

Necrotizing enterocolitis in very low birthweight infants: a four-year experience

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Abstract Fifty (13%) of 375 infants who weighed 1500 g or less at birth had necrotizing enterocolitis (NEC). Haematological changes suggestive of sepsis occurred in 83% and positive bacteriological cultures were found in 38%, the most common organism isolated being *Clostridium perfringens*. Complications included intestinal perforation in six patients and recurrence of NEC in five, of whom one subsequently developed an intestinal stricture. Five of the eight nursery deaths were secondary to peritonitis and overwhelming sepsis from NEC. In spite of the discontinuation of milk feeds for prolonged periods, satisfactory caloric intake and weight gain were achieved with parenteral nutrition in the survivors. Of the 41 long-term survivors, six (15%) were found to have a disability at 2 years of age, corrected for prematurity, compared with 48 (20%) of 241 very low birthweight survivors from the same study period who did not have NEC. None had evidence of gastrointestinal dysfunction. Six (15%) children remained below the 10th percentile for both weight and height. This study showed that early diagnosis and therapy for NEC in very low birthweight infants were associated with a favourable short- and long-term outcome.

Key words: very low birthweight infants; necrotizing enterocolitis; growth and development.

Necrotizing enterocolitis (NEC) is recognized as an important cause of morbidity and mortality in infants admitted to neonatal intensive care units.¹ As there are no proven preventive measures, current practice emphasizes early recognition and medical intervention to minimize the impact of the disease. Increasing awareness of the early signs and symptoms has led to the identification of a spectrum of manifestations of NEC which varies from a benign course and complete recovery following conservative treatment to those in whom gastrointestinal necrosis, perforation and septicæmic shock develop and who die despite aggressive medical and surgical management.² However, only a few studies have attempted clinical staging of the disease.^{2–4} In this study, the clinical features, complications and outcome of infants with mild or severe NEC based on a radiological classification are compared.

Recent studies indicate that 46–70% of NEC populations were of very low birthweight (VLBW, ≤ 1500 g).^{2,5,6} The mortality rate of NEC in this high-risk group remains high at 33–53%.^{5,7,8} Our experience with NEC is therefore reported in such a VLBW population. As only limited information is available on the late morbidity among survivors of NEC,⁹ we also report here the growth and development of survivors of NEC at 2 years of age corrected for prematurity.

PATIENTS AND METHODS

The study population consisted of 375 VLBW infants admitted

to the neonatal intensive care unit over the period 1977–1980. Overall neonatal survival was 79%; 56% for infants weighing 501–1000 g and 89% for infants weighing 1001–1500 g. Details of the patient profile and morbidity for this cohort have been reported previously.¹⁰

Criteria for diagnosis

The diagnosis of NEC was based on clinical and radiological data. Only at surgery or necropsy was there pathological confirmation of the disease. The criteria for diagnosis were similar to those used in two previous studies.^{2,3} The clinical presentation included evidence of systemic illness such as recurrent apnoea, lethargy, poor circulation, temperature instability and metabolic acidosis as well as signs attributable to gastrointestinal malfunction such as abdominal distension, blood in stools, gastric residue and diarrhoea. Patients who manifested these clinical features were classified according to their abdominal x rays into mild or severe NEC. X-ray findings in the mild cases included gaseous distension, asymmetry of gas pattern, suggestion of thickened bowel wall and intramural gas in the form of a granular or foamy pattern. Severe cases were defined as those who showed on x ray a curvilinear intramural gas pattern, pneumoperitoneum or hepatic portal venous gas. All patients were diagnosed unanimously by the consultants as having NEC. Abnormal haematological findings and positive bacteriological cultures were used to differentiate between patients with mild NEC and infants with transient abdominal distension and milk intolerance with non-specific x-ray signs. Perinatal data were coded prospectively by a research sister (B.B.) and were checked by paediatricians (V.Y.H.Y. and R.J.) before card punching. Inconsistent information was sought by computer and cross-checked before final transfer to magnetic tape.¹¹

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First received 22 June 1983. Resubmitted 22 August 1983.

Management

All infants with NEC were treated with the discontinuation of oral feeds, nasogastric decompression and intravenous therapy. Penicillin (50 000 units/kg per day) and gentamicin (5 mg/kg per day) were given to those infants who were not already receiving antibiotics. In the latter period of the study, metronidazole (20 mg/kg per day) was also given parenterally. Fresh blood transfusion was used for anaemia or circulatory support when indicated. Thrombocytopenia was treated with platelet transfusions and documented coagulopathy was managed either with fresh frozen plasma or with exchange transfusion. The protocol for supportive therapy including that for assisted ventilation and parenteral nutrition has been reported previously.¹²⁻¹⁴ Supine and lateral decubitus x-rays of the abdomen were taken every 12 h for the first few days after initial diagnosis and daily until disappearance of intramural gas. Cultures of blood, gastric aspirate, stool and other sites were taken as indicated. In addition, complete blood counts and serum biochemistry were obtained. The duration of treatment depended on resolution of clinical, radiological and haematological abnormalities and ranged from 7-21 days. Surgery was undertaken for pneumoperitoneum as a sign of intestinal perforation and its indication was reviewed with paediatric surgeons when possible if sudden clinical deterioration occurred or there was failure to show a progressive response to medical management. Operative therapy included resection of gangrenous or perforated intestine, peritoneal cultures and toilet, and either diversion enterostomy or primary anastomosis.

Follow-up

All 41 long-term survivors of NEC were followed at the Growth and Development Clinic with the exception of one child who lived interstate and was assessed by his own paediatrician. At the Clinic, the children were given a clinical and neurological examination by a developmental paediatrician (A.O.) and their development was assessed by a psychologist (J.A.) according to the Bayley scales of infant development which included a mental developmental index (MDI) and a psychomotor developmental index (PDI). The results of the assessment at 2 years of age were corrected for prematurity. Disability was defined as cerebral palsy, developmental delay (MDI more than 2 s.d. below the mean), sensory deficits, hydrocephalus or epilepsy. Methods of assessment and data collection and processing have been reported previously.^{15,16}

RESULTS

Incidence

Fifty (13%) VLBW infants developed necrotizing enterocolitis; 32 (8%) were classified as mild and 18 (5%) as severe. Fifteen (14%) of 107 infants 501-1000 g birthweight had NEC compared to 35 (13%) of 268 infants 1001-1500 g birthweight. The incidence of mild and severe cases in these birthweight subgroups was also similar (10% with mild NEC and 4% with severe NEC in the former group, compared to 8% and 5% respectively in the latter group). The mean birthweight of the NEC patients was 1122 g (s.d. = 240 g, range 560-1480 g) and

the mean gestation was 29 weeks (s.d. = 2 weeks, range 24-35 weeks). There were 27 boys and 23 girls. Seven (14%) were small for gestational age.

Clinical presentation

Although the age at diagnosis ranged from 1 day to 10 weeks, 80% occurred within the first 3 weeks (Fig. 1). All the severe cases occurred in the neonatal period. No difference in the frequency of systemic or gastrointestinal signs and symptoms was observed between the mild and severe cases (Table 1).

Forty (83%) of 48 NEC patients who had a complete blood count done on the day of diagnosis had one or more leucocyte abnormalities suggestive of sepsis according to the criteria used in a previous study.¹⁷ This was present in 24 (80%) mild cases and 16 (89%) severe cases. Details of the haematological changes are shown in Table 1. A total of 74% developed anaemia but only 9% were thrombocytopenic.

The majority of x-ray abnormalities were found to be equally common to mild or severe cases (Table 1). By virtue of the radiological classification used to determine mild or severe categories, only the severe cases had curvilinear intramural gas, pneumoperitoneum or portal vein gas. Nine (18%) patients did not have intramural gas of either the foamy or curvilinear pattern but had established systemic and gastrointestinal features of NEC supported with abnormal haematology. Four patients whose initial x ray had foamy intramural gas subsequently developed curvilinear intramural gas and were considered to have progressed from mild to severe NEC despite medical intervention. Three of the four patients with portal venous gas died.

Eighteen (38%) of 47 NEC patients who had bacterial studies done on the day of diagnosis had either positive blood or stool cultures. Thirty-one infants were either on antibiotics or had received a course of antibiotics prior to the onset of NEC. Two patients had *Escherichia coli* and one patient each had *C. perfringens*, *Klebsiella-Enterobacter* and anaerobic streptococcus in their blood cultures. Three of these five patients died. Stool cultures yielded *C. perfringens* (4), *Staphylo-*

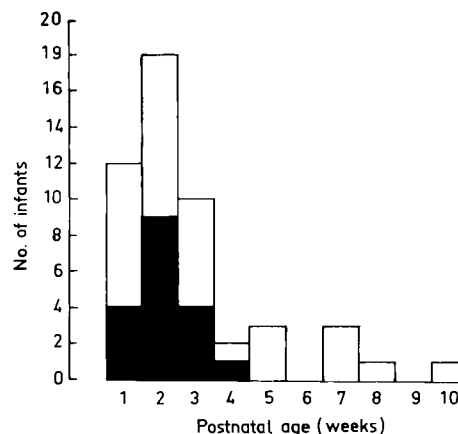


Fig. 1 Age of onset of necrotizing enterocolitis. Mild NEC (□), severe NEC (■).

Table 1 Clinical presentation of necrotizing enterocolitis.

	Mild NEC		Severe NEC		All patients	
	Number	%	Number	%	Number	%
Systemic features						
Recurrent apnoea	19	59	8	44	27	54
Lethargy	10	31	5	28	15	30
Poor circulation	7	22	7	39	14	28
Temperature instability	5	16	8	44	13	26
Metabolic acidosis	9	28	4	22	13	26
Gastrointestinal features						
Blood in stools	20	63	14	78	34	68
Abdominal distension	18	56	11	61	29	58
Gastric residue	15	47	8	44	23	46
Diarrhoea	10	31	8	44	18	36
Anaemia						
Immediate transfusion	12	38	7	39	19	38
Drop in haemoglobin (> 2 g%)	11	34	7	39	18	36
Leukocyte abnormalities*						
Neutrophilia	8	27	3	17	11	23
Neutropaenia	1	3	3	17	4	8
Increased immature cells	23	77	15	83	38	79
Toxic granulation	10	33	6	33	16	33
Vacuolization	7	23	6	33	13	27
Thrombocytopenia†						
	1	4	3	18	4	9
X-ray abnormalities						
Gaseous distension	26	81	14	78	40	80
Foamy intramural gas	23	72	15	83	38	76
Asymmetry of gas pattern	11	34	10	56	21	42
Curvilinear intramural gas	0	0	18	100	18	36
Thickened bowel wall	11	34	6	33	17	34
Free peritoneal fluid	2	6	4	22	6	12
Pneumoperitoneum	0	0	5	28	5	10
Portal vein gas	0	0	4	22	4	8
Fluid levels	2	6	2	11	4	8

*Data from 30 mild and 18 severe cases. †Data from 27 mild and 17 severe cases.

coccus aureus (4), *E. coli* (2) *Klebsiella enterobacter* (1), *Streptococcus agalactiae* (1), *Streptococcus viridans* (1) and *Pseudomonas aeruginosa* (1). The six peritoneal cultures grew *C. perfringens* (2), *E. coli* (1), *Klebsiella enterobacter* (1) and *S. aureus* (1). Viral serology and cultures were not carried out on the NEC patients in this study.

One patient had not been fed orally prior to onset of NEC. Twenty-eight (56%) were receiving fresh expressed breast milk from their own mothers supplemented with milk formula (Nan, Nestles) when the former was unavailable. Only five (10%) patients were receiving breast milk exclusively and 16 (32%) were completely formula fed. Breast milk was the predominant feed in 16 infants at the time NEC developed.

Short-term outcome

The overall nursery survival rate was 84%; 31 (97%) patients with mild NEC and 11 (61%) with severe NEC survived. Eleven (73%) of 15 NEC patients weighing 501–1000 g survived compared to 31 (89%) of 35 weighing 1001–1500 g. Eleven (22%) patients had one or more complications; six had intestinal perforation and five had a recurrence of NEC on reintroduction of oral feeds, one of whom subsequently was shown to have an intestinal stricture.

Oral feeds were reintroduced after a mean of 12 days treatment in the 42 nursery survivors; 26 (62%) had 7 days or more treatment, including all 11 survivors with severe NEC and

Table 2 Nursery deaths.

No.	Gestation (week)	Birthweight (g)	Sex	Age at onset (day)	Age at death (day)	Complications	Cause of death
1	26	710	F	18	18	Perforation	Fulminating sepsis
2	27	930	F	9	10	Perforation	Fulminating sepsis
3	28	1190	M	11	13	Perforation	Fulminating sepsis
4	30	560	M	22	28	Perforation	Progressive sepsis
5	35	1250	F	3	10	Perforation	Progressive sepsis
6	27	1190	M	17	60	Perforation	Pneumonia*
7	28	1170	M	15	58	Stricture	Meningitis*
8	30	890	F	3	10	—	Intraventricular haemorrhage*

*Deaths unrelated to NEC.

15 (48%) with mild NEC. Parenteral nutrition was given for a mean of 16 days for amino acids and glucose and a mean of 10 days for fat. Mean caloric intakes were 70, 100, 105 and 111 kcal/kg per day for the first 4 weeks respectively. The mean body weights were 1007, 1079, 1184 and 1322 g respectively, in the first four weeks after birth. The mean rate of weight gain over this period was 15 g/day. The survivors were discharged at a mean age of 78 days (s.d. 12 days, range 38–123 days).

Details of the eight nursery deaths are shown in Table 2. Case 1 died within 24 h of onset from fulminating sepsis: intestinal perforation was found at necropsy. The remaining five received surgery following the appearance of pneumoperitoneum. The NEC was found to be too extensive for resection in one patient (Case 2) who had the perforation repaired but died in the immediate postoperative period. Four had resection of gangrenous and perforated intestine of whom two had diversion enterostomy and two had primary anastomosis. Three died from sepsis due to NEC (Cases 3–5) and one died in the post-neonatal period from an unrelated pneumonia (Case 6). Another late death occurred from an unrelated meningitis (Case 7). The single death from the mild NEC group occurred owing to intraventricular haemorrhage (Case 8).

Long-term outcome

Of the 42 nursery survivors, one died at 8 months of age from aspiration pneumonia. At their 2-year assessment, there were two children with cerebral palsy (spastic quadriplegia and diplegia respectively) and two children with MDI scores of 59 and 63 respectively. In addition, one child had spastic quadriplegia and a MDI of below 50. The remaining child with a disability was physically and developmentally normal but had epilepsy. The mean score for the MDI was 89 (s.d. = 20) and that for the PDI was 86 (s.d. = 15) which approximate closely the figures reported in the test manual (mean = 100, s.d. = 16). Of the 50 VLBW infants with NEC in this series, nine (18%) died, six (12%) survived with a disability and 35 (70%) were considered to be normal. In comparison, of the 325 remaining VLBW infants who did not develop NEC, 84 (26%) died, 48 (15%) survived with a disability and 193 (59%) were considered to be normal. At 2 years post-term, six (15%) children remained below the tenth percentile for both weight and height although their head circumference distribution was normal (Table 3). None had evidence of recurrent diarrhoea or other gastrointestinal dysfunction.

DISCUSSION

Non-specific x-ray findings frequently accompanied or pre-

ceded the appearance of curvilinear intramural gas which is the radiological hallmark of NEC.¹⁸ The latter need not be demonstrated in all patients¹⁹ and in a recent series, 14% of patients who had pathological confirmation of NEC did not have this specific x-ray feature.²⁰ Non-confluent gas bubbles in the wall of the diseased bowel segment produce an x-ray appearance of 'cystic pneumatosis' or intramural gas with a granular or foamy pattern.^{21,22} The x-ray signs of curvilinear intramural gas, portal venous gas and pneumoperitoneum are probably late signs of severe bowel disease. For this reason, we commenced treatment in infants with early or mild disease, which involved 5–7 days of parenteral antibiotics and a concomitant period of parenteral nutrition via peripheral veins. In spite of this approach towards early diagnosis, our 14% overall incidence of NEC in VLBW infants was only slightly higher than the 8–10% incidence of NEC reported in other centres for the same birthweight category.^{5,23,24} This difference could probably be explained by the higher overall survival rate of VLBW infants in the present series compared with previous reports, as this would increase the proportion of VLBW infants who previously would have died before they had a chance to develop NEC. Our approach of early diagnosis and intervention may have contributed to our low 5% incidence of severe NEC which manifested the more specific x-ray signs.

Mortality was secondary to intestinal perforation, peritonitis and overwhelming sepsis, similar to two previous reports.^{7,8} Although only 38% documented systemic infections on bacterial cultures, the majority were either on antibiotics or had a preceding course of antibiotics prior to the cultures being taken at the onset of NEC. As 83% of the patients had haematological evidence of sepsis, infection appeared to play a central role in the pathogenesis of NEC. It has been proposed that bacterial growth may be enhanced by milk feeding, the intestinal mucosa may be compromised by hypoxia-ischaemia and may permit secondary bacterial invasion, and the nature of the bacteria in a specific environment may provide the appropriate setting for direct infection.²⁵ The most interesting bacteria implicated as primary pathogens for the development of NEC are the clostridia organisms.²⁶ These are obligate anaerobes which inhabit the intestinal tract and have a propensity to invade ischaemic and devitalized tissue and produce gas and virulent toxins. Clostridium was found in five patients and was the most common bacterial isolate in this series. Two of the five patients died and both had portal venous gas in their x rays.

A high incidence of rotavirus in the stools of asymptomatic infants has been reported.²⁷ No less than 50% of infants were found to excrete the virus by 4 days of age. Significantly more infants with diarrhoea excreted the virus than in the symptom free group. A significant association of NEC with coronavirus but not with rotavirus has been reported in another study.²⁸ Routine viral studies for NEC were only introduced after the

Table 3 Growth percentiles at 2 years.

Percentiles	Weight		Height		Head circumference	
	Number	%	Number	%	Number	%
Over 90th	0	0	0	0	4	10
50–90th	7	18	10	25	20	50
10–49th	25	62	18	45	14	35
Under 10th	8	20	12	30	2	5

Data from 40 children.

period of the study reported here and therefore data are not available on the prevalence of viruses in NEC patients. Further research needs to be done on this aspect which hopefully may lead to improvement in the management of NEC and measures for infection control.

A concern for the late outcome of survivors who recovered from NEC is as important as the concern for the prevention of death. The only detailed report of late morbidity among survivors of NEC included patients who were more mature at birth (mean 32 weeks) and had a higher birthweight (mean 1700 g).⁹ Despite the fact that intestinal injury is the main feature of the neonatal disease, none of the survivors were symptomatic from gastrointestinal sequelae. The growth potential of the six children who remained below the tenth percentile for weight and height needs to be ascertained with longer follow-up. The late non-gastrointestinal morbidity reported was probably not related to the NEC *per se*. Six (15%) of 41 VLBW survivors who had NEC were found to have a disability at 2 years compared with 48 (20%) of 241 VLBW survivors who did not have NEC ($\chi^2=0.6$, $P=n.s.$). The late outcome in VLBW children who have had NEC is therefore encouraging.

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