ORIGINAL ARTICLE

Necrotizing Enterocolitis Among Newborn Infants Suffering from Gastroenteritis A Clinical evaluation of 17 cases.

by

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Abstract

Seventeen infants with NNEC were evaluated. The diagnosis was based on clinacal, laboratory and rontgenographic findings. Twelve out of them had a low birth weight (less than 2500 grams) and 5 were prematures.

Since only 2 cases had asphyxia at 1 minute after birth, asphyxia apparently played only a small role as the perinatal factor in the development of NNEC. Beside gastro — enteritis, bronchopneumonia and meningitis were the accompanying diseases in 2 cases and 1 case respectively. Bacterial findings from the stool and cerebrospinal fluid were as follows :

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— *E. Colie 0111 K 58 (b), 0126 K 71 (B) H2 were cultured from the stool of 7 infants.*

— *Pseudomonas from cerebrospinal fluid was found in 1 case.*

Prior to the onset of symptoms, all of these infants were fed with milk formula. Therefore the authors believe that infections and formula feedings play an important role in the development of NNEC.

The survival rate of our cases was poor with 52% deaths (9 out of 17), and 2 of them had intestinal perforation. Anemia which develops rapidly should be taken into account in the management of NNEC.

Introduction

NNEC is an acute and serious disease of newborns and young infants resulting in a high mortality rate, usually being diagnosed in its advanced stage, and it is primarily found among premature infants.

With the many publications of this disease having been reported there seems to be an increased frequency of it. This increase of frequency is probably not only related to a better recognition of it, but also to the enchanced practice of bottle feeding. This disease is characterised clinically by lethargy, irritability, prolonged gastric emptying with or without vomiting, abdominal distention, apneaic episodes, and the passage of blood macroscopically or microscopically in the stools. Radiologically it is characterised by pneumo-intestinalis.

In advanced cases the infant may be in shock, with frequent apneaic episodes, may have septicemia, and signs of intestinal perforation with peritonitis.

The etiology of this disease is still unknown, although many factors have been explained which account for its pathogenesis. Among those factors are : Infection (Mizrahi et al., 1965), Cow's Milk (Barlow et al., 1974), early feeding with Bottle Milk (Krouskop et al., 1974) hypersmolar feedings (Book et al., 1976), and ischaemia of the gastrointestinal tract (Touloukian, 1976). The purpose of this paper is to report our experience with the epidemiological aspects, diagnosis, management, and outcomes of 17 cases.

Material and Methods

From December 1975 to September 1977, there were 17 newborns, being diagnosed as NNEC in the neonatal intensive-ward, Gunung Wenang Hospital, Manado, Indonesia. (Abbreviation used: NNEC : Neonatal Necrotizing Entero Colitis).

Clinical Diagnosis

The clinical diagnosis was based on the following criteria :

1. Clinical Findings :

— lethargy

— slight or severe abdominal distention and ileus

— apneaic episodes

— bloody stools or positive guaiac test,

2. Radiographyc Findings :

— Radiological findings confirmed the clinical diagnosis of NNEC

— Radiological findings may be pneumointestinalis, and a dynamic ileus with or without pneumoperitoneum or pneumoportalis.

Management

When the clinical diagnosis of NNEC was established, the management consisted of the following procedures :

1. Shock therapy was instituted, if a patient was in shock by using a mixture of electrolytes in dextrose 5% with a composition as follows :

— Na+ — 2 mg/100 ml
— K+ — 2 mg/100 ml
— Cl— — 4 mg/100 ml

2. Intravenous feedings of ½ strength aminofusin 600 in dextrose 10% at the rate of 140 ml/kg body weight/day which is the equivalent of 100 cal/kg body weight/day.

Oral feedings were ceased for 3 - 5 days.

This solution provided the nutrients as follows :

Nutrients	amount/kg body weight in 140 ml/kg b.w./day
— DL Isoleucine	240 mg
— L Leucine	168 mg
— L Lysine	140 mg
— DL Methionine	210 mg
— DL Phenyl alanine	280 mg
— DL Therenine	140 mg
— DL Tryptophane	70 mg
— DL Valine	224 mg
— L Arginine	448 mg
— L Histidine	70 mg
— DL Alanine	420 mg
— Glycine	980 mg
— L Proline	140 mg
Total amino acid	3.5 gm/kg body weight/day
B. Carbohydrate (gm/100 cc)	
— Sorbitol	5
— Glucose	10
C. Vitamins (mg/100 cc)	
— Ascorbic acid	20
— Inositol	25
— Nicotinamide	3
— Pyridoxine HCL	2
— Riboflavine 5 phosphate Sodium	0.12
— Rutin	10
D. Electrolyte (meq/l)	
— Na+	17.5
— K+	12.5
— Mg++	2.5
— Acetate	17.5
— Malate	11
— Cl	19

2. Parenteral antibiotics :

— Ampiclox : 100 mg/kg body weight/day administered intravenously in divided doses.

— Garamycin : 8 mg/kg body weight/day in divided doses.

3. Blood transfusion if necessary

4. After improvement of clinical and radiological findings, and negative guaiac test, gradual oral feedings are then begun concomitantly with the reducing of IVFD. Breast feeding was encouraged in all patients when deemed advisable. Oral feeding was started at the rate of 20 ml/kg body weight/day and by the 5 - 7th day the average daily intake of 120 cal/kg body weight, Apgar score, gestational age, and types of feeding were recorded.

Result

TABLE 1 : *Body weight and Gestational age*

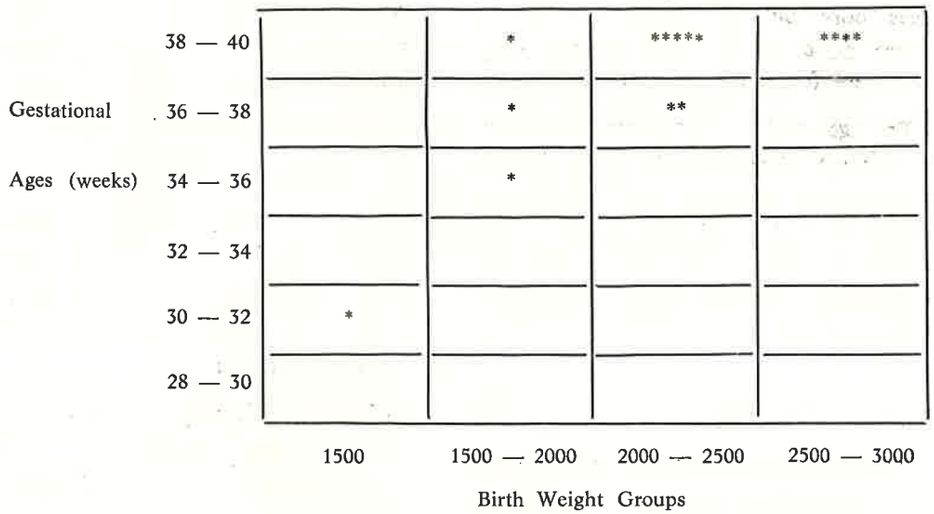
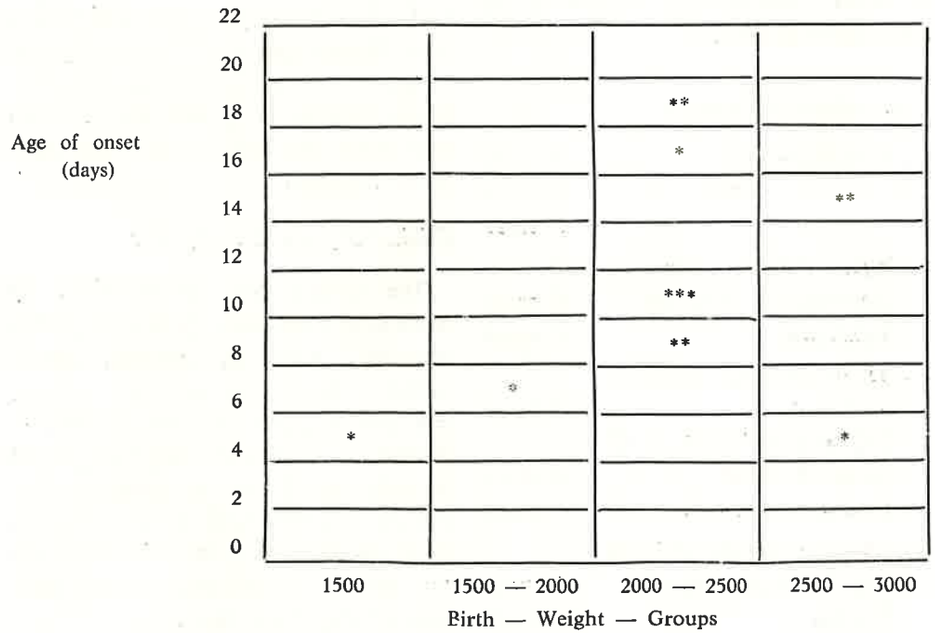


TABLE 2 : *Birth weight and Age of Onset*



Twelve of 17 cases (70.6%) were low birth weight infants, weighing less than 2500 grams, whereas 5 of these were preterms. The birth weight of 3 of our cases born outside the hospital was unknown, but on clinical assessment they were found to be fullterm infants.

The age of onset or the age at which the clinical diagnosis was established varied from 4 to 18 days (mean : 10.9 days). It seemed that there was no correlation between birth weight and day of onset.

Perinatal Conditions

There are many perinatal risk factors which have been reported and suspected of accounting for the development of NNEC. Among those factors in our cases were namely :

a. Maternal factors :

— Gestation : 1st	9 cases
2 - 5	5 cases
6	3 cases
— Blood Pressure : Normal	8 cases
Hypertension (130/90)	6 cases
Unknown	3 cases
— Antenatal care : Unbooked infants	4 cases
bad antenatal care (1 - 3 antenatal visits)	9 cases
good antenatal care	4 cases
— Anemia : Anemia with Hb less than 6 gm/100 ml	1 cases
Normal	16 cases

b. Neonatal Factors :

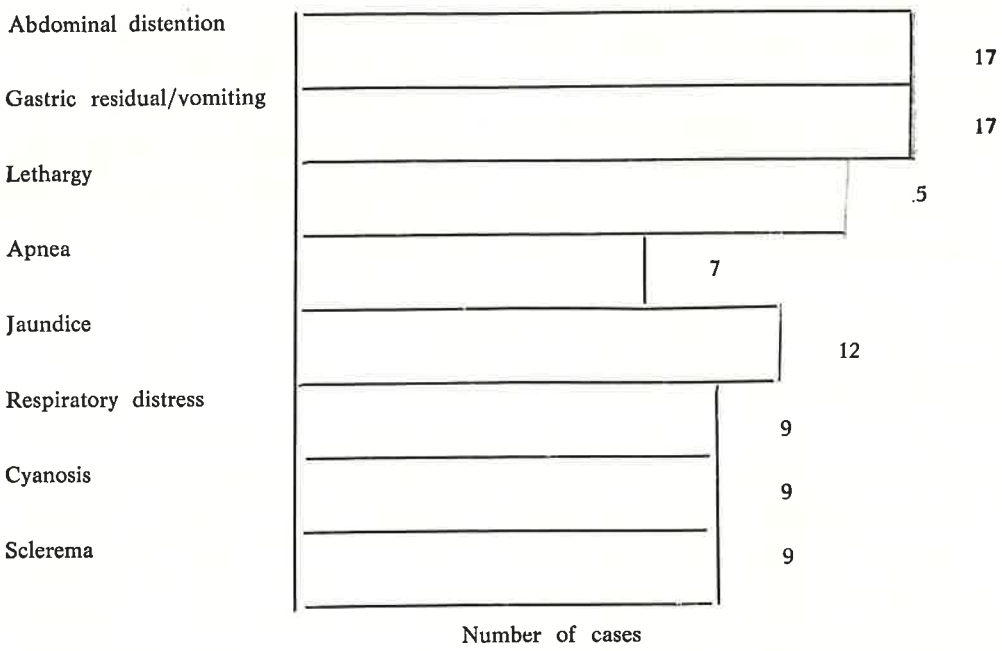
— Gastroenteritis	17 cases
— Bronchopneumonia	2 cases
— Meningitis	1 cases
— Recurrent apnea	1 cases
— Apgar Score (1 minute)	
0 — 3	2 cases
4 — 6	1 cases
7 — 10	11 cases
unknown	3 cases
— Type of feeding :	
— human milk only	—
— human milk and bottle feeding	3 cases
— bottle feeding	14 cases

All infants except 3 were fed with a milk formula prior to the development of the disease. In the history, inadequate breast milk or no production of breast milk were the main reasons for using bottle feedings.

Clinical Signs and Symptoms

The disease was characterized by abdominal distention, prolonged gastric emptying, vomiting, lethargy, apnea, jaundice, respiratory distress, cyanosis, and sclerema. But all these clinical manifestations might not always be present in each case. However, abdominal distention and prolonged gastric emptying were always present in each of our cases. Apnea, cyanosis and sclerema were seen among severe cases.

FIG. 1 : *Clinical Signs and Symptoms of 17 cases*



Radiological Investigations :

Radiological findings confirmed the clinical diagnosis.

Four radiological features may be found in NNEC, namely :

1. Intestinal distention with or without fluid levels.

This evidence can be used as warning sign in the development of pneumointestinalis, since it appears prior to the development of pneumointestinalis.

2. Pneumointestinalis.

Sometimes it is very difficult to demonstrate intramural air which can be easily misinterpreted as stool mixed with air. Hence serial x-rays are advisable to confirm the clinical diagnosis. The appearance of pneumointestinalis in the form of linear or curvilinear streaks of air within the bowel wall is pathognomonic.

3. Pneumoperitoneum.

Free peritoneal air can be seen in patients with intestinal perforation which varies from small volume seen only in erect position to a massive air appearence.

4. Portal Vein Gas.

Portal vein gas is an ominous radiological finding which can be considered as the terminal stage with a high mortality rate. Intestinal air enters the portal circulation through the necrotic intestinal mucosa. Death frequently occurs in

infants with portal vein gas finding. The cause of this death is septicemia due to gram negative organism. (Insert figure 2 and 3).

Radiological investigations among our 17 cases were as follows :

Pneumointestinalis	17 cases
Pneumoperitoneum	2 cases
Portal vein gas	4 cases

All of our cases with pneuperitoneum and portal vein gas died.

Stool cultures were done in all patients and yielded E. coli pathogens in 7 cases. Pseudomonas was found in the cerebrospinal fluid and stool culture of one infant.

TABLE 3 : *Laboratory Investigations*

Case	B.W.	Gestational age	Onset of disease	Hb (gm/100 ml)	Thromb
1. F	2100	38 — 40 weeks	18 days	9.8	114.000
2. F	1360	30 — 32	5	10.8	180.000
3. M	2760	38 — 40	15	8.2	197.000
4. M	2560	38 — 40	10	13.6	222.000
5. F	2100	36 — 38	8	13.6	210.000
6. M	2230	38 — 40	10	10.8	184.000
7. F	1770	36 — 38	12	12	186.000
8. M	2750	38 — 40	15	8	96.000
9. F	2450	38 — 40	8	11	210.000
10. F	2060	36 — 38	16	11	222.000
11. M	2440	38 — 40	11	11	186.000
12. F	2000	38 — 40	10	11	195.000
13. F	2280	38 — 40	10	10.5	156.000
14. M	1600	34 — 36	7	10.8	196.000
15. F	3000	38 — 40	8	8	125.000
16. M	2100	38 — 40	18	13.5	230.000
17. F	2820	38 — 40	4	6	54.000

Anemia and thrombocytopenia can be easily seen among severe cases. However, it seems that there is no correlation between Hb concentration with birth weight, and gestational age.

Discussion

The etiology of NNEC is still obscure and is considered to be multifactorial with many predisposing factors including low birth weight infant, particular-

ly prematurity (Hopkins et al., 1970; Frantz et al., 1975; Denes et al., 1970; Book et al., 1976, 1976a, 1976b), bottle feedings (Kroupkop et al., 1974; Bell et al., 1971) hyperviscosity syndrome (Leake et al., 1975), and umbilical catherization (Hopkins et al., 1970).

Hypoxia or ischaemic injury of the bowel wall (Touloukian et al., 1972; Barlow et al., 1974; Santuli et al., 1975), direct injury of the mucosal wall by hyper — osmolar feeding (Nasrallah et al., 1968; De Lemos et al., 1974; Book et al., 1976), and infection with gram negative microorganisms such as Salmonella (Stein et al., 1972); Klebsiella (Hill et al., 1974), Pseudomonas aeroginosa (Santuli et al., 1975), and E. Coli (Speer et al., 1976), have been suggested as etiological factors.

The current most accetable theory of the pathogenesis is hypoxia which evokes a reflex resulting redistribution of blood, shunted away from less vulnerable organs like the mesenteric, the renal and the peripheral vascular bed to the first class organs (the brain and the heart) which would suffer irreversible damage if deprived of adequate perfusion.

The mucosal cells, which are highly sensitive to ischaemia, stop secreting protective mucous. Hence, proteolyptic autodigestion of the mucosa occurs.

Once the integrity of mocusa is broken, it will be invaded by gas forming micro organisms. Bacteria are absorbed into the lymphatics and into the radicles of the portal venous system, leading to overwhelming sepsis and death (Touloukian et al., 1967; Barlow et al., 1974).

From our observation it can be seen that diarrhea, bottle feeding and infection are the most important multiple factors responsible for the development of NNEC. It is also thought that low birth weight infants born from mothers with hypertension and poor antenatal care, and infants with pneumonia were predisposed to the development of NNEC.

All our cases prior to the development of diarrhea received bottle feedings, and out of 17 cases in which a stool culture was made, 10 were found to contain E. Coli and Pseudomonas.

The role of bottle feedings in the development of NNEC may be as follows:

1. Cow's milk protein intolerance (de Peyer and Smith, 1977).

2. Although the prevalence of protein milk allergy is very low, less than 1% (Lebenthal, 1975), it cannot be eliminated as a factor which cause diarrhea in our cases. As far as we know there is no publication on the prevalence of protein allergy among neonates in Indonesia.

3. Formula feeding lack protective factors such as IgA, IgG, active lymphocyte and macrophages, specific antibodies againts many types of organisms (especially the most important bacterial pathogen of the neonate E. Coli), growth enchancer of gram positive lactobacilli,

an anti staphylococcal agent, lysozyme and lactoferrin (Goldman and Smith, 1973; Barlow et al., 1974). Therefore in premature infants where enteric immunity is still immature, formula feedings will cause overgrowth of enteric bacteria. The clinical onset of NNEC is varied from an insidious onset with increasing gastric retention of food and occult blood in stools, developing over several days, to a fulminating course within a few hours with lethargy, abdominal distention and peritonitis.

Figure 1 shows a variety of clinical signs and symptoms; abdominal distention, prolonged gastric residue and lethargy were the main clinical signs and symptoms of our cases.

Our criteria for the diagnosis of NNEC in this evaluation were too strict, whereas x-ray examination required pneumointestinalis and/or pneumoperitoneum and portal vein gas. Hence this may be one of the causes, of our delay in making an early diagnosis, with the result that the vast majority of our cases, 9 out of 17, were severe with frequent apnea, cyanosis, lethargy and sclerema. Anemia and thrombocytopenia were also encountered among our severe cases.

In an attempt to prevent severe cases and to reduce the mortality rate, an accurate early diagnosis should be made. Book et al. (1976), found that in testing stools from one day to four days prior to the onset of NNEC, 71% of the cases showed reducing substances to be strongly positive. In the authors' opinion, a neonate with diarrhea, especially of low birth weight, who has abdominal distention, a positive guaiac test, and positive reducing substances in the stool with unspecific radiological findings in the x-ray such as a foamy appearance or a bowel distention should be treated as a NNEC. A series of x-ray and blood examinations are advisable for detecting the progression of the disease.

Portal vein gas was first reported by Wolfe and Evans in 1955. Since then this finding has been widely reported by Goldstein et al., 1966, Touloukian et al., 1967; Stevenson et al., 1971; Miskian and Reilly 1969; and Yu et al., 1977), and suggested to be the ominous sign. (Wilson and Wooley 1969; Hopkins et al., 1970). Six of our cases with portal vein gas, accompanied by severe clinical symptoms and signs such as frequent apnea, cyanosis, lethargy and sclerema, died.

The management of all of our cases was mainly only conservative treatment by witholding oral feeding, institution of parenteral feedings and administration of antibiotics intravenously, the outcome of this regimen was rather poor where 9 out of 17 cases (51%), died.

Although some of our cases were absolutely surgically indicated such as perforation (Touloukian et al., 1967, Stevenson et al., 1971), sudden clinical deterioration or the obvious progressive clinical course of the disease (Stevenson et al., 1971), because of a lack of neona-

tal surgical facilities in our hospital, surgical intervention could not be conducted. Looking back to our severe cases, we felt that early surgical intervention before becoming moribund, where the infant was too ill to be operated upon, was absolutely necessary. The mortality rate can be reduced by conducting early surgical intervention among indicated cases. (Wayne et al., 1975; Touloukian 1976). Parenteral feeding may not be overlooked in the management of NNEC, because the infusion of amino acids can deteriorate the infant condition particularly among low birth weights, whose activities of certain amino acids will be imbalanced and elevated which may have harmful effects.

Our infusion which contain a higher concentration of amino acids compared to the advisable requirements (Fomon, 1974), particularly proline and cystein are a high risk as they frequently develop into metabolic complications. However, during these observations we did not see any complication as the result of parenteral feedings. This may be because our intravenous feeding procedures were too short to develop any complications, and because of the highly caloric contents of our infusates. But, further study of this solution is needed to find out the effect of short term parenteral feeding, compared to the low concentration of amino acids.

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