

An epidemiological study of neonatal necrotizing enterocolitis

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ABSTRACT

Objective: To study epidemiology including various risk factors incorporated in neonatal necrotizing enterocolitis in Kashmir.

Methods: A retrospective hospital based study on 3235 neonates admitted in Neonatal Intensive Care Unit of Sheri-Kashmir Institute, were evaluated. Forty two were diagnosed as cases of Neonatal Necrotizing Enterocolitis on the basis of various clinical and radiological parameters and grouped in 3 stages as per modified Bell's classification. The case records of these 42 babies and 303 of the control group were reviewed for the purported risk factors and recorded on pretested proforma and finally statistically analyzed.

Results: Over a period of 10 years, we documented necrotizing enterocolitis in 42 neonates, with an incidence of 1% of all Neonatal Intensive Care Unit admissions and 1% of all live births. Eighty one percent were less than 2000 gms and 76% less than 36 weeks of gestation. Twenty four percent had stage I disease, 33% had stage II, and 43% babies had stage III disease. Multiple risk factors were present in these babies, with significant differences among Necrotizing Enterocolitis and the control group of patients, particularly hypothermia ($P<0.001$), respiratory distress ($P<0.05$), polycythemia ($P<0.001$) acidosis ($P<0.01$), sepsis ($P<0.001$), enteral feeding and asphyxia ($P<0.001$). Of the 59 babies (<2000 gms) with

hypothermia ($<35^{\circ}\text{C}$), 39% developed Necrotizing Enterocolitis, compared to 4% babies (11/278), who did not have hypothermia, statistically a significant finding. Mean birth weight and gestational age were lower than in control group ($P<0.05$). The age of presentation was 5.2 ± 4.0 days and majority (81%) presented during first week of life, most severe cases presenting earlier than the mild cases. Severity of Necrotizing Enterocolitis as per modified Bell's classification and mortality was inversely related to birth weight and gestational age. One hundred percent mortality was noted in the babies, with birth weight less than 1000 gms and gestational age less than 28 weeks. The overall mortality was 45%, for stage I, 20%; for stage II, 36% and 67% for stage III. Necrotizing Enterocolitis cases accounted for maximum mortality in Neonatal Intensive Care Unit than in control group ($P<0.001$).

Conclusion: Recognition of factors such as prematurity, low birth weight, hypothermia, asphyxia and their timely prevention would help in reducing morbidity and mortality due to Necrotizing Enterocolitis.

Keywords: Necrotizing enterocolitis, neonate, hypothermia, very low birth weight, premature.

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Neonatal necrotizing enterocolitis (NEC) is one of the acquired gastrointestinal emergencies in very low birth weight (VLBW) and premature babies.^{1,2} With the increased survival of VLBW and premature babies, the incidence of NEC has been increasing and at present ranges between 1-5% of all admissions in NICU.²⁻⁹ Despite a definite drop, mortality over the

last decade still ranges between 20-50%.⁶⁻¹¹ It is therefore, important to identify various pathogenic factors in these high risk babies for prompt recognition, aggressive monitoring and early management of disease¹² and of course, prevention of these risk factors. We analyzed this condition over a period of 10 years, with the objectives of assessing

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the incidence, mortality and to obtain information about possible risk factors, keeping in view the climatic condition of Kashmir region, where most of the babies are hypothermic at the time of admission in NICU.¹³

Methods. During the study period of 10 years (January 1985-December 1995) 3240 neonates were admitted to the NICU of Sheri-Kashmir Institute of Medical Science Srinagar. Most of these babies were referred from district hospitals, peripheral centers and Children's Hospital Srinagar for intensive and level-III care. Out of these cases, 42 neonates were diagnosed as having necrotizing enterocolitis (NEC), based on their clinical features (abdominal distention, gastric residue or vomiting, guaiac positive stools, ascitis) and radiological findings (gaseous distention, pneumatosis intestinalis and pneumoperitonium). All these babies were finally grouped into three stages as per the modified Bell's classification.¹² However further subclassification such as a and b were not found necessary to avoid confusion and lengthening of tables. The case records of high risk low birth weight and premature babies were reviewed for the purported risk factors for NEC⁵ cases. Cases with incomplete data were excluded from the total number of 3230 admissions, which were however, without NEC. Birth asphyxia was defined as an Apgar score of < 6 at 1 minute and severe birth asphyxia with a score of <3 at one minute. Polycythemia was considered at PCV >60%. A rectal temperature <35°C was considered as hypothermia. All these relevant details, which included mode of delivery, history of birth asphyxia and resuscitation, polycythemia, type and time of first feeding, temperature instability, birth weight and gestational age of all these babies were recorded on a pretested proforma and the results thus obtained were tabulated and statistically analyzed using Chi-square test for discrete variable and Student's t-test for continuous variables. Significant variables associated with severe NEC were further evaluated in logistic regression analysis with establishment of OR and corresponding 95% confidence interval (CI). Significance was set at 5% probability.

Results. Of the total 3235 admissions in our NICU, 42 neonates were diagnosed for necrotizing enterocolitis, with an incidence of 1%. Male versus female ratio was 1.5:1. 40.5% of babies were born in our institute, comprising 0.2% of all livebirths. Seventeen (40.5%) were referred from the district and other peripheral hospitals and had to cover a distance of about 50-200 kms. Eight (19%) of babies were referred from Children's Hospital Srinagar, covering a distance of 14 kms. Most of the babies from peripheral hospitals were transferred in ambulances (76%) and private taxis (24%) wrapped

in blankets and hot water bottles. None of the babies were transferred in portable incubator. Incidence in inborn was 1% and transferred babies was 2%. The more severe (Group II & III) amongst transferred babies was 72%. These babies developed the disease after being admitted to our NICU. Seventy four percent presented during winter months (from October to ending February) with an incidence of 2% of total admissions during these 5 months compared to just 1% during the other 7 months (summer). Almost 81% babies were below 2000 gms and 76% below 36 weeks of gestation. Mean birth weight was 1579.30 ± 597.1 gms (range 795-3125) and mean gestational age was 32.7 ± 4.4 (25-40) weeks. From Table 1, it is clear that 24% cases had stage I disease, while 33% had stage II and 43% had stage III of the disease. The most severe disease was noted in extreme low birth weight and premature babies with 100% mortality in those with birth weight below 1000 gms and gestation below 28 weeks. From Table 2, it is clear that the condition is more prevalent in LBW and premature babies, associated with hypothermia. Of the 59 LBW babies (<2000 gms) with hypothermia, 23 (39%) developed NEC, compared to just 4% (11/278) in nonhypothermic group ($X^2=65.75$, $p<0.001$). However, hypothermia was a significant factor associated in both mature and > 2000 gms babies. A significant (78%) number of cases of stage III disease had associated hypothermia (<35°C). Prevalence of purported risk factors and their association with NEC is shown in Table 3 and Table 4. Tested individually each of the risk factors were statistically significant in the NEC group, when compared with 303 cases of the non-NEC group. Hypoglycemia and exchange transfusion were not significant factors noted in our study. Formula fed babies were more prone to develop NEC ($p<0.001$). Babies, who were not fed at all had significantly less chances of developing NEC ($p<0.001$). Birth asphyxia was more prevalent in NEC group ($p<0.001$) and incidence of severe asphyxia was significantly more in disease group than in non-NEC group ($X^2=6.34$ $p<0.05$). Average age of presentation was 5.2 ± 4.0 days and it was as early as 24 hours to 21 days. Majority of these presented during the first week of life (81%), the peak being 48-72 hours. Early onset was seen in more severe cases (stage II and III), whereas stage I disease was mostly seen with late onset. Early onset was also seen in low birth weight and premature babies since most severe disease was noted in extreme low birth weight and premature babies. Overall mortality was 45%, 20% for stage I, 36% for stage II and 67% for stage III. NEC contributed to significant ($p<0.001$) number of deaths to overall mortality in NICU, when compared to non-NEC group (Table 4). Mortality was noted in 60% surgical cases (9/15) as against 37% (10/27) medically treated cases. We did not notice any

Table 1 - Showing severity of NEC in relation to gestational age and birth weight.

Gestational age (weeks)	Total cases (%)	Stage I	Stage II	Stage III	Mortality (weeks)
≤28	8 (19)	-	-	8 (100)	8 (100)
29-32	12 (29)	2 (17)	5 (42)	5 (42)	6 (50)
33-36	12 (29)	4 (33)	4 (33)	4 (33)	4 (33)
≥37	10 (24)	4 (40)	5 (50)	1 (10)	1 (10)
Birth weight (gms)					
<1000	8 (19)	-	-	8 (100)	8 (100)
1001-1500	13 (31)	3 (23)	5 (38.5)	5 (38.5)	6 (46)
1501-2000	13 (31)	3 (23)	6 (46)	4 (31)	4 (31)
≥2001	8 (19)	4 (50)	3 (37.5)	1 (12.5)	1 (12.5)
Total	42	10 (24)	14 (33)	18 (43)	19 (45)
Mortality	-	2 (20)	5 (36)	12 (67)	-

epidemic form of disease in our NICU during this study.

Discussion. It is difficult to be certain about the true incidence of NNEC, since the frequency of its occurrence changes from time to time. Increased incidence in recent years is believed to be due to better neonatal care and survival of premature and VLBW babies.^{7,14} The incidence of 1% in the present study is comparable with the reported figures

of 1-5% of all NICU admissions²⁻⁹ our figure is much lower, however, agrees with other Indian authors (5/9). Three and a half percent incidence as reported by Narang et al⁵ is probably due to inclusion of high number of stage I (suspected NEC) cases in that study (57%) compared to just 24% cases of stage I in our study. Clusters of large number of cases have been reported from many earlier studies including from India.^{15,16} However, no such epidemic has been noticed in present series and others.^{5,9} The incidence

Table 2 - Showing NEC in premature and low birth weight babies with hypothermia.

Gestational age (weeks)	Temperature	Total	NEC cases (%)	X ²	P-value (weeks)
≤36	≤35°C	62	22 (35.5)	62.75	<0.001
≤ 36	>35°C	287	10 (3.5)		
≥ 36	≤35°C	568	7 (1)	16.06	<0.01
≥36	>35°C	2318	3 (0)		
Birth weight (gms)					
≤ 2000	≤35°C	59	23 (39)	65.85	<0.001
≤ 2000	>35°C	278	11 (4)		
≥ 2000	<35°C	571	6 (1)	15.50	<0.01
≥ 2000	>35°C	2327	2 (0)		
Total		3235	42		

Table 3 - showing prevalence of risk factors in 34 neonates with NEC and 303 without NEC of birth weight ≤ 2000 gms.

Risk factors	NEC cases (n=34)	Non NEC cases (n=303)	Univariate analysis or (95% CI)	Univariate analysis or (95% CI)
Hypothermia	23 (68)	36 (12)	15.5 (5.1-8.3)	13.2 (4.8-17.1)
Respiratory distress	12 (35)	61 (20)	2.16 (1.9-5.1)	2.2 (1.9-4.7)
Hypoglycemia	9 (26.5)	42 (14)	2.23 (1.2-4.0)	2.1 (0.2-3.1)
Polycythemia	9 (26.5)	18 (6)	5.70 (1.2-40)	3.2 (0.3-6.0)*
Exchange & cannulation	2 (6)	13 (4)	1.40 (0.1-1.3)	5.3 (0.2-3.2)
Acidosis	9 (26.5)	27 (9)	3.70 (1.2-4.0)	8.2 (1.1-9.1)*
Sepsis	17 (50)	46 (15)	5.6 (3.4-6.6)	5.2 (0.6-9.3)
Type of feed (initial)				
Breast milk	7 (21)	47 (15.5)	1.40 (0.7-3.3)	2.2 (0.4-8.0)*
Formulae	13 (38)	46 (15)	3.50 (2.2-5.4)	1.9 (1.0-9.2)
Both	9 (26.5)	59 (19.5)	1.50 (1.2-4.0)	1.0 (0.8-6.0)*
No feeding	5 (15)	151 (50)	0.20 (0.2-2.6)	2.2 (1.7-2.8)
Mean age of first feed (days)	2.49 \pm 1.3	2.20 \pm 1.9	NS	-
Frequency of feed				
1 hour	20 (69)	99 (65)	2.9 (5.3-8.5)	2.1 (2.8-10.3)*
2 hour	9 (31)	53 (35)	-	-
Mean quality per feed/kg (ml)	5.24 \pm 3.0	4.90 \pm 4.12	NS	-
Birth asphyxia	21 (62)	10 (32)	3.4(4.5-7.7)	1.2 (0.8-8.2)
*Not significant factors for NEC, NS - Not significant, CI - Confidence Interval				

and severity of NEC as noticed by us was inversely related to birth weight and gestational age of these babies. The incidence among low birth weight (<2000 gms) was 10%, which is nearer to reported figures of 13-17%.^{1,2} Narang et al⁵ reported an incidence of 6% in those, who had birth weight of < 1500 gms. Twenty one (50%) babies in present series had birth weight of < 1500 gms, which is in close conformity of 53% as reported by Narang et al.⁵ Full term babies account for 10% of cases of NEC.¹⁷ Preterm babies have more chance of developing NEC, most likely due to immature gastrointestinal tract and other associated factors in premature babies.^{7,18} Only 10 (24%) of cases in our study were above 36 weeks of gestation and therefore accounts for a strong reason for choosing 36 weeks as a cut-off point. Two previous studies from India have reported incidence of 82-85% in premature babies.⁵⁻⁹ In full term babies other associated risk factors might be playing a role in development and progression of NEC. Seven (1%) cases of our study (>36 weeks) had hypothermia as a risk factor, which was statistically significant ($p<0.001$) than

nonhypothermic group (0.1%). Although association of various risk factors with NEC was a significant finding, however it precludes us from implicating them in the etiology of NEC. Their risk factors may simply be a coincidental finding in these babies, who later on develop NEC. However, better understanding of significant findings might help in reaching to some conclusion and thereby proper prevention and management of these cases. Multivariate regression analysis showed hypothermia, polycythemia, sepsis, birth asphyxia and enteral feeding to be independent risk factors for development of NEC, however, the 95% confidence intervals were so wide, suggesting caution in interpreting these data and it is also possible multiple etiological factors operated in several babies.

Hypothermia (<35°C) was the significant factor found in the present series, particularly those with extreme prematurity. Sixty eight percent of cases with NEC had associated hypothermia compared to only 12% in the control group ($p<0.001$). Since transportation of very sick and LBW babies is usually delayed because of long distance over which

they have to be transported from far across areas of the Kashmir valley, particularly during winter months (outside mercury falls below 0°C), accounts for neonatal hypothermia. Almost 17% of babies are hypothermic at the time of admission to NICU of Sheri-Kashmir Institute, due to the distance of 50-200 kms that they have to travel. These babies account for the maximum mortality and other complications.¹³ Gut ischemia in response to cold stress might be a possible reason that these babies are more prone to develop NEC with inadequate facilities in most Indian units for monitoring and maintaining optimum temperature. Hypothermia may well be a significant factor as the incidence has been seen more in transferred babies than in inborn babies. In a few earlier studies^{1,9} hypothermia has been reported as a significant factor in association with NEC. However, Narang et al⁵ has noted hypothermia only in 4 cases of NEC. This low figure, although statistically significant, could be due to the higher temperature in the region of study compared to Kashmir.

Association between NEC and polycythemia has been reported in earlier studies^{1,5,9,17,19,20} hematocrit exceeding 60% even in term SGA infants²⁰ results in bowel ischemia and partial exchange through the umbilical vessels for their treatment might be a predisposing factor.¹² We noted polycythemia in 26.5% cases of NEC as against 6% in the control

group ($p<0.001$). Similar results have been noted by Narang et al,⁵ whereas higher results have been noted by Thomas et al,⁹ who noted polycythemia in about 52% cases. Exchange transfusion and umbilical cannulation are implicated as important risk factors for NEC¹² with an incidence of 1-2%.^{5,7,21} However, this was not a significant finding in our study. Since most of the cases, who were referred from peripheral hospitals were not cannulated at the time of admissions in our NICU. Acidosis and respiratory distress were other significant risk factors in this series, as have been reported in earlier studies also.^{1,5,7} NEC has rarely been observed in babies, who have never been fed^{1,5,22} and therefore, a possible association between feeding and NEC cannot be denied, particularly in progression of disease from mild to severe form.²³ Too much or too early feeding may also increase the chances of developing NEC^{24,25} Formula feeding is one of the significant ($p<0.001$) factors associated with NEC as has been observed in this series. This may be because of their hyperosmolar nature, leading to damage of the intestinal mucosal layer. Narang et al⁵ reported 75% babies of NEC who were on enteral feeds. A significant ($p<0.001$) number of cases, who were not fed at all did not develop NEC and all those 5 cases (without enteral feeding) had only mild disease (stage I) and did not progress to severe form. One can at least agree with the hypothesis put forth earlier^{5,23} that

Table 4 - Showing characteristics of 34 neonates with NEC.

Parameters	NEC cases (n=34)	Non NEC cases (n=303)		P-value
Birth weight (gms±SD)	1269±448.2	1498.3±369.3		<0.05
Gestational Age (Wks±SD)	29.8±3.2	3.1±3.3		<0.05
Apgar Score				
1 minute	4.7±1.7	5.8±1.2		<0.001
5 minute	7.4±2.2	8.9±1.9		<0.001
Mild asphyxia	7.0 (42.9)	62 (63.3)	$\chi^2=6.34$	
Severe	14 (57.1)	36 (36.7)	$\chi^2=23.65$	<0.05
Outcome				
Survival	16 (47)	251 (82.9)		
Deaths	18 (53)	52 (17.1)		<0.001

progression of disease can be prevented by withholding feedings in high risk babies such as in VLBW and asphyxiated babies. The association of NEC with the volume and schedule of feeding has been documented by many workers^{2,9}. However, we did not notice any significant difference in the diseased and control group. Ostertog et al⁴ also observed that early feeding did not increase incidence of NEC unless babies were very sick and VLBW. As noted in previous studies^{5,9} birth asphyxia is a significant ($p < 0.001$) risk factor associated with NEC. Presence of lower mean APGAR scores in association with NEC has been noticed in this study, which is in conformity with some previous studies.^{1,2,5,9} This probably gives some importance to the theory of a diving reflex producing gut ischemia and making baby prone to develop NEC.^{26,27}

Bacteria play a key role in the pathogenesis of NEC. We isolated various organisms in 17 (50%) cases as against 15% in control group ($p < 0.001$). *Klebsiella* (22%), *Esch. Coli* (17%) and *Staph aureus* (17%), were the most common organisms. These organisms may represent merely an overgrowth of normal gut flora leading probably to NEC in premature and high risk babies, since we did not notice any epidemic form of disease. However, association of NEC with micro-organism has been noticed earlier also.⁵ Mean age of presentation was 5.2 ± 4.0 days with 81% cases presenting in first week of life. Severe disease (stage III) had earliest onset (48-72 hours), whereas, most of the mild cases had late onset (beyond 3rd day). Contrary to earlier reports,⁵ early presentation was seen more in premature and LBW babies, being more prone to develop hypothermia, acidosis, asphyxia, sepsis. These findings are in contrast to earlier reports of early presentation in more mature babies.^{15,28}

The overall mortality was in close conformity with the earlier reports⁵ from India. Mortality due to NEC accounts for a significant number of deaths in NICU compared in the control group. Stage III disease had the maximum mortality than stage I cases. Similarly, VLBW and premature babies had 100% mortality as observed earlier by Narang et al.⁵ As expected, medically treated cases had less mortality than in surgically treated cases.

In conclusion, NEC is a disease predominantly affecting VLBW and premature babies and account for considerable mortality in NICU. However, mature and high birth weight babies are also prone to develop NEC, while keeping in view the risk factors these babies can face in our set up of developing countries. Considering the fact that hypothermia, birth asphyxia, polycythemia, sepsis, enteral feeding emerged as important risk factors in this series, recognition of these risk factors and their prevention, along with frequent monitoring would help in the reduction of morbidity and mortality due to NEC. Cautious approach in starting of enteral feeding may

help in reducing the incidence of NEC in premature babies and those suffering from birth asphyxia.

References

1. Yu VYH, Joseph R, Bajuk B, Orgill A, Astbury J. Perinatal risk factors for necrotizing enterocolitis. *Arch Dis Child* 1984; 59: 430-434.
2. Kliegman RM, Fanaroff AA. Neonatal necrotizing enterocolitis. A nine year experience. Epidemiology and uncommon observations. *Am J Dis Child* 1981; 135: 603-607.
3. Brown EG, Sweet AY. Neonatal necrotizing enterocolitis. *Pediatr Clin North Am* 1982; 29: 1149-1170.
4. Osterteg SG, Lagamma FE, Reisen CE, Fersentins FL. Early enteral feeding does not effect the incidence of necrotizing enterocolitis. *Pediatrics* 1986; 77: 275-280.
5. Narang A, Rao R, Bhakoo ON. Neonatal necrotizing enterocolitis: An epidemiological study. *Indian Pediatr* 1993; 30: 1207-1214.
6. Narang A, Rao R, Bhakoo ON. Neonatal necrotizing enterocolitis. A clinical study. *Indian Pediatr* 1993; 30: 1417-1422.
7. Yadav K, Narang A, Rao KLN, Chowdhary J, Katarira S. Neonatal necrotizing enterocolitis. *Indian Pediatr* 1983; 20: 87-90.
8. Buch NA, Hassan M, Wajid S. Neonatal necrotizing enterocolitis: In: 8th Asian Congress of Pediatrics. India; 1994. p. 12-13.
9. Thomas C, Krishnan L. Neonatal necrotizing enterocolitis. *Indian Pediatr* 1997; 34: 47-51.
10. Dolores C, Mastandrea J. Necrotizing enterocolitis: Factors affecting mortality in hundred and one surgical cases. *Surgery* 1984; 96: 648-655.
11. Dolan P, Azmy AF, Young DG. Necrotizing enterocolitis: Experience with fifty four neonates. *Scotland Medical Journal* 1984; 29: 166-170.
12. Walsh MC, Kliegman RM. Necrotizing enterocolitis. Treatment based on staging criteria. *Pediatr Clin North Am*. 1986; 33: 179-201.
13. Mir NA, Javied S. Transport of sick neonate: practical considerations. *Indian pediatr* 1989; 26: 755-764.
14. Bell MJ, Temberg H, Feigin RD. Neonatal necrotizing enterocolitis. Therapeutic decisions based on clinical staging. *Ann Surg* 1978; 187: 1-7.
15. Books LS, Overall JC(Jr), Herbst JJ, Britt MR, Epstein B, Jung AL. Clustering of necrotizing enterocolitis. *New Engl J Med* 1977; 297: 984-986.
16. Bhargava SK, Mittal SK, Saxena HMK, Sagreiya K. An outbreak of necrotizing enterocolitis in a special care new born nursery. *Indian Pediatr* 1973; 10: 551-555.
17. Pollin RA, Pollcak PF, Barlow B. Necrotizing enterocolitis in term infants. *J Pediatr* 1976; 89: 460-462.
18. Udall JN (Jr). Gastrointestinal host defense and necrotizing enterocolitis. *J Pediatr* 1990; 117: S33- S34.
19. Bunton GL, Durbin GM, McIntosh N, Shaw DGT, Aghizadeh A, Reynolds EOR. Necrotizing enterocolitis: Controlled study of 3 years experience in neonatal intensive care unit. *Arch Dis Child* 1977; 52: 772-777.
20. Hakanson DO, Oh W. Necrotizing enterocolitis and hyperviscosity in newborn infants. *J Pediatr* 1977; 90: 458-461.
21. Touloukian RJ, Kadar A, Spencer RP. The gastrointestinal complications of neonatal umbilical venous exchange transfusion. A clinical and experimental study. *Pediatrics* 1973; 51: 36-43.
22. Yu VYH, James B, Henry P, MacMahon RA. Total parenteral nutrition in very low birth weight infants: A controlled trial. *Arch Dis Child* 1979; 54: 653-661.

23. Marchildon MB, Buck BE, Abdenour G. Necrotizing enterocolitis in the unfed infants. *J Pediatr Surg* 1982; 17: 620-624.
24. Goldman HL. Feeding and necrotizing enterocolitis. *Am J Dis Child* 1980; 134: 553-555.
25. Eyal F, Sagi E, Arad I, Avital A. Necrotizing enterocolitis in the very low birth weight infants: Expressed breast feeding compared with parenteral feeding. *Arch Dis Child* 1982; 57: 274-276.
26. Kosloske AM. A unifying hypothesis for pathogenesis and prevention of necrotizing enterocolitis. *J Pediatr* 1990; 117: S68-S74.
27. Nowicki P. Intestinal ischemia and necrotizing enterocolitis. *J Pediatr* 1990; 117: S14-S19.
28. McAlmon KR. Necrotizing enterocolitis: Manual of Neonatal Care. 3rd ed. Boston: Brown and Co; 1991. p. 511-517.