Intrathecal antibiotic therapy for neonatal meningitis

C. Y. YEUNG

From Paediatric B Unit, Queen Elizabeth Hospital, Hong Kong

Yeung, C. Y. (1976). *Archives of Disease in Childhood*, 51, 686. **Intrathecal antibiotic therapy for neonatal meningitis.** Twenty infants with neonatal meningitis were treated with systemic and lumbar intrathecal antibiotics upon initial diagnosis. Failure to sterilize the CSF in 2–3 days was associated with evidence of ventriculitis in these infants who were then treated with intraventricular antibiotics. 4 infants died, but only 2 of them may be regarded as treatment failure. It is suggested that many deaths from neonatal meningitis may be preventable by early detection and treatment of ventriculitis with intraventricular antibiotics.

Neonatal meningitis is still a frequently fatal condition. Despite the remarkable advances in antibiotic and chemotherapy in recent years, the mortality has not been reduced to the extent anticipated (Riley, 1972). Fosson and Fine (1968) reviewed the experience of 16 centres in 1968 and noted 334 deaths among 478 affected infants. High mortality rate of 60% was noted a few years later in an analysis of the data from the Collaborative Perinatal Research Study (Overall, 1970). Two recent reports from South Africa (MacDonald, 1972) and Montreal (Fitzhardinge *et al.*, 1974) still show a mortality of 50% and 44% respectively.

Persistent ventriculitis has been implicated as the cause of treatment failure in many cases of neonatal meningitis (Lorber, Kalhan, and Mahgrefte, 1970; Salmon, 1972; Moellering and Fischer, 1972). Many workers (Stark, 1968; Lorber *et al.*, 1970; Salmon, 1972; Moellering and Fischer, 1972) have suggested that the level of antibiotics in the ventricular CSF is an important prognostic factor in treatment. This level often has to exceed the minimal inhibitory concentration for the organism many, many fold to be effective. The results of an attempt to treat neonatal meningitis with intrathecal antibiotic therapy and to detect and eradicate ventriculitis early are reported.

Materials and methods

All infants less than 28 days old admitted to the Paediatric B Unit of Queen Elizabeth Hospital with evidence of pyrogenic meningitis are included. The initial diagnosis (Overall, 1970) was made upon the presence of two of the following cerebrospinal fluid (CSF) findings. (1) Increased white cell counts, i.e. $>30/\text{mm}^3$; (2) demonstrable presence of bacteria on

direct smear; and (3) sugar concentration of $<50\%$ of that of the blood, or an absolute level of $<30 \text{ mg}/100 \text{ ml}$. The definitive diagnosis was based entirely on the demonstrable presence of positive culture in the CSF. Other conditions such as partially treated meningitis with sterile CSF and viral or toxoplasmosis encephalopathy which could result in CSF changes are therefore excluded.

Upon initial diagnosis all patients were treated with systemic and intrathecal antibiotics. All infants were started on intramuscular gentamicin $8 \text{ mg}/\text{kg}$ in 3 divided doses and intravenous ampicillin $200\text{--}400 \text{ mg}/\text{kg}$ in 4 divided doses. This combination of systemic antibiotics was given for at least 3 weeks or for a further week after discontinuing intrathecal therapy, whichever was longer. In addition, presence of Gram-positive cocci in the CSF was treated with parenteral cloxacillin. Subsequent adjustment of antibiotics was done entirely according to bacteria identification and sensitivity results.

Lumbar punctures were performed daily to monitor CSF changes and for intrathecal antibiotic therapy. Term infants with Gram-negative infection were given intrathecal gentamicin 4 mg daily and low birthweight infants 2 mg for 7 days. In those who showed persistent growth after 48 hours of therapy intrathecal administration was changed from the lumbar subarachnoid to the intraventricular route. Intrathecal antibiotic was continued after 7 days until the CSF showed all of the following changes: (1) negative growth for at least 3 days; (2) no demonstrable organism on Gram smear; and (3) change of inflammatory cellular response from polymorphonuclear to mononuclears, i.e. a decrease to $<50\%$ polymorph counts in smear. Follow-up lumbar punctures were done at 3- to 10-day intervals until the CSF had returned to normal.

Gram-positive infections were also initially treated with intrathecal gentamicin therapy until definitive identification of the organism, which usually took 24 to 36 hours. Antibiotic therapy would then be changed accordingly and intrathecal methicillin 25 mg daily would be given for staphylococcal infection, and penicillin

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10 000 units daily for pneumococcal and streptococcal infections. The duration of therapy and criteria for stopping therapy was similar to that in Gram-negative infection.

Infants who showed signs of increased intracranial pressure and features of midbrain compression (Williams, Swanson, and Chapman, 1964) were treated with intramuscular dexamethasone 1 mg 8 hourly for 3-5 days after starting antibiotics.

Results

Twenty infants with neonatal bacterial meningitis were included in this study. 16 had Gram-negative infections and 4 had Gram-positive pathogens. The mortality rate was 20%. 3 deaths were due to Gram-negative meningitis (Table I). 2 infants (Cases 17 and 13) died at 3 and

TABLE I
Features of infants with neonatal meningitis treated with intrathecal antibiotics

Case no.	Gestation (w)	Sex	Age (d)	Infecting organism	Before therapy		Associated conditions	Discharge		Follow-up	
					Onset (d)	Anti-biotics (d)		Age (d)	Condition	Age (m)	Findings
1	40	M	14	<i>Esch coli</i>	2	0	Septicaemia	45	Normal	4	Normal
2	39	M	12	"	1	0	Birth asphyxia	43	Normal	3	Normal
3	40	M	27	"	14	13		75	Deaf	30	Normal
4	36	F	21	"	3	3		65	Subdural effusion treated	—	—
5	39	M	9	"	$\frac{1}{2}$	0	Septicaemia Necrotizing enterocolitis	39	Normal	3	Normal
6	34	M	1	"	1	1	Birth asphyxia	38	Floppy	—	—
7	34	M	25	<i>Pseudomonas</i>	5	5	DIC necrotizing enterocolitis, septicaemia	55	Hydrocephalus	18	Arrested hydrocephalus, mildly retarded
8	36	M	24	<i>Pseudomonas</i>	4	4	Septicaemia, DIC, skin sepsis, necrotizing enterocolitis	26	Death		
9	41	M	27	<i>Bacillus subtilis</i>	2	2		58	Normal	4	Normal
10	35	M	23	<i>Bacillus subtilis</i>	5	5		51	Normal	—	—
11	34	F	1	<i>Mima polymorpha</i>	1	0	Unattended birth, septicaemia	31	Normal		
12	39	F	7	<i>Mima polymorpha</i>	2	0	DIC, pulmonary haemorrhage, septicaemia	9	Death		
13	40	M	10	<i>B. Proteus</i>	4	4		10	Death (9 h)		
14	40	M	3	<i>Klebsiella</i>	$\frac{1}{2}$	0	Severe jaundice	28	Normal	10	Normal
15	35	M	11	<i>Paracolon bacilli</i>	1	0	Skin sepsis	41	Normal	—	—
16	38	M	3	<i>Flavobacterium</i>	1	1		78	Hydrocephalus, subdural effusion treated		Died at 3½ m, cerebral bleeding at operation for hydrocephalus
17	39	F	19	<i>Pneumococcus</i>	2	0	Septicaemia, gastric perforation, neurogenic bladder	19	Death (3 h)		
18	40	F	22	<i>Pneumococcus</i>	5	5	Uncontrolled convulsions for 48 h	55	Cerebral palsy, subdural effusion	30	Cerebral palsy, severe retardation
19	41	M	26	β -haemolytic streptococcus	2	0	Septicaemia	45	Normal		
20	40	M	24	<i>Staph. aureus</i>	3	3	Skin boils, otitis, and pneumatoceles	62	Normal		

9 hours after admission, one (Case 17) deteriorating so rapidly that she never had the opportunity of receiving intrathecal therapy. The other 2 (Cases 8 and 12) died at 34 and 26 hours after admission, each having been treated twice with intrathecal antibiotic. Necropsy findings in these 4 infants showed acute pyogenic meningitis (Berman and Banker, 1966) with purulent exudates over the surface of the brain and in the ventricles, and varying degrees of cerebral oedema. Moderate ventricular dilatation was also seen in Case 12. 2 infants (Cases 8 and 12) who had evidence of disseminated intravascular coagulopathy (Corrigan, Walker, and May, 1968) during life, showed multiple bleeding foci at post mortem; Case 12 actually died of respiratory failure with massive pulmonary haemorrhage.

In addition to treatment with systemic gentamicin and ampicillin, and intrathecal gentamicin, Case 16 who had *Flavobacterium* infection was also treated with systemic erythromycin for 3 weeks and carbenicillin for 2 weeks because of sensitivity results. In 3 infants with Gram-positive pathogens the systemic antibiotics were changed appropriately to penicillin for the pneumococcal (Case 18) and streptococcal (Case 19) infection 2 days after initiation of antimicrobial therapy. The infant (Case 20) with staphylococcal meningitis was treated with combination of gentamicin and methicillin.

Six of the 16 infants with Gram-negative infections were found to have ventriculitis (Lorber *et al.*, 1970; Salmon, 1972) and were treated with daily intraventricular antibiotics (Table II). Cases 3

and 7 had meningitis for 14 and 5 days respectively before admission and were partially treated with antibiotics, Case 3 having also received two intrathecal gentamicin injections. Both continued to show positive growth from the lumbar CSF. They had immediate ventricular CSF analyses on admission showing florid pictures of pyogenic ventriculitis and were treated with intraventricular gentamicin.

Intraventricular antibiotics were given to the other infants because of signs of ventriculitis (Lorber *et al.*, 1970; Salmon, 1972) and failure of lumbar intrathecal therapy to sterilize the CSF in 2-3 days. 2 of the 4 infants with Gram-positive infections were also treated with intraventricular antibiotics. Case 18 was admitted in moribund condition with partially treated pneumococcal meningitis and was immediately given intraventricular penicillin therapy after finding thick purulent exudates from the ventricles. Case 20, who had multiple staphylococcal abscesses in the body, also showed thick pus discharging into the ventricles and was treated with intraventricular methicillin until the CSF showed signs of improvement and was free of organisms. He had a 6-week course of antibiotic treatment for multiple staphylococcal lesions, continuing 3 further weeks after CSF returned to normal.

Follow-up assessments were available on 9 of the 16 surviving infants ranging from 3 months to 2½ years (Table I). 6 infants were found to be normal at follow-up, 2 had minor neurological deficit, and one (Case 18) who had had decerebrate

TABLE II
Features of infants with pyogenic meningitis treated with IV antibiotics

Case no.	Gestation (w)	Sex	Age (d)	Infecting organism	Antibiotics	Duration (d)	Initial CSF findings				CSF conversion after treatment (d)	
							Protein	Sugar (mg/100 ml)	Cells (/mm ³)	Poly-morphs (%)	Absence of organism	Other
3	40	M	27	<i>Esch. coli</i>	IT	14	200	18	240	70	10	38
4	36	F	21	<i>Esch. coli</i>	IV	20	400	23	1200	60		
					IT	2	270	12	160	95		
7	34	M	25	<i>Pseudomonas</i>	IV	7	500	15	120	95	3	30
10	35	M	23	<i>B. subtilis</i>	IV	7	150	10	1240	90	2	24
					IT	3	120	15	128	100	5	28
					IV	5	150	10	150	90		
15	35	M	11	<i>Paracolon bacilli</i>	IT	2	200	50	220	90	4	10
					IV	7	250	20	250	100		
16	38	M	3	<i>Flavobacterium</i>	IT	1	500	10	200	90	12	40
					IV	16	450	<5	1500	100		
18	40	F	22	<i>Pneumococcus</i>	IV	14	500	10	2500	100	5	26
20	40	M	24	<i>Staph. aureus</i>	IT	1						
					IV	7	270	35	1240	95	3	21

IV, intraventricular;

IT, intrathecal (lumbar).

rigidity on admission was in an institution at 2½ years with cerebral palsy and marked mental retardation. Towards the end of the 5th week of gentamicin treatment deafness was noted in one infant (Case 3) shown by failure to respond to the rattles and musical box as he had earlier during the course of his illness. Gentamicin was withdrawn and ampicillin 400 mg/kg continued for another week because of persistent raised cells ($>200/\text{m}^3$) and low sugar ($<30 \text{ mg}/100 \text{ ml}$) in CSF. His hearing returned 5 weeks later and at 2½ years he was perfectly normal with a normal audiometry result. Of the other 7 survivors who failed to return for follow-up, 5 were clinically normal at the time of discharge from hospital.

Discussion

Effective treatment of neonatal meningitis depends on the eradication of the pathogen and adequate organization of the inflammatory response. Clearance of the micro-organisms from the meninges is facilitated by chemotherapeutic and antimicrobial agents which inhibit multiplication and kill the bacteria enhancing their removal by the host. Failure to achieve a therapeutic level may explain many treatment failures, since antibiotics vary greatly in their ability to penetrate the 'blood-brain barrier' (Rahal, 1972; McCracken, 1974), and even with the same agent, penetration of this barrier varies tremendously with the course of the meningitis (McCracken, 1974; Smith, 1973).

Antibiotics which are distributed poorly in the CSF, such as gentamicin, have been given intrathecally to treat Gram-negative meningitis with variable reported success (Newman and Holt, 1971; Smilack and McCloskey, 1972; Graybill, Mann, and Charache, 1973). The preliminary report of a large series (McCracken, 1975) from a multicentre collaborative study in the United States recently showed that lumbar intrathecal antibiotic therapy has produced an apparent but no significant improvement of survival rate. The central issue probably still lies with the achievement of adequate therapeutic levels of antibiotics in the CSF bathing the cerebral hemispheres and the ventricles.

Materials injected through the lumbar puncture needle may fail to diffuse beyond the lumbar space (Rieselbach *et al.*, 1962) due to technical or other reasons. It has been shown in radioactive studies that although radioactivities are demonstrable in the basal cisterns an hour after an intrathecal injection into the lumbar subarachnoid space (Di Chiro, 1964), in order to attain radioactivities beyond the basal cisterns a volume of at least 10–25% of the total estimated CSF volume may be necessary

(Rieselbach *et al.*, 1962). In the clinical situation the volume of antibiotic injected could hardly compare with this amount.

In an infant with pyogenic meningitis treated with the usual dosage of intramuscular gentamicin, persistent infection and very low concentration of the antibiotic was detected in the lumbar CSF (Moellering and Fischer, 1972). Intrathecal treatment through lumbar puncture with 1–2 mg gentamicin also failed to produce both sterilization and adequate concentration in the ventricular CSF. Only direct injection of the antibiotic into the ventricle was able to raise it to effective therapeutic levels. We have had similar experience in 2 infants with *Esch. coli* meningitis at the McMaster University Neonatal Unit recently (unpublished observation).

Six infants with Gram-negative infections and 2 Gram-positive ones in the present study were found to have evidence of ventriculitis (Lorber *et al.*, 1970; Salmon, 1972). Intraventricular antibiotic therapy in these infants has been associated with 100% survival. Apparently raising the antibiotic concentration in the ventricular CSF has produced good results. Follow-up assessment was available in 6 infants treated intraventricularly (Cases 3, 7, 10, 15, 18, 20); 4 showed no neurological deficit (Table II).

Since the institution of intrathecal antibiotic therapy in the hospital in which this series was collected, the mortality of neonatal meningitis has been markedly reduced from 70% to 20%. 2 of the 4 deaths occurred in less than 9 hours after admission and in one infant (Case 17) intrathecal therapy was not even started. These deaths apparently could not be attributable to failure of the therapeutic measures. The other 2 infants died within 48 hours of admission and post-mortem examination showed features of acute meningitis and pyogenic ventriculitis in both. This finding raises the question of whether more aggressive search for evidence of ventriculitis and earlier intraventricular therapy might have prevented these deaths.

No clinical complications were encountered in the infants who received intraventricular antibiotic therapy, except in Case 16 (Table II) who developed unilateral subdural effusion which was chemically identified as CSF and believed to be the result of leakage from the ventricle. The condition resolved after three subdural taps draining the effusion. Neurotoxicity from direct intrathecal or intraventricular injection of antibiotics should be entertained (Lerner, Smith, and Weinstein, 1967; Arcieri *et al.*, 1970). Only one infant (Case 3)

developed transient deafness, which has not been recorded as a feature of gentamicin toxicity (Arcieri *et al.*, 1970) though very high levels of gentamicin in the ventricular system could have been responsible. No other complications were encountered.

Long-term follow-up studies were available in 9 of the survivors. 6 were found to be normal on follow-up visits, and a further 5 infants were clinically normal at the time of discharge from hospital, although behavioural and learning difficulties may not have come to the surface in such short-term assessment.

This study supports the idea that ventriculitis may be an important factor (Lorber *et al.*, 1970; Salmon, 1972; Moellering and Fischer, 1972; Stark, 1968) in the outcome of neonatal meningitis. Early detection and treatment of pyogenic ventriculitis may improve survival. This may not necessarily be achieved by lumbar intrathecal injection of antibiotics. In cases of persistent signs of infection, search for evidence of ventriculitis is warranted and direct intraventricular instillation of antibiotic has proved to be highly effective.

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Correspondence to Dr. C. Y. Yeung, Department of Pediatrics, McMaster University Medical Centre, Hamilton, Ontario, Canada L8S 4J9.