Necrotizing Enterocolitis

Craig Sitzman, MD, FAAP

1

Disclosures

- No relevant financial disclosures
- Will discuss off label use of products

2

Agenda

- Introduction and basic pathophysiology
- Diagnosis and management
- Prevention
- NEC in the News

3

What's New in the NICU

THE WALL STREET JOURNAL.

Abbott Ordered to Pay $495 Million in Baby-Formula Verdict

Jury says Similac maker failed to warn of risk; Abbott says it disagrees with verdict

FDA NEWS RELEASE

FDA Raises Concerns About Probiotic Products Sold for Use in Hospitalized Preterm Infants

Warning Letters Issued to Two Companies for Illegally Selling Probiotic Products to Treat Diseases in Preterm Infants

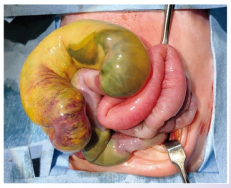
Here's what families need to know after a landmark $60 million verdict in baby-formula suit

Latest verdict against Reckitt offers hope for families whose newborns developed serious intestinal disease after consuming formula, law professor says

4

Introduction

- Most common GI emergency in newborn
- Ischemic necrosis of intestinal mucosa
  - Severe inflammation
  - Enteric organism invasion
- Substantial long-term morbidity
- Potential for high mortality



From Kim W, Seo J. Necrotizing Enterocolitis. New England Journal of Medicine 2022; 387:2418. Copyright © 2022 Massachusetts Medical Society.

5

Epidemiology

- Proven or severe NEC – 1-3 per 1000 live births
- 90% of cases → VLBW infants born at <32 weeks gestation
- Mortality – incidence decreases with increasing GA and BW

Table 3 Rate of disease and mortality from NEC by birth weight category (n = 71,808)

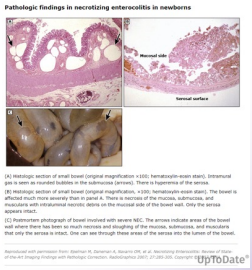
Birth weight category	Birth weight (g)	NEC n	Risk of NEC (%)	Mortality (%)	Adjusted OR (95% CI)
1	501-750				1.6 (1.4-1.8)
2	751-1000				3.6 (3.1-4.2)
3	1001-1250				7.5 (6.2-9.1)
4	1251-1500				9.9 (7.3-13.4)

OR indicates odds ratio; CI, confidence interval. Necrotizing enterocolitis risk ($P < .001$) and mortality ($P < .001$) decreased with higher birth weight category. Necrotizing enterocolitis was associated with a significant odds ratio for death for each birth weight category ($P < .001$). Adjusted odds ratio for NEC mortality increased with higher birth weight category ($P < .001$).

6

Pathology

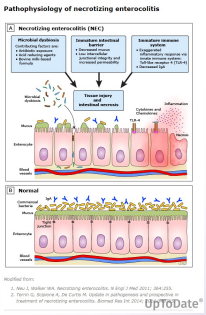
- Severe intestinal inflammation
  - Terminal ileum and colon
- Subserosal gas
- Gangrenous necrosis
- Bowel wall thickening
- Histology
  - Mucosal edema, hemorrhage, necrosis



7

Pathogenesis

- Multifactorial
  - Immaturity
  - Triggers
  - Dysbiosis
  - Exaggerated inflammatory response



8

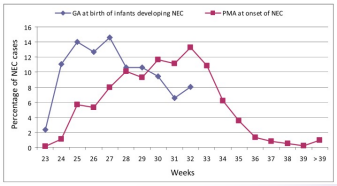
Presentation

- Preterm infants
  - Majority healthy and feeding well prior
  - Most frequent sign – sudden change in feeding tolerance
    - Abdominal wall erythema, apnea, lethargy, temperature instability
    - Gastric residuals – routine measurement – no evidence
      - Single-center study of 141 infants, 74 were randomized to undergo gastric residual checks while the other half did not have residuals checked.
        - No residual group
          - Achieve faster feeding rates
          - Consumed more feedings at weeks 5 and 6
          - Higher mean weights
          - Discharged earlier than the residual check group
        - No differences in risk for NEC, late-onset sepsis, or death

9

Presentation

- Timing
  - BW > 1000 g with NEC – mean 7 days
  - BW < 1000 g with NEC – mean 32 days



10

Laboratory findings

- CBC – nonspecific WBC alterations
- Coagulation studies – DIC frequent finding
- Serum chemistries – hyponatremia, hyperglycemia, metabolic acidosis
- CRP – nonspecific
- Ongoing research – intestinal fatty acid binding protein, stool NEC biomarker, microRNAs, cord blood biomarkers

11

Laboratory findings

Table 1 Clinical Characteristics of Study Patients

	Group 1 (Platelet <100,000/mm³), $n = 47$	Group 2 (Platelet ≥ 100,000/mm³), $n = 44$	p-Value
Gestational age (weeks)	28.0 (±4.1)	30.0 (±4.2)	0.02
Birth weight (g)	1165 (±749)	1454 (±769)	0.07
Male (%)	29 (61.7)	24 (54.5)	0.49
Breast milk fed (%)	14 (29.8)	16 (36.4)	0.5
Received postnatal steroids (%)	20 (42.5)	9 (20.4)	0.02
Received indomethacin (%)	17 (37.0)	10 (22.7)	0.14
Umbilical line placement (%)	32 (71.0)	29 (65.9)	0.6
Blood culture positive (%)	20 (42.5)	10 (22.7)	0.05

Table 2 Adjusted Odds Ratios for Clinical Outcomes Calculated for Those Patients in Group 1 vs Group 2

Clinical outcome	Group 1, $n = 47$	Group 2, $n = 44$	Adjusted OR*	p-Value	95% CI
Laparotomy performed (%)	38 (80.8%)	16 (36.4%)	16.33	<0.001	3.75–71.02
Died (%)	25 (48.9%)	6 (13.6%)	6.39	0.002	1.97–20.76
Short bowel/cholestasis (%)	27 (57.4%)	9 (20.4%)	5.47	0.006	1.64–18.29

*Variables adjusted for include birth weight, gestational age, gender, use of postnatal steroids, use of postnatal indomethacin, umbilical arterial line placement, and the type of feedings received (formula vs breast milk).

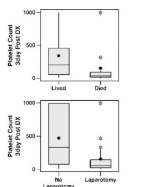


Figure 1. Box plot demonstrating the mean and median platelet counts of infants with NEC, according to outcome. Boxes indicate 25 and 75% interquartile ranges. Horizontal lines indicate median platelet counts. Dots represent the mean platelet count. Platelet count units are in $\times 10^3$/mm³.

12

Radiologic Evaluation

- Pneumatosis intestinalis on abdominal imaging is highly suggestive of NEC

Table 2 Probability analysis of radiological criteria as predictors of necrotising enterocolitis or perforation as stratified by birth weight[10]

Radiological finding	Group	Sensitivity (%)	Specificity (%)	Positive predicative value (%)	Negative predictive value (%)	Prevalence (%)
Pneumatosis	All	44 (n=27)	100 (n=19)	100	36	34
	EX LBW	35 (n=12)	100 (n=15)	100	41	24
	LBW	56 (n=15)	100 (n=4)	100	25	48
Portal venous gas	All	13 (n=8)	100 (n=19)	100	26	10
	EX LBW	12 (n=4)	100 (n=15)	100	50	8.1
	LBW	15 (n=4)	100 (n=4)	100	15	13
Pneumoperitoneum	All	52 (n=23)	92 (n=33)	88	61	29
	EX LBW	47 (n=15)	100 (n=17)	100	50	31
	LBW	67 (n=8)	84 (n=16)	73	80	26
Gasless abdomen	All	32 (n=14)	92 (n=33)	82	52	18
	EX LBW	41 (n=13)	82 (n=14)	81	42	27
	LBW	8.3 (n=1)	100 (n=19)	100	63	28

EX LBW, extremely low birth weight; LBW, low birth weight.

13

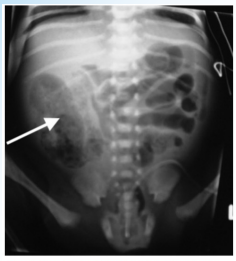


Figure 1 Soap bubble appearance (arrow) persisting at 48 hours into treatment for necrotising enterocolitis. Found to be necrotic ascending colon at laparotomy.

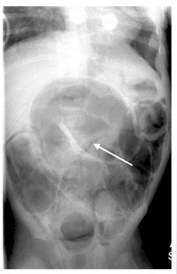


Figure 2 Widespread pneumatosis seen as crescents (arrow).

14

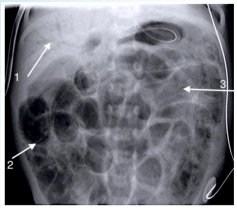


Figure 3 Arrow 1 shows the branching tree of the portal venous gas. Arrow 2 shows the crescents of pneumatosis. Arrow 3 shows widespread soap bubbling.

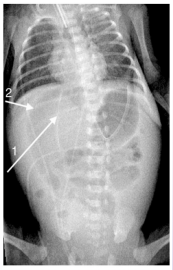


Figure 4 The 'football sign' is demonstrated with gas on either side of the falciform ligament (arrow 1). Arrow 2 shows the lucency over the liver, indicating pneumoperitoneum.

15

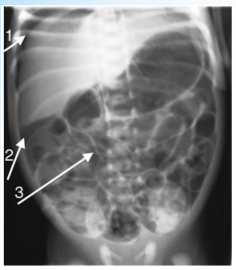


Figure 5 Arrow 1 shows gas under the diaphragm. Arrow 2 shows a 'triangle' under the liver. Arrow 3 points at the 'Rigler sign'.

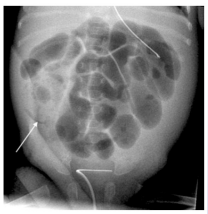
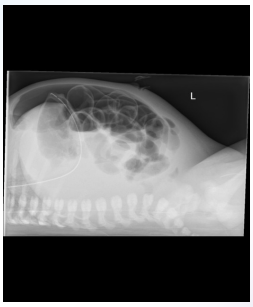


Figure 7 Crescent from pneumatosis.

16



17

Radiologic Evaluation

- Abdominal US
  - Increasingly helpful
  - Operator variability
  - Free air, fluid collections, bowel wall thickness
  - High specificity – low sensitivity

TABLE 3. Pooled Sensitivity and Specificity of Individual BUS Findings for Diagnosis of NEC in Neonates

BUS Findings	Studies	n	Sensitivity (95% CI)	Specificity (95% CI)	Hypothetical Cohort With NEC Prevalence of 49% (n = 100)			
					NEC Correctly Diagnosed (TP)	NEC Correctly Ruled Out (TN)	NEC Missed (FN)	Unnecessary Treatment (FP)
PVG	6	462	0.27 (0.15–0.45)	0.94 (0.89–0.97)	13	48	36	3
PI	5	414	0.48 (0.21–0.76)	0.91 (0.64–0.98)	24	46	25	5
Free air	3	270	0.27 (0.14–0.44)	0.99 (0.93–1.00)	13	50	36	1
Bowel wall thickening	5	414	0.31 (0.16–0.51)	0.67 (0.41–0.85)	15	34	34	17
Bowel wall thinning	4	234	0.22 (0.11–0.38)	0.96 (0.85–0.99)	11	49	38	2
Absent peristalsis	3	291	0.30 (0.15–0.53)	0.95 (0.90–0.98)	15	48	34	3
Simple ascites	5	414	0.45 (0.29–0.61)	0.92 (0.65–0.99)	22	47	27	4
Focal fluid collection	3	183	0.19 (0.04–0.59)	0.98 (0.92–1.00)	9	50	40	1

FN, false negative; FP, false positive; TN, true negative; TP, true positive.

18

Severity

Table 1 Modified Bell's staging criteria (Kliegman and Walsh[7])

Modified Bell's staging	Clinical findings	Radiographic findings	Gastrointestinal findings
Stage I	Apnoea, bradycardia and temperature instability.	Normal gas pattern or mild ileus.	Mild abdominal distension, stool occult blood, gastric residuals.
Stage IIA	Apnoea, bradycardia and temperature instability.	Ileus with dilated bowel loops and focal pneumatosis.	Moderate abdominal distension, haematochezia, absent bowel sounds.
Stage IIB	Metabolic acidosis and thrombocytopaenia.	Widespread pneumatosis, portal venous gas, ascites.	Abdominal tenderness and oedema.
Stage IIIA	Mixed acidosis, coagulopathy, hypotension, oliguria.	Moderate to severely dilated bowel loops, ascites, no free air.	Abdominal wall oedema, erythema and induration.
Stage IIIB	Shock, worsening vital signs and laboratory values.	Pneumoperitoneum.	Bowel perforation.

19

Differential Diagnosis

- Spontaneous intestinal perforation – absence of pneumatosis, timing earlier
- Hirschsprung's, atresia, volvulus, meconium ileus
- Infectious enteritis
- Anal fissures
- Septic ileus
- Cow's milk protein intolerance

20

Medical Management

- Supportive care
  - Bowel rest
  - Gastric decompression
  - TPN
  - Respiratory/CV support
- Antibiotic Therapy
  - 20-30% with bacteremia
  - Treat common pathogens – E. Coli, Klebsiella, Gram neg, Clostridium, Anaerobes
  - Amp/Gent/Metronidazole, Amp/Ceftoax/Metronidazole, Zosyn, Meropenem
- Serial Monitoring

21

Surgical Management

- Collaborative decision with surgery team
  - Perforation
  - Clinically deteriorate despite medical management
  - No single indicator sensitive or specific enough
- Surgical procedures
  - Exploratory laparotomy
    - Resection
  - Primary peritoneal drainage

22

NEST trial

- Prospective randomized trial conducted at 20 U.S. centers
  - Randomized laparotomy vs drainage
- Inclusion criteria were birth weight ≤ 1,000 grams, age ≤8 weeks, a decision to perform surgery for suspected NEC or IP
- Primary outcome was a composite of death or NDI at 18–22 months corrected age.
- No difference noted on primary outcome
- Secondary analysis

23

NEST Trial

Primary and major secondary outcomes by preoperative diagnosis

Outcome	Initial Laparotomy (N = 166) n/N (%)	Initial Drainage (N = 162) n/N (%)	Frequentist Adjusted Relative Risk (95% CI)	Bayesian Adjusted Relative Risk (95% CrI)	Bayesian Adjusted Risk Difference (95% CrI)	Bayesian Posterior Probability (%) of RD <0 with Laparotomy
Death or NDI						
NEC	29/42 (69%)	44/52 (85%)	0.81 (0.64, 1.04)	0.81 (0.63, 1.04)	−14% (−31, 1)	97
IP	66/99 (69%)	64/102 (63%)	1.11 (0.95, 1.31)	1.09 (0.94, 1.33)	6% (−7, 18)	18
Death						
NEC	17/42 (40%)	27/53 (51%)	0.77 (0.52, 1.15)	0.82 (0.53, 1.28)	−11% (−30, 8)	87
IP	24/144 (23%)	21/109 (19%)	1.28 (0.79, 2.06)	1.18 (0.74, 1.87)	5% (−7, 20)	20
Survival with NDI						
NEC	12/42 (29%)	17/52 (33%)	0.73 (0.42, 1.27)	0.76 (0.48, 1.18)	−19% (−45, 7)	92
IP	46/99 (46%)	43/102 (42%)	1.11 (0.85, 1.45)	1.04 (0.83, 1.42)	5% (−10, 20)	26
Death or moderate/severe cerebral palsy						
NEC	22/42 (52%)	38/52 (73%)	0.70 (0.47, 1.05)	0.73 (0.52, 0.96)	−18% (−34, −2)	99
IP	56/100 (56%)	41/105 (39%)	0.95 (0.76, 1.18)	0.93 (0.68, 1.22)	−2% (−16, 12)	62
Death or Bayley cognitive composite score < 85						
NEC	28/42 (67%)	41/50 (82%)	0.81 (0.61, 1.06)	0.80 (0.61, 1.01)	−15% (−32, 2)	96
IP	67/99 (68%)	59/101 (58%)	1.17 (1.01, 1.37)	1.15 (0.94, 1.42)	9% (−4, 22)	8

[1]Denominators in each cell reflect the number of infants with complete data for each outcome reported

24

Complications

- Infectious
  - Sepsis, DIC, CV, metabolic
- Late GI
  - Strictures, intestinal failure, recurrent NEC
- Short bowel syndrome

Table 1. Complications (47%)

Sepsis	23 (9%)
Stricture	23 (9%)
Short gut	22 (8.7%)
Wound infection	15 (5.9%)
Stoma	12 (4.7%)
Bowel obstruction	9 (3.5%)
Renal failure	8 (3.1%)
Disseminated intravascular coagulation	8 (3.1%)
Intraabdominal abscess	6 (2.3%)

25

Outcome

Table V. NEC morbidity

NEC morbidity

Authors	Year	Population	Definition of NEC	Definition of NDD	Number with NDD	n	NDD %
Ganapathy et al[23]	2013	All neonates	ICD-9	At 24-36 mo–definition unclear	26	105	24.8
Hayakawa et al[24]	2015	<1500 g BW	Bell 2a+	18 mo of corrected age: developmental quotient <70, or the presence of neurologic sequelae	11	18	61.1
Fullerton et al[22]	2017	<1000 g BW	Bell 2a+	Any severe disability (including BSID: MDI or PDI <70)	267	866	30.8
Fullerton et al[22,*]	2017	<1000 g BW + surgery	Surgical NEC	Any severe disability (including BSID: MDI or PDI <70)	169	449	37.6
Wadhawan et al[44]	2014	<1000 g BW + Surgery	Surgical NEC	1 or more of: moderate/severe CP, bilateral blindness, bilateral hearing loss needing amplification, MDI or PDI <70.	125	220	56.8

Authors	Year	Population	Definition of NEC	Definition of intestinal failure	Number with intestinal failure	n	intestinal failure rates%
Duro et al[19]	2010	All neonates	Bell 1 -3	Failure to achieve full enteral feeds at 90 d	60	394	15.2
Murthy et al[31]	2014	Surgical NEC	Surgical NEC	>90 d PN	171	753	22.7
Bhatt et al[16]	2017	Surgical NEC (<37/40)	Surgical NEC	Failure to achieve full enteral feeds at 90 d	78	223	35.0

BSID, Bayley Scales of Infant Development; *CP*, cerebral palsy; *MDI*, Mental Developmental Index; *PDI*, Psychomotor Developmental Index.
*Subgroup outcome data reported in study.

26

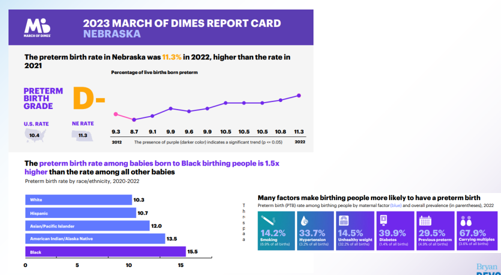
Outcome

Table IV. Meta-analyses of NEC mortality by subgroup

Groups	n	Mortality % (95% CI)	Figure
All neonates with NEC (Bell 1-3)	21 349	15.3 (10.8-20.4)	2
All neonates with NEC (Bell 2a+)	7540	23.5 (18.5-28.8)	2
All neonates with surgical NEC	8303	34.5 (30.1-39.2)	2
Neonates with birthweight <1500 g (Bell 2a+)	19 228	30.1 (24.3-36.2)	3
Neonates with birthweight <1000 g (Bell 2a+)	3089	41.3 (25.0-58.7)	3
Neonates with birthweight <1500 g and surgical NEC	6383	40.5 (37.2-43.8)	3
Neonates with birthweight <1000 g and surgical NEC	3668	50.9 (38.1-63.5)	3

27

Prevention



28

Prevention

- Antenatal corticosteroids
  - BMJ article 2017: 117k infants between 2009-2013 – Pediatrix US NICU - prospective

Table 2 | Mortality and composite outcomes of infants born 23 0/7 to 34 6/7 by gestational age and exposure to antenatal corticosteroids (ANS). Values are numbers (percentages) unless stated otherwise

	23 weeks	24 weeks	25 weeks	26 weeks	27 weeks	28 weeks	29 weeks	30 weeks	31 weeks	32 weeks	33 weeks	34 weeks
Death before discharge												
ANS	439/754 (58.2)	642/1781 (36.0)	432/2161 (20.0)	302/2602 (11.6)	213/3315 (6.4)	141/4237 (3.3)	90/5019 (1.8)	75/6466 (1.2)	45/8556 (0.5)	44/13203 (0.3)	22/16810 (0.1)	9/16928 (0.1)
No ANS	331/447 (74.0)	182/352 (51.7)	114/381 (29.9)	77/444 (17.3)	51/468 (10.9)	46/685 (6.7)	30/813 (3.7)	22/1172 (1.9)	21/1591 (1.3)	18/3070 (0.6)	18/5954 (0.3)	37/20732 (0.2)
AOR (95% CI)	0.47 (0.36 to 0.62)	0.51 (0.40 to 0.64)	0.52 (0.41 to 0.67)	0.55 (0.42 to 0.74)	0.50 (0.36 to 0.71)	0.48 (0.34 to 0.69)	0.44 (0.29 to 0.68)	0.66 (0.41 to 1.12)	0.42 (0.25 to 0.74)	0.61 (0.36 to 1.08)	0.43 (0.23 to 0.80)	0.32 (0.14 to 0.63)
Severe intracranial hemorrhage or death												
ANS	493/754 (65.4)	774/1781 (43.5)	607/2161 (28.1)	449/2602 (17.3)	329/3315 (9.9)	247/4237 (5.8)	162/5019 (3.2)	132/6466 (2.0)	95/8556 (1.1)	75/13203 (0.6)	47/16810 (0.3)	21/16928 (0.1)
No ANS	364/447 (81.4)	214/352 (60.8)	144/381 (37.8)	128/444 (28.8)	90/468 (19.2)	70/685 (10.2)	52/813 (6.4)	46/1172 (3.9)	35/1591 (2.2)	28/3070 (0.9)	27/5954 (0.5)	47/20732 (0.2)
AOR (95% CI)	0.40 (0.29 to 0.53)	0.47 (0.37 to 0.60)	0.57 (0.45 to 0.72)	0.48 (0.38 to 0.60)	0.43 (0.33 to 0.57)	0.55 (0.41 to 0.73)	0.47 (0.34 to 0.66)	0.53 (0.38 to 0.76)	0.53 (0.36 to 0.80)	0.64 (0.42 to 1.01)	0.60 (0.37 to 0.97)	0.56 (0.33 to 0.9[illegible]
Necrotizing enterocolitis ≥stage 2 or death												
ANS	464/754 (61.5)	704/1781 (43.5)	536/2161 (24.8)	427/2602 (16.4)	322/3315 (9.7)	276/4237 (6.5)	225/5019 (4.5)	212/6466 (3.3)	175/8556 (2.0)	176/13203 (1.3)	122/16810 (0.7)	52/16928 (0.3)
No ANS	342/447 (76.5)	198/352 (56.3)	127/381 (33.3)	99/444 (22.3)	76/468 (16.2)	69/685 (10.1)	53/813 (6.5)	57/1172 (4.9)	40/1591 (2.5)	56/3070 (1.8)	45/5954 (0.8)	97/20732 (0.5)
AOR (95% CI)	0.47 (0.36 to 0.62)	0.48 (0.37 to 0.60)	0.58 (0.46 to 0.74)	0.62 (0.49 to 0.81)	0.52 (0.39 to 0.69)	0.62 (0.47 to 0.83)	0.64 (0.47 to 0.89)	0.66 (0.49 to 0.91)	0.85 (0.60 to 1.23)	0.71 (0.53 to 0.98)	0.93 (0.67 to 1.33)	0.67 (0.47 to 0.94)

29

Prevention

- Human milk feedings - In 1997 and again in 2005, the American Academy of Pediatrics published position statements recommending human milk (HM) for premature infants
  - Lower gastric pH, enhances motility, gut microbiota
  - Dose dependent

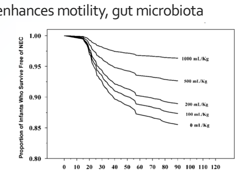


Figure 1.
Adjusted survival curves for necrotizing enterocolitis (NEC) or death by amount of human milk (ml kg^{-1}) over the first 14 days of life. Survival curves adjusted for birth weight, small for gestational age, race, patent ductus arteriosus (PDA), antenatal steroids, duration of mechanical ventilation and Network Center. Survival curves represent predicted survival time free of NEC or death and do not directly correspond to the number of infants.

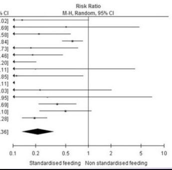
30

Prevention

- Donor Breast Milk
  - Cochrane Meta-analysis 2024 : donor human milk reduces the risk of NEC
    - Risk ratio: 0.53 - high certainty evidence
- Standardized feeding protocol

Study or Subgroup	Standardised feeding Events	Standardised feeding Total	Non standardised feeding Events	Non standardised feeding Total	Weight	Risk Ratio M-H, Random, 95% CI
Brown 1978	1	932	14	1745	4.1%	0.13 [0.02, 1.02]
Hanson 2011	1	32	3	49	3.6%	0.51 [0.06, 4.69]
Kamitsuka 2000	5	467	23	477	8.7%	0.22 [0.09, 0.58]
Kuzma-O'Reilly 2003	94	2041	62	828	12.1%	0.62 [0.45, 0.84]
Mckallie R 2011	2	64	15	83	6.2%	0.17 [0.04, 0.73]
Patel 2015	5	170	35	219	8.9%	0.18 [0.07, 0.46]
Patole S 2000	1	298	30	250	4.2%	0.03 [0.00, 0.20]
Premji 2002	0	100	2	100	2.3%	0.20 [0.01, 4.11]
Sanchez-Tamayo 2016	1	115	12	155	4.1%	0.11 [0.01, 0.85]
Spritzer 1988	3	937	51	529	7.6%	0.03 [0.01, 0.11]
Stefanescu 2016	1	156	4	143	3.7%	0.23 [0.03, 2.03]
Street 2006	0	66	1	57	2.1%	0.29 [0.01, 6.95]
Talavera 2016	19	606	27	335	10.9%	0.39 [0.22, 0.69]
Viswanathan 2015	7	125	33	294	9.7%	0.50 [0.23, 1.10]
Wiedmeier 2008	37	4538	94	2249	11.8%	0.20 [0.13, 0.28]
Total (95% CI)		10647		7513	100.0%	0.22 [0.13, 0.36]
Total events	177		406			

Heterogeneity: Tau² = 0.51; Chi² = 54.54, df = 14 (P < 0.00001); I² = 74%
Test for overall effect: Z = 6.01 (P < 0.00001)



BEYOND 100

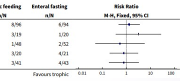
31

Prevention

- Early feeding regimen
  - Cochrane Review – 2013
    - Determine the effect of early trophic feeding versus enteral fasting on feed tolerance, growth and development, and the incidence of neonatal morbidity (including necrotizing enterocolitis and invasive infection) and mortality in very preterm or VLBW infants
    - 9 trials included

Analysis 1.2. Comparison 1 Effects of trophic feeding versus enteral fasting, Outcome 2 Incidence of necrotising enterocolitis.

Study or subgroup	Trophic feeding n/N	Enteral fasting n/N	Weight	Risk Ratio M-H, Fixed, 95% CI
Becerra 1996	8/96	6/94	19.82%	1.31[0.47,3.62]
Dunn 1988	3/19	1/20	3.18%	3.16[0.36,27.78]
McClure 2000	1/48	2/52	6.28%	0.54[0.05,5.78]
Meetze 1992	3/20	4/21	12.75%	0.79[0.2,3.09]
Mosqueda 2008	3/41	4/43	12.76%	0.79[0.19,3.3]



Bryan BEYOND 100

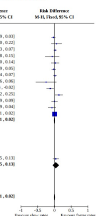
32

Prevention

- Progressive feeding regimen
  - Cochrane Review – 2021

Analysis 1.1. Comparison 1: Slow versus faster rates of feed advancement, Outcome 1: Necrotising enterocolitis - all infants

Study or Subgroup	Slow rate Events	Slow rate Total	Fast rate Events	Fast rate Total	Weight	Risk Difference M-H, Fixed, 95% CI
1.1.1 Infants at least partially fed with human milk						
Caple 2004	2	84	4	74	3.9%	-0.03 [-0.09 , 0.03]
Fayyaz 2020	1	16	0	15	0.8%	0.06 [-0.10 , 0.22]
Hasshemi 2018	2	100	0	40	2.9%	0.02 [-0.03 , 0.07]
Jain 2016	1	15	2	15	0.8%	-0.07 [-0.28 , 0.15]
Karagol 2013	5	46	4	46	2.3%	0.02 [-0.10 , 0.14]
Krishnamurthy 2010	1	50	2	50	2.5%	-0.02 [-0.09 , 0.05]
Modi 2015	2	65	1	66	3.3%	0.02 [-0.04 , 0.07]
Montealegre-Pomar 2021	0	12	2	8	0.5%	-0.25 [-0.56 , 0.06]
Raban 2014a	1	51	7	47	2.4%	-0.13 [-0.24 , -0.02]
Raban 2014b	9	52	2	50	2.6%	0.13 [0.02 , 0.25]
Saha 2019	3	55	2	38	2.3%	0.00 [-0.09 , 0.09]
Salhotra 2004	0	26	2	27	1.3%	-0.07 [-0.19 , 0.04]
SIFT 2016	78	1399	70	1394	69.9%	0.01 [-0.01 , 0.02]
Subtotal (95% CI)		**1971**		**1870**	**95.4%**	**0.00 [-0.01 , 0.02]**
Total events:	105		98			
Heterogeneity: Chi² = 18.24, df = 12 (P = 0.11); I² = 34%						
Test for overall effect: Z = 0.26 (P = 0.79)						
1.1.2 Infants exclusively formula fed						
Rayyis 1999	13	98	8	87	4.6%	0.04 [-0.05 , 0.13]
Subtotal (95% CI)		**98**		**87**	**4.6%**	**0.04 [-0.05 , 0.13]**
Total events:	13		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**2069**		**1957**	**100.0%**	**0.00 [-0.01 , 0.02]**
Total events:	118		106			
Heterogeneity: Chi² = 18.86, df = 13 (P = 0.13); I² = 31%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%						



BEYOND 100

33

Prevention

- Other Strategies
  - Avoid prolonged antibiotics
  - Avoid gastric acid suppression
  - Prevent severe anemia

Bryan BEYOND 100

34

Human milk derived fortification

- Blinded/randomized, <1250 grams
  - August 2014-Nov 2015
  - MBM/DBM – no formula
  - Primary – feeding interruption
  - 127 infants

Nutrient enrichment of human milk with human and bovine milk–based fortifiers for infants born weighing <1250 g: a randomized clinical trial

Deborah L O'Connor,[1,4,11] Alex Kiss,[7,8] Christopher Tomlinson,[1,2,4,5] Nicole Bando,[1] Ann Bayliss,[9] Douglas M Campbell,[2,5,10] Alan Daneman,[3,6] Jane Francis,[1,4] Kirsten Kotsopoulos,[11] Prakesh S Shah,[5,11] Simone Vaz,[12] Brock Williams,[1] and Sharon Unger[2,5,11] for the OptiMoM Feeding Group

[1]Translational Medicine Program and Divisions of [2]Neonatology and [3]Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada; Departments of [4]Nutritional Sciences, [5]Pediatrics, and [6]Medical Imaging; [7]Institute of Health Policy, Management and Evaluation; and [8]Evaluative and Clinical Sciences, Sunnybrook Research Institute, University of Toronto, Toronto, Canada; [9]Trillium Health Partners, Mississauga, Canada; [10]St. Michael's Hospital and Li Ka Shing Knowledge Institute, Toronto, Canada; [11]Department of Pediatrics, Sinai Health System, Toronto, Canada; and [12]Department of Pediatrics, William Osler Health System, Brampton, Canada

ABSTRACT
Background: Human milk-based fortifiers (HMBFs) are being adopted in neonatal care to enrich the nutrients in human milk for very low birth weight (VLBW) infants despite being costly and there being limited efficacy data. No randomized clinical trial has evaluated the use of HMBF compared with bovine milk–based fortifiers (BMBFs) in the absence of formula feeding.
Objective: We determined if HMBF compared with BMBF for routine nutrient enrichment of human milk improves feeding tolerance, reduces morbidity, reduces fecal calprotectin (a measure of gut inflammation), and supports the growth of infants <1250 g.
Design: In this blinded randomized clinical trial, infants born weighing <1250 g were recruited from neonatal units in Ontario, Canada between August 2014 and November 2015. The infants were fed mother's milk and donor milk as required. Fortification commenced

trial was registered at clinicaltrials.gov as NCT02137473. Am J Clin Nutr 2018;108:108–116.

Keywords: nutrient fortification, human milk, preterm infants, very low birth weight

INTRODUCTION
Mother's milk is the optimal source of nutrition for all infants (1). Among very low birth weight (VLBW) infants, mother's milk supplemented with donor human milk, instead of formula, when there is insufficient volume improves enteral feeding tolerance and reduces the risk of necrotizing enterocolitis (NEC), a life-threatening gastrointestinal condition (2, 3).

TABLE 3
Mortality and major morbidity diagnosed on or after study day 1 to hospital discharge[1]

	HMBF[2]	BMBF[2]	Unadjusted risk difference[3]	P value	Adjusted risk difference[3]	P value
Mortality and morbidity index[4]	23/64 (35.9)	30/61 (49.2)	−13.4 (−30.4, 4.0)	0.13	−14.5 (−29.9, 1.0)	0.07
Death	3/64 (4.7)	4/61 (6.6)	−1.9 (−10.0, 6.2)	0.65	—	
Late-onset sepsis	8/64 (12.5)	14/61 (23.0)	−10.5 (−23.8, 2.9)	0.12	−11.7 (−24.7, 1.3)	0.07
Necrotizing enterocolitis						
All stages	3/64 (4.7)	6/61 (9.8)	−5.2 (−14.2, 3.9)	0.27	—	
Stage ≥II	3/64 (4.7)	3/61 (4.9)	−0.2 (−7.7, 7.3)	0.95	—	
Oxygen support at 36 wk postconception	16/64 (25.0)	18/61 (29.5)	−4.5 (−20.1, 11.1)	0.57	−2.0 (−13.3, 9.3)	0.73
Severe retinopathy of prematurity	1/62 (1.6)	6/59 (10.2)	−8.6 (−16.9, −0.02)	0.04	—	
Severe brain injury[5]	11/64 (17.2)	8/61 (13.1)	4.1 (−8.5, 16.6)	0.52	—	

by a Programmatic Grant in Food and Health from Health Research (OptiMoM, FHG 129919). PSS is Research Chair in Reproductive and Child Health earch from the Canadian Institutes of Health Re- ased as part of routine clinical care (e.g., donor milk, ers) were provided by participating centers. Prolacta human milk–based fortifiers at manufacturing cost. ad no role in the design or conduct of the research data interpretation, or writing of the manuscript. -3 and Supplemental Figures 1–3 are available from link in the online posting of the article and from the ble of contents at https://academic.oup.com/ajcn/. e to DLO (e-mail: deborah.oconnor@utoronto.ca). MBF, bovine milk–based fortifier; CNN, Canadian BF, human milk–based fortifier; NEC, necrotizing natal intensive care unit; PN, parenteral nutrition; l trial; ROP, retinopathy of prematurity; SickKids, ildren; VLBW, very low birth weight. 018. Accepted for publication March 14, 2018.

108 Am J Clin Nutr 2018;108:108–116. Printed in USA. © 2018 American Society for Nutrition. All rights reserved.

BEYOND 100

35

Human milk derived fortification

- Journal of Peds – Sullivan Trial – 2010
  - 3 groups – 207 infants – BW 500-1250 grams
    - 2 human milk based fortifiers
      - Fortified at either 100 or 40 ml/kg
      - Donor breast milk if no maternal milk available
    - Bovine based fortifier
      - Fortified at 100 ml/kg
      - Preterm formula if no maternal milk available
  - Duration of study participation was the earliest of the following
    - 91 days of age
    - Discharge from hospital
    - 50% oral feedings (ie, 4 complete oral feedings per day).

Bryan BEYOND 100

36

Human milk derived fortification

- Journal of Peds – Sullivan Trial – 2010

Table III. Study outcomes

Outcome	HM100 (n = 67)	HM40 (n = 71)	BOV (n = 69)	*P* value
Parenteral nutrition, days	20* (14, 35)	20 (12, 33)	22 (14, 34)	.71
Length of stay, days	74 (61, 107)	79 (64, 110)	78 (67, 99)	.90
Mother's own milk, mL per study	4048 (841, 7479)	4544 (627, 8012)	5676 (1064, 8309)	.71
Mother's own milk, % enteral intake	73 (16, 82)	70 (18, 80)	82 (38, 100)	.002
Late-onset sepsis (LOS), n (%)	19 (28)	15 (21)	13 (19)	.39
LOS and/or NEC, n (%)	22 (33)	20 (28)	21 (30)	.84
Retinopathy of prematurity, n (%)	31 (46)	25 (35)	27 (39)	.41
Ventilator, days	25 (6, 54)	25 (12, 50)	34 (10, 58)	.54
Oxygen therapy, days	41 (24, 63)	48 (12, 78)	45 (19, 74)	.92
Central line, days	21 (15, 36)	22 (14, 30)	22 (16, 30)	.82
Bronchopulmonary dysplasia, n (%)	22 (33)	26 (37)	27 (39)	.74
Weight gain, (g/kg/day)	14.2 (11.9, 15.8)	14.2 (12.3, 16.3)	15.1 (12.8, 17.0)	.13
Length increment, (cm/wk)	0.86 (0.72, 1.08)	0.88 (0.70, 1.03)	0.94 (0.72, 1.16)	.35
Head circumference increment, cm/wk	0.76 (0.62, 0.85)	0.75 (0.61, 0.88)	0.75 (0.62, 0.86)	.99

*Median (25th, 75th percentile).

37

Human milk derived fortification

- Journal of Peds – Sullivan Trial – 2010

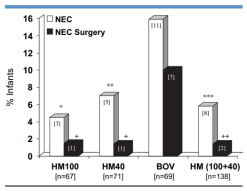
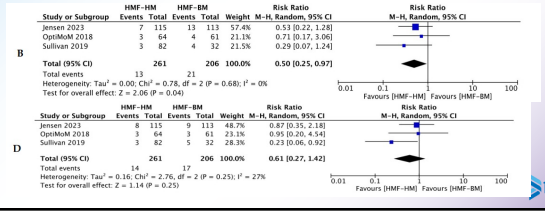


Figure 2. NEC and NEC surgery in study infants. There were significant differences in NEC among the 3 groups (P = .05), *P = .04 vs BOV, **P = .09 vs BOV, ***P = .02 vs BOV. There were significant differences in NEC requiring surgical intervention among the 3 groups (P = .02). †P = .03 vs BOV, ††P = .007 vs BOV. [ ] refers to number of infants.

38

Human milk derived fortification

- "Association of Fortification with Human Milk versus Bovine Milk-Based Fortifiers on Short-Term Outcomes in Preterm Infants-A Meta-Analysis" - 2024
  - 4 studies included



39

Human milk derived fortification

- "Human milk derived fortifiers are associated with glucose, phosphorus, and calcium derangements"
  - Journal of Perinatology
  - 2017 – Single center retrospective study
    - <30 weeks or <1250 grams
    - 2015-2019
    - Center switched from BOV TO HM-fort

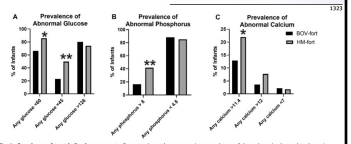
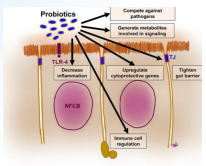


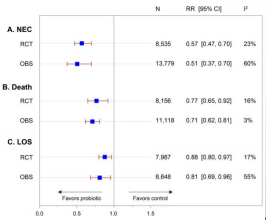
Fig. 1 Prevalence of metabolic derangements. Retrospective cohort comparing prevalence of hyperglycemia, hypophosphatemia, and hypercalcemia in infants born < 30 weeks who received Human milk derived (HM-fort) vs. Bovine derived fortifiers (BOV-fort). Infants receiving HM-Fort had more **A** hyperglycemia **B** hypophosphatemia. **C** Hypercalcemia. *Indicates comparison between cohorts with $p < 0.025$, **Indicates $p < 0.0001$.

40

Probiotics

- Live Micro-organisms which, when administered in adequate amounts, confer a health benefit on the host





41

WARNING REGARDING USE OF PROBIOTICS IN PRETERM INFANTS

Subject: Risk of Invasive Disease in Preterm Infants Given Probiotics Formulated to Contain Live Bacteria or Yeast

September 29, 2023

Dear Healthcare Provider:

The U.S. Food and Drug Administration (FDA) is providing important safety information to healthcare providers on the use of products containing live bacteria or yeast (commonly called probiotics) in preterm infants in hospital settings.

Risk of Invasive Disease with the Use of Probiotics in Preterm Infants

- The FDA is warning that preterm infants who are given probiotics are at risk of invasive, potentially fatal disease caused by the bacteria or fungi contained in probiotics.
- A preterm infant, birthweight <1000 g, who was administered a probiotic, Evivo with MCT Oil (Infinant Health), as part of in-hospital care, developed sepsis caused by the bacterium *Bifidobacterium longum* and subsequently died.
- Evivo with MCT Oil is a probiotic formulated to contain the live bacterium, *Bifidobacterium longum* subsp. *infantis*.
- The FDA is investigating the death of this preterm infant. Genomic sequencing data demonstrate the bacterium that caused sepsis in this infant was a genetic match to the bacteria contained in this probiotic.

Information on Probiotic Safety

The FDA cautions that microorganisms contained in probiotics have been reported in the medical literature as causing bacteremia or fungemia, sometimes with a severe clinical course, in very preterm or very low birthweight (VLBW) infants.[1-4]

Moreover, the American Academy of Pediatrics states "Given the lack of FDA-regulated pharmaceutical-grade products in the United States, conflicting data on safety and efficacy, and potential for harm in a highly vulnerable population, current evidence does not support the routine, universal administration of probiotics to preterm infants, particularly those with a birth weight of <1000 g."[5]

The FDA is also reminding healthcare providers that FDA has not approved any probiotic product for use as a drug or biological product in infants. The FDA is aware that some unapproved, unlicensed probiotics are nonetheless sold for use to treat or prevent a disease or condition in infants, including to reduce the

Risk of necrotizing enterocolitis (NEC) in preterm infants. Healthcare providers should be aware that these products have not undergone the FDA's rigorous premarket review evaluation for safety and effectiveness, nor have they been evaluated for compliance with the agency's rigorous manufacturing and testing standards for drugs and biological products, including testing for extraneous organisms.

The FDA reminds healthcare providers who administer probiotics containing live bacteria or yeast to treat, mitigate, cure, or prevent a disease or condition that they are required to submit an Investigational New Drug Application (IND) to the agency.

42

Probiotics

- Cochrane Review
  - 60 trials – 11,156 infants
  - Most common
    - Bifidobacterium
    - Lactobacillus
    - Saccharomyces
    - Streptococcus

Summary of findings 1. Probiotics compared to control in very preterm or very low birth weight infants — Open in table viewer

Probiotics compared to placebo or no probiotics in very preterm or very low birth weight infants

Patient or population: very preterm or very low birth weight infants
Setting: neonatal care centres worldwide
Intervention: probiotics
Comparison: placebo or no probiotics

Outcomes	Anticipated absolute effects* (95% CI)		Risk ratio (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)
	Risk with control	Risk with probiotics			
Necrotising enterocolitis (before hospital discharge)	60 per 1000	33 per 1000 (28 to 39)	**0.54** (0.46 to 0.65)	10,918 (57)	⊕⊕◯◯ Low[a,b]
All-cause mortality (before hospital discharge)	63 per 1000	48 per 1000 (42 to 57)	**0.77** (0.66 to 0.90)	10,484 (54)	⊕⊕⊕◯ Moderate[a]
Late-onset invasive infection (before hospital discharge)	173 per 1000	154 per 1000 (142 to 168)	**0.89** (0.82 to 0.97)	9876 (49)	⊕⊕⊕◯ Moderate[a]
Neurodevelopmental impairment (18 months to 3 years)	194 per 1000	200 per 1000 (163 to 245)	**1.03** (0.84 to 1.26)	1518 (5)	⊕⊕◯◯ Low[a,c]

Bryan BEYOND 100

43

Probiotics

- AAP – "Use of Probiotics in Preterm Infants" – 2021
- "Given the lack of FDA regulated pharmaceutical-grade products in the United States, conflicting data on safety and efficacy, and potential for harm in a highly vulnerable population, current evidence does not support the routine, universal administration of probiotics to preterm infants, particularly those with a birth weight of ,1000 g."

Bryan BEYOND 100

44

NEC in the News

Bryan BEYOND 100

45

SAIONTZ & KIRK, P.A.
www.YouHaveALawyer.com
800-522-0102
Free Evaluation | Call 24/7

BABY FORMULA RESOURCES: Case Info | Learn More

Enfamil Lawsuit Settlement Information

Was your premature baby diagnosed with necrotizing enterocolitis (NEC)? Enfamil Lawsuit Settlement benefits may be available.

Families throughout the United States may be eligible for an Enfamil NEC lawsuit settlement, providing financial compensation for:

- Hospital Bills and NEC treatments;
- Life-long therapy, medical equipment and services a child needs;
- Daycare and after-car services
- Support and counseling for you and your family

Find out if your family may be eligible for a Enfamil NEC lawsuit payout by requesting a free case evaluation, or calling our office toll free at 1-800-522-0102.

There are no fees or expenses unless we win your family a Enfamil settlement

Find Out If Eligible for a
ENFAMIL NEC LAWSUIT

Step 1 of 2

1. Was your baby born premature? *
2. Was your baby given Similac® or Enfamil® baby formula or milk fortifier in the NICU? *
3. Was your baby diagnosed with necrotizing enterocolitis (NEC)? *

NEXT ›

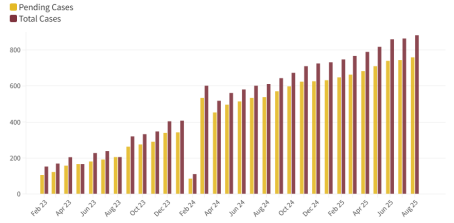
Bryan BEYOND 100

46

Baby Formula NEC Lawsuit:
Cases Filed (Feb 2023 - Aug 2025)

THL TorHoerman Law, LLC
Champions for Justice. Justice for People.

Pending Cases
Total Cases



Source: United States Judicial Panel on Multidistrict Litigation

A Flourish chart

Bryan BEYOND 100

47

Parents be aware

Parent Support Hotline
1-888-413-9885

NEC risk for premature infants

Lawsuits about cow milk-based nutrition used in NICUs and the life-threatening intestinal disease called NEC have worried many parents. Prolacta Bioscience isn't involved in any of these lawsuits, but the matter has highlighted why our 100% human milk-based nutrition is beneficial for the tiniest preemies.

Parent Support Hotline
1.888.413.9885

Learn more →

Bryan BEYOND 100

48

Journal of Perinatology www.nature.com/jp

REVIEW ARTICLE OPEN

The fifty billion dollar question: does formula cause necrotizing enterocolitis?

Mark A. Underwood[1]

The question of whether preterm infant formulas cause necrotizing enterocolitis (NEC) is the subject of multiple lawsuits and has daily relevance in the care of preterm infants. Research supporting the hypothesis that toxic components in infant formula cause NEC is limited to preclinical data while data from human infants are lacking. Human milk should be the first choice for most preterm infants, however, preterm infant formula is at times a critical alternative. It is the absence of human milk that increases NEC risk rather than toxic components in preterm infant formula.

Journal of Perinatology (2025) 45:565–571; https://doi.org/10.1038/s41372-025-02277-2

INTRODUCTION
Two separate lawsuits alleging that preterm infant formula caused necrotizing enterocolitis (NEC) in preterm infants resulted in awards of $60 M and $495 M against two formula companies in the United States in 2024. A third trial completed in October 2024 did not result in a judgment against a formula company. With about 1000 similar cases already filed, the potential impact of litigation on formula manufacturers and infant nutrition is significant [1]. NEC is a potentially devastating inflammatory intestinal disease with a global incidence of 7% among infants with birth weight less than 1500 g with high variability across studies [2]. Several studies have shown higher incidence among the smallest infants including those with lower gestational age, lower birth weight, and those who are small for gestational age [3–5]. Mortality rates are as high as 30%, and long-term consequences among survivors include short gut syndrome, malnutrition, chronic renal insufficiency, and poor neurodevelopmental outcomes. In multiple studies, the primary risk factor for NEC is preterm birth with the smallest and most preterm infants at the highest risk. The purpose of this review is to assess the evidence for a causal role of infant formula in the development of NEC.

Pathogenesis
NEC is likely not a single discreet entity, but rather a final pathway to intestinal inflammation and necrosis with multiple starting points. To switch analogies, NEC is likely a perfect storm at the intersection of one or more of the following: immature intestinal anatomy, physiology, immune responses, intestinal dysbiosis, and inconsistent intestinal perfusion and oxygenation. In many cases, the poorly regulated inflammatory response begins *in utero*.

Risk factors
In addition to preterm birth and low birth weight, several risk factors for NEC have been identified with some variation between

postnatal factors recognizing some degree of overlap. Table 1 presents odds ratios from recent papers for some NEC risk factors [6–13], and Table 2 presents odds ratios for some NEC protective factors in preterm infants [11].

Unpasteurized human milk
The studies in Table 2 are among several that have shown a lower incidence of NEC in preterm infants receiving unpasteurized mother's own milk. Human milk is a complex tissue containing an array of bioactive components that shape the infant's intestinal microbiota and impact the developing infant's immune system. Table 3 summarizes many of these components and includes potential protective mechanisms [14–26]. Studies comparing raw mother's milk (never frozen or pasteurized) to mother's own milk that has been frozen or pasteurized in preterm infants have been small with limited evidence for benefit [27].

Pasteurized donor human milk
The 2024 Cochrane review of pasteurized donor human milk (generally a pooled product from multiple donors) vs infant formula for preterm infants included 12 trials from Europe and North America (five of these studies were conducted more than 40 years ago). The meta-analysis found that donor human milk reduces the risk of NEC (RR 0.53, 95% CI 0.37, 0.76) but does not alter the risk of late-onset sepsis or death [28]. Donor milk is generally lower in protein content than mother's own milk. Pasteurization is effective at destroying potentially pathogenic bacteria and viruses but also denatures bioactive proteins and peptides. Table 3 also includes the impact of pasteurization on bioactive human milk components.

Fortifying human milk
Human milk is often fortified for premature infants to improve growth and minimize fluid overload. Commercially available fortifiers are either made from bovine milk or donor human milk.

49

$50 billion dollar question

- "Available evidence supports the hypothesis that it is the absence of human milk – rather than the exposure to formula – that is associated with an increase in the risk of NEC"
- "It is unknown whether human milk fortified with HMF, compared to human milk fortified with a BMF, could decrease the risk of NEC"

Table 2. Protective factors for NEC.

Factor	OR or adjusted OR (95% CI)
Prenatal	
Normal body mass index [9]	aOR 0.11(0.02, 0.58), $p = 0.009$
Perinatal	
Antenatal corticosteroids [8]	OR 0.38 (0.24, 0.60), $p < 0.001$
Antenatal corticosteroids (sNEC) [7]	OR 0.80 (0.64, 0.99), $p = 0.044$
Postnatal	
Breast milk feeding [6]	OR 0.26 (0.12, 0.57), $p < 0.01$
Breast milk feeding [8]	OR 0.31 (0.16, 0.62), $p < 0.001$
Probiotics [8]	OR 0.36 (0.25, 0.53), $p < 0.001$
Probiotics (in small for gestational age babies) [11]	OR 0.49 (0.30, 0.80), $p = 0.004$

sNEC surgical necrotizing enterocolitis.

50

Table 3. Some of the bioactive components of human milk [references 14–26].

	Growth factor	Enhanced barrier function	Prebiotic	Anti-inflammatory	Antimicrobial	Anti-oxidant	Degraded by pasteurization	Degraded by freezing
Immunoglobulins			X		X		X	
Lactoferrin	X	X		X	X	X	X	X
Lysozyme					X		X	
Alpha lactalbumin					X		X	
Human milk oligosaccharides		X	X	X	X	X		
Bile salt stimulating lipase					X		X	
Human milk fat globule membrane proteins		X			X	X	X	
Long chain PUFAs				X			X	
Epidermal growth factor	X			X			X	
Insulin-like growth factors 1/2	X						X	
Erythropoietin	X						X	
Insulin	X						X	
Adiponectin				X			X	
Melatonin		X		X		X	X	
Vascular endothelial growth factor	X						X	
Glycosaminoglycans		X	X	X	X			
Glutathione peroxidase						X	X	X
Superoxide dismutase						X	X	X
microRNAs		X		X			X	
White blood cells				X	X		X	
Stem cells	X						X	
Bacteria				X			X	
Exosomes	X			X	X		X	

PUFAs polyunsaturated fatty acids.

51

$50 billion dollar question

- FDA/NIH/CDC Statement
  - "There are two key points about feeding practices and NEC
    1. There is no conclusive evidence that preterm infant formula causes NEC
    2. There is strong evidence that human milk is protective against NEC
  - "While mother's milk is the preferred source of nutrition – with pasteurized donor milk as the next best alternative – preterm infant formulas are a critically important option for premature infants for whom parental or donor milk is not an option, or where a supplement to parental or donor milk is necessary for the health of the infant"

52

$50 billion dollar question

- Health and Human Services
  - NEC Working Group of Council
    - "a diet containing human breastmilk appears to be protective against the development of NEC. In addition, the use of human milk-based fortifier in the infant's diet, rather than bovine-based fortifier, may be useful in reducing the development of NEC"
  - CDC/NIH/FDA
    - "there is no conclusive evidence that preterm infant formula causes NEC" "there is strong evidence that human milk is protective against NEC"

53

$50 billion dollar question

- Openness and transparency
- Additional research
- Funding for human milk

54

References

- Soni R, et al. Arch Dis Child Educ Prac Ed 2020;**105**:50-57. doi;10.1136/archdischildl-2018-215252.
- Ginglen JG, Butki N. Necrotizing Enterocolitis. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK533157/
- Carlo W, et al. Exposure to any antenatal corticoseroids and outcomes in preterm infants by gestational age: prospective cohort study. British Medical Journal. 2017;356:j1039.
- Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. J Perinatol. 2009;29(1):57. Epub 2008 Aug 21.
- Donor human milk for preventing necrotising enterocolitis in very preterm or very low-birthweight infants. Quigley M, Embleton ND, Meader N, McGuire W . Cochrane Database Syst Rev. 2024;9(9):CD002971. Epub 2024 Sep 6.
- Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. JAMA. 2015 Sep 8;314(10):1039-51. doi: 10.1001/jama.2015.10244. PMID: 26348753; PMCID: PMC4787615.
- Fitzgibbons SC, Ching Y, Yu D, Carpenter J, Kenny M, Weldon C, Lillehei C, Valim C, Horbar JD, Jaksic T. Mortality of necrotizing enterocolitis expressed by birth weight categories. J Pediatr Surg. 2009 Jun;44(6):1072-5; discussion 1075-6. doi: 10.1016/j.jpedsurg.2009.02.013. PMID: 19524719.

55

References

- Parker LA, Weaver M, Murgas Torrazza RJ, Shuster J, Li N, Krueger C, Neu J. Effect of Gastric Residual Evaluation on Enteral Intake in Extremely Preterm Infants: A Randomized Clinical Trial. JAMA Pediatr. 2019 Jun 1;173(6):534-543. doi: 10.1001/jamapediatrics.2019.0800. Erratum in: JAMA Pediatr. 2019 Jun 1;173(6):610. doi: 10.1001/jamapediatrics.2019.1999. PMID: 31034045; PMCID: PMC6547072.
- Yee WH, Soraisham AS, Shah VS, Aziz K, Yoon W, Lee SK; Canadian Neonatal Network. Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. Pediatrics. 2012 Feb;129(2):e298-304. doi: 10.1542/peds.2011-2022. Epub 2012 Jan 23. PMID: 22271701.
- Cuna AC, Lee JC, Robinson AL, Allen NH, Foley JE, Chan SS. Bowel Ultrasound for the Diagnosis of Necrotizing Enterocolitis: A Meta-analysis. Ultrasound Q. 2018 Sep;34(3):113-118. doi: 10.1097/RUQ.0000000000000342. PMID: 29369246.
- Kenton AB, O'Donovan D, Cass DL, Helmrath MA, Smith EO, Fernandes CJ, Washburn K, Weihe EK, Brandt ML. Severe thrombocytopenia predicts outcome in neonates with necrotizing enterocolitis. J Perinatol. 2005 Jan;25(1):14-20. doi: 10.1038/sj.jp.7211180. PMID: 15526014.
- Jasani B, Patole S. Standardized feeding regimen for reducing necrotizing enterocolitis in preterm infants: an updated systematic review. J Perinatol. 2017 Jul;37(7):827-833. doi: 10.1038/jp.2017.37. Epub 2017 Mar 30. PMID: 28358382.

56

References

- Morgan J, Bombell S, McGuire W. Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. Cochrane Database Syst Rev. 2013 Mar 28;2013(3):CD000504. doi: 10.1002/14651858.CD000504.pub4. PMID: 23543508; PMCID: PMC11480887.
- Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2021 Aug 24;8(8):CD001241. doi: 10.1002/14651858.CD001241.pub8. PMID: 34427330; PMCID: PMC8407506.
- Patel RM, Underwood MA. Probiotics and necrotizing enterocolitis. Semin Pediatr Surg. 2018 Feb;27(1):39-46. doi: 10.1053/j.sempedsurg.2017.11.008. Epub 2017 Nov 6. PMID: 29275816; PMCID: PMC5844696.
- Ackley D, Yin J, D'Angio C, Meyers J, Young B. Human milk derived fortifiers are associated with glucose, phosphorus, and calcium derangements. J Perinatol. 2024 Sep;44(9):1320-1324. doi: 10.1038/s41372-024-01977-5. Epub 2024 Apr 24. Erratum in: J Perinatol. 2025 May;45(5):698. doi: 10.1038/s41372-025-02241-0. PMID: 38658693.
- Galis R, Trif P, Mudura D, Mazela J, Daly MC, Kramer BW, Diggikar S. Association of Fortification with Human Milk versus Bovine Milk-Based Fortifiers on Short-Term Outcomes in Preterm Infants-A Meta-Analysis. Nutrients. 2024 Mar 21;16(6):910. doi: 10.3390/nu16060910. PMID: 38542821; PMCID: PMC10975992.

57

Thank You!

58