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Bacterial meningitis – ten years experience

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SUMMARY

Between January 1968 and December 1977, 635 cases of acute bacterial meningitis were admitted to hospitals in the Birmingham Area Health Authority. The epidemiology of these cases was analysed and compared with the 270 cases which were admitted to the regional infectious diseases unit at East Birmingham Hospital (E.B.H.). In children and young adults the meningococcus was the commonest causative organism while over the age of 25 pneumococcal meningitis predominated. Although *Haemophilus influenzae* was the second commonest infecting organism it was a rare cause of meningitis in school children and adults, only four cases presenting in these age groups in the Birmingham Area.

A detailed analysis was made of the symptoms, signs, laboratory investigations and clinical course of the 270 cases treated at E.B.H.

The mortality in the patients with pneumococcal meningitis was 30%. In the meningococcal group it was 3·5% and in the haemophilus groups 7·7%.

An analysis of the various treatment regimes employed in the 270 E.B.H. patients supports the view that a single antibiotic is sufficient for the therapy of most forms of bacterial meningitis. Intrathecal antibiotic administration is unnecessary in pyogenic meningitis caused by meningococci, pneumococci or *H. influenzae*.

INTRODUCTION

Bacterial meningitis remains a major cause of mortality and morbidity, despite the availability of effective antibiotics. The mortality from pneumococcal meningitis ranges from 13–60% (Baird, Whittle & Greenwood, 1976) while the morbidity from *Haemophilus influenzae* meningitis has been reported as 35% (Sell *et al.* 1972) and in one American epidemic of meningococcal meningitis the mortality was 31% (Foster, Sanders & Ginter, 1971).

The aim of the present study was to define the current pattern of bacterial

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meningitis in an English hospital. The study was designed to identify the causative organisms, the type of patient affected, the factors in a patient's history, examination or investigation which are of diagnostic or prognostic importance and clinical measures which might improve outcome. Particular emphasis has been given to the rational use of antibiotics.

PATIENTS AND METHODS

The Hospital Statistics Register codes the principal diagnosis and associated diseases using the International Classification of Diseases. Hospital records were reviewed from all cases coded with numbers 3200 (pneumococcal meningitis), 3201 (haemophilus meningitis), 3209 (culture negative bacterial meningitis), 0360 (meningococcal meningitis) and 3208 (meningitis due to other organisms) admitted to East Birmingham Hospital between January 1968 and December 1977 inclusive.

Patients were included in the study if they were found to have one of the following: (i) culture of bacteria from purulent cerebrospinal fluid (CSF), (ii) purulent CSF plus positive blood culture, (iii) sterile but purulent CSF (culture-negative bacterial meningitis).

Patients with tuberculous meningitis were excluded. Patients were also excluded when the primary site of infection was elsewhere in the central nervous system, such as those with cerebral abscesses or infected ventriculo-atrial shunts.

Information was recorded on coded sheets and transferred to punched computer cards. The cards were read on an IBM 370/165 computer and analysed using Version 8 of the Statistical Package for the Social Sciences.

Four hundred and forty-one cases coded as bacterial meningitis were reviewed, of which 270 fulfilled the above criteria. The majority of the remaining 171 cases had lymphocytic meningitis, most frequently caused by the mumps virus, and had been miscoded as culture-negative bacterial meningitis.

East Birmingham Hospital (E.B.H.) contains the West Midlands Regional Infectious Diseases Unit. In order to compare our figures with other local hospitals the numbers of hospital inpatients with diagnoses in the relevant categories were obtained from the Birmingham Area Health Authority (BAHA) computer for the years 1969–78 inclusive. Because of the large numbers of incorrectly coded culture-negative cases at E.B.H. this category was excluded from the BAHA figures.

RESULTS

(1) *Epidemiology*

Neisseria meningitidis was the commonest cause of bacterial meningitis in our series and this was reflected in the BAHA figures (Table 1). Culture-negative figures are not given for BAHA (see Materials and Methods). Figures for adult and paediatric series from other countries are given for comparison in Tables 2 and 3. Splitting up the BAHA cases by age reveals that *N. meningitidis* is the commonest

Table 1. *Acute bacterial meningitis* – 1968–77

(East Birmingham Hospital (EBH) figures are given as % of total cases and % of culture positive cases, Birmingham Area Health Authority (BAHA) as % culture positive only.)

	Total no. of patients		Meningococcal (113 patients)	Haemophilus (52 patients)	Pneumococcal (40 patients)	Other organisms (17 patients)	Culture negative (48 patients)
EBH	270	% of total	42	19	15	6	18
		% culture positive	51	23	18	8	—
		% fatal	3·5	7·7	30	41	6
BAHA	635	% culture positive	47	20	25	8	—*
		% fatal	4·1	3·9	25	28	—*

* See text.

Table 2. *Cause of acute bacterial meningitis in four published studies* (% *mortality in parentheses*)

	Total cases	Meningococcal (%)	Haemophilus (%)	Pneumococcal (%)	Other organisms (%)	Culture negative (%)
U.S.A. 1948–58†	294	13 (8)	16 (11)	13 (19)	39 (24)	19 (12)
U.S.A. 1948–73‡	349	12 (17)	4 (7)	25 (31)	17 (61)	42 (14)
Denmark 1960–65§	356	29 (1)	18 (3)	21 (21)	13 (26)	18 (11)
Nigeria 1971–73‖	194	69·5 (*)	6 (*)	21·5 (48)	3 (*)	0

* Mortality not stated. † Eigler *et al.* 1961: ‡ Hodges & Perkins. 1975; § Jensen *et al.* 1969; ‖ Tugwell *et al.* 1976.

Table 3. *Causative organism in four published series of acute bacterial meningitis in children*

	Total cases	Meningococcal (%)	Haemophilus (%)	Pneumococcal (%)	Other organism (%)	Culture negative (%)
Canada 1962*	68	9	52	9	5	25
Australia 1953–59†	237	26	28	15	7	24
U.S.A. 1956–60‡	447	18	30	8	16	28
England 1969–73§	738	34	27	9	9	20

* Gossage, 1962. † Kneebone, 1961: ‡ Haggerty & Ziai, 1964. § Goldacre, 1976.

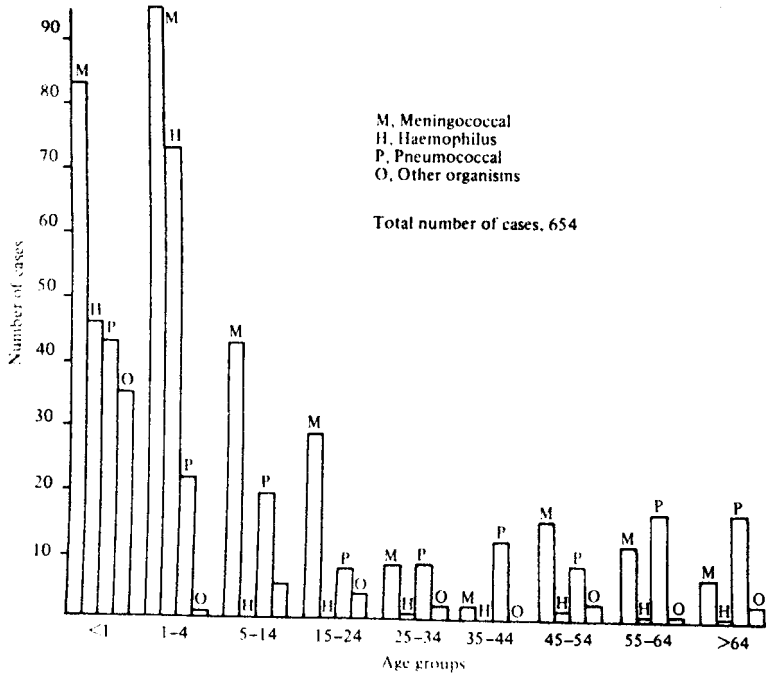

Fig. 1. Frequency of infection by different organisms by age group in the Birmingham Area Health Authority (Teaching).

organism for all ages up to 25 (Fig. 1). Over this age pneumococcal meningitis predominates.

The annual incidence of bacterial meningitis in Birmingham fluctuates (Fig. 2). In cases of meningococcal disease this was significant (χ^2 8 D.F. 57·9, $P < 0{\cdot}001$) but was not significant for pneumococcal or haemophilus meningitis (χ^2 8 D.F. 15·1 and 11·5; $P > 0{\cdot}05$ and $P > 0{\cdot}1$ respectively).

In the last year of the study the three principal organisms were equally common, but this was due to a decrease in meningococcal meningitis since 1973, and not to an increase in pneumococcal or haemophilus disease.

Organisms other than the three principal bacteria caused only 17 cases of meningitis at E.B.H. Thirteen of these patients were less than 1 year old; the causative organisms were *Escherichia coli* (7 cases), *Streptococcus pyogenes* (3 cases) *Staphylococcus albus* (2 cases) and *Pseudomonas aeruginosa* (1 case). The remaining four patients were between 15 and 30 years old; the causative organisms were: *Staphylococcus aureus* (2 cases) *Listeria monocytogenes* (1 case) and *Leptospira canicola* (1 case). An organism was cultured from the blood but not from the CSF in both of the patients with meningitis due to *S. aureus*.

In all of the groups except the culture negative one, there was a predominance

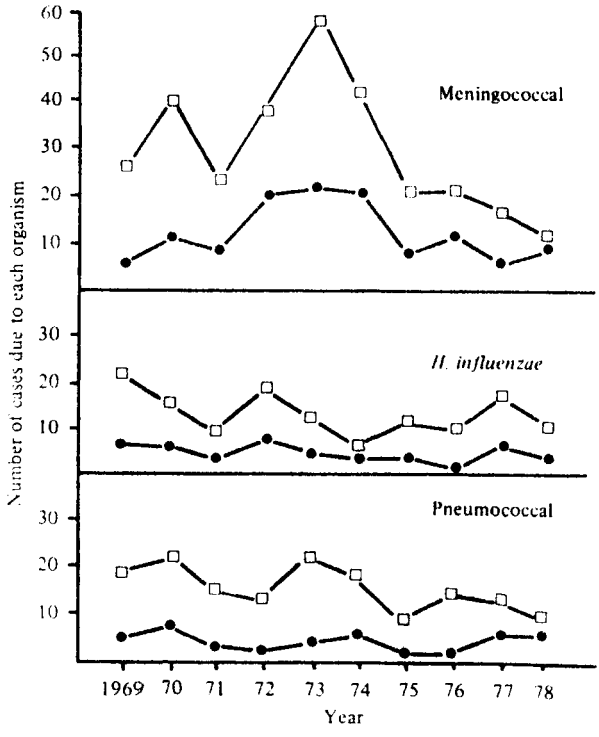

Fig. 2. The annual fluctuation for cases of meningitis in the Birmingham Area Health Authority (□, B.A.H.A.) and at East Birmingham Hospital (●, E.B.H.).

of males. The male to female ratios were as follows: meningococcal 1·5:1; haemophilus 1·7:1; pneumococcus 2·6:1; culture negative 1:1.

The following were considered to be events in the patients' past history which might predispose them to bacterial meningitis: lesions of the cranial vault, including the presence of CSF shunts; conditions associated with impaired resistance to bacterial infection, e.g. splenectomy, sickle cell disease, diabetes mellitus and previous history of bacterial meningitis. Fifty-five % of the patients with pneumococcal meningitis had a significant past history and in 12·5% there were multiple predisposing factors. In contrast, in the meningococcal, haemophilus and culture negative groups a significant past history was present in 18·5, 13·5 and 21 % of patients respectively and multiple factors were not recorded in any patient. There was a statistically significant difference between the number of patients in the pneumococcal group with a significant past history and the number in the other three groups (χ^2 1 D.F. 25·7; $P < 0{\cdot}001$). Four patients had had previous episodes of bacterial meningitis, two in the pneumococcal group and one each in the meningococcal and culture negative groups. The previous episodes in both of the latter patients were culture negative and both patients were found to have a familial complement deficiency (Hacney *et al.* 1980).

Contact with other cases of bacterial meningitis was recorded in only three patients, two with meningococcal and one with culture negative meningitis accompanied by a florid petechial rash. One of the meningococcal patients was a family contact; the type of contact was not defined in the other two cases.

(2) *Clinical history*

A history of headache or photophobia was recorded in only 44 and 13% of cases respectively. These complaints were recorded in significantly fewer haemophilus cases. All but seven patients had a history of fever and 45% of sore throat or other upper respiratory tract infection. Only 9% had a history of rigors.

A history of antibiotics taken before admission was recorded in 46% of the culture-negative group as opposed to 37% of the culture-positive group. This difference just failed to reach statistical significance (χ^2 1 D.F. = 3·7; $P > 0·05$).

Three patients had been taking long-term prophylactic antibiotics before admission; they were all in the culture-negative group.

(3) *Physical signs*

The temperature was between 36·8 and 37·2 °C in 15 cases. Six patients had subnormal temperatures on admission (temperature 35·4–36·7 °C); the remaining 229 patients were febrile (temperature 37·3–43·0 °C). Pulse rate remained normal in 18 cases and 217 patients had a tachycardia (pulse 90–200 beats per min). Lymphadenopathy and splenomegaly were present in 28 and 8 cases respectively. Fifty three cases had signs of pharyngitis. There was no significant difference between the organism groups for these signs.

A petechial rash was present in 65% of the meningococcal and 27% of the culture-negative cases. One haemophilus and two pneumococcal patients had petechial rashes.

Otitis media was present in 32·5% of the pneumococcal group but in only 11·5% of the other patients (χ^2, 1 D.F. 13·9, $P < 0·001$).

Neck stiffness was observed in 72% of cases. Meningism was most common in the culture-negative group (85%) and least common in the meningococcal group (66%). Other central nervous system signs were most common in the pneumococcal and haemophilus patients (Table 4).

(4) *Laboratory results*

The initial lumbar puncture was performed more than 24 h after admission in eight of the 40 pneumococcal cases but in only ten of the remaining 213 cases. Lumbar puncture was delayed until the fourth day in three of the pneumococcal cases.

Blood cultures were positive most frequently in the pneumococcal group and more often in the haemophilus than in the meningococcal group (Table 5); these differences were significant (χ^2 1 D.F. 7·9, $P < 0·001$ and χ^2 1 D.F. 4·9, $P < 0·05$ respectively). In nine cases an organism was isolated from the blood but not from the CSF. Gram staining of CSF was interpreted correctly in all but four cases (Table 5). A relevant organism was grown from seven of the 170 throat swabs; two

Table 4. *The percentage of patients with central nervous system signs on admission and the significance of the differences between organisms*

	Meningococcal	Haemophilus	Pneumococcal	Culture negative	Significance of differences*
Convulsions	10·6	32·7	27·5	10·4	H = P > M = CN ($P < 0·01$)
Cranial nerve signs	8	9·6	27·5	8·3	P > M = H = CN ($P < 0·001$)
Long tract signs	5·3	17·3	20·0	12·5	P = H > M = CN ($P < 0·05$)
Conscious Level:					
Normal	23	31	15	37·5	N.S.
Drowsy	62	61·5	57·5	50·0	N.S.
Unconscious	15	7·5	27·5	12·5	P > M = H = CN ($P > 0·02$)
Signs of raised intracranial pressure (papilloedema/bulging fontanelle)	30·6	35·3	40·0	17·0	N.S.
Total patients	113	52	40	48	

All tests of significance done by χ^2 with 3 D.F. (degrees of freedom)
* P, Pneumococcal; M, Meningococcal; H, Haemophilus; CN, Culture-negative; N.S., Not significant.

Table 5. *Results of CSF Gram stain and culture, and blood cultures in patients with bacterial meningitis*

	Gram stain of CSF			CSF culture		Blood culture	
	Negative	Correct	Wrong	Positive	Negative	Positive	Negative
Meningococcal	24	88	1	105	6	25	60
Haemophilus	9	40	2	52	0	20	13
Pneumococcal	4	32	1	37	3	19	7

Table 6. *CSF polymorph count and biochemistry results by organism given as percentages of total patients in each category*

	% meningococcal	% haemophilus	% pneumococcal	% culture negative
Protein (G/L)				
0–0·45 (normal)	8	6	0	14·0
0·46–1·00	16	9·5	10·5	23·5
1·01–10·00	76	84·5	89·5	62·5
Sugar (mmol/L)				
> 3·1 (normal)	19	12	11	17
Polymorphs (per mm^{-3})				
5–1000	16·5	29	25	27
1001–5000	25	38·5	35	31·5
50001–20000	40	25·0	30	29
> 20000	16	7·5	5	10·5
Total patients	113	52	40	48

in the culture-negative group and five in the meningococcal group. However, all of the organisms grown from the meningococcal patients were either streptococci or *H. influenzae*.

There was a tendency towards lower CSF protein levels in the culture-negative group and a higher CSF polymorph count in the meningococcal cases (Table 6). CSF sugar levels were > 3·1 mmol/l in 11–19% of each group, but cannot be analysed accurately since only 29 patients had simultaneous blood sugars. Thirty-one % of the patients were anaemic on admission. A platelet count < 100000 was no more frequent in the meningococcal than in the pneumococcal patients and did not correlate with the presence of a petechial rash. The numbers of patients who had platelet counts in the haemophilus and culture-negative groups are too small for statistical analysis. Coagulation tests were performed in only 30 patients so that detailed analysis of the presence of intravascular coagulation is not possible.

(5) *Outcome*

Outcome is analysed in terms of mortality and permanent complications for patients who were followed up at the hospital clinics (Table 7). The permanent complications were serious and included paresis, severe deafness or mental retardation. Only 31 patients had sufficiently detailed follow-up to assess more subtle complications such as mild deafness or impaired intelligence. These are not considered in the analysis since they are probably a highly selected subgroup.

Treatment-related temporary complications occurred in 10 patients (Table 7). These were drug fever in three cases, mild penicillin allergy in two and ulceration or abscess formation at the site of sulphonamide injection in three. One patient developed erythema nodosum whilst receiving oral sulphonamides and one an arteritic rash after multiple antibiotic therapy. In addition to these, one of the fatal

Table 7. *Number of deaths and complications in the four groups of patients*

(Permanent complications were recorded from out-patient follow-up notes; general practice records for other patients were not obtained.)

	Total	Deaths	Permanent complications	Disease related temporary complications	Drug related temporary complications	No complications
Meningococcal	113	4	8	12	4	85
Haemophilus	52	4	5	15	1	27
Pneumococcal	40	12	1	9	0	18
Culture negative	48	3	0	5	5	35

cases of meningococcal meningitis may have died from penicillin anaphylaxis, and one patient in the meningococcal group developed a haematoma and subsequent fibrosis of the thigh following intramuscular penicillin injections.

Disease related temporary complications occurred in 41 patients (Table 7). The complications involved the central nervous system (CNS) in 35 patients: convulsions; impaired consciousness; cranial nerve palsies; long tract signs and subdural effusions. The complications in the remaining six patients were aseptic arthritis; septic arthritis and, in one case, pericarditis and ophthalmitis.

The outcome in each group is now described in more detail.

Outcome – meningococcal group

Only one of the four patients in the meningococcal group who died had been ill for more than a day before death. This patient had a 'flu-like illness for 10 days before admission and was treated with tetracycline at home. He became seriously ill on the day of admission. Following one injection of penicillin he had a respiratory arrest; he was ventilated but died 4 days later. All four fatal cases were severely ill on admission with multiple CNS complications.

All of the patients with permanent complications of meningococcal meningitis had at least one temporary complication involving the CNS on admission. Fibrosis of the thigh in one patient resulted from a massive haematoma following intramuscular penicillin. This patient had a normal platelet count but did not have coagulation tests performed.

Twelve patients with temporary complications recovered without obvious long-term problems. One patient had ophthalmitis and pericarditis; these complications were not recorded in any other organism group. Aseptic arthritis was present in two patients.

Outcome – haemophilus group

Of the four deaths in this group, two occurred within 24 h of the onset of symptoms and both patients were comatose on admission. The other two deaths followed respiratory arrest during uncontrolled status epilepticus, one on day two and one on day 14 of the illness. Five patients had permanent complications. In two, these were present on admission to hospital.

Table 8. *Weiss score in 11 patients who died*

	Fatal	Temporary complications	Uncomplicated
Weiss score > 2	10	5	6
Weiss score ≤ 2	1	3	11

Eleven of the 15 other patients with temporary complications had convulsions, two had cranial nerve palsies, one ataxia and one septic arthritis. All resolved uneventfully.

Outcome – pneumococcal group

Twelve patients died. They all had a longer history than the fatal cases in the other organism groups and only three died within 24 h of admission. The mean duration of illness before admission in the fatal group was 3·75 days compared with 2·17 days in the group with no complications and 2·8 days in the group with temporary complications. These differences are not significant by the Mann–Whitney U-test. CNS complications were present in seven of the 12 fatal cases on admission.

Eleven out of 12 fatal pneumococcal cases had a significant past history as did two of the ten with temporary complications and 10/18 with no complications. The difference between the fatal and the combined non-fatal cases is significant (χ^2 1 D.F. 6·8, $P < 0{\cdot}01$) but the difference between the fatal and non-fatal cases without complications is not (χ^2 1 D.F. 2·2, $P > 0{\cdot}1$).

The only laboratory tests with significant differences between fatal and non-fatal groups were the CSF protein (higher in fatal group, $P < 0{\cdot}01$, Mann–Whitney U-test) and the serum urea (higher in fatal group $P < 0{\cdot}01$ Mann–Whitney U-test).

The higher mean CSF protein in the fatal group was due to five individuals. A scoring system has been devised (Weiss *et al.* 1967) for predicting mortality in pneumococcal meningitis. Weiss *et al.* assigned one point each to a CSF protein of more than 2·8 g/l, a CSF sugar of less than 0·8 mmol/l, the presence of coma, semicoma, delirium, convulsions and each underlying disease. All of their 13 fatal cases had a score of greater than two.

Information for assessing the Weiss score in our series was available in 11 fatal cases, eight cases with temporary complications and 17 uncomplicated cases (Table 8). The difference between the fatal and the combined non-fatal groups was significant ($P < 0{\cdot}05$) but the difference between the fatal and temporary complication groups was not.

Outcome–culture negative group

Three patients died. One was a 50-year-old man admitted with hemiplegia who had Gram-negative cocci seen on Gram stain but blood and CSF cultures were negative; he died on day 3 of his illness. Another was a 15-year-old boy with no complications on admission who died on the second day of illness following a convulsion terminating in cardiorespiratory arrest. Gram negative rods were seen

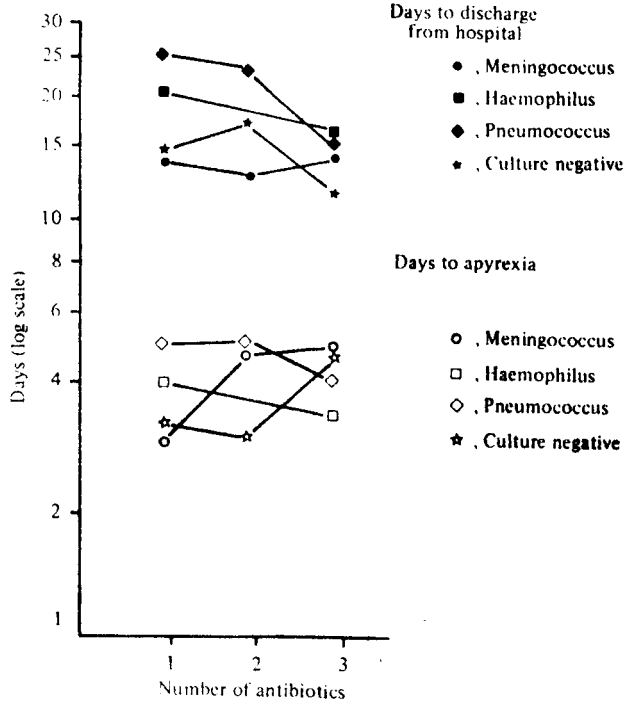

Fig. 3. Mean days (log scale) to apyrexia and to discharge by organism and by drug therapy.

on Gram stain of CSF and pus from frontal sinuses but cultures were negative. Neither had received antibiotics before admission. The third patient was a 20 year old woman who had a 36 h history and was admitted quadriplegic with fixed dilated pupils. She died soon after admission. She had been given intravenous ampicillin by her G.P., her CSF was typical of acute bacterial meningitis, although no organisms were seen or cultured.

(6) *Treatment*

There is no uniform treatment policy for bacterial meningitis at this hospital, the choice in an individual patient varying with different consultants. Almost all of the patients received a penicillin, chloramphenicol or a sulphonamide, alone or in combination. The outcome in patients who received a single drug was compared with those patients given a combination of bactericidal (penicillin or ampicillin) and bacteriostatic drugs (chloramphenicol or sulphonamide) throughout treatment. Patients were excluded if they had received a combination of drugs initially, followed by a single drug. Insufficient patients died or developed permanent complications to use these as criteria for analysis. Outcome was therefore analysed by rate of recovery. Patients with temporary complications were also excluded from the analysis, since almost all the patients who died or had permanent

Table 9. *Analysis of variance of the effects of infecting organism and type of therapy upon the days to apyrexia and days to discharge from hospital for 130 patients who recovered with complications*

Order of entry	Dependent variable / Effect	D.F.	Log days to apyrexia SS	F	p	Log days to discharge SS	F	p
1	Organism	3	0·293	0·687	0·562	0·709	4·784	0·003
2	Drug therapy	2	0·242	0·849	0·430	0·118	1·198	0·305
3	Organism × drug therapy	5	0·576	0·810	0·545	0·190	0·770	0·573
	Residual	120	17·070	—	—	5·928	—	—
	Total	130	18·180	—	—	6·946	—	—

D.F., Degrees of freedom; SS, Sum of squares; F, F-statistic; p, Probability associated with F-statistic.

complications presented with other temporary complications, which suggested more severe illness in these patients. This left 130 patients without complications who received either single, dual or multiple chemotherapy throughout. There were therefore three treatment groups for analysis.

Two indices of rate of recovery were used; the number of days until apyrexia, and the number of days until discharge from hospital. Since both measures were very skewed, a logarithmic transformation was applied to the figures before analysis. As in most retrospective analysis, there were unequal numbers of patients in each therapy organism sub-group, and hence a classical analysis of variance could not be used. Instead a hierarchical analysis of variance was used in which firstly, effects due to differences in organism type were removed, then effects due to differences between therapy and finally organism-therapy interactions were removed. Fig. 3 shows the mean (log) days to apyrexia and to discharge as a function of the therapy type and the organism, the sample size for each point being indicated. Table 9 shows the analysis of variance tables for the two dependent variables.

Organism and type of therapy had no significant influence upon the number of days until apyrexia. Organism type had a statistically significant ($P = 0{\cdot}003$) effect upon the time until discharge, the fitted effects indicating that, on average, the meningococcal patients were discharged in 13·2 days, haemophilus patients in 18·2 days, pneumococcal patients in 21·9 days. The culture-negative patients were discharged in 15·1 days. There were no significant effects of therapy type upon time until discharge from hospital.

DISCUSSION

This is the first major review of bacterial meningitis from a British hospital for over 10 years.

N. meningitidis was the commonest overall cause of bacterial meningitis in Birmingham and was responsible for the most cases up to 25 years old; in some

of the older age groups *Strep. pneumoniae* was the commonest cause. This contrasted with published adult series from the United States, where *Strep. pneumoniae* or unusual organisms were the principal agents (Table 2). In paediatric series from other countries *H. influenzae* predominated (Table 3) and *H. influenzae* is now the commonest *overall* cause of bacterial meningitis in the U.S.A. (Ward *et al.* 1979). There is, however, no reason why this should not change in the U.K. as it did in the U.S.A. and it is very important that there should be continuous monitoring of cases of meningitis. Unfortunately, analysis of notification rates is not sufficient. Goldacre (1976) showed that meningococcal meningitis was notified in 50% of cases from a community study of meningitis in children, whereas only 17% of pneumococcal and haemophilus cases were notified. Further, fatal cases were notified about half as frequently as non-fatal cases (Goldacre & Miller, 1976).

Meningitis due to uncommon organisms is much less frequent in our series than in comparable North American series (Carpenter & Petersdorf, 1962; Eigler *et al.* 1961; Hodges & Perkins, 1975) (Table 2). In a community-based study of bacterial meningitis in Olmsted County, U.S.A. from 1935–79, Fraser, *et al.* reported a trebling of disease due to unusual organisms when the years 1935–46 were compared with 1959–70 (Fraser, Henke & Feldman, 1973). During this period the mean age in the 'other organisms' group rose from 17·5 to 56 years. Between 1959 and 1970, 11 out of 16 cases of meningitis in patients over 60 were due to unusual organisms. From Fig. 1 it can be seen that only 12 cases of meningitis due to uncommon organisms in patients over 15 years old occurred in the entire Birmingham Area in 9 years. Fraser and colleagues could not attribute their findings to the increased survival of immunologically abnormal people since only three of the patients over 60 had significant underlying disease. This is in contrast to the findings of a study of meningitis in the elderly (Massanari, 1977) where it was found that uncommon organisms were not cultured from elderly patients without co-existent disease any more frequently than from young people.

The conclusion that the cases of meningitis due to less common organisms in American series are largely due to infection in compromised hosts is strengthened by the fact that in a review of cases of meningitis at Boston City Hospital during selected years from 1935–72, 30% of 572 cases were hospital-acquired. Almost all of these were due to less common bacteria and hospital-acquired cases accounted for 50–75% of cases due to the various unusual bacterial species (Finland & Barnes, 1977). None of the cases in our series was hospital-acquired. It is possible that this disparity is caused by a more aggressive approach to disease in the elderly in America. For example, Carpenter stresses the need for lumbar puncture in any elderly person with disturbance of consciousness, regardless of the absence of fever and meningism (Carpenter & Petersdorf, 1962). It must also be noted that the outlook in this group is very poor and that treatment makes little difference. Mortality in patients over 60 years old with culture-positive meningitis was 79% in Fraser's series for the years 1959–70 and in Finland's series mortality in this group was 77% both before, and after, the introduction of antibiotics in 1942.

The findings of an overall predominance of males and of patients with significant past history in the pneumococcal group are both similar to that reported in other

series (Carpenter & Petersdorf, 1962; Jonsson & Alvin, 1971; Richter & Brust, 1971). A history of case contact occurred only in the meningococcal group and the culture-negative group which, together with the greater fluctuation in annual incidence in the meningococcal group, is consistent with the reputation of the meningococcus for case to case spread. No secondary cases and no significant annual fluctuation was observed in the haemophilus group, although recent reports from America have documented case to case spread (Ward *et al.* 1979; Glode *et al.* 1980). It is, at present, our opinion that these sporadic secondary cases of haemophilus meningitis are insufficient justification for giving chemoprophylaxis to contacts of this disease (Davey & Cruickshank, 1979; Davey, Cruickshank & Geddes, 1980).

Clinical presentation

In a retrospective study it is difficult to draw conclusions about the absence of a symptom since the fact that it was not recorded does not mean that it was not present. The infrequency of headache in the haemophilus group is attributable to the fact that the majority were infants but this symptom was surprisingly infrequent in the other groups as well. Neck stiffness was not recorded in 28% of cases, the temperature was normal in 15 cases and 11–19% of each group had normal CSF sugar, although, unfortunately, few had measurements of blood sugar. This emphasizes that the classic signs and laboratory findings are not always present and that a clinical diagnosis of bacterial meningitis should not be discarded because some of these features are absent.

Otitis media was present significantly more frequently in the pneumococcal patients; other authors have also reported the higher incidence of primary sites of infection in this group (Carpenter & Petersorf, 1962; Jonsson & Alvin, 1971; Ruegsegger, 1942; Tugwell, Greenwood & Warrell, 1976). The only symptom or sign which is sufficiently specific to be of clinical value in identifying the causative organism is the petechial rash of meningococcal meningitis. However, even this is not absolutely reliable since it was also observed in two of the pneumococcal patients and one of the haemophilus patients. Petechial rashes in patients from these latter groups have been reported by other authors (Carpenter & Petersdorf, 1962; Hodges & Perkins, 1975; Jensen, Ranek & Rosdahl, 1969; Johnsson & Alvin, 1971; Laxer & Marks, 1977).

A history of antibiotics administered before admission was commoner in the culture-negative group but this did not reach statistical significance.

The subject of the influence of pre-admission antibiotics on the outcome of bacterial meningitis is controversial and has been well reviewed (Editorial, 1977). The concensus seems to be that whilst no overall adverse effect is noted, individual cases where diagnostic confusion has arisen have been reported (Mandal, 1976). Only one case of culture-negative meningitis from our series caused diagnostic difficulties, but there was no history of pre-admission antibiotics in this patient. Finally, it is interesting to note that in Fraser's series there was no change in the number of cases of culture-negative meningitis over the years 1935–70 despite the introduction of antibiotics during that time (Fraser *et al.* 1973). Thus, the

prescription of antibiotics before admission is not the major reason for the existence of culture-negative meningitis. If a patient is severely ill, particularly if a petechial rash is present, it is our opinion that the rapidly fatal course of bacterial meningitis is sufficient justification for the general practitioner to give parenteral penicillin before the patient is sent to hospital (Editorial, 1979).

Laboratory results

Delayed diagnosis and lumbar puncture were significantly more common in the pneumococcal group in this series, as has been previously reported (Carpenter & Petersdorf, 1962). In our series all of these cases recovered uneventfully, suggesting milder or earlier disease at presentation and no adverse effect of delayed diagnosis.

Gram stain examination of CSF proved a useful and reliable guide to organism type, being positive in 80% of cases due to the three commonest organisms and incorrectly interpreted on only four occasions. A high yield of positive cultures from blood was obtained, particularly in the pneumococcal and haemophilus groups, and in nine cases this was the only positive culture, emphasizing the importance of this investigation in meningitis. Throat swabs were found to be of no practical value, giving misleading results on the few occasions that an organism was cultured, an observation that has previously been made (Carpenter & Petersdorf, 1962; Swartz & Dodge, 1965).

Outcome

Meningitis caused by *Strep. pneumoniae* and by less common organisms has by far the worst prognosis. In the case of less common organisms this is largely attributable to the type of patient affected.

Detailed studies of pneumococcal meningitis have identified factors contributing to this poor prognosis (Tugwell *et al.* 1976). Alterations in brain carbohydrate metabolism, vascular damage and qualitative reduction in polymorph response were demonstrated. Post-mortem studies have emphasized the importance of meningeal collections of pus, cerebral abscess formation and venous sinus thrombosis (Quaade & Kristensen, 1962; Swartz & Dodge, 1965). As in other studies, fatal pneumococcal cases in our series were distinguished by clinical and laboratory evidence of severe disease at presentation. However, it is impossible to predict prognosis accurately in an individual patient (Table 8). As there is no clinically proven therapy for bacterial meningitis other than antibiotics, the value of any prognostic index is in any case purely academic.

Although prognosis was better in the meningococcal and haemophilus groups, death occurred within 24 h of presentation in seven of 11 fatal cases. Moreover, all but three of the 13 cases with permanent complications had complications present on admission and two of the three who did not had underlying disease which made assessment of the role of meningitis as a cause for those complications difficult. In Goldacre's community study of meningitis (Goldacre, 1976) 71% of deaths occurred before or within 24 h of admission to hospital. In epidemics of meningococcal disease, which are usually due to more virulent strains, mortality is higher than for sporadic cases. In two reports of epidemics from England and

America, mortality was 19 and 31 % respectively (Easton *et al.* 1974; Foster *et al.* 1971). In Easton's series all deaths occurred within 24 h of the onset of symptoms.

It has not been possible to assess fully the long term complications. One study, employing techniques such as I.Q. testing and audiometry, assessed serious morbidity from haemophilus meningitis at 35 % (Sell *et al.* 1972). The majority of patients with long term complications in Sell's study had significant complications at presentation.

The chances of improving outcome with new antibiotics therefore seem slight. More research is required into the patho-physiology of meningitis, particularly in the pneumococcal group. However, the area which offers the greatest hope for significantly affecting outcome in bacterial meningitis is prevention. The prevention of meningococcal and pneumococcal disease has been reviewed recently (Fallon, 1979; Emmerson, 1980).

Antibiotic therapy

Jawetz & Gunnison (1952) proposed certain general principles governing the use of combinations of antibiotics. These included a statement that a combination of a bactericidal with a bacteriostatic agent *might* be antagonistic. These were only general principles and must be interpreted in relation to the organism and site of infection (Rahal, 1978). It should also be noted that antagonism between bactericidal and bacteriostatic drugs is of two basic types. The bacteriostatic agent may inhibit the bactericidal action of the other drug, so that the effect of the combination is equivalent to the bacteriostatic drug given alone. Alternatively, the antagonism may be mutual, in which case the combination is less effective than either drug given alone.

The evidence from *in vitro* and animal experiments on the combination of penicillins and chloramphenicol is conflicting (Rahal, 1978). However, there is evidence that chloramphenicol inhibits both the bactericidal effect of penicillin on *Strep. pneumoniae* (Tomasz & Waks, 1975) and of ampicillin on *H. influenzae* (Mackenzie, 1979). More importantly, the only prospective randomized study comparing single with combination therapy showed a significant reduction in morbidity and mortality in 140 patients given ampicillin, chloramphenicol and streptomycin (Mathies *et al.* 1967). Retrospective studies, such as the present one, are obviously less satisfactory for analysing treatment but other studies have either failed to show any beneficial effect of multiple therapy (Laxer & Marks, 1977; Baird *et al.* 1976) or have shown a detrimental effect (Lindberg *et al.* 1977). A prospective study of the treatment of haemophilus meningitis with either chloramphenicol or ampicillin showed no difference in outcome between the two groups (Feigin *et al.* 1976).

In summary, there is no evidence that the combination of penicillins with chloramphenicol and/or sulphonamides is any more effective than either drug given alone. In view of the frequency of resistance to sulphonamides amongst meningococci in this country, their use in bacterial meningitis is now limited (Fallon, 1974).

The practice in this Unit is not to inject antibiotics intrathecally as we consider

that it is unnecessary and potentially hazardous to do so. The current policy is to treat all cases of bacterial meningitis due to the three common organisms with a single antibiotic – benzylpenicillin for meningococcal and pneumococcal infections and chloramphenicol for those caused by *H. influenzae*. Single therapy is also used when the organism has not been identified, except in neonates and compromised hosts. Benzylpenicillin is the drug of choice unless the patient is under 6 years of age when chloramphenicol is substituted in view of the possibility of haemophilus infections in the pre-school child. Infections caused by *H. influenzae* are extremely uncommon in older children and adults, only four cases being diagnosed in Birmingham during the period of ten years. When these do occur they frequently complicate serious underlying disease (Eykyn, Thomas & Phillips, 1974). The above approach has been advocated by Lambert (1979). Combination therapy is not only unnecessary; it exposes the patient to the risk of side-effects of more than one antibiotic.

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