Necrotizing Enterocolitis in Very Low Birth Weight Neonates: A Natural History Study

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Abstract

Objective We characterize the most recent natural history of necrotizing enterocolitis (NEC), as this is an essential first step in guiding the prevention and treatment of this disease in the present day.

Study Design We performed a retrospective cohort study of neonates who were born at 23 to 29 weeks' gestation and birth weight <1,500 g who received care from the Pediatrix Medical Group between 2004 and 2019. We assessed the incidence of medical and surgical NEC and the patterns of initial antibiotic treatment to develop a contemporary cohort for further analysis. Among patients discharged between 2015 and 2019, we characterized the stage-specific risk factors for patients diagnosed with medical or surgical NEC, as well as patterns of disease onset, progression, biomarkers, and outcomes. We used the same approach to characterize patients diagnosed with suspected NEC.

Results Among 34,032 patients in the contemporary cohort, 1,150 (3.4%) were diagnosed with medical NEC and 543 (1.6%) were diagnosed with surgical NEC. The temporal pattern of disease onset was different for medical and surgical NEC, with gestational age– and birth weight–specific risk disparities emerging earlier in surgical NEC. Thirty-day mortality was much greater among surgical NEC patients (medical NEC 16.4% vs. surgical NEC 43.0%), as were rates of various in-hospital and long-term outcomes. Suspected NEC was diagnosed in 1,256 (3.7%) patients, among whom risk factors and disease onset, progression, and outcomes closely resembled those of medical NEC.

Conclusion Analyzing data from a contemporary cohort enabled us to characterize the current, stage-specific natural history of NEC, including novel insights into suspected NEC. Future studies could leverage this cohort to characterize how specific patient characteristics, care processes, or biomarkers may influence or predict disease outcomes.

Keywords

- necrotizing enterocolitis
- neonate
- very low birth weight
- prematurity
- natural history

Key Points

- The incidence of NEC has reached a stable baseline in recent years.
- Risk factors for NEC vary in a stage-specific manner.
- The stage-specific onset and progression of NEC differ by gestational age and birth weight.

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Necrotizing enterocolitis (NEC) is a life-threatening disease characterized by inflammatory necrosis of the neonatal intestine.[1,2] Extremely premature and very low birth weight (VLBW) neonates are at greatest risk for NEC due to immaturity of intestinal anatomy, physiology, and immune function, as well as abnormal bacterial colonization of the gastrointestinal tract.[1–4] Interventions to prevent NEC target these risk factors and include antibiotic stewardship, promoting use of human milk, protocolized feeding, and avoidance of medications that alter the intestinal microbiome.[5–7] Despite these advances in neonatal intensive care, NEC remains a common cause of surgical intervention, long-term morbidity, and mortality in preterm and VLBW neonates.[8–15]

Understanding the natural history of NEC is essential to the development of novel interventions to prevent the disease or improve outcomes in affected neonates. Natural history studies can illustrate how patient characteristics, biomarkers, and care processes influence disease onset, progression, and resolution, and can frame this information in a relevant, contemporary context.[16,17] To achieve these aims, a natural history study ideally would leverage a robust source of data that reflects the full spectrum of a given disease and the general experience of specialists who treat that disease.[18]

The goal of this study was to characterize the natural history of NEC in preterm and VLBW neonates in a contemporary population cohort. By analyzing data from a large, national database, we sought to describe the relationship between key patient characteristics and the onset of NEC; provide new information about the stage-specific treatment and progression of NEC; and report all-cause mortality, biomarkers, and various patient-important outcomes after the diagnosis of NEC.

Materials and Methods

Study Design

We performed a historical cohort study utilizing data from the Pediatrix Clinical Data Warehouse (CDW). The CDW includes data on more than 1 million neonates cared for by the Pediatrix Medical Group (PMG). Data for the CDW are extracted directly from the electronic health record (EHR) of each patient. The same propriety EHR software system (BabySteps; MEDNAX, Inc., Sunrise, FL) is utilized at most PMG neonatal intensive care units (NICUs). To improve validity, data extraction occurs at the end of each patient's hospitalization, allowing providers numerous opportunities to review and verify documentation. This study was deemed exempt by the Mayo Clinic Institutional Review Board (Rochester, MN) as the data provided for the study was deidentified.

Study Setting and Population

We included all neonates who were admitted to a PMG NICU on day of life (DOL) 0 or 1 after being born at 23 to 29 weeks' estimated gestational age and weighing <1,500 g at birth between 2004 and 2019. Inborn neonates who died in the delivery room were not included in the CDW tables that we queried.

Patient Characteristics and Outcomes

We obtained baseline maternal and neonatal characteristics for each patient, including early care processes required by the patients. The primary outcome was the maximum stage of NEC as clinically diagnosed by the PMG neonatologists, categorized as suspected, medical, or surgical NEC in daily clinical notes.[4] Patients with more than one NEC stage diagnosed on the day-of-onset (NEC day 0) were classified by the highest NEC stage on that day. Patients who were diagnosed with intestinal perforation in the absence of a diagnosis of NEC were included among patients categorized as having no NEC, thus, patients diagnosed with spontaneous intestinal perforation would not be misclassified as having been diagnosed with surgical NEC.[4] To build a contemporary cohort for further analysis, we used Cox's proportional hazards regression to compare the incidence of medical and surgical NEC (together considered "definite NEC") across years, and characterized antibiotic utilization among these patients on NEC day 0 or 1.

Among contemporary patients diagnosed with NEC, we assessed stage-specific progression (i.e., progression from suspected NEC to medical or surgical NEC or progression from medical NEC to surgical NEC), as well as survival following the diagnosis of the maximum stage of NEC. We also characterized the antibiotic regimens and blood culture results at the onset of NEC (NEC day 0 or 1); vasopressor and inhaled nitric oxide use on NEC day 0 or 1; and biomarkers of post-NEC renal and hepatic function at 1-week intervals till NEC day 28 (creatinine, aspartate aminotransferase [AST], and alanine aminotransferase [ALT]). Last, among patients with NEC we also quantified the rates of clinically diagnosed post-NEC stricture, post-NEC intestinal ostomy creation, and cholestasis, as well as the rate of deoxycholate prescription.

Among all patients in the contemporary cohort, we assessed change in weight *z*-score between the day of birth and 36 weeks' corrected gestational age (CGA), as well as the rate of postnatal growth restriction (defined as <3rd percentile for weight at 36 weeks' CGA based on Olsen's growth curves).[19] We also quantified the rates of retinopathy of prematurity requiring treatment (tROP), chronic lung disease (CLD; defined as requirement for oxygen or other respiratory support among those still hospitalized at 36 weeks' CGA), and periventricular leukomalacia (PVL; among those examined for PVL). Finally, among discharged patients, we measured the presence of a gastrostomy tube and length of stay (LOS; defined as days between birth and day of discharge).

Estimated Hospital Costs

Using the above LOS data in concert with published information regarding the mean costs of NICU care,[20] hospital cost indices,[21] and U.S. vital statistics,[22] we estimated the percase and system-level costs of medical and surgical NEC. First, we determined the mean per-day cost of providing care to patients <28 weeks' gestation, irrespective of NEC status,

according to Russell et al ($1,555 in 2001).[20] While a small percentage of these patients would have been diagnosed with NEC, we considered this subgroup as being "without NEC" for use in subsequent calculations, noting that doing so would underestimate the impact of NEC on overall cost of care.

Compared with the benchmark subgroup above, Russell et al found that patients with NEC incurred 1.52-fold higher mean cost of hospitalization.[20] Thus, we estimated the per-day cost of providing care to patients with NEC to be $2,364 in 2001. To determine the current per-day cost of caring for patients with and without NEC, we adjusted for the change in the Personal Health Care-Hospital Care price index between 2001 and 2019 (a factor of 1.65 increase).[21] We then multiplied these adjusted per-day costs by the median LOS that we observed in patients without NEC and those with medical or surgical NEC. The difference between these values was our estimated per-case cost of NEC. To estimate the annual cost of NEC in the U.S. health care system, we multiplied this estimated per-case cost of NEC by the number of live births <1,500 g as per the National Vital Statistics Report (2019),[22] and by the combined incidence of medical and surgical NEC, we observed in our contemporary cohort.

Data Analysis

Continuous data are summarized using means and standard deviations (SD) or medians and interquartile ranges (IQRs) for continuous data; categorical data are summarized using frequencies and percentages. The Aalen–Johansen method was used to calculate the rates of suspected, medical, and surgical NEC, with patients who were transferred out of the NICU being censored at time of transfer and in-hospital mortality being considered a competing risk.[23] Cox's proportional hazards regression was used to assess risk factors for each NEC stage. Proportional hazards assumptions were checked, and all assumptions were met. In these models, we also assessed for interactions between gestational age and birth weight.

Similar survival methods were used to assess the secondary post-NEC outcomes of stage-specific progression, in-hospital mortality, cholestasis, ursodeoxycholate use, and post-NEC stricture. The remaining secondary outcomes were compared between groups (based on the maximum NEC stage diagnosed during hospitalization), using a Chi-square test for categorical data, analysis of variance (ANOVA) for normally distributed continuous data, and a Kruskal–Wallis test for nonnormally distributed continuous data. All tests were two-sided, and p-values of ≤ 0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 software (SAS Institute, Inc.; Cary, NC) and R version 4.0.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Incidence and Initial Antibiotic Treatment of Definite Necrotizing Enterocolitis: 2004–2019

To characterize the natural history of NEC, we first sought to determine a recent epoch during which the incidence of definite NEC was fairly stable. After reaching a peak in 2007, the annual incidence of definite NEC declined considerably, with a stable range of 4.8 to 6.1% between 2015 and 2019 (►Fig. 1A). Compared with 2019, there was no significant difference in the incidence of definite NEC from 2015 to 2018 ($p \geq 0.05$); however, prior to 2015, the incidence of definite NEC was significantly higher than it was in 2019 ($p < 0.001$), so we limited the data for our natural history study to this contemporary 5-year period.

The profile of antibiotics prescribed at the onset of NEC also changed between 2004 and 2019 (►Fig. 1B). Cefotaxime use declined (21.3–1.1%), while use of piperacillin and tazobactam increased (5.3–21.6%), though we observed only small increases in the use of cefepime and ceftazidime (►Fig. 1B). The rates of clindamycin and metronidazole prescription decreased and increased, respectively, by approximately 15% over this 16-year period. In contrast,

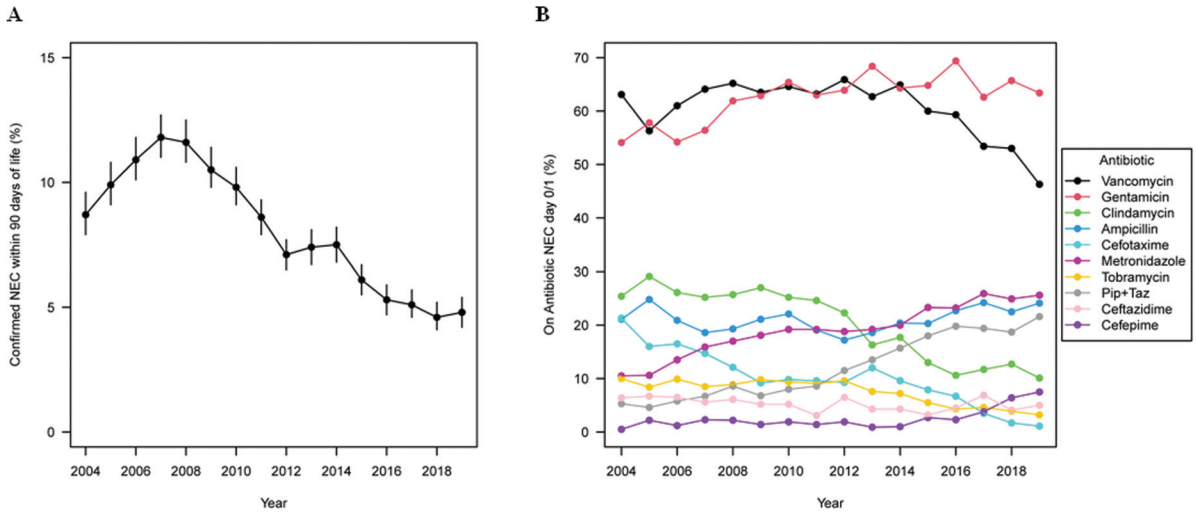

Fig. 1 Annual incidence of confirmed NEC within the first 90 days of life and the frequency of antibiotic use the time of NEC onset (NEC day 0 or 1). NEC, necrotizing enterocolitis; Pip, piperacillin; Taz, tazobactam.

between 2015 and 2019, the frequency with which each antibiotic was used changed by less than 10%, the lone exception being vancomycin (►Fig. 1B).

Stage-Specific Onset and Risk Factors

Among 34,032 patients in the 2015 to 2019 cohort, PMG neonatologists diagnosed 1,256 patients with suspected NEC, 1,150 patients with medical NEC, and 543 patients with surgical NEC (cumulative incidence by DOL 90 4.2, 3.9, and 1.8%, respectively). ►Supplementary Table S1 (available in the online version) presents the baseline maternal and neonatal characteristics according to maximum NEC stage, including no NEC. For each stage of NEC, the temporal pattern of disease onset varied according to gestational age and birth weight (►Fig. 2). As expected, the stage-specific risk of NEC was inversely related to gestational age and birth weight (►Fig. 2; ►Supplementary Fig. S1, available in the online version). ►Supplementary Fig. S1 (available in the online version) also displays the hazard ratios and confidence intervals (CIs) for other relevant characteristics and their association with each NEC stage. Among all these risk factors, multivariable analysis revealed that only four characteristics were independently associated with an increased risk of both medical and surgical NEC: gestational age 23 to 24 weeks, birth weight <1,000 g, male sex, and outborn birth status (►Table 1).

Stage-Specific Progression of Necrotizing Enterocolitis

Sixty-six patients initially diagnosed with suspected NEC progressed to either medical or surgical NEC, with 4.5% (95% CI: 3.2–5.7%) progressing within 7 days of diagnosis of suspected NEC. One hundred and three patients with medical NEC progressed to surgical NEC (7-day rate of progression = 8.5%, 95% CI: 6.6–10.2%). We did not observe a difference in rate-of-progression among either the gestational age or birthweight subgroups. Please refer to ►Supplementary Tables S2 and S3 (available in the online version) for additional information on progression rates in gestational age and birth weight subgroups.

Initial Stage-Specific Treatment of Necrotizing Enterocolitis

At the onset of NEC, the frequency with which a given antibiotic was prescribed varied according to stage of the disease (►Table 2). Perhaps as anticipated, broad-spectrum and anaerobic coverage most commonly were provided to patients with surgical NEC. Surgical NEC patients were four times as likely than those with medical NEC to require support with vasopressors and inhaled nitric oxide at the time of disease onset (►Table 2). Among surgical NEC patients for whom procedure type was documented ($n = 250$), 34% were treated with peritoneal drain placement alone, 51% underwent primary laparotomy and

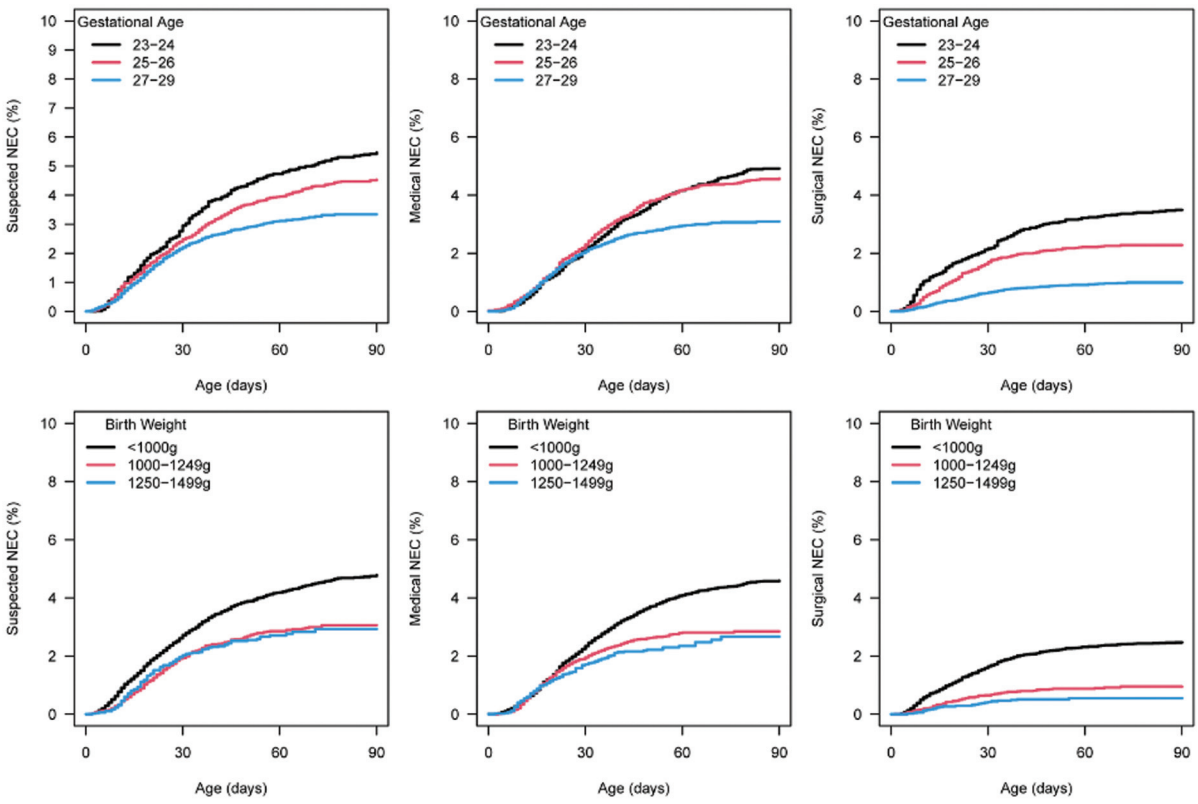

Fig. 2 Cumulative incidence of neonates diagnosed with NEC (suspected, medical, and surgical), accounting for the competing risk of death, by gestational age (23–24, 25–26, and 27–29 weeks) and birth weight (<1,000, 1,000–1,249, and 1,250–1,499 g). NEC, necrotizing enterocolitis. NEC, necrotizing enterocolitis.

Table 1 Stage-specific multivariable Cox's proportional hazards regression models

	Suspected NEC		Medical NEC		Surgical NEC	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Singleton birth	1.20 (1.04–1.38)	0.014	1.09 (0.94–1.27)	0.24	1.08 (0.87–1.34)	0.48
Smoking reported	1.05 (0.84–1.30)	0.67	1.04 (0.83–1.31)	0.75	1.61 (1.21–2.14)	0.001
Diabetes	0.77 (0.62–0.96)	0.021	1.00 (0.81–1.22)	0.97	1.23 (0.92–1.64)	0.17
Antenatal steroids	1.44 (1.20–1.72)	<0.001	1.13 (0.94–1.36)	0.19	1.01 (0.79–1.29)	0.94
PROM (>5 days)	0.88 (0.76–1.02)	0.096	1.08 (0.93–1.25)	0.32	0.85 (0.67–1.07)	0.16
Chorioamnionitis	0.84 (0.65–1.08)	0.18	0.76 (0.57–1.00)	0.052	0.51 (0.32–0.83)	0.006
Preeclampsia	0.84 (0.71–1.00)	0.055	0.98 (0.82–1.16)	0.79	0.97 (0.74–1.26)	0.81
Gestational age (wk)						
23–24	1.47 (1.22–1.76)	<0.001	1.38 (1.14–1.68)	<0.001	2.44 (1.84–3.21)	<0.001
25–26	1.08 (0.92–1.26)	0.37	1.16 (0.99–1.37)	0.067	1.55 (1.21–2.00)	<0.001
27–29	Reference		Reference		Reference	
Gender–male	1.18 (1.05–1.32)	0.004	1.13 (1.00–1.27)	0.048	1.27 (1.07–1.51)	0.006
Race						
White	Reference		Reference		Reference	
Asian	1.08 (0.78–1.49)	0.66	0.90 (0.62–1.31)	0.58	0.65 (0.34–1.23)	0.19
Black	1.03 (0.90–1.18)	0.67	1.17 (1.02–1.35)	0.029	0.96 (0.78–1.19)	0.72
Hispanic	1.13 (0.97–1.32)	0.11	1.16 (0.99–1.37)	0.071	1.32 (1.06–1.66)	0.015
Other	0.94 (0.76–1.17)	0.57	1.00 (0.79–1.25)	0.97	1.08 (0.79–1.48)	0.63
Outborn	1.44 (1.23–1.68)	<0.001	1.20 (1.01–1.44)	0.041	1.38 (1.09–1.73)	0.007
Birth weight (g)						
< 1,000	1.36 (1.09–1.70)	0.006	1.49 (1.18–1.87)	<0.001	2.62 (1.67–4.11)	<0.001
1,000–1,249	1.00 (0.80–1.24)	0.98	1.06 (0.84–1.33)	0.61	1.53 (0.97–2.41)	0.068
1,250–1,499	Reference		Reference		Reference	
Major anomaly	1.27 (1.11–1.45)	<0.001	1.46 (1.27–1.68)	<0.001	1.16 (0.94–1.42)	0.16
On vent DOL 0–2	1.14 (0.99–1.31)	0.078	1.07 (0.92–1.23)	0.38	1.24 (0.98–1.58)	0.070
Vasopressors DOL 0–2	1.10 (0.95–1.27)	0.20	1.04 (0.89–1.22)	0.63	1.16 (0.94–1.42)	0.16
PDA DOL 0–2	1.22 (1.08–1.38)	0.001	1.10 (0.97–1.26)	0.13	0.98 (0.82–1.17)	0.82
Severe IVH DOL 0–2	1.19 (0.96–1.46)	0.11	1.03 (0.81–1.30)	0.83	1.70 (1.32–2.19)	<0.001

Abbreviations: CI, confidence interval; DOL, day of life; iNO, inhaled nitric oxide; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PROM, prolonged rupture of membranes.

stoma creation, and 15% first were treated with peritoneal drainage before subsequent laparotomy and stoma creation. Post-NEC stricture was infrequent in both definite NEC subgroups (medical NEC = 2.3% and surgical NEC = 0.8%).

Maximum Stage-Specific Survival

Among all patients diagnosed with NEC, the all-cause mortality rate at 30 days of postonset was greater among patients with higher acuity, maximum-stage disease (suspected NEC = 6.1%, 95% CI: 4.7–7.5%; medical NEC = 16.4%, 95% CI :14.1–18.7%; and surgical NEC = 43%, 95% CI: 38.4–47.3%). The median time of death was similar among all three stages (suspected NEC = 1.5 days, IQR: 0–21 days; and medical and surgical NEC = 1 day, IQR: 0–6 days). The degree of prematurity was less consistently associated with stage-specific mortality than was birth weight category, with patients <1,000 g at birth most likely to die in each maximum-stage NEC category (►**Fig. 3**).

Post–Necrotizing Enterocolitis Blood Culture Microbiology

Among NEC patients for whom a blood culture was obtained within 7 days of onset, those with surgical NEC were twice as likely to have a positive culture as patients with suspected or medical NEC (suspected NEC = 20.6%, medical NEC = 20.2%, and surgical NEC = 40.2%; $p < 0.001$). Details on the organisms seen on positive cultures can be found in ►**Supplementary Table S4** (available in the online version).

Table 2 Stage-specific treatment and outcomes of NEC

	Suspected ($n = 1,095$) Mean ± SD)/n (%)	Medical ($n = 990$) Mean ± SD)/n (%)	Surgical ($n = 543$) Mean ± SD)/n (%)	p-Value
Lowest hemoglobin within 7 days prior to NEC[a]	10.26 ± 1.90	10.23 ± 2.07	9.64 ± 1.92	<0.001
Anemia (hemoglobin < 8) within 7 days prior to NEC[a]	77 (8.7)	69 (8.5)	72 (16.1)	<0.001
PDA diagnosis before NEC	677 (61.8)	511 (51.6)	284 (52.3)	<0.001
PDA ligated before NEC	72 (10.5)	80 (15.0)	34 (11.5)	0.034
IVH diagnosis before NEC				<0.001
Missing	81	127	96	
0	622 (61.3)	545 (63.2)	243 (54.4)	
1	134 (13.2)	159 (18.4)	54 (12.1)	
2	111 (10.9)	66 (7.6)	52 (11.6)	
3	59 (5.8)	37 (4.3)	35 (7.8)	
4	88 (8.7)	56 (6.5)	63 (14.1)	
Cholestasis prior to NEC	132 (12.1)	154 (15.6)	110 (20.3)	<0.001
Ursodeoxycholate prior to NEC	49 (4.5)	72 (7.3)	36 (6.6)	0.021
Positive culture on DOL 4 to NEC day 1 (out of no. with culture done)	182/536 (34.0)	203/552 (36.8)	108/286 (37.8)	0.47
Antibiotics on NEC day 0/1				
Ampicillin	247 (22.6)	259 (26.2)	89 (16.4)	<0.001
Gentamicin	712 (65.0)	715 (72.2)	287 (52.9)	<0.001
Tobramycin	41 (3.7)	44 (4.4)	30 (5.5)	0.25
Cefepime	43 (3.9)	40 (4.0)	32 (5.9)	0.15
Ceftazidime	51 (4.7)	36 (3.6)	36 (6.6)	0.030
Clindamycin	83 (7.6)	128 (12.9)	96 (17.7)	<0.001
Metronidazole	176 (16.1)	264 (26.7)	204 (37.6)	<0.001
Piperacillin + tazobactam	173 (15.8)	188 (19.0)	149 (27.4)	<0.001
Meropenem	70 (6.4)	64 (6.5)	86 (15.8)	<0.001
Nafcillin	64 (5.8)	62 (6.3)	15 (2.8)	0.010
Vancomycin	587 (53.6)	546 (55.2)	309 (56.9)	0.44
Vasopressors NEC day 0/1	112 (10.2)	144 (14.5)	317 (58.4)	<0.001
iNO NEC day 0/1	20 (1.8)	11 (1.1)	24 (4.4)	<0.001
Post-NEC stricture[b]	8 (0.8)	18 (2.3)	4 (0.8)	0.050
Cholestasis after NEC (among those without it prior to NEC)[b]	132 (13.3)	165 (18.1)	160 (37.5)	<0.001
Ursodeoxycholate after NEC (among those without it prior to NEC)[b]	97 (6.3)	118 (6.1)	110 (8.2)	<0.001

Abbreviations: DOL, day of life; iNO, inhaled nitric oxide; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; SD, standard deviation.
[a]Available in 2,148 (888 with suspected NEC, 814 with medical NEC, and 446 with surgical NEC).
[b]Rates are calculated using survival methods within 30 days after NEC, p-values are from Cox's proportional hazards regression model.

Biomarkers after the Onset of Necrotizing Enterocolitis

Creatinine levels on the day-of-onset (NEC day 0) were the highest among patients diagnosed with surgical NEC, but after 3 weeks, there were no differences between the three NEC subgroups (►**Supplementary Fig. S2**, available in the online version). Both AST and ALT levels likewise were the highest among surgical NEC patients on NEC day 0, but within 1 week, these liver enzymes were similar to those of patients diagnosed with suspected and medical NEC (►**Supplementary Fig. S2**, available in the online version). Interestingly, AST and ALT levels trended up by NEC day 21 in surgical NEC patients, with a difference in ALT still detected by NEC day 28. This latter finding is of interest given that the

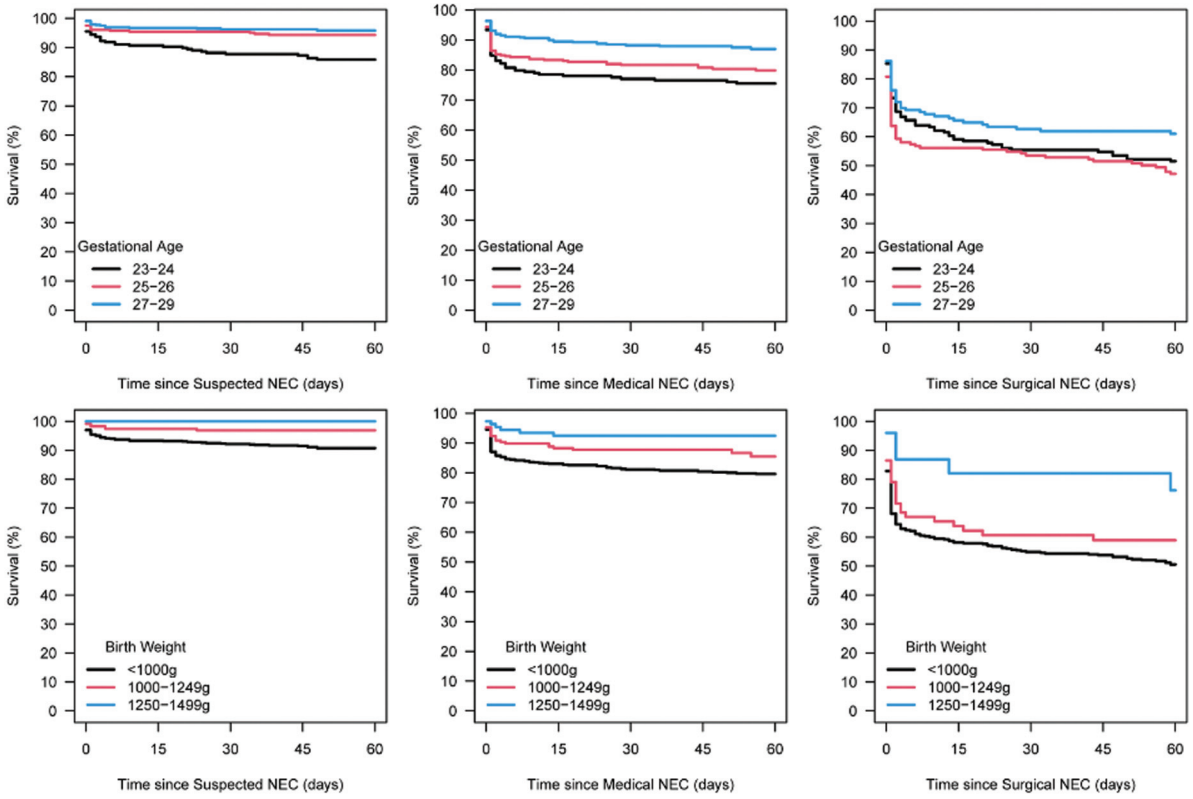

Fig. 3 Stage-specific in-hospital survival following diagnosis of NEC by gestational age (23–24, 25–26, and 27–29 weeks) and birth weight (<1,000, 1,000–1,249, and 1,250–1,499 g). NEC, necrotizing enterocolitis.

new-onset diagnosis of cholestasis and requirement for ursodeoxycholate therapy was the highest among patients diagnosed with surgical NEC as shown in ►Table 2.

Clinical Outcomes

Patients diagnosed with NEC had higher rates of postnatal growth restriction and various clinician-reported, patient-important outcomes than those without NEC (►Table 3). Patients in each of the NEC subgroups more often required postdischarge enteral feeding support via gastrostomy tube, as well as prolonged hospitalization (►Table 3). These descriptive data were derived from analyses in which we did not control for risk factors, thus they do not indicate independent stage-specific associations between NEC and each outcome.

Estimated Costs of Definite Necrotizing Enterocolitis

Among patients discharged home following a diagnosis of medical or surgical NEC, the median LOS was 101 days (IQR: 79–127), or 26 days longer than discharged patients without NEC (75 days, IQR: 58–97 days; $p < 0.001$). After adjusting for inflation in the Personal Health Care-Hospital Care price index,[21] this increased LOS translates to approximately $200,000 per case of NEC. Based on the 4.8% incidence of definite NEC that we observed in our patients born in 2019, and given that 51,716 neonates were born at <1,500 g that same year[22] that the total cost of NEC to the American Health Care System could approach or even exceed $500 million annually.

Discussion

Trends in the Incidence and Initial Treatment of Definite Necrotizing Enterocolitis

Among a large cohort of extremely premature neonates, we observed a recent decline in the rates of medical and surgical NEC,[10,24] with the incidence of disease leveling off between 2015 and 2019. As previously described for patients in this cohort,[24] favorable trends in the use of human breast milk and avoidance of prolonged early empiric antibiotic treatment likely contributed to these improved outcomes.[25–32] Over the same period of time, we observed shifts in the antibiotics selected to cover gram-negative and anerobic organisms at the onset of definite NEC. Given that the incidence of definite NEC and antibiotic prescription patterns were fairly stable between 2015 and 2019, we studied the stage-specific, natural history of NEC among patients born in this 5-year period. In the subsections below, we first discuss matters related to medical and surgical forms of NEC ("definite NEC"), then briefly address the more challenging topic of suspected NEC.

Risk Factors for Definite Necrotizing Enterocolitis

The risk of medical or surgical NEC was inversely related to gestational age and birth weight, as expected, with distinctly higher risk among patients born at 23 to 24 weeks or birth weight <1,000 g. Surprisingly, among patients with definite NEC, there was no significant interaction between gestational age and birth weight among patients with definite NEC (*p*-

Table 3 Stage-specific growth and patient-important outcomes of NEC

	None Median (IQR)/ mean ± SD)/*n* (%)	Suspected Median (IQR)/ mean ± SD)/*n* (%)	Medical Median (IQR)/ mean ± SD)/*n* (%)	Surgical Median (IQR)/ mean ± SD)/*n* (%)	*p*-Value
Weight at 36 weeks' CGA,[a]	2,207 ± 360	2,073 ± 360	2,076 ± 369	2,014 ± 421	<0.001
Weight *Z*-score at birth	−0.1 ± 1.0	−0.2 ± 1.1	−0.2 ± 1.1	−0.1 ± 1.0	<0.001
Weight *Z*-score at 36 weeks' CGA	−1.1 ± 0.7	−1.4 ± 0.8	−1.3 ± 0.8	−1.5 ± 0.9	<0.001
Change in weight *Z*-score	−1.0 ± 0.8	−1.2 ± 0.8	−1.1 ± 0.8	−1.3 ± 1.1	<0.001
≤3rd percentile	3,032 (12.7)	209 (24.4)	167 (23.7)	86 (33.5)	<0.001
ROP requiring treatment[d]	937 (3.8)	57 (6.3)	56 (7.3)	54 (18.0)	<0.001
Chronic lung disease[e]	7,388 (35.1)	341 (44.1)	319 (49.1)	135 (56.0)	<0.001
Periventricular leukomalacia[f]	1,099 (3.9)	57 (5.3)	50 (5.2)	42 (7.9)	<0.001
Gastrostomy at discharge[g]	54 (0.2)	5 (0.7)	4 (0.7)	4 (2.0)	<0.001
LOS for survivors[g]	75 (58, 97)	89 (69, 114)	95 (74, 118)	122 (101, 152)	<0.001

Abbreviations: CGA, corrected gestational age; IQR, interquartile range; LOS, length of stay, NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity, SD, standard deviation.
[a]Available in 23,811 without NEC, 859 with suspected NEC, 705 with medical NEC, and 257 with surgical NEC.
[b]Available in 20,637 without NEC, 719 with suspected NEC, 591 with medical NEC, and 207 with surgical NEC.
[c]Available in 21,889 without NEC, 794 with suspected NEC, 651 with medical NEC, and 229 with surgical NEC.
[d]Available in those with ROP evaluated (24,915 without NEC, 905 with suspected NEC, 767 with medical NEC, and 300 with surgical NEC).
[e]Available in those still in the neonatal intensive care unit at CGA ≥ 36 weeks (21,023 without NEC, 774 with suspected NEC, 750 with medical NEC, and 241 with surgical NEC).
[f]Available in those examined (28,158 without NEC, 1,069 with suspected NEC, 964 with medical NEC, and 531 with surgical NEC).
[g]Among those discharged alive (23,241 without NEC, 766 with suspected NEC, 612 with Medical NEC, and 197 with surgical NEC).

values >0.65). Our multivariable analysis likewise did not identify small for gestational age birth size as an independent risk factor for NEC. These findings clarify that among all VLBW neonates those who are least mature and the lowest birth weight require special consideration in clinical processes, such as standardized feeding protocols.[24]

Our analysis of other risk factors allowed us to build on our earlier work and compare our current findings to others' observations. While Fang et al identified a small increase in the risk of NEC among outborn VLBW neonates born between 2000 and 2014,[33] our present study suggests that this outcome disparity increased over the subsequent 5 years (►Table 1). The presence of congenital anomalies is another baseline patient characteristic that others have associated with NEC,[34,35] though we observed only an increased risk of medical NEC after adjusting for other variables. Perhaps due to differences in study design, we did not identify early exposure to inotropes as an independent risk factor for definite NEC as did Wong et al.[36] Because this care process may influence the risk of NEC, we analyzed the rate at which at least one inotrope was prescribed DOL 0 to 2 and found that it decreased over time (2004–2014: 24.4% v. 2015–2019: 18.1%, $p < 0.001$). Among patients with definite NEC, prior diagnosis of anemia (Hgb <8 g/dL) within 1 week prior to the onset of NEC were most common among patients with surgical NEC.[37] Similarly, we identified that preexisting cholestasis may be a diagnostic harbinger of more advanced forms of NEC to our knowledge, a novel finding.

Stage-Specific Onset, Treatment, and Progression of Definite Necrotizing Enterocolitis

The temporal pattern of disease onset differed considerably between medical and surgical NEC. The risk of medical NEC increased linearly among all gestational age and birth weight subgroups over the second and third week of life, at which point the risk began to plateau for patients born at >26 weeks or >1,000 g. The risk for less mature and lower birth weight patients did not appreciably level off until nearly 8 weeks of life. The onset of surgical NEC was characterized by immediate distinctions in risk among the three gestational age subgroups during the second week of life. Among the birth weight subgroups, there was a clear difference between patients born <1,000 g and patients of greater birth weight. Understanding these stage-, gestational age–, and birth weight–specific patterns of onset could improve the precision with which clinical neonatologists discuss prognosis with VLBW patients' families.

While the initial antibiotic treatment of definite NEC has stabilized in recent years (►Fig. 1B), we observed a broad array of drug classes prescribed at the onset of both medical and surgical NEC (►Table 2). This variability in antibiotic prescription patterns mirrors recent reports from single centers,[38,39] and likely reflects the lack of clear evidence on which to develop specific guidance.[40,41] With this in mind, we note that approximately one in nine patients with medical NEC progressed to surgical NEC in our cohort, most within 1 week of the onset of medical NEC. Bacteremia was most common among surgical NEC patients in our cohort as well.[42] Thus it is important to be mindful of VLBW patients' response to initial antibiotic

regimens, with careful attention for signs of progression and surveillance for bacteremia, as changes in antibiotic coverage may be warranted.

Stage-Specific Survival in Definite Necrotizing Enterocolitis

Among patients with definite NEC most mortality occurred within a few days of disease onset. There was an inverse, stratal relationship between survival and both gestational age, and birth weight among patients with medical NEC. This was less, so the case for surgical NEC. Survival was similar among the least mature and lowest birth weight subgroups, and patients >1,250 g gestation were notably most likely to survive surgical NEC. The relatively high risk of mortality among surgical NEC patients appears to be reflected in the high rates of bacteremia (40.2%) and requirement for vasopressors (58.4%) that we observed after disease onset. Late-onset sepsis, particularly with gram-negative organisms, like those we observed, is strongly associated with death in neonates,[43] while vasopressor treatment has been independently associated with death among patients with NEC.[14]

Biomarkers of Disease: Relevance to Surgical Necrotizing Enterocolitis

Creatinine levels on the day of diagnosis suggested that surgical NEC patients may have experienced some degree of acute kidney injury at the time of disease onset. While their creatinine levels were similar to those of suspected and medical NEC patients after 3 weeks, it is conceivable that this biomarker portended an increased LOS among surgical NEC patients.[44] Our limited transaminase data also suggest that surgical NEC patients experienced transient liver injury on the day of diagnosis, perhaps followed by the evolution of more chronic liver disease. Indeed, the prevalence of cholestasis among surgical NEC patients was twice that of patients with medical NEC, and quite similar to that of surgical NEC patients in a contemporary, prospectively studied cohort.[42]

Growth and Other Patient-Important Outcomes of Definite Necrotizing Enterocolitis

Consistent with other contemporary studies of growth outcomes among VLBW neonates,[45,46] we identified significant postnatal growth failure among patients with medical and surgical NEC. Severe restriction (<3rd percentile) in weight was most prevalent among surgical NEC patients. We attribute this finding to the high prevalence of intestinal stoma in our cohort (17%),[47] but cannot resolve whether this factor per se contributes to the adverse neurodevelopmental outcomes observed in patients with surgical NEC.[42] Nevertheless, the observed restriction in postnatal growth is especially concerning, considering the high rates of tROP, CLD, and serious brain injury (severe intraventricular hemorrhage and PVL) among surgical NEC patients.[48,49]

Length of Stay and Estimated Costs of Definite Necrotizing Enterocolitis

In our cohort, the diagnosis of definite NEC was associated with a 26-day increase in the median LOS. While several multicenter studies have demonstrated similarly prolonged hospitalizations,[10,42,44,50] the literature regarding the surgical and overall hospital costs of NEC is limited.[20,51] While Russell et al provided LOS and mean hospital cost data,[20] we only could estimate and compare the per-day cost of hospitalization for patients with and without NEC. To understand the cost implications of NEC more clearly, future studies of the Nationwide Inpatient Sample or other government databases will be essential.[20,51] For now, though, it seems as though our approach to cost estimation is valid, when comparing our patients' likely total cost of care with those reported by Stey et al.[51]

Suspected Necrotizing Enterocolitis

There is virtually no literature describing the risk factors or natural history of suspected NEC, perhaps because the nonspecific nature of this diagnosis has prevented or disincentivized investigation into its origins and outcomes.[3] While patients diagnosed with suspected NEC might be affected by other non-NEC diagnoses (e.g., bacteremia with septic ileus and feeding intolerance of prematurity),[3] we reasoned that these selected patients could serve as a "least acute" comparator for patients with medical or surgical NEC, a group that may be considered collectively as those with "definite" forms of NEC.[37]

We were surprised to see many similarities between patients with suspected and medical NEC. There was substantial overlap in the patient characteristics of these two subgroups, as well as similar patterns of disease onset, early care requirements, survival, biomarkers, and outcomes of disease. These similarities could indicate that suspected and medical NEC exist on a continuum of disease (i.e., infectious inflammation that does not lead to intestinal perforation) or they could reflect patients' risks for and gastrointestinal complications of other life-threatening systemic diseases (e.g., bacterial sepsis). Without better diagnostic and prognostic tools for NEC,[52] it is unlikely that we will resolve this question with certainty.

Limitations

We acknowledge that our analyses are limited by the diagnostic imprecision inherent to NEC.[53] In our classification system, we applied concepts and methods previously described for the study of NEC using CDW data[3,4] and critically assessed prior studies of NEC outcomes that leveraged these data.[14,24,33,54] We also could not resolve exactly which surgical procedures were required for a given patient, and recognize that initial placement of a peritoneal drain versus laparotomy is associated with different clinical outcomes among extremely low birth weight neonates.[42] Lastly, while there is a considerable interest in the role of probiotics might play in the prevention of NEC, we did not analyze probiotic exposure among patients in our cohort. Prior study of CDW patients revealed significant variability in probiotic organisms and no information about dosing,[55] and given recent

guidance from the American Academy of Pediatrics, our decision seemed prudent.[56]

Conclusion

We present the natural history of NEC in large, contemporary cohort of VLBW patients who received care from neonatologists who practice in more than 300 NICUs in the United States. Among these patients, the incidence and initial antibiotic treatment were stable over a period of 5 years. Studying these patients allowed us to characterize in detail the stage-specific patterns of onset, progression, and survival of NEC, including novel information about suspected NEC. Perhaps most importantly, we identified the extent to which all stages of NEC impact the in-hospital outcomes of these patients, as they represent key opportunities for disease prevention in future clinical studies.

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Conflict of Interest

W.A.C. reports serving on a scientific advisory board of Plakous Therapeutics (Winston-Salem, NC). The other authors have no conflicts of interest relevant to this article to declare.

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