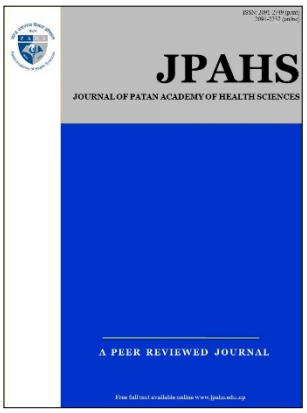

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Necrotizing enterocolitis: clinical characteristics and outcome of a cohort of 106 cases at a children's hospital in North China

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Abstract

Introduction: Necrotizing enterocolitis (NEC) in neonates, especially in the preterm, is a life-threatening condition. This study aims to analyze the clinical profile of NEC to get an insight for better understanding and management.

Method: This was a retrospective analysis of neonatal NEC during the six-year period from 2014 to 2019. The prevalence and time for the development of NEC, clinical profile (term and preterm, low birth weight, gender, breast and formula feeding, abdominal distension, vomiting, hematochezia, apnea, fever, altered mental status, blood transfusion, breast or formula-fed, intestinal perforation, Bell's stage and time for the development of NEC) and maternal factors (gestational hypertension, diabetes, premature rupture of membranes PROM, intrauterine fetal distress, placenta previa) were analyzed. Features in preterm and term neonates were compared. Ethical approval was obtained.

Result: There were 106 NEC (0.87% of 12,184 neonatal admissions), 62 (58.49%) male, 90 (84.91%) preterm, and 85 (80.19%) LBW. Overall, 88 (83.02%) were Bell's stage II, and severe stage III was seen in eight (19.04%) out of 42 babies with formula feeding as compared to one (1.56%) out of 64 in breastfeeding. The median time for the development of NEC was 6 days of life. The yearly prevalence of NEC per thousand neonates admitted during 6-years increased from 2.90 in 2014 to 12.06 in 2019. Overall mortality was 14 (13.20%).

Conclusion: The yearly incidence of NEC increased with a higher incidence in preterm, in low birth weight and formula-fed neonates.

Keywords: formula feeding, necrotizing enterocolitis (NEC), neonatal intensive care unit, premature rupture of membrane

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Introduction

Necrotizing enterocolitis (NEC), a life-threatening condition with an incidence of 2-5% and fatality of 16-50%, more common in preterm and formula-fed neonate. It is characterized by inflammation, necrosis and perforation of colon, terminal ileum and cecum.[1-5] Possible pathogenesis and associated factors of NEC include impaired intestinal mucosal barrier, microbial dysbiosis, presence of food particles and bacteria in the colon generating inflammatory mediators leading to damage in the bowel wall and further systemic inflammatory response, preterm, low birth weight (LBW), premature rupture of membrane (PROM), hypoxia, formula feeding and blood transfusion etc.[3,6-9] Some of the preventive measures include breast feeding, bioactive nutrients, probiotics, and trophic factors in human milk.[4,5]

The clinical features vary widely from mild to severe presentations of nausea, vomiting, abdominal distension, intolerance of feedings, diarrhea and blood in stool, apnea and shock, intestinal obstruction, causing significant psychological and economic burden to families, health care system and society.[10,11] This study aims to analyze clinical features and outcomes of NEC to further explore the strategies for early detection, prevention and treatment to improve neonatal survival.

Method

This was a retrospective analysis of cases of NEC during 6-year period from January 2014 to December 2019 at Yulin children's hospital, in northernmost prefecture in Shanbei region bordering inner Mongolia, in Shanxi Province, China. Data of all the neonates aged ≤28 days after birth, gestational age of 28-42 weeks, and diagnosed clinically with NEC as per Bell's stage and managed in neonatal intensive care unit (NICU) were included. Hospital record files with incomplete data, neonates >28 days of life were excluded. Variables analyzed were clinical signs and symptoms (prevalence and time for development of NEC, term and preterm, low birth weight (LBW), gender, breast and formula feeding, abdomen distension, vomiting, hematochezia, apnea, fever, altered mental status, blood transfusion, breast or formula-fed, intestinal perforation); perinatal factors (gestational hypertension, diabetes, premature rupture of membranes PROM, intrauterine fetal distress, placenta previa), clinical stage of NEC as per modified Bell's stage, Table 1,[6,7]

Table 1. Modified Bell's stage for NEC, adapted and modified from[6,7]

Stage	Systemic findings	Abdominal findings	Radiological findings	Treatment
I. Suspected				
A	Temperature instability, apnea, bradycardia	gastric stasis, abd distension, OB	Normal or mild ileus	NPO, antibiotics x 3 days
B	IA	+ gross blood in stool	IA	IA
II. Definite				
A-Mildly ill	IA	I+ absent BS, abd tenderness	Ileus, PI	NPO, antibiotics 7-10 days
B-Moderately ill	IA+ metabolic acidosis, thrombocytopenia	IIA+ abd cellulitis, mass	IIA+ PV gas, mild/ no ascites	NPO, antibiotics 14 days
III Advanced				
A- Severely ill	IIB+ hypotension, resp acidosis, DIC, neutropenia	IIB+, peritonitis, marked distension of abdomen	IIB, plus definite ascites	IIB+ inotropic, ventilator, paracentesis
B- Severely ill	IIIA	IIIA	IIIA+ bowel perf	IIIA+ surgery

.abd- abdomen, OB- occult blood, NPO- nil per os, BS- bowel sound, PI- pneumatosis intestinalis, PV- portal vein, resp- respiratory, DIC- disseminated intravascular coagulopathy, bowel perf- perforation pneumoperitoneum

and short-term outcome of in-hospital mortality were analyzed, and comparison was made between preterm and term neonates. Ethical approval was obtained from the hospital ethical committee

Statistical analysis was performed by SPSS 21.0. Data were expressed as percentage (%) and mean±SD. For theoretical frequency of $1 \leqq T < 5$ the χ^2 continuity correction formula was used; and for frequency T<1, Fisher's exact test was used. p<0.05 was considered statistically significant.

Result

Data on 106 neonates who developed NEC were analyzed (after excluding 10, six age >28 days and four incomplete data). The incidence of NEC during study period was 0.87% among 12,174 neonatal admissions. The preterm were 3,001 (24.65%) of total neonatal admissions. The median time for development of NEC was six days of life. Among 106 NEC, preterm were 90 (84.91%), LBW 42 (39.62%), and male 62 (58.49%). Overall mortality due to NEC was 14 (13.21% of 106) and 12 (85.71%) in preterm, Table 2.

The yearly trend percentage increase in NEC was observed, from 0.29% (6 out of 2,066) in 2014 to 1.22% (26 out of 2,155) in 2019. Preterm babies of total neonatal admissions increased from 18.26% (319 of 2,066) in 2014 to 40.85% (625 of 2,155) in 2019. Among preterm, NEC increased from 1.57% (5 out of 319) in 2014 and 3% (23 out of 625) in 2019. The overall mortality of NEC decreased from 16.7% (1 out of 6) to 7.7% (2 of 26) in 2019, Figure 1.

Clinical demographics including gender, mode of delivery and blood transfusion had no statistically significant association with NEC. In clinical signs and symptoms, apnea was significantly common in preterm than term, ie. 30 (33.33%) vs. one (6.25%), p<0.05. The Bell's stages I-III were seen in both term and preterm, p>0.05. In perinatal factors, the PROM was significantly common in preterm than term, ie. 40 (44.44% of 90) vs. one (6.25% of 16), p<0.05, Table 2.

Severe presentation of stage III was seen in formula fed vs. breast fed neonates, eight (19.04%) vs. one (1.56%), p<0.05, Table 3.

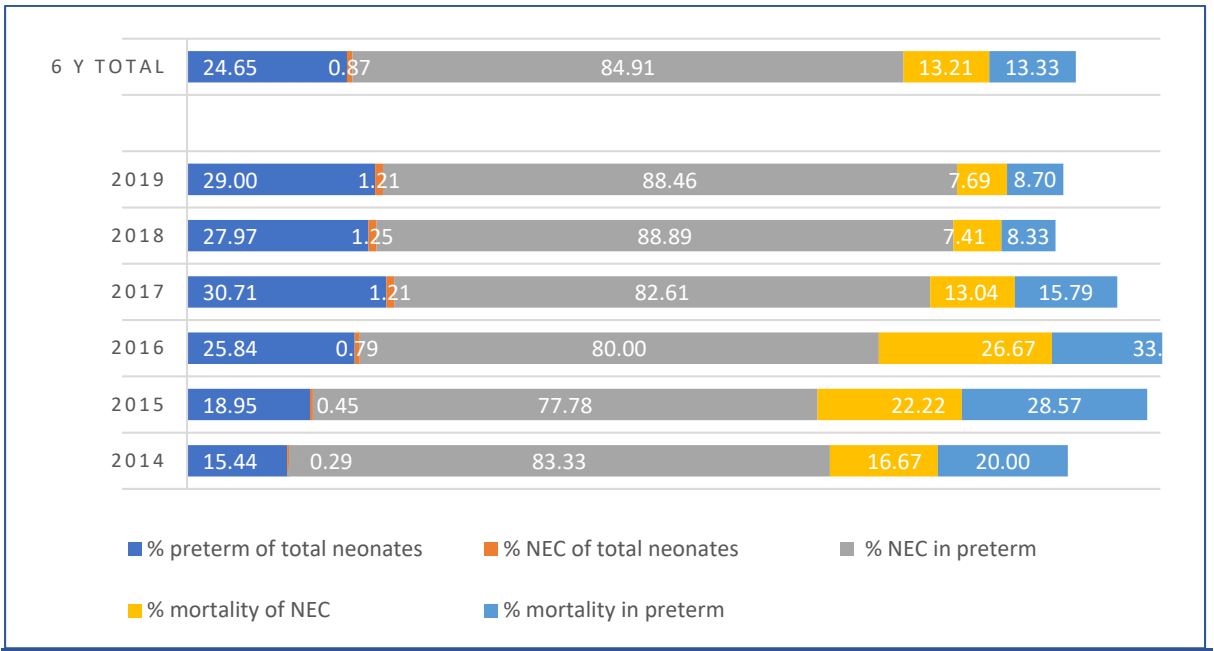

Figure 1. The yearly trend in percentage of preterm neonates, NEC in total and in preterm, mortality of NEC in total and in preterm

Table 2. Neonatal admission and necrotizing enterocolitis (NEC, N=106)

Year	2014	2015	2016	2017	2018	2019	Total
Total neonates	2066	1989	1900	1908	2156	2155	12174
Preterm	319	377	491	586	603	625	3001
Total NEC	6	9	15	23	27	26	106
Preterm	5	7	12	19	24	23	90
Total NEC mortality	1	2	4	3	2	2	14
Preterm	1	2	3	2	2	2	12

Table 3. Clinical profile of NEC in preterm and term neonates, N=106

Presentation	Preterm (N=90)	Term (N=16)	χ^2	p
Demographics				
Gender (male)	60 (66.67%)	9 (56.25%)	0.29	0.78
Mode of delivery (normal)	52 (57.78%)	9 (56.25%)	0.30	0.79
Blood & blood products transfusion	32 (35.56%)	4 (25.00%)	1.89	0.35
Clinical sign and symptoms				
Abdomen distension	74 (82.22%)	15 (93.75%)	2.01	0.19
Vomiting	34 (37.78%)	9 (56.25%)	2.74	0.10
Hematochezia	48 (53.33%)	11 (68.75%)	2.18	0.17
Gastric stasis	52 (57.78%)	6 (37.50%)	3.12	0.29
Apnea	30 (33.33%)	1 (6.25%)	5.27	0.02
Fever	58 (64.44%)	10 (62.50%)	0.92	0.43
Altered mental status	82 (91.11%)	11 (68.75%)	0.04	1.02
Intestinal perforation	18 (20.00%)	1 (6.25%)	0.72	0.51
Bell's stage				
First stage	42 (46.67%)	5（31.25%)	9.12	0.98
Second stage	30 (33.33%)	9（56.25%)	5.24	0.69
Third stage	18 (20.00%)	3（18.75%)	1.06	0.26
Perinatal factors				
Gestational hypertension	22 (24.44%)	2 (12.50%)	0.62	0.59
Gestational diabetes	16 (17.78%)	1 (6.25%)	0.00	1.00
Premature rupture of membrane PROM ≥18h	40 (44.44%)	1 (6.25%)	5.12	0.01
Intrauterine fetal distress	8 (8.89%)	2 (12.50%)	1.26	0.42
Placenta previa	7 (7.78%)	1 (6.25%)	0.008	0.09
Meconium liquor	21 (23.33%)	4 (25.00%)	0.01	0.17

Table 4. The NEC stages among breast fed and formula fed neonates, N=106

Project	Breast feeding N=64 (60.38%)	Formula feeding N=42 (39.62%)	χ^2	p
First stage	18 (28.13%）	16 (38.10%）	4.26	0.04
Second stage	45 (70.31%	18 (42.86%	2.89	1.09
Third stage	1 (1.56%）	8 (19.04%）	8.27	0.03

Discussion

Our findings show an increasing trend of NEC annually, significantly more common in preterm neonates, and those with PROM. We also found that NEC was significantly associated with apnea in preterm, and severe Bell's stage III in formula-fed babies compared to breast-fed. The overall incidence of NEC was 0.87% (106 NEC out of 12,174 neonatal admissions), but it was 4-times higher in preterm at 3.0% (90 NEC in 3,001 preterm). Similarly, preterm accounted for majority of NEC, with 90 (84.91% of 106) cases, and more

in LBW 85 (80.19% of 106). Bell's stage III was seen in 8 (19.04%) out of 42 babies who were formula-fed but only in one (1.56%) out of 64 who were breast-fed.

Above findings are in line with reported studies showing higher incidence in premature neonates. Possible causes of this higher incidence in preterm neonates are immature bowel, intestinal mucosal barrier dysfunction and poor mucosal blood supply. This is further aggravated by hypoxia, hypothermia, sluggish peristalsis and accumulated food in intestine leading to bacterial overgrowth, and inflammatory mediators induced inflammation of bowel wall. The inflammation further progresses to necrosis, perforation and sepsis.[12-15] The overall reported incidence of NEC ranges from 0.1%-0.3%, and is as high as 5%-10% in very LBW with a higher mortality.[1-3,16-18] In preterm neonates, the epithelial cells of the intestinal wall are loosely connected and have high permeability. This, combined with inadequate secretion of gastric acid and digestive enzymes, weak peristalsis and food retention in intestine are ideal environment for bacterial overgrowth, fermentation with gaseous dilation, further compromise in blood flow, increase in permeability for harmful molecules and bacteria, leading to inflammation and damage of intestinal wall and development of NEC.[10,18,19] We found that preterm was an independent risk factor for NEC and poor outcome.

The clinical features of NEC is manifested in various combinations of signs and symptoms. We found that abdominal distension, vomiting, hematochezia, gastric stasis, apnea, altered mental status and intestinal perforation were common in both term and preterm, but apnea was significantly higher in preterm, occurring in 30 (33.33%) in preterm vs. one (6.25%) in term, ($p<0.05$). Also, the percentage of gastric stasis, altered mental status and intestinal perforation were higher in preterm compared to term, but the differences were statistically not significant. In our series, among 14 (13.20%) deaths due to NEC, majority of deaths i.e. 12 (85.71%) occurred in preterm. Similar findings of rapid progress of disease with marked abdominal distension, intestinal perforation and poor prognosis has been reported in preterm.[14] In bowel perforation, the abdominal USG is a useful adjunct to radiography and more sensitive for bowel ischemia.[20] In our review, due to retrospective data, we could only analyze radiological findings of perforation, and could not separately analyze the findings of abdomen radiography and sonography.

Among perinatal factors of 'gestational hypertension, diabetes, PROM, fetal distress, placenta previa, meconium liquor', only the PROM was significantly associated with NEC, occurring in 40 (44.44% out of 90 preterm) compared to one (6.25% out of 16 terms). Other studies have similar observation, viz. longer the time of PROM, greater the risk of intrauterine infection, especially for premature infants.[21] In very low birth weight (VLBW; <1500 g) infants, prolonged initial empirical antibiotics for ≥ 5 days and cumulative days of antibiotic exposure, especially gentamicin and meropenem, is associated with an increased risk of developing NEC.[22]

In our findings, the advanced Bell's stage III NEC was significantly higher in formula-fed (19.04%) than in breast fed (1.56%). This highlights the importance of breastfeeding. Recent review reaffirms the importance of 'human breast milk' which contains bioactive components (immunoglobulins, growth factors, cytokines, and immune cells) and nutrients necessary for infant's growth, immunity, intestinal maturation, gut microbial colonization and homeostasis. The formula-fed preterm, and extremely premature infants have up to 10-times greater risk of NEC.[23] Meta-analysis of RCTs has shown that oropharyngeal administration of colostrum in preterm infants has positive effect on the incidence of NEC, late-onset sepsis, and mortality.[24] However, the benefit of early feeding in ultra-LBW requires further studies.

Our data suggest neonatal factors (gender, mode of delivery, blood transfusion) had no

significant association with NEC in either preterm or term neonates. However, some studies suggest transfusion may be an aggravating factor.[25-27] But this may be because of the presence of anemia and not the transfusion aggravating the NEC.[28] Pre-terms frequently require transfusion to improve oxygen delivery to the vital organs during the crucial phase of growth and development, but there are still controversies regarding optimal management of anemia in pre-term neonates.[29] The causal relationship of whether blood transfusion increases severity of NEC or the severity of NEC requires blood transfusion, is still unclear and needs further research.

Our findings of short term outcome in terms of in-hospital mortality of 14 (13.20%) out of 106 NEC is comparable and somewhat better than published reports.[24,29,30] The year by year increase in the incidence of NEC from 2.90 in 2014 to 12.99/1000 in 2018 may be the reflection of improvement in overall maternal and child health care, with better survival of preterm and LBW babies, and increase in NEC. The babies who survive the assault of NEC have the possibility of poor physiological and neurodevelopmental growth, due to intestinal failure, strictures, short bowel syndrome, frequent hospitalization. This requires more research to better understand long term prognosis and outcome.[30]

Some of the imitations of our study are those inherent to the retrospective data analysis from a single center. We could not analyze complete antenatal and perinatal data, the protocol of antibiotics, transfusion and feeding for in-depth subgroup analysis. It is possible that there were differences in management by different neonatologists and surgeons during the six-year period. Also, we could not analyze the actual reason and timing of blood transfusion, whether it was for anaemia or for critical illness before or after the diagnosis of NEC; nor was the role of colostrum and addition of probiotics studied in this review. To address these limitations, a prospective, possibly multicenter pooled data, is needed to better understand and manage NEC in neonates with serious short- and long-term consequences.

Conclusion

Our study of 6-year data shows less than 1% overall incidence of NEC among neonatal admissions, majority in preterm, low-birth weight, premature rupture of membrane and formula-fed neonates. The clinical presentation varies from mild manifestation to intestinal perforation, from Bell's stage I to III. Overall mortality was 14%, majority in preterm.

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Conflict of Interest

None.

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Author Contribution

All authors participated in concept, design and preparation of manuscript. All authors have read and approved final manuscript.

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