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Treatment of necrotizing enterocolitis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review

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Abstract

Objective: The optimal treatment of necrotizing enterocolitis (NEC) is a common challenge for pediatric surgeons. Although many studies have evaluated prevention and medical therapy for NEC, few guidelines for surgical care exist. The aim of this systematic review is to review and evaluate the currently available evidence for the surgical care of patients with NEC.

Methods: Data were compiled from a search of PubMed, OVID, the Cochrane Library database, and Web of Science from January 1985 until December 2011. Publications were screened, and their references were hand-searched to identify additional studies. Clinicaltrials.gov was also searched to identify ongoing or unpublished trials. The American Pediatric Surgical Association Outcomes and Clinical Trials Committee proposed six questions deemed pertinent to the surgical treatment of NEC.

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Recent Cochrane Reviews examined three of these topics; a literature review was performed to address the additional three specific questions.

Results: The Cochrane Reviews support the use of prophylactic probiotics in preterm infants less than 2500 grams to reduce the incidence of NEC, as well as the use of human breast milk rather than formula when possible. There is no clear evidence to support delayed initiation or slow advancement of feeds. For surgical treatment of NEC with perforation, there is no clear support of peritoneal drainage versus laparotomy. Similarly, there is a lack of evidence comparing enterostomy versus primary anastomosis after resection at laparotomy. There are little data to determine the length of treatment with antibiotics to prevent recurrence of NEC.

Conclusion: Based on available evidence, probiotics are advised to decrease the incidence of NEC, and human milk should be used when possible. The other reviewed questions are clinically relevant, but there is a lack of evidence-based data to support definitive recommendations. These areas of NEC treatment would benefit from future investigation.

Necrotizing enterocolitis (NEC) is a devastating intestinal disease occurring primarily in premature infants. As neonatal respiratory care continues to improve, NEC is poised to become the leading cause of death in the premature population. Practicing pediatric surgeons are confronted daily with controversies in care of infants with NEC, and guidelines for definitive therapy are not always clear. Many studies aimed at prevention and medical therapy for NEC have yielded mixed results, and few standards for surgical care exist. The aim of this study is to review systematically the currently available evidence focusing on surgical care of the patient with NEC.

1. Material and methods

1.1. Questions

In an effort to summarize and categorize current therapies for infants with NEC, the American Pediatric Surgical Association (APSA) Outcomes and Clinical Trials Committee posed several questions which are pertinent to the daily care of infants with NEC. These questions were chosen based on common clinical scenarios.

1. Does the use of prophylactic probiotics reduce the rate of NEC in newborn infants?
2. Does exclusive use of human breast milk rather than formula affect the rate of NEC in newborn infants?
3. Does the rate of feeding affect development of NEC in newborn infants?
4. Does peritoneal drainage versus laparotomy as treatment for perforated NEC affect mortality or long-term sequelae, such as neurodevelopmental outcomes and stricture rates?
5. Does primary anastomosis at laparotomy versus enterostomy as treatment for NEC affect mortality or long-term sequelae, such as neurodevelopmental outcomes and stricture rates?
6. Does length or type of antibiotic treatment affect recurrence rate of NEC?

1.2. Search methods

Data were compiled from a search of PubMed, OVID, the Cochrane Library database, and Web of Science from January 1985 until December 2011. Clinicaltrials.gov was searched for ongoing and unpublished trials.

Studies were limited to human subjects, English language, and children aged 0 to 18 years. Search terms were determined by the questions posed. Randomized clinical trials were utilized when available, and observational studies were evaluated when randomized controlled studies were not available. Smaller case reports and series (fewer than 10 subjects) as well as review papers were excluded. Titles and abstracts were screened, and potentially eligible papers extracted for further assessment. References were hand-searched to identify additional studies.

1.3. Data extraction

Extracted data included sample size, age range, gender distribution, study design, study period and duration of follow up, description of NEC, description of surgical procedures performed, information on postoperative outcomes including length of stay, morbidity and mortality, and any other outcomes measured. Methodological quality of the studies was assessed and the evidence graded based on the Oxford Centre for Evidence-Based Medicine scale (CEBM) [1]. When all included studies were non-randomized, the Methodological Index for Non-Randomized Studies (MINORS) checklist was also used to assess the quality of each study [2]. This validated index involves 12 items: the first 8 specifically designed for non-comparative studies and additional 4 items applied to comparative studies. Items are scored as 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The total best score is 24 for comparative studies and 16 for non-comparative studies.

2. Results

The Cochrane Collaborative addressed the first three of these questions with recent systematic reviews that are summarized in this report. The last three questions were evaluated with the methods described.

2.1. Does the use of prophylactic probiotics reduce the rate of NEC in preterm infants?

A Cochrane review published in 2011 addressed this question [3]. In this review, the authors were specifically interested in evaluating both the safety and efficacy of the use of prophylactic probiotics (before NEC developed), compared to placebo or no treatment. Predetermined primary outcomes were the incidence of severe (Bell Stage≥II) NEC or nosocomial sepsis [4]. There were sixteen eligible trials which included almost 3000 infants. The review specified *a priori* that infants<37 weeks gestation and/or with a birth weight of<2500 grams were to be included [5-18]. The examined trials included enteral administration of any live microbial supplement at any dose for more than seven days compared to placebo or no treatment.

The included studies used variable formulations and duration of treatment of the probiotics. *Lactobacillus, Bifidobacterium, Saccharomyces boulardii*, and a mixture preparation of two or three probiotics were also used. Initiation of probiotics was within the first 24 hours of life, at the time of the first feed, or when feeds were tolerated. They were continued for a minimum of two weeks and as long as until discharge.

Despite variability in the studies, the combined results demonstrated that probiotics significantly reduced the incidence of severe NEC, with a relative risk of 0.35 (95% CI 0.24 to 0.52). In subgroup analysis, infants under 1500 grams treated with prophylactic probiotics had a similar reduced relative risk of 0.34 (95% CI 0.23 to 0.50) for development of severe NEC. In addition, both overall and NEC-specific mortality was significantly lower in the probiotics groups. The probiotics groups had a significant reduction in total hospitalization days and time to reach full enteral feeds compared to controls, although days on total parenteral nutrition did not differ. There were no differences in long term neurodevelopmental outcomes. No systemic infections due to the probiotic organisms were reported. No conclusions regarding probiotic use in ELBW (<1000 grams) infants could be extrapolated from the studies due to limited data.

SUMMARY: Substantial data support routine supplementation of enteral intake with probiotics in premature infants to reduce the incidence of severe NEC (Grade A/B). No formal recommendations regarding the formulation, timing or duration of supplementation could be determined, but at least one probiotic formulation initiated in the first week of life and continued for at least two weeks appears appropriate.

2.2. Does exclusive use of human breast milk rather than formula affect the rate of NEC in newborn infants?

The Cochrane Collaborative addressed this question in two separate reviews, both published in 2008.

The first review detailed the use of formula versus donor breast milk for feeding preterm (<37 weeks gestation) or low birth weight infants (less than 2500 grams) [19]. This study searched for randomized controlled trials and evaluated predetermined primary outcome variables of growth and development, with secondary outcomes of death in the neonatal period, NEC, time to full enteral feeds, feeding intolerance, and incidence of invasive infection. Eight studies fulfilled the criteria, most of which were conducted in the late 1970's and early 1980's [20-27]. The studies included about 1000 infants, most were less than 32 weeks gestation and less than 1800 grams. On meta-analysis, formula feeding was associated with a significantly higher rate of weight gain, increase in length, and increase in head circumference. Formula compared to breast milk feeding was associated with a higher incidence of NEC, with a relative risk of 2.5 (95% CI 1.2 to 5.1), as well as an increased rate of feeding intolerance. Subgroup analyses included term formula versus donor breast milk, preterm formula versus donor breast milk, formula as a sole diet versus donor breast milk as a sole diet, formula milk as a supplement to maternal breast milk versus donor breast milk given as a supplement to maternal breast milk, and formula milk versus nutrient-fortified donor breast milk. Due to the smaller numbers of patients in each group, only a marginal increase in the incidence of NEC with formula feeding was found in any of the subgroup analyses.

The second Cochrane review evaluated formula versus maternal breast milk for preterm (<37 weeks) or low birth weight (<2500 grams) infants [28]. Randomized controlled trials which compared maternal breast milk versus formula feedings for preterm infants were examined. The predefined primary outcome variables included weight gain, growth and development, with secondary outcome variables of mortality and morbidity including NEC, time to full enteral feeds, feeding intolerance, and the occurrence of invasive infections. Six studies identified for evaluation were subsequently excluded because they were either not randomized studies or the infants received both maternal and donor breast milk. The review therefore produced no formal recommendations regarding the use of maternal breast milk versus formula for preterm infants, but referenced the prior Cochrane study to recommend the use of donor human milk if possible.

SUMMARY: Although formula fed preterm and low birth weight infants gain weight, length, and head circumference faster than infants who receive donor breast milk,

they appear to have an increased risk of developing NEC as a result of this intervention (Grade A/B).

2.3. Does the introduction and rate of feeding affect development of NEC in preterm infants?

The Cochrane Collaboration addressed impact of feeding practices on development of NEC with two separate reviews published in 2011 – one addressed when to initiate enteral feeds in very low birth weight (<1500 grams) infants, and the other addressed how quickly to advance enteral feedings in very low birth weight infants once they have been started [29,30].

The first review based the question on two observational studies that suggested that a delay in introduction of enteral feeds for 5 to 7 days after birth might confer a benefit in avoiding NEC [31,32]. They included studies that randomized very low birth weight (<1500 grams) or very preterm (<32 weeks gestation) infants to a delay in initiation of enteral feeds (for more than four days after birth) versus earlier introduction of enteral feeds. The primary outcome variable was the development of any stage of NEC or neonatal mortality, with secondary outcomes of growth and development. Five trials with 600 infants total were identified [33-37]. There was no significant benefit to the delay of enteral feeds in this population, relative risk of NEC 0.89 (95% CI 0.58 to 1.37). Delay in initiation of enteral feeds resulted in a delay in time to full enteral feeds. While the available evidence does not support delay of enteral feeds in very low birth weight infants, there are wide confidence intervals and pooled estimates of effect which could suggest a decrease in NEC incidence of up to 40% with delay of enteral feeds. These findings make the recommendation of delay in enteral feeding initiation controversial.

The second Cochrane review focused on the rate at which feeds are advanced, and evaluated randomized studies in which feeds in very low birth weight (<1500 grams) infants were advanced at a maximum of 24 ml/kg/day (slow advance) or faster. Four randomized controlled trials that included almost 500 patients were identified [38-41]. Meta-analysis of these trials (slow advancement in daily increments of 15–20 ml/kg, fast advancement of 30–35 ml/kg) did not identify an association between quicker advancement of feeds and development of NEC, relative risk 0.91 (95% CI 0.47 to 1.75). Infants who had slow feed advancement took longer to regain their birth weight and reach full enteral feeds.

SUMMARY: While smaller studies have suggested that a delay in initiation of feeds in preterm infants (>4 days after birth) may aid in the avoidance of NEC, pooled estimates do not statistically support delaying enteral feeds in this population (Grade B). Once started, slow progression of feeds is not supported to prevent NEC (Level IV). The timing of initiation of feeds and speed at which they are advanced is unlikely to affect future development of NEC.

2.4. Does peritoneal drainage versus laparotomy as treatment for perforated NEC affect mortality or long-term sequelae, such as neurodevelopmental outcomes and stricture rates?

Historically, exploratory laparotomy with resection of involved bowel and creation of stomas has been the treatment of choice for perforated NEC. In 1977, a report was published in which placement of a peritoneal drain was used as initial treatment for neonates with intestinal perforation due to NEC [42]. This intervention was later suggested by others as a definitive treatment, since a significant number of drained patients required no further operations to regain bowel function [43]. Inherent in comparing treatments for neonatal intestinal perforation is recognizing that two distinct disease processes may lead to this end result – intestinal perforation as a result of NEC and diffuse bowel ischemia, and spontaneous intestinal perforation which affects an isolated segment of intestine, usually in the terminal ileum. Often it is difficult to categorize patients as to the cause of their intestinal perforation, particularly if full abdominal exploration is not carried out. The intent of this review is to include studies of patients with perforated NEC, though this cannot definitively be confirmed in all cases.

We identified one Cochrane review and five studies that dealt with the outcomes of survival and neurodevelopment after drainage or laparotomy for perforated NEC [44-49]. There was one large retrospective study and two randomized trials with mortality as a primary endpoint [45-47], and a single prospective multicenter observational cohort reported over two publications which addressed neurodevelopmental outcomes [48,49].

2.4.1. Mortality

Choo et al. performed a retrospective analysis of 4,657 patients from a combination of the Nationwide Inpatient Sample (NIS) and Kids' Inpatient Database (KID) from 1988 to 2005 [45]. Multiple logistic regression analyses were performed for in-hospital mortality associated with peritoneal drainage, laparotomy (bowel resection) or both procedures for management of NEC. Patients undergoing peritoneal drainage had a 5.7 times higher odds of death compared to patients treated with laparotomy alone ($p<0.05$). Those who received both procedures did not have significantly higher odds of death compared to the laparotomy group. Shorter length of stay (43 days; $p<0.05$) and lower total hospital charges ($173,850; $p<0.05$) was demonstrated in the drainage patients in comparison to patients in the laparotomy group and higher yet in the combined group (not statistically significant compared to laparotomy alone).

A Cochrane review was published in 2011 that addressed peritoneal drainage versus laparotomy as the intervention for perforated NEC or spontaneous intestinal perforation [44]. This review included the only two prospective, randomized trials that exist and we will outline in detail [46,47].

In 2006, Moss and colleagues reported the results of a multi-institutional prospective randomized trial that evaluated infants with perforated NEC weighing less than 1500 grams treated with either primary peritoneal drainage or primary laparotomy [46]. Patients were included when there was a clinical suspicion of bowel perforation as determined by the attending neonatologist and pediatric surgeon. Peritoneal drainage was intended to be definitive management, and in the peritoneal drainage groups subsequent laparotomy was allowed but not encouraged. With an expected reduction in mortality from 50% to 25% for peritoneal drainage compared with laparotomy for a power of 0.82, the sample size calculated was 130 patients. Patients were stratified by birth weight (<1000 grams vs. 1000 to 1499 grams), and randomized.

This study randomized 117 infants, all of which had complete follow up through the 90 day study period. The study closed when funding ended. There was no difference in survival at 90 days with a 34.5% mortality for peritoneal drainage and 35.5% mortality for laparotomy (p=0.92). Secondary outcomes of dependence on total parenteral nutrition at 90 days and length of hospital stay for 90 day survivors also did not differ between the two groups. Patients were analyzed by intent to treat, but 21 of the drainage group ultimately underwent either early (n=5) or delayed (n=16) laparotomy. The initial type of surgical intervention for perforated NEC did not influence the short-term outcomes, and neurodevelopmental outcomes were not evaluated in this trial.

More recently, Rees and colleagues reported a prospective, randomized trial in infants with perforated NEC weighing less than 1000 grams [47]. Performed in 8 countries outside of North America, this trial differed in three respects from the Moss trial: 1) only infants weighing <1000 grams were included, whereas the Moss study included up to 1500 grams; 2) patients were required to have documented pneumoperitoneum, whereas the Moss study allowed entry into the trial for clinical suspicion of bowel perforation as determined by the attending neonatologist and pediatric surgeon; and 3) laparotomy was allowed as a "rescue" therapy as soon as 12 hours after peritoneal drainage, whereas the Moss study advocated peritoneal drainage as a definitive procedure.

The primary outcome measure was survival at 1 and 6 months, and secondary outcome measures were length of stay, ventilator dependence, and need for parenteral nutrition at 1 and 6 months. The sample size calculation of 208 patients was based on a 20% difference in survival with 0.90 power. Sixty-nine patients were randomized, and enrollment ended due to slow accrual. Of the 69 infants randomized, there was no significant difference in the 1 and 6 month survival of the peritoneal drainage versus laparotomy groups (1 month 65.7% vs. 75.8% respectively, p=0.4; 6 month 51.4% vs. 63.6% respectively, p=0.3). There were also no statistically significant differences in secondary outcomes. However, 74% of patients in the drainage group underwent "salvage" laparotomy due to failure of clinical stabilization an average of 2.5 days after drainage, compared to 9% early crossover in the Moss trial. As a result of this, Rees and colleagues do not recommend treatment with peritoneal drainage for NEC, and only recommend its use as a temporizing measure if absolutely necessary.

SUMMARY: Although two well-designed (but underpowered) prospective, randomized trials have attempted to answer the question of whether primary peritoneal drainage or laparotomy is the optimal intervention for perforated NEC with regard to affecting short-term outcomes, neither trial showed a statistically significant difference in survival between the two treatments (Grade B). In a large retrospective review of patients with NEC, mortality was higher in patients who underwent peritoneal drainage than those who had bowel resection and enterostomy and those who underwent both procedures. However, risk stratification using prematurity, birth weight, and number of concurrent diagnoses yielded equivocal results. Therefore, a definitive recommendation for treatment intervention based on expected survival cannot be made.

2.4.2. Neurodevelopmental outcomes

Neither of the previously described randomized controlled trials evaluated outcomes beyond the 6 month time point. However, there is one ongoing study that compares laparotomy to peritoneal drainage for operative NEC with a primary endpoint of death or neurodevelopmental impairment from 18–22 months corrected age [50]. Background data for this study comes from two publications from the NICHD Neonatal Research Network [48,49]. These two papers evaluated a single group of infants identified prospectively through a cohort study at 16 neonatal intensive care units associated with the Neonatal Research network. Patients included infants <1000 grams who were thought by the pediatric surgeon and neonatologist to require surgical intervention. The type of surgical procedure was not randomized. Of the 156 infants enrolled, 76 (49%) had an initial laparotomy and 80 (51%) had initial peritoneal drainage. Again, there was no significant survival difference, 43% with laparotomy and 54% with drainage (p=0.2). In the first paper, intestinal stricture was the most common postoperative complication, but occurred in about 10% of both the laparotomy and peritoneal drainage groups [48]. Less common and also not different between the two groups, were the incidence of intraabdominal abscess and wound dehiscence.

In the second paper from this non-randomized cohort of patients, there is a suggestion that patients treated with initial laparotomy had improved long-term neurodevelopmental outcomes compared to those in the peritoneal drain group, with 38% of survivors of initial laparotomy suffering neurodevelopmental impairment while 63% of patients treated with initial peritoneal drainage were similarly affected [48]. When death or neurodevelopmental impairment were combined as a non-favorable outcome, the data indicated a possible advantage of laparotomy over peritoneal

drainage, with a risk-adjusted odds ratio of 0.56(95%CI 0.19–1.69) although the confidence interval is wide and does include 1.0 and is therefore not statistically significant. The authors acknowledged that the infants receiving peritoneal drainage were a higher risk group and adjusting for these differences is difficult.

SUMMARY: A very limited number of studies have evaluated long-term surgical complications and neurodevelopmental outcomes after laparotomy or peritoneal drain placement for NEC. Thus, no formal recommendations for treatment can be made based on the currently available data (Level IV).

2.5. Does primary anastomosis at laparotomy vs. enterostomy as treatment for NEC affect mortality or long-term sequelae, such as neurodevelopmental outcomes and stricture rates?

2.5.1. Studies

The traditional approach at laparotomy for NEC has been resection of necrotic or perforated bowel and creation of an enterostomy with or without mucous fistula. Risks of anastomotic complications such as leak or stricture have been considered high when performing a primary anastomosis in the setting of infection and perforation. However, starting in the 1970's and 1980's some surgeons empirically treated both localized and diffuse NEC with resection and primary anastomosis instead of enterostomy [51,52]. Ten studies that addressed the above question were included in this review (Table 1) [53-62].

No randomized clinical trials were identified. All the studies were retrospective case series or cohort studies (Level IV) [1].

Comparison using the MINORS checklist showed considerable variation in the quality of the reviewed studies, with scores ranging from 8 to 16 with comparative items, and 5 to 11 if only non-comparative items were scored. Only 2 of the 10 studies had comparison of enterostomy and primary anastomosis for NEC as a stated aim [53,56]. No study had a clearly defined comparison group or ensured baseline similarities of groups. Although most studied contemporary groups, one study included historical controls. Five studies did not perform any statistical analyses, and the other studies performed uni- and bivariate analyses with reported *p* values. No study included multivariate analysis, or reported confidence intervals or relative risks.

2.5.2. Study outcomes

Table 1 shows the studies included in this systematic review of the current evidence base for whether enterostomy or primary anastomosis is more effective at laparotomy for NEC in infants.

Ta et al. assessed clinical and motor skill in survivors aged 6 to 13 years who had undergone previous operation for NEC [53]. Choice of primary anastomosis (n=5) or enterostomy (n=14) was based on the surgeon's assessment. Patients in the enterostomy group scored lower on total and verbal intelligence scales but the difference was clinically small and statistically borderline. Eltayeb et al. prospectively followed 23 surgical patients stratified into 2 categories based on disease severity and concluded primary anastomosis was procedure of choice [54]. No statistical analysis was performed and selection bias likely existed, as all 12 primary anastomosis cases were from the moderate disease group and 8 of 11 enterostomy cases were from the advanced disease group.

Hall et al. reviewed 26 infants under 1000 grams who had laparotomy for NEC [55]. Their procedure of choice was resection and primary anastomosis if clinical condition of the infant permitted (12 patients) or enterostomy if the infant was too unstable or had a complex perioperative course (14 patients); therefore, selection bias could not be excluded. No statistical analysis was performed. However, 83% in the anastomosis group had advanced disease compared with 57% in the enterostomy group, indicating likely important differences in the treatment groups. They stated the two surgical procedures were comparable with respect to stay in the intensive care unit and postoperative dependence on parenteral nutrition, and argue their data on mortality and morbidity may be used as evidence to suggest benefit of primary anastomosis. Hofman et al. argue that primary anastomosis is superior to enterostomy after resection for acute NEC [56]. They found no difference in mortality or complication rate in their review, but they included only 63 patients total. Hospital stay was longer for enterostomy patients although time to full feeds was not different. Discharge of patients to other hospitals was not recorded, and enterostomy patients typically remained hospitalized until after enterostomy closure.

Fasoli et al. reviewed different surgical treatments according to extent of disease [57]. They found no difference between primary anastomosis and enterostomy for NEC isolated to a single loop in a small number of patients. Bivariate analysis showed higher mortality for the enterostomy group in multifocal disease, but the authors acknowledged that selection bias could not be excluded. Ade-Ajayi et al. concluded that primary anastomosis is appropriate, safe and effective treatment for most infants [58]. Apart from their study being subject to selection bias, they did not include statistical analysis, and the numbers were small. Griffiths et al. also promoted primary anastomosis, but again their study had the aforementioned limitations [59]. Of 143 laparotomy patients, Cooper et al. "carefully selected" 27 patients for primary anastomosis [60]. Their observed higher mortality in the primary anastomosis group did not reach statistical significance. Sparnon et al. compared a small series of resection and primary anastomosis with historical enterostomy patients [61]. The authors concluded that primary anastomosis has definite short- and long-term advantages without adding to mortality and morbidity. Pokorny et al. acknowledged their bias towards primary anastomosis based on extent of disease and the patient's condition [62].

Table 1 Studies to evaluate whether enterostomy or primary anastomosis is preferred at laparotomy for NEC in infants.

Study [Reference]	Design	Anastomosis				Enterostomy				MINORS
		n	Gestational age (weeks)	Mortalityn (%)	Other outcome	n	Gestational age (weeks)	Mortalityn (%)	Other outcome	
Ta 2011 [52]	Case series	5	29 * (n/a)	n/a [a]	VIQ 101 +/− 15	14	31 * (n/a)	n/a	VIQ 85 +/− 12 [b]	16
Eltayeb 2010 [53]	Case series	12	n/a	2 (17)	2 complications	11	n/a	9 (82)	4 complications	15
Hall 2005 [54]	Case series	12	25 [#] (23–28)	4 (33)	1 complication	14	25 [#] (23–28)	8 (57)	8 complications	13
Hofman 2004 [55]	Case control	34	30 (3) [*]	6 (18)	12 complications	29	32 [*] (4) [c]	9 (31)	7 complications	9
Fasoli 1999 [56]	Case series [d]	18	30 [#] (25–40)	2 (11)	5 complications	7	31 [#] (26–40)	1 (14)	2 complications	15
Fasoli, cont. [56]	Case series [e]	26	31 [#] (26–40)	4 (15)	8 complications	20	30 [#] (24–40)	10 (50) [f]	9 complications	-
Ade-Ajayi 1996 [57]	Case series	18	31 * (25–39)	2 (11)	-	8	28 * (25–31)	5 (63)	-	12
Griffiths 1989 [58]	Case series	29	32 * (25–40)	7 (24)	4 complications	13	32 * (25–40)	8 (62)	3 complications	14
Cooper 1988 [59]	Case series	27	n/a	14 (52)	-	116	n/a	33 (28) [g]	-	11
Sparnon 1987 [60]	Case control	10	35 * (n/a)	3 (30)	3 complications	7	36 * (n/a)	3 (43)	3 complications	8
Pokorny 1986 [61]	Case series	28	n/a	3 (11)	-	24	n/a	9 (38)	-	11

MINORS: Methodological Index for Non-Randomized Studies.
n/a, not available.
* Mean.
[#] Median (SD or range).
[a] Overall mortality 34% for complete NEC cohort (medically and surgically treated).
[b] VIQ, verbal intelligence quotient; $p=0.04$ versus anastomosis, Student's t-test.
[c] $p<0.01$ versus anastomosis, Student's t-test. Birth weight and age at operation also different between the two groups.
[d] Isolated NEC – limited to single segment.
[e] Multifocal NEC – included two or more intestinal segments.
[f] $p=0.03$ versus anastomosis, chi-square test.
[g] $p=0.06$ versus anastomosis, chi-square test.

Prospective multicenter trials are ongoing to establish whether primary anastomosis or enterostomy is superior in patients who need surgical intervention for NEC.

SUMMARY: There is lack of comparative evidence to support primary anastomosis over enterostomy after intestinal resection during laparotomy for acute NEC in infants. Currently, only Level IV, Grade D data exist.

2.6. Does length or type of antibiotic treatment affect recurrence rate of NEC?

2.6.1. Studies evaluated

Recurrence of NEC after medical or surgical management of a first episode occurs in 4% to 6% of cases [63,64]. Historical studies have demonstrated that different antibiotic regimens can decrease the variety and quantity of gram negative and anaerobic organisms in the flora of the neonatal intestine, but the clinical consequences of these changes are unclear [4,65].Three articles were identified that (1) addressed factors which contributed to NEC recurrence, and (2) compared the clinical outcomes of parenteral antibiotic regimens used in the treatment of NEC (Table 2) [63,66,67]. These included one randomized clinical trial that did not directly address the issue of recurrence but did compare outcomes of different parenteral antibiotic regimens. The two remaining studies were a non-concurrent cohort study and a retrospective case series (Levels II and IV, respectively). The cohort study examined recurrence within the context of complications occurring after treatment of NEC; the case series did not specifically examine the role of antibiotics. No study had a blind evaluation of study endpoints. The two non-randomized studies did not calculate sample size.

The Surgical Infection Society and the Infectious Disease Society of America recommend ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem for medical management of NEC (Level II, Grade B). They recommended the use of vancomycin instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection [68]. Current World Health Organization (WHO) recommendations use ampicillin or penicillin, gentamicin, and metronidazole [69]. In their treatises, these organizations did not mention NEC recurrence rate as an outcome for their recommendations.

2.6.2. Study outcomes

Only Scheifele et al. specifically examined the effect of antibiotic choice on recurrence of NEC [66]. This cohort study evaluated the difference in complication rates between two different antibiotic regimens used to treat NEC diagnosed by clinical signs combined with pneumatosis or pneumoperitoneum. Ampicillin and gentamicin were used in combination during 1982 and 1983; cefotaxime and vancomycin were used during 1984 and 1985. The recurrence rate was 5 of 46 patients (10.9%) in the ampicillin/gentamicin group, and 0 of 44 patients in the cefotaxime/vancomycin group, with most recurrences in the first group occurring among patients less than 2200 grams (4 of 5 recurrences) However, the difference in recurrence was not statistically significant. The non-contemporary nature of the comparison groups may have affected study results as all recurrences occurred in the earlier time period.

The study by Stringer et al. was a retrospective case review addressing recurrence but did not examine the role of antibiotics [63]. This study included 10 premature infants and 6 full term infants, including 4 with major congenital anomalies, mostly heart disease, who experienced recurrent episodes of NEC out of a cohort of 200 infants with NEC from 1981–1991 at a referral center. Twelve of the 16 patients had undergone surgery before developing recurrence (9 for initial episode of NEC, 3 for other conditions). The

Table 2 Studies evaluating the length and type of antibiotic treatment regarding recurrence of NEC.

Study [Reference]	Design	Comparison	n	Group 1		n	Group 2		MINORS
				GA/BW	Recurrence		GA/BW	Recurrence	
Scheifele 1987 [65]	Cohort (non-concurrent)	Ampicillin and gentamicin vs. cefotaxime and vancomycin	46 8 38	1828 g * >2200 g <2200 g	5/46 1/8 4/38 **	44 14 30	1980 g * >2200 g <2200 g	0/44 0/14 0/30 **	10/14
Stringer 1993 [62]	Case Review		16	32 wk † / 1260 g ††	16/200				6
Faix 1988 [66]	Randomized Controlled Trial	Standard+ clindamycin vs. standard	20	29.2 wk±2.7 § / 1290 g±560 §	n/a	22	29.6 wk±3.7 § / 1310 g±590 §	n/a	n/a

GA, gestational age; BW, birth weight.
* mean.
** p=0.07.
† median (range 27–40 weeks).
†† median (range 790–3230 grams).
§ mean±SD.

authors did not find an association between recurrent NEC and feeding patterns, or method of management of the original episode (medical or surgical), however the study was retrospective and sample size small. This study defined NEC and its recurrence by clinical, radiographic, or operative evidence consistent with Bell stage II or III disease.

The last study by Faix et al. addressed antibiotic choice, but not NEC recurrence [67]. In a randomized, controlled trial of 42 patients, 20 received parenteral clindamycin in addition to a standard antibiotic regimen (ampicillin and gentamicin). The study aim was to determine if the addition of clindamycin, an anaerobic agent, would reduce the rate of NEC progression to gangrene and perforation. Treatments were otherwise standardized between groups. NEC was defined by pre-determined clinical signs and radiographic evidence of pneumatosis or portal venous gas. The study found that the group receiving clindamycin had a much higher stricture rate than the control group (6/15 vs. 1/18, $p = 0.022$). The study was terminated early due to this finding and the low perforation rate in the overall cohort. While this study demonstrated that antibiotic choice can affect outcomes, it did not address the issue of recurrent NEC.

SUMMARY: There is a lack of evidence upon which to base recommendations for antibiotic protocols that may decrease NEC recurrence. The only study that directly addresses the interaction between antibiotics and recurrence is underpowered to draw statistically or clinically significant conclusions.

3. Summary of findings

In conclusion, definitive studies to aid the pediatric surgeon with care of infants with NEC are lacking (Appendix). Several studies do support probiotics as being effective in preventing NEC, and the Cochrane Collaboration recommends routine use in practice, though the precise formulation and timing is not determined. Human milk generally should be fed to preterm infants when available, as there is an increased risk of NEC when formula is used. Feeds can be initiated early in life, which is particularly important in avoiding complications of parenteral nutrition. Unfortunately, due to small patient numbers in randomized clinical trials, the definitive association of the type of surgical procedure with long term outcomes is not yet determined. Correlation of optimal antibiotic intervention with survival and morbidity outcomes cannot be determined at this time. These findings speak to the strong need for further work in this devastating disease.

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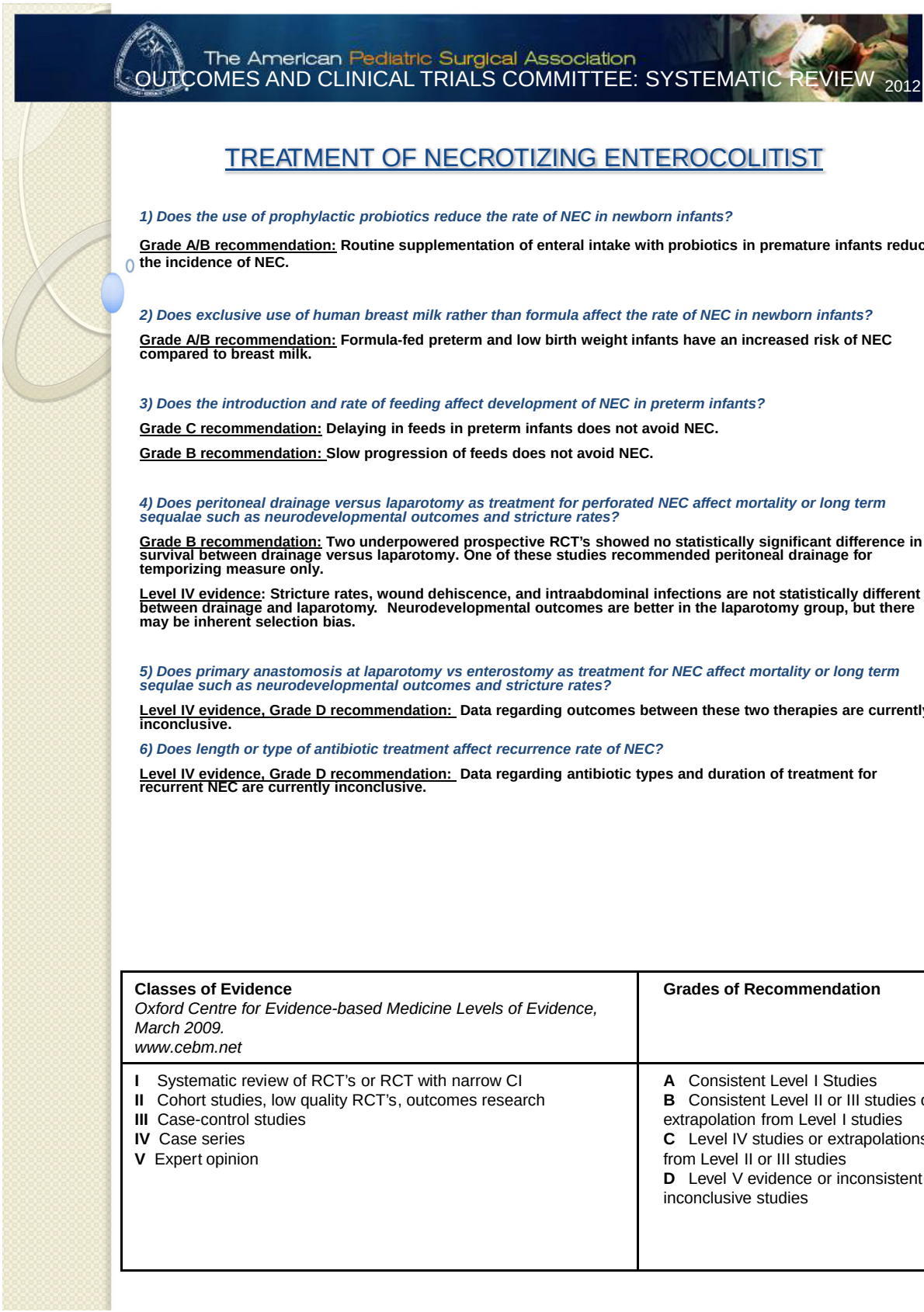
Appendix



Classes of Evidence *Oxford Centre for Evidence-based Medicine Levels of Evidence, March 2009.* *www.cebm.net*	**Grades of Recommendation**
I Systematic review of RCT's or RCT with narrow CI **II** Cohort studies, low quality RCT's, outcomes research **III** Case-control studies **IV** Case series **V** Expert opinion	**A** Consistent Level I Studies **B** Consistent Level II or III studies or extrapolation from Level I studies **C** Level IV studies or extrapolations from Level II or III studies **D** Level V evidence or inconsistent or inconclusive studies

Summary of systematic review of treatment of NEC.