THE DIAGNOSIS AND TREATMENT OF ACUTE MENINGITIS, EXCLUDING TUBERCULOSIS, IN INFANCY AND CHILDHOOD*

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SUMMARY

A retrospective study is made of 376 case records of acute non-tuberculous meningitis in infants and children admitted during 1967 to the Emergency Ward at the Red Cross War Memorial Children's Hospital, Cape Town, with regard to aetiology, incidence, diagnosis, and results with standard triple therapy. Specific diagnostic problems, with the emphasis on early diagnosis, and general therapeutic measures, are discussed. In addition, the use of ampicillin in the treatment of acute bacterial meningitis is reviewed.

Epidemic meningitis with a rash of 'purple spots' was clearly described by Vieussieux[1] following an outbreak in Geneva in 1805. But it was not until 1886 that causative organisms were first isolated from the cerebrospinal fluid.[2] Despite this advance, bacterial meningitis remained almost uniformly fatal until the discovery, in 1935, of the sulphonamides, which were especially effective against the meningococcus.[3] Since then, the mortality rate has fallen considerably as first penicillin, and then chloramphenicol, were found to penetrate the blood - brain barrier. In the last decade, however, the mortality rate, especially in infants, has not been significantly lowered in spite of improved diagnostic procedures and broad-spectrum chemotherapeutic regimens.[4-10]

In 1967, 666 patients were admitted to the emergency ward at Red Cross War Memorial Children's Hospital, Cape Town, with the initial diagnosis of meningitis. Of these, 376 case records, excluding those of tuberculous meningitis, were traced and this article is a retrospective assessment of diagnostic criteria and the efficacy of standard treatment of all types of acute non-tuberculous meningitis at this hospital during 1967.

AETIOLOGY

Of the 376 case records studied the 3 main organisms isolated from the cerebrospinal fluid (CSF) were *Neisseria meningitidis* (126), *Haemophilus influenzae* (28), and *Diplococcus pneumoniae* (23). In 187 cases no evidence of bacteria, not even on stained smear of centrifuged sediment, was found. Of this unknown group, 114 were suspected to be aseptic meningitis, either on clinical evidence and/or the finding of a suggestive CSF (normal sugar with or without normal protein and cell content) or in retrospect by their clinical course. The remaining undiagnosed 73 had frankly purulent spinal fluids. Since diagnostic isolation of viruses from cerebrospinal fluid is not undertaken at the Red Cross Hospital, the unknown group will be regarded as 'unknown aseptic' and 'unknown purulent' if merely to aid discussion and illustrate a few points.

More unusual organisms isolated were: Salmonella BO species (2), *Escherichia coli* (3), *Staphylococcus aureus* (2), *Klebsiella pneumoniae* (1), Torula (1), *Listeria monocytogenes* (1) and 2 cases of cerebral vein thrombosis yielded a CSF imitating meningitis.

*Date received: 19 February 1971.

AGE, SEX AND SEASONAL INCIDENCE

Age

Meningitis was commonest between 2 months and 1 year of age (39%); other age groups being more or less equally affected (Table I).

TABLE I. AGE: SEX DISTRIBUTION

	Male		*Female*		
Age	*No. of cases*	*Deaths*	*No. of cases*	*Deaths*	*Total deaths*
<1 month	9	1	—	—	1
2 months - 1 yr	114	6	31	4	10
1 - 3 years	46	—	24	1	1
3 - 5 years	58	1	26	1	2
6 - 10 years	36	1	28	1	2
>11 years	2	—	2	—	—
Total	265	9 (3·4%)	111	7 (2·4%)	16 (4·3%)

Meningococcal meningitis was not as common in infants (90% over the age of 3 years) as were influenzal meningitis (76% under 1 year) and pneumococcal meningitis (53% under 1 year). Surprisingly, the unknown aseptic group also showed a high predilection for infants (56%),[11-13] but this may reflect the diagnostic difficulties in the very young leading to empiric antibiotic use before lumbar puncture,[14] resulting in a sterile CSF. Few cases over the age of 10 years were found.

Neonatal cases were frequently associated with abnormalities in labour. Three of these patients could not be followed up owing to insufficient data.

Sex

Over-all, the disease favoured males (7:3). This difference was less marked in meningococcal (3:2), but more noticeable in *Haemophilus influenzae* (4:1) and in patients under 1 year of age (4:1). The susceptibility of the male infant to infection is well documented.[15]

Seasonal Incidence

Of the meningococcal cases, 71% occurred between June and October (winter months). Aseptic meningitis was more common between September and February (summer months). The increase in meningococcal cases towards the end of winter,[4,5] presumably due to concomitant upper respiratory infection, and the viral incidence in summer and autumn,[11,13,16] is shown in Fig. 1.

DIAGNOSTIC CRITERIA

Clinical Evidence

'The signs and symptoms of meningitis occur not only as a result of the meningeal inflammatory reaction but also because of the local process from which invasion of the pia-arachnoid arises, from the occasional focal or diffuse cerebral injury and from the systemic response to infection'.[9]

Symptoms[3-5,7,10,11,13,16-18]

The relative frequency of symptoms and signs found in the various groups is tabulated in Tables II and III.

The average duration of symptoms before admission was 2½ days. In 50% of cases the onset was so acute that symptoms had lasted 24 hours or less. The most common symptoms occurring in all groups were nausea, vomiting (often producing a worm), fever, convulsions, headache, irritability and cough. Other symptoms were variable, occurring with more or less equal frequency and indicating either meningeal, cerebral or systemic involvement.

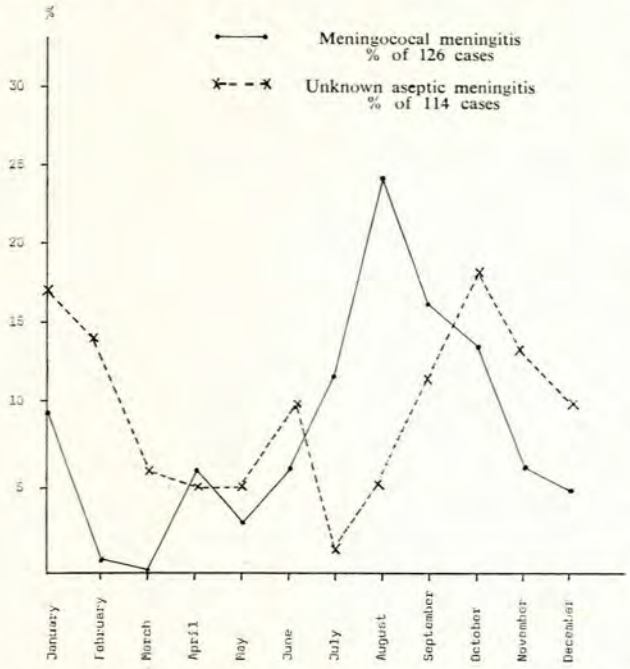

Fig. 1. Seasonal incidence of meningococcal and unknown aseptic meningitis (January - December 1967).

TABLE II. SYMPTOMS IN NON-TUBERCULOUS MENINGITIS

Symptoms	*Total % of 376 cases*	*Meningococcal % of 126 cases*	*Unknown aseptic % of 114 cases*	*<1 year % of 145 cases*
Nausea and vomiting	52	44	50	35
Fever	42	23	38	44
Convulsions, fits	24	6	17	33
Headache	23	30	17	
Irritability	21	8	25	34
Cough	21	28	25	25
Anorexia/ refusing feeds	16	7	15	19
Diarrhoea	15	6	16	21
Stiff neck or back	14	9	15	11
Joint or body pain	9			
Drowsiness or apathy	8			
Becoming stiff or limp	6			
Confusion	5			
Photophobia	4			

Headache was not as common as expected, although found slightly more often in meningococcal meningitis and usually of increasing severity, radiating from a frontal or diffuse localization into the neck and back.[18] Obviously, headache appeared to be more common in those children old enough to complain.

TABLE III. CLINICAL SIGNS IN NON-TUBERCULOUS MENINGITIS

Signs	*Total % of 376 cases*	*Meningococcal % of 126 cases*	*Unknown aseptic % of 114 cases*	*<1 year % of 145 cases*
Neck stiffness	64	84	43	55
Positive Kernig's sign	31	39	21	22
Irritability, apathy or drowsiness	30	24	25	38
Bulging fontanelle	19	—	19	44
Positive Brudzinski sign	17	27	13	15
Rash	14	24	10	11
Doubtful neck stiffness	13	6	7	20
Dehydration	10	8	11	
Coma, convulsions, fits	9	4	7	
Impaired consciousness	7	14	2	
Abnormalities of reflexes, tone or paralysis	7	8		
Abnormalities of cranial nerves	6	5		
Otitis media	6	8		
Photophobia	5	7		

Irritability and convulsions were often seen in infants, the former expressed as resentment of handling; the latter anything from a rolling up of the eye-balls or a twitching limb to a grand-mal seizure.

Cough preceded the onset of meningitic symptoms, often by as much as a week.

The suspicious triad in infants[10] of fever, vomiting and irritability with no other signs was found in one-fifth of cases and convulsions alone were found in one-tenth of the infants.

Photophobia, confusion, drowsiness and coma were important, if uncommon, symptoms of cerebral involvement.

Signs

The classical picture of an opisthotonic child, lying turned away from the light, with neck and back extended, knees flexed and drawn up to his body, resenting interference and covered in petechiae,[3] was not often seen.

Neck stiffness was the most frequent sign and may be graded 'terminal' (doubtful), 'definite' and 'with neck retraction' (this is arbitrary although meningitis is believed to progress through these stages).[3,18]

Positive Kernig's sign[19] was seen in one-third of cases but, though more common than Brudzinski's sign, was probably sought more often. Irritability, apathy and drowsiness (30%) were frequently found.

Meningococcal cases usually showed 'definite' neck rigidity, but in a significant number of cases, commonly of the fulminating variety, neck stiffness was absent.

Cerebral involvement was not often recorded, although this may reflect the fact that when the emphasis was on urgent treatment for the acutely ill child, careful records were not made.

Unknown aseptic cases appeared milder, presenting more diagnostic problems—mild or doubtful neck stiffness and irritability were often the only signs.

In infants, neck stiffness was difficult to evaluate but was nevertheless found in 55% of cases. Kernig's and Brudzinski's signs were unreliable and definitely present in fewer cases. Irritability was common. In this group a bulging fontanelle was a frequent indication of meningitis. (Table III.)

CEREBROSPINAL FLUID

Lumbar puncture was performed on admission in suspected cases of meningitis and when diagnosis was in doubt. A subsequent lumbar puncture after a 48-hour interval was used to assess treatment and to follow the course of the disease. In 14 cases the cerebrospinal fluid was sterile and its chemistry normal. One case showed an essentially normal fluid but meningococcus was cultured. The CSF in 14 cases was of little value owing to faulty technique (bloody tap).

Concomitant blood cultures and blood sugar levels are not performed as a routine at the Red Cross Hospital.

Sugar Levels

This study supports the view that the absence of sugar in the CSF is pathognomonic of *bacterial* meningitis, but that a normal CSF sugar level does not exclude it. It appears that altered brain metabolism in the presence of both bacteria and pleocytosis in the CSF is responsible for the reduction in sugar,[20] although Cooper *et al.*[21] described decreased influx of sugar into the CSF and increased utilization by cells and organisms in experimental pneumococcal meningitis.

A total of 61% (77 cases) of meningococcal meningitis, 43% (12 cases) of influenzal meningitis and 50% (10 cases) of pneumococcal meningitis showed no evidence in the CSF of sugar while the corresponding figures for normal sugar levels were meningococcal 11% (14 cases), influenzal 14% (4 cases) and pneumococcal 25% (5 cases). None of these cases received treatment before lumbar puncture.

In the unknown aseptic group, on the other hand, 99% of cases had a normal sugar level, the remaining 1% showing a raised CSF sugar.

Of interest is the large number of cases showing normal CSF sugar levels in the unknown purulent group. This could illustrate the dangers of indiscriminate use of antibiotics before lumbar puncture, leading to a mild, sterile CSF and delayed diagnosis,[22] although Dalton[24] found, in a controlled study, that CSF chemistry was not materially altered by previous antibiotic treatment (Table IV).

TABLE IV. CSF SUGAR LEVELS*

	Sugar level				
Aetiology	*Increased*	*Normal*	*Slightly decreased*	*Decreased*	*Absent*
Meningococcal (% of 126 cases)	—	11	9	19	61
Unknown aseptic (% of 114 cases)	1	99	—	—	—
Unknown purulent (% of 70 cases)	2	38	8	35	17
H. influenzae (% of 28 cases)	—	14	14	29	43
D. pneumoniae (% of 20 cases)	—	25	—	25	50

*Normal range, dependent on blood sugar level = 40 - 75 mg/100 ml

Cell Counts

Bacterial meningitis in most cases, but not exclusively, caused a polymorphonuclear pleocytosis above 500 cells/mm³. If lymphocytes were also found, and this was common, they never amounted to more than 30% of the total cell count. In the unknown aseptic group the pleocytosis was invariably mixed, polymorphonuclear cells only occasionally predominating exclusively in the more acute cases. Lymphocytes predominated in 40% of cases in the unknown aseptic group. The total number of cells rarely (3%) exceeded 500/mm³ in this group (Table V).

TABLE V. CSF CELL COUNTS

I. **Polymorphs**

	No. of cells/mm³							
Aetiology	*⩽10*	*10 - 50*	*50 - 100*	*100 - 250*	*250 - 500*	*500 - 1 000*	*1 000 - 3 000*	*3 000 - 20 000*
Meningococcal (% of 126 cases)	—	2	—	3	6	19	34	36
Unknown aseptic (% of 114 cases)	22	33	24	13	5	1	2	—
Unknown purulent (% of 70 cases)	2	4	3	8	23	26	28	6
H. influenzae (% of 28 cases)	—	3	4	11	29	14	25	14
D. pneumoniae (%of 20 cases)	—	—	5	15	—	40	25	15

II. **Lymphocytes**

	No. of cells/mm³						
Aetiology	*⩽10*	*10 - 50*	*50 - 100*	*100 - 200*	*200 - 300*	*>300*	*>600*
Unknown aseptic (% of 114 cases)	47(4)*	24(12)	9(6)	11(9)	4(4)	5(5)	
Meningococcal (% of 126 cases)	<30% total cell count if present						

*Figures in brackets represent % of 114 cases showing lymphocyte predominance.

TABLE VI. CSF PROTEIN LEVEL*

Aetiology	Protein level mg/100 ml							
	⩽10	10 - 20	20 - 40	40 - 80	80 - 150	150 - 300	300 - 600	>600
Meningococcal (% of 126 cases)	1	3	2	11	23	38	18	4
Unknown aseptic (% of 114 cases)	38	21	21	10	7	3	—	—
Unknown purulent (% of 70 cases)	3	4	18	19	23	25	8	—
H. influenzae (% of 28 cases)	—	—	18	32	14	18	14	4
D. pneumoniae (% of 20 cases)	—	—	—	20	25	40	15	—

*Normal range = 10 - 45 mg/100 ml

Protein

In this study a CSF protein level above 80 mg/100 ml suggested bacterial meningitis (83%), whereas a level below 80 mg/100 ml indicated aseptic meningitis but these criteria were not infallible (10% aseptic cases were above 80 mg while 17% meningococcal cases had levels below 80 mg and 6% were normal). There was no correlation between protein, cell count or sugar levels, nor between CSF picture and prognosis (Table VI).

Globulin (normally absent)

This parameter was found to be useful, tending to parallel the protein rise, but not always (Table VII).

TABLE VII. GLOBULIN

Aetiology	Amount present measured as degree of flocculation					
	Absent	±	+	++	+++	++++
Meningococcal (% of 126 cases)	3	8	31	31	22	5
Unknown aseptic (% of 114 cases)	68	14	16	1	1	—
Unknown purulent (% of 70 cases)	6	30	32	20	12	—
H. influenzae (% of 28 cases)	22	15	45	10	8	—
D. pneumoniae (% of 20 cases)	10	10	35	35	10	—

Bacteriology

(*a*) *Culture.* No organisms could be cultured after 48 hours growth in 214 cases (57%); the apparent reasons being (*i*) viral aetiology, (*ii*) previous treatment, (*iii*) delay in transport of specimen to laboratory, and (*iv*) faulty lumbar puncture (bloody tap).

(*b*) *Stained smear* of the centrifuged CSF sediment showed organisms in 140 cases (26%) with 95% accuracy. False interpretations were due either to unusual organisms (torula resembling Gram-negative bacillus) or faulty staining.

(*c*) *Other cultures.* Blood culture at the height of fever, culture of a scraping of a petechial rash and throat and nasal swab cultures were not performed frequently enough to be of value statistically, but were occasionally useful in cases of doubtful aetiology.

TREATMENT

Treatment of non-tuberculous meningitis at the Red Cross Hospital is standard. Immediate intrathecal injection of 5 000 - 10 000 IU of crystalline penicillin was given at lumbar puncture if the CSF was abnormal. This was followed by intravenous penicillin, chloramphenicol, and sulphisoxazole (Gantrisin) for at least 48 hours. When clinical improvement was evident, intravenous therapy was discontinued and replaced by oral chloramphenicol and sulphisoxazole with intramuscular penicillin for 7 - 10 days.

When the causative organism was known, one drug, determined by sensitivity tests, was dropped or specific antibiotic therapy was added, if necessary.

Neonatal meningitis (0 - 3 months of age) was treated mainly with kanamycin and penicillin but streptomycin and chloramphenicol were often used in addition.

Summary of Treatment

Intrathecal injection stat: 5 000 - 10 000 IU penicillin; intravenous: (crystalline) penicillin 2 000 000 IU 6-hourly, chloramphenicol 80 mg/kg/day, sulphisoxazole 180 mg/kg/day; oral: chloramphenicol 80 mg/kg/day, sulphisoxazole 180 mg/kg/day; intramuscular injection: (procaine) penicillin 20 000 IU/kg/day.

RESULTS (OF 376 CASES)

In a review of 6 000 cases in the literature (1955 - 65) Rose and Condon[5] gave average mortality figures of 10% for meningococcal meningitis, 40% for pneumococcal meningitis and 15% for influenzal meningitis. The average mortality from neonatal meningitis was as high as 60%.

This study (Tables VIII and IX) demonstrates that although pneumococcal and influenzal meningitis were most often fatal and resulted in the highest number of complications, the results, especially for pneumococcal meningitis, compare very well.

TABLE VIII. MORTALITY BY AETIOLOGY (376 CASES)

Aetiology	Mortality	
	No.	%
Meningococcal	3	2·4
Unknown aseptic	2	1·8
Unknown purulent	5	6·8
Influenzal	2	7·3
Pneumococcal	3	13·0
Salmonella BO	1	50·0
Total	16	4·3

In the unknown purulent group, mortality was comparatively low, but complications were common.

The low incidence of death in meningococcal meningitis compares favourably with other series. A mortality under 2% has been achieved during epidemics, albeit in fit,

TABLE IX. COMPLICATIONS BY AETIOLOGY (376 CASES)

Aetiology	*Complications (No. of cases)*					
	Hydro-cephalus	*Subdural effusion*	*Neuro-logical deficit*	*Recurrent meningitis*	*Nerve deafness*	*Spast-icity*
Meningococcal	—	—	—	—	—	1
Unknown aseptic	—	—	2	1	—	—
Unknown purulent	2	3	—	3	1	—
Influenzal	3	1	1			
Pneumococcal	1	1	1			
Total	6	5	4	4	1	1

healthy army recruits.[23] Complications due to infection by this organism are uncommon.

Hydrocephalus was most frequently found as a complicating feature, especially in *Haemophilus influenzae* infections. Subdural effusions, neurological deficiencies, recurrent meningitis and occasionally complete nerve deafness or spasticity were also encountered.

Associated Factors

An associated upper respiratory tract infection or gastro-enteritis were each found in 10% and pneumonic infection in 12% of all cases. Common misdiagnoses were measles, papular urticaria and chicken pox in cases of rash, bronchopneumonia, influenza, gastro-enteritis, tetanus and malnutrition.

Factors Predisposing to Death

In all except 3 cases the patients died less than 24 hours after admission; most of these died within 12 hours of the initiation of treatment.

In 11 fatal cases convulsions occurred, 3 patients were in coma and 2 more were confused.

In fatal cases of pneumococcal meningitis, pneumonia was a constant finding.

Two patients, labelled aseptic meningitis died, but in both autopsy revealed other causes of death.

Males were more susceptible if less than 1 year old.

Otitis media was found in two-thirds of fatal cases.

SUMMARY OF RESEARCH FINDINGS

A specific aetiological organism could not be isolated in 50% of cases. In 30% of cases in aseptic meningitis was suspected. *Haemophilus influenzae* and *Diplococcus pneumoniae* predominated in meningitis cases under 1 year of age, whereas more unusual organisms tended to cause meningitis in neonates. Meningitis was commonest in males less than 1 year old. Symptomatology and clinical signs of meningeal irritation were not invariable manifestations of meningitis and were less marked in meningitis of suspected viral aetiology and presented less reliably in infants and neonates. Examination of the cerebrospinal fluid was invaluable in the diagnosis of meningitis, although CSF chemistry was normal in a significant number of cases. The incidence of mortality and complications with conventional triple therapy was found to compare favourably with other series. Mortality was highest in infants under 1 year of age and fatal cases were frequently associated with either an acute onset, convulsions or some underlying disease.

Diagnosis and management will be discussed.

DISCUSSION

Bacterial meningitis remains a disease with a significant mortality rate despite advances in diagnosis and treatment. Since antibiotics now in use are known to be capable of sterilizing the cerebrospinal fluid, factors other than unchecked infection are thought to be responsible.[24] Delay in diagnosis, the presence of associated disease,[7] the route of drug administration and drug antagonism,[25-27] relative immunological incompetence (as seen in neonates[28] and infant males[15]), the deleterious effects exerted within the rigid confines of the cranial cavity by the inflammatory exudate itself,[29,30] and acute intrathecal hypersensitivity to bacterial products[30,31] have all been implicated at one time or another to account for this persistent mortality.

Good results obtained in this study with conventional triple therapy and intrathecal penicillin, however, may indicate the awareness at the Red Cross Hospital of the problem of meningitis and its treatment, since it is a common disease among Cape Coloured people.

The essence of successful management of bacterial meningitis lies in early diagnosis, early and intensive chemotherapy, and thorough treatment of complications.[15]

EARLY DIAGNOSIS

Examination of the spinal fluid is the only method for immediate confirmation of the diagnosis.[32]

Steps in Examination of Spinal Fluid in Meningitis

(*i*) Intrathecal pressure recording, (*ii*) appearance, (*iii*) immediate microscopical examination of Gram-stained, air-dried loopful of uncentrifuged cerebrospinal fluid, (*iv*) cell count and differential analysis, quantitative glucose and protein determinations, (*v*) examination of Gram- and acid fast-stained centrifuged sediment and also a wet preparation for yeast forms, unstained or with methylene blue or India ink; and (*vi*) culture of centrifuged sediment on heart infusion and chocolate agar, in nutrient broth and thioglycollate (for anaerobic and micro-aerophitic bacteria), also Saboraud's medium for fungi, Lieuwenstein's medium for *Mycobacterium tuberculosis.*

Lumbar Puncture

Lumbar puncture should be performed in all cases where meningitis is suspected clinically and in infants and children with unexplained pyrexia, irritability or vomiting.[33] A history of a convulsion in a child should not be attributed to fever or epilepsy before lumbar puncture has excluded meningitis.[34]

Technique.[32] An examination of the optic fundi should precede lumbar puncture. The presence of papilloedema

should alert the physician to the dangers of lumbar puncture when intracranial pressure is raised. After adequate skin preparation the patient should be restrained firmly with knees drawn up in the right lateral decubitus, or sitting, position. The bore of the needle should be parallel with the trunk in order to minimize dural tear.

Problems encountered include: (*i*) a dry tap—this may indicate epidural abscess or some other obstruction or merely that the needle has been inserted too far down the spinal cord,[35] (*ii*) gelatinous fluid with a few elliptical cells —this represents fluid from the nucleus pulposus rather than spinal fluid, and (*iii*) blood in the first part of fluid withdrawn—this indicates rupture of a blood vessel (bloody tap). Results should be interpreted with caution if erythrocytes are seen in the cerebrospinal fluid specimen.[35] It is imperative that spinal fluid pressure be recorded and the flow carefully controlled during collection.

Unfortunately a lapse of from 1 to 2 days may occur before a definitive bacteriological laboratory report is available. For this reason antimicrobial therapy (*vide infra*) is usually initiated until the drug of choice can be determined. If the cerebrospinal fluid is abnormal (hazy or purulent) or if the child is acutely ill with obvious clinical meningitis, intrathecal kanamycin or penicillin may be administered at lumbar puncture.

Smear

Stained smear of the centrifuged CSF sediment as used in most hospitals for diagnosis was frequently found unsatisfactory by Biegeliesen *et al.*[36] due to the small number of organisms (as in meningococcal meningitis) or due to misinterpretation of the shape or staining characteristics of organisms. Over- or under-decolorization during the staining process may also be misinterpreted and yeasts may be mistaken for bacteria. Although Biegeliesen[36] and Fox[37] recommend, as a rapid screening test, fluorescent antibody techniques, which they found to be more sensitive and specific than Gram-stained smears and of the same order of sensitivity and specificity as bacterial culture, Wehrle *et al.*[17] maintain that conventional methods, in the hands of experienced laboratory technicians, are of sufficient value. Fluorescent microscopy has also been reported useful in identifying fungi[30,37] and viruses[38] and is of special use for aetiological confirmation of infection in which antimicrobial therapy has preceded lumbar puncture.[37] However, it is at present only available in a few special centres.

Chemistry

Beck *et al.*[39] report accurate results for the assessment in the ward of CSF protein levels with a reagent strip. Sugar levels estimated by this method were less reliable, but indicated whether sugar was present or absent. Pandy's test for globulin and Benedict's reagent for sugar may also give rapid quantitative information of CSF chemistry.

Gram stain of petechial smears, 1 (and preferably 2)[32] blood cultures, throat and nasal swab cultures and blood for sugar estimations should all be taken before instituting therapy.

Following the steps set out on p. 690 and in Table X, few cases of meningitis due to the more common organisms should escape diagnosis.

TABLE X. DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN MANAGEMENT OF MENINGITIS IN INFANTS AND CHILDREN

Diagnostic procedures	*Therapeutic procedures*
Complete history	Initiation of antimicrobial therapy
Physical examination	Isolation
Neurological examination	Maintenance of optimum hydration and electrolyte balance
Lumbar puncture and cerebrospinal fluid studies	Maintenance of ventilation
Bacteriological studies of CSF, blood, skin lesions, nasopharynx	Reduction in increased intrathecal pressure
Blood glucose estimation	Management of bacteraemic shock
	Control of seizures
	Control of extremes of temperature
	Correction of anaemia

DIAGNOSTIC AND THERAPEUTIC PROBLEMS

Neonatal and Infantile Meningitis[32]

This is the greatest period of risk for bacterial meningitis. Neonates are susceptible to a wide variety of organisms. Gram-negative organisms are commonly found under 3 months of age whereas *Haemophilus influenzae*, and less often *Diplococcus pneumoniae*, predominate in meningitis in infants.

Signs of meningeal irritation are often minimal or absent, but neck rigidity may be recognized earlier in the disease if the child is seated with his legs outstretched when flexion of the neck is attempted. The infant appears fretful and is often anorectic. Frequent stroking of the head or a frown are characteristic counterparts of headache in an infant. Vomiting appears early and ensuing dehydration is likely to prevent the appearance of a full fontanelle until late in the course of the disease. Fever is often absent; indeed, a subnormal temperature may indicate the poor circulation of bacteraemic shock.

The examination of the patient should include a careful search for otitis media, pneumonia and signs of other foci of infection.

Unidentified Organisms

Viral meningitis (meningo-encephalitis)[12] was suspected in 114 of the 187 cases in this study when no organisms were found in the CSF. Grounds for suspicion were a mild clinical course with varying emphasis on meningitic or encephalitic signs, and CSF profile of aseptic meningitis (normal sugar level and mixed pleocytosis with lymphocyte predominance—except in the early stages of the disease). In several instances associated viral syndromes were recognized (post-infectious encephalomyelitis, mumps, infectious mononucleosis, poliomyelitis). However, a differential diagnosis of viral meningitis should include[12] tuberculous meningitis, neighbourhood syndrome, leptospirosis, and infections due to *Mycoplasma pneumoniae*, torula, and *Listeria monocytogenes*. Partially-treated or early bacterial meningitis[12] may also stimulate the aseptic CSF profile of meningitis and for this reason all meningitides of indeterminate origin should be treated initially as bacterial meningitis (*vide infra*).

Various deleterious or beneficial effects[25] have been ascribed to empiric antibiotic therapy before examination of the spinal fluid. The fact remains that it does considerably delay the diagnostic process in some instances[34] and treatment should only be instigated before lumbar puncture if time is of the utmost importance, and then treatment should be comprehensive and thorough.

Fulminant Cases

In this study, 13 out of the 16 patients who died, succumbed within 24 hours of admission and most of these died within 12 hours of starting therapy. Convulsions[8] were a bad prognostic sign. Garrod and O'Grady[25] report other features associated with a bad prognosis including hyperacute onset (12 hours or less), coma, and absent cerebrospinal-fluid sugar.

It appears that in some instances the patient is overwhelmed by an infection before therapy can become effective. It is important, therefore, to recognize both the urgency of such cases and the danger signs listed above. Overwhelming septicaemia associated with meningitis is most commonly due to meningococcae,[40] although other organisms may be responsible (including *Haemophilus influenzae, Diplococcus pneumoniae, Staphylococcus aureus* and Gram-negative bacilli).[17] The characteristic petechial rash is more common in fulminating meningococcaemia than in the average case of meningococcal meningitis. However, 5 different types of rash (ranging from a morbilliform rash early in the disease to large ecchymoses) have been described during the bacteraemic phase of meningococcal disease.[32] In addition, petechiae have been described in meningitis due to other organisms.[32,40]

Prompt recognition of bacteraemic shock[32,40,41] is as essential as is the intravenous administration of plasma volume expanding fluids and isoprenaline in its treatment. Pharmacological doses of glucocorticoids may be used, although clinical proof of their efficacy is lacking.[42] Central venous pressure monitoring is essential in the presence of an unstable blood pressure.

Glynn-Jones[40] points out the discrepancy of attributing collapse in meningococcal septicaemia to adrenal failure (the 'largely abandoned' Waterhouse-Friderichsen syndrome), since adrenal function has been found to be adequate in such cases, and ablation of the adrenals does not ordinarily cause immediate collapse. He describes, in addition, two theoretical mechanisms of septic shock (vasoconstriction and vasodilatation) as predominating at different times and discusses the possibilities in treating each.

Mathies *et al.*[17] however, emphasize the rare but possible occurrence, in meningococcal disease of intra-adrenal haemorrhage. The administration of glucocorticoids, in an attempt to raise low plasma cortisol levels reported in these patients, has yet to be proved beneficial.

ANTIMICROBIAL THERAPY

It was general practice before the advent of ampicillin[43] to begin treatment of purulent meningitis with a combination of penicillin, chloramphenicol and sulphonamide[25] (either sulphadimidine or sulphadiazine—which penetrates into the CSF more readily than sulphadimidine but is more liable to cause crystalluria). One of these agents is dropped when bacteriological diagnosis has been made. Otherwise triple therapy is continued for 2 - 4 days after clinical recovery (usually not more than 10 days).

Two factors[25] thought to be responsible for consistent failure rates with triple therapy have been antagonism between pairs of simultaneously administered drugs,[26,27] and failure to administer drugs intrathecally thereby failing to achieve the requisite high concentrations in the CSF.

Ampicillin in high dosage intravenously[17,35,44] is presently being favoured in treatment of meningitis before definitive diagnosis can be made. This follows reports that ampicillin (*a*) penetrates, with facility, the blood-brain barrier producing sufficiently high CSF concentrations,[45] (*b*) clears the CSF more rapidly and consistently than triple therapy,[45] (*c*) is as effective as penicillin against both meningococcae and pneumococcae and is less toxic than sulphonamides,[25,32,41] (*d*) is as effective as and less toxic than chloramphenicol in treating *Haemophilus influenzae* infections,[44,46-48] and (*e*) obviates the possibility of drug antagonism[27,48] that may occur with penicillin and chloramphenicol.

Recently published reports[49-51] describe isolated cases of persistent or recurrent meningitis due to *Haemophilus influenzae* (type B) during ampicillin therapy. Mathies *et al.*[46], however, have encountered no such cases in their experience with ampicillin. It appears that two factors[52] may be responsible for relapse:

1. Failure to achieve[51] or maintain[50] adequate cerebrospinal-fluid levels of ampicillin. CSF ampicillin levels[45] are dependent on dosage, route of administration and the degree of inflammation of the meninges (i.e. previous antibiotic treatment or advanced stages of the disease[44] may decrease the penetration into the CSF of ampicillin, secondary to decreasing the inflammatory exudate).
2. Residual sequestration[40] into foci (e.g. the ethmoid sinus) where the organisms cannot be reached by the antibiotic and from where they may recede into the blood stream.

Yow[44] stresses, however, that relapse in *Haemophilus influenzae* meningitis has been reported during other antibiotic regimes and that no resistance to ampicillin of *Haemophilus influenzae* has been established. Ampicillin in high doses intravenously remains the treatment of choice in meningitis due to *Haemophilus influenzae*. Undue alarm may be caused by apparent resistance[44] of the organism to ampicillin when tested by the disc method rather than the more reliable tube-dilution technique.

Sulphonamides are being discarded following reports of the growing incidence in the number of meningococcae resistant to the drug.[27]

Experiments with enzymes in an attempt to reduce intrathecal exudation have been disappointing.[25] Glucocorticoids have no value in the treatment of bacterial meningitis,[53,42] except perhaps in cases where Waterhouse-Friderichsen syndrome is recognized. They have been reported useful in aseptic meningitis.[54]

Route of Administration

Dowling *et al.*[55] demonstrated that choice of antibiotic, dosage used and route of administration could all influence the outcome of the disease.

TABLE XI. SELECTION OF ANTIBIOTICS FOR THE TREATMENT OF MENINGITIS IN INFANTS AND CHILDREN[6,11,17,32]

Initial Therapy

Age	*Most likely pathogens in order of importance*	*Initial therapy until organism identified*
<3 months	Enteric bacilli including Salmonella species *Haemophilus influenzae* *Streptococcus pyogenes* *Diplococcus pneumoniae*	Ampicillin 75 - 150 mg/kg/day I.V. + kanamycin 15 mg/kg/day I.V. ± intrathecal injection *stat* of kanamycin 5 - 10 mg
>3 months	*Diplococcus pneumoniae* *Haemophilus influenzae* *Neisseria meningitidis*	Ampicillin 150 mg/kg/day I.V. ± intrathecal penicillin 5 000 - 10 000 IU

Definitive Therapy—Drugs of choice (Dependent on Sensitivity Tests)

Organism	*Drug*	*Dose*	*Route of administration and duration**
Meningococcus	Ampicillin	75 - 150 mg/kg/day	I.V.
	Penicillin G	2 000 000 - 4 000 000 IU 6-hourly	I.V. for 48 hours then I.M. in lower doses
Pneumococcus	Penicillin G	4 000 000 IU 6-hourly	I.V. for 48 hours then I.M. in lower doses
H. influenzae	Ampicillin	75 - 150 mg/kg/day	I.V.
Gram-negative bacilli	Kanamycin	15 mg/kg/day	I.V.
Pseudomonas sp.	Polymixin B	2 - 4 mg/day	I.T.
		2·5 mg/kg/day	I.M.
Streptococcus	Penicillin G	4 000 000 IU 6-hourly	I.V. for 48 hours then I.M. in lower doses
Staphylococcus aureus	Sodium methicillin	20 - 25 mg/day	I.T.
	or	100 - 150 mg/kg/day	I.V.
	Erythromycin + Chloramphenicol	40 - 80 mg/kg/day + 40 - 80 mg/kg/day	I.V.
Actinomycosis *Listeria monocytogenes*	Penicillin G	10 000 000 - 20 000 000 IU per day	I.V. for 8 weeks
Nocardiosis Cryptococcosis	Amphotericin B	0·25 - 1 mg/kg/day	I.V. over 6 - 8 hours daily for 8 weeks
	or		
	Sulphonamides	2 g/day	

*In general intravenous therapy for 48 hours or until clinical recovery, then oral or intramuscular therapy for a further 7 days.

Intrathecal injection. Direct intrathecal injection especially of penicillin is advocated by Garrod[25] despite views of its harmful effects and uncertainty of its intrathecal distribution on lumbar injection. No good evidence of improved results with this route of administration exists, although nothing seems to be lost in its implementation. In the treatment of pseudomonas infections, intrathecal administration of Polymyxin-B is essential as this drug diffuses poorly from the blood into the CSF.[6,17,25,32]

Parenteral administration. Studies have shown that for practical purposes,[24] intermittent intravenous infusions (4 - 6-hourly) produce the highest level of penicillin in the cerebrospinal fluid. Intravenous therapy may be replaced after clinical recovery by oral or intramuscular administration. Evidence for the production of satisfactory intrathecal levels of ampicillin after intramuscular injection is not yet concrete.[44]

Duration

Usually not more than 10 days of therapy are required.[25] Therapy may be withheld 5 - 7 days after clinical recovery.[32,48]

GENERAL THERAPEUTIC CONSIDERATIONS[17,32,41]

Isolation.[41] It is advisable in a childrens' ward to isolate all patients with purulent meningitis for the first 48 hours or until the aetiologic agent is identified.

Hydration.[17,40,41] Glynn-Jones[40] emphasizes the dangers of circulatory overload and raised intra-cranial pressure resulting from over-enthusiastic intravenous fluid therapy and water intoxication. Symptoms and signs of electrolyte disturbances may be wrongly attributed to meningitis.

It is important, therefore, bearing in mind the large doses of intravenous antibiotics being used and the increased renal flow promoted by sulphonamides, and that shock may be misinterpreted as dehydration,[40] to limit intravenous therapy initially to replacement of basic deficits and maintain a low level of fluid intake thereafter.[41]

Ventilation.[17,41] Airway obstruction, decreased respiratory effort, irregular respiratory rate, secondary to increased intracranial pressure or seizure activity may present problems of ventilation and oxygenation.

Reduction of increased cranial pressure.[41] Signs of this complication (irregular respiration, increase in systolic blood pressure, bradycardia, persistent convulsive activity, papilloedema and slanting of sutures) should be carefully sought. Cerebral swelling as a cause of raised intracranial pressure may be treated with hypertonic urea or mannitol infusions although proof of their efficacy has been shown more convincingly in the treatment of non-infective causes than in inflammatory causes of raised intracranial pressure.

The use of glucocorticoids for bacterial meningitis complicated by increased intracranial pressure has not been thoroughly evaluated.

Convulsions.[17,32,41] Because of the high incidence of seizures in children with bacterial meningitis, prophylactic anticonvulsant therapy may be initiated as soon as the patient is admitted to hospital. Sedation, however, may

obscure important neurological signs. Phenobarbitone 7·5 - 60 mg or phenytoin sodium 20 - 50 mg may be used. Convulsions occurring after infection is under control suggest the presence of subdural effusion or water intoxication.

ASSESSMENT[37, 32, 43]

Assessment of the patient's progress depends on the febrile course, improvement in sensorium, improvement in cerebrospinal fluid findings and return of peripheral blood count to normal. Fever lasts a variable period of time. Persistent fever (more than 5 days) may be due to continued sepsis in a subdural effusion, the formation and persistence of a brain abscess, lateral sinus thrombosis, tissue necrosis, ecchymotic cutaneous lesions, sinusitis or mastoiditis, a urinary tract infection, pneumonia or drug fever.

A repeat lumbar tap should be performed 36 - 48 hours after initiation of therapy by which time, although the cell count and protein level may be higher than the initial count, viable organisms will be absent from the CSF provided the appropriate drug has been administered (except in neonatal meningitis caused by enteric bacilli, which may be viable for several days).

Therapy should be continued until the patient is afebrile for 7 days, the cerebrospinal fluid cell count is 30 cells or less and the sugar and protein levels have returned to normal (this is usually not more than 10 - 14 days after admission). Persistent pleocytosis or increased protein values at this stage may indicate subdural effusion or some other septic focus such as mastoiditis.

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