Today's Treatment

Use of antibiotics

Meningitis

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The great variety of different organisms that may cause meningitis and the resulting range of possible treatments make for much concern and confusion. Nevertheless, for most patients with meningitis, a clear line of diagnosis and treatment may easily be achieved. The first point to determine is whether the meningitis is caused by a pyogenic bacterium; this is normally established by the florid nature of the illness, the high neutrophil count in the cerebrospinal fluid (CSF), and sometimes by the characteristic rash of meningococcal septicaemia. Occasionally, in severe septicaemia, the CSF may be taken before many neutrophils have accumulated in it (and indeed bacteria may be found in acellular CSF), but the severe acute illness with, sometimes, a purpuric rash help to diagnose the illness correctly. The next step is to exclude for separate consideration meningitis in the neonate or in patients with CNS defects or immune suppression.

For the rest, three organisms only account for most cases of pyogenic meningitis: *Neisseria meningitidis*, which is common in children and young adults but rare in the elderly; *Haemophilus influenzae*, rarely encountered in patients more than 5 years old; and *Streptococcus pneumoniae*, found in all age groups including infancy and becoming the dominant cause in the elderly. The centrifuged CSF deposit is examined by an experienced observer to detect organisms characteristic of each species. Other methods are becoming available to supplement Gram-staining of the CSF—notably, countercurrent immunoelectrophoresis for detecting bacterial antigen in CSF, blood, or urine—a method that sometimes yields positive results when conventional staining has failed to do so. Results of CSF and blood cultures will later become available, but treatment must be started as soon as the relevant specimens have been taken and the CSF deposit examined. In the most severe forms of meningococcal septicaemia even this delay may not be justified, and treatment should start as soon as a blood culture has been taken.

Meningococcal meningitis

Sulphonamide resistance is now common enough to bar using this drug as the sole initial choice for meningococcal disease, despite its excellent record in the 25 years before resistance emerged. Benzylpenicillin is effective if given by a dose and route that achieves adequate CSF as well as serum concentra-

tions. Frequent large intramuscular injections are painful; the best method is to establish an intravenous infusion and to give bolus injections of benzylpenicillin at four-hourly intervals in a dose of about 250 000 units (0.15 g)/kg/day—that is, 2-3 mega-units (1.2-1.8 g) every four hours in an adult. If the organism is susceptible to sulphonamide, treatment may then be changed when the patient is generally well, is not vomiting, and has satisfactory renal function to a sulphonamide by mouth for the remaining week of treatment. Sulphadiazine and sulphafurazole are superior to sulphadimidine for this *in vitro* but they all work about as well in practice, given in an initial dose of 50 mg/kg up to a maximum of 3 g, followed by 100 mg/kg/day for adults and 200 mg/kg/day for infants (four doses at six-hourly intervals).

Meningococcal septicaemia and meningitis, especially in their more acute presentation, provoke much natural anxiety among the patient's contacts. The risk of contact disease is closely related to social conditions, especially crowding, and is greatest for contacts in the first years of life. Since tests of individual susceptibility to meningococcal disease are not easily or rapidly available, all household contacts and all under-5-year-old contacts in playgroup or nursery school should be treated. Contacts in older age groups will be treated only if evidence of an institutional outbreak becomes apparent. This decision about treating contacts should be made as soon as possible after the first case is identified and should not wait for the results of cultures of any nasopharyngeal swabbing. Sulphadiazine, 1 g thrice daily for three days for an adult and correspondingly less for a child, clears the meningococcal carrier state effectively. If the organism is sulphonamide-resistant rifampicin or minocycline may be necessary. Both are unsatisfactory; the former because the small proportion of meningococci not cleared are likely to be rifampicin resistant, and the latter because some patients complain of dizziness or vertigo. Effective as it is in treatment, penicillin does not clear the meningococcal carrier state.

Pneumococcal meningitis

Pneumococcal meningitis carries a high mortality rate. It may occur, especially in tropical countries, in healthy patients of all ages, but is also often associated with old age, chronic illnesses, and an impaired resistance to infection. *Strep pneumoniae* is also by far the most common causal organism in meningitis associated with head injury. Antimicrobial treatment consists of high doses of benzylpenicillin given by intravenous bolus injection as for meningococcal meningitis.

Penicillin resistance has been recorded in pneumococci causing septicaemia and meningitis in South Africa: serious difficulties will be encountered in managing pneumococcal disease if these strains become widespread. Cephaloridine given by intramuscular and intrathecal injection has been used successfully in pneumococcal meningitis but, with this exception, available cephalosporins are not suitable for treating pyogenic meningitis.

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Haemophilus influenzae

Haemophilus influenzae meningitis mainly affects children below school age. Good results have been achieved with various antimicrobial regimens—notably, chloramphenicol and ampicillin. In recent years high-dose ampicillin by intravenous bolus injection (200–400 mg/kg/day) has been widely used but the emergence since 1974 of plasmid-mediated ampicillin resistance in *H. influenzae* has led doctors to reconsider a return to chloramphenicol as drug of first choice. Resistance to chloramphenicol has rarely been reported and, although the possible complication of aplastic anaemia must always be remembered, the drug has many pharmacokinetic and antibacterial properties that favour its use in meningitis, being well absorbed after oral administration and giving high CSF:serum ratios. Treatment starts with intravenous administration, and oral treatment follows as soon as possible, using a total dose of 100 mg/kg/day—that is, 0.25 g six-hourly in a 1-year-old child.

Chloramphenicol is also a suitable single-drug treatment for meningitis of uncertain cause and for patients with meningococcal or pneumococcal meningitis who are unequivocally hypersensitive to penicillin. The former practice of treating patients with pyogenic meningitis with a mixture of penicillin, chloramphenicol, and sulphonamide may be discontinued. There is no reason to believe that the results of this treatment are better than those obtained using chloramphenicol alone, while the use of three drugs increases the risks of unwanted effects and tends to induce half-heartedness in the dose of the individual components. Nor is intrathecal treatment indicated in managing the three common varieties of pyogenic meningitis since this procedure is of dubious benefit, and too many tragic errors have been made by injecting excessive doses of penicillin into the subarachnoid space.

A decision tree suitable for treating the common forms of meningitis is shown in the figure.

Other aspects of management

Few drugs other than the appropriate antimicrobials are needed in meningitis. The chief need in conscious patients is for analgesics to combat headache. In infants and in patients of any age who have had fits, phenobarbitone in normal anti-convulsant dosage should be prescribed. Most important is the

nursing care of a patient who may be restless, unconscious, and incontinent.

Uncommon forms of pyogenic meningitis

The less common varieties of pyogenic meningitis are usually encountered in association with immune suppression, chronic inner ear infection, or defects of the central nervous system, but unusual organisms are sometimes found in patients with no identifiable predisposing cause. The causal organisms vary so much in their type and antibiotic sensitivity pattern that only general guides to treatment can be given, and careful bacteriological study of each patient is particularly important.

Neonatal meningitis, caused mainly by coliform bacteria and streptococci, is discussed in another article in this series by Dr P Davies, and the special problems that the treatment of coliform meningitis poses apply also to older age groups. Streptococcal meningitis is treated with large doses of penicillin by intravenous injection, while for staphylococcal meningitis both benzylpenicillin and flucloxacillin are given at first until the antibiotic sensitivity of the causal strain is established. *Listeria monocytogenes* varies a good deal in its antibiotic sensitivity; several regimens have been used successfully, most commonly ampicillin by intravenous injection as for *H. influenzae* meningitis.

Tuberculous meningitis

Tuberculous meningitis is often hard to diagnose and hard to treat. Optimal methods of management with modern anti-tuberculosis drugs are still uncertain, since no controlled studies of the type that have transformed the treatment of pulmonary tuberculosis are available for tuberculous meningitis. Treatment has therefore to be based on known antibacterial and pharmacokinetic properties of the available drugs rather than on the results of clinical trials. Isoniazid must be given in generous doses, 10–15 mg/kg/day, together with rifampicin, 600 mg daily.

In the first two or three months of treatment additional chemotherapy should also be included, either streptomycin (1 g daily injected intramuscularly) together with ethambutol (25 mg/kg/day by mouth), or pyrazinamide (0.5 g thrice daily by mouth). Intrathecal treatment is now rarely included, and whether or not this would give additional benefit to current

Decision tree for treating common forms of meningitis.

chemotherapeutic regimens is unknown. Treatment should be continued for a total of one year.

Cryptococcal meningitis

Amphotericin B and flucytosine have each, used alone, cured several patients with cryptococcal meningitis, but use of the former is limited by toxicity and the latter by the development of resistance. The demonstration that the two agents can act in synergy, both in vitro and in animals, enabled this property to be exploited in disseminated fungal diseases in man, and combined treatment by the two agents is now the preferred method.

Little toxicity has been encountered using 20 mg amphotericin B daily by intravenous infusion (after initial smaller test doses) together with oral flucytosine in a dose of 150 mg/kg day. Treatment should be continued for at least six weeks. Additional amphotericin B has sometimes been given by the intrathecal route.

Viral meningitis

No specific antiviral drugs are available for treating the ordinary varieties of viral meningitis, most commonly caused, when a pathogen is identified, by enteroviruses or by mumps. The problem here is rather to identify, among the patients with a low cell count in the cerebrospinal fluid, those few who have unusual causes of aseptic meningitis carrying special implications for management. Especially important are tuberculous and cryptococcal meningitis; meningeal reactions in association with brain abscess; and partly treated pyogenic meningitis; while among the enteroviruses, the now rare possibility of encountering a patient with poliomyelitis has to be remembered. Leptospirosis is also worth remembering in certain areas and among particular occupations.

Duration and assessment of response to treatment

Surprisingly little is known about how long treatment ought to continue in the ordinary forms of pyogenic meningitis. It is conventional to continue for about 10 days, although it has been shown in Nigeria that good results are obtained in meningococcal meningitis using a five-day course of treatment. The shorter courses will be applied to those forms, exemplified by meningococcal meningitis, in which no focal collections of infection are found. Longer courses tend to be given for 14 days or more, when meningitis is caused by a "difficult" organism or is associated with immune suppression or chronic illness. If the chosen treatment includes intravenous or intramuscular injections it is best to continue the chosen regimen for the whole duration of treatment rather than to change to doses and routes of administration that are ineffective in meningitis—for example, from high-dose parenteral ampicillin to oral ampicillin or amoxycillin.

It is often hard to judge the progress in patients with meningitis. Fever may continue for many days, and neurological signs may also persist for a variable time. It is important to review the whole body of evidence on which the diagnosis was made; whether the treatment chosen was correct; and whether it is actually being delivered in the right dose—at the proper intervals and by the chosen route. If the treatment was indeed rationally based and used as planned antibiotic failure is unlikely, and the cause of unsatisfactory progress is likely to be found elsewhere. For example, thrombophlebitis at sites of intravenous infusions or areas of damage at the sites of intramuscular injections may cause fever, or the fever of meningitis may be supplanted by a drug hypersensitivity when the temperature will return to normal as soon as treatment is stopped. Less often metastatic foci of infection such as arthritis in meningococcal septicaemia may be found.

Slow neurological progress may also have several different causes. Focal events such as subdural effusion, brain abscess, or

thrombophlebitis of the cerebral sinuses must be considered, but metabolic causes may be more common—for example, neurological signs may be found in hyponatraemia resulting from injudicious administration of large volumes of glucose solutions in a patient with impaired renal function. Repeated lumbar puncture as a routine may complicate the condition by giving the patient a worse headache and serves no useful purpose, since it is rare to recover organisms shortly after starting effective treatment. When progress is satisfactory therefore, only the initial diagnostic lumbar puncture is performed, and the cerebrospinal fluid is examined further only in those patients whose progress is unsatisfactory or in whom a problem in diagnosis remains.

MATERIA NON MEDICA

Gardens of Hesperides

It isn't my fault if Kirsty has the wrong idea of the Outer Hebrides. At least, I can accept only partial responsibility. It is true that I have told the family for years how close to the gates of paradise lie these islands of the blessed. This may constitute brain-washing of a kind, I suppose. But, dear Lord, to give us 10 days, from Lochboisdale to Stornoway, and never a cloud in the sky, that was really laying it on a bit thick; and do you wonder that the girl thinks sun on silver sand the norm? Why, we went swimming in the sea, twice on the same day. My protestations that it is not always like this fall on deaf and un-receptive ears. Nor in recollection is it otherwise, for she has the photographs to prove it—photographs of a jewelled sound of Harris sparkling in the reflection of a cloudless sky, the very stuff of song and saga.

Memories of Hebridean hospitality embroider recollections evoked by photography. To countless strubagan or "quick cups of tea" is added the memory of those oh-so-blessed girdle scones. None the worse, dear God, for cooking on the electric, rather than the peat, fire. And that's not the half of it. In fact, we might very well say "Hospitality, thy name is Hebrides."

Can you picture a hotel where the manager stays up until 2.00 am to welcome travellers when the boat is four hours late in arriving (because it was four hours late in leaving Oban) and who then provides tea and biscuits "because you will be needing something"? Lochboisdale is the place and, merciful heaven, he was English.

Kirsty, I take it all back. You are right. Forget my carping. The sun shines always, silver sands stretch forever, virginal and untrodden, and the sparkling sea beckons ever westward. Hebrides or gardens of Hesperides?—KENNETH M LEIGHTON (Vancouver, British Columbia).

Unexpected encounter

To the experienced rock climber, Amphitheatre Buttress in North Wales is little more than a scramble—a pleasant route to climb in winter, when conditions preclude more serious undertakings. To the inexperienced, city-softened registrar it presented problems enough and one in particular that could hardly have been predicted.

About half way up the 950 feet of this slabby, heathery climb you encounter a little nose of rock, worn and polished. The guide book warns that this is the crux, but there were so many holds that I felt comparatively secure as I pulled myself up. The precipitous drop which appeared on the right prompted me to adjust my footing and it was then that I heard a strange yelping immediately above. I looked up and saw a dark silhouette, wings swept back and blunt nosed like a torpedo. It flew close over at great speed and then turned in the air to reveal a pale face with black moustache. As soon as it had passed, it turned again and, to my amazement and considerable peril, stooped viciously on an unfortunate seagull gliding blamelessly in the gully.

I nearly fell off in astonishment. To see a peregrine falcon was rare enough, but to encounter one stooping at 150 mph a few yards away did little to promote composure and equilibrium in one so delicately poised. I regained safety with difficulty, which is more than could be said for the seagull.

It was a female bird which had so distracted me. For the rest of the climb she and her mate were frequently visible in every detail, flying and at rest. Their cries filled the valley and they came very near. We completed the route in safety and congratulated ourselves on so doing. Such undertakings never fail to produce an adrenergic response, but on this occasion the rock took second place.—G D OAKLEY (cardiac registrar, London).