NEONATAL NECROTIZING ENTEROCOLITIS AN EPIDEMIOLOGICAL STUDY

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ABSTRACT

Necrotizing enterocolitis (NEC) was diagnosed in 77 infants among 2200 admissions to the NICU during the period January 1986 to September 1990. The incidence was 0.5% of all live births and 3.5% of NICU admissions. Majority (57.1%) had Stage I of the disease while 23.4% had Stage II and 19.5% had Stage III of the disease. The average birth weight of the babies was 1650 ± 577 g and gestational age 33.3 ± 2.6 weeks. Majority(53.2%) were very low birth weight (VLBW) babies. Incidence was significantly more (5.7% vs 0.25%, $p < 0.001$) in VLBW infants and in preterm infants of gestational age less than 32 weeks (5.2% vs 0.09%, $p < 0.001$).

Multiple risk factors were present in these babies while 8 babies did not have any risk factor. Risk of developing NEC was significantly more if infants had any of these risk factor ($p < 0.001$). Incidence of severe birth asphyxia was more in Stage I cases (35.7% vs 10.3%, $p < 0.05$).

The age at presentation was 4.9 ± 4.8 days and majority (96%) presented during the first 14 days. The overall survival was 61% and was 70.5, 77.8 and 13.3% in Stages I, II and III, respectively. VLBW and preterm infants had a higher mortality.

Key words: *Necrotizing enterocolitis, Neonate, Epidemiology, Very low birth weight infants.*

Necrotizing enterocolitis (NEC) is the most common surgical emergency in neonatal intensive care units (NICU)(1). Even though it has significant mortality and morbidity, the initiating events in its pathogenesis are yet to be established. It is generally believed to arise from an interaction of 3 elements: (*i*) intestinal injury, usually ischemic, (*ii*) bacterial colonization of the gut, and (*iii*) presence of a substrate, usually formula feedings in the lumen of the gut, in a susceptible infant(2). The disease is suspected whenever gastrointestinal manifestations predominate in an infant with signs and symptoms suggestive of neonatal sepsis and is confirmed by the radiologic sign of pneumatosis intestinalis or portal venous gas or both(3). Alongwith the proliferation of NICUs, the incidence of NEC has been increasing and is not uncommon in our country too(4-6). We present here our experience of the disease during a 5-year period. Our objectives were: (*i*) to find the incidence of the condition; (*ii*) obtain information about possible predisposing factors; and (*iii*) study factors associated with mortality.

Subjects and Methods

Among the 15,346 live births during the period January 1986 to September 1990, 2200 babies were admitted to our Neonatal Intensive Care Unit (NICU). Seventy seven babies were diagnosed to have NEC. The

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diagnosis was based on the clinical features of prefeed gastric residue and/or vomiting, abdominal distension and presence of blood in the stool, together with evidence from a plain *X*-ray of the abdomen of gaseous distension of bowel loops, gas in the bowel wall or portal venous system or intestinal perforation. Infants were grouped into 3 stages according to modified Bell's criteria(7).

The records of these infants were reviewed for the purported risk factors for NEC. Birth asphyxia was defined as an Apgar score of ≤ 6 at 1 minute. A score of ≤ 3 at 1 minute was considered as severe birth asphyxia(8). Polycythemia was considered whenever venous PCV exceeded 65%. A temperature variation of more than 1°C within a period of 6 hours was considered as unstable temperature and a rectal temperature ≤ 35° was considered hypo-thermia.

The clinical presentation, course and management as well as outcome were studied and the results were tabulated as the mean or the number and percentage of infants with the specific factors. Statistical analysis was done by χ^2 test and Student's 't' test.

Results

Patient Population: Among the 77 infants with NEC, 45 (58.4%) were male and 32 (41.6%) were female infants. All infants except 2 were born in our Institute and developed the disease after being admitted to our NICU. The overall incidence was 0.5% of all live births and 3.5% of NICU admissions. The incidence during 1986, 1987, 1988, 1989 and 1990 was 1.6, 2.7, 3.8, 4.6 and 4.7%, respectively.

The average birth weight of these infants was 1650 ± 577 g (range: 880 g to 4250 g) and their gestational age was 33.3 ± 2.6 weeks (range 28 weeks to 40 weeks). The average Apgar score at 1 and 5 min was 5.5 ± 2.6 and 8.2 ± 1.9, respectively. Forty four (57.1%) infants had suspected NEC

TABLE I—*Characteristics of Infants with NEC.*

Parameter	Modified Bell's Stage			
	Stage I	Stage II	Stage III	Overall
No. of cases	4	18	15	77
Birth weight (g)	1667±649	1505±277	1777±579	1650±577
Gestational age (wk)	33.5±2.4	33.0±2.6	33.1±2.9	33.3±2.6
Apgar score 1 min	4.9±2.8	6.4±2.3	6.3±1.9	5.5±2.6
5 min	7.9±2.1	8.4±1.6	8.9±1.4	8.2±1.9
Age at onset (days)	3.8±3.2	5.2±3.5	7.5±7.7	4.9±4.8
Outcome				
Survival	31(70.5)	14(77.8)	2(13.3)	47(61.0)
Death	13(29.5)	4(22.2)	13(86.7)	30(39.0)

Figures in parentheses are percentages.

(Stage I) while 33 (42.9%) had definite NEC (Stages II and III) (*Table I*). The condition was more prevalent in very low birth weight (VLBW) infants (5.7% *vs* 0.25%, $\chi^2 = 422.35$, $p < 0.001$). Premature infants of gestational age less than 32 weeks were the most vulnerable group to develop NEC (5.2% *vs* 0.09%, $\chi^2 = 346.20$, $p < 0.001$) (*Table II*).

Prevalence of the purported risk factors and their association with NEC is shown in *Table III*. In addition, 14 (18.7%) had patent ductus arteriosus, 11 (14.7%) had antecedent diarrhea and 56 (74.7%) were on enteral feedings, before developing NEC. Eight babies (6 in Stage I, one each in Stages II and III) did not have any risk factor other than prematurity. Tested individually, the incidence of NEC was significantly more ($p < 0.001$) in infants with each of these risk factors. The Apgar scores in various stages did not differ significantly. However, the incidence of severe birth asphyxia (Apgar ≤ 3 at 1 minute) was significantly more in Stage I cases (35.7% *vs* 10.3%, $\chi^2 = 5.26$ $p < 0.05$) (*Table IV*).

The average age at presentation was 4.9 ± 4.8 days (range: less than 24 hours to 29th day of life). Majority (80.8%) presented during the first 7 days, second and the third days being the most common days of presentation (40/75, 53.3%). Twelve cases (16.0%) presented between days 8 and 14, only 3(4.0%) beyond that period (*Table V*).

Outcome: The overall recovery rate was 61%(47/77). It was 70.5% (31/44) for Stage I and 48.5% (16/33) for Stages II and III. The mean age at the time of death was 11.4 ± 7.6 days. The mean interval between the onset and death was 4.7 ± 5.8 days (range 1 to 22 days). *Table VI* shows the survival in relation to birth weight and gestational age.

NEC and its complications were the cause of death in 4.13% of all neonatal deaths. In infants weighing less than 1500 g and of gestational age less than 32 weeks, NEC accounted for 5.4% of all deaths during the neonatal period.

Discussion

NEC is usually a disease of ill premature infants of NICU. The overall incidence varies between 1 and 5% of all NICU admissions(9). In the present study it was 0.5% of all live births and 3.5% of NICU admissions. Since 1970s the incidence of NEC has been

TABLE II—*Incidence of NEC*

Parameter	Live births	Cases of NEC	Significance	
			χ^2	p
(*a*) According to birth weight (g)				
≤ 1500	715	41 (5.7)		
>1500	14631	36 (0.25)	422.35	<0.01
(*b*) According to gestatinal age (wk)				
≤ 32	734	38 (5.2)		
33-36	2450	28 (1.1)		
≥ 37	12162	11 (0.09)	346.20	<0.001

Figures in parentheses are percentages.

TABLE III–*Prevalence of Risk Factors in Infants and their Association with NEC*

Risk factor	No. of infantswith risk factor	No. of cases of NEC	Significance	
			χ^2	p
Respiratory distress	734	27	157.86	<0.001
Hypothermia	47	4	62.62	<0.001
Hypoglycemia	146	15	227.13	<0.001
Hyperglycemia	57	8	110.75	<0.001
Exchange transfusion	146	19	461.02	<0.001
Polycythemia	140	24	790.45	<0.001
Birth asphyxia*	2035	35	72.69	<0.001
Severe	1073	18	32.19	<0.001
Septicemia**	254	21	313.14	<0.001

* Apgar score ≤6 at 1 minute; severe, ≤3 at 1.
** Done in 61 cases only.

TABLE IV–*Birth Asphyxia and NEC.*

Parameter	Modified Bell's stage		Overall
	Stage I	Stages II & III	
(*a*) Apgar score			
1 min	4.9±2.8	6.3±2.1	5.5±2.6
5 min	7.9±2.1	8.6±1.6	8.2±1.9
(*b*) Incidence of birth asphyxia*			
Mild	9 (21.4)	8 (27.6)	17 (23.9)
Severe	15 (35.7)**	3 (10.3)	18 (25.4)
(*c*) Age at presentation (days)			
Mean	3.8±3.2	6.3±6.0	4.9±4.8
No asphyxia	3.9±3.2	5.5±3.5	4.7±3.5
With asphyxia	3.9±3.3	8.9±9.0	5.4±6.1
With severe asphyxia	3.7±3.6	11.0±8.8	5.1±5.7

Figures in parentheses are percentages.
* Definition of birth asphyxia–Mild: one minute Apgar 4 to 6; Severe: one minute Apgar 3 less (8).
** $\chi^2 = 5.26$, $p < 0.05$. All other differences are not significant.

TABLE V—*Age at Presentation and Mean Gestational Age of Infants with NEC*

Parameter	Stage of NEC		Overall	Mean gestational age (wk)
	I	II & III		
Mean age at onset	3.8±3.2	6.3±6.0	4.9±4.8	-
Age at presentation (days)				
≤ 24 hours	4 (9.3)	-	4 (5.3)	35±2.7
2nd & 3rd	26 (60.7)	14 (43.8)	40 (53.3)	33.8±2.7
4th - 7th	8 (18.6)	8 (25.0)	16 (21.3)	33.2±2.5
8th - 14th	4 (9.3)	8 (25.0)	12 (16.0)	32.0±1.5
15th - 21st	1 (2.1)	-	1 (1.3)	32.0
22nd - 28th	-	1 (3.1)	1 (1.3)	32.0
after 28th	-	1 (3.1)	1 (1.3)	32.0

Figures in parentheses are percentages.

TABLE VI—*Survival in Relation to Birth Weight and Gestational Age*

Variable	No. of babies	Survival	Death
(*a*) Birth Weight (g)			
≤ 1500	41	21 (51.2)	20 (48.8)
1501-2499	27	19 (70.4)	8 (29.6)
≥2500	9	7 (77.8)	2 (22.2)
(*b*) Gestational Age (wk)			
≤ 32	38	20 (52.6)	18 (47.4)
33-36	28	18 (64.3)	10 (35.7)
≥37	11	9 (81.8)	2 (18.2)
Total	77	47 (61.0)	30 (39.0)

Figures in parentheses are percentages.

increasing all over the world, and it was true in our study also. This trend is attributed to the improved survival of premature infants in NICUs who otherwise would not have survived the early neonatal period(6).

There are atleast two distinct epidemiological classifications of NEC: a low background or endemic incidence of 0-2 cases per month over which are superimposed clusters of large number of cases(7). Such

epidemics have been reported from our country also(5). However, no such epidemic was seen in the present series.

Majority (85.7%) of the infants in the present series were preterm. A preterm infant of gestational age of less than 32 weeks had 58 times more chance of developing NEC than a full term infant. This increased risk may be because of the immaturity of the gastrointestinal tract(10) or due to various stress factors these premature infants are exposed to in the NICUs(6).

Full term infants account for 10% of cases of NEC(11). In the present study 11 (14.3%) infants were full term. As described by Thilo *et al.*(12), majority of these (91%) were ill with birth asphyxia(two), respiratory distress (two) and sepsis (two). Two of these infants had polycythemia. In addition, 5 had one or more exchange transfusions prior to the development of NEC. The onset of illness in these infants was earlier than in preterm infants (2.36 ± 0.88 days *vs* 5.3 ± 5.0 days, $p > 0.05$) and had better prognosis (81.8% *vs* 57.6%).

Except for nine, the birth weight of the babies in the present series was below 2500 g. Majority (53.2%) were of very low birth weight. Seventy five to 90% of infants with NEC weigh less than 2500 g at birth and VLBW infants are particularly vulnerable with the incidence in them approaching 12%(9). The incidence in VLBW infants in our series was 5.7%.

Purported risk factors were present in 89.3% of infants. Most of these factors produce ischemia of the gut either directly or through the 'diving reflex'(13). Although association of NEC with each of these factors was statistically correlated, the study design precludes us from implicating them in the etiology of NEC. However, certain of our findings may be helpful in better understanding the cause and treatment of the disease.

Thirty five (46.7%) infants had birth asphyxia, 18 (24%) of them having an Apgar Score of less than 3 at one minute. Infants with perinatal asphyxia develop NEC earlier and unless enterally fed, do not develop pneumatosis intestinalis even in later stages(14). In our series also majority of the infants with birth asphyxia did not progress beyond Stage I of NEC. However, birth asphyxia did not affect the age at onset of NEC as well as its course and prognosis.

NEC following exchange transfusion is a well known entity with an incidence of 1.5 to 2%(6). Colon is the most common site of involvement and prognosis is generally good. In our series, excluding the six babies in whom indication for exchange transfusion was septicemia, the rest were larger (birth weight: 2011 ± 650 g *vs* 1597 ± 547 g) and more mature (gestational age 35 ± 3 weeks vs 33 ± 3 weeks). The better survival rate of them (76.9%; 10/13) compares well with the other reports(15).

Polycythemia is another risk factor which has been consistently demonstrated to be associated with NEC in controlled studies(16). It was present in 24 (32.0%) of our infants. Hyperviscocity associated with polycythemia resulting in ischemia, and the partial exchange transfusions through the umbilical vessels for its treatment may predispose these infants to NEC(7).

Diarrhea is said to be a common antecedent feature especially in our country(17). Apart from the local infection of the gastrointestinal tract, thrombosis of the small vessels of the intestine due to Schwartzman reaction is thought to cause NEC in infants with diarrhea(18). The incidence of diarrhea in the present study was 14.7%, much lower than the incidence of 67% quoted by others(4).

Bacteria are the second and probably the key factor in the pathogenesis of NEC. Micro-organisms were isolated in 21 (34.4%) of our cases. They were a reflection of the nursery isolates of that period and not necessarily the etiologic agents as no micro-organism was consistently seen in all cases. Blood cultures are positive in approximately one third of patients with NEC(3) and Klebsiella, as in our series, is the most common micro-organism isolated(2).

Other data have indicated oral feeding as an etiologic factor, more than 95% of affected patients having been fed by mouth before the onset of disease(9). Fifty six (74.7%) of the infants were on enteral feeds in the present study. While all the 15 babies with Stage III were on enteral feeds, only 25 (56.8%) babies with Stage I were fed by mouth prior to the development of the disease ($\chi^2 = 5.08, p < 0.05$) while many of these infants with Stage I NEC probably would not have progressed beyond that stage, we are tempted to hypothesise that atleast in some of these infants (*e.g.*, those with birth asphyxia) withholding of enteral feedings might have prevented them from developing a severe form of the disease. Hence, a cautious introduction of feeding in a stressed VLBW infant may be a useful approach in the prevention of the disease(19).

The age at oneset of the condition in the series was 4.9 4.8 days with 96% occurring during the first 14 days of life. The disease usually develops during the first 2 weeks of life. The more immature the infant is at birth, the later is the onset of NEC(20). In four (5.3%) of our cases, the onset was on first day of life. These infants were larger (1813 659 g) and more mature (35.0 2.7 wks) than other infants in whom the disease occurred beyond first day of life. All these infants had Stage I of the disease only.

The overall mortality in the present study was 39%. The survival rate of 70.5%, 77.8% and 13.3% in Stages I, II and III, respectively is lower than expected(1). Very low birth weight and prematurity were associated with higher mortality.

In conclusion, NEC is a disease that predominantly affects VLBW infants and accounts for considerable mortality in them. Prevention of NEC is the ultimate goal, but unfortunately, this can be accomplished only by preventing premature birth. Until such time, recognition of risk factors and their prevention or treatment along with frequent monitoring would help in the reduction of mortality and morbidity due to NEC.

REFERENCES

1. Kosloske AM, Musemeche CA. Necrotizing enterocolitis of the neonate. Clin Perinatol 1989, 16: 97-111.
2. Kosloske AM. A unifying hypothesis for pathogenesis and prevention of necrotizing enterocolitis. J Pediatr 1990, 117: S68-S74.
3. Kliegman RM. Models of the pathogenesis of necrotizing enterocolitis. J Pediatr 1990, 117: S2-S5.
4. Karan S, Pathak A. Necrotizing enterocolitis in the newborn. Indian Pediatr 1973, 10: 279-286.
5. Bhargava SK, Mittal SK, Saxena HMK, Sagreiya K. An outbreak of necrotizing enterocolitis in a special care newborn nursery. Indian Pediatr 1973, 10: 551-525.
6. Yadhav K, Narang A, Rao KLN, *et al.* Neonatal necrotizing enterocolitis. Indian Pediatr 1973, 20: 87-90.
7. Walsh MC, Kilegman RM. Necrotizing enterocolitis: Treatment based on staging criteria. Pediatr Clin North Am 1986, 33: 179-201.
8. Definitions for Neonatal Morbidity. *In:* Neonatal Nomenclature and Data Collection, Eds Singh M, Paul VK, Bhakoo ON. National Neonatology Forum, 1989, p 67.

9. Kilegman RM, Fanaroff AA. Necrotizing enterocolitis. N Engl J Med 1984, 310: 1093-1103.
10. Udall JN Jr. Gastrointestinal host defense and necrotizing enterocolitis. J Pediatr 1990, 117: S33-S34.
11. Polin RA, Pollcak PF, Barlow B, *et al.* Necrotizing enterocolitis in term infants. J Pediatr 1976, 89: 460.
12. Thilo EH, Lazarte RA, Hernandez JA. Necrotizing enterocolitis in the first 24 hours of life. Pediatrics 1984, 73: 476.
13. Nowicki P. Intestinal ischemia and necrotizing enterocolitis. J Pediatr 1990, 117: S14-S19.
14. Marchildon MB, Buck BE, Abdenour G. Necrotizing enterocolitis in the unfed infant. J Pediatr Surg 1982, 17: 620.
15. Joshi VV. Clinicopathological spectum of neonatal necrotizing enterocolitis. Indian Pediatr 1978, 15: 447-450.
16. Yu VYH, Joseph R, Bajeek B, *et al.* Perinatal risk factors for necrotizing enterocolitis. Arch Dis Child 1984, 59: 430-434.
17. Karan S. Neonatal necrotizing enterocolitis. *In:* Pediatric and Neonatal Emergencies. Eds Srivastava RN, Man Mohan, Sachdev HPS, Puri RK. Delhi, Indian Pediatrics, 1990, pp 430-434.
18. Stein H, Beck J, Solomon A, *et al.* Gastroenteritis with necrotizing enterocolitis in premature babies. Br Med J 1972, 2: 616-619.
19. Brown EG, Sweet AY. Neonatal necrotizing enterocolitis. Pediatr Clin North Am 1982, 29: 1149-1170.
20. McAlmon KR. Necrotizing enterocolitis: *In:* Manual of Neonatal Care, 3rd edn. Boston,Little, Brown and Company, 1991, pp 511-517.

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