Archives of Disease in Childhood, 1985, **60**, 542–546

Neonatal septicaemia

T VESIKARI, M JANAS, P GRÖNROOS, N TUPPURAINEN, M RENLUND, P KERO, M KOIVISTO, M KUNNAS, K HEINONEN, R NYMAN, O PETTAY, AND K ÖSTERLUND

Department of Clinical Sciences, University of Tampere, the Departments of Paediatrics, the University Hospitals of Tampere, Helsinki, Turku, Oulu, and Kuopio, State Maternity Hospital, Helsinki, the Central Hospital of Lahti, and the Department of Microbiology, Tampere University Central Hospital, Tampere, Finland

SUMMARY A total of 410 proved cases of neonatal septicaemia from seven Finnish hospitals seen between 1976 and 1980 were reviewed. The annual incidence of neonatal septicaemia was 3 per 1000 births, and overall mortality was 23%. Onset was early in most patients. Symptoms of septicaemia occurred within the first 24 hours of life in 44% and within the first week of life in 90%. In the very early onset disease (within 24 hours) mortality was 30%, compared with 17% in all other cases. Group B streptococcus was the leading cause in very early onset disease (52%) but mortality from infection with this organism was similar to that in other very early onset cases. It is concluded that very early onset neonatal septicaemia, probably of intrauterine origin and caused by group B streptococcus in one half of the cases, constitutes the major form of neonatal septicaemia in Finland and should receive the highest priority in preventive measures.

Neonatal septicaemia remains a major problem in perinatology and paediatric infectious disease. In the past few years attention has been focussed on the growing role of group B streptococcus in neonatal septicaemia in the United States and in Europe.[1–4] Based on an attack rate of 1·3 per 1000 live births and a mortality rate of 55% and 23% for early and late onset infections respectively,[1] Baker estimated that approximately 6000 deaths attributable to group B streptococcus would occur in the United States each year.[2] Thus early onset group B streptococcal infection is more common and carries a greater risk than the late onset form. Late onset disease, however, which accounts for some 30% of all group B streptococcus infections in the United States and United Kingdom,[2 3] may represent a particular problem as it is associated with a high incidence of meningitis.[2] The division line between early and late onset neonatal septicaemia has usually been at 5 or 7 days of age,[2] although some authors have preferred to group cases according to onset before or after the first 48 hours of life.[5 6]

We carried out a five year, multicentre survey of neonatal septicaemia in Finland, the purpose of which was to evaluate the importance of group B streptococcus in relation to other pathogens. We paid particular attention to the time of onset of disease to differentiate between early and late onset cases, because this is important in determining the origin of infection. We also studied the serotypes of group B streptococcus isolated, to see if cases of early or late onset were associated with different serotypes.

Materials and methods

The survey included all the five university hospitals in Finland (Helsinki, Turku, Tampere, Kuopio, and Oulu), the State Maternity Hospital in Helsinki, and the Central Hospital of Lahti. These seven hospitals covered approximately 43% of all births in Finland. Over the five year study period (1976 to 1980) the practice of microbiological diagnosis of suspected neonatal septicaemia was uniform in the seven hospitals; that is, blood and cerebrospinal fluid cultures were routinely taken in all such cases.

Furthermore, access to a microbiological laboratory was good in these hospitals, and it is likely therefore that the overall diagnostic accuracy was good.

The patients included in the survey met the following two criteria: (1) clinical diagnosis of septicaemia or meningitis within the first 28 days of life; and (2) a positive blood or cerebrospinal fluid culture, or both. (It turned out that all the patients with a positive cerebrospinal fluid culture also had a

positive blood culture.) The medical records of all these patients were available for review and the relevant information from these was transferred to identical forms in all seven hospitals. Only information that was uniformly and reliably available from all the hospitals was collected; we chose not to analyse clinical laboratory data in this retrospective survey.

Most of the blood or cerebrospinal fluid culture isolates of group B streptococcus held in the laboratories at Helsinki and Tampere were available for serotyping. Serotyping was performed at the Department of Microbiology, Tampere University Central Hospital, with antisera prepared according to Jelinková.[7] The specificity of the sera was checked by exchanging reference strains and sera with the World Health Organisation Collaborating Center for Reference and Research on Streptococci, Institute of Hygiene and Epidemiology, Prague. Many strains, however, reacted with antisera against both serotypes Ib and Ic, and therefore these strains were grouped together. It was not specifically determined if the strains possessed the bc protein antigen.[8]

Results

A total of 410 cases of neonatal septicaemia were reviewed in the survey. Patients who also had lethal congenital malformations (mainly chromosomal abnormalities and left heart hypoplasia), which were diagnosed but left untreated, were excluded. The overall incidence of neonatal septicaemia in the area and time covered was 3·02 per 1000 live births, and the annual variation was from 2·64 to 3·50 per 1000 with no trend towards increase or decrease over the five year period.

A complete list of bacterial pathogens is given in Table 1. Although a total of 27 different bacteria were implicated as causative organisms, only three accounted for a major share in the aetiology: group B streptococcus 32%, *Staphylococcus aureus* 22%, and *Escherichia coli* 20%. All the remaining 24 bacteria accounted for one fourth of the total cases and these were taken as a fourth aetiologic group in the analyses, in the realisation that the group was very heterogeneous indeed. Ninety three patients died, making the overall mortality 23%.

The onset of symptoms and its relation to mortality of neonatal septicaemia is illustrated in Fig. 1. Almost half the infants had symptoms occurring within the first 24 hours of life, which in many cases meant immediately after birth, and this group had the highest mortality (30%). Infants suffering septicaemia in the first day of life were clearly separable from the remainder and there was no apparent division line in incidence or mortality

Table 1 *Blood culture isolates from 410 cases of neonatal septicaemia in 7 Finnish hospitals between 1975 and 1980*

Bacteria	*No*	*(%)*
Group B streptococcus	130	(32)
Staphylococcus aureus	90	(22)
Escherichia coli	81	(20)
Staphylococcus epidermidis	16	
Streptococcus faecalis	15	
Listeria monocytogenes	9	
Klebsiella	8	
Alfa haemolytic streptococci	7	
Peptostreptococci	4	
Proteus	4	
Enterobacter cloacae	3	
Salmonella typhimurium	3	
Acinetobacter	3	(27)
Haemophilus influenzae	3	
Diphtheroides	3	
Bacteroides fragilis	2	
Clostridium sp	1	
Propionibacter	1	
Moraxella	1	
Aerobacter	1	
Bacillus subtilis	1	
Pseudomonas aeruginosa	1	
Salmonella newport	1	
Streptococcus pneumoniae	1	
Streptococcus bovis	1	
Group C streptococcus	1	
Group D streptococcus	1	
Mixed infection	18	

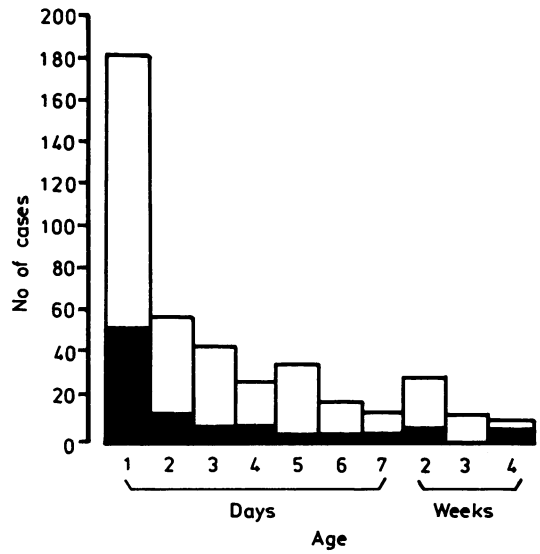

Fig. 1. *Distribution of 410 blood culture positive cases of neonatal septicaemia in relation to the onset of symptoms.*

Open columns represent the number of cases and black columns the number of deaths.

later (Fig. 1). We then divided the cases conventionally into those with symptoms occurring within the first week (early onset) or during the second to fourth weeks (late onset) of life (Table 2).

In cases presenting within the first 24 hours of life, group B streptococcus was the major causative organism, with *E coli* second and *S aureus* third (Table 2). There were seven cases (4%) caused by listeria and in the remaining 40 cases a large number of bacteria were implicated. Septicaemia with onset in the first 24 hours carried a higher mortality than the later onset disease (30% *v* 17%, P<0·001), but mortality from very early onset disease was not dependent on the causative organism. In fact mortality attributable to each pathogen was directly proportional to the aetiologic importance of that pathogen; for example group B streptococcus was responsible for 52% of the deaths, which equalled 30% death rate, or exactly the same as in the total group (Table 2).

The aetiologic distribution in cases presenting during the first week but after the first 24 hours was different from that in the very early onset group, and the outcome was dependent on the causative organism (Table 2). Group B streptococcus infection accounted for only 14% of the cases with zero mortality. *S aureus* was the most common pathogen in this group, but was associated with a relatively low mortality. In contrast, *E coli* was responsible for only 24% of the cases but for 47% of the deaths in the group, equalling to 31% mortality.

The late onset group comprised only 10% of the cases (Table 2). Mortality was 22·5%, which is actually the same as in all the cases with onset in the first week combined. There was one death from group B streptococcus infection, but this was the only fatality among 37 patients with onset after the first 24 hours.

The 'profiles' of the major individual pathogens in relation to onset of symptoms and mortality are presented in Fig. 2. Group B streptococcus infections were characterised by the very early onset: 71·5% began within the first 24 hours and all but one of the deaths were in this group. Most *E coli* infections were also of early onset, but many were clustered around days two to four of life. *Staph aureus* infections occurred rather evenly throughout the neonatal period, and carried a lower mortality than group B streptococcus or *E. coli.*

There were 51 cases of meningitis (determined by positive cerebrospinal fluid culture). Mortality in these cases was 24%, that is the same as in the total group. The two most important pathogens were group B streptococcus and *E coli,* which accounted for 41% of the cases each. The outcome in these two groups was different, however: none of the 21 patients with group B streptococcus meningitis died, whereas *E coli* meningitis was associated with a 33% mortality.

Low birthweight was associated with high mortality from neonatal septicaemia (Table 3) and was thus another important determinant of poor prog-

Table 2 *Neonatal septicaemia with very early, early, and late onset of disease in relation to causative organisms and mortality*

Aetiology	*Very early onset (<24 hrs)*		*Early onset (>24 hrs–7 days*		*Late onset (8–28 days)*	
	No (%)	*Mortality (%)*	*No (%)*	*Mortality (%)*	*No (%)*	*Mortality (%)*
Group B streptococcus	93 (52)	28 (30)	26 (14)	0 (0)	11 (27)	1 (9)
Escherichia coli	26 (14)	8 (31)	45 (24)	14 (31)	10 (10)	3 (30)
Staphylococcus aureus	14 (8)	3 (21)	64 (34)	7 (11)	12 (30)	1 (8)
Other	47 (26)	15 (32)	55 (23)	9 (16)	7 (17)	4 (57)
Total	180 (100)	54 (30)	190 (100)	30 (16)	40 (100)	9 (23)

Table 3 *Outcome of neonatal septicaemia in relation to birthweight and causative organisms*

Aetiology	*Birthweight*					
	≤1500 g		*1500–2500 g*		*>2500 g*	
	No	*Mortality (%)*	*No*	*Mortality (%)*	*No*	*Mortality (%)*
Group B streptococcus	15	11 (73)	36	10 (28)	79	8 (10)
Escherichia coli	15	11 (73)	19	8 (42)	47	6 (13)
Staphylococcus aureus	9	4 (44)	26	4 (15)	55	3 (5)
Other	18	12 (67)	21	7 (33)	70	9 (13)
Total	57	38 (67)	102	29 (28)	251	26 (10)

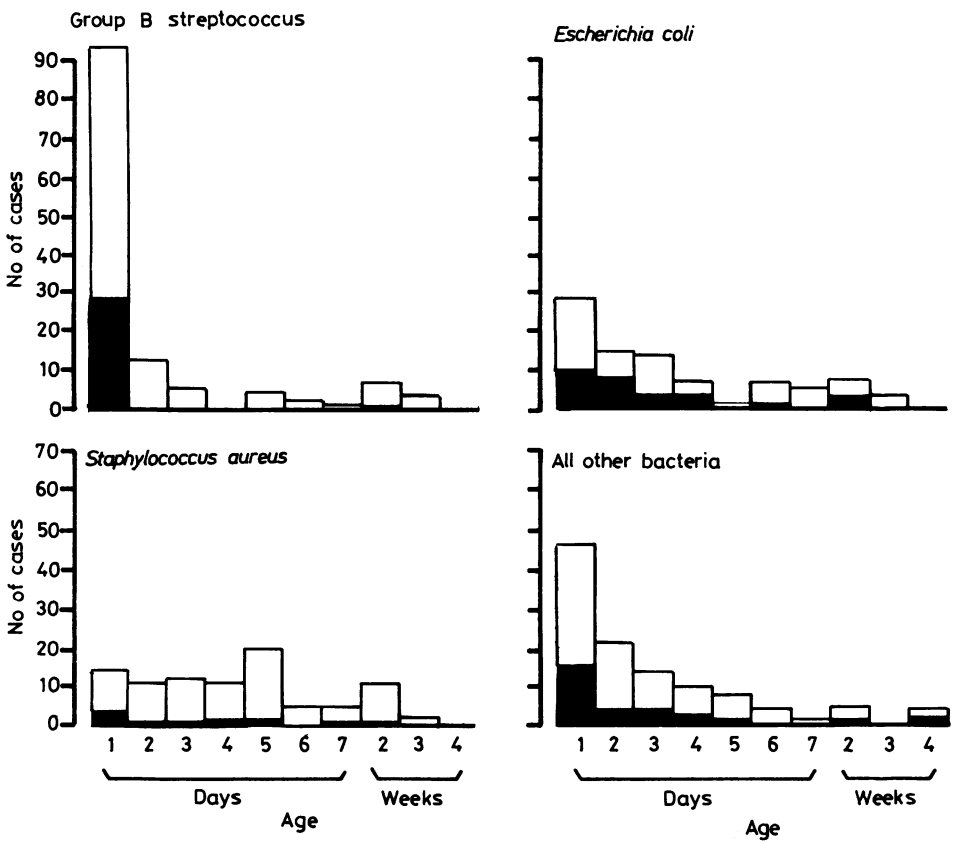

Fig. 2 *Relation between onset of symptoms and outcome of infection in the four major aetiologic groups of neonatal septicaemia in Finland.*

nosis in addition to early onset of symptoms. While the mortality of infants weighing 2500 g or more was only 10%, however, they still accounted for 28% of all deaths.

Altogether 43 blood culture isolates of group B streptococcus were available for serotyping and 41 were typable. The predominant serotypes were Ib or Ic, or both, with 28 (65%) isolates. There were no cases of type Ia, nine cases (21%) of type II, and four cases (9%) of type III. Three of the four isolates of serotype III were from cases with meningitis, but of early onset. Three isolates came from patients with late onset disease; two of them were of serotype I bc and one was not typable.

Discussion

The present survey confirms that neonatal septicaemia is a major problem in perinatology and paediatric infectious disease today in Finland. The survey also showed epidemiological features of neonatal septicaemia that may help direct future preventive measures. These findings were made because of the large study population which resolved any minor fluctuations and variations between hospitals which might have occurred.

The overall incidence of neonatal septicaemia in Finland, 3 per 1000 births, was of the same magnitude as that reported from Sweden for the years 1974–8, with the claim that the incidence in Sweden is increasing.[9 10] We do not have any comparable figures for Finland from previous years, but within the five year study period there was no apparent trend towards an increase. It will be important, however, to continue surveillance of neonatal septicaemia to determine the trend.

Mortality from neonatal septicaemia in Finland was found to be relatively low for all the diagnosed cases combined, for all patients with group B streptococcus septicaemia, and for early and late onset disease separately. At the same time, how-

ever, it is important to note that even with a mortality of 23% and with the present incidence there still are approximately 40 to 50 deaths annually from neonatal septicaemia in Finland. This figure exceeds mortality from any other paediatric infectious disease today.

Very early onset septicaemia was found to be of particular importance. The 'emergence' or virulence of group B streptococcus can hardly alone explain the high incidence and poor prognosis of very early onset disease. Group B streptococcus was responsible for only one half of the cases, and the mortality was the same as in other cases with very early onset. Infection of later onset carried only a 3% mortality, suggesting that group B streptococcus infection is a 'manageable' infection when the host defences are better prepared.

It seems that the outcome of the very early onset form of neonatal septicaemia may be determined by the intrauterine progression of the infection rather than the nature of the pathogen. These infections seem to originate from the birth canal, and the causative organism may colonise the infant before delivery or, alternatively, may be introduced with obstetric examinations or procedures.[10] In any case, it seems (as already suggested by Baker in 1978)[11] that in many cases intrauterine infection must take place well before delivery to allow the infection to reach an overwhelming magnitude by the time of delivery. Amniotic fluid seems to be ineffective against the growth of group B streptococcus,[12] which may partly explain the enhanced role of this pathogen in the very early onset disease. The infection route is probably via lungs, and it has been shown experimentally that alveolar macrophages before birth are unable to restrict the growth of group B streptococcus.[13] Thus the infant may be born with intrauterine pneumonia, with septicaemia and shock either already present or developing shortly thereafter. The management of these patients creates a problem far beyond antimicrobial treatment. Early and rapid diagnosis may be crucial for successful management; this calls for future development of intrauterine diagnostic procedures.

In view of the importance of very early onset disease, we would propose that classification into three groups based on time of onset of symptoms may be justified. By definition the 'very early onset' disease is likely to have its origin in utero, and is therefore separable as one entity. Infections with early onset, perhaps up to the age of one week, may also originate from intrauterine colonisation, but more probably have their origin in the delivery process, whereas disease with a later onset may be the result of a nosocomial or environmental source of infection.

The distribution of group B streptococcus serotypes in neonatal septicaemia in Finland was found to be different from that in the United States and United Kingdom,[2 3] perhaps reflecting the predominance of early onset and the relative absence of late onset disease. In the United States, serotype III is responsible for 90% of the late onset cases, which constitute one third of the total cases.[2] In addition serotype III is found in one third of the early onset cases in these countries.[3] These results are in contrast to the 10% found in the present series. Thus, a vaccine against group B streptococcus serotype III[14] would be of little value in Finland. Further studies in Finland should include serological surveys to determine if the distribution of group B streptococcus serotypes could be correlated with prevalence of type-specific antibodies in mothers. Identification of at risk mothers could then form the basis for future prevention of group B streptococcus septicaemia in the newborn.[4]

References

1 Anthony BF, Okada DM. The emergence of group B streptococci in infections of the newborn infant. *Ann Rev Med* 1977;**28**:355–69.

2 Baker CJ. Group B streptococcal infections in neonates. *Pediatrics in Review* 1979;**1**:5–15.

3 Parker MT. Infections with group-B-streptococci. *J Antimicrob Chemother* 1979;**5**(Suppl A):27–37.

4 Christensen KK, Christensen P, Hägerstrand I, Linden V, Nordbring F, Svenningsen N. The clinical significance of group B streptococci. *J Perinatol Med* 1982;**10**:133–46.

5 Placzek MM, Whitelaw A. Early and late neonatal septicaemia. *Arch Dis Child* 1983;**58**:728–31.

6 Jeffery H, Mitchison R, Wigglesworth JS, Davies PA. Early neonatal bacteraemia. Comparison of group B streptococcal, other Gram-positive and Gram-negative infection. *Arch Dis Child* 1977;**52**:683–6.

7 Jelinková J. Group B streptococci in the human population. *Curr Top Microbiol Immunol* 1977;**76**:127–65.

8 Johnson DR, Ferrieri P. Group B streptococcal I bc protein antigen: distribution of two determinants in wild-type strains of common serotypes. *J Clin Microbiol* 1984;**19**:506–10.

9 Bennett R, Eriksson M, Zetterström R. Increasing incidence of neonatal septicaemia: causative organisms and predisposing risk factors. *Acta Paediatr Scand* 1981;**70**:207–10.

10 Bergvist G, Eriksson M, Zetterström R. Neonatal septicaemia and perinatal risk factors. *Acta Paediatr Scand* 1979;**68**:337–9.

11 Baker CJ. Early onset group B streptococcal disease. *J Pediatr* 1978;**93**:124–5.

12 Evaldson G, Nord CE. Amniotic fluid activity against Bacteroides fragilis and group B streptococci. *Med Microbiol Immunol* 1981;**170**:11–7.

13 Sherman M, Goldstein E, Lippert W, Wennberg R. Group B streptococcal lung infection in neonatal rabbits. *Pediatr Res* 1982;**16**:209–12.

14 Baker CJ, Edwards MS, Kasper DL. Immunogenicity of polysaccharides from type III, group B streptococcus. *J Clin Invest* 1978;**61**:1107–10.

Correspondence to Dr T Vesikari, Department of Clinical Sciences, University of Tampere, 33520 Tampere, Finland.

Received 25 January 1985