Necrotizing enterocolitis

Controlled study of 3 years’ experience in a neonatal intensive care unit


From the Departments of Paediatrics, Radiology, and Morbid Anatomy, University College Hospital and Medical School, London

SUMMARY During the 3 years 1972–74, 17 infants were treated for necrotizing enterocolitis (NEC) in the Neonatal Unit at University College Hospital. The incidence of the illness was 0·2% of live births in the hospital and 2·7% of those referred from elsewhere. The mean birthweight of the affected infants was 1832 g (range 878–3850 g) and mean gestational age 33 weeks (range 28–40 weeks). The illness was diagnosed at a mean age of 16 days (range 3–33 days). 14 infants (82%) survived. One infant developed NEC because of a volvulus, and another because of an apparently abnormal arterial supply to a segment of bowel. Each of the remaining 15 infants was matched with 3 control infants in order to see whether any factors predisposing to the development of NEC could be identified. Birth asphyxia, the use of umbilical catheters, the length of time that these catheters were in place, and complications of catheterization were all significantly more frequent in the infants who developed NEC than in the controls. These findings support the view that hypoxia and ischaemia of the gut wall are important in the pathogenesis of NEC.

Necrotizing enterocolitis (NEC) has been increasingly recognized in recent years as an important cause of serious illness and death in infants admitted to neonatal intensive care units (Waldhaussen et al., 1963; Mizrahi et al., 1965; Touloukian et al., 1967; Fetterman, 1971; Stevenson et al., 1971; Stein et al., 1972; Hill et al., 1974; Roback et al., 1974; Livaditis et al., 1974; Virnig and Reynolds, 1974; Frantz et al., 1975; Santulli et al., 1975; Leonidas and Hall, 1976; Polin et al., 1976). The pathogenesis of the condition is imperfectly understood, though damage to the bowel mucosa followed by invasion with gas-forming organisms have been suggested as important factors. The extensive literature has been reviewed by Santulli et al. (1975). We report details of infants with NEC admitted to the Neonatal Unit at University College Hospital (UCH) during a 3-year period. In order to obtain information about possible predisposing factors, clinical data from the affected infants and from a control group have been compared.

Patients and methods

Infants with NEC. During the 3-year period, January 1972 to December 1974, 17 infants were diagnosed as having NEC. 9 were boys and 8 were girls. 10 were born in UCH and 7 were referred from other hospitals. Diagnosis was based on the presence of blood in the stool, abdominal distension, and vomiting, together with evidence from a plain x-ray film of gas in the bowel wall or portal venous system, fluid levels in the small intestine, or intestinal perforation. Clinical information from the 17 infants is in Table 1. In addition, 10 infants appeared peripherally vasoconstricted, and 8 had unstable rectal temperatures which varied by more than 1°C within a period of 6 hours. Haematological data were available from all 17 infants and detailed coagulation studies were carried out as previously described (Jones et al., 1972; Rivers, 1975) on 8.

Details of the total population of infants admitted to the neonatal unit during 1972–74 have been summarized by Blake et al. (1975). The perinatal mortality rate for infants born in UCH in the 3 years was 16·2 per 1000 births. The incidence of NEC was 0·2% of infants born in the hospital, and 2·7% of those referred from elsewhere, giving an overall incidence of 1·3% of admissions to the unit. One of the affected infants was referred because of NEC. The remainder developed the condition there.

Management and outcome. Except in one mildly
affected infant, oral feeding was stopped and intravenous infusions of glucose and electrolytes were started as soon as the diagnosis was made. Nasogastric suction was started and all except 2 of the infants were treated with parenteral penicillin and gentamicin. 4 needed mechanical ventilation. None of the infants was given oral antibiotics though one was receiving colistin orally when NEC developed. 4 infants also received total parenteral nutrition as described by Shaw (1973).

Laparotomies were performed on 5 infants (Table 1), but in only one case (Case 12) during the acute stage of the illness. This infant was found to have infarction of the whole small intestine and ascending colon. She died after operation. The remaining 4 infants were operated upon aged 32–68 days, 8–45 days after NEC had been diagnosed. Surgery in one of these infants (Case 7) was for persistent bleeding from an ulcer in the transverse colon, which was excised, and in the others because of progressive abdominal distension and vomiting, together with radiological evidence of stricture formation. Strictures in the ileocaecal region were excised from 2 infants and the bowel was anastomosed. All made an uneventful recovery. A segment of the transverse colon in the remaining infant was found to be in spasm; this was left and she recovered spontaneously.

Two infants died without laparotomy. One (Case 5) arrived moribund from another hospital, and the other (Case 4) had extremely poor lung function due to hyaline membrane disease and massive pulmonary haemorrhage which precluded surgery.

Necropsies were performed on the 3 infants who died and pathological examination was carried out on the specimens removed at laparotomy. In one infant (Case 12), infarction of the bowel was found to be associated with a volvulus that had caused obstruction of the superior mesenteric artery. In another (Case 17) 3 strictures in the ileum were associated with an excess of thick walled and occluded small arteries which may have been congenital. Areas of necrosis and ulceration involving the mucosa and muscular layers of the bowel wall, particularly in the ileocaecal region were always found, and in 4 cases had resulted in perforation and peritonitis. Gas was seen in the bowel wall of 3 infants. The small blood vessels were ulcerated and thrombosed in all the infants except the one with the volvulus (Case 12), but apart from Case 17, no thrombic or embolic obstruction of the regional arteries could be shown. In the specimens removed at laparotomy the repair processes of the bowel wall were found to be well developed. A more detailed description of the pathological findings from infants treated in this hospital for NEC during the past 10 years will be published separately.

**Controls.** 3 control infants were selected for each of the 15 infants with NEC whose illness was not associated with a volvulus or a possible congenital abnormality (Cases 12 and 17). These 3 controls were admitted immediately before or after each NEC-affected infant, and their birthweights were within 7.5% of that of the affected infant. Controls

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**Table 1 Clinical and radiological features of the infants with necrotizing enterocolitis**

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Birthweight (g)</th>
<th>Gestation (w)</th>
<th>Day of diagnosis</th>
<th>Abdominal distension</th>
<th>Vomiting</th>
<th>Blood in stool</th>
<th>Rh disease</th>
<th>Umbilical catheter*</th>
<th>Gas in bowel wall†</th>
<th>Gas in portal veins</th>
<th>Fluid levels in small intestine</th>
<th>Perforation</th>
<th>Surgery (day)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1</td>
<td>878</td>
<td>33</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>suspect, l</td>
<td>1</td>
<td>+</td>
<td></td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1123</td>
<td>29</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>l</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Died, day 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1155</td>
<td>28</td>
<td>26</td>
<td>+</td>
<td>+</td>
<td>a + v</td>
<td>+</td>
<td>s + l</td>
<td>-</td>
<td>+</td>
<td></td>
<td>Died, day 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1332</td>
<td>28</td>
<td>8</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>s + l</td>
<td>l</td>
<td>+</td>
<td></td>
<td>Died, day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1438</td>
<td>30</td>
<td>17</td>
<td>+</td>
<td>+</td>
<td>v</td>
<td>+</td>
<td>s + l</td>
<td>+</td>
<td>+</td>
<td></td>
<td>Died, day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1540</td>
<td>30</td>
<td>24</td>
<td>+</td>
<td>+</td>
<td>l</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1595</td>
<td>31</td>
<td>24</td>
<td>-</td>
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<td>a</td>
<td>+</td>
<td>l</td>
<td></td>
<td>+</td>
<td></td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1630</td>
<td>31</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>suspect, l</td>
<td>1</td>
<td></td>
<td></td>
<td>Died, day 4</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>1641</td>
<td>31</td>
<td>33</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>l</td>
<td></td>
<td></td>
<td></td>
<td>Died, day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2200</td>
<td>35</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>l</td>
<td></td>
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<td></td>
<td>Died, day 4</td>
<td></td>
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</tr>
<tr>
<td>11</td>
<td>2220</td>
<td>35</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>l</td>
<td></td>
<td></td>
<td></td>
<td>Died, day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2250</td>
<td>37</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>s + l</td>
<td>l</td>
<td></td>
<td></td>
<td>Died, day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2350</td>
<td>35</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>l</td>
<td></td>
<td>+</td>
<td></td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2550</td>
<td>36</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>a</td>
<td>+</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>2640</td>
<td>34</td>
<td>24</td>
<td>+</td>
<td>+</td>
<td>a + v</td>
<td>+</td>
<td>l</td>
<td></td>
<td></td>
<td></td>
<td>Died, day 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1832</td>
<td>33</td>
<td>16 Total 10</td>
<td>+</td>
<td>+</td>
<td>a + v</td>
<td>+</td>
<td>suspect, l</td>
<td>1</td>
<td></td>
<td></td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>878–3850</td>
<td>28–40</td>
<td>(3–33) % 59</td>
<td>+</td>
<td>+</td>
<td>a + v</td>
<td>+</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>5 infants 14 survived</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* = artery; *v* = vein; † = large intestine; *s* = small.
with rhesus haemolytic disease were selected for the 5 NEC-affected infants with this disorder, but no attempt was made to match controls and infants with NEC for other illnesses.

The notes of all the infants were reviewed for factors which might have had an influence on the development of NEC. Statistical analysis was with the Pike Test for matched controls, and the Wilcoxon test.

Results

The results of comparisons between the infants with NEC and the controls are given in Table 2. Birth asphyxia, defined by a low Apgar score or delayed establishment of breathing, was more frequent in the infants who subsequently developed NEC. The presence of umbilical catheters, the length of time that they were in place, and the frequency of complications of catheterization, including decreased blood flow to the legs (2 infants), embolus to a toe (1 infant), recatheterization of the artery (3 infants), or umbilical sepsis (2 infants), were all significantly more common in the infants with NEC. The arterial catheters were 3-5F or 5F Argyle catheters with their tips sited at the level of the second to fourth lumbar vertebrae. When the umbilical vein was catheterized the catheter tip was in the inferior vena cava or portal sinus. The only infant with NEC among the 15 in the controlled study whose umbilical vessels were not catheterized (Case 6) received total parenteral nutrition via a silicon rubber catheter inserted percutaneously into the long saphenous vein at the ankle, with its tip at the level of the 12th thoracic vertebra.

The 5 NEC-affected infants with rhesus haemolytic disease received a total of 14 exchange transfusions (median 2, range 1–7, per infant). 8 were done through the artery and 6 through the vein. The umbilical arteries of 3 of the 5 infants were recatheterized for exchange transfusion. The veins were not recatheterized. 8 of the 15 control infants received 20 exchange transfusions through the artery and 8 through the vein; the umbilical artery of one infant and the umbilical veins of 4 control infants were recatheterized. No significant differences relating to exchange transfusion could be shown between the NEC-affected and control infants with rhesus haemolytic disease.

Coagulation findings from the 8 cases of NEC studied after the onset of illness showed thrombocytopenia (platelets <150,000/mm³; 150 × 10⁹/l) in 2 (Case 9, 107,000/mm³, 107 × 10⁹/l; Case 12, 71,000/mm³, 71 × 10⁹/l), evidence of hypercoagulability with a raised level of circulating fibrin monomer in 4 (Cases 9, 11, 12, 13) and a high fibrinogen level (>600 mg/100 ml) in 2 (Cases 7 and 11). Disseminated intravascular coagulation was thought to exist in one infant (Case 12) because of very prolonged clotting times, thrombocytopenia, hypofibrinogenaeemia, and high levels of fibrin degradation products. Haematological results from the 17 infants showed anaemia (Hb<10 g/dl) in 4 (Cases 2, 6, 7, 8), and an absolute neutropenia

Table 2 Comparison between infants with necrotizing enterocolitis and controls

<table>
<thead>
<tr>
<th></th>
<th>Infants with necrotizing enterocolitis (n = 15)</th>
<th>Controls (n = 45)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g, mean ± SD)</td>
<td>1805 ± 603</td>
<td>1805 ± 605</td>
<td>NS</td>
</tr>
<tr>
<td>Gestation (w, mean ± SD)</td>
<td>32 ± 2 ± 0-9</td>
<td>32-0 ± 3-1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>8:7</td>
<td>24:21</td>
<td>NS</td>
</tr>
<tr>
<td>Birth asphyxia* (n)</td>
<td>10 (67%)</td>
<td>10 (33%)</td>
<td>&lt;0·0025</td>
</tr>
<tr>
<td>Hyaline membrane disease (n)</td>
<td>13 (87%)</td>
<td>24 (53%)</td>
<td>NS</td>
</tr>
<tr>
<td>Rhesus haemolytic disease (n)</td>
<td>5 (33%)</td>
<td>15 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mechanical ventilation for respiratory illness (n)</td>
<td>6 (40%)</td>
<td>11 (24%)</td>
<td>NS</td>
</tr>
<tr>
<td>Umbilical catheters (n)</td>
<td>14 (93%)</td>
<td>29 (64%)</td>
<td>&lt;0·0325</td>
</tr>
<tr>
<td>Duration of umbilical catheterization (h, median + range)</td>
<td>60 (0-140)</td>
<td>30 (0-144)</td>
<td>&lt;0·025</td>
</tr>
<tr>
<td>Complications of umbilical catheterization† (n)</td>
<td>8 (53%)</td>
<td>7 (16%)</td>
<td>&lt;0·0025</td>
</tr>
<tr>
<td>Pathogenic bacteria isolated† (n)</td>
<td>8 (53%)</td>
<td>22 (49%)</td>
<td>NS</td>
</tr>
<tr>
<td>Antibiotics‡ given before diagnosis (n)</td>
<td>9 (60%)</td>
<td>24 (53%)</td>
<td>NS</td>
</tr>
<tr>
<td>Antibiotics‡ being given on day of diagnosis (n)</td>
<td>2 (13%)</td>
<td>12 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Feeding started with human milk (n)</td>
<td>13 (87%)</td>
<td>25 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Feeding with human milk continued until day of diagnosis (n)</td>
<td>5 (33%)</td>
<td>14 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>Minimum volume of oral feed/day during the 3 days before diagnosis (ml/kg per 24 h; median + range)</td>
<td>200 (75-230)</td>
<td>195 (50-240)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Apgar score <5 at one minute of age, <7 at 5 min; or intubated and ventilated for more than 10 min.
† Embolus, impaired circulation to the legs, recatheterization, or umbilical sepsis (see text).
‡From admission or weekly routine cultures of nose, oropharynx, umbilicus, rectum, conjunctivae, or from daily cultures from endotracheal aspirate in intubated babies, or from blood cultures in sick babies. The only positive blood culture grew a Bacteroides (Case 1, Table 1). Peritoneal fluid from one infant (Case 4) grew Actinobacter.
§ Penicillin and gentamicin.
(polymorphonuclear granulocytes <1500/mm³; 
<1·5 × 10⁹/l) in 1 (Case 4). No infant had been 
polycthaemic (venous haematocrit >65%).

Discussion

The results of this investigation confirm that factors 
which cause hypoxia or ischaemia of the bowel wall 
are involved in the pathogenesis of NEC. One infant 
had a volvulus and another an apparently congenital 
abnormality of the blood supply to the gut. More 
affected infants than controls had low Apgar scores 
or were slow to breathe at birth and were therefore 
probably asphyxiated. Also, the incidence of hyaline 
membrane disease tended to be higher, though this 
difference was not significant. Asphyxia is known to 
provoke a redistribution of the circulation, including 
a large reduction in blood flow to the intestines 
(Lloyd, 1969; Touloukian et al., 1971, 1972), and 
Touloukian et al. (1972) showed in piglets that 
mucostral capillary engorgement and infarction 
ocurred during recovery from ischaemia.

Catheterization of the umbilical vessels has 
previously been implicated in the pathogenesis of 
NEC (Beck et al., 1971; Hardy et al., 1972; 
Touloukian et al., 1973). In our study a higher proportion 
of affected than control infants had had their 
ubmilical arteries or veins catheterized, and 
complications of catheterization, such as the replacement 
of arterial catheters, were much more common. Plastic 
catheters introduced through the umbilical artery 
to the aorta cause thrombus formation (Neal et al., 
1972) which could compromise blood flow to the 
gut or encourage embolization. Necrosis and per-
formation of the bowel is a well recognized complica-
tion of exchange transfusion through the umbilical 
vein, probably because of stasis in the portal venous 
system (Orme and Eades, 1968; Rogers and Dunn, 
1969; Beck et al., 1971; Hardy et al., 1972; 
Touloukian et al., 1973). The combination of asphyxia 
with umbilical catheterization seems especially likely 
to produce hypoxic or ischaemic damage to the 
bowel wall. The release of plasticizers from catheters 
is an additional factor that has been invoked in the 
pathogenesis of NEC (Rogers and Dunn, 1969; 
Hillman et al., 1975). A difficulty in directly relating 
ubmilical catheterization to subsequent NEC in our 
investigation was that the illness did not develop 
until 2–29 (mean 13) days after the catheters were 
removed.

Other factors which may cause a reduction in 
blood flow or oxygen supply to the bowel are the 
presence of a large shunt (in either direction) through 
a patent ductus arteriosus (Kitterman, 1975); a high 
blood viscosity due to a high haematocrit; anaemia; 
hypotension; local inflammation due to the chemotactic 
effect of endotoxin released by Gram-negative 
organisms invading the bowel wall; and thrombosis 
in the microcirculation caused by the endotoxin-
stimulated release of a clot-promoting substance 
from monocytes (Rivers et al., 1975). Only one of 
the affected infants had the physical signs of a patent 
ductus arteriosus, and none were known to have 
been polycythemic or hypotensive. However, the 
Presence of anaemia in 4 infants may possibly have 
contributed to their illness by reducing oxygen 
delivery to the intestines. Evidence of hypercoagul-
ability of the blood in another 4 suggests that endo-
toxin-stimulation of monocytes had occurred.

Engel et al. (1973) and Barlow et al. (1974) have 
shown in experimental animals that bacterial 
Colonization and the presence of a nutritive sub-
strate in the bowel are necessary for the development 
of NEC-like changes following hypoxia. Barlow 
et al. (1974) further showed an effect of species-
specific milk in preventing these changes from taking 
place. Although there was no difference in the 
proportion of breast milk fed infants in the NEC-
affected and control infants in the present study, the 
overall incidence of NEC was low when compared 
with previous reports from neonatal intensive 
care units; the illness was generally mild and the 
survival rate was high, so breast milk may have been 
exerting a protective effect on our population of 
infants (Hanson et al., 1975). Any such effect could 
well have been incomplete, since the milk was 
usually pasteurized, which would be expected to 
destroy macrophages and inactivate other anti-
bacterial substances in the milk. The remaining 
infants who developed NEC were being fed SMA, 
and none had received hyperosmolar feeds, which 
are capable of damaging the bowel wall (de Lemos, 
1975).

Prevention. In the future, some of the factors impli-
cated in this and previous studies in the development 
of NEC should become preventable. Asphyxia 
should become less frequent with improved fetal 
and postnatal monitoring. Silicon rubber may re-
place plastic as the material used for the manufacture 
of umbilical catheters (Boros et al., 1975), thereby 
reducing the risk of thrombosis and removing 
potential dangers associated with the presence of 
plasticizers. Also, the length of time that umbilical 
arterial catheters remain in situ is likely to become 
shorter as improvements continue to be made in the 
management of respiratory illnesses and in methods 
for transcutaneous monitoring of blood oxygen and 
carbon dioxide levels (Huch et al., 1972; Delpy and 
Parker, 1975). There is a case for feeding sick infants
with fresh breast milk. We agree with Stein et al. (1975) that once NEC has developed a conservative approach to surgery is likely to yield the best results.

We are grateful to the staff of the Neonatal Unit and Professor J. F. Smith for help.

References


Necrotizing enterocolitis


Correspondence to Dr. G. M. Durbin, Department of Paediatrics, University of Birmingham, East Birmingham Hospital Teaching Unit, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST.

The following articles will appear in future issues of this journal:


Pressure and volume changes during the first breath of human neonates. A. D. Milner and R. A. Saunders.


Increased protoporphyrin in erythrocytes in a child with acute intermittent porphyria. Anita Gregor, Ewa Kostrzewska, Halina Prokurat, Zofia Pucek, and Emilia Torbicka.


Lung function in children after repair of congenital diaphragmatic hernia. A. A. Kerr.