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Outcome of neonatal necrotising enterocolitis: results of the BAPM/CDSC surveillance study, 1981–84

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SUMMARY Neonatologists in 100 special care baby units in the United Kingdom and Ireland collaborated in a four year surveillance study of neonatal necrotising enterocolitis. The average overall annual reporting rate of necrotising enterocolitis for infants in England and Wales was 0·3/1000 live births, but ranged from 9·5/1000 live births in infants weighing less than 1000 g at birth to 0·2/1000 live births in infants weighing 2500 g or more. There were more deaths among girls, infants who weighed less than 1500 g at birth, those whose bleeding was abnormal or who had low peripheral platelet counts, infants with Gram negative bacteraemia, and very low birthweight infants who developed it during the first few days of life. In both boys and girls, and in all birthweight groups, operation was associated with increased mortality.

National surveillance of necrotising enterocolitis was set up by the British Association of Perinatal Medicine (BAPM) and the PHLS Communicable Disease Surveillance Centre (CDSC) in 1980.[1] The objectives were to describe the clinical features of necrotising enterocolitis, to monitor its pattern of occurrence, and to study factors associated with mortality. A pilot study of a clinical reporting scheme began in July 1980, and the definitive scheme began in July 1981 and ended in July 1984. The main findings of the first two years of the study were that outbreaks of necrotising enterocolitis occurred in six neonatal units, there was an inverse relationship between birth weight and age at onset, and there were more deaths among girls.[1] We now report the final results of the project.

Method of evaluation

Neonatologists who were members of the BAPM working in 100 neonatal units were asked to report all cases of necrotising enterocolitis diagnosed in their units to the CDSC using forms that requested data on main clinical features, date of birth, sex, birth weight, gestational age, date of onset of symptoms of necrotising enterocolitis, outcome, evidence of infection, and findings at operation or necropsy, or both. Criteria for reporting necrotising enterocolitis were the presence of at least two of the four following features: abdominal distension; blood in the faeces; hypotonia, lethargy or apnoeic episodes; and pneumatosis cystoides intestinalis. Cases were considered confirmed if they had either pneumatosis cystoides intestinalis, gas in the portal venous system or free air in the abdomen on abdominal radiograph, or histological evidence of necrotising enterocolitis.

From July 1981 to December 1982 cases from 60 units were reported. Neonatologists in the remaining 40 units were sent a questionnaire to ascertain if any cases of necrotising enterocolitis had been diagnosed; 23 (58%) replied and in 20 (87%) of these cases of necrotising enterocolitis had been diagnosed but not reported. After the questionnaire had been sent, reports were received from 15 of the 40 units until July 1984 including seven units that had not replied to the questionnaire.

Infants below the 10th centile for distribution of birth weight for gestational age were identified using published centile charts.[2] Data on live births were obtained from the Office of Population Censuses and Surveys.[3] Statistical comparisons were by χ^2 with Yates's correction and Fisher's exact test.

Results

Reports of 240 confirmed, and 158 unconfirmed, cases of necrotising enterocolitis were received. In

219 confirmed cases (91%), pneumatosis cystoides intestinalis was present. Of the remaining 21 confirmed cases, seven were confirmed on histological examination and 14 others were reported to have intestinal perforations or gas in the portal vein. Of the 158 unconfirmed cases, 97 had visible blood in the faeces (61%), and 24 (15%) had occult blood together with either abdominal distension or systemic signs, or both. Only 20 (13%) were diagnosed only by the presence of abdominal distension and systemic signs.

BIRTH WEIGHT AND GESTATIONAL AGE

The distribution according to birth weight and gestational age of confirmed and unconfirmed cases is shown in tables 1 and 2. The birthweight distribution of all infants born in England and Wales in 1982 is shown in table 3 for comparison. Incompleteness of reporting does not permit the calculation of the incidence of necrotising enterocolitis, but the average yearly birthweight specific reporting rates give an indication of the relative incidence of necrotising enterocolitis within birthweight groups.

Table 1 *Deaths among confirmed and suspected cases by birth weight*

Birth weight (g)	*Confirmed cases*			*Unconfirmed cases*		
	Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*
<750	10	4 (40)	0	9	3 (33)	0
750–999	36	15 (42)	0	26	3 (12)	0
1000–1249	42	14 (33)	0	27	2 (7)	0
1250–1499	34	15 (44)	1	17	1 (6)	0
1500–1999	38	5 (13)	1	32	1 (3)	0
2000–2499	25	3 (12)	3	12	0	1
≥2500	45	4 (9)	2	33	0	1
Not known	3	2 (67)	0	0	0	0
Total:						
<1500	122	48 (39)	1	79	9 (11)	0
≥1500	108	12 (11)	6	77	1 (1)	2
All cases	233	62 (26)	7	156	10 (6)	2

Table 2 *Deaths among confirmed and suspected cases by gestational age*

Gestational age (weeks)	*Confirmed cases*			*Unconfirmed cases*		
	Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*
≤28	59	21 (36)	0	40	6 (15)	0
29–30	40	17 (42)	2	26	3 (12)	0
31–32	46	12 (26)	0	22	1 (4)	0
33–36	41	6 (15)	3	27	0	1
≥37	40	3 (8)	2	36	0	1
Not known	7	3 (43)	0	5	0	0
Total	233	62 (27)	7	156	10 (6)	2

Table 3 *Confirmed cases in England and Wales 1981–84, and total live births in England and Wales, 1982*

Birth weight (g)	*No (%) with confirmed necrotising enterocolitis 1981–84*	*Total live births 1982 (% with necrotising enterocolitis)*	*Average annual reporting rate/1000 live births*
<1000	41 (20)	1442 (0·002)	9·5
1000–1499	70 (34)	3330 (0·006)	7·0
1500–1999	36 (18)	7529 (1·3)	1·6
2000–2499	22 (11)	27 632 (4·6)	0·3
≥2500	35 (17)	558 646 (93)	0·2
Total	204 (100)	598 579 (100)	0·3

The average annual reporting rate for confirmed necrotising enterocolitis ranged from 9·5/1000 live births among those that weighed less than 1000 g at birth to 0·2/1000 live births among those that weighed 2500 g or more.

The mortality among very low birthweight (VLBW) infants (those who had weighed less than 1500 g at birth) who were confirmed as having necrotising enterocolitis was 48/122 (39%). This was significantly higher than the 12 of 108 (11%) among infants who had weighed 1500 g or more at birth ($p<0·001$, table 1). In confirmed cases, as the birth weight increased the mortality remained constant until 1500 g, when it dropped by 67%. In the unconfirmed cases there was a steady fall in mortality as birth weight increased. The mortality increased steadily as gestational age decreased until 29–30 weeks' gestational age in confirmed cases (table 2). Of the 192 singleton confirmed cases, 38 (20%) were below the tenth centile of weight for gestational age; mortality among these infants was not increased.

OUTCOME BY CLINICAL FEATURES

One VLBW infant and 11 other confirmed cases had only pneumatosis cystoides intestinalis and blood in the faeces, but no abdominal distension or tenderness or systemic signs, and none died. VLBW infants who were confirmed cases and who had an abnormal bleeding tendency or low peripheral platelet counts ($<100\times10^9$/l) had a higher mortality (20 of 38) compared with other VLBW infants (28 of 84, $p=0·07$).

Infants who had weighed 1500 g or more at birth with abnormal bleeding or low platelet counts also had a higher mortality (nine of 24 compared with five of 87, $p<0·001$). Sixteen of 37 VLBW infants with bacteraemia died compared with 32 of 85 who did not develop bacteraemia ($p=0·7$), and three of 19 who had weighed 1500 g or more at birth who developed bacteraemia died compared with nine of 89 who did not ($p=0·4$). The commonest organisms isolated from blood were *Staphylococcus epidermidis* and *Escherichia coli* (table 4). The mortality for VLBW confirmed cases with Gram negative bacteraemia (11 of 17) was significantly higher than for infants from whose blood other organisms had been isolated (five of 20, $p=0·04$). Similarly, infants who had weighed 1500 g or more at birth who developed Gram negative bacteraemia had a significantly higher mortality (three of six compared with none of 13, $p=0·02$).

One third of the confirmed cases had operations (table 5); the mortality among these cases was almost twice that among other infants ($p=0·016$). This was most pronounced among infants who had weighed 1500 g or more at birth. Details of the indications for operation were not collected in the study, but in 164 confirmed cases there was no report of an abdominal radiograph showing free gas in the abdomen. Seven of 30 of the infants who had operations died, compared with 20 of 134 who did not ($p=0·28$).

Among unconfirmed cases the mortality for VLBW infants and those who had weighed 1500 g or more at birth was 11% and 1% (table 1). Uncon-

Table 4 *Deaths among confirmed and suspected cases by organism isolated from blood*

Organism	*Confirmed cases*		*Unconfirmed cases*	
	Total No	*No of deaths*	*Total No*	*No of deaths*
S epidermidis	14	1	9	0
E coli	13	7	2	1
Staphylococcus aureus	6	1	2	0
Clostridium species	6	4	1	0
Pseudomonas species	5	5	1	0
Streptococcus species	5	1	3	2
Serratia species	1	1	0	0
Klebsiella species	3	1	3	2
Candida	1	0	0	0
Anaerobic diphtheroids	1	0	0	0
Bacteroides species	0	0	1	0
S epidermidis and Klebsiella species	1	0	0	0
S epidermidis and Bacteroides species	1	0	0	0
S epidermidis and diphtheroids	0	0	1	0
Total	57	21	23	5

firmed cases among VLBW infants with abnormal bleeding or low platelet counts had a significantly higher mortality: six of 22 compared with three of 57 (p=0·01). Five of 20 VLBW unconfirmed cases that developed bacteraemia died, compared with four of 59 that did not (p=0·05). Three of nine VLBW unconfirmed cases that had operations died, compared with only five of 65 that did not (p=0·05).

AGE AT ONSET

Age at onset of confirmed cases of necrotising enterocolitis ranged from 1 to 138 days, and was inversely related to birth weight. The median age of onset for infants who had weighed less than 750 g, 750–999 g, 1000–1249 g, 1250–1499 g, 1500–1999 g, 2000–2499 g, and 2500 g or more at birth was 15, 15, 12, 8, 10, 5, and 3 days, respectively. In VLBW infants with confirmed necrotising enterocolitis the median age of onset was 11 days and mortality decreased steadily as the age of onset increased. In infants who were heavier at birth no trend was found (table 6).

SEX

The mortality among girls with confirmed necrotis-

Table 5 *Deaths among confirmed cases by birth weight, sex, and whether they underwent operation*

Birth weight (g)	*Sex*	*Number operated on*			*Number not operated on*			*Total number*		
		Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*
<1500	Male	23	10 (43)	0	27	6 (21)	1	50	16 (32)	1
	Female	20	10 (50)	0	47	19 (40)	0	67	29 (43)	0
≥1500	Male	18	2 (10)	2	38	3 (8)	0	56	5 (9)	5
	Female	15	5 (33)	1	36	2 (5)	0	51	7 (14)	1
Unknown	Male	0	0	0	0	0	0	0	0	0
	Female	1	1 (100)	0	2	1 (50)	0	3	2 (67)	0
Total:										
<1500		43	20 (47)	0	74	25 (33)	1	117	45 (38)	1
≥1500		33	7 (22)	3	74	5 (8)	0	107	12 (11)	6
	Male	41	12 (30)	2	65	9 (14)	1	106	21 (20)	6
	Female	36	16 (43)	1	85	22 (26)	0	121	38 (31)	1

It was not recorded whether six babies had operations, and the outcome was not known for three other boys. Five weighed <1500 g (two girls, one death; three boys, one death), and four weighed ≥1500 g (one girl, survived; three boys, unknown).

Table 6 *Deaths among confirmed cases by birth weight, sex, and age at onset of necrotising enterocolitis*

Birth weight (g) and sex	*Age at onset (days)*								*Total*		
	0–6			*7–13*		*14–20*		*≥21*			
	Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Total No*	*No of deaths (%)*	*Total No*	*No of deaths (%)*	*Total No*	*No of deaths (%)*	*Outcome unknown*
<1500:												
Male	13	8 (62)	1	12	4 (33)	11	2 (18)	15	3 (20)	51	17 (32)	1
Female	21	10 (48)	0	21	11 (52)	7	4 (57)	19	5 (26)	68	30 (44)	0
≥1500:												
Male	34	4 (12)	4	12	0	2	1 (50)	8	0	56	5 (9)	4
Female	35	5 (14)	1	12	1 (8)	2	0	3	1 (33)	52	7 (13)	1
Total:												
<1500	34	18 (53)	1	33	15 (45)	18	6 (33)	34	8 (24)	119	47 (39)	1
≥1500	69	9 (13)	5	24	1 (4)	4	1 (25)	11	1 (9)	108	12 (11)	5
Male	47	12 (26)	5	24	4 (17)	13	3 (23)	23	3 (13)	107	22 (20)	5
Female	56	15 (27)	1	34	13 (38)	9	4 (44)	23	6 (26)	122	38 (32)	1

Age at onset was not recorded for three babies who weighed <1500 g (two boys and a girl, the girl died) and for one boy who weighed ≥1500 g (outcome not recorded). Birth weight was not recorded for one girl aged 7–13 days who died and one aged ≥21 days who survived. Neither were recorded for one further girl who died.

ing enterocolitis of 40 of 124 (32%) was higher than the 22 of 109 (20%) among boys (p=0·05, table 5), and this was not accounted for by differences in the distribution of birth weight or gestational age. Of VLBW boys, 23 of 50 (46%) had operations compared with 20 of 67 (30%) girls. In the VLBW girls the increased mortality was seen particularly in those who did not have operations: 19 of 47 compared with six of 27 (p=0·18), but in those who had weighed 1500 g or more at birth it was among those who did have operations, although the numbers were so small (five of 15 compared with two of 18) that this difference might not be significant. When mortality was examined by age at onset of necrotising enterocolitis, the rate for VLBW girls was higher in each period except for onset in the first week of life, when there was a higher rate among boys (table 6) and this applied both to those who had operations and those who did not.

FINDINGS AT OPERATION OR NECROPSY

Histological findings at operation or necropsy, or both, were recorded for 72 of the 108 confirmed cases that had operations or died. In 24 cases only the small bowel was diseased; the sites of the lesions were: jejunum (n=2), terminal ileum only (n=10), ileum (n=8), jejunum and terminal ileum (n=1), and the whole of the small bowel (n=3). In 12 cases the large bowel alone was diseased, and the sites of the lesions were: ascending colon (n=1), ascending and transverse colon (n=2), transverse colon (n=1), sigmoid colon (n=7), and rectum (n=1). In 24 cases both small and large bowel were diseased, and the sites of the lesions were: the whole of the small and large bowel (n=8), the terminal ileum and caecum (n=4), the terminal ileum and colon (n=8), and the caecum and colon (n=4). The colon seemed more likely to be diseased in infants who had been heavier at birth, but this difference was not significant.

Discussion

Population surveillance based on reporting by physicians is a useful method of characterising diseases of unknown aetiology—for example, Reye's syndrome.[4 5] Surveillance data may show epidemiological and clinical patterns that warrant more detailed study, and programmes are being developed to study several newly recognised diseases of children.[6] In our study, which relied upon members of the BAPM initiating reports, there was underreporting and no reports were received from a few large neonatal units. The survey of units that did not send any reports during the first part of the study suggested that at least 20% of units had diagnosed cases of necrotising enterocolitis. For this reason rates of reporting based on national birth rates must be considered only a minimum estimate of incidence. These estimates, however, do emphasise the strong association between low birth weight and necrotising enterocolitis. Our experience with clinical surveillance confirms the need to encourage more complete reporting by regularly contacting clinicians and confirming the presence or absence of cases by methods such as those now used for Reye's syndrome in the United Kingdom.[7]

The highest mortality was associated with very low birth weight and low gestational age, although surprisingly a trend of decreasing mortality with increasing birth weight was not seen within the VLBW group with confirmed necrotising enterocolitis; the mortality among these infants compares favourably with earlier studies.[8–11] In VLBW infants, onset in the first week of life and an abnormal bleeding tendency or low platelet counts were associated with significantly higher mortality. The mortality among infants with evidence of intrauterine growth retardation was not increased. Gram negative bacteraemia was associated with a higher mortality and this observation might be used to support the use of prophylactic antibiotics. It should be borne in mind, however, that antibiotic resistant organisms may cause severe morbidity.[12] Strict infection control, especially attention to hand washing, must be maintained at all times.[13 14]

Infants who had operations had a significantly higher mortality. A possible explanation for this is that operation was only undertaken when the clinical condition was deteriorating, and when the outcome was poor. In this surveillance study we did not collect data on the indications for operation, but the fact that mortality was not lowered by operation in this and other studies[11 15] indicates the urgent need for controlled trials to evaluate the role of operation in the management of necrotising enterocolitis. Kliegman and Fanaroff[16] suggest that in the absence of intestinal perforation (shown on abdominal radiographs or by paracentesis) operation should be avoided; even in infants with perforations, conservative management may be successful.[17] In our study 38% of infants who had operations were not reported as having radiological evidence of perforation. In infants considered to have necrotising enterocolitis without pneumatosis cystoides intestinalis the outcome without operation was excellent, and referral of such cases to a paediatric surgeon would not generally be indicated.

The persistently higher mortality among girls is intriguing and cannot be explained by their lower birth weights and gestational ages. In VLBW infants who had necrotising enterocolitis confirmed during the first week of life there was an increased

mortality, but in infants who did not develop necrotising enterocolitis until the second or third week mortality fell steadily among boys but increased among girls. One possible explanation is that a higher proportion of girls survived other more common life threatening diseases associated with low birth weight and prematurity, but that these ill survivors were less able to withstand the additional stress of necrotising enterocolitis. This may also explain the finding that VLBW girls were less likely to have operations, perhaps because they were considered less able to withstand operation, although the mortality was higher among those who did have them.

The clinical criteria for reporting were broad enough to include infants who did not have pneumatosis cystoides intestinalis. Whether these unconfirmed cases, who usually presented with abdominal distension and blood in the stools, did have necrotising enterocolitis is debatable[18] although histologically proved necrotising enterocolitis can occur without radiological features.[19] Infants in whom the disease was not confirmed were more mature at birth, and developed less serious disease earlier in life. Possibly these cases were diagnosed and treated before radiological signs became apparent, or in these cases the disease was caused by bacteria that do not produce gas. Some cases may have been associated with feeding intolerance.[18] In our study clinicians were not asked to distinguish suspected from confirmed cases so that all cases were diagnosed and managed as necrotising enterocolitis and most suspected cases did have abdominal distension and blood in the stools. Infants with gastrointestinal symptoms attributed to other diseases would not have been reported to us. Bell *et al*[20] have proposed a clinical staging system for necrotising enterocolitis, but the criteria for inclusion as definite, as opposed to suspected, necrotising enterocolitis are not sufficiently specific to apply to our cases. Most of our suspected cases, however, had gross blood in the stool and these seem closer to their stage II (definite) than stage I (suspect).

It may be that both confirmed and suspected necrotising enterocolitis share a common initiating aetiological factor (for example, a specific infection) that causes mucosal necrosis, and that various host factors may modify the presentation of disease, including the development of pneumatosis cystoides intestinalis. Evidence in favour of this hypothesis comes from the often epidemic presentation of cases.[1] Such clustering suggests that infection may play an important part, and outbreaks are usually terminated by strict control of cross infection. It also seems that during clusters of confirmed necrotising enterocolitis the incidence of unconfirmed cases also increases. Sherertz and Sarubbi[21] reported a small outbreak of necrotising enterocolitis associated with *Clostridium difficile* infection in the nursery; four cases were confirmed and one was suspected (with bloody faeces, abdominal distension but no pneumatosis cystoides intestinalis). Cashmore *et al*[22] reported a larger outbreak in which 11 cases were confirmed and nine suspected during a four week period. In six clusters reported in the United Kingdom study in 1981–82, 11 of 24 cases were not confirmed radiologically, but this proportion was not significantly different from the 21 out of 32 sporadic cases in those units.[1] These data suggest that suspected and confirmed necrotising enterocolitis may be different responses to the same initial stimulus.

The necrotising enterocolitis surveillance scheme was successful in clarifying the clinical presentation of necrotising enterocolitis, it highlighted the occurrence of outbreaks,[1] and has helped to elucidate factors associated with mortality. Furthermore, it provided the basis for a multicentre case control study that identified risk factors for necrotising enterocolitis.[23] The under reporting, however, prevented the calculation of incidence rates for necrotising enterocolitis for the United Kingdom, and prevented regional comparisons. Future incidence surveys of necrotising enterocolitis should adopt active surveillance methods[6] rather than depending upon the physicians to initiate the reporting.

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