Bloodstream infections and perinatal mortality

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SUMMARY Bloodstream infection is demonstrable at necropsy in 21.1% of perinatal deaths but is almost invariably a secondary event, often terminal, contributing to death as a secondary cause. In only 3.8% is infection recorded as the primary cause of death. *Escherichia coli* predominates, and postmortem and antemortem studies alike confirm the tendency of this and other microbes to involve the meninges in the course of bloodstream infection. Fatal viral and fungal infections are rare, and life-threatening disease is overwhelmingly of bacterial origin.

A separate, prospective study of septicaemia in the newborn is reported, and the data are tabulated. The overall incidence in inborn and outborn populations, together with the incidence of specific infections, is stated, and the relationship to birthweight is analysed. The overall mortality for treated cases is 40.7%, the mortality being inversely proportional to birthweight, and highest at 62.5% in those born weighing less than 1000 g. The advent of meningitis (1 in 5 cases of septicaemia) aggravates the mortality (83%). The potential hazard of nursing seriously infected babies is emphasised.

Neonatal sepsis

Neonatal sepsis is defined as a clinical syndrome characterised by systemic signs of infection and accompanied by bacteraemia, occurring in the first month of life.¹ The difficulties of recognising the clinical stigmata of bloodstream infection in the newborn have been emphasised by Davies² and by Klein *et al.*,³ the early signs may be insidious and non-specific, and those of infectious and non-infectious processes are similar.

Klein *et al.*³ estimate that as many as 2% of fetuses are infected *in utero* and up to 10% of infants during delivery or in the first few months of life. Although, clearly, figures are influenced by the clinical acumen of the neonatologist and the vigour with which he pursues microbiological investigation, the reported incidence of neonatal sepsis varies from 1 to 5.2 cases per 1000 livebirths. Low birthweight is the most important factor in its genesis, and wherever rates can be stated with any degree of confidence there is general agreement that they will be 5 to 100 times higher for babies weighing less than 2500 g. Sophisticated life support systems in neonatal intensive care units now allow survival to many babies of birthweight less than 1000 g (Table 1), with corresponding risk of serious sepsis intervening as an intercurrent or terminal event. Thus, paradoxically, despite the advances that have been made in

Table 1 Survival of very low birthweight babies*

Survey	Year	Birthweight (g)	
		< 1000	1000-1500
Maternity Survey	1946	Nil	14 survived
British Perinatal Mortality Survey	1958	7%	27%
British Birth Survey	1970	12%	57%
Queen Charlotte's and Hammersmith Hospitals Survey	1978-91 ³	30%	80%
Lancet 1980	Now	30-50%	85%

*Lancet 1980;i:461-3.

the care of the newborn, the total number of serious infections encountered in specialist neonatal units has increased, with a concomitant rise in the risk of dissemination of pathogens to unaffected babies. Two forms of neonatal sepsis are recognised.

EARLY ONSET DISEASE

Early onset disease occurs in the first week of life as a fulminant systemic illness in babies who are usually premature and of low birthweight and who have been born to women who have undergone abnormal pregnancies and deliveries. Premature and prolonged rupture of the membranes with premature labour, obstetric complications leading to operative or instrumental delivery, maternal or fetal

distress, haemorrhage, maternal anaemia or intercurrent illness, and peripartum fever are all factors prejudicial to the birth of an uninfected baby. The causal bacteria of early onset sepsis are derived from the birth canal and are acquired as a result of an ascending infection in intrauterine life or during passage through the birth canal. Transplacental transmission occurs rarely, but the child may be born with a true congenital bacteraemia. The bacteria associated with early onset sepsis are usually those that are indigenous to the maternal genital tract (Table 2), but rarely adventitious microbes such as β -haemolytic streptococci (Lancefield group A) or *Clostridium perfringens* are isolated. These, too, derive from the infected genital tract. The mortality rate of early onset sepsis is high, lying between 20 and 50%, but it is almost certainly underestimated, for recorded rates usually take no account of stillbirths or of those who survive insufficiently long to allow clinical and microbiological investigation to proceed.

Table 2 Incidence of bacteria potentially pathogenic for the newborn in the maternal vaginal vault (280 subjects)

Bacteria	% Incidence
<i>Staphylococcus epidermidis</i>	66.1
Faecal streptococci	34.3
Anaerobic and microaerophilic streptococci	21.7
<i>Escherichia coli</i>	19.3
β haemolytic streptococci*	8.9
<i>Proteus</i> species	6.1
<i>Staphylococcus aureus</i>	4.6
Non-haemolytic streptococci	4.3
<i>Klebsiella aerogenes</i>	0.7
<i>Pseudomonas aeruginosa</i>	0.4

*Lancefield group A, 0; B, 5.4; C, F, G, 0.7; not groupable, 2.9.

LATE ONSET DISEASE

Late onset disease occurs after the first week of life, although it has been recognised on the fourth day. There are fewer prejudicial maternal peripartum events, but the babies are often afflicted by congenital malformations or illness, or other disease. The microbes responsible are usually those that are being disseminated in the infants' environments, reflecting epidemiologically the distribution of pathogens at large in a particular nursery or intensive care baby unit. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Klebsiella aerogenes* are examples of such pathogens. Cooke *et al.*⁴ and Shinebaum *et al.*⁵ have described the mode of acquisition of *Ps. aeruginosa* and *Kl. aerogenes* in the newborn; both are acquired from the ward environment, and only rarely is the mother the source. Group B streptococci and *Escherichia coli* are causally related to both early onset and late onset disease. However, although the infant usually

acquires *E. coli* from the mother, some babies are colonised by strains from other sources, and there may be spread within the ward.⁶⁻⁸ Postnatal acquisition of group B streptococci has also been documented.⁹ The mortality is lower in late onset neonatal sepsis and is of the order of 10-20%.

It is often difficult to determine the precise onset of neonatal sepsis in babies who are weakly and marasmic from birth, but the diagnosis must be considered in almost every sick newborn infant.¹⁰ Suspicion of serious infectious disease arises in about one-third of babies on our intensive care unit, and 25% to 30% of them are treated with systemic antibiotics. A smaller number have proven bacterial infections (see below). In some seriously handicapped babies, it is no kindness to diagnose or to treat neonatal sepsis as it arises, and early, late onset, or terminal septicaemia is diagnosed definitively at necropsy.

Whether acquired by the fetus *in utero* or by the infant at birth or in early postnatal life, neonatal sepsis is an important cause of perinatal mortality. Pryse-Davies and Hurley¹¹ combined morbid anatomical, histological, and microbiological investigations in a 10-year study of 835 necropsies performed on 130 aborted fetuses of more than 500 g, 371 still-born fetuses, 307 neonates dying in the first week, and 27 neonates dying later in the first month of life, obtaining specimens for microbiological examination from 96.2% of necropsies. Body storage and post-mortem delay did not affect the microbiological findings. Although infection was recorded as a primary cause of death in 32 instances (3.8%) (Table 3) other than in listeriosis and the two cases of intra-uterine infection, septicaemia or neonatal sepsis did not figure as a primary cause of death, and in all cases in which bloodstream infection was demonstrated (21.1%), death was ascribed to other disease or deformity. Bloodstream infection, though very frequent in this necropsy series, was, therefore, almost invariably a secondary event, often terminal, contributing to death in the course of other disease processes. Widely disseminated infection, with some

Table 3 Infections as primary causes of death in 835 perinatal necropsies 1967-76

Diagnosis	% Incidence
Pneumonia	2.5
Meningitis	0.5
Peritonitis	0.3
Intrauterine infection (stillbirth)*	0.2
Coxsackievirus infection	0.1
Listeriosis	0.1
Total	3.8

**Clostridium perfringens*, β haemolytic streptococcus (Lancefield group A).

histological evidence of the same, and the isolation of the same pathogen from the heartblood, cerebrospinal fluid, and bronchi, occurred in 4.4% of 340 necropsies. The causative microbes are shown in Table 4.

Table 4 *Disseminated infection in the perinatal period*

Bacteria	% Incidence in 340 necropsies
<i>Escherichia coli</i>	2.1
<i>Klebsiella aerogenes</i>	0.9
<i>Clostridium perfringens</i>	0.3
Group B streptococcus	0.3
<i>Proteus mirabilis</i>	0.3
<i>Pseudomonas aeruginosa</i>	0.3
Coagulase-positive staphylococcus	0.3
Total	4.4

Thus in the newborn there is a tendency, of the approximate order of 1 in 5, for the meninges to become involved in the course of bloodstream infection. This observation is borne out in clinical practice (see Table 15). Further analysis of the data shows that infection of the bronchial tree with the same microbe as that present in the bloodstream occurs in over 80% of cases of bloodstream infection.

Fatal viral infection is rare in the newborn period, and life-threatening disease is overwhelmingly of bacterial origin. Only five cases (Table 5) have come to necropsy in our hospital in a 17-year period, that is, in 58 160 births. In a further case, intranuclear and intracytoplasmic inclusions suggestive of cytomegalovirus were noted in the lungs of a 28-week gestation baby who survived 37 days; the causes of death included disseminated intravascular coagulation, patent ductus arteriosus, intraventricular haemorrhage, and degenerative changes of the brain. Antemortem blood cultures had been positive and *Kl. aerogenes* was isolated from the heart blood, cerebrospinal fluid, and bronchi at necropsy. Disseminated candidosis is also rare, six cases having been encountered over the same period.

Table 5 *Fatal viral infections as primary causes of death in the perinatal period: rates per 1000 births, 1963-79*

Varicella-Zoster	0.017
Coxsackievirus B ₁	0.017
Herpesvirus hominis	0.051

The microbiological data of Pryse-Davies and Hurley¹¹ have been re-examined, and Tables 6 and 7 show the incidence of neonatal sepsis confirmed or first demonstrated definitively at necropsy in those of the population born at Queen Charlotte's Maternity Hospital for the years 1972-76. They are

expressed as rates per 1000 of the total birth numbers of 17 740. The rate, though low, is appreciable as a percentage of all perinatal mortality, septicaemia contributing to death in about one-fifth of all necropsies performed in those years. The pre-eminent position of the Gram-negative rods as causes is shown in Table 6, and the nature of the infecting microbes, showing the preponderance of *E. coli* among the Gram-negative rods and group B streptococci among the Gram-positive cocci, is shown in Table 7. These figures take no account of successfully treated cases and are concerned only with fatalities. They include stillbirths and late abortions.

Table 6 *Neonatal septicaemia confirmed or demonstrated at necropsy: rates per 1000 births, QCMH 1972-76*

	No. of cases	Rate
All microbes	46	2.59
Gram-negative rods	36	2.03
Gram-positive cocci	9	0.50
<i>Listeria monocytogenes</i>	1	0.06

Table 7 *Neonatal septicaemia confirmed or demonstrated at necropsy: rates per 1000 births, QCMH 1972-76*

	No. of cases	Rate
<i>Escherichia coli</i>	19	1.07
<i>Pseudomonas aeruginosa</i>	7	0.39
<i>Klebsiella aerogenes</i>	6	0.34
Other Gram-negative rods	4	0.23
Group B streptococci	5	0.28
Other streptococci	2	0.11
Staphylococci	2	0.11
<i>Listeria monocytogenes</i>	1	0.06
Total	46	2.59

Septicaemia

A separate study of septicaemia was undertaken for the years 1978-79. As before, microbiological data on the necropsy population were available. The incidence of neonatal sepsis diagnosed during life is shown in Table 8, expressed in terms of rates in all births, and rates in live births only, and based only on babies born at Queen Charlotte's Hospital. Again, Gram-negative rod sepsis predominates; there are few cases (2) of group B streptococcal sepsis, with no fatalities. The only baby with listeriosis was successfully treated. Table 9 expresses the total incidence of all bloodstream infections per 1000 total births for the Queen Charlotte's population and includes those diagnosed and successfully treated, those unsuccessfully treated, stillborn babies with intrauterine infections, and those in whom terminal septicaemia was established at necropsy by histo-

Table 8 *Septicaemia: incidence per 1000 births 1978-79 (QCMH)*

	No. of cases	Per 1000 total births	Per 1000 live births
Antemortem diagnosis (all microbes)	17	2.10 (0.74)	2.11 (0.75)
Gram-negative rods	14	1.72 (0.74)	1.74 (0.75)
Group B streptococcus	2	0.25	0.25
<i>Listeria monocytogenes</i>	1	0.12	0.12

The figures in parentheses are mortality/1000.

logical and microbiological examination. The combined rate gives the total incidence of septicaemia, including neonatal sepsis, intrauterine infection, and terminal septicaemia, in the population under study (8095 births; 150 necropsies; necropsy rate 86.5%). Gram-negative rods outnumber all other microbes by a factor of six. The only instance of bloodstream infection with *Staph. aureus* occurred in the premature fresh stillborn child of a febrile mother transferred to Queen Charlotte's Hospital in labour when signs of fetal distress supervened. The mother was being treated with ampicillin. Pryse-Davies and Hurley¹¹ recorded an incidence of bloodstream infection of 21% in their 10-year series of necropsies, from which the figure of 22% recorded here does not differ.

Twenty-four perinatal deaths in babies born at Queen Charlotte's Hospital were complicated by septicaemia in 1978 and 1979. Only six of these had been definitively diagnosed during life although some had been treated before death for suspected neonatal sepsis. Treatment had been withdrawn in two cases and was never started in others. Five babies weighed more than 2000 g at birth (Table 10),

Table 10 *Perinatal deaths complicated by septicaemia in 24 babies, QCMH 1978-79*

Birthweight (g)	≤1000	≤1600	>2000
Gestational age	10	19	5
	≤30 weeks	≤33 weeks	≥36 weeks
Survival time	18	20	4
	0-5 days	10-30 days	30-55 days
	14	6	4

septicaemia terminating lives that were handicapped and crippled by multiple congenital abnormalities (4) and brain death due to total infarction of the brain (1). The other 19 babies (79%) weighed less than 1600 g (18 < 1500 g; 1 1600 g), and 10 (41.7%) weighed less than 1000 g. The series includes four stillborn babies with intrauterine infections. Survival time of the liveborn ranged from 27 hours to 55 days.

The total number of babies under special or intensive care in 1978 was 559, of whom 43 (7.7%) were referred from other hospitals (Table 11). The Table shows the overall mortality, with the mortality in the two groups of inborn and outborn babies. Naturally, the death rate is much higher in the group of very sick babies referred from other hospitals, and deaths associated with sepsis, established either antemortem (Table 12) or postmortem, are very high indeed at 88%. One-fifth of all referred cases had neonatal sepsis, and 55% of these died (Table 12). The mortality was highest in those with *E. coli* septicaemia, but one child with group B streptococcal sepsis died. The incidence of group B streptococcal sepsis (Table 13) was higher in the outborn babies (7%) than in the inborn (0.25/1000; 0.19% of admissions to the special care baby unit). Although in two of the outborn babies the diagnosis of streptococcal septi-

Table 9 *Septicaemia: incidence per 1000 births 1978-79 (QCMH)*

	No. of cases	Combined rate	Diagnosed		% Incidence in necropsy series
			Antemortem	Postmortem	
Combined antemortem and postmortem diagnosis (all microbes)	33	4.08	2.10	1.98	22.0
Gram-negative rods	28	3.45	1.72	1.73	18.6
Group B streptococcus	2	0.25	0.25	—	1.33
Anaerobic streptococcus	1	0.12	—	0.12	0.67
<i>Listeria monocytogenes</i>	1	0.12	0.12	—	0.67
Coagulase-positive staphylococcus*	1	0.12	—	0.12	0.67

Figures include two stillbirths and one abortion.

*Transferred in labour, baby stillborn.

Table 11 *Babies under special or intensive care, 1978*

	Number	All deaths	Deaths complicated by septicaemia	% of deaths complicated by septicaemia
Total	559	62 (11.1)	30 (5.37)	48.4
From same hospital	516	45 (8.7)	15 (2.9)	33.3
From other hospitals*	43	17 (39.5)	15 (34.9)	88.0

*Includes two cases transferred in utero.

The figures in parentheses are % mortality of total numbers.

Table 12 Septicaemia in 43 babies admitted from other units (1978)

	No. of cases	% of admissions
Antemortem diagnosis	9	20.9 (55.5)
Gram-negative rods	8	18.6 (37.5)
<i>Escherichia coli</i>	3	7.0 (67.0)
<i>Pseudomonas aeruginosa</i>	2	4.7 (0.0)
Other	3	7.0 (0.0)
Group B streptococcus	1	2.3 (100)

The figures in parentheses are % mortality rates.

Table 13 Septicaemia in 43 babies admitted from other units (1978)

	No. of cases	% of admissions	% Incidence in necropsy series
Combined antemortem and postmortem rate	17	39.5	19.3
Gram-negative rods	14	32.5	15.9
Group B streptococci	3	7.0	3.4

caemia was not established during life, it does seem unlikely that the infection could have been acquired from the environment of a unit where streptococcal infection is so infrequent, suggesting that the type of disease was early onset. This diagnosis accords with the clinical history; the babies survived only a few hours.

Relation to birthweight

The relation of the incidence of neonatal sepsis and of septicaemia disclosed at necropsy to birthweight is shown in Table 14. The incidence is highest and the fatality greatest in those weighing less than 1500 g. Of all babies admitted to the unit 2.1% died of neonatal sepsis or had terminal infections complicating other conditions.

Table 14 Septicaemia* in patients in special care baby unit, 1978-79

	No. of admissions	No. of cases	% of admissions
Weight $\leq$ 1500 g	197	22	11.17 (7.1)
Weight $\leq$ 2000 g	343	23	6.7 (4.1)
All admissions	972	36	3.7 (2.1)

*Based on antemortem and postmortem findings.
The figures in parentheses are case fatality percentages.

Table 15 shows the outcome in 27 cases of treated neonatal sepsis. The overall mortality for the group is 40.7%, and the mortality rate is inversely proportional to the birthweight, being highest, at 62.5%, in those born weighing less than 1000 g. One death occurred in babies weighing more than 2000 g. The

Table 15 Mortality in 27 cases of treated neonatal sepsis (septicaemia) 1978-79

Birthweight (g)	No. dead/ No. in group	% mortality
$\leq$ 1000	5/8	62.5
>1000- $\leq$ 1600	4/8	50.0
>1600- $\leq$ 2000	1/3	33.3
$\geq$ 2000	1/8	12.5
Thus,		
$\leq$ 1000	5/8	62.5
$\leq$ 1600	9/16	56.3
$\leq$ 2000	10/19	52.6
In babies in whom meningitis supervened, irrespective of birthweight	5/6	83.0
Whole group	11/27	40.7

mother, from another hospital, was delivered by emergency lower segment caesarean section for fulminating pre-eclamptic toxemia, and the baby survived five days. After initial septicaemia with *Ps. aeruginosa* meningitis supervened on the fourth day and was regarded as the cause of death.

Meningitis

Meningitis is far less frequent than neonatal sepsis and, uncomplicated by septicaemia, did not occur during 1978 and 1979. It occurred with septicaemia in six of the 27 babies treated for neonatal sepsis. In three cases the causative organism was *E. coli*, in two it was *Ps. aeruginosa*, and in one it was *Listeria monocytogenes*. Only the last baby survived. In the necropsy series over the same period, group B streptococci were isolated from the cerebrospinal fluid and bronchi of a 30 weeks' gestation baby (birthweight 1240 g) who survived 40 hours after birth by emergency caesarean section. The mother was transferred in labour, the membranes, which appeared necrotic at delivery, having been ruptured for more than 48 hours. The placenta showed chorioamnionitis with clusters of cocci on and just beneath the amniotic epithelium; clearly, the infection was intrauterine. The microbiological findings were complicated by the isolation of xanthomonas from the heart blood and bronchi.

Discussion

Neonatal sepsis and terminal septicaemia are diseases with an appreciable incidence (2.1%) in babies admitted to the special care baby unit of our hospital. The former is one of the major reasons for the transfer of sick babies from other hospitals, being diagnosed after arrival in just over 20% of all referrals. Either neonatal sepsis or terminal septicaemia contributes to death in 88% of those who

die having been admitted from other units, and in 33% of those inborn babies who die having received intensive or special care (Table 11). They are, thus, major problems of neonatology for, leaving aside the high overall mortality rate (41%) of neonatal sepsis (rising to 62.5% in those of birthweight less than 1000 g and to 83% in those in whom meningitis supervenes), the decision to withdraw or not to institute treatment may add to the microbial hazards of the uninfected who are under active care. Our necropsy studies have shown that over 80% of those with neonatal sepsis or terminal septicaemia harbour the same microbe in the bronchial tree, whence, during life, it may contaminate the attendant's hands and clothing, adjacent fomites, or the larger environment of the special care unit. Containment isolation of dying babies, desirable though it may be, is scarcely feasible in the cramped confines of most intensive care neonatal units. We have drawn attention elsewhere to the danger,¹² alluding to the increasing difficulty of avoiding and controlling late onset disease in units that are already overloaded and overworked with the primary care of low birth-weight babies.

Our studies show that neonatal sepsis and terminal septicaemia are important associated causes of death in the perinatal period, neonatal sepsis caused predominantly by *E. coli* contributing to a perinatal mortality rate of 2.59/1000 total births. While, following recommendations from the British Paediatric Association and the Royal College of Obstetricians and Gynaecologists (1978), there is every hope that infant care will improve and perinatal and neonatal mortality be reduced, it is important that we should continue to study associated causes of death that are both preventable and avoidable.

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