

Neonatal group B streptococcal meningitis

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SUMMARY Bacteriological and clinical data on 68 children with neonatal group B streptococcal meningitis were analysed as part of a wider study of bacterial meningitis undertaken between 1976 and 1982. Twenty five per cent of patients died and there was no difference in the mortality rate between early and late onset disease. Sixteen per cent of the infants weighed less than 2500 g at birth but in 50% no predisposing aetiological factor was found. *Streptococcus agalactiae* type III was isolated in 57% of the patients.

In 1935 Lancefield and Hare¹ first isolated group B streptococci from the vaginas of women postpartum and in 1938 Fry² found group B streptococci in vaginal cultures from both symptomatic and asymptomatic women at the time of delivery. Despite these early observations, however, group B streptococcus continued for many years to be considered primarily as the organism responsible for mastitis in cows and was therefore named *Streptococcus agalactiae*. Eickhoff³ stressed the importance of group B streptococci as a cause of neonatal infection in 1964.

Group B streptococcus is now recognised as the first or second most common cause of neonatal meningitis in the United States.⁴ Together with *Escherichia coli*, and for reasons that are largely unknown, it accounts for most cases of meningitis in infants between birth and age 27 days.^{5,6} In the Netherlands, *Escherichia coli* causes 47% and group B streptococcus 24% of neonatal meningitis.

A collection of strains of bacterial isolates from patients with meningitis has been built up in our laboratory in collaboration with other laboratories in the Netherlands over the past 24 years. Between 1959 and 1975 strains of *Neisseria meningitidis* only were collected but from mid-1975 strains of all bacterial species causing meningitis have been included.

To analyse the problem of neonatal meningitis in the Netherlands more precisely we examined retrospectively clinical information on the collected strains. Almost all published reports on neonatal meningitis have come from university hospitals; only a minority of our collected strains, however, were isolated from patients in these hospitals.⁷ We report our experience of neonatal group B streptococcal meningitis in the Netherlands between 1976 and 1982; we have tried to analyse the causes and the

relation between bacterial data and clinical outcome in this potentially curable disease.

Patients and methods

Samples of cerebrospinal fluid obtained between the day of birth and age 27 days were positive for bacteriological culture in all the neonates included in the study. Between January 1, 1976 and December 31, 1982 isolated strains were sent to our laboratory and were identified by biochemical and physiological characteristics as described by Cowan and Steel.⁸ Serotyping was performed by Dr H W B Engel and Dr D G Groothuis and co-workers at the State Institute of Health (Rijks Instituut voor de Volksgezondheid, Bilthoven). Bacteriological strains and clinical information were collected in collaboration with bacteriologists and paediatricians looking after the infants.

Each case was examined for the following risk factors found during pregnancy, delivery, and subsequent physical examination:

- (1) Low birthweight (2500 g, or less);
- (2) Maternal urinary tract infection during the last month of pregnancy;
- (3) Prolonged rupture of membranes (longer than 12 hours);
- (4) Maternal fever during labour (temperature of 37.5°C, or more);
- (5) Endometritis postpartum;
- (6) Prematurity (gestational age less than 37 weeks);
- (7) Postmaturity (gestational age 42 weeks, or more);
- (8) Small for gestational age (according to the paediatrician);
- (9) Twin birth;

- (10) Delivery assisted (forceps, vacuum), prolonged (one hour, or more), or caesarean section;
- (11) Congenital defects.

We considered the case mortality rate in district general and university hospitals. Infants with meningitis transferred from a general hospital to a university hospital for intensive care were considered to be 'general' neonates.

Statistical methods. χ^2 test with Yates's correction and Fisher's exact test were used.⁹ Differences with a probability of 0.05 by the appropriate null hypothesis were considered significant.

Results

Age at diagnosis. The age at diagnosis of the 68 infants ranged between 0 and 25 days (Fig. 1). Most infants were diagnosed between day 0 and day 4 of life. Forty six infants (68%) had early onset (between day 0 and day 4) meningitis and 22 suffered late onset (day 5 to day 27) disease.

Seasonal variation. There was a seasonal variation in group B streptococcal meningitis. Only 7 of the 68 cases (10%) occurred during the months of May, June, and July (Fig. 2).

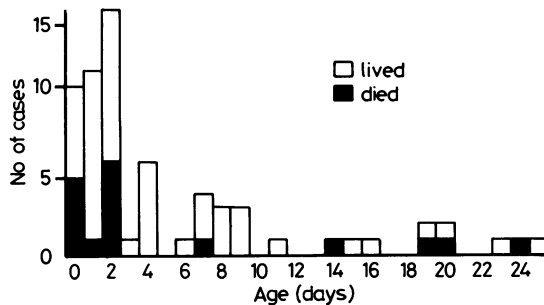


Fig. 1 Number of cases related to age at diagnosis (n=68).

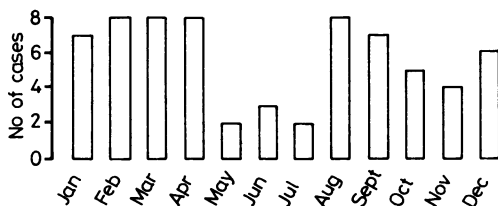


Fig. 2 Number of cases related to seasonal variation (n=68).

Congenital defects. No recognised congenital defects were found among these infants.

Boy:girl ratio. There were 34 boys and 34 girls—a ratio of 1.0. The early onset group comprised 23 boys and 23 girls and the late onset group 11 boys and 11 girls.

Mortality related to sex and age. The case mortality rate was 25% (17 of 68; 11 boys and 6 girls). No difference in the mortality rate was seen between the early onset group (26%; 12 of 46) and the late onset group (23%; 5 of 22).

Birthweight. Sixteen per cent (11 of 68) of the neonates weighed 2500 g, or less at birth (Table 1). The case mortality rate in this low birthweight group was 55% (6 of 11); in the group weighing 2501 to 3000 g it was 42% (5 of 11) and in the infants of birthweight greater than 3000 g it was 13% (6 of 45). The difference in the case mortality rate between the low birthweight group (less than 2500 g; 6 of 11) and the group weighing more than 2500 g (11 of 57) was significant (P=0.0036).

Gestational age at birth. A gestational age of less than 35 weeks seemed to be a special risk factor for a fatal outcome of the disease (Table 2). The case mortality rate in the group with a gestational age of 35 weeks or more was much lower (18%; 11 of 60) than that of the group born at less than 35 weeks' gestation (75%; 6 of 8). (P=0.0023).

Infections in the mother. Three of the 68 infants (4%) were delivered to mothers with recognised fever during labour (temperature 37.5°C, or more). No bacterial strains were isolated from samples of

Table 1 Mortality related to birthweight in 68 neonates with early and late onset group B streptococcal meningitis

Birthweight (g)	Early onset (0-4 days)	Late onset (5-27 days)	Total	Case mortality rate
1001-1500	3 (3)	—	3 (3)	1.0
1501-2000	3 (2)	1	4 (2)	0.5
2001-2500	2	2 (1)	4 (1)	0.25
2501-3000	9 (3)	3 (2)	12 (5)	0.42
3001-3500	15 (2)	7 (1)	22 (3)	0.14
3501-4000	13 (2)	7	20 (2)	0.1
4001-4500	—	2 (1)	2 (1)	0.5
4501-5000	1	—	1	0.0
Total	46 (12)	22 (5)	68 (17)	
Case mortality rate	0.26	0.23		0.25

No of dead patients in parentheses.

Table 2 *Mortality related to gestational age in 68 infants with early and late onset neonatal group B streptococcal meningitis*

Gestational age (weeks)	Early onset (0-4 days)	Late onset (5-27 days)	Total	Case mortality rate
≤26 to <28	2 (2)		2 (2)	1.0
28 to <32	2 (2)		2 (2)	1.0
32 to <35	2 (1)	2 (1)	4 (2)	0.5
35 to <37	5 (1)	2	7 (1)	0.14
37 to <42	31 (5)	18 (4)	49 (9)	0.18
≥42	4 (1)		4 (1)	0.25
Total Case mortality rate	46 (12)	22 (5)	68 (17)	0.25

No of dead patients in parentheses.

blood or urine taken from these mothers during labour.

Two neonates contracted meningitis after their mothers developed endometritis. The first developed meningitis (late onset disease) 16 months after her brother (in this series) had suffered neonatal meningitis (late onset disease). The brother and sister had no recognised risk factors (except endometritis in the mother after delivery of the girl). Brother and sister were both positive for group B streptococcus type III. No cervical swab from the mother was cultured. The second child in this series who developed meningitis (early onset) after maternal endometritis postpartum died; her nurse was positive (culture of hands) for group B streptococci (not serotyped). None of the mothers suffered urinary tract infections in the last month of pregnancy.

Prolonged rupture of maternal membranes. This occurred in 10 (15%) of labours. All of these neonates developed early onset disease. Four of the 10 (40%) had a gestational age of less than 37 weeks and two of these died.

Other risk factors. Three twins, two of whom were second born developed neonatal meningitis (Table 3). All these infants died. Two weighed less than 2000 g and the third 3200 g at birth. There were obstetrical problems during delivery in 12 infants, most of whom (9 of 12) developed meningitis between day 0 and day 4 of age. Four neonates were small for gestational age.

Meningitis in neonates with no known risk factors. In 51% (35 of 68) meningitis occurred in the absence of any known risk factor (Table 4). This occurred in 48% (22 of 46) of the early onset cases and in 60%

Table 3 *Mortality related to each risk factor in 68 infants with early and late onset neonatal group B streptococcal meningitis*

Risk factor	Early onset (0-4 days)	Late onset (5-27 days)	Total	Case mortality rate
Prolonged rupture of membranes (> 12 hours)	10 (3)		10 (3)	0.3
Maternal fever during labour	2 (1)	1	3 (1)	0.33
Endometritis postpartum	1 (1)	1	2 (1)	0.5
Small for gestational age	2 (1)	2 (1)	4 (2)	0.5
Twin birth	3 (3)		3 (3)	1.0
Forceps/vacuum assisted delivery	4 (1)	2	6 (1)	0.16
Caesarean section	2 (1)	1	3 (1)	0.33
Prolonged delivery (≥1 hour)	3 (2)		3 (2)	0.67

No of dead patients in parentheses.

Table 4 *Mortality related to presence or absence of risk factors in 68 infants with early and late onset neonatal group B streptococcal meningitis*

	Early onset (0-4 days)	Late onset (5-27 days)	Total	Case mortality rate
Absence of risk factor(s)	22 (2)	13 (3)	35 (5)	0.14
Presence of risk factor(s)	24 (10)	9 (2)	33 (12)	0.36
Total Case mortality rates	46 (12)	22 (5)	68 (17)	0.25

No of dead patients in parentheses.

(13 of 22) of the late onset cases. The case mortality rate in the group with one or more risk factors was 36% (12 of 33) compared with 14% (5 of 35) in the group with no recognised risk factors ($P=0.05$).

Complications. No relapses of meningitis occurred after completion of the course of antimicrobial treatment. A ventriculoperitoneal shunt was placed in only one infant because of hydrocephalus caused by meningitis.

Death. Meningitis was diagnosed at necropsy and by postmortem culture of cerebrospinal fluid in two neonates of 27 and 33 weeks' gestation. The clinical diagnosis had been idiopathic respiratory distress syndrome in both cases.

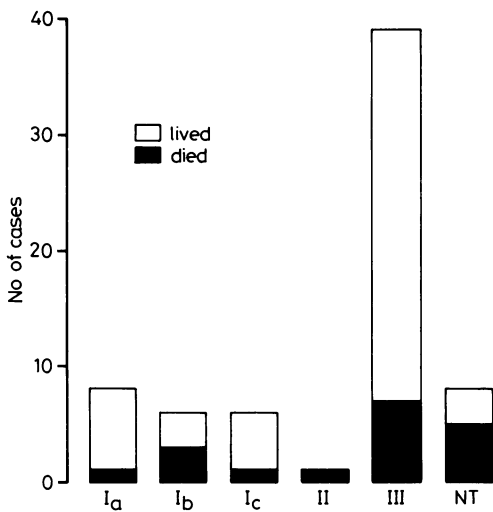


Fig. 3 Serotyping of strains in relation to mortality (n=68).

Ninety three per cent of infants (14 of 15) diagnosed during life died within three days after meningitis was diagnosed. Seven neonates died on the day of diagnosis.

Death related to type of hospital. Most strains (50) of group B streptococcus were isolated in general hospitals; only 18 strains were isolated in the university hospitals. The case mortality rate in the general hospitals was 20% (10 of 50) compared with 39% (7 of 18) in the university hospitals ($P=0.12$).

Serotyping in relation to death, (Fig. 3). Serotype III was the most commonly isolated and was found in 57% (39 of 68) infants. Type IA was isolated in 12% (8 of 68) infants, type IB in 9% (6 of 68), IC in 9% (6 of 68), and type II in one infant. Eight strains were non-typable (NT). Type III was more frequently isolated in late onset (68%; 15 of 22) than in early onset meningitis (52%; 24 of 46). The case mortality rate in the neonates with group B streptococcus type III was low (18%; 7 of 39) compared with neonates with other serotypes (34%; 10 of 29). In the type III group, 14 of 39 neonates (36%) had recognised risk factors compared with 19 of 29 in the remainder (66%) ($P=0.029$).

Discussion

From 1940 to 1964 sporadic cases of group B streptococcal meningitis were reported to occur congenitally and in neonates. Nowadays most reported cases are in infants under the age of 3

months.^{3 10-12} Two distinct clinical types have been defined in neonates;^{10 11} the first, early onset, is observed in neonates aged 5 days or less. Acquisition of group B streptococcus in this age group is from the maternal genital tract in utero or during passage through the birth canal.¹³ The fact that all our neonates with prolonged rupture of maternal membranes (over 12 hours) and most of those whose delivery was assisted developed meningitis between day 0 and day 4 of life supports this.

Late onset in contrast with early onset disease, occurs after the first week of life and is not often associated with maternal obstetrical complications.^{3 11 13 14} Our results confirm this finding.

Our data suggest that there is a dip in the occurrence of meningitis during late spring and early summer.

In contrast with neonatal meningitis caused by *E. coli* (personal communication) none of our infants with group B streptococcal meningitis had congenital defects.

The boy:girl ratio of 1.0 in our series is in agreement with the findings of Baker¹⁵ who noted 55% girls. Thirumoorthi and Dajani,¹⁶ however, found a preponderance of girls (68%).

The case mortality rate was 25% in our series and was strongly associated with risk factors found during pregnancy, delivery, and on physical examination. Other papers report a case mortality rate of about 50%¹⁵ but in almost all the work was undertaken in university hospitals with more underlying diseases in neonates and mothers. Only a minority of our bacterial strains were isolated in university hospitals. Seventy two per cent (13 of 18) of the neonates at the university hospitals had one or more abnormalities compared with 40% (20 of 50) at the local hospitals. The high risk infants—those of gestational age less than 35 weeks (case mortality 6 of 8 in our series), twin pregnancies (3 of 3), and amniotic membranes ruptured for longer than 12 hours (6 of 10)—were over represented in the university hospitals. Other authors have reported a greater number of very small infants with neonatal meningitis.^{17 18} Most (84%) of the neonates in our series weighed more than 2500 g at birth. Preterm infants with a high case mortality rate were a minority in our series.

In our infants only one nosocomial infection was suspected but other studies report that nosocomial transmission may play a role in neonatal meningitis. Paredes *et al*¹⁹ showed that 40% of neonates became colonised in the newborn nursery. Medical staff must be vigilant and swab cultures of the environment, equipment, and staff should be taken if there is any evidence of hospital infection.

About 50% of our neonates who developed meningitis had no recognised risk factor. Most of these infants developed meningitis caused by the *S agalactiae* type III (71%; 25 of 35). The overall frequency of the type III strain in our series was high (57%) as it has been in other reports on neonatal meningitis.²⁰ This supports the view that *S agalactiae* type III has a special ability to invade the cerebrospinal fluid of the neonate.

The recommended treatment for group B streptococcal infection is benzylpenicillin, either alone or in combination with an aminoglycoside.²¹ The choice of treatment in our population of infants varied too much to evaluate. All received benzylpenicillin or ampicillin in combination with or without an aminoglycoside, chloramphenicol or co-trimoxazol.

Most deaths occurred within three days after the onset of meningitis. Seven neonates died on the first day of illness. These neonates must probably be considered too critically ill to be cured.

The differential diagnosis of idiopathic respiratory distress syndrome and group B streptococcal meningitis is difficult.²² We would advise blood cultures, a gastric aspirate culture, and a lumbar puncture in every neonate who does not improve after treatment for idiopathic respiratory distress syndrome. To examine the question of whether neonatal infections are being missed, prospective studies of postmortem cultures (lumbar punctures, intracardial puncture etc) are needed, especially in neonates who die in the first week of life.

The aim of our study was to analyse the relation between bacteriological data and clinical outcome in neonatal group B streptococcal meningitis in the Netherlands. We will continue this study to enlarge our knowledge of this disease.

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References

- Lancefield RC, Hare R. Serologic differentiation of pathogenic and non-pathogenic strains of hemolytic streptococci from parturient women. *J Exp Med* 1935;**61**:335-49.
- Fry RM. Fatal infections by hemolytic streptococcus group B. *Lancet* 1938;**i**:199-201.
- Eickhoff TC, Klein JO, Daly K, Ingall D, Finland M. Neonatal sepsis and other infections due to group B beta-hemolytic streptococci. *N Engl J Med* 1964;**271**:1221-8.
- Anthony BF, Okada DM. The emergence of group B streptococci in infections of the newborn infant. *Annu Rev Med* 1977;**28**:355-69.
- Communicable Disease Surveillance Centre. Neonatal septicaemia and meningitis. *Br Med J* 1978;**i**:55.
- Faden H. Etiologic agents for meningitis in early life. *NY State J Med* 1981;**81**:1618-20.
- Zanen HC. Bacteriële meningitis in Nederland. Annual reports 1976-82. Amsterdam: University of Amsterdam, 1983.
- Cowan ST. Cowan and Steel's manual for the identification of medical bacteria. Cambridge: Cambridge University Press, 1974.
- Fischer RA, Yates F. Statistical tables for biological, agricultural and medical research. 6th ed. London: Longmans, 1974.
- Franciosi RA, Knostman JD, Zimmerman RA. Group B streptococcal neonatal and infant infections. *J Pediatr* 1973;**82**:707-18.
- Baker CJ, Barrett FF, Gordon RC, Yow MD. Suppurative meningitis due to streptococci of Lancefield group B: a study in 33 infants. *J Pediatr* 1973;**82**:724-9.
- Anthony BF, Concepcion NF. Group B streptococcus in a general hospital. *J Infect Dis* 1975;**132**:561-7.
- Baker CJ, Barrett FF. Transmission of group B streptococci among parturient women and their neonates. *J Pediatr* 1973;**83**:919-25.
- Vollman JH, Smith W, Ballard ET, Light JJ. Early onset group B streptococcal disease: clinical roentgenographic, and pathologic features. *J Pediatr* 1976;**89**:199-203.
- Baker CJ. Summary of the workshop on perinatal infections due to group B streptococcus. *J Infect Dis* 1977;**136**:137-52.
- Thirumoorthi MC, Dajani AS. Systemic infections due to group B streptococci: a 7 year experience at a children's hospital. In: Parker MT, ed. *Basic concepts of streptococci and streptococcal diseases*. Windsor, Berks: Reedbooks, 1982.
- Quirante J, Ceballos R, Cassidy G. Group B beta-hemolytic streptococcal infection in the newborn, early onset infection. *Am J Dis Child* 1974;**128**:659-65.
- Stewardson-Krieger PB, Gotoff SP. Risk factors in early-onset neonatal group B streptococcal infections. *Infection* 1978;**6**:50-3.
- Paredes A, Wong P, Mason EO, Clark D, Yow MD, Barrett FF. Nosocomial transmission of group B streptococci in a newborn nursery. *Pediatrics* 1977;**59**:679-82.
- Baker CJ, Barrett FF. Group B streptococcal infections in infants, the importance of various serotypes. *JAMA* 1974;**230**:1158-60.
- Jacobs MR, Kelly F, Speck WT. Susceptibility of group B streptococci to 16 beta-lactam antibiotics, including new penicillin and cephalosporin derivatives. *Antimicrob Agents Chemother* 1982;**22**:897-900.
- Menke JA, Giacoia GP, Jockin H. Group B beta hemolytic streptococcal sepsis and the idiopathic respiratory distress syndrome: a comparison. *J Pediatr* 1979;**94**:467-71.

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