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Coliform meningitis in the newborn

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Heckmatt, J. Z. (1976). *Archives of Disease in Childhood*, **51**, 569. **Coliform meningitis in the newborn.** Thirty-six patients with coliform meningitis in the 15-year period 1960–1974 are reported. Only 9 patients survived unscathed though the other 5 survivors were not seriously affected. During the septicaemic phase of the illness the cerebrospinal fluid (CSF), though positive on culture, may be otherwise normal. Meningitis can ensue even when the patient is receiving antibiotics to which the organism is sensitive and the possible disadvantages of using a nondiffusible antibiotic must be appreciated. The CSF in *Esch. coli* meningitis can be persistently haemorrhagic which may cause difficulties in the initial diagnosis. It must be emphasized that infective illness in the newborn is often nonspecific in its presentation and that repeated bacteriological investigations are essential in neonates who are unwell.

The treatment of neonatal coliform meningitis even in modern times has been thoroughly unsatisfactory (Yu and Grauaug, 1963). This paper reports our experience of this disease in Glasgow in the past 15 years in an attempt to analyse the causes of failure and to assess the value of the various forms of treatment in use.

Subjects and methods

There were 36 newborn infants with coliform meningitis in the period between 1960 and 1974 at the Queen Mother's Hospital, Royal Maternity Hospital, and the Royal Hospital for Sick Children, Glasgow. The criterion of diagnosis was the presence of a purulent cerebrospinal fluid (CSF) (with a positive CSF culture in all but one in whom *Esch. coli* was grown from the blood), or the histology of the meninges in 4 patients who died before diagnosis. All the 14 survivors were traced and 13 have been examined. Preschool children were assessed on the Mary Sheridan Scale of development and school reports were obtained on the children of school age.

Results

Of the total number of 36 patients, 22 survived the acute infection and 14 died. Of the 22 who survived, 8 died later, leaving 14 survivors. Of the 14 survivors 7 are of school age and all are attending normal school. One girl is in a class one year below that expected for her age and one boy has a large head (62·5 cm at 9½ years) above the 98th centile (Nellhaus, 1968), probably due to arrested hydrocephalus but air studies were not thought to be justified. His scholastic performance is average, he has difficulties with co-ordination but not with spatial orientation. The other 5 children are performing normally at school.

Six of the 7 preschool children are developing normally, though 2, a boy and a girl, have large heads (51·5 cm and 51 cm at 18 months) above the 98th centile (Nellhaus, 1968). The seventh is slow, development being about 2½ years at a chronological age of 3¼ years and she has a drain for hydrocephalus. Unsatisfactory social circumstances may also be a factor in this child's delayed development.

Seven of the 8 children who died later had a drainage operation for hydrocephalus, the ages of death being from 5 months to 9 years. The other patient died of a pseudomonas urinary infection at the age of 2 months and he had dilated ureters and a large bladder.

Table I shows that *Esch. coli* was the commonest organism, unclassified coliforms, proteus, salmonella, pseudomonas, and mixed coliforms forming the rest. Of the 14 survivors 12 had *Esch. coli* infection. In one the coliform was unclassified and there was one case of proteus infection. The 14 survivors had a greater mean birthweight than the 14 patients who died from the infection (Table II). They were older at the time of diagnosis

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TABLE I

Incidence of infecting organisms

Organism	
Esch. coli	22
Unclassified coliforms	4
Proteus	5
Salmonella	1
Pseudomonas	2
Mixed coliforms	2
Total	36

after the first lumbar puncture. In these 2 cases the organism was sensitive *in vitro* to the aminoglycoside prescribed. When the second lumbar puncture was performed in one of these patients the CSF was blood stained with a xanthochromic supernatant fluid which remained so throughout her illness.

Two other patients who had *Esch. coli* meningitis had heavily blood-stained CSF specimens throughout the illness. In one of them the first CSF specimen grew only contaminants and CSF taken after a convulsion 3 days later grew *Esch. coli*,

TABLE II

Distribution of birthweights, age at diagnosis, and length of interval from onset of symptoms to time of diagnosis in three groups of patients

	Mean birthweight (kg) (range)	Mean age at diagnosis (d) (range)	Mean symptom to diagnosis interval (d) (range)
Survivors (n = 14)	3·3 (1·3–4·4)	14½ (1–29)	4 (<1–12)
Late deaths (n = 8)	2·9 (2–3·5)	13 (10–23)	2 (<1–10)
Early deaths (n = 14)	2·4 (1·5–3·6)	8 (2–23)	1½ (<1–6)

and there was a longer interval between the onset of symptoms and the time of diagnosis. There was, however, some overlap between the groups. The most common early signs (Table III) were convulsions, failure to feed, and pyrexia. A bulging fontanelle was less common and neck stiffness and head retraction very uncommon.

The initial CSF specimen was virtually clear in 3 patients (Table IV) and sterile in 2 of these. All 3 had meningitis with a positive *Esch. coli* culture on the second lumbar puncture, though 2 of these patients received an aminoglycoside antibiotic

TABLE III

Early presenting signs

Sign	No. of cases
Convulsion	21
Failure to feed, lethargy	18
Pyrexia	13
Irritability	13
Pallor/cyanosis/collapse	11
Bulging fontanelle	9
Respiratory distress	5
Neck stiffness	2
Head retraction	2

TABLE

3 cases in which meningitis was not

Case no.	Birthweight (kg)	Clinical presentation	First	
			Sugar (mg/100 ml)	Protein (mg/100 ml)
*3 1971	1·7	At 22 d diarrhoea, dehydration	23	558
*11 1973	4·4	At 3 d pyrexia, a convulsion	44	–
*14 1974	3·8	At 16 d hypertonic dehydration	118	240

*See Appendix

though it is likely that meningitis was present at the time of the first lumbar puncture. In neither was the diagnosis made until the second lumbar puncture. In all these 5 patients the blood culture grew *Esch. coli* at the time of the first lumbar puncture.

Chloramphenicol was the drug most often used of the antibiotics started at the time of diagnosis (Fig.) (see Appendix). 4 patients died before a diagnosis of meningitis was made and another died before any antibiotics could be given. All patients received more than one antibiotic throughout the illness and various dosages were used. Chloramphenicol was used in a dose of 50 mg/kg per 24 hours in most cases and the only case of the 'grey baby' syndrome survived. 17 patients received intrathecal antibiotics, 8 surviving. 7 of the 8 patients who had a drain for hydrocephalus received steroids which were started within one day of diagnosis in 5 and later in 2. None of these patients survived. 10 patients in all received steroids started within one day of diagnosis and 4 survived though one has a large head.

One patient relapsed after treatment was stopped. He had received treatment for 18 days and CSF was sterile on culture after 7 days of treatment. He had an intermittent pyrexia after stopping treatment though two lumbar punctures and two blood cultures were sterile. Purulent *Esch. coli* meningitis was found after a convulsion 7 days after stopping treatment. 4 infants were breast fed until the time of the illness. One of these had a mixed coliform infection and there was prolonged rupture of the amniotic membranes in another (48 hours). 3 of these 4 patients survived.

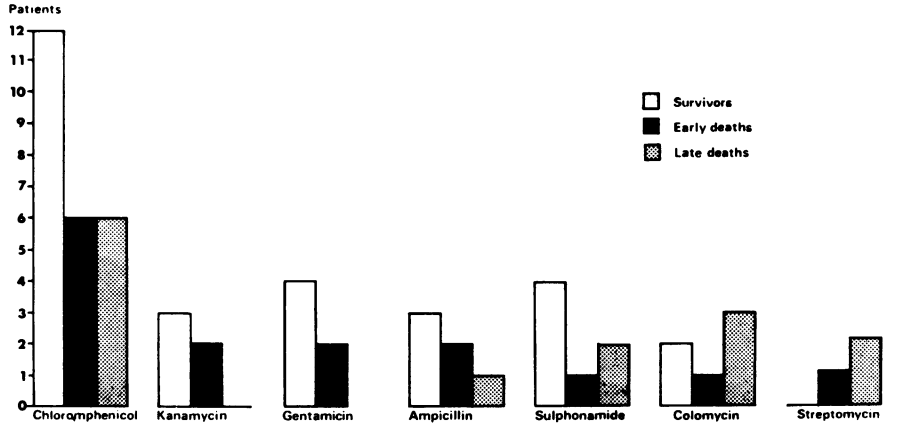

FIG.—*Intramuscular and intravenous antibiotics started at, or within, one day of diagnosis.*

IV

present on the first lumbar puncture

CSF		Antibiotics (mg/kg per day)	Reason for repeat lumbar puncture	Organism
Cells	Culture			
0	Neg	Kanamycin 20 mg Cloxacillin 36 mg	Convulsion	*Esch. coli* sensitive to kanamycin
0	*Esch. coli*	Gentamicin 5 mg Cloxacillin 36 mg	CSF culture +	*Esch. coli* sensitive to gentamicin
20 W 65 R	Neg	None	Blood culture +	*Esch. coli*

Discussion

The poor prognosis in coliform meningitis is illustrated by the survival of only 9 patients out of a total of 36. Early diagnosis of coliform meningitis can be difficult because of the nonspecific presentation and our experience (Table III) is in accord with that of Yu and Grauaug (1963) and many others. The difficulties with early diagnosis may contribute to the poor prognosis (Gellis, 1974). Our survivors, however, tended to be diagnosed at an older age and there was usually a longer interval between the onset of symptoms and the time of diagnosis (Table IV).

Of particular interest are the 3 patients who did not have meningitis at their first lumbar puncture. These 3 patients had a septicaemic illness at the time of presentation and 2 of them received antibiotics which are commonly used in the newborn period. Although the organism was sensitive *in vitro* to the aminoglycoside antibiotic used these 2 patients developed meningitis. Aminoglycosides do not cross the uninflamed meninges (Riley *et al.*, 1971; Garrod, Lambert, and O'Grady, 1973) and it is likely that bacterial colonization of the CSF occurred before inflammation of the meninges could permit an antibiotic to cross into the CSF. Unfortunately, even the use of an antibiotic which diffuses more readily into the CSF such as chloramaphenicol may not always prevent the above sequence of events. One patient who died received chloramphenicol as antibacterial prophylaxis for prolonged rupture of the amniotic membranes but the dosage was inadequate at only 30 mg/kg body weight (Case 27 in Appendix).

The CSF was heavily blood stained in 3 patients, remaining so throughout their illness. Subarachnoid haemorrhage without infection should not be diagnosed in the neonatal period without careful consideration of the possibility of *Esch. coli* meningitis. The patient who relapsed after 18 days of treatment and the other 5 patients not diagnosed at initial lumbar puncture illustrate the importance of obtaining repeated specimens for bacteriology in unwell babies even though they are receiving antibiotics.

It is not possible to be definite about the efficacy of the antibiotics used because of the variety of treatments given. However, apart from the sulphonamides, chloramphenicol diffuses more readily into the CSF than any of the other antibiotics used (Garrod *et al.*, 1973). Bacterial resistance to chloramphenicol is low if chloramphenicol is not routinely used in the newborn nursery (Dery, Marks, and Mackay, 1975).

At present all *Esch. coli* are sensitive to gentamicin (Dery *et al.*, 1975; McAllister, 1975). Gentamicin has been used to treat coliform meningitis without intrathecal injection (Zoumboulakis *et al.*, 1972) and adequate CSF levels without intrathecal injections have been achieved in some cases (Riley *et al.*, 1971; McCracken, 1972). Unfortunately the giving of antibiotics intrathecally at lumbar puncture may only serve to sterilize the lumbar CSF as the antibiotics may not rise to the basal cisterns (Rieselbach *et al.*, 1962; Di Chiro, 1964; Rahal *et al.*, 1974). Further, a controlled trial of 110 patients with neonatal meningitis due to enteric bacteria showed that intrathecal gentamicin was of little therapeutic advantage (McCracken, 1975). This was so in spite of the fact that on intravenous or intramuscular therapy alone it can be difficult to obtain kanamycin or gentamicin levels in the CSF which are consistently greater than the minimum inhibitory concentration of the organism (McCracken, 1972; Moellering and Fischer, 1972).

Although in some patients the infection is well advanced and irreparable damage has already occurred at the time of diagnosis, in others prompt sterilization of the CSF may favourably affect the outcome (McCracken, 1972). Unless the disadvantages of intraventricular or cisternal injection of antibiotics are accepted an antibiotic which diffuses relatively readily into the CSF has an obvious advantage.

It may be that further co-operative studies are needed to assess the value of chloramphenicol and other antibiotics in this disease for even in a large centre such as ours the numbers are too small for a controlled therapeutic trial. It seems clear that the vulnerability of the newborn brain will make meningitis a dangerous condition even when treated early: some other approach such as the investigation of a possible means of prohylaxis may be more successful.

I am grateful to Dr. R. A. Shanks for suggesting this study and guidance in its preparation; to Drs. J. M. Scott and A. A. M. Gibson for reviewing the histology; to Dr. P. Stansfield for help in the follow-up of 2 patients; and to my senior colleagues for permission to study the the cases under their care.

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Addendum

Since the submission of this paper there have been 6 more patients with coliform meningitis. One died shortly after admission to hospital and 5 survive but only 2 apparently unscathed (mean birthweight 3·3 kg; organisms, *Esch. coli* 3, proteus 1, mixed and unclassified coliforms 2). Chloramphenicol 50–75 mg and gentamicin 6–8 mg/kg body weight/day were the antibiotics used in the 5 survivors. The nonspecific presentation of coliform infection undoubtedly contributed to late diagnosis and the poor results of treatment in 2 cases.

In one patient the CSF was evenly blood-stained (sugar 2 mmol/l; 36 mg/100ml) and there were very few white cells present. There were, however, scanty organisms on the Gram film and the culture was positive for *Esch. coli*. This case particularly shows the importance of examining blood-stained CSF with great care when infection is suspected in the newborn.

Appendix overleaf

Appendix

Details of treatment in

Case no.	Year of birth	Birthweight (kg)	Age at diagnosis (d)	Infecting organism	Antibiotics before diagnosis
Final survivors (n = 14)					
1	1960	3·4	22	*Esch. coli*	Pen V
2	1963	3	29	UC	Tetra
3	1964	3·3	½	Proteus	
4	1965	3·4	16	*Esch. coli*	
5	1965	3·5	16	*Esch. coli*	
6	1967	4·0	22	*Esch. coli*	
7	1968	4·0	17	*Esch. coli*	
8	1971	1·3	26	*Esch. coli*	Kana Clox
9	1973	3·4	3	*Esch. coli*	
10	1973	1·5	3	*Esch. coli*	Kana Clox
11	1973	4·4	4	*Esch. coli*	Genta Clox
12	1973	2·8	29	*Esch. coli*	
13	1973	3·8	16	*Esch. coli*	Amp
14	1974	3·8	19	*Esch. coli*	
Initial survivors who died later (n = 8)					
15	1962	3·3	13	Proteus	Erythro Chlor
16	1962	2·7	15	*Esch. coli*	Pen Chlor
17	1963	2	12	UC	
18	1965	3·5	16	Proteus	
19	1965	2·7	11	*Esch. coli*	
20	1966	3	11	*Esch. coli*	Tetra
21	1968	2·7	10	Proteus	
22	1968	3·3	12	Mixed coliforms	Amp
Patients who died of acute infection (n = 14)					
23	1963	2·2	23	UC	
24	1963	3·6	6	*Esch. coli*	Strep
25	1964	3·4	5	Proteus	
26	1964	2·1	8	Pseudomonas	Pen Strep
27	1964	1·5	5	*Esch. coli*	Chlor
28	1965	2·6	7	Pseudomonas	Amp Clox
29	1966	2·3	3	*Esch. coli*	Amp Clox
30	1967	2·2	2	*Esch. coli*	
31	1967	2	10	UC	Amp Clox
32	1968	3·4	13	Salmonella	Amp Clox
33	1970	3·1	20	Proteus	
34	1970	2·9	5	Mixed coliforms	
35	1972	1·6	3	*Esch. coli*	Clox Klana
36	1973	2·0	6	*Esch. coli*	

Amp, ampicillin; Carben, carbenicillin; Ceph, cephaloridine; Chlor, chloramphenicol; Clox, cloxacillin; Colo, colomycin; Dexa, dexasulphonamide; Tetra, tetracycline. LP, administration by lumbar puncture; IV, intraventricular administration; UC, unclassified coliforms;

Treatment for meningitis (mg or units/kg bodyweight per day) Days treated given as age in days in brackets	Intrathecal antibiotics	Steroids	Outcome
Chlor 60–80 mg (22–37) Pen 300 000 u (22–27) Sulph 300 mg (22–32)	Pen LP 10 000 u × 1		
Chlor 100 mg (29–31) Sulph 300 mg (20–33) Strep 60 mg (31–40)	Strep I,V 12·5 mg × 4	Pred 3 mg (33–40)	
Chlor 25–30 mg (½–20) Pen 100 000u (1–2) Sulph 300 mg (1–45)		Pred 5 mg (½–20)	
Chlor 60 mg (16–38) Colo 40 000 u (16–38) Sulph 200 mg (16–18) Amp 15 mg (38–41)	Colo LP 1500 × 3		
Chlor 50 mg (16–44) Colo 125 000 u (16–37)		Pred 3 mg (16–44)	Large head
Chlor 50 mg (22–42) Amp 200 mg (22–42)		Pred 2 mg (22–27)	1 yr behind at school
Amp 50 mg (17–23) Kana 15 mg (17–23) Chlor 50 mg (23–35)			
Kana 20 mg (23–42) Chlor 30 mg (26–42) Amp 300 mg (42–73)			H (Dr)
Kana 12 mg (3–7) Genta 6 mg (7–15) Kana 12 mg (15–23) Chlor 50 mg (17–31) Sulph 300 mg (31–38)			+ CSF at 16d, large head
Genta 5 mg (3–10) Chlor 50–25–60 mg (4–35) Genta 5 mg (16–35)	Genta LP 1 mg × 5		Grey baby syndrome
Chlor 50–100 mg (4–24) Amp 150 mg (24–31)	Genta LP 1 mg × 1		
Amp 100 mg (29–31) Genta 5–7 mg (29–50) Chlor 50 mg (3–5) Kana 15 mg (4–5) Sulph 200 mg (36–51)	Genta LP 3 mg × 3	Pred 5 mg (30–56)	Large head
Chlor 50 mg (16–34) Genta 6 mg (16–34)	Pen LP 3000 × 1		
Chlor 60–70 mg (19–36) Genta 2·5–7·5 mg (19–24) Chlor 100 mg (43–49) Genta 7·5 mg (43–65)	Genta LP (mg × 3 (5 mg ×) 14 after relapse		Relapse at 43 d
Strep 50 mg (13–25) Chlor 50 mg (14–31)	Strep 25 mg LP & IV × 6	Pred 7 mg (25–57)	Died 2 yrs H (Dr)
Sulph 300 mg (15–23) Chlor 50 mg (15–42) Strep 30–50 mg (30–79) Colo 200 000 u (25–31)	Colo 100 000 u IV × 1	Pred 5 mg (15–46)	Died 5 yrs H (Dr)
Chlor 40 mg (12–21) Strep 40 mg (12–17) Colo 150 000 u (13–40) Amp 100 mg (18–37)	Strep 25 mg IV R & L × 5	Pred 5 mg (12–21)	Died 15 m H (Dr)
Chlor 25 mg (16–53) Sulph 150 mg (17–33) Colo 175 000 u (27–60)		Pred 6 mg (19–44)	Died 4 m H (Dr)
Chlor 25–30 mg (11–39) Colo 100 000 u (11–19) Sulph 180 mg (23–39)		Pred 5 mg (11–)	Died 9 yrs H (Dr)
Amp 100 mg (11–35) Sulph 160 mg (14–32)	Ceph 25 mg LP × 4	Pred 6 mg (12–29)	Died 1½ yrs H (Dr)
Chlor 60 mg (10–15) Colo 100 000 u (10–14) Kana 50 mg (13–43)	Colo LP × 1 Carben IV 4 × 8, 5 mg	Pred 6 mg	Died 5 m
Ceph 66 mg (12–26) Chlor 25 mg (14–23)	Ceph LP 3 mg × 5		Died 2 m Urinary infection
			Died 23 days
Strep (6–8) Chlor 50 mg (8) Sulph 250 mg (8)	Pen LP 5000 u × 1 Strep 25 mg × 1		Died 8 days
Chlor 100 mg (5–6)			Died 6 days
Chlor 40 mg (8–9)			Died 9 days
			Died 5 days
Chlor 25 mg (7) Clox 60 mg (7) Amp (7)			Died 7 days
			Died 3 days
			Died 2 days
Chlor 50 mg (10) Colo 150 000 u (10) Sulph 250 mg (10)		Pred 10 mg (10)	Died 10 days
			Died 13 days
Amp 200 mg (20) Kana 15 mg (20)			Died 20 days
Amp 160 mg (5–12) Kana 16 mg (5–12)	Pen LP 5000 u × 1		Died 12 days
Genta 4–6 mg (3–6)		Dexa 1 mg (3–6)	Died 6 days
Chlor 50 mg (6–16) Genta 3 mg (6–16)	Genta LP 1 mg × 5		Died 16 days

methasone; Erythro, erythromycin; Genta, gentamicin; Kana, kanamycin; Pen, penicillin; Pred, prednisolone; Strep, streptomycin; Sulph, H, hydrocephalus; Dr, drainage operation for hydrocephalus.