

# Association of H2-Blocker Therapy and Higher Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants

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## ABSTRACT

**OBJECTIVE.** We sought to determine if an association exists between the use of histamine-2 receptor (H2) blockers and the incidence of necrotizing enterocolitis (NEC) in infants of 401 to 1500 g in birth weight.

**STUDY DESIGN.** Data from the National Institute of Child Health and Human Development Neonatal Research Network very low birth weight (401–1500 g) registry from September 1998 to December 2001 were analyzed. The relation between the diagnosis of NEC (Bell stage II or greater) and antecedent H2-blocker treatment was determined by using case-control methodology. Conditional logistic regression was implemented, controlling for gender, site of birth (outborn versus in-born), Apgar score of <7 at 5 minutes, and postnatal steroids.

**RESULTS.** Of 11 072 infants who survived for at least 12 hours, 787 (7.1%) developed NEC (11.5% of infants 401–750 g, 9.1% of infants 751–1000 g, 6.0% of infants 1001–1250 g, and 3.9% of infants 1251–1500 g). Antecedent H2-blocker use was associated with an increased incidence of NEC ( $P < .0001$ ).

**CONCLUSIONS.** H2-blocker therapy was associated with higher rates of NEC, which is in agreement with a previous randomized trial of acidification of infant feeds that resulted in a decreased incidence of NEC. In combination, these data support the hypothesis that gastric pH level may be a factor in the pathogenesis of NEC.

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### Key Words

prematurity, cimetidine, ranitidine, famotidine, necrotizing enterocolitis, H2 blockers

### Abbreviations

NEC—necrotizing enterocolitis  
H2—histamine-2 receptor  
VLBW—very low birth weight  
NICHD—National Institute of Child Health and Human Development  
OR—odds ratio  
CI—confidence interval

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**N**ECROTIZING ENTEROCOLITIS (NEC) is a neonatal disorder that affects 1 to 3 in 1000 live births and 1% to 5% of infants who are admitted to NICUs.<sup>1</sup> Prematurity is the primary risk factor for development of NEC.<sup>2</sup> Additional risk factors seem to include bowel ischemia, enteral feedings, and the presence of pathogenic organisms in the gastrointestinal tract. Alteration in gastrointestinal colonization by common NICU practices such as use of broad-spectrum antibiotics or enteral feeding practices<sup>3</sup> also may have an effect.

In animal models of NEC, various factors have been identified that may play a role in the development of the disease.<sup>4</sup> In a porcine model of a lethal form of NEC, the etiologic agent is thought to be excessive Gram-negative bacteria growth.<sup>5</sup> The incidence of the disease is highest in the first postnatal week of life when the animals are achlorhydric and have elevated gastric pH levels. On the basis of this observation, Carrion and Egan<sup>6</sup> conducted a relatively small ( $n = 68$ ) prospective, double-blinded trial to compare preterm infants supplemented with 0.01 to 0.02 mL of 1 N HCl/mL milk with infants receiving milk supplemented with a similar volume of water. Their data demonstrated that acidification decreased gastric bacterial colonization and significantly reduced the incidence of NEC ( $P = .02$ ).<sup>6</sup>

Histamine-2 receptor (H2) blockers are used in neonates to increase the gastric pH level in a variety of clinical situations, often without data proving benefit. They are administered to neonates with proven or presumed gastroesophageal reflux to minimize esophagitis and also may be given to neonates who are receiving steroids to minimize the associated gastritis. In some instances, H2 blockers are added to the intravenous fluids of neonates who are not receiving enteral feeds and are believed to be at risk for stress-associated gastritis. Although administration of H2 blockers may serve to protect the mucosa from excessive acid production, as limited as that may be in the premature neonate, it may also counteract a natural defense against gastric bacterial overgrowth.

Our study was undertaken to determine the incidence of NEC and the association between treatment with H2 blockers and this condition in very low birth weight (VLBW) infants.

## METHODS

### Study Population

Our population included infants of 401 to 1500 g in birth weight who were cared for in 1 of the 19 National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers from September 1998 to December 2001.

### Data Collection

Demographic and clinical data were obtained from the infant's medical chart by trained research nurses, coded

by using written uniform definitions, deidentified, and entered into the NICHD generic database. Approval for data collection and analysis was obtained from the institutional review boards of each of the participating NICU centers.

NEC was defined as "absent/suspect" when there was no NEC present or in the presence of Bell stage IA or IB. It was defined as "proven, no surgery" if it met Bell stage IIA, IIB, or IIIA criteria and as "proven, surgery" if it met Bell stage IIIB criteria. Criteria for Bell staging were those modified by Walsh and Kliegman.<sup>7</sup> The date of the first episode of NEC was recorded in the database. Spontaneous gastrointestinal perforation was recorded separately from NEC and is not included in this review.

H2-blocker treatment was documented in the database if the infant ever received (either enterally or parenterally) ranitidine (Zantac), famotidine (Pepcid), or cimetidine (Tagamet) before 120 days of age, death, or discharge. The specific agent used, the particular route of administration, and the dosage were not recorded. The reason for use of H2 blockers was not documented in the database and thus is unavailable. The dates that treatment was started and discontinued were recorded.

Treatment with steroids was documented in the database if the infant received any postnatal systemic steroids to prevent or treat bronchopulmonary dysplasia. The date of the first dose of steroids was recorded. However, neither the dosage nor the total duration of steroid exposure was recorded. Inhaled steroids and doses of steroids used solely for extubation or stridor were not included.

Additional data based on documented risk factors for NEC were also retrieved for each infant and included participating NICHD Neonatal Research Network center, whether the infant was inborn or outborn, gestational age as determined by the best obstetric estimate, birth weight, gender, mother's race, and 5-minute Apgar score. The limitations of the database precluded the inclusion of detailed fluid and feeding regimens in the analyses. The use of formula versus maternal breast milk was not documented and could not be assessed separately. It was also difficult to unambiguously differentiate infants with late-onset sepsis without NEC from those with NEC as the reason for a full course of antibiotics in the database; thus, data on late-onset sepsis were not analyzed as a function of H2-blocker treatment.

### Statistical Methods

A case-control study was conducted, and the results were analyzed with conditional logistic regression. Three controls were matched to each NEC case on the basis of birth-weight category (401–750, 751–1000, 1001–1250, and 1251–1500 g), race (black versus nonblack), and center. Each of these factors is highly associated with the likelihood of NEC. H2-blocker use was truncated such that H2 blockers received by case infants the day before

NEC diagnosis or later were not counted. Likewise, H2-blocker use in matched control infants was truncated on the same postmenstrual age and, in a second analysis, chronologic age so that truncation occurred in the identified case. Conditional logistic regression was implemented by using the PHREG procedure in SAS 8.02 (SAS Institute, Inc, Cary, NC). The regression model predicted NEC based on H2-blocker use while controlling for the effect of gender, site of birth (inborn versus outborn), postnatal steroids, and 5-minute Apgar score of <7.

## RESULTS

Of 11 936 infants born between September 1, 1998, and December 31, 2001, 11 072 survived for at least 12 hours. Complete data including presence or absence of NEC, birth weight, center, race, gender, whether they were outborn or inborn, use of postnatal steroids, and 5-minute Apgar score were available for 10 903 infants. The overall incidence of NEC was 7.1% (787 of 11 072), with approximately half of the infants undergoing surgery. When stratified by birth weight the incidence was 11.4% in infants 401 to 750 g (5.0% receiving no surgery, 6.4% receiving surgery), 9.0% in infants 751 to 1000 g (4.5% receiving no surgery, 4.5% receiving surgery), 6.0% in infants 1001 to 1250 g (3.2% receiving no surgery, 2.8% receiving surgery), and 3.8% in infants 1251 to 1500 g (2.1% receiving no surgery, 1.7% receiving surgery). Several neonatal variables were associated with increased risk for NEC (Tables 1 and 2). Infants with proven NEC were more likely to be black ( $P < .0001$ ), of lower birth weight ( $P < .0001$ ), and outborn ( $P < .0001$ ). In addition, both the incidence of NEC and frequency with which infants were treated with H2

blockers at any time during their hospitalization varied by clinical center (NEC: 4.26–11.25%,  $P < .0001$ ; H2-blocker use: 6.5–72.2%,  $P < .0001$ ). The Pearson correlation between H2-blocker use and NEC at each center is 0.33, which is not statistically significant ( $P = .165$ ).

To determine if there was an association between the incidence of NEC and treatment with H2 blockers, a case-control analysis was done as described above. There were 787 NEC cases. Of the planned 2361 matched controls (3 per case), 2357 controls were matched successfully. In 1 center, only 21 of 24 controls could be matched because of unavailability of black control infants; in another center, only 5 of 6 controls could be matched because of unavailability of nonblack control infants. Thus, 3144 observations were used in a conditional logistic regression.

As described in "Methods," H2-blocker use the day before diagnosis of NEC or later was not included as H2-blocker exposure. H2 blockers were started a mean of  $18.9 \pm 15.5$  days before NEC (median: 14; range: 2–76 days).

The results of the conditional logistic regression with H2-blocker use truncated by postmenstrual age and those truncated by chronologic age were similar (Tables 3 and 4). H2-blocker use was associated with an increased incidence of NEC (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.34–2.19;  $P < .0001$ , when data collection was truncated by postmenstrual age; OR: 1.49; 95% CI: 1.18–1.89;  $P = .0010$ , when data collection was truncated by chronologic age). In this analysis in which controls were matched for birth-weight category, race, and center, of the additional factors tested, only outborn versus inborn was significantly associated with the incidence of NEC.

**TABLE 1 Neonatal Demographic Data (n = 10 903): Entire Population**

Neonatal Variable	% of Patients With Variable and NEC	OR	95% CI	P
<b>Race</b>				
Black	8.8	1.58	1.34–1.86	<.0001
Non-black <sup>a</sup>	6.1			
<b>Gender</b>				
Male	7.6	1.15	0.99–1.33	.0684
Female <sup>a</sup>	6.8			
<b>Birth weight, g</b>				
401–750	11.5	3.30	2.62–4.16	<.0001
751–1000	9.1	2.43	1.94–3.05	<.0001
1001–1250	6.0	1.58	1.24–2.00	.0090
1251–1500 <sup>a</sup>	3.9			
<b>Site of birth</b>				
Outborn	10.2	1.54	1.25–1.90	<.0001
Inborn <sup>a</sup>	6.9			
<b>Apgar score &lt; 7 at 5 min</b>				
Yes	8.8	0.96	0.81–1.14	.6401
No <sup>a</sup>	6.6			
Network center				<.0001

<sup>a</sup> Reference groups.

## DISCUSSION

In a large cohort of >11 000 VLBW infants, treatment with H2 blockers was associated with a higher incidence of NEC, which is consistent with the results of a small randomized trial of acidification of feeds<sup>6</sup> that showed that a lower gastric pH level was associated with a decreased incidence of NEC.

Previous studies of premature infants cared for in the NICHD Neonatal Research Network centers have suggested that there are many identifiable risk factors for NEC in the VLBW population. Uauy et al<sup>8</sup> found (as did we in the current study) that the most significant factor in determining NEC prevalence was the center in which the infant was cared for. Our analysis, however, was limited by our inability to completely quantify illness severity at the time of birth or transfer to the tertiary center. Some referral hospitals may have chosen to transfer only the most vigorous infants to tertiary centers, whereas others would transfer only the sickest infants. It is also possible that some infants who were outborn were transferred to the network center because

**TABLE 2 Neonatal Demographic Data (n = 3144): Cases and Matched Controls**

Characteristic	Controls (n = 2357), n (%)	NEC cases (n = 787), n (%)	$\chi^2$ P	Total (n = 3144), n (%)
Race	1182 (50.2)	395 (50.2)	.9837	1577 (50.2)
Black				
Gender	1213 (51.5)	374 (47.5)	.0555	1587 (50.5)
Male				
Site of birth	257 (10.9)	121 (15.4)	.0008	378 (12.0)
Outborn				
5-min Apgar score <7	796 (33.8)	268 (34.1)	.8851	1064 (33.8)
Postnatal steroids	592 (25.1)	212 (26.9)	.3106	804 (25.6)
Yes				
Birth weight			.9999	
401–750 g	776 (32.9)	260 (33.0)		1036 (33)
751–1000 g	696 (29.5)	232 (29.5)		928 (29.5)
1001–1250 g	510 (21.6)	170 (21.6)		680 (21.6)
1251–1500 g	375 (15.9)	125 (15.9)		500 (15.9)

**TABLE 3 Conditional Logistic Regression: H2-Blocker Use Truncated According to Gestational Age**

Variable	OR	95% CI	P
H2 blocker	1.71	1.34–2.19	<.0001
Male vs female	1.12	0.95–1.31	.1910
Outborn vs inborn	1.51	1.18–1.92	.0008
Apgar score < 7 at 5 min	0.96	0.80–1.16	.6868
Postnatal steroids	1.02	0.83–1.25	.8389

**TABLE 4 Conditional Logistic Regression: H2-Blocker Use Truncated According to Chronologic Age**

Variable	OR	95% CI	P
H2 blocker	1.49	1.18–1.89	.0010
Male vs female	1.13	0.96–1.33	.1585
Outborn vs inborn	1.51	1.19–1.91	.0008
Apgar score < 7 at 5 min	0.97	0.81–1.17	.7761
Postnatal steroids	1.05	0.86–1.29	.6256

they had NEC in a NICU with no surgeon and arrived with both the diagnosis of NEC and use of H2 blockers. This may have contributed to the center differences in outcome. Uauy et al<sup>8</sup> also reported an increased incidence of NEC associated with prolonged rupture of membranes, maternal age of <25 years, birth weight of <1000 g, Apgar score at 5 minutes of <7, and maternal hemorrhage. Decreased incidence of NEC was associated with maternal prenatal care, high maternal blood pressure, and delivery by cesarean section. Additional analyses suggested that early fluid and feeding regimens, which varied from center to center, may relate to NEC prevalence. Those centers with more aggressive fluid and feeding regimens tended to have a higher prevalence of NEC. The use of either prenatal or postnatal steroids was not examined, nor was the use of H2 blockers. In our study, although there was a significant difference in both the incidence of NEC and the frequency with which H2 blockers were prescribed among centers,

the correlation between the 2 was not statistically significant.

Stoll et al<sup>9</sup> examined the relationship between postnatal steroid exposure (beginning at 2 weeks of age) and late-onset sepsis in VLBW infants cared for in NICHD Neonatal Research Network centers and entered into a randomized, controlled trial that compared early and late exposure to dexamethasone. Although not the original hypothesis, they observed that treatment with dexamethasone and with H2 blockers was associated with an increased risk of bacteremia/sepsis and meningitis. The increased risk of infection in infants treated with H2 blockers before randomization to the study drug (steroid or placebo) was postulated to be the result of a change in small-bowel colonization after the development of hypochlorhydria. Similarly, in a prospective observational study, Beck-Sague et al<sup>10</sup> reported that 12 (36%) of 33 VLBW neonates who received H2 blockers developed bloodstream infections, whereas only 30 (9%) of 343 of those not treated with H2 blockers developed bacteremia. In logistic-regression analysis, the risk of a bloodstream infection was independently associated with lower birth weight, respiratory illness at the time of admission, and receipt of H2 blockers. They postulated that gastric acidity may be a protective mechanism against respiratory and gastrointestinal tract colonization with nosocomial pathogens and subsequent bacteremia. The incidence of NEC was not examined separately in either study.

In a study of 34 infants who were <37 weeks' gestation with a mean birth weight of 1500 g, Hyman et al<sup>11</sup> reported that hypochlorhydria (pH > 4) was present in 19% of their study population at 1 week of age, 16% at 2 weeks of age, and 8% at 3 weeks of age. No infant had a basal gastric pH level of >4 after 6 weeks of age. In addition, stimulated acid output increased both as a function of postnatal and postmenstrual age ( $P < .01$ ). Similarly, Kelly et al<sup>12</sup> showed that in 22 infants who

were <30 weeks' gestation there was a trend for increasing gastric acidity with increasing postnatal age. However, even the infants who were born at 24 to 25 weeks' gestation had recorded gastric pH levels of 3 to 4 during the first 3 days after birth, and the pH level declined to <2 by day 16. In the infants who were 26 to 29 weeks' gestation, gastric pH levels were <3 throughout the testing period from days 1 to 17. These findings were in contrast with those of Carrion and Egan,<sup>6</sup> who reported that in infants of <1250 g birth weight, the median gastric pH level was 4.0 for the first 4 weeks after birth. They were able to decrease the median pH level to 3.0 with the addition of 1 N HCl to the study infants' feeds. Higher gastric enteric bacterial colony counts were strongly correlated with gastric pH level of >4 ( $P < .001$ ). In the Carrion and Egan study, there was a concomitant decrease in the reported incidence of NEC over the study period in those infants whose formula or maternal breast milk had been acidified (1 of 34 in infants receiving acidified feeds vs 8 of 34 in controls;  $P = .02$ ).

In light of the findings of Carrion and Egan,<sup>6</sup> we postulated that maintenance of a relatively less acidic gastric milieu would be associated with an increased incidence of NEC, possibly through bacterial overgrowth. There was no clear evidence of benefit of the use of H2 blockers; in fact, H2-blocker therapy seemed to be a significant risk factor for the development of NEC. This result is consistent with the literature on adult intensive-care patients in whom use of H2 blockers has been associated with an increase in the incidence of pneumonia.<sup>13</sup> However, we cannot dismiss the possibility that the use of H2 blockers may be a marker for clinical signs of fragility, inflammation, or other problems that are harbingers for NEC. In this retrospective study, without information on the indication for H2 therapy use, the use of such therapy may be an indication of the level of illness among the study cohort rather than a cause of disease.

NEC is a complex disease with multiple predisposing factors. Although focusing on one factor at a time may contribute to our understanding of the etiology of this disease, it is unlikely that a single intervention will markedly change its overall incidence. Between-center differences far outweigh any of the biological factors examined in this and other studies. However, it seems prudent to not use prophylactic H2-blocker therapy in VLBW infants without additional data from a randomized, controlled trial. Additional basic science research and a more global approach to modifying the care of extremely low birth weight infants, perhaps by using "benchmarking" techniques, may be alternatives to a randomized, controlled trial in gaining a greater understanding of gastrointestinal development and iatrogenic or environmental factors contributing to the risk of NEC.<sup>14</sup>

#### NICHD NEONATAL RESEARCH NETWORK MEMBERS

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