Leading articles


**Antibiotics in suspected neonatal meningitis**

Meningitis in the first month of life is unique and should be considered as a separate clinical entity, because the offending pathogens, the clinical presentation and still the unacceptably high mortality are strikingly different from meningitis afflicting all other age groups. The incidence varied from 0.26/1000 live births (Goldacre, 1976) in a defined population in the North-west Metropolitan Region between the years 1969–73, to 0.46/1000 live births between 1959 and 1966 in the collaborative Perinatal Research Study Group in the United States (Overall, 1970). Moreover, for birth weights above and below 2500 g, it was 0.37/1000 and 1.36/1000 live births, respectively. Therefore, the incidence of neonatal meningitis may be comparatively higher in countries with a high low-birth-weight rate. *Escherichia coli* and Group B streptococcus together account for the majority of cases, followed by other Gram-negative bacteria, e.g. *Proteus, Klebsiella-Enterobacter-Serratia* species, *Pseudomonas* species.
Listeria and from time to time the only pathogen encountered in neonatal meningitis rather than E. coli (Chattopadhyay, 1980). Mixed infections (Lorber, 1974) as well as infections due to two different serotypes of the same organism (Goldenberg & Neter, 1977) have been documented.

Suspected meningitis in the neonate is rather difficult to treat because of the dilemma faced by the paediatricians of selecting the right combination of antibiotics to have the desired effect on the wide range of potentially infective organisms and the rationale of intrathecal or intraventricular therapy. The commonest treatment regime in practice is to give systemically a penicillin like ampicillin plus an aminoglycoside such as gentamicin. However, this may not be adequate since it is well known that the aminoglycosides penetrate the blood brain barrier poorly. Lorber (1974) successfully treated a series of infants with a systemic combination as above plus lumbar intrathecal therapy along with intrathecal cortisol (10 mg) and defended this subsequently (Lorber, 1976). However, the US Neonatal Meningitis Co-operative Study Group failed to establish any superiority of lumbar intrathecal gentamicin (1 mg daily) instilled for at least three days in association with systemic ampicillin plus gentamicin over systemic combination therapy alone (McCracken & Mize, 1976). This is because even after intrathecal instillation, the antibiotic level in the ventricle fails to reach adequate concentrations bearing in mind that ventriculitis is a common feature of neonatal meningitis (Berman & Banker, 1966). Also it has been observed that in Gram-negative meningitis the CSF seems to remain culture positive for a significantly longer time than in meningitis caused by Gram-positive organisms. Even when the antibiotic level in the lumbar CSF exceeds the minimum inhibitory concentration, the survivors persist in that fluid (McCracken, 1972). There may be several explanations for this peculiar phenomenon. Firstly the organisms survive probably due to inadequate ventricular fluid drug concentration in the presence of persisting ventriculitis, which may lead to relapse following a course of lumbar intrathecal aminoglycosides (Helms, 1977). Secondly much larger numbers of organisms are present in the CSF when the treatment is initiated (Feldman, 1976).

Although intraventricular administration of gentamicin has been attempted, producing very high levels locally, the report of the Second Neonatal Meningitis Co-operative Study Group from the United States has concluded that in neonatal meningitis caused by Gram-negative enteric bacilli intraventricular gentamicin should not be used as routine treatment because of the significantly higher mortality rate (42-9%) as opposed to systemic therapy only (12.5%), (McCracken, Mize & Threlkeld, 1980). Also there was no significant difference between the two groups so far as the duration of positive CSF cultures and morbidity were concerned. The concept of intraventricular administration rests on the assumption that as in adults at least there is rapid and uniform distribution of gentamicin in the CSF space (Kaiser & McGee, 1975), so in neonates also the case fatality rate might be reduced and the CSF sterility achieved more quickly by this route. Unfortunately, however, in this group, drug concentrations in the lumbar CSF are usually found to be only marginally higher than those after systemic therapy alone (McCracken et al., 1980). The procedure of ventricular tap itself has inherent danger particularly in immature infants. The needle may cause excessive bleeding while penetrating the highly vascular germinal matrix (Davies, 1977; McCracken et al., 1980), and puncture tracts and repeated needle aspirations of ventricular fluid may lead to the formation of porencephalic cysts (Lorber & Emery, 1964; Salmon, 1967). These cysts have been demonstrated at the needle track sites by computerized axial tomography (McCracken, 1980). In healthy adult rabbits intracisternal inoculation of gentamicin consistently produces glial cell necrosis, axonal degeneration and myelin swelling in the brain stem and cervical spinal cord (Watanabe et al., 1978).

Therefore, although combination of ampicillin and gentamicin in treating suspected neonatal meningitis has been suggested by many leading workers in the field (Lorber 1976; McCracken, 1977; Feigin, 1977; Black, 1979), others have endeavoured to use equally effective yet less damaging alternatives in this situation. One should also bear in mind that many E. coli strains are resistant to amoxycillin, that in vitro synergism of the combination of amoxycillin and gentamicin has been demonstrated in approximately 30% of E. coli isolates, and that the peak level of aminoglycosides in the lumbar CSF after systemic administration barely reaches the
minimum inhibitory concentration for the majority of Gram-negative bacilli causing meningitis. Therefore these bacteria persist in the CSF for several days after the commencement of antibiotics (McCracken, 1972; McCracken & Mize, 1976). In the second US Neonatal Meningitis Study Group 67% of the infants with meningitis and ventriculitis who died had ampicillin-resistant organisms, compared with 38% who survived. Moreover in experimentally infected rabbits ampicillin was shown to be less effective than aminoglycosides in lowering colony counts of Gram-negative enteric bacteria in CSF (Schaad et al., 1980).

The alternatives suggested have been either chloramphenicol or co-trimoxazole because both will penetrate the blood brain barrier and reach effective CSF levels when given systemically. However, neither of them is active against Ps. aeruginosa. When the infecting organism and its sensitivities are unknown chloramphenicol is perhaps the best choice for initial treatment as it penetrates the CSF adequately after intravenous administration (Davies, 1979; Drug and Therapeutic Bulletin, 1981). By using a lower intravenous dosage and, later on, once-daily oral dosage the rare though serious haematological side effects and 'potentially fatal' grey baby syndrome can be avoided (Burns et al., 1959; Schröter, 1974; Chang et al., 1975). It is best given intravenously for maximum absorption rather than intramuscularly. The recommended dosage is 12.5–25 mg/kg 8-hourly. Even in full-term infants (>37 weeks gestation) the total daily dose should not exceed 75 mg/kg. For preterm infants (<37 weeks gestation), it should be given 12-hourly in the first week of life (Davies, 1979). It is continued for about 2 weeks after the CSF becomes sterile (Black, 1979). It should be remembered that newborns receiving chloramphenicol plus phenobarbitone may have a diminished serum level of chloramphenicol leading to reduced CSF level. This is because before excretion chloramphenicol is metabolized by conjugation with glucuronide (Garrod, Lambert & O'Grady, 1981), whereas the barbiturate induces the liver microsomal enzymes responsible for glucuronide conjugation (Winforder & Pringstein, 1977). Maintenance of adequate level is of paramount importance in the treatment of meningitis. Co-trimoxazole has been used as an alternative therapy for Gram-negative bacterial meningitis in the newborn with good results though it should be avoided in icteric or very immature infants and probably should not be used during the first week of life (Sabel & Brandberg, 1975).

Instead of chloramphenicol alone, a combination of chloramphenicol and gentamicin has recently been advocated in suspected neonatal meningitis by some workers (Lorber, 1976; Lambert, 1977; Black, 1979). Virtually all organisms causing neonatal meningitis are susceptible to one of them, and so they can be used together beneficially until relevant bacteriological information is available. This is also based on the principle that whereas one has adequate penetration into the CSF when given parenterally, the other is suitable for both parenteral and intrathecal or intraventricular administration. Antagonism between chloramphenicol and gentamicin has been demonstrated experimentally in vivo in rabbits with meningitis (Strausbaugh & Sande, 1978) though the relevance of these findings to the human neonate is difficult to judge. As no single centre will have enough cases to dictate rational antibiotic therapy in suspected neonatal meningitis, without properly controlled collaborative study the problem of resolving these questions remains a mammoth task and a daunting one.

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References


The outlook for antifungal prophylaxis in the compromised host

Over the last two decades considerably more progress has been made in the prophylaxis and treatment of the serious bacterial infections occurring in the compromised host than in preventing and treating serious infections caused by opportunistic fungi. In retrospect, the rapid proliferation of antibacterial agents is likely to have contributed to this new set of infectious problems. Time and time again it has been found that nature will not allow an ecological vacuum to persist: rapid elimination or suppression of the endogenous bacterial flora of the gut, upper respiratory passages, or skin may pave the way for fungal superinfection. Thus, 8 years ago we reported a marked upsurge in invasive aspergillosis in neutropenic patients with neoplastic disease (Meyer et al., 1973). Indeed, more than 40% of patients dying of acute leukaemia who were autopsied during one observation period were found to have histological evidence of disseminated aspergillosis. Like many infectious problems occurring in compromised hosts the predisposing or contributing factors were difficult to segregate and individually analyse, but in retrospect it appears that two were important: (1) introduction of potent combinations of antimicrobial agents such as carbencillin and gentamicin for initial empirical therapy of presumed or documented Gram-negative bacterial infection; (2) aggressive use of anti-neoplastic agents in combination, thereby creating an intensely immunosuppressed state.

Disseminated candidiasis appears to be an even greater problem than aspergillosis in the compromised host and the available data are equally discouraging: Edwards has summarized reports of systemic candidiasis and