Published in final edited form as:
Adv Neonatal Care. 2008 October ; 8(5): 285–290. doi:10.1097/01.ANC.0000338019.56405.29.

RISK FACTORS FOR NEC IN PRETERM INFANTS: HOW RACE, GENDER AND HEALTH STATUS CONTRIBUTE

Brigit M. Carter, RN, MSN, CCRN [Pre-Doctoral Fellow]
UNC Chapel Hill School of Nursing

Diane Holditch-Davis, PhD, RN, FAAN [Professor]
Duke University School of Nursing

Abstract

Purpose—To examine 5 infant characteristics and health factors that might be risk factors for necrotizing enterocolitis (NEC) in preterm infants.

Subjects—134 preterm infants at high risk for NEC due to either having a birthweight of <1500 grams or requiring mechanical ventilation at birth.

Design—Descriptive secondary analysis using data from a larger longitudinal study.

Methods—Weekly review of infant's medical record until discharge. Demographic questionnaire completed by mothers at time of enrollment. Data analysis done with logistic regression, Fischer's exact tests and correlations.

Outcome Measures—Total number of days infant required mechanical ventilation, birthweight in grams, number of infections prior to NEC diagnosis, maternal race (Black, White or Asian), and infant gender were used to predict the development of NEC.

Results—Maximum likelihood estimates indicated that mechanical ventilation had a positive relationship with developing NEC, such that as the number of days of mechanical ventilation increased so did the risk of developing NEC. There was also a very strong positive relationship between the number of nosocomial infections and NEC indicating that as the number of infections increased the likelihood of developing NEC increased. Although the relationship between race and NEC was not significant in the logistic regression, a Fisher's exact test showed that Black preterm infants had increased incidence of NEC as compared to other races. This relationship was not due to correlations between race and mechanical ventilation or infections. No relationship between gender on NEC was noted. Birthweight was not significantly associated with NEC in the logistic regression but was correlated with NEC, probably because of its correlation with mechanical ventilation and number of infections.

Conclusions—In this sample, number of infections and length of mechanical ventilation were the primary predictors of NEC in preterm infants. In addition, the frequency that Black infants are diagnosed with NEC is significantly higher than that of other races. Knowledge of risk factors for NEC can allow healthcare providers to evaluate and adjust care practices for preterm infants who present with higher risk for NEC based on empirical data.

Address all correspondence to: Brigit M. Carter 1403 Ainsworth Boulevard Hillsborough, North Carolina 27278 Home: 919-732-6370 Work: 919-681-5551 Cell: 919-801-9620 Fax: 919-681-7770 Primary email: E-mail: bmcarter@email.unc.edu Secondary email: E-mail: carte025@mc.duke.edu.

Original Research Work completed at: University of North Carolina at Chapel Hill School of Nursing

Keywords

premature infant; necrotizing enterocolitis; risk factors; race; gender

Necrotizing enterocolitis (NEC) is a gastrointestinal emergency that predominately affects preterm infants.[1] To date there is no one theory as to the etiology of NEC; however, most researchers agree that the pathogenesis is multifactorial and is often been associated with enteral feedings, ischemia and infectious causes.[2] The process leading to NEC is thought to be preceded by an ischemic or toxic event that causes damage to the immature gastrointestinal mucosa and loss of mucosal integrity.[3] The initiation of enteral feedings allows for bacterial proliferation at which time the damaged mucosa is invaded by gas producing bacteria. This process may lead to necrosis which can cause either perforation of the bowel or sepsis.[4]

Surgical NEC is the leading cause of morbidity for preterm infants, followed by chronic lung disease, nosocomial infections and retinopathy of prematurity.[5] Necrotizing enterocolitis affects approximately 10% (per 100,000) of preterm infants who are born >1500 grams. [6] The mortality rate for preterm infants classified as extremely low birthweight (<1000 grams) who are diagnosed with NEC is 35-50% .[6] Infants classified as very low birthweight (<1500 grams) who are diagnosed with NEC have a mortality rate between 10 to 30%, and this mortality rate has not significantly decreased over the past 30 years.[1] Because several studies have identified interventions that resulted in only minor reductions in the incidence of NEC (such as breast milk feeding, enteral antibiotic prophylaxis, use of probiotics, and slow progression of enteral feeds), additional approaches to NEC prevention are needed.[1,7-10] Identifying risk factors for NEC might lead to the development of interventions to decrease the rate of NEC in preterm infants. Therefore, the purpose of this study was to examine 5 infant characteristics and health factors that might be risk factors for NEC in preterm infants.

Race may be one risk factor for NEC. Epidemiologic studies showed that mortality rates due to NEC were higher for Blacks than Whites, and have found that the racial differences remained statistically significant even after controlling for birthweight, sex, gestational age, Apgar scores and geographical region.[11] The overall incidence for NEC for non-Hispanic Blacks was significantly greater than that for non-Hispanic Whites and continued to be significant after correction for birthweight.[12]

Gender might also be a risk factor for NEC. Most studies either did not investigate gender or found a statistically non-significant relationship between male gender and NEC. Although the results were not statistically significant one study found that the incidence of NEC was lower in females than in males. [12] Thus, whether gender is a risk factor for NEC is unclear. However, when males and female preterm infants of similar gestational age were compared, mortality rates were greater for males (51%) than for females (35%).[13] This possible gender effect should be investigated further to determine the contribution of NEC to these mortality rates.

The number of nosocomial infections experienced by preterm infants and the development of NEC may also be related. Extremely low birthweight infants with NEC were found to have more culture-proven sepsis than infants without NEC.[14] It has also been found that infants with proven NEC have associated bacteremia and were more likely to have late-onset sepsis. [15] It has been suggested that preterm infants with predisposing clinical conditions, when exposed to an infective agent, could experience intestinal ischemia leading to NEC. [16] Preterm infants with the history of gut injury such as that with NEC developed a higher number of infections when compared to infants without bowel injury.[17]

Several investigators have suggested that very low birthweight and mechanical ventilation are also risk factors for NEC. Infants with birthweights of <1500 grams and NEC had a greater

need for mechanical ventilation prior to the development of NEC than infants of the same birthweight without NEC. [18] Preterm infants, due to increased metabolic demands, demonstrated signs of respiratory decompensation before signs of intestinal inflammation due to NEC, resulting in infants with NEC requiring increased respiratory support including intubation and mechanical ventilation.[19] In addition, preterm infants who required surgery for NEC required mechanical ventilation more often than those that could be managed medically for NEC suggesting these infants presented sicker earlier in life.[20]

Correlations may exist between race, gender, birthweight, number of infections experienced by preterm infants and mechanical intubation. These variables should be studied together to determine which ones are more significant for the development of NEC. Therefore, the purpose of this study was to examine these five infant characteristics and health factors that might be risk factors for NEC in preterm infants.

METHODS

This study was a secondary analysis of data from Assessment of Biological and Social Risk in Preterm Infants.[21] In the larger longitudinal study 4 biological risk indices and 2 social risk indices were evaluated for predicting developmental and health outcomes of high-risk preterm infants. This study will examine total number of days infant required mechanical ventilation, birthweight in grams, number of infections prior to NEC diagnosis, maternal race (Black, White or Asian), and infant gender to evaluate how they contribute to the development of NEC in the preterm infant.

Participants

The sample was drawn from the larger study of 134 preterm infants (75 from North Carolina, 54 from Ohio, and 5 from Pennsylvania) who were at high risk for NEC due to either having a birthweight of <1500 grams or requiring mechanical ventilation at birth. All were <35 weeks gestation at birth. In the larger longitudinal study, the preterm infants were excluded if they had congenital neurological problems or were symptomatic from substance exposure. They were also excluded if their social situations precluded follow-up for 2 years or if their family situation was such that asking for consent would be impossible or intrusive.[21]

For the purposes of this analysis, NEC was defined as either having confirmed documented NEC on radiograph by the hospital radiologist or a surgical intervention for NEC. Medical NEC was defined as a preterm infant who had pneumotosis intestinalis on x-ray and was treated with antibiotics for more than 2 days. Surgical NEC was defined as any surgical intervention (peritoneal drainage; exploratory laparotomy with diverting ostomy, intestinal resection or primary anastomosis or stoma creation). Chart reviews indicated that of the 26 infants listed as having NEC in the data set, 24 met the criteria for NEC in this analysis. The other 2 only received antibiotics for 2 days to rule out NEC. Fifty four percent of the infants with NEC had 1 or more infections prior to the diagnosis of NEC (defined as treatment with antibiotics > 2 days), and 63% had 1 or more infections after the NEC diagnosis, not including the NEC diagnosis. Table 1 provides demographic information for the 134 infants in the study.

Procedures

In the larger longitudinal study, the participants were recruited from the neonatal intensive care and intermediate care units of the participating hospitals. Mothers of infants that met the study criteria were contacted by phone and the study was explained. If the mothers were willing to have their infants participate, consent was obtained during a hospital visit. Enrollment questionnaires and a 1-page demographic questionnaire were completed at time of enrollment.

The infant's medical records were reviewed weekly for medical course information until hospital discharge.

Variables

Five neonatal risk factors that are known to be associated with necrotizing enterocolitis were the variables of interest. These variables were birthweight, mechanical ventilation, number of infections before the NEC diagnosis, race and gender. Variable data was obtained from the medical record and the demographic questionnaire was completed by the mother.

Data Analysis—The primary method of analysis utilized to determine the effect of the categorical (race and gender) and continuous variables (birthweight in grams, number of days on mechanical ventilation and number of infections prior to NEC diagnosis) on NEC was logistic regression; *alpha* ≤ 0.05 was deemed statistically significant. In addition, secondary analyses were conducted using Fischer's exact tests and correlations.

RESULTS

Table 2 presents the results of the logistical regression. Maximum likelihood estimates indicated that mechanical ventilation had a positive relationship with developing NEC, such that as the number of days of mechanical ventilation increased so did the risk of developing NEC. There was also a very strong positive relationship between the number of infections and NEC. The log odds ratio indicated that each additional infection increased the odds of developing NEC by 2.6 times. Fifty percent of the 24 infants with NEC had one or more infection prior to developing NEC while only 31% of the remaining 110 infants without NEC had infections during their hospitalization.

Because infection was so significant in predicting NEC, this variable may have overwhelmed the other variables when it was included in the model. Therefore, additional analyses were conducted to explore the effects of the variables that were not statistically significant in the logistical regression: Black, female and birthweight. To address the relationships between Black race, gender and NEC, the frequency of NEC and black or male infants was compared using the Fisher's exact test. Table 3 indicates increased frequency of NEC in Black preterm infants. No relationship was identified between gender and NEC.

Table 4 presents the results of Pearson correlations among the variables. NEC was correlated with infection, mechanical ventilation, birthweight and race. The correlation between race and NEC did not appear to be due to infections or mechanical ventilation as those factors were not correlated with race. The correlation between NEC and birthweight, such that decreased birthweight was associated with greater risk of NEC, could be explained by the correlations between birthweight and mechanical ventilation and infection. There was a significant negative correlation between infection and gender, indicating that the number of infections were lower for female preterm infants than for males.

DISCUSSION

The rate of NEC in the current sample was similar to NEC rates documented in other studies. Of 134 preterm infants there were 24 cases of NEC. The frequency of NEC often differs between NICUs, averages between 9-19% and is in keeping with this sample's frequency of approximately 18%.[22] This similarity provides support for the findings of this study. There was also a significant positive relationship between infection and NEC and mechanical ventilation and NEC. When examined alone, Black infants exhibited an increased rate of NEC that could not be explained by a correlation of race with birthweight, infections or days of mechanical ventilation.

This study showed that as the number of infections increased the risk for NEC increased. Ascertaining if there is a cause-effect between infection and NEC is difficult. Vulnerability to infection could be caused by the over-utilization of antibiotics leading to the overgrowth of pathogens and in antibiotic resistant bacteria subsequently increasing number of infections.[23] On the other hand, infections prior to NEC could indicate that being subjected to increased number of infections potentially decreases infant's immunological competence, thereby increasing vulnerability to successive pathogens. Most investigators acknowledge that infants are at increased risk for NEC due to presence of pathogen or possible imbalances in the intestinal microbial flora.[3] However, no literature identified by authors of the current study has examined the mechanism by which the number of infections experienced by preterm infants affects their risk for developing NEC.

The risk of NEC also increased as the need for mechanical ventilation increased. This is in keeping with previous research that showed mechanical ventilation increased preterm infants' risk for NEC.[20] Extremely low birthweight infants' initial survival often depends on intubation at birth potentially increasing the risk of infections including NEC. The act of intubation and the indwelling endotracheal tube may destroy the integrity of the infant's esophageal mucosal barriers, increasing the risk for infection.[27] Invasions of the esophagus could possibly lead to the introduction of pathogens to the bowel initiating the NEC process. On the other hand, having NEC increases the need for mechanical ventilation. The intestinal inflammation caused by NEC increases metabolic demands causing respiratory decompensation, which can lead to intubation.[23]

Low birthweight has been recognized as a contributor to increased mortality and morbidity of the preterm infant.[7] The frequency and severity of NEC increase with decreasing birthweight.[26] Infants with lower birthweight (<1000 grams) had more episodes of nosocomial sepsis than those of higher birthweight (>1000 grams) and require more mechanical ventilation.[20] However, there was not a significant relationship between birthweight and NEC on the logistic regression. There was an inverse correlation between birthweight, NEC, mechanical ventilation and infection indicating that lower birthweight infants had higher rates of NEC, days of mechanical ventilation and number of infections prior to NEC. This suggests that infants who are of lower birthweight present with multiple risk factors that are associated with NEC.

Gender has not been recognized as a risk factor of NEC and was not significant in this study. This factor should continue to be evaluated however because these results did show that of the 24 infants that experienced NEC, 15 males and 9 females experienced NEC, suggesting that females experience less NEC. Some other studies have also found that there are more males than females who develop NEC although this difference was non-significant.[10] Also, the mortality rate for NEC is higher for males than females.[7]

Race may be one of the newer predictors of NEC in preterm infants. Although there was not a significant relationship between black race and NEC when studied along with other variables, the frequency with which Black infants were diagnosed with NEC was significantly higher than that of other races. The connection between race and NEC is not well studied; thus, there is a need to investigate not only the infant risk factors but the maternal factors of Black women that might contribute to preterm delivery. For example, Group Beta Streptococcus (GBS) colonization was found to occur more often in Black women due to lower access to prenatal care.[21] Factors such as GBS positive colonization could contribute to decreased oxygenation to the bowel or proliferation of bacteria which can contribute to NEC in the preterm infant. Black women who experience such infections during pregnancy have an increased risk of preterm birth.[22] Hence, the GBS positive state of the Black mother potentially not only contributes to the preterm delivery but also to the development of NEC in the preterm infant.

Investigation of the role of race in the development of NEC must extend to maternal factors in order to understand their level of contribution.

LIMITATIONS

As a secondary analysis, the original data was not collected with the intention of investigating the effects of multiple variables on NEC in preterm infants. Another limitation of this study is the geographic region from which the sample was drawn. The 3 hospitals were all from the southeastern part of the United States. A sample drawn from various parts of the United States might provide a greater ability to generalize results to other parts of the country.

Knowledge of risk factors for NEC can allow healthcare providers to evaluate and adjust care practices such as feeding regimes for the preterm infants who present with higher risk for NEC based on research data. Better outcomes can result from more successful management of preterm infants if major risk factors are known and taken into account in clinical and dietary management.

The results of this study suggest the need for further research to determine additional risk factors for NEC. Further investigation should focus on the number of infections a preterm infant experiences prior to NEC as well as the effects of race. The correlation between infection and mechanical ventilation was expected as it has been demonstrated in the literature.[13] Increased awareness of the length of intubation and number of infections a preterm infant can experience before increasing the risk of NEC may provide additional evidence to support early extubation and crucial infection control practices in the health care setting. Infants with lower birthweights (<1500 grams) tend to present with multiple risk factors that are associated with NEC. [6,11] Because the frequency and severity of NEC increase with decreasing birthweight, further investigation is needed to determine how associated co-morbidities contribute to the risk of NEC in this population.[26] Although race and gender are not variables that can be altered, further research to determine their level of contribution to NEC in the preterm infant can provide health care providers with necessary information to alter plan of cares to account for potential increased sensitivity of the bowel in Black male preterm infants and in infants with longer mechanical ventilation or more infections.

Acknowledgements

This paper was supported in part by University of North Carolina at Chapel Hill T32 NR07091 to University of North Carolina at Chapel Hill, National Institute of Nursing Research to the first author and NR01894 from National Institute of Nursing Research, NIH to second author.

The authors thank Todd Schwartz, DrPH for statistical consultation and Mark Scher for collaboration in the original project.

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Table 1

Demographic Characteristics of the 134 Preterm Infants

	Mean (SD)	%
Gestational Age	**28.8 (2.6)**	
Birthweight in Grams	**1218 (432)**	
Gender (Male)		**53.7%**
Race: African American		**46.3%**
White (Non-Hispanic)		**52.2%**
Asian		**1.5%**
Mechanical Ventilation (Days)	**11.5 (18.7)**	
% with Infections		**48.5%**
Number of Infections	**1.3 (1.7)**	
Maternal Age in Years	**27.6 (6.5)**	
Maternal Education in Years	**13.8 (2.4)**	
Percent Married		**56.7%**

	Mean (SD)		%	
	NEC N = 24	**No NEC N = 110**	**NEC N = 24**	**No NEC N = 110**
Gestational Age	28.0 (1.9)	29.0 (2.7)		
Birthweight in Grams	989.0 (304)	1273.7 (437)		
Gender (Male)			11.2	42.5
Race: African American White (Non-Hispanic) Asian			11.9 6.0 0	34.3 46.3 0.75
Mechanical Ventilation (Days)	21.4 (23.9)	8.9 (16.4)		
% with Infections			91.7	39.1
Number of Infections	2.9 (2.2)	0.77 (1.2)		
Maternal Age in Years Maternal Education in Years Percent Married	25.8 (5.7) 13.8 (2.4)	28.1 (6.6) 13.8 (2.0)	9.7	46.3

Abbreviation: SD, Standard Deviation

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Table 2

Analysis of Maximum Likelihood Estimates Using Chi-Square on NEC for the 134 infants

Parameter	Estimate	p-value for Chi Square	Odds Ratio
Ventilation	0.0517	0.0470*	1.053
Birthweight	0.00131	0.1635	1.001
Infection (# of)	-0.9712	<.0001†	0.379
Black	-0.5603	0.3172	0.571
Female	-0.1118	0.8465	0.894

*p<.05

†p<.001

Table 3

Frequency procedure between NEC and all variables for the 134 infants

Total Sample (134 Infants)	w/NEC N (%)	w/o NEC N (%)	Fisher's Exact Test Two-sided p-value
Blacks	16 (12%)	47 (35%)	0.0436*
Others	8 (6%)	62 (47%)	
Females	9 (7%)	52 (39%)	0.4979
Males	15 (10%)	57 (43%)	

* $p<.05$

Table 4

Pearson Correlations between all variables for the 134 infants

Parameter	Correlation with NEC		Correlation with Race		Correlation with Gender		Correlation with Vent		Correlation with Infection	
	r	p value	r	p value	r	p value	r	p value	r	p value
Infection	0.5	<.0001†	0.15	0.07	-0.21	0.012*	0.73	<.0001†	--	--
MechVentilation	0.25	0.002*	0.08	0.35	-.11	0.20	--	--	0.73	<.0001†
Birthweight	-.022	0.02*	-0.13	0.12	0.03	0.69	-0.49	<.0001†	-0.43	<.0001†
Black	0.18	0.03*	--	--	0.09	0.28	0.08	0.35	0.15	0.07
Female	-0.07	0.36	0.09	0.28	--	--	-.11	0.20	-0.21	0.012*

Abbreviation: r, Pearson Correlation

*p<.05

†p<.001