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EPIDEMIOLOGY OF NECROTIZING ENTEROCOLITIS

Barbara J. Stoll, MD

Necrotizing enterocolitis (NEC) is the most common emergency of the gastrointestinal tract occurring in the neonatal period. First described in the nineteenth century, NEC has been recognized as an important neonatal disorder since the 1960s. Dozens of descriptive studies and more than 20 case-control studies have been published in the English literature since 1965. Nonetheless, the cause and pathogenesis of NEC remain enigmatic.

CASE DEFINITION

Necrotizing enterocolitis is characterized by gastrointestinal and systemic signs and symptoms including feeding intolerance, delayed gastric emptying, abdominal distention or tenderness, occult or gross blood in the stool, lethargy, apnea, respiratory distress, and poor perfusion. In advanced cases, associated acidosis, shock, bacteremia, and disseminated intravascular coagulopathy are found. The diagnosis is suspected from clinical presentation. However, to be proved, clinical impressions must be confirmed by results of diagnostic radiographs, surgery, or autopsy.

In 1978, Bell et al[9] proposed a system for the uniform clinical staging of patients with NEC. With this system, infants are classified as having stage I (suspect), stage II (definite), or stage III (advanced) disease. Walsh and Kliegman[72] modified Bell's staging criteria to include systemic, intestinal, and radiographic signs and to suggest treatment based on stage and severity of illness. Infants with suggestive clinical signs and symptoms but nondiagnostic results of radiographs are classified as stage I (suspect NEC). Infants

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with stage II disease (definite NEC) have diagnostic abdominal radiographs (that is, pneumatosis intestinalis) and are mildly ill (stage IIA) or moderately ill (stage IIB, with systemic toxicity including acidosis, thrombocytopenia, or ascites). Infants with stage III disease (advanced NEC) are critically ill with impending (stage IIIA) or proven (stage IIIB) intestinal perforation. This staging system has been widely accepted and has improved the ability of the clinician and investigator to compare patients with diseases of uniform severity.

DESCRIPTIVE EPIDEMIOLOGY

Incidence, Sex, Race, and Seasonality

The incidence of NEC varies considerably from nursery to nursery, both within a similar geographic region and from region to region. Most descriptive studies of NEC report numbers of cases in a single institution for a designated time period and report the percentage of all neonatal intensive care unit (NICU) admissions with NEC or extrapolate to the number of cases per 1000 live births at a particular institution (Table 1). The incidence of NEC in selected studies has ranged from fewer than 1% to approximately 5% of NICU admissions, or fewer than 1 case per 1000 live births to approximately 3 cases per 1000 live births at these centers.[2,5,6,19,23,25,36,40,42,53,60,66]

Some studies have collected data on NEC from multiple institutions during the same time period. Fewer population-based studies have reported the number of cases in an entire state or geographic region over time (Table 2). In these multicenter and population-based studies, infants with NEC account for 0.3 cases per 1000 live births to 2.4 cases per 1000 live births (median value, 1.3 cases per 1000 live births).[26,51,58,75,77] If these data are extrapolated to all live births in the United States each year, NEC is clearly an important national problem. With approximately 4 million births each year[50] and NEC case rates of 0.3 to 2.4 cases per 1000 live births, 1200 to 9600 newborns are estimated to develop NEC in the United States each year (Table 3).

Most infants with NEC are born prematurely. In reported clinical series, 62% to 94% of patients are premature.[5,19,25,39,42,66] Several investigators have noted an increased incidence of NEC with decreasing birth weight and gestational age.[20,21,44,58,65,79] Wilson et al[75] studied all 148 cases of NEC reported from a single state during a 1-year period. The highest case rates occurred in infants weighing less than 1000 g (42.1 cases per 1000 live births); rates declined with increasing birth weight to 39.0 cases per 1000 live births for infants weighing 1000 to 1500 g, 3.8 cases per 1000 live births for infants weighing 1501 to 2500 g, and 0.11 cases per 1000 live births for infants weighing more than 2500 g at birth. A sharp decrease in the attack rate for NEC occurred at 35 to 36 weeks postconceptual age.[76] These data support the hypothesis that the risk of NEC is determined by maturity of the gastrointestinal tract. Palmer et al[51] studied 100 newborn units in the United

Table 1. LARGE DESCRIPTIVE STUDIES OF NECROTIZING ENTEROCOLITIS FROM SINGLE INSTITUTIONS: CASE RATES, SELECTED COMPLICATIONS, AND SURVIVAL RATES*

Author	Years Studied	Number of Cases	NICU Admissions (%) or Number of Cases/ 1000 Live Births	Preterm (%)	Positive Blood Culture (%)	Surgery (%)	Surgical Survival (%)	Overall Survival (%)
Frantz[25]	1970–1973	54	4.7%	91	37	70	31	35
Teasdale[66]	1974–1978	62	1.2%	69	11	31	—	76
Schullinger[60]	1955–1979	116	—	71	17	34	38	44
Kliegman[39,40]	1970–1978	123	3.7%	93	35	41	54	55
Dykes[23]	1972–1983	80	—	—	—	36	69	76
Barnard[2]	1976–1982	51	—	—	—	27	79	94
Pokorny[53]	1982–1983	55	3.0/1000	—	—	31	65	76
Beasley[5]	1975–1984	202	2.3%†	66	—	36	58	67
Holzman[36]	1980–1984	61	1.3%	—	—	36	77	69
Leong[42]	1971–1985	87	1.3/1000	94	21	23	60	74
Beeby[6]	1984–1991	82	—	90	24	37	53	72

* Studies include 50 or more cases each.
† For years 1981 to 1983.

Table 2. SELECTED MULTICENTER STUDIES OF NECROTIZING ENTEROCOLITIS: INCIDENCE AND CASE-FATALITY RATE

Author	Population Studied	Number of Births	Number of Cases	Cases per 1000 Live Births	Case-Fatality Rate (%)
All birth weights					
Ryder[58]	12 US hospitals	37,370	125	2.4	41
Wilson[75]	State of Georgia	161,886	148	0.9	38
Freeman[26]	Grampian, Scotland	—	92	2.2	9
Wiswell[77]	All US Army hospitals	264,789	338	1.3	11
Palmer[51]	100 NICUs in the United Kingdom and Ireland	—	204	0.3	27
Very low birth weight†				**% of VLBW**	
Uauy[69]	7 US hospitals	2681	269	10%	29
Vermont-Oxford[67]	36 US and Canadian hospitals	2961	178*	6%	—

* Six percent of 2961 cases.
† Under 1500 g birth weight.

Kingdom and Ireland during a 4-year period. They reported average annual rates of 0.3 cases per 1000 live births, ranging from 9.5 cases per 1000 live births in infants weighing less than 1000 g to 0.2 cases per 1000 live births for those weighing more than 2500 g at birth. Wiswell et al[77] studied the records of all infants with NEC born in US Army hospitals from 1980 to 1985. During this 6-year period, NEC developed in 338 of 264,789 babies (1.3 cases per 1000 live births). Case rates were 100 times higher in preterm (16.9 cases per 1000 live births) than full-term infants (0.17 cases per 1000 live births).

Two multicenter networks, the National Institute of Child Health and Human Development Neonatal Network (NICHD Neonatal Network) and the Vermont-Oxford Trials Network studied NEC in very low birth weight (VLBW = 501 to 1500 g) infants (Table 2). In 1991, the NICHD Neonatal

Table 3. ESTIMATES OF ANNUAL NECROTIZING ENTERCOLITIS DISEASE BURDEN IN THE UNITED STATES

Total live births*	~4,000,000/year
Necrotizing enterocolitis cases†	0.3 to 2.4 cases/1000 live births ↓ 1200 to 9600 cases/year
Necrotizing enterocolitis case fatality‡	9% to 28% ↓ 108 to 2688 deaths/year

* National Center for Health Statistics, 1992.[50]
† Based on multicenter studies.[26,51,58,75,77]
‡ Based on studies published since 1990.[8,26,44]

Network reported that NEC developed in 10.1% of 2681 VLBW infants cared for at seven university centers during an 18-month period.[69] Wide center-to-center differences were found, with percentage prevalence ranging from a low of 3.9% to a high of 22.4% at different institutions. A recent update of their data revealed a minimal change in NEC rates (8% of 1804 VLBW infants) and continued wide intercenter differences (4% to 19%).[30] Rates for infants weighing 501 to 750 g (9%; range, 2% to 19%) were similar to those of larger VLBW infants: 751 to 1000 g (9%; range, 2% to 25%) and 1001 to 1500 g (8%; range, 1% to 17%), with wide center-to-center differences in each birth weight group as well. The Vermont-Oxford Trials Network reported the experiences of 36 centers (including university hospitals, university affiliates, and unaffiliated hospitals) caring for 2961 VLBW infants.[67] Results were similar to those of the NICHD Neonatal Network: NEC developed in 6% of VLBW infants (ranging from 9% of those weighing 501 to 750 g to 5% of those weighing 1251 to 1500 g at birth), again showing variability among centers. The striking center-to-center variability in NEC prevalence found by both networks raises intriguing questions about differences in perinatal factors, birth weight distribution, severity of underlying illness, case identification, infectious milieu, and clinical management.

No consistent association between sex and NEC incidence has been found. In most studies, male and female infants are equally affected.[14,23,28,47,59,75,79] This is in contrast to a reported male predominance for both gram-negative and gram-positive neonatal sepsis and meningitis.[38]

Some studies have noted an increased incidence of NEC among black infants. Mizrahi et al[47] reported an increased ratio of black to white infants (1.7:1) in 1965. Wilson et al[75] reported significantly higher case rates for black than white infants (1.6 compared with 0.5 cases per 1000 live births; $P = 0.01$). Uauy et al[69] reported a significantly higher prevalence rate for black boys (but not girls) compared with white boys (14.4% compared with 5.8%; $P < 0.0001$). However, some case-control studies have not identified an increased risk of NEC for any race.[29,58,65] No seasonal pattern for NEC and no association between NEC and socioeconomic status have been reported consistently.

Necrotizing enterocolitis is primarily a disease of premature infants who have survived the immediate neonatal period. The introduction of new technology, especially artificial surfactants, has allowed smaller, more immature neonates to survive—the infants at greatest risk for NEC.[37] Whether this phenomenon will increase the numbers of babies with NEC is unknown. Population-based studies to evaluate trends in birth weight-specific incidence of disease will be especially important as early VLBW mortality continues to improve.

Age of Onset

The age of NEC onset is (like incidence) inversely related to birth weight and gestational age.[6,21,42,44,65,66,69,76] Stoll et al[65] reported a mean age at diagnosis of 20.2 days for infants born at 30 or fewer weeks' gestation,

13.8 days for those born at 31 to 33 weeks, and 5.4 days for those born at 34 or more weeks. All infants 36 weeks or more were diagnosed by age 7 days. Similarly, Wilson et al[76] reported that NEC developed after the age of 10 days in 45 of 86 (52%) infants weighing 1500 g or less at birth after 10 days of age compared with only 4 of 62 (6%) infants weighing more than 1500 g at birth.

Some investigators studied NEC in full-term infants and found an earlier age of onset in these infants.[1,22,68,77] Wiswell et al[77] reported that the median age of onset of NEC among 43 full-term infants was 2 days, with 42% presenting on the first day of life. Similarly, Andrews et al[1] and DeGamarra et al[22] reported that most full-term infants were symptomatic by 7 days of age. Thilo et al[68] studied 13 infants in whom NEC developed on the first day of life and reported that they were significantly more mature than 66 babies in whom NEC developed after day 1 (mean gestational age, 37.9 $\pm$ 2 weeks compared with 32.0 $\pm$ 3.5 weeks; $P < 0.001$).

Although NEC develops in full-term or near-term infants within the first few days of life, immature infants continue to be at prolonged risk for NEC. The clinician must be alert to the signs and symptoms of NEC in growing premature babies who have survived what is often a difficult early neonatal period and then appear to be feeding and progressing well. Strategies to prevent NEC will probably target the preterm baby and focus on issues related to gastrointestinal maturation, enteral nutrition, mucosal immunity, inflammatory mediators, and infectious agents.

Selected Complications and Death Secondary to Necrotizing Enterocolitis

The early clinical presentation of NEC may be indistinguishable from that of the sepsis syndrome. Necrotizing enterocolitis is associated with bacteremia in 11% to 37% of patients in large series (that is, more than 50 patients each; Table 1). Whether bacteremia is primary or secondary in these cases is unknown.

Surgery is performed in 23% to 70% of patients in selected series (Table 1). The age at time of surgery is inversely related to gestational age and birth weight.[53,55] In a review of 100 consecutive surgical patients at a single university, Ricketts reported that 93% of infants weighing less than 1000 g had surgery after 10 days of age compared with only 26% of infants weighing more than 1500 g.[55] Complications of surgery contribute to morbidity and death.

Death associated with NEC results from refractory shock, disseminated intravascular coagulation, multiple-organ failure, intestinal perforation with sepsis, extensive bowel necrosis, and complications of the short bowel syndrome after surgery. Birth weight and gestational age are important determinants of risk for death from NEC. Several investigators reported increased NEC case-fatality rates with decreasing birth weight and gestational age.[19,40,42,46,51,53,55,58,60,65,75,77] Case-fatality rates for infants weighing less than 1500 g range from 10% to 44%, whereas those for infants weigh-

ing more than 2500 g range from 0% to 20%.[44,51,60,65,69,75] Death rates are particularly high for extremely low-birth-weight infants (less than 750 g), ranging from 40% to 100%.[51,53,75] Wiswell[77] reported that 2 of 43 (4.7%) full-term infants died compared with 35 of 295 (11.9%) preterm infants. Whether NEC is less severe in full-term infants or if they are better able to withstand the disease is not known.

In most case series, NEC death rates are increased in those infants who require surgery compared with those who do not (Table 1), possibly because surgery is required in infants who have more severe disease, are deteriorating, or both. Surgical survival rates also decrease with decreasing birth weight.[55]

Epidemiologic evidence shows that death rates from NEC have decreased over time.[5,21,28,35,40,60,70] Although large series from the 1960s and 1970s reported mortality rates of 24% to 65%,[25,66] case series published since 1990 report mortality rates ranging from 9% to 28%.[6,28,43,44] Most series continue to report higher mortality rates for VLBW babies. The introduction of standardized therapeutic protocols, including criteria for medical management and surgical intervention, as well as a high index of suspicion for the disease and general improvements in neonatal intensive care presumably have decreased the mortality rate.

In 1979, the International Classification of Diseases (ICD) established a unique code for NEC that distinguished it from other gastrointestinal causes of death. Holman et al[35] used this new ICD code and analyzed data from the National Center for Health Statistics to describe trends in deaths related to NEC among infants in the United States. From 1979 to 1985, 3327 NEC deaths were reported, with an average annual mortality rate of 13.1 deaths per 100,000 live births. Annual mortality rates for NEC decreased during the study period from 14.5 deaths per 100,000 live births in 1979 to 10.2 deaths per 100,000 live births in 1985 (30% decrease). Because ICD coding alone was used to determine the number of NEC-related deaths, this study probably underestimates the total number of deaths (Table 3). Nonetheless, death rates decreased for male and female infants and for black and white infants. Male infants were more likely to die than were female infants, perhaps reflecting the higher birth weight-specific infant mortality rate reported for boys overall.[34] Black infants were more than three times as likely to die as were white infants. The increased mortality rate for blacks may be due to the increased low birth weight rate among black infants.[50] In another population-based study, Wilson et al[75] did not find a difference in NEC case-fatality rates between black and white infants after controlling for birth weight.

Endemic Compared with Epidemic Necrotizing Enterocolitis

Most large institutions have a low rate of endemic NEC—that is, sporadic cases that occur periodically throughout the year. In fact, most cases of NEC occur sporadically. However, NEC also occurs in temporal and geo-

graphic clusters or outbreaks (epidemic NEC). Superimposed on their baseline rate, several centers have reported alternating periods of endemic and epidemic NEC.[56] Different etiologic factors may be involved in endemic and epidemic NEC.

The first epidemics of NEC were reported in South Africa in 1972[18,64] and India in 1973.[10] The first outbreak in the United States was reported in 1974 and included five cases of NEC that occurred during a 3-week period in a nursery that had only 16 other cases in the previous eight years.[71] Many outbreaks of NEC have been identified, studied, and reported since these early epidemics. They have occurred throughout the United States and in all seasons of the year.

During epidemics, affected infants had different characteristics than during endemic periods. Guinan et al[29] studied three epidemics from three states. Affected infants had higher birth weights and Apgar scores, fewer perinatal complications, and lower case-fatality rates than did those reported for sporadic cases. Moomjian et al[49] found similar distinguishing features of epidemic cases.

Several observations during epidemics of NEC led to speculation about possible transmissible etiologic agents, including aerobic and anaerobic bacteria and viruses. Nonspecific gastrointestinal disturbances may increase during outbreaks of NEC and an increased frequency of gastrointestinal illness among NICU staff has been described before, during, and after epidemic periods.[12,27,64] Well-known temporal variations in gastrointestinal microflora and general NICU flora may affect the rate of NEC. A wide variety of organisms have been associated with outbreaks of NEC, including *Klebsiella pneumoniae,*[33] *Escherichia coli,*[62] clostridia,[16] coagulase-negative staphylococcus,[48] rotavirus,[57] coronavirus,[17] and others. Organisms have been cultured from stool, blood, and peritoneal fluid and have been identified in tissue specimens. However, in many epidemics, no specific pathogen has been identified.

The most compelling evidence that NEC is etiologically related to infection comes from the occurrence of epidemics. Although no single agent has been associated consistently with NEC, it may be due to an as yet unidentified pathogen. It is more likely that a variety of organisms, their toxic products, or both are related to NEC and are responsible for epidemic cases. Outbreak investigations have been limited by several weaknesses. Most notably, they have usually been retrospective studies, in part because of a lag time in identifying the "epidemic." They have included small numbers of patients, often without controls, and have involved nonuniform or inadequate specimen collection and processing. Continued and improved outbreak investigations are needed in the search for pathogens of possible etiologic importance. Such studies must be planned before the outbreak, must be ready for implementation with the earliest cases, and must include careful prospective collection of uniform samples from both cases and concurrent unaffected NICU controls. Furthermore, in an era of rapidly expanding diagnostic technology, the latest techniques to identify both routine and unusual organisms must be applied (Table 4).

Nursery crowding increases the risk of epidemic NEC.[61] This finding

Table 4. EPIDEMIC INVESTIGATIONS

Establish work plan before outbreak.
Be ready to implement investigation with earliest cases.
Study cases and concurrent matched unaffected nursery controls.
Collect uniform samples (stool, blood) from affected infants and controls.
Use most sophisticated diagnostic technology available.

either supports the role of a transmissible agent (that is, higher attack rate with crowding) or simply reflects an increased number of susceptible hosts with increased nursery census (that is, increased population of premature infants). The clinician and clinical investigator must respond to the first case of NEC as if it were the first case of an epidemic. During periods of particularly high attack rates, a nursery may need to be closed to new admissions until the epidemic is controlled. Infection-control measures include strict handwashing, use of gowns and gloves, cohorting and isolation of confirmed cases, separate care givers for confirmed cases (who do not care for unaffected infants), and exclusion of visitors or staff with gastrointestinal symptoms from the nursery.[56] Book et al[12] showed a reduction in NEC incidence from 3.6% to 0.7% when strict infection-control measures were introduced. However, Bell et al[7,8] reported changing rates of NEC with time without special isolation procedures. Given the fluctuating nature of this disease, strict care must be used in interpreting the results of interventions introduced to stop NEC outbreaks.

Associations and Risk Factors

Controversy surrounds the concept of "risk factors" for NEC. In 1975, Santulli et al[59] suggested that the pathogenesis of NEC involved three factors: bowel ischemia, oral feedings (metabolic substrate), and pathogenic organisms. A series of studies followed that linked risk factors related to this triad to the development of NEC.

The role of bowel ischemia was supported by studies that identified risk factors including low Apgar scores/birth asphyxia,[14] umbilical vessel catheterization,[14,61] and, recently, decreased in utero umbilical artery and aortic blood flow[31,45] in infants in whom NEC subsequently developed. Several observations support a role for milk feeding in the pathogenesis of NEC. Most NEC patients have been fed before disease onset.[19,28,44,66,74] Necrotizing entercolitis occurs less often in infants who are never fed, are fed human breast milk, or who are placed on a cautious feeding regimen.[13,43,63] Evidence suggesting an infectious etiology for NEC includes identification of outbreaks of NEC, investigations of these epidemic cases, a decreased risk or modification of disease with antibiotic therapy, and the association of particular pathogens with NEC.[8,12,27,56] However, some carefully performed case-control studies comparing affected infants with birth weight– and gestational age-matched unaffected controls did not identify risk factors for NEC independent of prematurity.[21,41,44,65,78] These studies argue that pre-

maturity (with immaturity of the gastrointestinal tract or host defense mechanisms) is the greatest risk factor for the development of NEC.

Some investigators suggest that risk factors may vary with birth weight and gestational age.[6,52,74] Necrotizing entercolitis may, in fact, be a different disease in preterm and full-term infants. Several observations suggest that in full-term infants, NEC may result more directly from an injury to the gastrointestinal tract, and that gut immaturity may be less important. In full-term infants, NEC has been associated with congenital heart disease[54] and polycythemia,[11,73] conditions that may compromise gastrointestinal oxygenation, blood flow, or both. In the largest published case-control study of full-term infant NEC, Wiswell et al[77] found a substantially higher incidence of asphyxia, respiratory distress, intrauterine growth retardation, and exchange transfusion in affected infants than in controls. Because NEC usually develops in full-term infants within a few days of birth,[1,68,77] a causal association between perinatal events and NEC is more plausible. Based on their observations of 82 infants with NEC, Beeby and Jeffery[6] proposed a model of susceptibility to NEC that depends on gestational age. In their model, all infants born before 30 weeks' gestation are at risk on the basis of extreme prematurity, and NEC may be unrelated to early perinatal events in these infants. Between 30 and 36 weeks' gestation, infants suffering asphyxia or growth retardation are at increased risk. At term, a major predisposing event is usually required for NEC to develop in the infant.

Although no proven unifying hypothesis for this disease exists, NEC is probably the result of a complex interaction between mucosal injury caused by a variety of factors (ischemic, infectious, intraluminal) and host response to that injury (circulatory, immunologic, inflammatory). Several articles in this volume of *Clinics in Perinatology* discuss issues related to the pathogenesis of NEC and present novel approaches to this disease.

Role of Future Randomized Trials: Prevention/Therapy

Prevention of NEC would contribute to a decrease in neonatal morbidity and death. Few clinical trials have addressed the issue of prevention.[3] Several potential preventive strategies have been suggested, including induction of gastrointestinal maturation with antenatal or early postnatal steroids,[4,32] improvement in gastrointestinal host defense with human breast milk feeding[43] or oral immunoglobulins,[24] change in bacterial colonization with antibiotics or novel feeding modification,[15] reduction of or antagonism of inflammatory mediators, and alteration in enteral feeding schedules.[63] In the future, strategies to prevent or modify this disease must be studied in carefully planned prospective randomized trials. Because the overall incidence of NEC at an individual institution is relatively low and may be episodic, collaborative multicenter studies are needed to recruit sufficient numbers of patients, in a timely fashion, to achieve statistically valid results.

Because the pathogenesis of NEC is complex and probably multifactorial, it is unlikely that a single intervention will be found to prevent this

disease. The most important preventive strategies will be those aimed at preventing prematurity, the greatest risk factor for NEC.

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