

NECROTIZING ENTEROCOLITIS IN SAUDI ARABIA: EXPERIENCE IN A REFERRAL NEONATAL INTENSIVE CARE UNIT

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Necrotizing enterocolitis (NEC) is the most common acquired gastrointestinal emergency in the newborn.¹⁻⁴ The incidence of this condition constitutes 1% to 5% of admissions in neonatal intensive care units worldwide.²⁻⁴ Necrotizing enterocolitis is frequently associated with multiple factors, such as gastrointestinal and immunological immaturity, intestinal ischemia, colonization and subsequent invasiveness by pathogenic enteric bacteria.^{3,5-7} Hypertonic milks or medicines, or too rapid feeding protocols, may contribute to mucosal injury. The disease is characterized by rapid necrosis and perforation of the bowel, involving largely the ileum and colon.⁴

To our knowledge, there has only been one report on NEC in Saudi Arabia, in which 20 proven cases were documented in a Riyadh hospital during the period 1983-1988.⁸ We retrospectively studied all 36 patients with NEC treated in the neonatal intensive care unit (NICU) of Asir Central Hospital (ACH), Saudi Arabia, during a three-year period. The aim of the study was to determine the pattern of the disease in infants referred from general hospitals in the Asir region to the NICU of ACH. It is hoped that the results will guide nursery staff of hospitals in the Asir region and beyond to recognize infants at risk, so as to institute timely and optimum medical and surgical intervention.

The diagnosis and the severity of the disease were based on the modified Bell's staging criteria for NEC.³ Stage I of the disease involves mild systemic disturbance, abdominal distension, increasing gastric residual, occult or frank blood in the stool, with radiological evidence of intestinal dilatation and thickening of the bowel wall. Stage II involves features of stage I plus radiological finding of intestinal intramural gas (*Pneumatosis intestinalis*), and stage III presents with progressive deterioration of the vital signs, shock, and intestinal perforation with or without gangrene.

Patients and Methods

All infants treated for NEC in ACH during a three-year period from January 1995 to December 1997 constitute the subject of this study. ACH serves as the only tertiary and referral center for all the secondary and primary health care institutions in the Asir region of Saudi Arabia. The hospital has no obstetric service of its own, therefore, the NICU of the hospital is entirely a referral unit which serves the whole region with a population of approximately two million. Based on the American standard,⁹ Asir Central Hospital is the only facility which can provide level 3 neonatal service in the region with 19 hospitals. Indeed, it is the only hospital in the area that provides pediatric and neonatal surgical services. The NICU has a bed capacity of 20, and admits an average of 250 infants per year. Except for two patients who were admitted directly from home, all the patients in this study were referred from other hospitals in the region, with a diagnosis of NEC based on both the clinical symptoms and radiological findings as confirmed on arrival.

A study of the ward registers and patients' charts was undertaken. Data obtained included gestational age, sex, date and place of birth and birth weight. Other data included feeding regimen, laboratory reports, including serial radiographs of the abdomen, details of medical and surgical treatment, operative findings and outcome (dead or discharged). Data on hemogram, coagulation and renal profiles were not studied.

As a routine in our NICU, septic work-up (blood, cerebrospinal fluid and urine cultures) was conducted on every infant upon admission. In all cases, especially where perforation was suspected, a horizontal beam cross-table lateral radiograph of the abdominal was taken every six hours during the acute period to monitor any free peritoneal air. The diagnosis of NEC was based on clinical, radiological and laboratory findings, and ultimately confirmed at surgery. Standard treatment of the patients consisted of decompression of the stomach with nasogastric tube, discontinuation of enteral feeding, administration of intravenous infusion, and triple antibiotics, which consisted of ampicillin, gentamicin and metronidazole, until

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culture results were available. Patients in shock were treated with sufficient volumes of fresh frozen plasma (as a volume expander), together with inotropics (dopamine 5-10 µg/kg/min and dobutamine 10-40 µg/kg/min) to maintain blood pressure and urine output. Postoperatively, patients were maintained on total parenteral nutrition for one or two weeks, depending on the stage of the disease. Generally, we used the modified Bell's staging criteria for NEC to guide our therapeutic decisions regarding the duration of antibiotics and when to reintroduce enteral alimentation. No autopsy was performed on any of the deceased infants.

Results

Of a total of 738 newborns admitted into the NICU during the three-year period, 36 newborn babies with proven NEC were treated, constituting 4.9% of total neonatal admissions in the hospital. The sex distribution of the patients was equal, with 18 males and 18 females. The admission frequency for NEC from the years 1995 through 1997 remained virtually the same for each consecutive year (Table 1).

Records regarding the gestational ages and birth weights were only available on 33 subjects. A majority of the infants were premature: 8 (24%) were 28 weeks and below; 14 (42%), 29-32 weeks; 8 (24%) 33-36 weeks; and 3 (10%) were 37 weeks and above. No infant weighed below 750 g. Two infants (6%) weighed 750-999 g, 16 (48.5%) weighed 1000-1499 g, 12 (36.4%) weighed 1500-2499 g, and 3 (9.1%) weighed 2500 g and above.

Regarding enteral milk feeds, only two of the infants had received nothing by mouth before the onset of the disease. The average age at initiation of feeds in the other 34 infants was 4 days (range 1-10 days). All 34 infants had received cow's milk-based formula, but other details on the feeding protocol were lacking, such as the specific milk formula or the volumes fed. Breast milk feed was not mentioned. Eighteen of the infants had received total parenteral nutrition before they were transferred. Umbilical

TABLE 1. Yearly total and NEC admissions.

Year	Admissions per year	NEC admissions (%)
1995	231	12 (5.2)
1996	288	14 (4.8)
1997	219	10 (4.6)
Total	738	36 (4.9)

TABLE 2. Radiological/operative findings in 36 patients with NEC.

Condition of the intestine	No. of patients (%)
Intramural gas only	4 (11)
Perforation only	5 (14)
Perforation with gangrene	23 (64)
Gangrene only	4 (11)
Total	36 (100)

arterial catheter (UAC) was inserted in eight (22.2%) of the infants in the referring hospitals, but Apgar scores were not stated for any of the infants in the series.

Age at Onset

From the history, a majority of the patients (47.2%) developed symptoms of NEC in the first week, 10 (27.8%) in the second, and 9 (25%) in the third and following weeks. Three of the infants, all referred from one hospital, were admitted at the ages of 41, 44 and 47 days, respectively, with active disease. These infants were extreme preterm (corresponding gestational ages were 26, 24 and 28 weeks), who had a prolonged hospitalization before they developed signs of NEC. For the purpose of this study, the three infants were still regarded as neonates, as their postconceptional ages at the point at which they developed the disease were all below 37 weeks.

All the infants had received antibiotics before referral, but 18 (50%) still had positive blood culture from blood specimens taken on admission into our NICU. The organisms cultured were all gram-negative bacilli—10 cases of *Klebsiella pneumoniae*, 6 of *Serratia marcescens* and 1 each of *Enterobacter* spp. and *Escherichia coli*. The type of bacteria tallies with the common organisms prevalent in our hospital newborn population.¹⁰

Findings/Specific Management Measures

Four patients, admitted with *pneumatosis intestinalis* or stage II NEC, improved with medical treatment only. Five patients admitted *in extremis* with grossly distended and bluish abdomen were decompressed with bilateral peritoneal drains. All five infants died within 12 hours of admission. The remaining 27 patients underwent exploratory laparotomy, which involved resection with enterostomy in 19 infants, enterostomy only in seven, and an "open and close" surgery in one infant whose entire bowel up to the stomach was too gangrenous to be resected or exteriorized. The infant succumbed within 24 hours of the procedure. Table 2 shows a summary of a combination of both the radiological and operative findings, which can be utilized in defining the stage of the disease in each of the patients. Thus, of the 36 infants, four (11%) presented with stage II and 32 (89%) with stage III NEC. No stage I NEC case was admitted.

One of the two infants who had not received any enteral feeds prior to developing NEC presented with extensive gut gangrene, fecal peritonitis, and *Klebsiella pneumoniae* septicemia that led to death. The other infant also had *Klebsiella* septicemia with gangrene involving the jejunum and proximal part of the ileum, but that infant survived.

Mortality Rate

Sixteen of the 36 patients died, giving a fatality rate of 44.4%. During the three-year period under review, there were a total of 102 neonatal deaths in the unit, thus NEC contributed to 15.7% of neonatal deaths in the hospital. The

yearly contribution by NEC to the mortality in the NICU was fairly similar, though there was a tendency towards a decline (Table 3).

Discussion

It was not possible from this retrospective study to determine the true prevalence of necrotizing enterocolitis in our area, since it was obvious that neonates whose disease did not go beyond stage I NEC were presumably treated in their hospitals of origin and, therefore, not referred. Some infants with the disease in its severe form may perhaps have died without being diagnosed or before a transfer could be effected.

In spite of these missing links, the present study has demonstrated some interesting baseline features of the disease in our area. The condition accounts for 5% of total neonatal admissions in the hospital. This observation tallies with global experience that NEC constitutes 1% to 5% of all NICU admissions.^{2-4,8} It also confirms a worldwide experience that NEC is predominantly a disease of the premature and low birth weight infants.^{1-9,11} In the present series, 90% of the babies were preterm/low birth weight. In all major reported case series, at least 80% of patients are preterm or of low or very low birth weight.^{1-9,11,12} Among preterm infants, the incidence of NEC is inversely proportional to the gestational age. Preterm neonates are known to have decreased gastric acid secretion, decreased proteolytic enzyme activity, poor intestinal motility, reduced secretory IgA, reduced T-cell numbers and increased mucosal permeability.¹³ All these operate in concert to create intestinal host defence deficiencies, thus facilitating bacterial overgrowth and the destruction of the infected intestinal epithelial cells.

The majority of patients (89%) referred to our NICU with NEC reported in the late or lethal stage of the disease (stage III). This may indicate a failure on the part of nursery staff in the referring centers within the Asir region to recognize the early or warning signs of the disease, resulting in the delay in initiating treatment and appropriate monitoring in order to determine when to transfer to a tertiary center for optimal supportive and surgical care. This revelation from the study may, therefore, alert pediatricians in the region to hold a high index of suspicion over this very severe disease. Referring every patient at the stage of suspected or "rule out NEC" may, however, lead to the transfer of superfluous cases, since most infants in this group may not have NEC but the more usual feeding intolerance problem common among low birth weight infants.³ We advocate that suspected cases should be closely monitored and transferred for specialist management when there is no improvement on conservative management or when serial clinical and distension or intramural gas (stage II NEC). Intestinal perforation (stage III) has, however, been documented in

TABLE 3. NEC contribution to yearly neonatal mortality at ACH.

Year	No. of neonatal deaths	NEC mortality (%)
1995	35	6 (17.1)
1996	38	6 (15.8)
1997	29	4 (13.8)
Total	102	16 (15.7)

some patients within the first 24 to 48 hours after the onset of NEC.³

Enteral alimentation has traditionally been considered a risk factor for NEC. The age at which enteral feeds were offered to the newborns in the present series varied from 1 to 10 days. This wide range tends to suggest that the age at onset of feeds may not be contributory to the pathogenesis of NEC. This impression had earlier been made by other workers who studied the effect of early feeding on premature infants.^{14,15} Moreover, two of our patients who did not receive any enteral alimentation developed the disease in its most severe form. In a composite review of six studies involving 537 infants with NEC, Kliegman and Fanaroff found that 6.8% of the patients had never been fed.¹⁶ The paucity of information from the patients' charts regarding details of feeding practices in the subjects limited our efforts to further evaluate the contribution of enteral alimentation to the development of NEC among the patients in this series.

Twenty-two percent of the patients also had umbilical arterial line inserted. Umbilical catheterization has been associated with the development of NEC, but this claim remains controversial.^{17,18}

Clostridium species and some strains of coagulase-negative *Staphylococcus* have been frequently isolated from NEC patients and are, therefore, implicated as specific causes of NEC.^{2-4,8} Epidemics of NEC have been reported with *E. coli*, *Klebsiella*, *Enterobacter*, *Pseudomonas* and *Salmonella*.¹⁶ Fifty percent of our subjects were septicemic on admission—the isolates were largely *Klebsiella pneumoniae*, *Serratia marcescens* and other gram-negative bacilli. These are the dominant organisms which cause neonatal sepsis in our environment.¹⁰ This experience, therefore, suggests that the organisms prevalent in our newborn population are the ones participating in the intestinal injury in infants vulnerable to NEC. This revelation regarding the bacterial pattern in this local survey should be useful in guiding chemotherapeutic decisions in NEC patients in the Asir region.

The fatality rate of 44% at our center agrees with the rate of 45% reported by Abdullah et al. from Riyadh,⁸ but is higher than the global average of 20%-40%.²⁻⁴ This high figure in our unit can be explained on the basis that, being a purely referral center, the NICU in ACH is exposed largely to subjects in the advanced stage of the disease. To have a good NEC outcome, a high index of suspicion and early transfer to a specialized center is mandatory.

Most neonatal units worldwide still regard perforation as the only indication for surgical intervention in NEC patients.² This may explain why a vast majority of the cases in this series were referred in stage III of the disease. Perforation should not be the only indication for laparotomy, since perforation with or without gangrene carries a poor prognosis for NEC. Relative indications for earlier surgery for NEC with a good outcome include radiographic finding of a single fixed bowel loop, erythema of the abdominal wall, palpable abdominal mass, and failed medical treatment.^{2,4} Each of these features, especially when associated with persistent metabolic acidosis and thrombocytopenia, suggests the existence of a necrotic loop of bowel and impending perforation.⁴ In the present series, 11% of the patients had gangrenous bowel without showing any radiological evidence of perforation. It would be ideal to be able to identify those infants with gangrenous bowel and proceed to resection of necrotic bowel and external ostomy diversion before the peritoneum is soiled with fecal matter. Koloske and Goldthorn have advocated *paracentesis abdominis* as a method of selection. A brown peritoneal fluid usually confirms gangrene, although a dry tap does not exclude it.¹⁹ In certain situations, even with gut perforation, peritoneal drainage alone under local anesthesia with antibiotic therapy has resulted in the recovery of patients.²⁰

A striking feature of this study is that a large majority of the NEC patients were referred in the advanced and lethal stage of the disease. Even without comparison with other centers, this figure of 89% is quite alarming and worrisome, and therefore, calls for urgent intervention. A high index of suspicion in recognizing infants at risk is essential. Intensive therapy is advisable for suspected as well as diagnosed cases. A surgeon should be consulted early in the course of treatment and early transfer of patients to a tertiary center cannot be overemphasized. Finally, a more detailed prospective multicenter survey on NEC in our environment is desirable. The feeding regimen, sociodemographic and other etiological correlates need to be scrutinized in a subsequent study in order to proffer possible effective preventive strategies.

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