Necrotizing Enterocolitis in the Newborn:

Operative Indications

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Fifty-two premature, low birth weight infants presented mainly in the first week of life with sudden manifestations of intestinal ileus and an x-ray picture of pneumatosis intestinalis. Twenty-two of 32 patients treated with gastric decompression, antibiotics, intensive supportive therapy and intravenous hyperalimentation survived. Twenty other patients had progression of their disease and required operation. Twelve of these patients survived. Review of this material indicated that some medically treated patients might have survived if they had been operated upon. Indications for operation included free perforation and clinical signs of deterioration. Abdominal physical findings and x-rays were not reliable except as signs of far advanced pathology. Confirmation of ascites by paracentesis and gram stain of fluid was helpful when present. If patients were adequately treated and then developed sudden hyponatremia or progressive acidosis, they invariably had gangrenous bowel and required operation. The most striking finding was that a sudden, profound drop in the platelet count to levels below 100,000 reliably predicted the presence of gangrenous bowel and the need for operation. Other clotting studies indicated that disseminated intravascular coagulation is an important accompaniment of NNE with the complication of bowel gangrene prior to perforation. Gastrostomy and resection of involved bowel with staged anastomosis proved to be the most successful form of surgical management. Overall survival was 66 per cent.

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THE CLINICAL and pathological features of neonatal necrotizing enterocolitis (NNE) were described in 1891 by Genersich, but in succeeding years apparently the same entity was described as functional ileus, idiopathic perforation of the colon and colonic perforation due to exchange transfusion to name just a few.[3] In 1964 Berdon, Barlow, Santulli and their group at Columbia University first noted an increase in the incidence of this disease and then took the opportunity to accurately describe the clinical manifestations of a single entity which they called necrotizing enterocolitis.[1]

They described the typical subject as a low birth weight infant who had undergone significant stress at the time of or immediately following birth. Others have stressed the occurrence of an hypoxic episode as the main feature common to all those with the disease.[12] These infants then appear to have no gastrointestinal problems for the first few days and even began enteral feedings, but 3 to 10 days following birth they may present with a clinical picture of sepsis with intestinal ileus, gastric retention, bilious emesis, abdominal distention, and bloody stools. Lethargy, apneic spells, hypothermia and circulatory collapse follow rapidly.

It is clear that some infants are capable of recovering from apparently severe enterocolitis with supportive therapy alone while others will require surgical intervention. However, selection of subjects for operation has been difficult since the presence of physical findings has proven to be unreliable in tiny infants or, at best, a sign of far advanced pathology. This report describes a plan of management for such infants with an analysis of criteria indicative that surgical intervention is in order.

Clinical Material

During the last five years approximately 2,000 infants were admitted to the Vanderbilt Neonatal Intensive Care Unit and 52 of these or 2.5 per cent were considered to have NNE on the basis of postmortem or operative information or clinically on the basis of a combination of physical signs plus radiographic findings of pneumatosis intestinalis (Fig. 1). Infants suspected of having this problem but who did not fit all of the above criteria, even though treated as such, were not included in this review.

Treatment Protocol

Although some aspects of treatment have changed over the last several years, the essential features have been the same. All infants suspected of having NNE are followed jointly by the neonatology and pediatric surgical teams.

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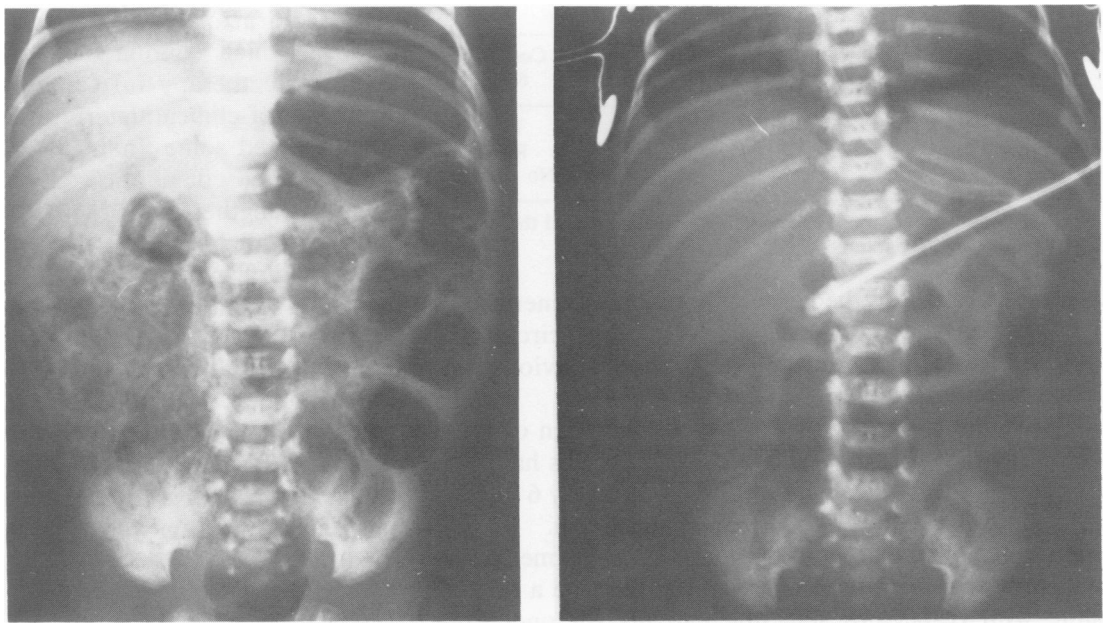

FIG. 1. The abdominal radiograph on the left demonstrates typical findings of extensive collections of intramural intestinal gas and gas in the portal venous tree. Most of these findings have disappeared 24 hours later as seen in the radiograph on the right. Now increased amounts of peritoneal fluid can be seen.

Once the diagnosis is suspected, oral or tube feedings are withheld and orogastric tube drainage instituted. A Silastic catheter is placed into the superior vena cava, preferably via the common facial vein, in order to repair volume depletion first and then in order to provide total parenteral nutrition. Ten per cent glucose and electrolytes are started initially and this is gradually increased to 20 per cent glucose along with crystalline amino acids* as dictated by the infant's glucose tolerance. Small amounts of insulin are occasionally required. Every effort is made to provide maximal caloric and protein input as well as optimum red cell and plasma volume, and electrolyte balance. Nasopharyngeal, stool, urine, endotracheal, cerebrospinal fluid and serial blood cultures are obtained. Intravenous ampicillin and gentamicin are administered routinely and occasionally other antibiotics as well, depending upon culture data.

Infants are examined jointly at least every 8 hours. Recumbent and left lateral decubitus x-rays are obtained at similar intervals. These intervals are lengthened or shortened as indicated by changes in the infant's clinical status. If significant ascites is noted on x-ray, parcentesis is performed and fluid obtained is cultured and a gram stain performed. Serial bilirubin, hematocrit, white blood cell count, electrolyte, pH and blood gas determinations are performed as well. In the last two years serial platelet count, partial thromboplastin generation, and prothrombin times have been determined. Heel sticks are performed every four hours for estimation of blood glucose.

The decision to operate is individualized and is based on clearcut signs of perforation or evidence of continued physiologic deterioration as indicated by the various laboratory studies mentioned above.

*Travasol kindly supplied by Travenol Laboratories, Morton Grove, Illinois.

Results

There were 24 males and 26 females. The range of birth weight was from one pound 14 ounces to 7 pounds 6 ounces with a mean of about 4 pounds. Gestational age was estimated to be from 24 to 40 weeks, however, the vast majority were low birth weight, premature infants. The mothers of forty-seven of the 52 patients had one or more of the following findings: premature rupture of membranes, severe meconium staining of amniotic fluid as a sign of intrauterine fetal distress, and prolonged or difficult labor. The infants had low Apgar ratings for up to 10 minutes following birth, a prolonged hypoxic episode, shock in the early neonatal period, or sustained respiratory difficulty. The most striking feature was severe respiratory distress and hypoxia noted in 70% of this series. One third of the patients had been on a respirator at some time during the period prior to the onset of enterocolitis. No definite predisposing factors could be elicited in 5 instances.

Initial symptoms and signs included sudden temperature instability, usually hypothermia, ileus with gastric retention, vomiting of bilious and/or guaiac positive material, abdominal distention, and lethargy. Experienced nurses often noted subtle changes in an infant's activity or the character of skin circulation. Stools were diminished in volume and invariably contained gross or occult blood. Subsequently, apneic spells, hyperbilirubinemia, oliguria, and abnormal bleeding became evident.

Prior to the onset of symptoms five infants had ex-

TABLE 1. *Platelet Counts in Infants With NNE*

Status	Number of Patients	Avg. Platelet Count	Count in 6 hrs
Gangrenous bowel	15	74,000	Fell
Recovered	2	130,000	Rose
Recovered	8	260,000	No change

Partial thromboplastin and prothrombin times paralleled the platelet count findings in 10 patients.

change transfusions because of hyperbilirubinemia. In five instances the first sign noted was sudden circulatory collapse, tight abdominal distention and obvious evidence of an intra-abdominal catastrophy.

Thirty-one patients or 60% had the first sign of NNE within the first five days of life. Fifteen infants had their first symptoms between 6 and 10 days and only 6 had the onset between 15 and 30 days following birth.

Although physical examination was performed carefully on a serial basis, this did not prove to be a reliable guide with respect to selecting patients for operation. Tenderness was minimal in some patients with perforation, and impressive in others who responded well to supportive therapy. Redness and edema of the abdominal wall indicated pathology requiring operation in two instances but was also present in an infant who recovered without surgery.

Radiologic Findings

Abdominal x-rays on all patients demonstrated intestinal distention, and varying amounts of intramural intestinal gas were noted in 45 instances. Pneumatosis generally cleared within 72 hours. Gas within the intrahepatic portal venous tree was noted in 6 instances (Fig. 1). Portal vein gas indicated extensive bowel involvement in three patients who required operation and one who died on supportive therapy, but it was also present in two infants who recovered without surgery. The latter finding was transient in all 6 patients and cleared within 18 hours in all. Pneumoperitoneum was seen in 8 patients. Apparent progressive generalized or localized collections of intra-abdominal fluid were noted in 5 patients. Paracentesis was performed in 3 of these 5 infants and bacteria were found on smear in two; this was an accurate indication that operation was needed. Barium contrast studies were not performed and were felt to be contraindicated.

Laboratory Findings (Table 1)

Forty patients had sufficient numbers of serial laboratory determinations to be helpful. Anemia occurred in most patients but did not indicate that a change in therapy was in order. A sudden drop in serum sodium indicated that sepsis with significant third space fluid loss was in progress. This occurred in two patients already on supportive therapy and it was accurately construed as a sign of deterioration due to bowel necrosis. Metabolic acidosis which continued longer than 4 hours despite appropriate therapy in 6 infants was also an accurate indication of clinical deterioration. Over half the infants demonstrated some findings suggestive of disseminated intravascular coagulation. A sudden drop in platelet count or lengthening of the PTT or PT which worsened over a 6 hour period always correlated with bowel gangrene and/or perforation. Serial platelet counts performed in 15 patients with gangrenous bowel ranged from 5,000 to 126,000 and usually followed a fall of 150,000 or greater. On followup two demonstrated an increase in platelet counts from 130,000 to 160,000 and 132,000 to 239,000 respectively, and both recovered without operation. These findings occurred in patients who had no other obvious cause for a fall in the platelet count. PTT and PT prolongation were noted in 10 patients and paralleled the findings of the platelet counts.

Results of Treatment

Supportive Therapy

Thirty-two patients were treated intensively as described above. Twenty-two or 69% survived. Ten patients died. It was elected not to operate on two of these 10 because of irreversible central nervous system damage; four died while on medical therapy and might have been helped by operation. One of the survivors required operation at two months of age because of stenosis of the splenic flexure of the colon. The remainder of this group and the child who required repair of colonic stenosis recovered without incident.

Operative Therapy

Twenty patients either presented with perforation or demonstrated signs of deterioration while on the supportive regimen. These patients had more extensive disease and were more seriously ill than the group treated without operation. Twelve or 60% survived. Two of the 8 who died following operation had involvement of essentially the entire gastrointestinal tract and were not amendable to surgical therapy; one of these latter patients had a second laparotomy within 12 hours without success. The other 6 who died were operated upon late in the course of their disease and might have responded had operation been performed earlier.

Two of the 8 patients who died had uncontrollable bleeding due to disseminated intravascular coagulation. Two of the operative survivors also had severe bleeding but responded to administration of platelets and exchange transfusion with fresh blood.

Three infants had resection with anastomosis and two had anastomotic leaks. The remaining 17 patients all had resection with exteriorization. Gastrostomy was gener-

ally performed in addition. Reanastomosis was performed in survivors from 2 to 10 months later.

Pathology

Information related to extent of disease was available in 30 patients on the basis of postmortem or operative data. Necrosis of the entire colon and such extensive amounts of small intestine as to be incompatible with life was the case in 5 infants. Four infants had necrosis of the entire colon and short segments of terminal ileum, and the remainder had cecal, ileocecal or right colonic necrosis with occasional segmental small intestinal necrosis. The gross and microscopic findings in involved bowel were typical of NNE as described by Santulli and his group.[8]

Cultures

Cultures of stool, blood and/or peritoneal fluid which appeared to correlate with the pathologic process were *E. coli,* Aerobacter-Klebsiella, and Pseudomonas, in the majority, *Staph. aureus* in three instances along with *E. coli,* and Clostridium species in one instance.

Comments

NNE, a common disorder of the low birth weight infant, has proven to be highly lethal in several series reported. Recent reported survivals ranged from 22 to 73%.[6,8,10,11] Overall survival in this series was 66%, but survival over the last two years has been 80%.

The marked increase in the number of reported cases has paralleled the rapidly increasing survival of low birth weight infants in neonatal intensive care units around the world. Technological improvements have provided such small subjects an opportunity to survive long enough to develop the disease. For example, such cases were rarely recognized at our medical center prior to 1967 whereas 52 instances have been encountered over the last 5 years. We have also treated a large number of infants who displayed some but not all of the characteristic findings of NNE. Although these probably represent early instances of the disease, these cases are not included here.

The precise etiology is unknown but it seems likely that neonatal asphyxia, hypoxia, hemorrhage, endotoxema or shock from any such factor may result in diminished splanchnic flow, focal mucosal necrosis, invasive bacterial proliferation and transmural gangrene. Exchange transfusion techniques may result in altered portal flow in infants with a closed ductus venosus. Also it may well be that the patent ductus syndrome of premature infants contributes to splanchnic flow abnormalities in the first week of life since many of these infants develop NNE. The fact that the colon and terminal ileum are the most common and most severe sites of involvement tends to implicate bacterial factors as well as flow factors since flora is more profuse and blood flow more peripheral in these areas than elsewhere in the GI tract. *E. coli,* Aerobacter-Klebsiella, and Pseudomonas were the main organisms encountered and are capable of producing gas. The bacteria appear to come from the patient's own flora entering the bowel wall and blood stream through altered gut mucosa. Virnig studied the epidemiology of this disease since it appeared to occur in sporadic outbreaks but no transmissible cause could be implicated.[13] In another study Hill and coworkers presented data implicating a resistant strain of Klebsiella which was found in a large group of infants in their nursery where the incidence of NNE was high at that time.[5] The possible deleterious effects of hyperosmolar and artificial milk feedings as a stimulus to dumping and altered flow have also been questioned.[8] No doubt multiple factors are involved.

It is clear that many infants who develop NNE with pneumatosis are capable of complete recovery without operation. In fact, 40% of our patients did recover without surgery. We operate on fewer infants than we did previously with better results, and others have reported similar experience. On the other hand, methods of supportive care have improved. Such infants receive no enteral feedings for two weeks or longer, and total parenteral nutrition has added significantly to their well-being. Patients such as these with bacteremia would be expected to require increased utilization of glucose at the same time they had impaired gluconeogenesis.[4] Also, rapid repletion of red cell and plasma volume using appropriate vascular monitoring and maintenance of normal acid-base and electrolyte status has been helpful.

However, despite the excellence of supportive care, the pathologic process will progress in some subjects and operation will provide the only opportunity for survival. Free perforation is an absolute operative indication but the ideal is to select patients who have not yet perforated before they develop signs of pneumoperitoneum or a localized abscess. A few patients may recover but develop stenosis in areas which had marginal blood supply.[7]

Repeated physical examination of the abdomen was not a dependable early indication that operation would be needed. At best, it was occasionally an indication of far-advanced pathology. Abdominal tenderness was equivocal and redness of the abdominal wall occurred too infrequently to be helpful.

Serial x-rays of the abdomen were relatively helpful. Pneumatosis generally cleared within 72 hours in those who recovered without operation. Portal vein gas was a sign of extensive disease in four infants who needed operation but was also present in two who recovered. Others have reported a higher incidence of portal pneumatosis but it did not occur often enough in this series to be a reliable guide. Evidence of localized or generalized abdominal fluid occurred infrequently but

when combined with paracentesis accurately predicted the need for operation.

Sudden hyponatremia and metabolic acidosis indicated deterioration. If these abnormalities did not respond to appropriate therapy within four hours in patients when first seen or if they occurred in adequately treated patients already on therapy, operation was generally needed.

The most striking finding was related to the course of the platelet count and the PTT. Modest falls in platelet counts to a level above 100,000 without further fall and modest prolongation of the PTT did not indicate a need for operation. However, platelet counts which fell below 100,000 or which continued to fall from higher levels over a period of hours were invariably associated with gangrenous bowel. The PTT data were similar to the platelet findings. It may be that gangrenous intestine releases sufficient tissue thromboplastin to initiate clotting and utilization of platelets. Similarly intravascular gas may produce thrombotic effects because of altered hemodynamics.[9] Finally, excessive binding of platelets with endotoxin may result in platelet injury and loss.[2] Regardless of the causal relationship, profound, sustained falls in the platelet count which could not be explained on another basis reliably predicted that gangrene with or without bowel perforation had occurred.

The surgical experience gained with these patients would indicate that exteriorization resection and anastomosis after a few months is likely to be the best approach. Anastomosis of potentially compromised bowel has been hazardous in our experience. Precise evaluation of the vascular status of the intestine in these patients is difficult, and the late occurrence of stenosis, especially in the distal colon, is another reason to stage the anastomosis.[7]

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Discussion

Dr. Thomas V. Santulli (New York): Dr. O'Neill and his group, I believe, have made an important contribution to this knotty problem of surgical indications in these desperately ill infants. They are to be congratulated for their excellent overall results.

The role of surgical intervention in this disease has been unclear. Pneumo-peritoneum or peritonitis resulting from perforation but without free air are clearcut indications. However, a decision to operate on the basis of progressive clinical deterioration may be very difficult.

Dr. O'Neill has placed emphasis on the development of metabolic acidosis, sudden hyponatremia and abnormalities in blood coagulation in these infants, as more objective evidence of intestinal gangrene, than the clinical examination which is so frequently unreliable in these very sick and small infants. I think this is an important contribution.

But, I would hasten to point out that these infants are usually suffering with many other problems as well. They may have hyaline membrane disease with periodic apnea, hyperbilirubinemia, and, especially sepsis, all of which or any one of which could account for some of these abnormal parameters. Hence, they must be evaluated in conjunction with the clinical picture.

Although we have had difficulty in interpreting most of the blood clotting parameters in the very young premature infant, the one reliable value is the platelet count since anything under a 100,000 is clearly abnormal, even in the tiniest premature infant.

In this regard, our data do not totally support Dr. O'Neill's conclusion that a drop in platelet count below a hundred thousand is indicative of intestinal gangrene and therefore requires operation. In 26 of our 69 patients whose platelet counts were under a hundred thousand, 20 died, six survived. In three of the survivors, no operation was done. They were managed on the type of intensive, aggressive, medical regimen that Dr. O'Neill has shown you. Their severe thrombocytopenia was on the basis of gram negative sepsis; they did not have gangrene of the intestine.

Finally, I wish to discuss the prophylaxis which I think is eminent in this very serious problem in the newborn infant. The laboratory data is quite convincing. It now remains to be documented in the human subject and a good deal of information is beginning to filter in.

Very briefly, in our laboratory, my resident, Barbara Barlow, was able to produce the disease in newborn rats which were made hypoxic. Three separate litters were used. One was contaminated by the environment, the second by introduction of an inoculum of klebsiella by mouth soon after birth, and the third by the transvaginal route in the mother about 24 hours before delivery. These were all split litters.

One group was allowed to feed on the mother's breast; another group was fed simulated breast milk formula which we had tried in many preliminary experiments.

None of the newborn rats that were fed breast milk developed the disease, whereas *all* that were fed the formula died two to five days later