A New Look at Infectious Diseases

Bacterial Meningitis and Tuberculous Meningitis

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Despite the wide range of antimicrobial drugs available today the mortality and morbidity from bacterial meningitis is disappointingly high. This disappointment is all the more poignant when one appreciates that some 75% of pyogenic meningitis in Britain results from infection by one of three organisms—namely, *Neisseria meningitidis, Streptococcus pneumoniae,* or *Haemophilus influenzae.* Though meningococcal infection still ranks as the main cause it is less dominant over the other two than it once was; the remaining 25% of cases result from a wide variety of organisms, many of which are involved in the problem of neonatal infection and have less relevance to pyogenic meningitis as a whole.

Before 1968 only meningococcal and tuberculous meningitis were statutorily notifiable, but since then all forms of acute meningitis, irrespective of the causative organisms, have been included. Nevertheless, official statistics indicate that the disease is still poorly notified and the figures for 1970 (table I) bear this out when compared to the unofficial analyses produced by the Public Health Laboratory Service (table II). The latter figures, admittedly incomplete and mainly concerned with England and Wales, show that some 1,500 cases of bacterial meningitis occur annually. Probably the real total exceeds 2,000 cases per annum—and even this figure could well be doubled if cases due to viral infection were included.

Estimates of the *overall* mortality of bacterial meningitis lie between 5% and 15%, but definite variation occurs with age and the responsible organism. For example, pneumococcal meningitis in people over 50 years of age may have a death rate as high as 50% and a similar picture may be found in unselected series of neonatal meningitis, where infection by Gram-negative organisms predominates.

Patients dying from, or being appreciably maimed by, bacterial meningitis are likely to do so for three main reasons. Firstly, because the infection has been so fulminant or occult that irreparable damage, or even death, has occurred by the time medical help is sought. Secondly, because there is delay in reaching the correct diagnosis in the home or in hospital. Lastly, because the treatment employed is basically wrong in the selection of therapy or incorrect in its application.

Short of prevention, which is discussed later, there is little that can be done about the first of these points but the other two can surely be improved by a better appreciation of the clinical presentation of the disease and more knowledgeable application of treatment.

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TABLE I—*Acute Meningitis.* Corrected Notifications England 1970: (1,255 cases)*

Age group	Meningococcus	Other Specified Organisms	Unspecified Organisms
All ages	494	353	408
0-	121	59	55
1-	67	32	24
2-	55	16	18
3-	29	27	15
4-	25	12	18
5-	64	65	82
10-	32	29	49
15-	50	33	60
25 and over	48	78	85
Unknown	3	2	2

*Extracted from the *Annual Report of the Chief Medical Officer of the Department of Health and Social Security for the year 1970.*

TABLE II—*Number of Cases of Bacterial Meningitis Reported 1967-71**

Bacterial Species	1967	1968	1969	1970	1971	Totals
Neisseria meningitidis	358	438	478	554	519	2,347
Haemophilus spp.	354	314	347	329	354	1,698
Pneumococcus	292	303	312	269	245	1,421
Escherichia coli	60	62	77	92	94	385
Mycobacterium tuberculosis	58	43	39	47	91	278
Staphylococcus spp.	33	59	60	60	52	264
Streptococcus spp.	36	44	38	47	50	215
Proteus spp.	20	42	36	20	26	144
Listeria monocytogenes	22	21	19	25	16	103
Pseudomonas spp.	24	17	25	22	13	101
Klebsiella spp.	10	10	12	14	17	63
Other coliforms	16	10	22	3	7	58
Other species	4	10	16	17	12	59
Totals	1,287	1,373	1,481	1,499	1,496	7,136

*Based on reports to the Public Health Laboratory Service quoted in the *British Medical Journal.*

Diagnosis

The diagnostic features of meningitis may show considerable variation with age and the nature of the infecting agent. Furthermore, the clinical features may be significantly suppressed by antimicrobial therapy introduced at an early, non-specific stage of the illness. It requires little clinical skill to recognize the mature picture of pyogenic meningitis, characterized by such features as unbearable headache, severe nuchal rigidity, opisthotony, delirium, and coma. Such an advanced case has already a diminished chance of survival and a significant risk of permanent cerebral damage.

Diagnosis, wherever possible, should be made early and the medical practitioner to this end must exercise his clinical acumen. The history in most cases will be brief, often lying between one and three days, though cases may be encountered where this period is as short as hours or as protracted as ten days.

The most common symptom, irrespective of age, is malaise soon followed by fever, headache, vomiting, and generalized aching. These features intensify and are joined by photophobia and alteration in the level of consciousness, manifested by increased irritability, restlessness, and delirium; thereafter progressive drowsiness and possibly coma set in. Nuchal rigidity and a positive Kernig's sign become more readily elicitable and further delay in diagnosis or treatment makes the occurrence of convulsions increasingly likely, together with focal neurological signs. The latter often present as paralytic squints, facial palsy, or hemiplegia.

The earliest signs of meningitis are quite non-specific and several conditions cause considerable confusion with their associated meningism. Among the most likely are tonsillitis, cervical adenitis, lobar pneumonia, pyelonephritis, bacillary dysentery, and hypernatraemic acidosis. Subarachnoid haemorrhage is usually distinguishable by its dramatic, clear-cut onset, while among rarer conditions causing confusion are epidural abscess and osteitis of the spine.

Many cases of meningitis may be said to be primary in the sense that no local focus of infection is found, but in others invasion of the meninges succeeds infection elsewhere in the body or results from a mechanical breach of the defence mechanisms. Hence it is important to inquire about—and to search for—such associated conditions as pneumonia, otitis, sinusitis, meningomyelocele, spina bifida, fracture of the skull, and less common primary sources of infection in the bowel, uterus, or kidneys.

Some types of meningitis merit particular emphasis and these include cases due to *N. meningitidis, S. pneumoniae, H. influenzae, Mycobacterium tuberculosis,* and neonatal infection.

MENINGOCOCCAL MENINGITIS

Meningococcal meningitis, the commonest type of pyogenic meningitis in the United Kingdom, is mainly a disease of young children but no age is immune (table 1). It is more likely to have special features than other forms of meningitis and the most important of these is the associated rash. This usually starts as fine, roseolar papules which rapidly develop into petechial or purpuric spots. These may only total 20 or 30 and have a haphazard, generalized distribution but there is some predilection for the eruption to occur around the pelvic or shoulder girdles. On occasion the rash is very profuse and associated with fulminating septicaemia (purpura fulminans); in this instance purpuric patches may take the form of irregular, flat ecchymoses with deep button-like induration, and some progress to frank ulceration. At the other extreme the rash may be very sparse and only show as an enanthem over the buccal mucous membranes or conjunctivae.

A clinical picture suggestive of pyogenic meningitis coupled with a haemorrhagic rash will usually add up to meningococcal infection though isolated examples are known where infection due to *S. pneumoniae* and *H. influenzae* have presented in this manner. Rashes are also encountered in some forms of aseptic meningitis due to picornaviruses, especially where Echoviruses type 4, 9, and 16 and certain Coxsackie A viruses are involved. These eruptions usually have a fine maculo-papular character but a petechial component may occur and cause confusion. The generally milder illness in these viral infections and the nature of the changes in the cerebrospinal fluid usually make differentiation quite clear.

Meningococcal infections may also cause focal lesions in the pericardium, eyes, joints, bones, or lungs. Furthermore, associated circulatory collapse may be present, and though this may indicate the dreaded complication of adrenal apoplexy (Waterhouse-Friderichsen syndrome), it may also be a manifestation of shock consequent to the severe toxaemia found in more serious cases.

H. INFLUENZAE MENINGITIS

The frequency of meningitis due to *H. influenzae* now ranks second to meningococcal infection in Britain though in some areas—including the United States—it is now the predominant aetiological agent. Though the prodromal illness may be quite brief, Haemophilus meningitis tends to evolve slowly and a week may elpase before definitive meningeal signs become apparent; not infrequently it occurs in the context of a respiratory tract infection—even when antibiotics are being used. It is essentially a disease of the infant and preschool child and cases in older children or adults are rare, probably reflecting a high incidence of Haemophilus type b antibody contracted through prior subclinical infection.

In recent years a higher incidence of septicaemic illness has resulted from infection with *H. influenzae,* usually an encapsulated typable strain and principally type b. Meningitis remains the most common single outcome but acute epiglottitis, osteomyelitis, pyarthrosis, pneumonia, empyema, cellulitis, and cardiac involvement may also occur—either individually or in association with meningeal invasion.

PNEUMOCOCCAL MENINGITIS

The introductory illness of pneumococcal meningitis is often longer than that of the meningococcal variety—extending over two or four, rather than one or two, days. Young infants and adults over 40 are most commonly involved and in the latter the illness can be dramatically sudden, to the extent that subarachnoid bleeding is suspected. Pneumococcal is the commonest type of pyogenic meningitis in British adults and certain predisposing, or associated, factors may be involved. These include fracture of the skull, less severe head injuries, chronic otitis media, sinus infection, and pneumonia.

TUBERCULOUS MENINGITIS

Tuberculous meningitis differs from the other types described in that a lymphocytic, rather than a pyogenic, meningitis is produced and by the less acute nature of tuberculous infection. It may well be possible to suspect the diagnosis before abnormal signs have developed; the illness often starts with an "influenzal-like" episode which fails to resolve and such an event in a patient who has a family contact with tuberculosis or in an immigrant (especially of Asian origin), should provoke a high index of suspicion. By the time these patients reach hospital the illness has often been present for two, or even three, weeks. Increasing drowsiness and mild neck stiffness have by then become apparent and signs of raised intracranial pressure soon follow. External ocular palsies are common, papilloedema is more likely than in pyogenic forms, and careful examination of the optic fundi may show choroidal tubercles.

While the history and physical findings may arouse the suspicion of tuberculous meningitis, examination of the cerebrospinal fluid is all important. Reported figures for bacteriological proof of this disease may be as low as 20-30% but more experienced laboratories can raise this figure to 80-90%. Nevertheless, in some instances treatment has to be started without this reassuring confirmation and in such cases the cytological and biochemical findings from examination of the C.S.F. will help, as may the finding of radiological signs of tuberculosis in the chest—e.g., a primary tuberculous focus or miliary mottling. Furthermore, most cases will have a positive tuberculin test, but this is not an exclusive feature and examples are on record where B.C.G. vaccination had been performed in earlier life. Recent reports indicate that additional diagnostic help in the difficult case may be provided by the bromide partition test.

NEONATAL MENINGITIS

Unfortunately the neonate shows a less dramatic and less specific response to meningitis than his older siblings or parents. The disease is most often encountered by paediatricians and especially by those working in special baby care units and in such centres as those dealing with spina bifida. Preceding septicaemia is usually present, often involving Gram-negative organisms or staphylococci. These bacteria are frequently hospital strains and may show significant resistance to antibiotics.

Nevertheless, cases do arise in the home and there is a wide range of possible presenting features. These include a reluctance to be handled, a reluctance to feed, repeated vomiting, gastro-enteritis, failure to thrive, sudden collapse, apnoeic attacks, hypothermia, head retraction, convulsions, persistent irritability, and a bulging anterior fontanelle This underlines the non-specific presentation and to some extent we must expect to admit many infants to hospital so that a lumbar puncture can exclude, or confirm, meningitis as the cause of illness. Such an approach seems fully justified in a disease with a potential mortality of 50-60%—especially as this figure can be appreciably lowered in specialized centres with unusual expertise in this field.

Diagnosis and Management

The definitive diagnosis and treatment of meningitis are essentially hospital exercises. The possible presentations of meningitis in general practice must be appreciated, as well as the dangers that result from the empirical introduction of antibiotic therapy in undiagnosed, febrile illness; should such a patient be developing meningitis the characteristic signs may be masked and the true diagnosis delayed. Undoubtedly some cases of partially treated, suppressed meningitis progress less well and empirical therapy used before diagnosis often makes an exact, aetiological diagnosis impossible in hospital. Trivial doses of antibiotics may result in negative smears of the cerebrospinal fluid and prevent the culture of the responsible organisms from this source as well as from the blood.

Patients with suspected meningitis should be admitted to hospital without delay as this disease constitutes a potential medical emergency. At hospital such cases must be expeditiously assessed and this concern must also be exercised by the laboratory staff. Estimates of the time interval between notification of a case of meningitis and the start of appropriate treatment sometimes show undue delay and every effort must be made to keep this interval to a minimum. Treatment is best introduced after the appropriate specimens have been taken for laboratory examination, but such an approach becomes invalid if undue delay occurs.

Specific Treatment

There is considerable diversity of opinion regarding the specific treatment of meningitis and in some varieties several alternative courses of action may provide equally satisfactory results. Nevertheless, certain principles remain paramount: wherever possible antibiotic treatment should be guided by the isolation of the responsible organisms, which should then be tested for their antibiotic sensitivity. Sometimes the latter is predictable but this is not necessarily true of such organisms as the coliforms and staphylococci. Knowledge of the chosen drug's ability to reach the C.S.F. is important and if the doctor has to use an agent with poor penetration its dosage and the route of administration may have to be adjusted. Many now consider intrathecal therapy unnecessary, and one should welcome the reduction in the use of this route of administration which has always provided some degree of risk. In some instances, however, antibiotic penetration is sufficiently poor to justify the continunace of intrathecal therapy at the acute stage of the illness. The exact duration of therapy is also somewhat controversial: too short a period may lead to relapse, whereas prolonged therapy may cause drug fever.

INDIVIDUAL INFECTIONS

Meningococcal Meningitis

Meningococcal meningitis is now best treated by penicillin alone. An increasing percentage of meningococcia (perhaps 9%) show significant resistance to the sulphonamides and if they are prescribed today penicillin should also be employed. Some clinicians favour ampicillin, but it has no advantage over penicillin itself.

H. influenzae Meningitis

Some years ago chloramphenicol became established as the treatment of choice for H. influenzae meningitis but the introduction of ampicillin, without any attendant risk of bone-marrow depression, stimulated a change to this form of therapy. However, many clinicians have been disappointed in its efficacy, coupled with the necessity for continuous parenteral administration, and have tended to revert to chloramphenicol.

Pneumococcal Meningitis

Penicillin remains the drug of choice for pneumococcal meningitis. Trials with tetracycline, chloramphenicol, and various drug combinations have shown poorer results than with penicillin alone, and, though cephaloridine shows promise, experience with it is still limited.

Tuberculous Meningitis

Standard combined treatment with streptomycin, isoniazid and para-amino-salicylic acid is still suitable for most cases of tuberculous meningitis and many experienced clinicians still favour the use of intrathecal streptomycin in the earliest stages. Drug-resistant acid-fast bacilli may be a problem and newer drugs such as rifampicin, ethambutol, and others may be indicated. Changes in the drug regimen may also be dictated by the development of hypersensitivity to the agents in use. Unlike pyogenic meningitis, where the course of treatment will usually be completed in one or two weeks, drug treatment of tuberculous meningitis should probably be continued for a minimum of two years.

Neonatal Meningitis

Probably the greatest therapeutic problems arise with this form of meningitis. Quite apart from the fact that a wide variety of bacteria is likely to be incriminated, antibiotic sensitivity is unpredictable with this group of agents and laboratory guidance is often paramount. Gram-negative infections are likely to predominate and among drugs employed are ampicillin, chloramphenicol, cephaloridine, kanamycin, gentamicin, and colistin. In staphylococcal meningitis cloxacillin provides the first-line treatment, though resistant strains may be encountered and alternatives such as cephaloridine may require to be used.

Combined, rather than single, antibiotic therapy is frequently preferred in treating neonatal meningitis and the agents used are often given by continuous infusion supplemented by intrathecal injection. The exact treatment employed depends very much on the preference and experience of the clinician.

No Organisms Isolated

Cases will arise where clinical and laboratory findings obviously point to pyogenic meningitis but no organisms can be isolated. After the neonatal period most cases are likely to result from the three common varieties of bacterial, or pyogenic, meningitis mentioned above. Thus antibiotic treatment should be selected with

these possibilities in mind and combinations such as chloramphenicol with penicillin are often successful. The problem is more complex in the neonatal period and in these circumstances paediatricians often favour some "triple antibiotic" combination in an attempt to produce cover for the wide spectrum of organisms that may be involved.

Supportive Treatment

NURSING

Skilled nursing is essential in meningitis for a variety of reasons—including the management of parenteral drug therapy and ensuring adequate fluid and electrolyte balance. Severe cases, often complicated by copious vomiting, will frequently require intravenous fluid therapy and such treatment is also mandatory when shock is present.

CONVULSIONS

Fits must be considered a potentially serious complication of meningitis and should be energetically suppressed. On occasion this may involve the use of anticonvulsant drugs before arrival in hospital and many clinicians employ these agents prophylactically in patients who have not yet had a convulsion. Personal preference often dictates the drugs employed though phenobarbitone is perhaps the most popular. However, this agent is not always effective and phenytoin provides a valuable alternative. Diazepam may also be used as an immediate choice in view of its rapidity of action.

CORTICOSTEROIDS

Corticosteroids may be used for a variety of reasons including their general anti-inflammatory action, for combating shock, and as replacement therapy when adrenal involvement is suspected in meningococcal disease. In general their value is not proved, but many paediatricians believe they have a valuable role in neonatal infection, when they may be given intrathecally as well as systemically. Some also advocate their routine use in tuberculous meningitis but others confine such therapy to cases with proved or threatened spinal block. Steroids have been used widely in meningococcaemia but their apparent success has often resulted from benefit to the associated shock rather than by influencing adrenal insufficiency. Indeed, in the latter situation there are at least theoretical grounds for believing steroids may predispose to further haemorrhage and that the underlying defect of disseminated intravascular clotting is better treated with heparin. Finally, severe and advanced cases of meningitis showing acute cerebral oedema may show significant improvement when dexamethasone is employed.

Complications

Most of the acute complications of meningitis are transient and respond to the basic treatment. More serious consequences do arise, such as acute obstructive hydrocephaly and subdural effusions.

The former may occur at any age and with any form of bacterial meningitis. Nevertheless, it is more common in neonates and where diagnosis and treatment have been delayed. When suspected, diagnostic tapping through the fontanelle or burr holes should be performed and where active infection is confirmed the local instillation of appropriate antibiotics is required while systemic treatment is maintained. More severe cases may require continuous external drainage by catheter. If obstruction remains after resolution of infection an appropriate valve will require insertion to produce permanent relief; either a ventriculo-atrial or a ventriculo-peritoneal shunt may be used, the latter having a lower incidence of complicating bacteraemia.

Subdural effusions (or subdural collections) seem more common than formerly and reflect the increasing incidence of Haemophilus meningitis, with which there is a clear association, as well as with inadequate treatment—which is also a predisposing factor. This complication usually responds to frequent subdural tapping but the later removal of scar tissue is sometimes required.

Other complications include cortical thrombophlebitis, venous sinus thromobosis, deafness, visual impairment, epilepsy. and mental insufficiency. Some of these may become apparent only after a latent interval and careful follow-up of meningitis cases is desirable. Children should be placed on an "at risk" register so that health departments may pay particular attention to their progress and discover any scholastic handicap at an early stage.

Prophylaxis

Relatively few types of bacterial meningitis are communicable and the routine treatment of contacts is not widely employed in this country, though it is usually practised in North America. Meningococcal infection provides the greatest danger, and prophylaxis among contacts merits consideration. Where several cases are shown to have a common factor, such as children from the same school, and where parents show understandable anxiety about spread to siblings, chemoprophylaxis should be used.

Despite a small percentage of meningococci in this country being resistant to the sulphonamides, this remains the best empirical choice and only three days' treatment will usually clear a carrier state. Nevertheless, if sulphonamide resistance is present, the use of alternatives such as penicillin has proved disappointing though recent reports indicate that rifampicin is promising. It is unusual to find secondary cases of Haemophilus meningitis in contacts but if there are any particular anxieties in any individual context a short course of chloramphenicol or ampicillin would seem desirable.

Chemoprophylaxis of other forms of meningitis is not normally required, though in recurrent meningitis this may be considered. The pneumococcal variety is the most common, and continuous prophylaxis with penicillin has been tried with apparent success.

General Prevention

As many of the agents responsible for bacterial meningitis are commensals, particular preventative measures are wellnigh impossible. However, most cases in Britain follow infection by one or other of three main organisms and specific prevention certainly merits consideration. The existence of numerous types of pneumococci are an obvious difficulty with this organism, and meningococci are also subdivided into several different groups. Attempts have been made to produce group-specific meningococcal vaccines and some success has followed the use of the group C variety; this certainly seems a field where further research might be valuable. In theory *H. influenzae* infection would seem to provide the most fruitful field for immunization, as only Pittman type b is involved. Nevertheless, the results of limited work in preparing Haemophilus vaccines for use in chronic respiratory disease have been disappointing.

In conclusion, it would be wrong to forget that before the introduction of sulphonamides bacterial meningitis virtually amounted to a death sentence, and today the prognosis is unbelieveably better. Nevertheless, the continuing mortality and morbidity remain challenges and undoubtedly the extent of the problem could be better appreciated if all types of acute meningitis were conscientiously notified.

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