PURULENT MENINGITIS IN 204 BANTU CHILDREN

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With the advent of penicillin and the broad-spectrum antibiotics it was hoped that the problem of therapy for acute purulent meningitis was about to be solved. However, the diversity of present therapeutic regimens indicates that there is still no entirely satisfactory approach. Furthermore, with similar treatment, the cure rate varies in different reports. In the following analysis we have attempted to show that the prognosis of acute purulent meningitis is affected not only by the dosage and mode of administration of antibiotics, but also by certain clinical features which develop during the course of the illness. Against this background, we have tried to evaluate a number of therapeutic regimens used at this and other hospitals.

Material and Methods

The series consists of 204 consecutive cases of purulent meningitis in Bantu children under 10 years of age admitted to this hospital from a poor socio-economic environment during the period 1 January 1954 - 31 July 1958. The cases are classified as follows according to the bacteria that were found: Pneumococci 54, *Haemophilus influenzae* 32, meningococci 49, other organisms 6, no organisms found 63.

In 141 cases the diagnosis was made by demonstrating the causative organism in the cerebrospinal fluid (CSF) either microscopically or on culture. In the remaining 63 cases no organism was either seen in the CSF or cultured, and the diagnosis was made on the clinical condition and the cytology and biochemistry of the CSF, which suggested a bacterial rather than a viral aetiology.[50,51] Tuberculous meningitis was excluded, and so were relapses after an apparently satisfactory remission.

In all but 2 cases the diagnosis of meningitis was made on admission after a lumbar puncture. The exceptions were: (1) a 2-weeks-old infant with severe bronchopneumonia and suspected congenital heart disease, in whom pneumococcal meningitis was found at autopsy; and (2) a 7-months-old girl admitted in status epilepticus, in whom the CSF was found to be normal on 2 separate occasions (lumbar puncture and cisternal puncture), yet autopsy revealed an acute purulent meningitis of unknown aetiology.

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The organisms isolated from the CSF were tested by the disc method (Baragwanath modification[1]) for sensitivity to penicillin, streptomycin, chloramphenicol, tetracycline, oxy- and chlortetracycline, and sulphonamides.

Each treatment group contained cases of all degrees of severity and there was no selection of cases for different therapeutic regimens. Patients who died within 6 hours of admission to hospital were excluded from the evaluation of treatment.

The nutritional state of each child was assessed. In this we were guided by the body weight and the stigmata of protein malnutrition.[2]

In this paper the term 'focal neurological signs' signifies spasticity, cranial nerve lesions and Jacksonian fits, whereas the term 'convulsions' is reserved for generalized seizures with loss of consciousness. Subdural effusions were looked for in all cases where the clinical progress was inexplicably unsatisfactory. Where found, these effusions were treated by repeated aspiration through the anterior fontanelle. Surgical exploration was not required in this series.

PNEUMOCOCCAL MENINGITIS

The age of the 54 patients with pneumococcal meningitis ranged from 2 weeks to 7 years; 42 (78%) were under 1 year of age. There were almost as many children in the 6 - 12 months group as in the group under 6 months. There were 29 girls and 25 boys.

All patients received intramuscular (IM) penicillin as follows: 20 cases (group I) received 1 mega-unit hourly, 23 cases (group II) received 1 mega-unit 2-hourly, and 1 patient received 1 mega-unit 3-hourly. This therapy was continued for at least 24 hours and not more than 72 hours, after which the interval was gradually increased, the dose remaining constant. Seven patients (group III), who were all admitted before 1955, received less than 0·5 mega-unit of penicillin per dose, usually every 4 or 6 hours. Three patients died before treatment could be commenced.

Intrathecal (IT) penicillin was given to 25 patients in doses of 10,000 - 25,000 units and 1 patient received 50,000 units on 2 occasions. IT penicillin was instilled from 1 to 10 times, half the patients receiving not more than 2 injections.

Sulphonamides were given to 47 children, in amounts of 2 grains per pound body-weight per day (per lb. bw per day).

Results

Of the 54 patients 33 (61%) survived but 8 (15%) of these remained with neurological sequelae (Table II) (4 with decerebrate rigidity, 2 with hemipareisis, 1 with lower motor neurone palsy of the VIIth nerve and 1 with hydrocephalus).

All 21 deaths in the series ocurred within 72 hours of admission, whatever the mode of treatment; 15 patients died within 24 hours of admission, including 11 cases admitted in coma (Table I); 3 of the deaths occurred within 6 hours of admission. Of the 22 fatalities 17 occurred among the girls and 5 among the boys.

TABLE I. STATE OF CONSCIOUSNESS ON ADMISSION TO HOSPITAL IN 21 FATAL CASES OF PNEUMOCOCCAL MENINGITIS

Survival in hospital	*Fully conscious*	*Comatose or stuporose*	*Total*
Less than 24 hours	4	11	15
24 - 48 hours	1	3	4
49 - 72 hours	1	1	2

Subdural effusions were found in 8 patients (15%), and hospitalization was prolonged for more than 28 days in 4 of these. All survived and 6 recovered completely. All except 1 were diagnosed within 7 days after admission.

Factors of Prognostic Significance

Age. Among the children under 6 months of age 11 (50%) died and 11 recovered, 4 of them only partially.

TABLE II. INFLUENCE OF AGE OF PATIENT ON OUTCOME OF PNEUMOCOCCAL MENINGITIS

Age of patient	*Full recovery*	*Recovery with sequelae*	*Deaths*	*Total*
Under 6 months	7 (32%)	4 (18%)	11 (50%)	22
6 months - 1 year ..	13 (65%)	2 (10%)	5 (25%)	20
Over 1 year	5 (42%)	2 (16%)	5 (42%)	12
	25 (46%)	8 (15%)	21 (39%)	54 (100%)

Of the 20 children aged 6 months - 1 year, 5 died and 15 recovered, 2 with sequelae. Of the 12 patients over 1 year, 5 died and 7 recovered, 2 with sequelae (Table II).

Duration of illness before admission. Table III shows that of the 25 children who had been ill for 2 days or less before admission 15 recovered, 4 with neurological residua; of the 19 children who had been ill 3 - 7 days before admission 15 recovered, 2 with sequelae; and of the 9 patients who had been ill for more than 7 days 6 died and 1 recovered completely.

TABLE III. INFLUENCE OF DURATION OF ILLNESS BEFORE COMMENCEMENT OF TREATMENT ON OUTCOME OF PNEUMOCOCCAL MENINGITIS

Duration of illness before treatment	*Full recovery*	*Recovery with sequelae*	*Deaths*	*Total*
2 days or less	11 (44%)	4 (16%)	10 (40%)	25 (46%*)
3 - 7 days	13 (68%)	2 (11%)	4 (21%)	19 (35%*)
More than 7 days ..	1 (11%)	2 (22%)	6 (67%)	9 (17%*)
Not recorded	—	—	1 (100%)	1 (2%*)

* Percentage of total cases.

Associated lesions. Pneumonia was present in 6 of the 54 children, pertussis and pulmonary tuberculosis in 1 each, purulent otitis media in 8, and advanced malnutrition in 4, of whom 3 died and 1 was discharged blind, deaf and spastic (Table IV).

TABLE IV. INFLUENCE OF ASSOCIATED LESIONS ON OUTCOME OF PNEUMOCOCCAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
Acute pneumonia ..	2	—	4	6
Other pulmonary pathology	2	—	—	2
Purulent otitis media ..	7	—	1	8
Malnutrition	—	1	3	4

Neurological manifestations. Of the 25 patients with clouding of consciousness on arrival in hospital 5 recovered completely, whereas of the 29 who were conscious 20 made a full recovery. Convulsions occurred in 29 patients

TABLE V. INFLUENCE OF NEUROLOGICAL MANIFESTATIONS ON OUTCOME OF PNEUMOCOCCAL MENINGITIS

	Complete recovery	*Recovery with sequelae*	*Deaths*	*Total*
Comatose on admission ..	2	1	8	11
Stuporose on admission ..	3	4	7	14
Conscious on admission ..	20	3	6	29
Convulsions with clouding of consciousness ..	4 } 10	4 } 5	11 } 14	19 } 29
Convulsions with full consciousness	6 }	1 }	3 }	10 }
No convulsions	15	3	7	25

and were distributed among all age groups. Fourteen of the deaths (66% of total deaths) occurred in the patients who had convulsions. (Table V.)

Fever. All 7 patients whose temperature returned to normal within 4 days or less after admission recovered completely. Of those whose temperature remained elevated for 5 - 10 days 13 (76%) did well; 6 of the children with subdural effusions fell into this group. The incidence of neurological sequelae was high in patients in whom pyrexia persisted for more than 10 days (Table VI). The height of the pyrexia on or after admission was of no prognostic significance.

TABLE VI. PROGNOSTIC SIGNIFICANCE OF DURATION OF PYREXIA AFTER COMMENCEMENT OF TREATMENT IN 33 NON-FATAL CASES OF PNEUMOCOCCAL MENINGITIS

Duration of pyrexia	*Full recovery*	*Permanent neurological damage*	*Transient subdural effusions*	*Total*
4 days or less	7	—	—	7
5 - 10 days	13	4	6	17
More than 10 days	5	4	2	9

Period of illness in hospital. From Table VII it can be seen that 7 children were clinically well within 14 days, 14 others had recovered by the 28th day; and 7 remained in hospital for more than 28 days, including 4 with subdural effusions and severe neurological sequelae. These 4 were kept in hospital until there was no further improvement and/or until they could take feeds by mouth. One of these patients remained in hospital for 74 days. Only 3 of all these patients relapsed and required re-admission to hospital.

TABLE VII. DURATION OF HOSPITAL STAY IN RELATION TO COURSE OF PNEUMOCOCCAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Subdural effusion*	*Total*
14 days or less	7	—	—	7
15 - 28 days	14	5	4	19
Over 28 days	3	4	4	7

Bacterial Sensitivity to Antibiotics

Cultures from 22 patients were tested for sensitivity to antibiotics. All were sensitive to penicillin and oxytetracycline, all but 2 were sensitive to chloramphenicol and chlortetracycline, and all but 1 were sensitive to tetracycline; 7 strains were completely insensitive to sulphonamides; and 4 were resistant to streptomycin.

TABLE VIII. MODE OF PENICILLIN ADMINISTRATION AND RECOVERY RATE FROM PNEUMOCOCCAL MENINGITIS

Treatment Group	*Full recovery*	*Recovery with sequelae*	*Deaths*	*Total*
I. (*a*) 1 million units IM penicillin hourly	7	–	4	11
(*b*) As above + IT penicillin	6 } 13 (65%)	1 } 1 (5%)	2 } 6 (30%)	9 } 20
II. (*a*) 1 million units penicillin IM every 2 hours	4	1	7	12
(*b*) As above + IT penicillin	4 } 8 (35%)	6 } 7 (30%)	1 } 8 (35%)	11 } 23
III. 1 million units IM penicillin 3 hourly	1	–	–	1
IV. (*a*) Low doses of IM penicillin 4 - 6 hourly	2	—	–	2
(*b*) As above + IT therapy	1 } 3	—	4 } 4	5 } 7
V. Death before commencement of treatment	—	—	—	3

IM = intramuscular. IT = intrathecal

Treatment

The effect of penicillin dosage on recovery. Table VIII shows that there was no significant difference in death rate between group I (hourly injections) and group II (2-hourly injections); but the number of complete recoveries in group I was 13 (65%), whereas it was only 8 (35%) in group II. The results in group I(*a*) (IM penicillin only and I(*b*) (IM penicillin and IT penicillin) were similar; but in group II(*a*) there were 7 deaths and 1 recovery with sequelae, and in II(*b*) 1 death and 6 recoveries with sequelae. The latter group received 2-hourly IM penicillin with IT penicillin.

Discussion

Prognosis

Our results show that there are a number of factors which affect the prognosis of pneumococcal meningitis adversely. The most outstanding of these was a depressed level of consciousness on admission, which was found in 48% of cases.

A bad result was also commoner in children under 1 year of age, who comprised 78% of our cases. Where a poor nutritional state coexisted with meningitis the final result was always bad. Other adverse factors of less significance were the presence of pneumonia and a pyrexia which persisted for more than 10 days after commencement of treatment. Results were also poor in children in whom meningitis remained untreated for 7 days or more.

However, patients with an illness of less than 48 hours before admission still had a significant mortality, but those with an illness for 3 - 7 days had the lowest number of deaths. A possible explanation for this difference is that children with overwhelming infection are brought to hospital early, whereas a delay may occur before the parents seek medical advice for those children in whom the disease is less acute. We are unable to explain why the mortality was significantly higher in girls than in boys. This has not been reported elsewhere.

While most of our findings are in agreement with those of other authors,[3-13] there are some points of variance. The incidence of clouding of consciousness and convulsions was much higher in our series than in those of others,[10,14] and this may help to account for our poor results. A small series reported with outstandingly good results had a very low incidence of coma and stupor.[10]

The deleterious effect of malnutrition on the outcome has not been noted elsewhere, but we cannot overlook it because malnutrition is common in children attending this hospital.[15]

Other associated lesions were an infrequent occurrence in our survey in comparison with other reported series.[4,14]

Focal neurological signs, either with or without clouding of consciousness, had little bearing on the outcome, which is in contrast with conclusions drawn by Zilberg.[13] It has often been stressed that the outcome of meningitis may be improved if subdural effusions are discovered and treated early.[6,10,16] This was borne out in our series, and of the 8 patients in whom effusions occurred, 6 recovered completely.

Treatment

As many of the 15 patients who died within 24 hours of admission received energetic treatment, it seems un-

likely that any form of therapy employed would have been effective in these children. If these are excluded from the series the mortality rate becomes considerably reduced.

Penicillin

In this series the pneumococcus was always highly sensitive to penicillin in *in vitro* testing. Unfortunately penicillin does not cross the blood-brain barrier easily[17,18] even in the presence of inflamed meninges.[19] This barrier is penetrated adequately only when the blood level of penicillin reaches a very high peak such as one obtains with an IM injection of 1 mega-unit.[20] Similar levels are not reached with continuous intravenous therapy.[21] Massive IM doses given every 2 hours usually result in CSF levels ranging from 0·08 to 1·25 u./ml.[22] These levels, however, are reached only about 8 hours after commencement of 2-hourly IM injections and this makes it advisable to give an IT injection of 10,000 - 20,000 u. of penicillin at the beginning of treatment.[22] In our series better results were obtained when this initial IT dose was given in addition to 2-hourly IM penicillin (Table VIII, group II*b*).

After an IM injection of 1 million units of penicillin the peak serum level is usually attained within 20 minutes, and the level then falls rapidly in the first hour to a quarter of the peak concentration, and to an eighth in the second hour.[20] Penetration of the blood-brain barrier, therefore, occurs only during a part of this 2-hour period. Thus it seems reasonable to assume that hourly injections would maintain higher penicillin levels in the CSF than 2-hourly injections. We have used this hourly regimen in 20 patients with a marked reduction in the sequela rate (Table VIII, group I).

Complications from this massive penicillin dosage are rare. In a few patients injection abscesses were noted and occasionally oedema of both lower limbs occurs in very small children; allergic manifestations have not been noted in this series. Repeated injections inflict considerable pain in conscious patients and may cause psychological trauma. Nevertheless, this drastic form of therapy is justified by the improved results we achieved.

It might be thought that the type of therapy outlined above could be matched by widely-spaced IM injections and repeated IT instillations of penicillin for many days. This approach has been tried,[5,10,23] but was finally discarded in favour of 2-hourly IM injections without IT therapy.[14]

The rôle of sulphonamides cannot be evaluated from this series, because we lacked controls, since there were only 7 patients who did not receive them. There was a high incidence of *in vitro* resistance to these drugs, which were used mainly for their supposed synergistic effect with penicillin.[24,25]

Broad-spectrum Antibiotics

Of the broad-spectrum antibiotics in use at present chloramphenicol and tetracycline appear to be the most promising in the treatment of pneumococcal meningitis.

Concentrations of chloramphenicol in the CSF have been consistently high after oral and parenteral administration, and in some cases even higher than the serum level.[26] To our knowledge the use of chloramphenicol in pneumococcal meningitis has been limited to only a few patients.[27,28] As its administration is easy and side-effects few,[29] we consider that this drug should be afforded a more extensive trial notwithstanding that two cultures from our cases were resistant to it.

The oral administration of tetracycline, even in high dosage, results in inadequate levels in the CSF[30] and parenteral use is therefore essential.[30] To achieve adequate CSF levels of 0·75 - 3·0 μg./ml., the dosage recommended is 75 mg. per kg. bw per day (initially IM), but this leads to necrosis and abscess formation at the site of injections.[30]. In the only series reported in which this drug was used alone, 22 mg. was administered per kg. bw per day. There was a recovery rate of 73% with 14% sequelae.[13]

Chlortetracycline and oxytetracycline do not cross the blood-brain barrier as readily as tetracycline[29,31-33] and have similar disadvantages.

INFLUENZAL MENINGITIS

During the period under review there were 32 patients with meningitis caused by *Haemophilus influenzae*. Their ages ranged from 3 months to 2 years; 6 (19%) were under 6 months, 17 (53%) between 6 months and 1 year, and 9 (28%) between 1 and 2 years (Table IX). There were 18 boys and 14 girls.

Thirteen patients received both streptomycin (20 mg. per lb. bw per day) and sulphadiazine (2½ gr. per lb. bw per day); and 9 patients received chloramphenicol palmitate, of which 6 were also given sulphadiazine. A further 9 children were treated with a combination of streptomycin, sulphadiazine and chloramphenicol. Chloramphenicol was given to 7 patients in doses of over 60 mg. per lb. bw per day (Table XIII).

Results

Of the 32 patients 28 (88%) survived, but 8 remained with neurological sequelae. All but one of the 4 deaths occurred within 24 hours of admission; the exception was a malnourished child who had a 3 weeks' history of convulsions, remained stuporose in hospital, and died after 7 days. All the fatal cases were 6 - 12 months old (Table IX).

TABLE IX. INFLUENCE OF AGE OF PATIENT ON OUTCOME OF INFLUENZAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
Less than 6 months ..	5	1	–	6 (19%)
6 months - 1 year ..	8	5	4	17 (53%)
Over 1 year	7	2	–	9 (28%)
	20 (63%)	8 (25%)	4 (12%)	32 (100%)

Subdural effusions were discovered in 7 (22%) cases; none of these patients died, but 2 were left with neurological sequelae (Table XIII).

Factors of Prognostic Significance

Duration of illness before admission to hospital. Table X shows that of the 13 children who had been ill for 2 days or less before admission to hospital, 11 recovered,

TABLE X. INFLUENCE OF DURATION OF ILLNESS BEFORE COMMENCEMENT OF TREATMENT ON OUTCOME OF INFLUENZAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
Less than 2 days	8	3	2	13
3 - 7 days	7	3	—	10
More than 7 days ..	5	2	2	9

3 with residua. All 10 children who had been ill for 3 - 7 days before admission survived but 3 remained with

neurological sequelae. Of the 9 patients who had been ill for more than 7 days 2 died; of the survivors 2 had neurological residua.

Associated lesions. Five children were malnourished, and of these 2 died and 3 remained with residua. Other associated lesions were found in 11 patients and were limited to pneumonia (6) and purulent otitis media (5).

Neurological manifestations. Of the 13 patients with clouding of consciousness on arrival in hospital 3 recovered completely, whereas of the 19 who were conscious 17 made a full recovery. In 18 (56%) of the patients

TABLE XI. INFLUENCE OF NEUROLOGICAL MANIFESTATIONS ON OUTCOME OF INFLUENZAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
Coma on admission	2 } 3	2 } 6	1 } 4	5 } 13
Stupor on admission	1 }	4 }	3 }	8 }
Conscious on admission	17	2	0	19
Focal neurological signs	2	2	0	4
Convulsions + clouding of consciousness	1 } 8	5 } 6	4 } 4	10 } 18
Convulsions + full consciousness	7 }	1 }	0 }	8 }
No convulsions	12	2	0	14

convulsions occurred. All the fatalities took place in this group, while only 8 cases (44%) recovered fully. Of the cases without convulsions 11 (78%) recovered completely. (Table XI.) Of the total of 8 patients with neurological damage 5 had decerebrate rigidity, 2 remained with a spastic hemiparesis, and 1 had a flaccid paralysis of an arm. These 8 patients were evenly distributed among all age-groups (Table IX).

Fever. There were 13 patients who became apyrexial within 10 days of admission and only 1 of these had neurological sequelae. In 15 patients the fever persisted for more than 10 days and 7 of these had neurological damage.

Period of illness in hospital. The duration of the patients' stay in hospital is analysed in Table XII in relation to their degree of recovery. Only 3 cases were clinically well within 14 days after arrival in hospital. A

TABLE XII. DURATION OF HOSPITAL STAY IN RELATION TO COURSE OF INFLUENZAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Subdural effusions*	*Total*
14 days or less	3	—	—	3
15 - 21 days	11	2	2	13
More than 21 days	6	6	5	12

further 13 patients recovered by the 21st day, among which were 2 patients with subdural effusions and 2 with neurological sequelae. Twelve children remained in hospital for more than 21 days; these included 6 with neurological residua and 5 with subdural effusions. One patient remained in hospital for 68 days; this child had a brainstem lesion with cortical atrophy. A relapse occurred in 2 children; both were readmitted to hospital and survived, 1 with sequelae.

Bacterial Sensitivity to Antibiotics

Cultures from 18 patients were tested for sensitivity to antibiotics. All were sensitive to chloramphenicol; 3 were resistant to streptomycin, 1 to tetracycline, 3 to oxytetracycline and 4 to chlortetracycline.

Treatment

Of the 13 patients who received a combination of streptomycin and sulphadiazine without chloramphenicol, 3 died and 10 recovered, 3 with residua. Of the 18 patients

TABLE XIII. EFFECT OF TREATMENT ON OUTCOME OF INFLUENZAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
Streptomycin + sulphadiazine	7	3	3	13
Streptomycin + sulphadiazine + chloramphenicol	5	3	1	9
Chloramphenicol	7	2	—	9
Tetracycline	1	—	—	1

to whom chloramphenicol was administered either alone or with streptomycin, 1 died and 17 recovered, 5 manifesting neurological damage. (Table XIII.)

Discussion

The incidence of influenzal meningitis at this hospital is lower than that of pneumococcal meningitis;[12] similar observations have been made elsewhere in South Africa.[3,13] Outside this country this situation is reversed.[6,27,34,35] Although the mortality of influenzal meningitis is relatively low, the high incidence of residua still makes it a dreaded disease in the Bantu.

In spite of the small number of cases, some factors of prognostic significance have emerged from this survey. The most important single adverse factor was clouding of consciousness; others were malnutrition, and a pyrexia which persisted for 10 days or more after commencement of treatment. Where convulsions were not associated with clouding of consciousness their presence did not seem to affect the outcome (Table XI).

As reported by others, the incidence of subdural effusions was slightly higher than in pneumococcal meningitis.[16,36,37] The occurrence of these effusions did not appear to affect the outcome adversely.

It was impossible to draw conclusions from the results obtained with the 3 treatment schemes used in the series, because the individual groups were too small. A study of the literature shows that the question of the antibiotic of choice is still undecided.[13,35,38-42] In recent years chloramphenicol appears to have become the most favoured drug,[35] and it is worthy of note that all the cultures from our patients were sensitive to it. The superiority of crystalline chloramphenicol over the esterized form has been pointed out.[26,37,43] Only the esterized form was used in this series, and our results would probably have been better if the crystalline form had been used.

MENINGOCOCCAL MENINGITIS

There were 49 sporadic cases of meningococcal meningitis in this survey; no epidemic of the disease occurred during the period. The ages of the patients ranged from 12 days to 9 years; 10 (21%) were under 6 months of age, 16 (33%) between 6 months and 2 years, and 22 (46%) over 2 years (Table XIV). There were 30 boys and 19 girls.

All but 1 patient received IM penicillin in doses ranging from 250,000 u. 6-hourly to 1 mega-unit hourly. All patients received sulphonamides, usually sulphadiazine, in amounts of 2 grains per lb. bw per day, initial dose usually being given parenterally, and subsequent doses orally.

Results

Of the 49 patients 42 (85%) survived, 4 of these with neurological sequelae.

All 7 deaths occurred within 48 hours of admission to hospital; 5 patients died within the first 6 hours. One of the 2 fatal cases with purpura came to autopsy and the adrenal glands were found to be normal.

Subdural effusions were encountered in 3 patients, who were all less than 6 months of age. None had been ill for more than 2 days before admission to hospital and all recovered fully.

Factors influencing the Prognosis

Age. Table XIV shows that 1 death occurred among the 10 children under 6 months of age, while 9 recovered, 2 with neurological damage. Of the 16 children between

TABLE XIV. INFLUENCE OF AGE OF PATIENT ON OUTCOME OF MENINGOCOCCAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
Less than 6 months ..	7	2	1	10 (21%)
6 months - 2 years ..	13	—	3	16 (33%)
Over 2 years	18	2	3	23 (46%)
	38 (77%)	4 (8%)	7 (15%)	49 (100)%

6 months and 2 years, 3 died and the others recovered completely. Of the 23 patients over 2 years of age 3 died and 20 recovered, 2 with neurological sequelae.

Duration of illness before admission to hospital. Deaths were confined almost entirely to children who had been

TABLE XV. INFLUENCE OF DURATION OF DISEASE BEFORE COMMENCEMENT OF TREATMENT ON OUTCOME OF MENINGOCOCCAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
2 days or less	18 (69%)	2	6 (23%)	26
3 - 7 days	15	1	—	16
More than 7 days ..	4	—	1	5
	37	3	7	47

ill for less than 48 hours before admission to hospital (Table XV). Excluding patients who died within 6 hours of admission, there were only 2 deaths among the 43 children receiving treatment.

Neurological manifestations. Of the 16 patients who showed clouding of consciousness on admission to hospital 5 died, whereas of the 33 who were admitted conscious

TABLE XVI. INFLUENCE OF NEUROLOGICAL MANIFESTATIONS ON OUTCOME OF MENINGOCOCCAL MENINGITIS

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*
Comatose on admission	1	1	2	4
Stuporose on admission	9	—	3	12
Conscious on admission	28	3	2	33
Focal neurological signs	1	—	1	2
Convulsions + clouding of consciousness ..	3 } 5	— } 1	2 } 2	5 } 8
Convulsions + full consciousness	2	1	—	3
No convulsions	33	3	5	41

only 2 died; there were 8 patients with convulsions and of these 2 died (Table XVI). Neurological damage occurred in 4 patients; 1 developed nerve deafness and mental retardation, 2 hydrocephalus and 1 severe disturbance of personality.

Other prognostic criteria. Purpura was noted in 7 patients (13%), 2 of whom died. All had been ill for less than 2 days before admission. Fever subsided within 10 days in 30 (71%) of the patients who survived; 28 of these recovered completely. Only 5 children required hospitalization for more than 28 days and of these 3 had neurological damage.

Discussion

In this series meningococcal meningitis occurred slightly less frequently than pneumococcal meningitis. Excluding the 5 patients who died within 6 hours of admission to hospital, the fatality rate was 3·8%, which is similar to that found in other series.[6,34,44] In contrast to other observers, our mortality was not affected by the age of the patient.[44,45]

As in pneumococcal and influenzal meningitis, clouding of consciousness was the most outstandingly adverse prognostic sign. As almost all the deaths occurred in the group which had been ill for less than 2 days before admission to hospital, the presence of fulminating septicaemia was likely[44,46] and may have led to the fatal outcome in these cases. Complications are rare in meningococcal meningitis,[6,14,44,45] and this was substantiated in this survey. The incidence of neurological damage did not appear to be related to the severity of the illness.

Sulphadiazine remains the drug of choice in meningococcal meningitis.[14,35,47-49] It crosses the blood barrier easily. A CSF level of 7 - 10 mg. per 100 ml. is necessary to obtain effective bacteriostasis, and this can be achieved with doses of 2 - 2½ grains per lb. bw per day.[14,47,49] Theoretically, in order to obtain a high blood level of sulphonamide as quickly as possible it is advisable to administer an initial dose intravenously.[37,49] However, in our series the initial dose was administered IM in most cases, and the results have been satisfactory. Provided the patient is not vomiting, subsequent doses may be given orally or by stomach tube.

It has been found in this series that if a minimal fluid intake of 2½ fl. oz. per lb. bw per 24 hours is maintained no renal complications occur, and the additional use of intravenous or oral alkalinizing solutions[49] appears to be unnecessary.

In view of the excellent results obtained with sulphadiazine there seems to be no need to resort to treatment with broad-spectrum antibiotics except in the rare case which fails to respond to sulphonamides. Penicillin, 250,000 u IM 6-hourly, however, should be given in addition to sulphadiazine to combat any septicaemia.[37,48] Being bactericidal, penicillin is preferable for this purpose to sulphadiazine, which is only bacteriostatic.

MENINGITIS CAUSED BY OTHER ORGANISMS

Salmonella meningitis occurred in 4 patients under 6 months of age; 3 died, and 1 recovered completely. *B. coli* was isolated from the CSF of 1 patient and a non-haemolytic streptococcus from the CSF of another; both these children recovered completely.

PURULENT MENINGITIS OF UNKNOWN ORIGIN

The largest individual group in the survey was formed by patients in whom no organism was found in the CSF microscopically or by culture. This may be due to the present day tendency to use antibiotics indiscriminately for apparently minor illnesses, and an increasing number of patients with meningitis are admitted after a varying period of chemotherapeutic or antibiotic treatment at home.[34] Using the diagnostic criteria laid down by Anglin[50] and Wallgren[51] for the diagnosis of aseptic meningitis,

the 63 cases included in this series were considered to be bacterial in origin. Tuberculous menigitis was carefully excluded.

The age incidence of the patients in this group ranged from 6 days to 8 years; 22 (35%) were under 6 months, 19 (30%) between 6 months and 1 year, and 22 (35%) over 1 year (Table XVIII). There were 33 boys and 30 girls.

Six children died before treatment could be started. The remaining 57 patients fell into 3 treatment groups (Table XVII), viz. (1) 12 patients who received IM penicillin in doses ranging from 0·25 mega-unit 6-hourly to

TABLE XVII. MODE OF THERAPY AND RECOVERY RATE IN MENINGITIS OF UNKNOWN AETIOLOGY

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*	*Refused hospital treatment*
Group I (penicillin + sulphadiazine) ..	5 (42%)	2 (17%)	4 (33%)	12	1
Group II (penicillin + sulphadiazine + streptomycin)	15 (60%)	6 (24%)	3 (12%)	25	1
Group III (penicillin + sulphadiazine + chloramphenicol) ..	12 (60%)	4 (20%)	4 (20%)	20	—

1 mega-unit hourly as well as oral sulphadiazine (2 gr. per lb. bw per day); (2) 25 patients who received IM streptomycin (20 mg. per lb. bw per day) as well as penicillin and sulphadiazine; and (3) 20 patients who received oral chloramphenicol ester in doses varying from 30 to 100 mg. per lb. bw per day as well as penicillin and sulphadiazine (Table XVII).

The clinical picture in these patients was not uniform, because most of them were probably suffering from one of the commoner types of meningitis, viz. pneumococcal, influenzal or meningococcal, each of which has some clinical characteristics of its own.

Results

Of the 63 patients 44 (69%) survived but 12 of these remained with neurological sequelae. This appears in Table XVIII, which also shows the difference in these respects in the three age-groups. The nature of the neurological lesions was similar to that found in the meningitides

TABLE XVIII. INFLUENCE OF AGE ON OUTCOME OF MENINGITIS OF UNKNOWN ORIGIN

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*	*Refused hospital treatment*
Less than 6 months ..	11 (50%)	3 (9%)	8 (36%)	22 (35%*)	—
6 months - 1 year ..	7 (57%)	5 (26%)	5 (26%)	19 (30%*)	2 (11%)
Over 12 months ..	14 (64%)	4 (23%)	4 (23%)	22 (35%*)	—
	32 (50%)	12 (19%)	17 (27%)	63 (100%)	2 (4%)

* Percentage of total cases.

mentioned earlier. No subdural effusions were found. As with the other meningitides all deaths occurred soon after admission to hospital, only 4 of the 17 fatal cases surviving for more than 72 hours.

Factors influencing Prognosis

Clouding of consciousness was the most outstanding factor which affected the prognosis adversely. Of the 29 patients (46%) with clouding of consciousness on arrival in hospital 11 (38%) died and 5 (18%) suffered neurological sequelae, whereas of the 34 patients (54%) who were conscious 6 died (18%) and 7 (21%) were left with neurological damage; the outcome was not affected by

TABLE XIX. INFLUENCE OF NEUROLOGICAL MANIFESTATIONS ON OUTCOME OF MENINGITIS OF UNKNOWN AETIOLOGY

	Full recovery	*Recovery with sequelae*	*Deaths*	*Total*	*Refused hospital treatment*
Comatose on admission	4	3	6	13	—
	12 (41%)	5 (18%)	11 (38%)	29(46%*)	
Stuporose on admission	8	2	5	16	1 (2%*)
Conscious on admission	20 (59%)	7 (21%)	6 (18%)	34 (54%*)	1 (2%*)
Focal neurological signs	3	3	3	9	
Convulsions + clouding of consciousness	6	4	7	18	—
	12	6	8	27	
Convulsions + full consciousness	6	2	1	9	1
No convulsions	20	6	9	36	1

* Percentage of total cases.

convulsions provided the patients regained consciousness between seizures (Table XIX).

A bad result was common in patients suffering from malnutrition or diarrhoeal disorders. Advanced malnutrition was present in 8 children; of these 3 died and 4 survived with neurological sequelae. Of the 5 patients with gastro-enteritis 3 died and 2 had neurological residua. There were 17 patients who were known to have received some antibiotic therapy before arrival in hospital; 9 of them had been treated for more than 7 days. A long illness, both with and without treatment, before admission, or fever persisting for more than 10 days after commencement of hospital therapy, had an adverse effect on the outcome.

As in pneumococcal and influenzal meningitis, the prognosis was better in children over 1 year of age. The initial CSF cell-count or sugar level had no detectable prognostic significance.

Discussion

Despite the fact that purulent meningitis of unknown aetiology is becoming increasingly frequent,[34,37] therapy appears to have aroused very little interest. As stated above, most of the patients have probably received inadequate treatment for meningococcal, influenzal or pneumococcal meningitis. Our investigations have shown that the last two diseases are not confined to young infants and that they occur almost as frequently in older children. For this reason best results should be obtained with a combination of drugs effective against *Diplococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*.

In our series a fairly extensive trial was given to two combinations of drugs. However results in group II (Table XVII), which was treated with penicillin, sulphadiazine and streptomycin, did not differ significantly from those in group III, treated with penicillin, sulphadiazine and chloramphenicol. In view of the fact that neither penicillin nor chloramphenicol was used in optimum dosage in these two groups, better results might have been expected if patients had been given penicillin, 1 mega-unit IM hourly and an initial IT injection of 10,000 - 20,000 u., in combination with sulphadiazine, 2½ grains per lb. bw per day initially (parenterally), and crystalline chloramphenicol 100 mg. per lb, bw per day.

Chloramphenicol, although it crosses the blood-brain barrier easily and has a wide range of antibacterial activity,[26] should probably not be used as the only drug, because some of the pneumococcal cases in this survey were shown to be resistant to it. Furthermore no extensive trial has been carried out with chloramphenicol alone.[27,28]

The question of mutual antagonism is raised whenever a combination of antibiotics is used.[39,52,53] It has been shown, however, that this danger, if it exists at all, is only of importance when drugs are used in inadequate amounts.[39,54]

We, therefore, feel that the therapy recommended above is the best available at present for purulent meningitides of unknown aetiology.

SUMMARY

1. 204 cases of purulent meningitis treated at Baragwanath Hospital over 3½ years ending 31 July 1958 are reviewed.

2. Pneumococcal meningitis occurred in 54 patients, of whom 33 survived; influenzal meningitis in 32 patients, of whom 28 survived; and meningococcal meningitis in 49 patients, of whom 42 survived.

In 6 patients less common organisms were found in the CSF. In 63 patients, of whom 44 survived, no organism was found.

3. Prognostic criteria in the clinical picture were evaluated.

4. Treatment regimens used were assessed. The following treatment schemes are recommended:

(*a*) Pneumococcal meningitis:
1 mega-unit of penicillin IM hourly, with an initial IT injection of 10,000 - 20,000 u., with or without sulphadiazine, 2½ gr. per lb. bw per day.

(*b*) Influenzal meningitis:
crystilline chloramphenicol, 100 mg. per lb. bw per day either orally or parenterally.

(*c*) Meningococcal meningitis:
sulphadiazine, 2½ gr. per lb. bw per day initially parenterally, and penicillin, 250,000 u. 6-hourly IM.

(*d*) Purulent meningitis of unknown aetiology:
Penicillin, 1 mega-unit IM hourly, with an initial IT injection of 10,000 - 20,000 u.; sulphadiazine, 2½ gr. per lb. bw per day; and crystalline chloramphenicol, 100 mg. per lb. bw per day.

We wish to express our thanks to Dr. I. Frack, Superintendent of Baragwanath Hospital, for permission to publish these figures, and to Dr. E. Kahn and Dr. S. Wayburne for allowing us to use the clinical material from their wards. Special thanks are due to Dr. E. Kahn and Dr. H. Stein for their help and encouragement in preparing this paper.

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