in childhood (including nine neonates). In the majority recrudescence/relapse could be explained by inadequate dosage of antibiotics, inadequate length of course, or persistent infection in meningeal or parameningeal sites, for example, subdural empyema, brain abscess, or ventriculitis. They concluded that a lumbar puncture at the end of therapy was unnecessary if the clinical response was otherwise uneventful, as they found that normal CSF findings may not exclude a relapse and abnormal CSF findings may not be predictive of relapse. A survey of practice among 109 paediatricians/neurologists in northwest England indicated that the majority (82%) do not routinely repeat lumbar punctures in proven neonatal meningitis.

It is probably true that in cases of neonatal meningitis with prompt CSF sterilisation and a benign clinical course the examination of CSF at the end of therapy is unnecessary, as it may not assist in management. However, in neonates where abnormal neurological findings persist, especially focal deficits, or where CSF cultures are positive for more than 48–72 hours into therapy, prolonging therapy may assist in preventing a relapse of infection. Examination of the CSF as well as neuroimaging in these circumstances can assist in determining an optimal duration of antibiotic therapy.

Adjunctive therapy

In the light of the benefits reported with dexamethasone treatment in childhood meningitis, corticosteroids were an obvious consideration for the management of neonatal meningitis. A very early non-randomised study in Australia suggested that steroid use was associated with an improved outcome. In a study from Jordan, 52 cases of neonatal meningitis (84% Gram negative) in full term neonates were alternately assigned to dexamethasone treatment (0.15 mg/kg every 6 hours for four days). The mortality (22% dexamethasone vs 28% controls) and the morbidity at two years (30 vs 39%) were not significantly different, and it was concluded that adjunctive dexamethasone therapy does not have a role in neonatal meningitis. The Fourth Neonatal Meningitis Collaborative Study also set out to determine the role of adjunctive dexamethasone in neonatal meningitis. This study was not completed, as follow up information on cases was inadequate. However, there was no impact of dexamethasone on mortality or morbidity at discharge (G McCracken, personal communication).

Because of the continuing mortality and morbidity from neonatal sepsis, attention has been focused on means to enhance neonatal immune responsiveness. Examples of this include granulocyte transfusions and pentoxifylline in established sepsis. Trials of haemopoietic colony stimulating factors have not yet shown a definitive role in the treatment of sepsis. Standard intravenous immunoglobulin is associated with an overall reduction in mortality when used as adjunctive therapy for neonatal sepsis. However, its place in therapy will be better defined following the outcome of a large international study in progress (www.npeu.ox.ac.uk). Although each of these studies has not focused on meningitis per se, bacteraemia is a prerequisite for meningitis and thus strategies that prevent or improve the outcome of sepsis may have similar benefits with meningitis.

Intensive care support

The appropriate and early use of supportive care, including fluid management, inotropes, anticonvulsants, and ventilation appear to be a critical part of neonatal meningitis management. There are no clinical trials, however, which address this. Similarly, in dealing with such an infrequent infection, the experience of those caring for the neonate may be an important factor in the infant’s outcome, but this hypothesis is not evidence based.

IMAGING

Neuroimaging is recommended to detect the complications of meningitis. Complications should be suspected when the clinical course is characterised by shock, respiratory failure, focal neurological deficits, a positive CSF culture after 48–72 hours of appropriate antibiotic therapy, or infection with certain organisms. *Citrobacter koseri* and *Enterobacter sakazakii* meningitis, for example, are frequently associated with the development of brain abscesses, even in infants who have a benign clinical course. The most useful and non-invasive method early in the course is ultrasonography, which will provide information regarding ventricular size and the presence of haemorrhage. Computed tomography will be useful in
detecting cerebral abscesses and later in the treatment course in identifying areas of encephalomalacia that may dictate prolonged therapy.

DETERMINANTS OF OUTCOME

A retrospective study of 101 cases of neonatal bacterial meningitis admitted between 1979 and 1998 identified early predictors of adverse outcome at 1 year of age (death or moderate/severe disability). Twenty-four hours after admission the important predictors of adverse outcome were presence of seizures, presence of coma, use of inotropes, and leucopenia ≤5000x10^9 (sensitivity 68%, specificity 99%). Ninety six hours after admission, predictors of adverse outcome were seizure duration of >72 hours, coma, use of inotropes, and leucopenia (sensitivity 88%, specificity 99%). There was no difference in outcome by pathogen, consistent with other reports. The study excluded infants <35 weeks of gestation and infants with criteria for intrapartum asphyxia, and thus cannot be used in assessing the risk of disability in such infants.

PREVENTION

It seems likely that delay in the commencement of treatment for neonatal meningitis will affect the outcome; however, there are no data to support this hypothesis. Delay may be less of an issue for neonates who are in a neonatal unit at the onset of symptoms as antibiotics generally are administered promptly in a neonate who becomes unwell. Obviously a lumbar puncture is required to document meningitis as blood cultures may be negative. Without detection of meningitis, antibiotic selection, dosing, and duration may be inappropriate. Late onset disease with presentation at home may be associated with delayed recognition and initiation of therapy. Possible strategies for prevention of neonatal meningitis include intrapartum antibiotic prophylaxis (IAP) for pregnant women, improvements in hospital infection control procedures, the use of prophylactic haemopoietic colony stimulating factors, and passive and active immunisation.

Currently, the best means of neonatal GBS prevention is the use of maternal IAP to prevent early onset GBS disease. However, IAP only prevents early onset GBS disease, and the majority of GBS meningitis cases are of late onset. The recent national UK surveillance study, for example, indicated that only 40 of the 122 cases (33%) presented in the first week of life (P Heath, unpublished data).

The source of infection in cases of late onset GBS disease (including meningitis) may be through nosocomial or community spread. It follows that any steps taken to prevent the spread of organisms in a neonatal unit may reduce the likelihood of late onset meningitis. Judicious antibiotic use, including the use of narrow spectrum antibiotics, stopping antibiotics when cultures are negative, and not using antibiotics to treat colonisation or as prophylaxis, as well as enforcement of hand hygiene policies, are obvious prevention strategies for neonates remaining in the hospital. Breast feeding appears to be protective against nosocomial infection in general, although its main benefit seems to be in preventing infections caused by *Staphylococcus epidermidis*. Maternal vaccination against GBS offers the best hope of protection against both early and late onset GBS meningitis. The leading vaccine candidates are serotype specific polysaccharide-protein conjugate vaccines. In the UK, four GBS serotypes account for more than 90% of disease strains (unpublished data, PHLS); similar data have been reported from the United States. There are also candidate vaccines against *E coli*. It may be that the most efficient use of an *E coli* vaccine is in generating specific antibody preparations that can be used for prophylaxis of late onset meningitis.

CONCLUSIONS

Have there been advances in the management of neonatal meningitis since the annotation in 1990? The incidence and the morbidity of this condition have changed very little. However, mortality has diminished. It is unclear whether improved survival from neonatal meningitis reflects general improvement in supportive care or the increased use of third generation cephalosporins. The pathogens remain similar though antibiotic resistance patterns, especially among Gram negative organisms isolated from premature infants, may be changing. The number of available antibiotics with proven safety and efficacy in the newborn infant has changed very little. Use of intraventricular therapy is not recommended except in very select circumstances. Now, as then, the role of adjunctive therapy remains enticing but unproven. The best hope for dealing with neonatal meningitis is in prevention.

RESEARCH PRIORITIES

There is a lack of longitudinal, prospectively collected data on neonatal infection/meningitis in the UK. Other countries have successfully established neonatal infection surveillance networks. The establishment of such a network in the UK would allow a better understanding of the epidemiology of neonatal infection and the risk factors for infection, and provide trials of interventions.

The prevention of GBS and *E coli* through maternal vaccination or the use of specific antibody preparations administered to at-risk neonates should be a research priority. The prevention of these two infections could reduce the incidence of neonatal meningitis in the UK by two thirds. As new antibiotics are introduced, they should be compared with established best therapy. The increased use of meropenem in neonatal meningitis, for example, should now be accompanied by a randomised controlled trial comparing it with ceftazidime and an aminoglycoside.

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