Advanced Necrotizing Enterocolitis Part 1: Mortality

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Abstract

Aim of the Study The aim of this study was to investigate the factors associated with mortality in infants referred for the surgical treatment of advanced necrotizing enterocolitis (NEC).

Methods Retrospective review of all infants with confirmed (Bell stage II or III) NEC treated in our unit during the past 8 years (January 2002 to December 2010). Data for survivors and nonsurvivors were compared using Mann-Whitney test and Fisher's exact test and are reported as median (range).

Results Of the 205 infants with NEC, 35 (17%) were medically managed; 170 (83%) had surgery; 66 (32%) infants died; all had received surgery. Survivors and nonsurvivors were comparable for gestational age, birth weight, and gender distribution. Overall mortality was 32%, the highest mortality was in infants with pan-intestinal disease (86%) but remained significant in those with less severe disease (multifocal 39%; focal disease 21%). The commonest cause of mortality was multiple organ dysfunction syndrome and nearly half of the nonsurvivors had care withdrawn.

Conclusion Despite improvement in neonatal care, overall mortality (32%) for advanced NEC has not changed in 10 years. Mortality is significant even with minimal bowel involvement.

Keywords

- necrotizing enterocolitis
- mortality
- multiple organ dysfunction syndrome

Introduction

Necrotizing enterocolitis (NEC) remains a devastating disease affecting newborn infants and is often associated with significant mortality and morbidity, especially in the very preterm and extremely low birth weight (ELBW) infants.[1,2] The mortality rates are high particularly in those infants requiring surgical intervention.[3] At laparotomy, the extent of disease varies from focal disease to multifocal or pan-intestinal disease, affecting varying lengths of bowel.[3,4] Previous reports have shown mortality rates increasing with more advanced and extensive disease.[4] While advances in perinatal care have contributed to an improvement in survival of extremely premature and ELBW infants, the mortality in infants with NEC has remained high despite advances in both medical and surgical treatment.[5,6] The aim of this study was to characterize the factors associated with mortality in infants with NEC referred to our unit.

Materials and Methods

With institutional ethical approval, we reviewed case notes of all infants with confirmed (Bell stage II or III) NEC treated in our unit during the past 8 years (January 2002 to December 2010). NEC was defined by Bell's criteria, as modified by Kliegman and Walsh.[7,8] Data retrieved included demographic, clinical, radiological, and operative details. Using mortality as our main outcome, we compared two groups (survivors and nonsurvivors) for factors predicting mortality. Data were compared using Mann-Whitney test,

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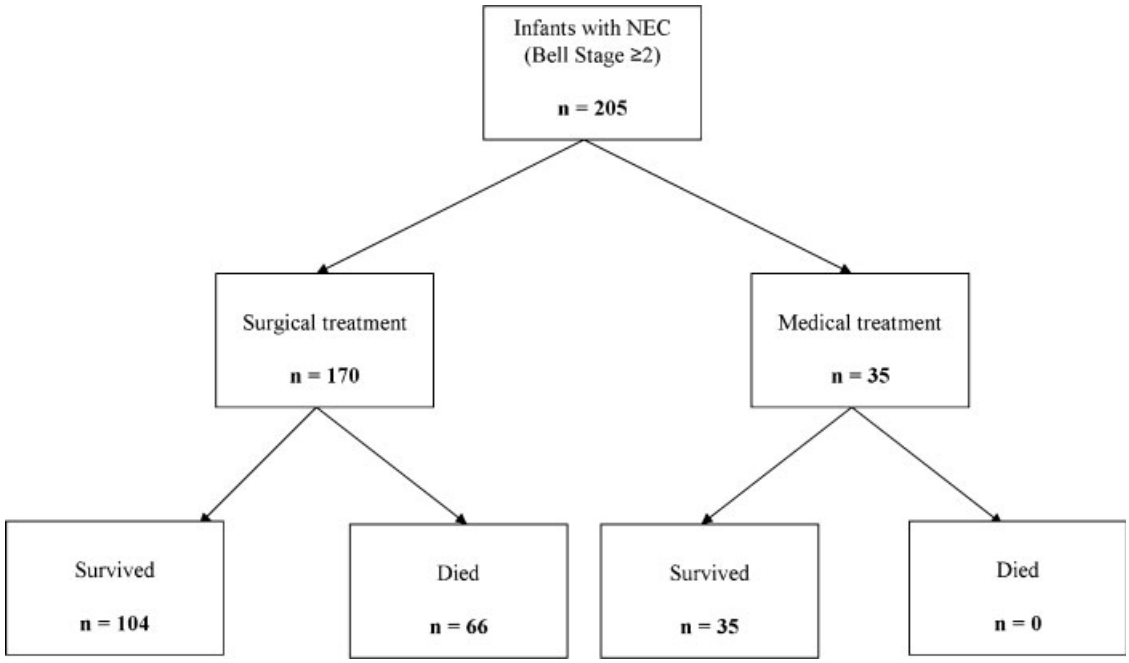

Figure 1 Cohort of NEC infants.

Fisher's exact test, and chi-square test as appropriate. Binary logistic regression analysis was also performed to determine the effect of predictors of mortality. Data reported as median (range), and the level of significance was set at $p < 0.05$.

Results

During the study period (2002 to 2010), 205 infants with confirmed NEC (Bell stage II or III) were admitted to our unit for further surgical evaluation. Of these, 35 (17%) were managed medically and 170 (83%) required operative intervention.

The overall mortality rate was 32%. All deaths ($n = 66$) occurred in infants who had surgery for NEC, giving a mortality following surgery for NEC of 39%. Mortality was significantly higher in infants receiving surgery compared with those receiving medical treatment ($p < 0.0001$, ►**Fig. 1**).

There was no significant difference, using Mann-Whitney test, Fisher's exact test, or binary logistic regression analysis, between survivors and nonsurvivors in terms of birth weight, gestational age, or gender distribution (►**Table 1**, ►**Fig. 2**). Of the 170 infants receiving surgery, there was a significant difference in the extent of intestinal involvement between those who died and those who survived (►**Table 2**). Those who died had a significantly higher incidence of more extensive intestinal involvement ($p < 0.0001$) as indicated by a higher proportion of patients of pan-intestinal involvement (29% in the on-survivors vs. 3% in the survivors) and a lower proportion with focal disease (►**Fig. 3A**). The majority of infants undergoing surgery had a primary laparotomy ($n = 161$; 95%); nine infants (5%) had peritoneal drain (PD) insertion as the first procedure as part of a previously reported randomized controlled trial.[9] All those receiving PD required a subsequent laparotomy for clinical deterioration (►**Table 3**).

Cause of death is summarized in ►**Table 4**. Among nonsurvivors, 32/66 (48%) of the deaths followed a decision to withhold or withdraw intensive care. In the infants who had care withdrawn, most (15 [47%]) had care withdrawn due to multiple organ dysfunction syndrome (MODS) refractory to

Table 1 Characteristics of Infants with NEC: Survivors and Nonsurvivors

	Survivors	Nonsurvivors	*p* Value
	$n = 139$	$n = 66$	
Birth gestational age (wk)	27 (22–42)	27 (23–42)	0.62
Corrected gestational age (wk)	32 (24–137)	32 (23–47)	0.63
Birth weight (kg)	0.92 (0.40–4.72)	0.96 (0.48–3.43)	0.50
Admission weight (kg)	1.28 (0.58–4.40)	1.30 (0.52–3.45)	0.95
Gender, male [*n* (%)]	80 (58)	42 (65)	0.45

Data reported as median (range) or number (percentage); $p < 0.05$.

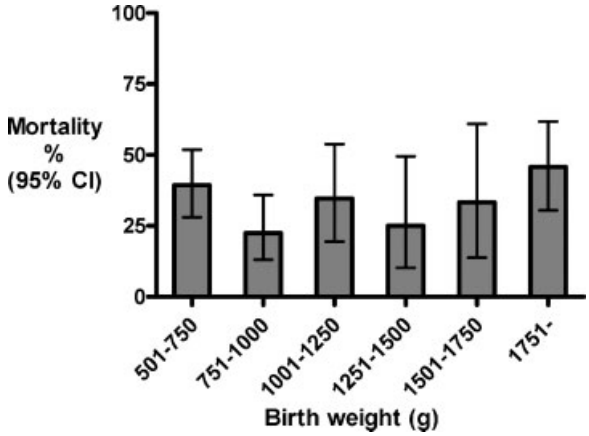

Figure 2 Mortality by birth weight.

maximal medical treatment with presumed poor outcome and 4 (13%) because of NEC totalis and the decision not to perform surgical resection of the entire gastrointestinal tract (►**Table 4**). A total of 34 infants died without care being actively withdrawn, predominantly from MODS or sepsis.

Discussion

Mortality rates among infants treated for NEC remains high, especially among ELBW infants, those requiring surgery and those with multiorgan failure.[1,3] As more extremely premature and low birth weight infants survive with improved perinatal care, the population of infants with risk factors for development of NEC increases. In parallel with these trends, advances in preventive, medical, and surgical treatment of NEC have failed to appreciably reduce the mortality rates in infants with NEC.[10,11]

Fitzgibbons et al, using data from Vermont Oxford Network showed a trend of increasing mortality from NEC with decreasing birth weight categories; the highest mortality (42%) observed in infants weighing 500 to 750 g.[12] In our study patients there was no significant association between birth weight, admission weight, birth gestational age or corrected gestational age, and mortality. This apparent contradiction may be due to the following reasons: (1) exclusion of suspected NEC (Bell stage I) in our study; (2) the inclusion in our study of only infants referred for surgical assessment rather than all infants with NEC; and (3) in our institution, we use the same criteria for surgical treatment in extremely premature infants, whereas other centers may consider ex-

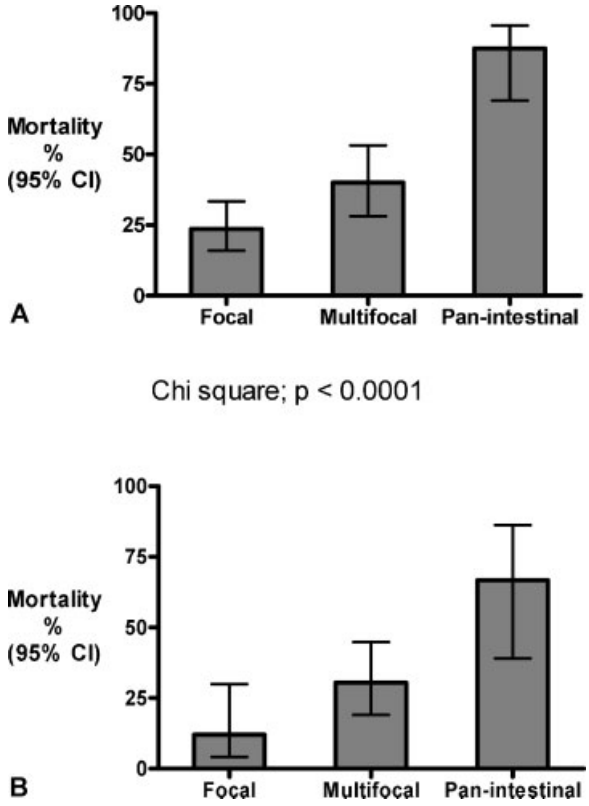

Figure 3 (A) Extent of disease and mortality. (B) Mortality by extent of disease in 1986 to 1996. Data redrawn from Fasoli et al.[4]

treme prematurity as a contraindication for laparotomy. This is reflected in our series in which there is preponderance for surgery in infants with NEC in contrast to other series.

In this study, we have shown that overall mortality in infants with confirmed NEC remains high, and these rates mirror the extent of disease found at laparotomy, with highest rates among infants with pan-intestinal disease.[13] This concurs with our unit's published previous experience where Fasoli et al[4] showed overall mortality rate of 30%, the highest mortality (67%) occurring in the infants with pan-intestinal disease (►**Fig. 3B**). This may be because either (1) there has been no improvement in the treatment of infants with NEC or (2) we are now referred sicker infants with NEC. It is notable that there remains a significant mortality rate (21%) in the infants with less extensive, focal NEC. This may signify that extent of disease alone may not be the only factor affecting mortality.

Table 2 Extent of Disease at Laparotomy

	Survivors	Nonsurvivors	*p* Value
	n = 105	*n* = 65	
Focal, *n* (%)	68 (65)	21 (32)	<0.0001
Multifocal, *n* (%)	34 (32)	22 (34)	
Pan intestinal, *n* (%)	3 (3)	22 (34)	

Data reported as number (percentage); $p < 0.05$.

Table 3 Infants Who Underwent Surgery ($n = 170$)

Procedure	Survivors ($n = 104$)	Nonsurvivors ($n = 66$)
Laparotomy	($n = 99$)	($n = 62$)
Stoma (± bowel resection)	59	31
Anastomosis	42	20
Open and close	1	11
Clip and drop	2	2
Peritoneal drain	($n = 5$)	($n = 4$)
Drain alone	0	0
Drain followed by laparotomy		
Stoma	4	3
Anastomosis	1	0
Open and close	0	1

Table 4 Cause of Death

Reason	*n*
Following withdrawal of care	32
Multiorgan failure	15
Open and close (NEC totalis)	4
Single organ failure	8
Neurological (IVH: $n = 2$, infarction: $n = 1$)	3
Disseminated coagulopathy	1
Others	1
Not following withdrawal of care	34
Multiorgan failure	11
Sepsis	9
Profound bleeding	7
Cardiac arrest	3
Single organ failure	4

IVH, intraventricular hemorrhage.

Nearly half of nonsurvivors had care withdrawn, mainly as a result of MODS. This is a particular group where the decision to withdraw care followed multidisciplinary meeting involving neonatal intensive care team, pediatric surgeon, and parents. In this particular group, no post mortem studies were requested by the coroner, and therefore we could not further substantiate extent of disease progression following withdrawal of care. Similarly, the infants with NEC totalis ($n = 4$) who had care withdrawn based on the fact that surgery was deemed not feasible with survival. These infants had an "open and close" laparotomy with no bowel resection.

Although this study is also limited by its retrospective nature, we have shown that despite the advances in the neonatal and surgical care of infants with NEC over the past decade, the mortality for advanced NEC has not changed in a single tertiary referral center. There is a desperate need to improve survival through preventive remedies such as breast milk promotion, judicious introduction and advancement of enteral feeds, probiotic therapy,[14,15] as well as novel therapeutic interventions such as therapeutic hypothermia[16] and stem cell therapy[17] in vulnerable, at-risk groups.

Conclusion

Despite improvement in neonatal care, overall mortality (32%) for advanced NEC has not changed in the past 10 years. Mortality, while highest in infants with extensive NEC, is significant even with minimal bowel involvement. In those infants with definite NEC, mortality does not appear to be related to low birth weight or prematurity. The commonest cause for mortality due to NEC is MODS. Further attempts at prevention of NEC and treatment of established disease are desperately needed.

Conflict of Interest

None

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