Bacterial meningitis

Some aspects of diagnosis and treatment

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Antimicrobial therapy has made few more dramatic conquests than that of bacterial meningitis, which it has transformed from the almost universally fatal illness of 30 years ago into one with a relatively low mortality. Yet the disease, which has its greatest impact in early childhood, poses a continuing threat and must be regarded as one of the most challenging of medical emergencies. In the United Kingdom and Eire in 1973, at least 109 children under 15 years of age were reported to have died from it (Public Health Laboratory Service, 1974); and in the United States more than a quarter of survivors from *Haemophilus influenzae* meningitis alone have been found to have significant neurological handicaps (Sproles *et al.*, 1969; Sell *et al.*, 1972a). Moreover, survivors of that illness considered normal by their physicians and families functioned significantly less well on a battery of tests than matched controls from the same classrooms at school (Sell *et al.*, 1972b). Though such disappointing results are by no means the rule (Lawson, Metcalfe, and Pampiglione, 1965), even more unfavourable reports come from follow-up of survivors of neonatal meningitis. It is important then to keep under review old and new methods of treatment and newer aids to diagnosis if this hard core of death and disability is to be reversed. We shall concentrate mainly, though not exclusively, on diagnosis and management of bacterial meningitis, and refer readers elsewhere for a wider discussion of other aspects (Hambleton and Davies, 1974).

Children at special risk

Children aged 6 months to 1 year are at greatest risk (Fraser *et al.*, 1973); and it has been estimated that over 80% of all cases occur in the first 5 years of life, with 35% in the first year (Wehrle *et al.*, 1967; Mathies, 1971-1972; Yow *et al.*, 1973). Poor socioeconomic conditions (Fraser *et al.*, 1973),

the male sex (Washburn, Medearis, and Childs, 1965), congenital anomalies of or injury to the central nervous system, and primary infection elsewhere, especially that adjacent to the meninges, are other well established predisposing factors. Children who have impaired defence mechanisms for a variety of reasons are a tiny minority but are nevertheless being kept alive in increasing numbers for much longer now, and are consequently in jeopardy. For instance, an association between pneumococcal infection and sickle cell disease, a condition which may be associated with a defect in the properdin system (Johnston, Newman, and Struth, 1973) is well known, and Smith *et al.* (1973) have calculated that 1 in every 27 children with the disease may develop pneumococcal meningitis by the age of 4 years. Others with the rare inborn errors of host defence, and children being treated with immunosuppressant and cytotoxic drugs for such conditions as leukaemia, malignant disease, and the nephrotic syndrome are all more liable to bacterial infection. In the newborn, low birthweight, a prolonged interval between membrane rupture and delivery, and a complicated obstetric and neonatal course are all factors which may be associated with a later development of meningitis.

Infecting organisms

After the first 2 months of life three organisms predominate: *Haemophilus influenzae*, *Neisseria meningitidis*, and *Diplococcus pneumoniae*. They are responsible for most cases of childhood meningitis. In the neonatal period and the ensuing 4 weeks virtually any bacteria can cause the disease, though Gram-negative organisms are most evident in many parts of the world. Some reasons for this have been discussed previously (Davies, 1971). Neonatal meningitis caused by *Esch. coli* is associated with a significantly higher morbidity and

mortality when the pathogen contains K1 capsular polysaccharide antigen compared with non-K1 strains (McCracken *et al.*, 1974). The emergence of the group B β -haemolytic streptococcus, now ranked second in importance to *Esch. coli* as a cause of neonatal meningitis in the United States (Barton, Feigin, and Lins, 1973), has been recent. Older children with impaired host defense share with the newborn a liability to infection with opportunist invaders such as *Pseudomonas aeruginosa*; and those who have cerebrospinal fluid shunts are most likely to be infected with *Staphylococcus albus*. Organisms causing meningitis in childhood, and the currently appropriate antibacterial drugs for treatment are shown in Table I.

It is worth discussing the two principal offenders, *H. influenzae* and *N. meningitidis*, in greater detail. Of the various encapsulated strains of *H. influenzae*, type b is responsible for almost all cases of meningitis (Turk and May, 1967), and the disease has become more common in recent years (Michaels, 1971; Smith and Haynes, 1972). Defence mechanisms have recently been summarized by Coulter, Whisnant, and Marks (1974) in their discussion of haemophilus meningitis in the identical twin pair of

a triplet sibship. Both anticapsular and/or bactericidal antibody, and genetic factors associated with the distribution of white and red cell antigens may determine individual susceptibility. Many years ago Fothergill and Wright (1933) showed that the blood's bactericidal activity to *H. influenzae* was age dependent, and that adult levels were not reached until 7 years. Recently, Graber *et al.* (1971) found that only 25% of mothers possessed such bactericidal antibodies compared with 90% previously, and consequently postulated a shift in neonatal susceptibility due to absence of the antibodies in the placentally transferred IgG fraction of immunoglobulins. Though their findings have been disputed on technical grounds (Mpairwe, 1972), others have cited similar evidence (Norden, Callerame, and Baum, 1970). Type b strains of *H. influenzae* have virtually all been sensitive to ampicillin in the past, but ampicillin-resistant isolates have now been reported from various parts of the world including the United Kingdom (Thomas *et al.*, 1974; Schiffer *et al.*, 1974; Thornsberry and Kirven, 1974; Clymo and Harper, 1974; Turk, 1974; Williams and Cavanagh, 1974; Schulte and Vollrath, 1974).

TABLE I
Antibacterial drugs useful in meningitis

Drug	Dose* (mg/kg per d) IM or IV	Peak serum levels (μ g/ml)	CSF/ serum ratio (%)	Minimum inhibitory concentration (μ g/ml)	Intrathecal* dose (mg)	Infecting organisms for which most appropriate
Ampicillin	150-400	6-38	10-50	2	10	<i>H. influenzae</i> ; <i>Esch. coli</i> ; <i>Listeria monocytogenes</i>
Benzylpenicillin	150-300	1.2-12	1-6	0.003-0.06	1-6 (1000 units=0.6 mg)	<i>N. meningitidis</i> ; <i>Dip. pneumoniae</i> ; β -haemolytic streptococci; <i>Staph. aureus</i> ; <i>Str. faecalis</i>
Carbenicillin	50-600	50-400	nil	2.5-125	10-20	<i>Ps. aeruginosa</i>
Chloramphenicol	100	10-40	10-60	8-10		<i>H. influenzae</i> ; <i>Esch. coli</i> ; <i>Proteus</i> spp.; <i>Listeria monocytogenes</i> ; <i>Klebsiella</i> spp.; <i>Bacteroides</i> spp.
Cloxacillin	50	8-17	nil	0.25-0.5	3-10	<i>Staph. aureus</i> (penicillinase producing)
Erythromycin	10	20-80	nil	0.1-1.6		<i>Staph. aureus</i> (penicillinase producing)
Gentamicin	6	5-7	nil	0.3-1.0	1-2	<i>Esch. coli</i> ; <i>Ps. aeruginosa</i> ; <i>Proteus</i> spp.; <i>Klebsiella</i> spp.
Kanamycin	15-50	10-20	20-40	0.5-5.0	2-10	<i>Esch. coli</i> ; <i>Proteus</i> spp.; <i>L. monocytogenes</i> ; <i>Klebsiella</i> spp.

Notes:

Many sources have been consulted in compiling this data and are referred to in full in Hambleton and Davies (1974).

Erythromycin: the intramuscular preparation is very irritant and should be avoided whenever possible. The drug is only necessary when the patient is penicillin-sensitive, or if infected with a methicillin-resistant *Staph. aureus*. These organisms are usually also resistant to cloxacillin and the cephalosporins.

Co-trimoxazole (sulphamethoxazole-trimethoprim): isolated case reports suggest this may prove to be a useful drug in treatment of meningitis. A dose of 30-40 mg sulphamethoxazole, 6-8 mg trimethoprim/kg per d is said to give high levels in serum and CSF (Sabel and Brandberg, 1975).

Other infecting organisms: meningitis may be caused by organisms not listed in this table, especially in the neonatal period. Other members of the Enterobacteriaceae (e.g. *Serratia marcescens*, *Edwardsiella tarda*, *Paracolonobacterium* spp., *Aerobacter aerogenes*, and *Citrobacter* spp.), and such organisms as *Pastuerella multocida*, and *Moraxella (Mima)* spp., *Vibrio fetus*, and *Flavobacterium meningosepticum*, all of them Gram-negative, should be sensitive to the combination of ampicillin and gentamicin, or to chloramphenicol.

* For dosage in neonatal period see Table II.

N. meningitidis has a number of serological groups, but A, B, and C are the ones mostly responsible for disease. Their geographical and age distribution varies. Group B strains are most common, and group A least common in the United Kingdom, whereas in many other parts of the world, excluding the United States, group A strains are responsible for most meningococcal illness (*British Medical Journal*, 1974; *Lancet*, 1974). Group B strains may be particularly important under 1 year of age, whereas C strains are more prevalent in later childhood (McCormick *et al.*, 1974). It appears that the acquisition rate of *N. meningitidis*—the number of new carriers over a short period of time—is more important than the carrier rate (Wenzel *et al.*, 1973), and Fallon (1974) has pointed out that as in poliomyelitis, meningococcal infection is really a 'failure of carriage'. Meningococcal meningitis has increased significantly in the last few years (*British Medical Journal*, 1974; *Lancet*, 1974). Sulphonamide-resistant strains of *N. meningitidis* have been noted since 1943 (Feldman, 1972) and are now predominant in the United States. Bennett and Young (1969) found such resistance to 92% of group C, 72% of group A, and 41% of group B strains. Sulphonamide-resistance is still relatively uncommon in Britain (Abbott and Graves, 1972), but the extent is debatable (Fallon, 1974; Jones and Abbott, 1974; Emond and Smith, 1974). There are many technical factors to be taken into account when determining resistance of various organisms, and Stokes (1968) has pointed out that statements of minimum inhibitory concentrations have little meaning without details of the method used and some standards of comparison.

Atypical forms of bacteria, known as L forms or spheroplasts, are sometimes found with classical bacteria in the early stages of acute bacterial meningitis (Kenny, 1973). Most bacteria have the ability to convert to this form if cell wall synthesis is not favoured by environmental conditions, so that they become resistant to antibiotics inhibiting such synthesis. However, Kenny did not find L forms to be associated with meningitis taking a prolonged or relapsing course.

Diagnosis

The first essential for improved results is early diagnosis, and it is in the younger child and infant that delay most often occurs. The early signs of meningitis are entirely nonspecific in the newborn, and unless the disease is positively excluded when they appear, or before any antibiotic therapy is started, mortality and morbidity rates will continue to be high. In the older infant, too, such signs as neck stiffness, a bulging fontanelle, and altered

sensorium are not present initially. The long-cherished belief of one of us—that the disappearance of the spontaneous social smile of the infant was a constant feature of early meningitis—has recently been rudely shattered; a cheerful countenance and *Esch. coli* in the cerebrospinal fluid (CSF) are not mutually exclusive. There are several helpful analyses of the early signs of meningitis to which we refer our readers (Smith, 1956; Heycock and Noble, 1964; Smith *et al.*, 1973).

It is usually not possible to distinguish the various causes of meningitis on clinical grounds, though illness during the winter and spring favours bacterial rather than viral meningitis. A purpuric rash is most often, though not exclusively, seen in meningococcal infection, which may occur in epidemics. Middle ear disease might suggest pneumococcal meningitis. *H. influenzae* meningitis is the commonest of the bacterial meningitides of childhood.

Routine examination of CSF. Lumbar puncture is obligatory. Papilloedema is not a contraindication provided only 1–2 ml of CSF are removed. Though there is some experimental work to show that meningitis can be produced if cisternal puncture is done within 2 minutes of an intravenous dose of infecting organisms (Petersdorf, Swarner, and Garcia, 1962) there is little evidence in the human that lumbar puncture causes meningitis if bacteraemia or septicaemia are present (Pray, 1941), and it, or cisternal or ventricular puncture if necessary, should always be performed. The greatest care should be taken over the procedure in very sick children with cardiac or respiratory disease (Margolis and Cook, 1973). A styletted-needle should always be used (Joyner, Idriss, and Wilfert, 1974). Gram-stain and differential cell count give the most useful information initially, and there are few if any situations in which the immediate help of an experienced bacteriologist is more necessary. The method of Gram-staining involves washing the stains at a certain stage, and can be misleading when performed by the inexperienced. The pleomorphism of *H. influenzae* must also be remembered. The cell count in bacterial meningitis may range from 10 cells to 100 000/mm³, and in viral meningitis from 15–2000/mm³. (Meade, 1963). While the cells in viral meningitis are predominantly lymphocytic, an early polymorph preponderance can cause confusion, and may persist for several days (Smith *et al.*, 1973).

The CSF glucose level should be interpreted in relation to the blood level taken at the same time, the latter usually being greater by 10 mg/dl. This

is particularly important in the early neonatal period. The CSF level is usually lowered in bacterial meningitis and unaltered in viral disease. However, interpretation of a normal level is made difficult if the CSF is free of cells (Feinbloom and Alpert, 1969), which may be the case in very early meningitis (Moore and Ross, 1973). The levels may also be normal when cells and bacteria are present in significant quantities. The factors influencing the amount of glucose in the CSF are complex and and not fully understood (Menkes, 1969). The CSF protein level provides nonspecific information, but is generally higher in bacterial than viral meningitis.

Other CSF investigations. When the Gram-stain and differential cell count are unhelpful, differentiation between bacterial and viral meningitis can be difficult, and other diagnostic measures have been sought in recent years.

(a) *Counterimmunoelectrophoresis.* This technique allows detection of bacterial antigen in the CSF by the use of specific antisera against the common pathogens, and can offer a result within 1–2 hours. The patient's CSF is exposed to the various antisera placed in wells in a suitable gel across which an electric field is exerted. The appearance of precipitation lines indicates a positive result. The reliability of the method rests on the specificity of the antisera, which should ideally be prepared from locally-occurring bacteria in the area of the hospital concerned. There are reports of the successful application of this technique in meningitis due to *H. influenzae* (Edwards, Muehl, and Peckinpaugh, 1972) and *N. meningitidis* (Greenwood, Whittle, and Dominic-Rajkovic, 1971; Tobin and Jones, 1972). False positive results have not been encountered, and false negatives are few. The technique's main advantage is in the rapidity with which reliable results can be obtained compared with bacterial culture.

(b) *Flourescein-labelled antibody.* Similarly the presence of bacterial antigen or cell constituents can be detected by fluoresecein-labelled antibody (Fox *et al.*, 1969), and antisera-coated latex particles (Newman, Stevens, and Gaafar, 1970; Goodman, Kaufman and Koenig, 1971).

(c) *Limulus tests for endotoxaemia.* A lysate prepared from the horseshoe crab, *Limulus polyphemus*, will form a gel in the presence of endotoxin, thus allowing nonspecific detection of Gram-negative organisms (Nachum, Lipsey, and Siegel, 1973). These authors claim the test is relatively simple and that a result can be provided within 15 minutes of diagnostic lumbar puncture.

(d) *Spinal fluid immunoglobulins.* These are altered in meningitis but there is no specific pattern which will differentiate between bacterial and viral causes (Kaldor and Ferris, 1969; Smith *et al.*, 1973). CSF IgM is also raised in noninfective inflammatory disease of the central nervous system Kolar and Ross, (1973).

(e) *CSF enzymes.* Levels of lactic dehydrogenase and glutamo-oxaloacetic transaminase are raised in bacterial, though not in viral, meningitis (Williams and Hawkins, 1968; Neches and Platt, 1968; Shoeb *et al.*, 1970).

For practical purposes, it seems likely that of all these possibilities counterimmunoelectrophoresis alone may offer rapid help when conventional CSF examination is ambiguous.

CSF in partially treated meningitis. In so far as symptoms or signs of upper respiratory infection or otitis media often precede meningitis it is not surprising that children presenting at hospital have frequently been given oral antibiotics in conventional dosage. This may obscure the clinical course of the illness and make bedside diagnosis difficult. Previous antibiotic therapy may have sterilized the CSF so that Gram-stain and culture are negative. However, this appears to be less of a problem than one might expect. Various published studies (Winkelstein, 1970; Jarvis and Saxena, 1972; Converse *et al.*, 1973) show that the rate of bacteriologically positive CSF is only some 10% less in treated patients as compared with untreated. In practical terms the clinician is faced with the problem of aetiology rather than diagnosis: the CSF is virtually always abnormal, and the difficulty lies often not in deciding whether meningitis is present, but whether it is viral (or very rarely tuberculous) or bacterial. Though they can usually be distinguished on levels of protein, glucose, and cell type and number, there is considerable overlap, and as already stated an early polymorph preponderance in some cases of viral meningitis can be confusing.

Feigin and Shackelford (1973) found that if the patient had *not* had prior antibiotic therapy, it was possible, by deferring such treatment and repeating lumbar puncture within 8 hours, to make a confident diagnosis of viral meningitis in doubtful cases, for the change to lymphocyte predominance had then occurred in the great majority. However, 8 hours is a long time in the natural history of bacterial meningitis, and withholding therapy when some has already been given calls for very fine clinical judgement in which the most careful history and clinical examination, the peripheral blood

total neutrophil count, the season of the year and the presence or otherwise of a community epidemic, may all give help. The wider use of counterimmunoelectrophoresis may provide the answer to this predicament, but if any reasonable doubt still exists, further effective antibiotic therapy must surely be mandatory without further delay.

Further investigations. Bacteraemia accompanies meningitis frequently and blood culture should be made as a routine, for it can provide an answer if the initial CSF culture is negative. A smear from a purpuric skin lesion may also yield the pathogen either on Gram-stain or culture. Nose and throat swabs are of limited value, for nasopharyngeal flora shows a poor correlation with the organism causing meningitis (Butler and Johnson, 1974) except in the early neonatal period. Haemoglobin and total and differential white blood count should be done at the outset; platelet count and blood content of fibrin degradation products may be necessary.

Treatment

Initial.

Antimicrobial therapy. This should be started at once, either intravenously or intramuscularly, and where necessary (see below) intrathecally. If clinical and bacteriological evidence based on initial CSF findings indicates a specific organism, then the appropriate antibiotic (see below and Table I) should be used. If such evidence is not forthcoming immediately and uncertainty exists, it is necessary after the first 2 or 3 months of life to cover the three common pathogens—*H. influenzae*, *N. meningitidis*, and *Dip. pneumoniae*.

Ampicillin alone (Wehrle *et al.*, 1967) and chloramphenicol alone (Murray *et al.*, 1972) have been used successfully. Ampicillin has been shown to be as effective singly at a dose of 150 mg/kg per day as combined with chloramphenicol 100 mg/kg per day and streptomycin 40 mg/kg per day, the latter for 2 days only (Mathies *et al.*, 1967). However, an ampicillin dosage of 300–400 mg/kg per day has also been recommended (Barrett *et al.*, 1966) in view of reports of relapses of *H. influenzae* meningitis. This problem is discussed in more detail below. In experimental meningitis a bacteriostatic drug such as chloramphenicol has been shown to interfere with the action of a bactericidal one such as penicillin, and there may be some support for this in clinical practice (Mathies *et al.*, 1967). In the first months of life a combination of ampicillin and gentamicin is to be preferred.

Intravenous antibiotics should not in general be mixed with acidic infusion fluids such as dextrose; benzylpenicillin and ampicillin may in particular lose their activity, and therefore should be given separately as a bolus over several minutes. Heparin and hydrocortisone should not be injected in the same syringes, for they may interfere with each other's activity (*Drug and Therapeutics Bulletin*, 1970).

Intrathecal therapy. There has always been controversy about the role of intrathecal therapy in meningitis. Excessive dosage and drug impurities in the early years led to serious reactions, and determined opponents such as Hoyne (1953) found more favour (e.g. Smith, 1956) than supporters (Weinstein, Goldfield, and Adamis, 1953; McKendrick, 1954). In one British series with generally good follow-up results (Lawson *et al.*, 1965) intrathecal therapy was more often used initially and has its continued advocates (Lorber, 1974). However, as Lawson *et al.* point out, their good results may have been due to favourable socioeconomic factors leading to early diagnosis by alert parents and family doctors. In the absence as yet of large controlled trials in childhood, and until early diagnosis is generally achieved, initial intrathecal therapy may well give best results. It must be acknowledged, however, that concentrations of intrathecally injected drugs are not uniform (Walker and Johnson, 1945). Furthermore, in the experimental situation, significant concentrations of a drug at cerebral, subarachnoid, and ventricular levels were only present if injection at the lumbar site was made in a volume equivalent to 25% of estimated CSF volume (Rieselbach *et al.*, 1962), a situation rarely achieved in clinical practice.

Supportive treatment.

Shock. Peripheral circulatory failure demands certain actions, irrespective of the causative organism. These include the use of plasma expanders and corticosteroids, correction of acidosis (Dietzman and Lillehei, 1968–1969; Murray *et al.*, 1972), and monitoring of central venous pressure. Phenoxylbenzamine 1 mg/kg every 2–4 hours, a blocker of α -adrenergic receptors, has been used successfully in shock syndrome, though has not been reported in meningitis. The use of corticosteroids in the absence of shock has no benefit; and two reports have cited evidence that morbidity and complications are worse (Lepper and Spies, 1957–1968; deLemos and Haggerty, 1969). It is known that most children have raised levels of plasma cortisol in meningitis (Migeon *et al.*, 1967). Those

with low levels are in an advanced state of shock which is usually fatal, even when corticosteroids are given.

Fits. These may be caused by the disease or by fever. Intramuscular paraldehyde, or intravenous diazepam will be the most helpful drugs. Short-term anticonvulsant therapy should be continued with phenobarbitone (4–8 mg/kg per d) or phenytoin (8–10 mg/kg per d) intramuscularly, and later orally. Phenobarbitone achieves therapeutic blood levels almost at once (Jalling, 1974) but 1–4 days are required for phenytoin, though larger loading doses can be used to achieve an effect within 24 hours (Wilder, Serrano, and Ramsay, 1973). A careful watch on blood pressure should be kept because of the risk of drug-induced hypotension. There is a reduction in regional cerebral blood flow and in cerebral metabolic rate of oxygen in adults with meningitis (Paulson *et al.*, 1974), and there is no reason to suppose these findings are not relevant to children. Thus any factors leading to hypotension or hypertension, hypercapnia, hypoxia, and increased cerebral metabolism are to be avoided whenever possible.

Cerebral oedema. This is likely to be a consequence both of hypoxia and of the infection and therefore to some extent preventable if the meningitis is diagnosed early and treated vigorously. If established, dexamethasone (0.5 mg/kg per d) for 48 hours or other corticosteroids (Reynolds, 1966) have been advocated. Mannitol 20% in a dose of 1–1.5 mg/kg in 20–30 minutes has also been used in meningitis (Murray *et al.*, 1972).

Treatment of specific infections

H. influenzae meningitis. As already indicated, ampicillin and chloramphenicol are equally effective in treatment and are the drugs of choice. A dozen or so reports of ampicillin failure—that is, positive CSF or blood culture persisting or recurring either early or late in the course of treatment—have caused much debate in the past few years. Some, though not all, have been due to inadequate dosage, and, as various reviewers have pointed out, there has probably been some underreporting of chloramphenicol failure (Yow, 1969; Wehrle, Mathies and Leedom, 1969). Meningeal inflammatory change is not essential for the penetration of chloramphenicol into the CSF, and most of the ampicillin failures have improved after substitution of chloramphenicol.

The debate concerning the two drugs is not easily resolved. Where ampicillin is concerned there is the possibility, as with any penicillin, of a serious sensitivity reaction, or the development of staphylo-

coccal enteritis. To these potential hazards must be added the emergence of ampicillin-resistant strains of *H. influenzae*, and the recently reported possibility of a significantly higher incidence of deafness among high-dose ampicillin-treated cases compared with those treated with benzylpenicillin, sulphonamide, and chloramphenicol, or a combination of both (Gamstorp and Klockhoff, 1974). 2 of the last 3 cases of haemophilus meningitis treated by us with high doses of ampicillin have become deaf early in the course of the illness.

On the other hand, with chloramphenicol, there is the possibility of drug-induced aplastic anaemia, which has a mortality rate of over 50% and which often develops weeks or months after the drug has been stopped. Schröter (1974) has reviewed published reports on chloramphenicol toxicity. It is clear that unlike the relatively common, easily reversed, dose-related suppression primarily involving the erythroid series, the much more serious bone marrow aplasia is unrelated to dose, and the risk is approximately 1 death for every 25 000 treated patients.

A current regimen for ampicillin, probably widely used in the United States, is to give 300–400 mg/kg per day intravenously in 4 or 6 divided doses for 10–14 days (Smith *et al.*, 1973). Maintenance of an intravenous drip for this length of time may pose problems in young children, and substitution of intramuscular therapy after 5 days, and for a further 5 days is acceptable (Wilson and Haltalin, 1975). While it is probably true to say that many young children would find an intravenous drip preferable to 4 or 6 intramuscular injections daily while very ill, once they feel like moving about they would probably wish to be rid of it.

Alternatively, chloramphenicol may be given at a dosage of 100 mg/kg per day either intramuscularly or intravenously for the same period. Lorber (1974) advocates another personally successful regimen of 10–20 mg (according to age) ampicillin or chloramphenicol intrathecally, in a volume not greater than the amount of CSF removed at the time of the diagnostic lumbar puncture. In children under 1 year 10 mg hydrocortisone is also injected intrathecally 'to minimize the risk of hydrocephalus.' Systemic treatment, either as ampicillin (200 mg/kg per d) or chloramphenicol (100 mg/kg per d), both in 4 divided doses, is rarely continued for more than 10 days, and daily intrathecal treatment for no longer than 2–3 days. Except in very ill, dehydrated children, the systemic antibiotic is given intramuscularly.

At present we do not believe there is an unequivocal answer to the question of preferred treat-

ment of *H. influenzae* (or unknown) meningitis, though this may be forthcoming if ampicillin resistance to the organism becomes widespread. As we go to press we marginally favour chloramphenicol. Lorber (1974) states that he has had no deaths with his method of treatment. If he can prove on detailed assessment at follow-up that neurological sequelae are also fewer than those recently reported, then his advocacy of initial intrathecal treatment may find wide support.

Meningococcal meningitis. The drug of choice is benzylpenicillin, and the initial dose 250 000 units/kg per day, given 4 or 6 hourly intravenously. It is no more effective than sulphonamides alone (Lepper *et al.*, 1952; Stiehm and Damrosch, 1966), providing of course that the organisms involved are sulphonamide sensitive, but since the possibility of resistant organisms exists, the sulphonamides need not now be used in treatment at all. Ampicillin (Mathies *et al.*, 1965) and chloramphenicol are also effective. In a controlled trial of the treatment of sulphonamide-resistant group A meningococcal meningitis in Africa, the latter proved as effective as, and much cheaper than, penicillin, for adults and older children were soon able to take it by mouth which reduced the cost and simplified treatment, both factors of overriding importance in that country (Whittle *et al.*, 1973).

Patients with meningococcal septicaemia have a bad prognosis (Stiehm and Damrosch, 1966), particularly if meningitis is not present. Treatment for shock may be necessary and in some cases disseminated intravascular coagulation occurs (Fox, 1971). Various authors have reported the successful use of heparin in this condition (Abildgaard *et al.*, 1967; Winkelstein *et al.*, 1969; Ellman, 1971), while others have reported failure (Hitzig, 1964; McGehee, Rapaport, and Hjort, 1967). Patients have survived the condition without the use of heparin (Corrigan, Jordan, and Bennett, 1973). It is not possible to give general advice about the treatment of disseminated intravascular coagulation, except to say that clear laboratory evidence of its occurrence must be obtained before considering the use of heparin.

Pneumococcal meningitis. Benzylpenicillin is again the drug of choice, with ampicillin an acceptable alternative (Mathies *et al.*, 1965). The previously favoured triple combination of benzylpenicillin, sulphonamides, and chloramphenicol is no more effective (Weiss *et al.*, 1967). Benzylpenicillin can be given intravenously in the same dosage as for meningococcal meningitis. If intrathecal therapy

is given for the first few days, CSF levels of the drug must be carefully monitored, particularly in the youngest patients and those with underlying disease, for their mechanisms for metabolism and excretion of drugs may be impaired, with drug-induced cerebral toxicity a real possibility. Beyond the neonatal period the intrathecal dose of benzylpenicillin can range from 2000–10 000 units, depending on age. Relapsing pneumococcal meningitis, associated with the isolation of an organism with decreased susceptibility to benzylpenicillin, in a child with sickle cell disease has recently been reported (Naraqi, Kirkpatrick, and Kabins, 1974).

Staphylococcal meningitis. In the early 1950s, when most newborn babies left maternity units colonized with *Staphylococcus aureus*, meningitis associated with this organism was by no means unknown, but it is rare at older ages (Finland, Jones, and Barnes, 1959; Quaade and Kristensen, 1962). Cloxacillin and methicillin are still the most appropriate drugs for most of the penicillinase-producing strains. Children with CSF shunts are at risk from meningitis, and particularly that caused by *Staphylococcus albus*. In general the same antibiotics are suitable, but recent trials have shown that systemic therapy alone is unlikely to be curative (Shurtleff *et al.*, 1974). These authors state that the initial treatment should be both systemic and intraventricular, providing the shunt system includes a reservoir allowing direct access to the CSF. However, complete shunt replacement using the opposite ventricle and a different distal shunt site in addition may be essential for cure.

Neonatal meningitis. Neonatal meningitis is characterized by a very wide range of infecting organisms, and there can be few bacterial species which have not been responsible for the disease. Satisfactory cure can follow intramuscular treatment alone (Zoumboulakis *et al.*, 1973). However, late diagnosis is too often made, and preliminary results of the U.S. Cooperative Neonatal Meningitis Study Group suggest that for meningitis due to Gram-negative enteric bacteria, uncorrected mortality is lower with intrathecal treatment, though this improvement is offset by a higher rate of serious sequelae (McCracken, 1975). Nevertheless, at present initial systemic treatment with ampicillin and gentamicin, and intrathecal treatment with gentamicin offer the most favourable combination for all eventualities, and should be given without delay. Chloramphenicol would be an acceptable alternative for most of the more commonly encountered organisms with the exception of *Pseudo-*

monas aeruginosa. Once the infecting organisms is known with certainty, modification may be necessary. For instance, benzylpenicillin would be the drug of choice for meningitis caused by group B β -haemolytic streptococci, usually a maternally transmitted infection. Carbenicillin and gentamicin should be used for *Ps. aeruginosa* infections.

CSF in meningitis due to Gram-negative organisms may show positive cultures for several days after treatment is started despite adequate antibiotic concentrations, whereas in that due to Gram-positive organisms it is usually promptly sterilized (McCracken, 1972). Daily intrathecal therapy should continue for 4-5 days after the last positive culture. Systemic therapy should probably be given for a total of 14-21 days, depending on progress. If the lumbar fluid is sterile, but clinical progress unsatisfactory, the possibility of a persisting ventriculitis should be remembered (Berman and Banker, 1966), and if present, therapy must be continued intraventricularly. Dosage for the neonatal period is given in Table II.

Monitoring and complications

Patients should show a good clinical response to therapy within a few hours depending on the severity of the presenting illness. Pulse, respiration, circulation, level of consciousness, and general demeanour should at minimum remain static or improve within 2-6 hours. If this does not

occur it suggests either that some element in the treatment regimen is inadequate or lacking, or that the disease state was irreversibly advanced before treatment started. Fever sometimes settles rapidly, as in meningococcal disease, or more slowly over the course of a few days. Continued accurate clinical assessment is crucial, and poor progress at any stage should provoke a critical review of the management and a search for complications. Frequent skull circumference measurements should be made in infants.

A repeat lumbar puncture after 24 hours or so is useful to ascertain CSF sterility. In the first 2 days the pleocytosis and protein content may show deterioration. However, if Gram stain and culture are negative and clinical progress good, this need not cause alarm, though further examination of CSF should be undertaken immediately if indicated. Antibiotic levels in CSF and serum may provide useful information, especially in patients who appear to be progressing less well, and are particularly important in the neonatal period. The assessment of patients with a persistently impaired level of consciousness is exceedingly difficult, and usually implies severe, established disease before treatment was started.

Specific early complications include subdural effusions, hydrocephalus, cerebral infarction, and sinus thrombosis. Persistent fever needs careful investigation. It may be caused by a relapse of the

TABLE II. *Suggested dosage for neonatal meningitis*

Drug	Intrathecal* (Daily dose)	Intramuscular	
		Single dose (per kg)	Frequency
Ampicillin Benzylpenicillin Carbenicillin Cloxacillin Methicillin	1000-2000 units 5.0 mg 2.5 mg	50 mg 25 000 units 100 mg 25 mg 50 mg	<i>For term infants (>37 weeks' gestation)</i> Every 12 h in first 48 h of life 8-hourly between 3rd d & 2 w 6-hourly if over 2 w <i>For preterm infants (<37 weeks' gestation)</i> Every 12 h in 1st week of life 8-hourly between 1 & 4 w 6-hourly after 4 w
Chloramphenicol		12.5 mg (maximum daily dose should not exceed 25 mg for first week of life in term babies, for first 4 weeks in preterm)	Kanamycin need not be given more than 12-hourly Gentamicin need not be given more than 8-hourly
Kanamycin	1-2 mg	7.5 mg (increase to 10 mg after 1st 48 hours of life in term babies, and after first week in preterm)	
Gentamicin	1-2 mg	2.5 mg	

*Lower dose is for preterm infants. Where hydrocephalus is present Lorber, Kalhan, and Mahgreffe (1970) state that much higher doses are needed, given *intraventricularly*, to achieve bactericidal concentrations in CSF. They have used up to 8 mg gentamicin and up to 20 mg cloxacillin in this situation.

Co-trimoxazole (sulphamethoxazole-trimethoprim): isolated case reports suggest this may prove to be a useful drug in treatment of meningitis, though it should be avoided in the first week, and in very immature or jaundiced newborn infants. A dose of 30-40 mg sulphamethoxazole, 6-8 mg trimethoprim/kg per day is said to give high levels in serum and CSF (Sabel and Brandberg, 1975).

meningitis, or by infection elsewhere—such as in the middle ear, urine, joints, bones, lungs, or pericardium. Dehydration, inflammation at intramuscular injection sites, or thrombophlebitis at intravenous sites are other possibilities. Frequently no cause for persistent fever is found, and it settles promptly when antibiotic treatment is stopped.

Late complications must not be forgotten, and long-term follow-up is required to exclude such conditions as insidiously developing hydrocephalus, cerebral palsy, deafness, epilepsy, or, later still, school learning difficulties with or without intellectual retardation.

Prophylaxis

Prevention of disease should always be as important to paediatricians as efficient diagnosis and treatment. It is uncertain to what extent this will be possible in the future where bacterial meningitis is concerned, but the development of vaccines against *N. meningitidis* and *H. influenzae* is a first step. We shall only mention here the controversial question of prophylaxis of meningococcal infection once the index case has presented to the paediatrician. Those at greatest risk are household contacts, particularly where very young, and where overcrowding exists, and the very young contacts in day nurseries (*Lancet*, 1974). It has been our policy to give sibs in these circumstances prophylactic treatment immediately, without waiting for any results of nasopharyngeal culture. There are three drugs which will eradicate *N. meningitidis*—sulphonamide, rifampicin, and minocycline. At present in this country it is probably still justifiable to prescribe sulphonamide in full dosage (100 mg/kg per d for 4 or 5 d), unless sulphonamide resistance of the organism in an epidemic is already known. Prophylactic rifampicin (20 mg/kg per d for 2 d) or minocycline (4 mg/kg initially, then 4 mg/kg per d for 3 d) does have a higher incidence of side effects, and resistance to rifampicin develops quickly (*Lancet*, 1974), which makes their use less attractive.

Although penicillin is so effective in the management of meningococcal meningitis it does not eradicate the organism, and successfully treated cases may return home still carrying it in the nasopharynx (Khuri-Bulos, 1973). Discussing this situation, Feldman (1975) points out that the presentation of a second case in a household is usually, though not invariably, within 96 hours of the index case, and he believes it is 'co-primary' rather than secondary. Thus, he advocates a therapeutic course of penicillin therapy, or alternatively—though surely this may not be possible throughout the first 24 hours except in hospital—

careful observation of contacts and prompt treatment at the first symptom. He concludes that prophylaxis may protect only for the period of its administration, and that infection may recur if an immune response is prevented. As Feldman rightly point out, a second case in a small circle engenders considerable emotional response, and this may have clouded judgement on this important issue; the last word on this subject has clearly not been written.

Conclusions

Bacterial meningitis is still a damaging and sometimes fatal disease. Prognosis has in the past been directly correlated with age, and is worst in the neonatal period. Late diagnosis in the youngest children is one of the most important reasons for this. If improvements are to occur, our efforts must be directed towards recognition of apparently trivial early signs in those at greatest risk, and towards ensuring that effective but not damaging levels of antibacterial drugs reach the CSF as quickly as possible.

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