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ORIGINAL ARTICLE

Experiences on Necrotizing Enterocolitis in Neonates and Young Infants in North Sulawesi

by

MUZIEF MUNIR

(From the Department of Child Health, Gunung Wenang Hospital Medical Faculty, Sam Ratulangi University, Manado – Indonesia).

Abstract

Since the predisposing factors of necrotizing enterocolitis in newborns and young infants in developed and developing countries are totally different, the evaluation of epidemiological, clinical and management problems of 20 of our newborn cases and 3 young infants was conducted.

It is evident that gastroenteritis and severe pulmonal infections are indeed the most important risk factors in developing necrotizing enterocolitis in our cases.

Rooming-in and breast feeding practices reduce sharply the incidences of diarrheal diseases in newborn infants, and in turn, cause a decline in the prevalent rate of necrotizing enterocolitis.

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Introduction

Necrotizing enterocolitis is a lethal disease in newborns, particularly in premature and small-for-gestational-age infants, and it is also sometimes found in young infants. This disease is characterised by a variety of gastrointestinal wall necrosis, ranging from mucosal ulceration to transmural necrosis which is usually fatal.

During the last ten years this disease has been widely reported in western countries where the prevalent rate of this disease varies from one centre to another, even to the point of near epidemic proportions. On the other hand the reports from developing countries are too few (Karan and Pathak, 1973, Munir et al., 1980). The lack of reports in developing countries might not only be caused by a lack of proper attention to this disease, but might also be caused by a low prevalent rate of this disease.

Many factors should be taken into consideration which account for determining the prevalent rate of this disease, such as : the ability to maintain or to prolong high risk infants life particularly premature infants, the prevalence of infection, and the type of feeding and infant care in the hospital. Since all of these factors in developed and the developing countries are totally different, the highlighting of this disease in this report is an attempt to prevent or to reduce the prevalent and the mortality rates of this disease.

Material and Methods

This on going evaluation of necrotizing enterocolitis, started in January 1976, is attempting to highlight all problems including. clinical, epidemiological, and management problems in neonates and young infants admitted in the neonatal intensive care ward or in the child-intensive care ward at Gunung Wenang Hospital, Manado, Indonesia.

I. Criteria For Diagnosis

Necrotizing enterocolitis is diagnosed clinically based on the existing syndromes of lethargy, abdominal distention, gastric retention with or without vomiting, bloody stools or positive guaiac test, and confirmed radiological findings such as pneumointestinalis or dynamic ileus with or without pneumoperitoneum or pneumoportalis.

II. Management

Once the clinical diagnosis of necrotizing enterocolitis had been established, the regiment of management was as follows :

1. If the patient was in shock, a shock therapy of 30 cc/kg bw of solution was instituted immediately.

   The solution were as follows :

   1.1. For NNEC cases : A solution which consists of a mixture of electrolytes :

Na	20 meq/1
K	20 meq/1
Cl	40 meq/1

   And to overcome : acidosis 2 cc/kg bw of 40% sodium bicarbonate solution was given intravenously.

   1.2. Young infants with necrotizing enterocolitis : A Ringer lactate solution.

2. Oral feedings were ceased for at least 3 – 5 days, and intravenous feedings were started by using half-strength aminofusin or aminovel, diluted with 10% dextrose solution at the rate of 140 – 150 cc/kg bw/day for newborns or equivalent to 75 cal/kg bw/day.

   150 cc of this half strength solution provided the nutrients as follows :

   A. Protein (Aminoacids)

Nutrient	amount/kg bodyweight in 150 cc/kg bw/day
Isoleucine	240 mg.
Leucine	180 mg
Lysine	150 mg
Methionine	225 mg
Phenylalanine	300 mg
Threonine	150 mg
Tryptophane	75 mg
Valine	240 mg
Arginine	465 mg
Histidine	75 mg
Alanine	450 mg
Glycine	1050 mg
Proline	150 mg
Total amino acids	3,75 gm/kg body weight/day

   B. Carbohydrate (gm). 15 grams

   C. Vitamins :

Ascorbic Acids	30 mg
Inositol	37,5 mg
Nicotinamide	4,5 mg
Pyridoxine HCL	3 mg
Riboflavine	0,18 mg
Rutin	15 mg

3. Parenteral antibiotics : Ampiclox 100 mg /kg bw/day (for neonates, gentamycin was added).
4. Blood transfusions as necessary.
5. Gastric decompression was done by using a nasogastric tube.
6. After the improvement of clinical and radiological findings as well as negative guaiac test, gradual oral feedings were then begun concomitantly with the reducing of ivfd.
   Breast feeding was encouraged.
7. Radiological examinations were repeated on days 1, 3, 5 and 7 after establishing the diagnosis.

III. Other Examinations and Follow up

Stool specimens were taken for 3 consecutive days for stool cultures, macroscopic and microscopic examinations, and guaiac tests.

A daily guaiac test was conducted until it became negative.

Birth weight, gestational age, type of feedings, associated diseases or problems, and body weights were recorded.

Careful physical examinations were conducted.

Results

During the 6 years period from 1976 to 1981, there were 23 cases, comprising 20 newborns and 3 infants diagnosed as having necrotizing enterocolitis.

After the rooming-in care procedure for newborns was put into practice in June 1980, no cases of necrotizing enterocolitis were found in the neonatal ward, except for 2 refered from maternity clinics.

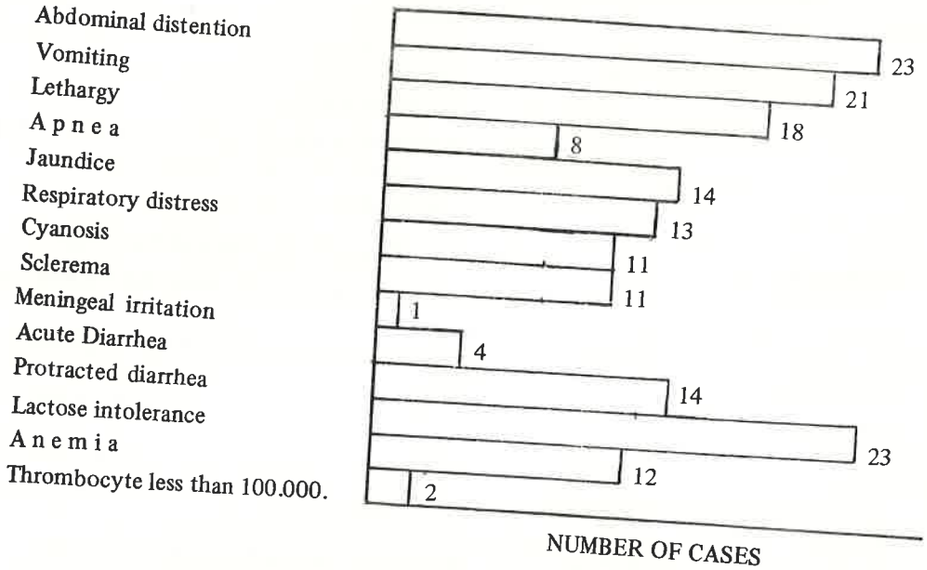
The clinical and radiological investigations:

The clinical signs and symptoms can be seen in figure 1.

Abdominal distention, gastric residue, vomiting and lethargy were the main clinical symptoms and signs found in cases with necrotizing enterocolitis, either in neonates or in infants.

Apnea, cyanosis, sclerema and severe paralytic ileus were seen among severe cases.

Figure 1 : Clinical Signs and Symptoms



Radiological findings confirmed the clinical diagnosis. Three types of radiological pictures were recurringly found in our cases (Fig. 2,3,4,5 and 6).

1. **Pneumointestinalis.**

   It is not easy to demonstrate intramural air which is sometimes misinterpreted as stool mixed with air.
   Serial X-rays are advisable to confirm the clinical diagnosis.
   The appearance of pneumointestinalis is in the form of lineairs, curvilineairs, or bubbles.

2. **Pneumoperitoneum in 4 cases.**

   Free peritoneal air could be seen in patients with intestinal perforation, which varied from small volume, seen only on erect position, to a massive appearance. Surgical intervention with a massive intestinal resection was conducted in only one case. All of these 4 cases died.

3. Portal vein gas was found in 4 cases and all of these cases died.

Risk - Factors

Many risk factors should be taken into consideration in the development of necrotizing enterocolitis.

Some of risk factors in our cases were as follows :

Gastroenteritis	20 cases
Severe pneumonia	5 cases
Type of feeding :	
human milk only	– case
human milk and bottle feeding	2 cases
bottle feeding	17 cases
baked ripe Banana + breastmilk	1 case

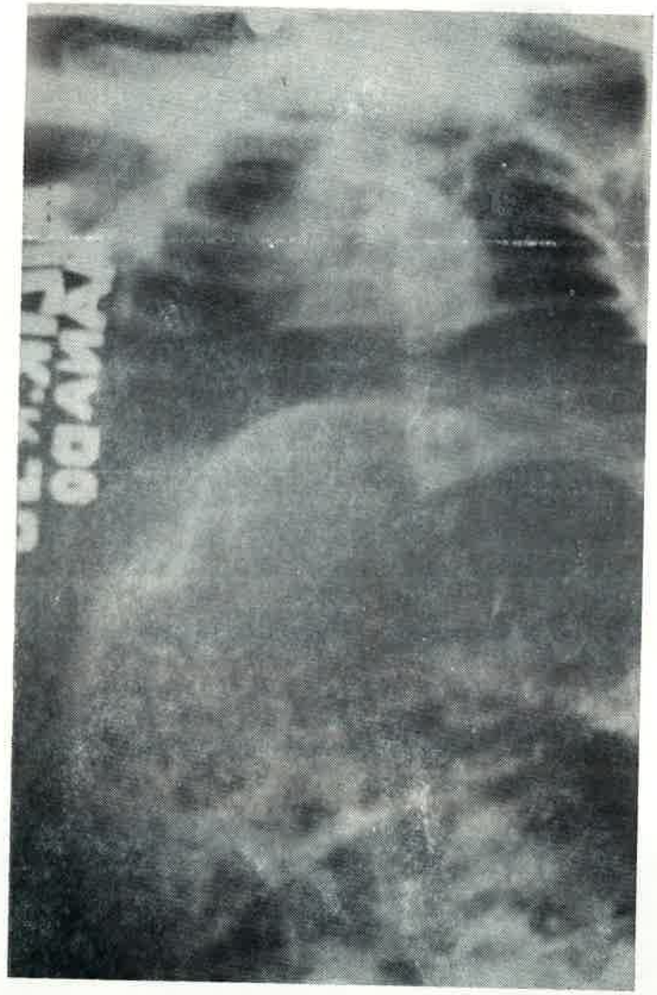


Figure 2 : *X ray of abdomen of a 7 day old baby showing marked bowel distention with evidence of free air under the dome of the diaphragm; a foamy appearance of intramural air on the right quadrant.*
The chest shows pneumonia.

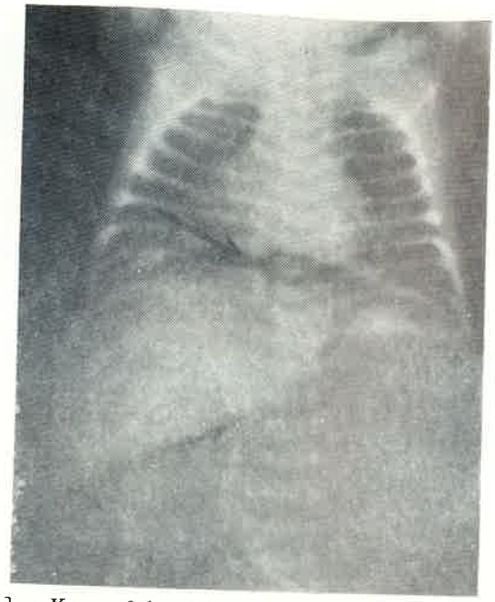


Figure 3 : *X ray of the abdomen of a 14 - day old baby indicating : Giant distention of stomach cavity with a foamy appearance intramural air throughout the stomach. The top arrow indicates free air under the dome of the right side of the diaphragm; the middle arrow shows portal vein gas; and the two bottom arrows indicates bubbly appearance of intramural air.*

Figure 4 : *The above x ray shows a marked – foamy appearance of intramural air.*

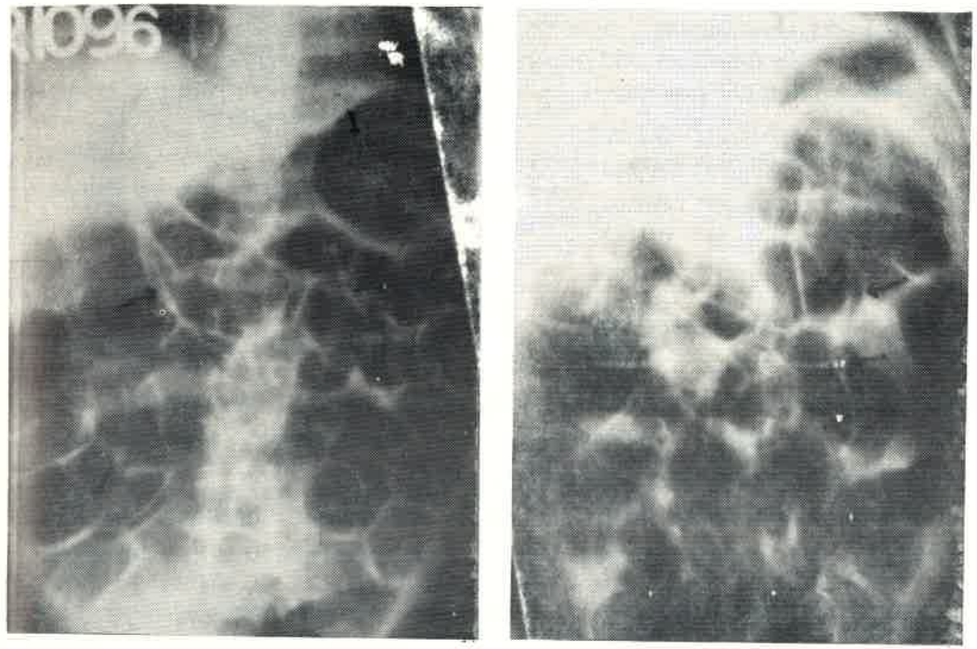


Figure 5 : (A) (B)

Extensive pneumatosis intestinalis with linear appearance of intramural air. (B) Extensive pneumatosis with linear appearance of intramural gas in a 17/12 years old case with severe pneumonia and empyema of the right side of the chest.

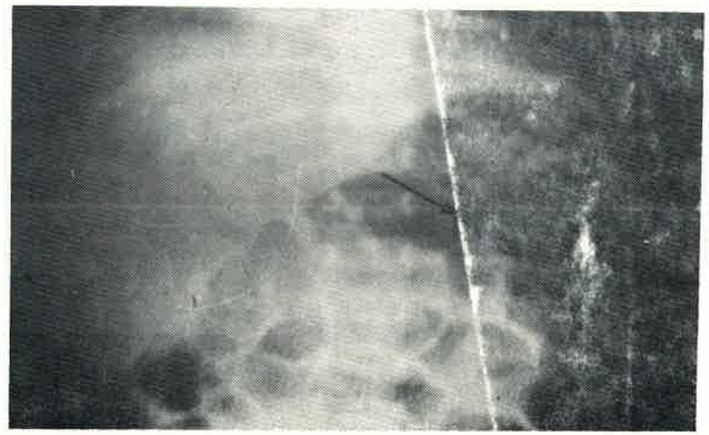


Figure 6 : ***Extensive pneumointestinalis with a culvilinear and bubble appearance of intramural gas.***

Birth weight or body weight :
low birth weight (less than 2500 grams) 15 cases consisting of 5 preterms.

normal birth weight of fullterm	5 cases
malnutrition	1 case
normal body weight	2 cases

Apgar score or asphyxia :

0 – 3 or severe asphyxia	2 cases
4 – 6 or moderate asphyxia	1 case
7 – 10 or vigorous baby	15 cases
Unknown	2 cases

Laboratory investigations can be seen in table 1.

Table 1 : Laboratory Investigations

Case	B.W. (in kg)	Gestational Age	Onset of Disease	Hb (gr/100 ml)	Throm-bocyte	Stool culture
1.F	1.360	30 – 32	5 days	10.8	180.000	Negative
2.F	2.820	38 – 40	4 days	6	54.000	Ecoli 0 55 K59(B)
3.F	3.000	38 – 40	8 days	8	125.000	Ecoli 0 111 K58(B)
4.M	2.100	38 – 40	18 days	13.6	230.000	Negative
5.F	2.280	38 – 40	10 days	10.5	156.000	Negative
6.M	1.600	34 – 36	7 days	10.8	196.000	Negative
7.M	2.440	30 – 40	11 days	11	186.000	Ecoli 0 126 K71(B) H
8.F	2.000	38 – 40	10 days	11	195.000	Negative
9.M	3.200	38 – 40	12 days	13.8	230.000	Ecoli 0 111 K58(B)
10.M	2.400	36 – 38	16 days	9.2	220.000	Negative
11.F	3.100	38 – 40	9 days	10	210.000	Negative
12.F	2.100	38 – 40	18 days	9.8	114.000	Negative
13.M	2.760	38 – 40	15 days	8.2	197.000	Ecoli mixed 0 111 K58 (B) and 0 126 K71 (B) H2
14.M	2.560	38 – 40	10 days	13.6	222.000	Ecoli mixed 0 111 K58 (B) and 0 126 K71 (B) H2
15.M	2.230	38 – 40	10 days	10.8	184.000	Ecoli mixed o 111 K58 (B) and 0 126 K71 (B) H2
16.F	1.770	36 – 38	12 days	12	186.000	Ecoli 0111 K59 (B)
17.M	2.750.	38 – 40	15 days	8	96.000	Negative

Case	B.W. (in kg)	Gestational Age	Onset of Disease	Hb (gr/100 ml)	Throm-bocyte	Stool pulture
18.F	2.450	38 – 40	8 days	11	210.000	Ecoli 0111 K58 (B)
19.F	2.060	36 – 38	16 days	11	222.000	Ecoli 0 111 K58 (B)
20.F	2.100	36 – 38	8 days	13.6	210.000	Negative
21.M	11 kg	–	2 7/12 yrs	6.8	165.000	Negative
22.M	3.4	–	1/12 yrs	9.8	220.000	Negative
23.M	7.7	–	1 7/12 yrs	8	245.000	Negative

Discussion

In spite of the fact that the etiology of necrotizing enterocolitis is still obscure, it is considered to be multifactorial with many predisposing factors such as low birth weight, particularly prematurity (Hopkins et al., 1970; Frantz et al., 1975; Book et al., 1975), bottle feedings (Krouskop et al., 1974; Bell et al., 1971) and hyperviscosity syndrome (Leake et al., 1975), and umbilical catheterization (Hopkins et al., 1970). The most acceptable theory is the hypoxia theory where hypoxia evokes a reflex resulting in the redistribution of blood hunted away from less vulnerable organs such as mesentery and the renal to the brain and the heart, first class which are liable to be damaged irreversibly if deprived of adequate perfusion.

The change of microcirculation in the gastrointestinal tract system which leads to gastrointestinal ischaemia might be found in severe pulmonal infection or in shock, whatever the cause is. Gastrointestinal ischaemia causes a decrease in the protective mucous secretion by mucosal cells which are highly sensitive to ischaemia affecting proteolytic autodigestion of the mucosa. Once the integrity of mucosa is broken, it will be invaded by gas-forming micro-organisms. Bacteriae might be absorbed into the lymphatic system and the radicles of the portal system, leading to an overwhelming sepsis and death (Touloukian, 1976; Barlow et al., 1974). On the otherhand Lehmiller and Kanto (1978) proposed that the development of NEC is the result of the occurrence of mesenteric thromboembolism in infants receiving oral feedings, while with an umbilical catheter.

Severe pulmonal infection and diarrheal diseases with or without other associated diseases account for the development of necrotizing enterocolitis either in neonates or in infants in this report. Severe pulmonal infection with or without empyema will cause general hypoxia leading to some degree of gastrointestinal hypoxia. One of the 3 young infants suffering from severe pulmonal infection was associated with empyema.

The adverse role of bottle feedings which influence the development of necrotizing enterocolitis in neonates, particularly in pre-

mature infants is fairly certain, since all, except one of the neonates were fed by bottle feedings which might account for the development of diarrhea. All of these neonates prior to the development of necrotizing enterocolitis suffered from diarrhea.

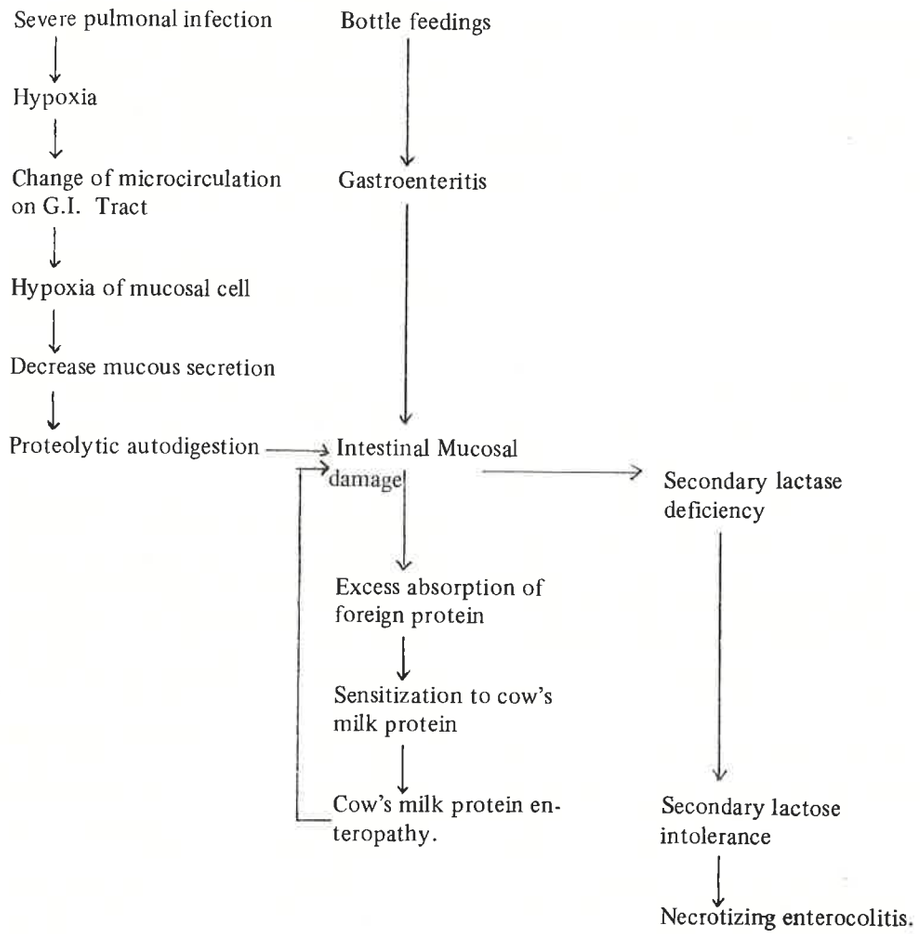
The development of diarrhea in bottle feedings may be closely related to infections or to cow's protein allergy(Lebenthal, 1975) so that cow's milk protein allergy in turn accounts for the development of NEC (de Peyer and Smith 1977). It is well known that formula feedings in comparison to breast feedings lack protective factors such as IgA, IgG, Lysozyme, active lymphocytes and macrophages, lactoferin, the growth enhancer of gram positive lactobacilli which acts as an anti staphylococcal agent, and specific antibodies against many types of organisms, particularly E.coli, the most important bacterial pathogen of the neonates (Goldman and Smith, 1973; Barlow et al., 1974). E. coli pathogen was found in the stool of 10 out of 20 neonates in this investigation.

Since enteric immaturity is still found in premature infants, formula feeding will cause an over growth of enteric bacteriae which accounts for the development of diarrhea will cause small mucosal damage with an excess of foreign protein absorption, causing cow's milk protein enteropathy (Harrison et al.,1976; Iangkaran et al.,1978). Cow's milk protein enteropathy will in turn increase the mucosal damage which will then be easily invaded by gas forming bacteriae. The formation of gas by gas forming bacteriae is made possible by the presence of lactose, caused by a secondary lactase deficiency (fig.7).

It is obvious from this report that incidences of diarrhea in neonatal wards is closely related to the type and the quality of newborn care, which in turn determines the incidence of necrotizing enterocolitis. Since rooming-in care has been put into practice in newborn care, the morbidity of diarrheal diseases in neonatal wards dropped sharply and none of the newborns developed necrotizing enterocolitis (Mustadjab and Munir).

This sharp drop may be caused not only by an increase in breast feeding practices among mothers delivering in the hospital, but also by the improvement in the quality of newborns care, since mothers are the best nurses for their babies. A deterioration of the lactation process will occur in the mother who is separated from her baby being cared for by the hospital. This separation will not enable the mother and the infant to establish a close interaction which serves as the basis for the proper development of mothering attitudes.

Figure 7 : *The possibilities of the pathogenesis of necrotizing enterocolitis in this report.*



The clinical picture of cases in this report was fairly characteristic, and this might be closely related to a strict observance of clinical criteria. A clinical diagnosis based on strict criteria necessitates the presence of pneumointestinalis on X-ray examination might account for a delay in making an earlier diagnosis, with the result that 12 out of 23 cases became severe with frequent apnea, cyanosis, lethargy, sclerema and severe lactose intolerance; 4 of them were even associated with pneumoperitoneum and another 4 showed the presence of portal vein gas. The presence of portal vein gas and pneumoperitoneum is suggested to be the ominous sign since all cases with portal vein gas and pneumoperitoneum died.

There was no difference in the clinical symptoms and signs and the average day of onset of necrotizing enterocolitis between low birth weight and fullterm infants. The average age of onset in low birth weight infants was 11.5 days, while in fullterms it was 10.4 days. On the contrary Polin et al. (1976) reported that the average age of onset in fullterm infants was longer than in premature ones. The difference between our findings and those of Polin's et al. (1976) might be caused by the differences in risk factors and the strict clinical diagnosis criteria used. The main risk factors in our cases were gastroenteritis and severe pulmonal infection, while in theirs, 44% of the cases in premature infants were associated with severe asphyxia. None of our premature infants with necrotizing enterocolitis was associated with the history of asphyxia, except in 2 fullterm infants.

Surgical intervention is absolutely indicated in cases with perforation (Touloukian et al., 1967; Stevenson et al., 1971), or in cases with a sudden clinical deterioration, or the obvious progressive course of the disease (Stevenson et al., 1971). Early surgical intervention is important indeed in reducing the mortality rate of severe cases (Wayne et al., 1975; Touloukian, 1976). A great majority of our cases absolutely required surgical intervention; however, during the period from 1976 to 1980, due to the lack of neonatal surgical facilities, particularly the facility of neonatal anaesthesia, the management of cases was merely conservative, involving the witholding of oral feedings, the institution of parenteral feedings, and antibiotics. The outcome of this regimen was rather poor, in that 12 out of 23 cases, or 52% died. Surgical intervention was conducted in only one case, after the facilities for neonatal surgery were available in our hospital.

An accurate early diagnosis is important indeed in reducing the incidences of severe cases, which will in turn reduce mortality rates. The presence of lactose intolerance and a bowel distention with air or an asymmetry of gas pattern on X-ray examination could indicate the development of necrotizing enterocolitis, particularly in cases with protracted diarrhea or severe pulmonal infections. All of the 23 cases in this report were associated with lactose intolerance either in mild or in severe form, and 14 of them were associated with protracted diarrhea. Book et al. (1976) reported that 71% of necrotizing enterocolitis cases, showed that reduced substances in the stools were strongly positive from day one to day four prior to the onset of the disease.

Parenteral feeding, which needs to be highlighted, is another aspect of clinical management, since the infusion of aminoacids can deteriorate the clinical condition of cases, particularly in premature infants

through the imbalance and elevation of certain blood aminoacids. In spite of the fact that our infusates contain nonfat solutions with a high concentration of aminoacids, which are high risk in developing metabolic complications, during the 6 year experience of using periferal parenteral feeding we did not see any serious complication, except phlebitis which was immediately reversed when the infusion was stopped. It should always be kept in mind proline and cysteine might give a harmful effect which can deteriorate the clinical conditions of infants.

Other complications which might occur during parenteral feedings are septicemia, osmotic diuresis which can be very serious in the neonate, particularly in premature infants, (Filler and Coran, 1976) and pulmonary edema which is the result of using a large volume of solution. In spite of the prevailing fear of overhydration during parenteral feedings, Coran and Weintraub (1977) reported that non of their cases receiving 250 – 275 cc/kg. bw/day of infusate developed overhydration.

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