Office of Evidence Based Practice (EBP) – Critically Appraised Topic: Starting Enteral Feedings after Medical NEC

Specific Care Question

For the patient in the NICU with medical necrotizing enterocolitis (mNEC) when is the optimal time to restart enteral feedings?

Recommendations from the XXXXX Team

No recommendation can be made on the timing of the re-initiation of enteral feedings after Stage IIa or IIb NEC. Three cohort studies are included, that show no difference in NEC recurrence or intestinal stricture if feedings are restarted early, and catheter related sepsis is lower when feedings are restarted early. However, the definition of early and late refeeding varied among the studies, which makes the studies inconsistent, and the time frame over which data was collected is wide. Other changes in neonatal care may have occurred to influence the outcomes.

When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.

Literature Summary

Background. Necrotizing enterocolitis is a condition that affects premature infants. In its most severe form, NEC causes severe inflammation and necrosis of the intestinal mucosa (Kim, 2019, Shenk 2019). It also presents in less severe forms. Medical NEC (mNEC) is when surgery is not required. A staging system, known as Bell staging, has been developed to describe the symptoms:

Name	Bell Stage	Symptoms
Suspected	Stage I	Emesis, abdominal distension, bloody stool
Proven	Stage II a	All the above, plus abdominal tenderness and lack of bowel sounds
Proven	Stage IIb	All the above, plus abdominal cellulitis
Advanced	Stage III	All the above, plus hypotension, pH imbalance, bradycardia, neutropenia

Note: from (Kim, 2019; Shenk et al., 2019)

Necrotizing enterocolitis is managed by stopping enteral feedings, initiating antibiotics, and continuing other supportive treatment, such as temperature regulation (Hock et al., 2018). There is a lack of standardization of when to re-start enteral feedings after a mNEC event. From a survey sent to 34 Intensive Care Nurseries (*n* = 22 responses) participating in the Children's Hospitals Neonatal Consortium (O'Donnell et al., 2019):

60% (13/22)- began enteral feeding on the day after antibiotics were completed
23% (5/22)- began enteral feeding on the day of discontinuation of antibiotics
18% (4/22-) starting feeds after resolution of pneumotosis and the return of bowel function

It is unknown if early or late reinitiation in feeding plays a role in NEC recurrence, time to full feeds, growth, or hosptial length of stay. In the calendar year 2017-2018, the NICU at Children's Mercy Kansas City discharged 13 patients with mNEC (Younger, 2019). Variation of timing of the restart of enteral feeds after mNEC is unknown.

The goal of the NICU is to standardize the initiation of enteral feedings after mNEC and to identify process points for feeding infants after mNEC to decrease patient important outcomes such as NEC recurrence, time to full feeds and hospital length of stay. This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on December 6, 2019. A. Khmour, MD and Denise Smith, RN, NNP-BC reviewed the 105 titles and/or abstracts found in the search and identified[b] 10 single studies believed to answer the question. A systematic review/meta-analysis was identified by ancestry search and led to two additional? studies that answered the question. After an in-depth review of the fourteen articles[c], four answered the question (see Figure 1).

Optimal time to start feedings after mNEC. Hock et al. (2018) is a systematic review/meta-analysis of two cohort studies that evaluated the timing of re-initiation of enteral feedings after mNEC. The two cohort studies are Bohnhorst et al. (2003) and Brotschi, Baenziger, Frey, Bucher, and Ersch (2009). Hock et al. (2018) reported on the outcomes (a) NEC recurrence, (b) catheter related sepsis, and (c) occurrence of intestinal stricture. Both studies compared shortening of time to initiate enteral feedings after mNEC to a historical cohort. The cohort study Arbra, Oprisan, Wilson, Ryan, and Lesher (2018) is a retrospective cohort that evaluated patients with early or late feeding after mNEC. The data from Arbra et al. (2018) has been added to the meta-analysis in this synthesis (see Table 1 and Figure 2).

Variation in time to feeding. The included studies differed in the definition of early and late enteral feeding.

Study	Arbra et al. (2018)	Bohnhorst et al. (2003)	Brotschi et al. (2009)
Early Feedings	Feeds started < 7 days after diagnosis of NEC, *n* = 40	Feeds started after 3 days without evidence of gas bubbles in the portal vein, *n* = 26	Feeds started < 5 days after NEC diagnosis, *n* = 30
Dates collected	July 2006 to June 2016	January 1998 to December 2001	January 2000 to December 2006
Delayed Feedings	Feeds started ≥ 7 days after diagnosis of NEC, *n* =98	Per the neonatologist, *n* = 18	Feeds started > 5 days after NEC diagnosis (median 5 days), *n* = 17
Dates collected	July 2006 to June 2016	April 1993 to March 1997	January 2000 to December 2006

Summary by Outcome

***NEC recurrence*.** Three studies (*n* = 229) measured NEC recurrence after early initiation of feeds after mNEC (Arbra et al., 2018; Bohnhorst et al., 2003; Brotschi et al., 2009). The studies reported the number of NEC recurrences as counts for early and late re-initiation of enteral feeding, and they are included in the meta-analysis (see Figure 2 and Table 1). The odds of NEC recurrence was not significantly different from restarting feedings later, *OR* = 0.46, 95% CI [0.15, 1.48].

Certainty of the evidence for NEC recurrence. The certainty of the body of evidence was very low based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have very serious risk of bias, very serious imprecision, not serious indirectness and serious inconsistency. Very serious risk of bias was assessed due to design, it is a cohort study, subjects were not randomized into feeding treatments, nor were subjects, providers, or outcome assessors blinded. Imprecision is serious due to the small number of subjects included in the papers. The studies are inconsistent in the definition of both early and late feeding. Furthermore, the date ranges from which the data was pulled was wide. For the Late Feeding group, data was pulled from 1993 to 2006. Time varying confounding occurs when the intervention received can change over time (Sterne, Higgins, & Reeves, 2014). Research published in the time between 1993 and 2006 may have suggested other changes in the care of the patient with mNEC that may have influenced the outcomes.

Catheter related sepsis. Two studies (*n* = 91) measured catheter related sepsis (Bohnhorst et al., 2003; Brotschi et al., 2009). The studies reported results as counts of catheter related sepsis events, and they are included in the meta-analysis (see Figure 3 and *Table 1).* The odds of catheter related sepsis were not significantly different from restarting feedings later, *OR* = 0.2, 95% CI [0.01, 3.29].

Certainty of the evidence for catheter related sepsis. The certainty of the body of evidence was very low based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have serious risk of bias, very serious imprecision, not serious indirectness and serious inconsistency. Very serious risk of bias was assessed due to design, it is a cohort study, subjects were not randomized into feeding treatments, nor were subjects, providers, or outcome assessors blinded. Imprecision is serious due to the small number of subjects included in the papers. The studies are inconsistent in the definition of both early and late feeding. Time varying confounding occurs when the intervention received can change over time (Sterne et al., 2014). Research published in the time between 1993 and 2006 may have suggested other changes in the care of the patient with mNEC that may have influenced the outcomes.

***Intestinal stricture*.** Three studies (*n* = 229) measured intestinal stricture (Arbra et al., 2018; Bohnhorst et al., 2003; Brotschi et al., 2009). The studies reported results as counts of stricture occurrence, and they are included in the meta-analysis (see Figure 4 and Table 1). The odds of intestinal stricture were not significantly different from restarting feedings later, *OR* = 0.15, 95% CI [0.15, 2.37].

Certainty of the evidence for intestinal stricture. The certainty of the body of evidence was very low based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have very serious risk of bias, very serious imprecision, not serious indirectness and serious inconsistency. Very serious risk of bias was assessed because by design, it is a cohort study, subjects were not randomized into feeding treatments, nor were subjects, providers, or outcome assessors blinded. Time varying confounding occurs when the intervention received can change over time (Sterne et al., 2014). Research published in the time between 1993 and 2006 may have suggested other changes in the care of the patient with mNEC that may have influenced the outcomes.

Identification of Studies

Search Strategy and Results (see Figure 1)

PubMed(1/6/2019)
(mNEC[tiab] OR ((nonoperative* OR nonsurgical OR medical[tiab]) AND ("Enterocolitis, Necrotizing"[Mesh] OR "Necrotizing Enterocolitis" OR NEC))) and (infants OR infant OR neonate OR "intensive care units, neonatal"[mesh] OR "intensive care, neonatal"[mesh] OR "intensive care nursery") AND ((time OR timing OR early OR duration OR standard OR delay OR restart* OR resume* OR reintroduc* OR initiat*) AND (enteral OR "enteral nutrition"[mesh] OR feed* OR refeeding))
Records identified through database searching *n* = 105
Additional records identified through other sources *n* = 3

Studies Included in this Review

**Studies included from meta-analysis*

Citation	Study Type
Arbra et al. (2018)	Cohort
Hock et al. (2018)	Systematic Review Meta-Analysis
*Bohnhorst et al. (2003)	Cohort
*Brotschi et al. (2009)	Cohort

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Downard et al. (2012)	Does not answer the question, included in the antibiotic review
Jayanthi, Seymour, Puntis, and Stringer (1998)	Does not answer the question, recommends feeding type for patients with gastroschisis
Kasivajjula and Maheshwari (2014)	Narrative review
Kosloske and Musemeche (1989)	Narrative review
Panigrahi (2006)	Narrative review
Sisk, Lovelady, Dillard, Gruber, and O'Shea (2007)	Does not answer the question, does not address post mNEC
Stringer et al. (1993)	Case series, does not address post mNEC
Thompson and Bizzarro (2008)	Narrative review
Wu, Caplan, and Lin (2012)	Narrative review

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings table(s) for this analysis.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

[d]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

[d]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

Office of Evidence Based Practice (EBP) – Critically Appraised Topic: Starting Enteral Feedings after Medical NEC

Question Originator
Ayman Khmour, MD
Denise Smith, RN, NNP-BC
Medical Librarian Responsible for the Search Strategy
Keri Swaggart, MLIS, AHIP
EBP Scholar's Responsible for Analyzing the Literature
Teresa Bontrager, MSN, RN, CPEN
Kori Hess, PharmD
Lucy Pappas, MS RD CSP LD
Ashley Wilson, BSN, RN, CPN
EBP Team Member Responsible for Reviewing, Synthesizing, and Developing this Document
Nancy H. Allen, MS, MLS, RD, LD, CPHQ

Acronyms Used in this Document

Acronym	Explanation
CAT	Critically Appraised Topic
CMH	Children's Mercy Hospital
EBP	Evidence Based Practice
mNEC	Medical necrotizing enterocolitis
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB	Risk of bias
SD	Standard deviation
sNEC	Surgical necrotizing enterocolitis

Date Developed/Updated
March 2020

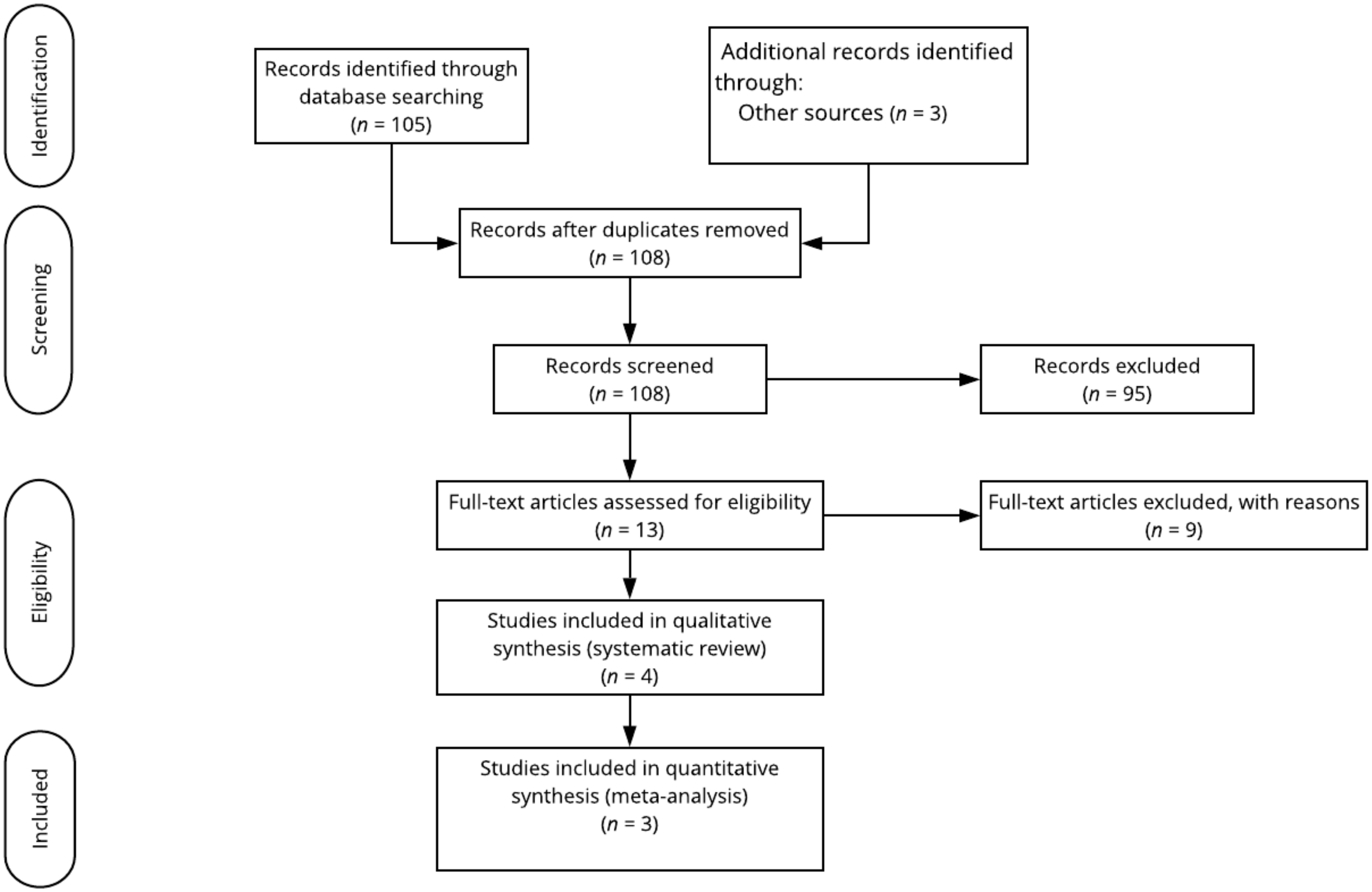

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[c]

Table 1.

Summary of Findings Table: Re-initiation of Enteral Feeds after mNEC

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**With Delayed initiation of enteral feeds**	**With Early re-initiation of enteral feeds after mNEC**	**Relative effect (95% CI)**	**Risk with Delayed initiation of enteral feeds**	**Risk difference with Early re-initiation of enteral feeds after mNEC**
NEC recurrence, lower is better											
229 (3 Cohort)	very serious [a,b]	serious [c,d]	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	15/133 (11.3%)	5/96 (5.2%)	**OR 0.46** (0.15 to 1.48)	113 per 1,000	**58 fewer per 1,000** (from 94 fewer to 46 more)
Catheter related sepsis, lower is better											
91 (2 Cohort)	serious [a,b]	serious [c,d]	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	10/35 (28.6%)	5/56 (8.9%)	**OR 0.20** (0.01 to 3.29)	286 per 1,000	**212 fewer per 1,000** (from 282 fewer to 283 more)
Intestinal Stricture											

Certainty assessment							Summary of findings					
229 (3 cohort)	serious [a,b]	serious [c,d]	not serious	very serious [d]	none	⨁◯◯◯ VERY LOW	6/133 (4.5%)	3/96 (3.1%)	**OR 0.59** (0.15 to 2.37)	45 per 1,000	**18 fewer per 1,000** (from 38 fewer to 56 more)

CI: Confidence interval; OR: Odds ratio

Notes:

a. It is a cohort study, by design, so it starts at lower level of evidence.
b. Time varying confounding, which is a selection bias occurs due to the wide range of dates in which subjects were enrolled
c. The definition of early and late feeding varied among the studies.
d. Low number of studies that include a low number of subjects.

Meta-analyses

Study or Subgroup	Early Events	Early Total	Delayed Events	Delayed Total	Weight	Odds Ratio M-H, Random, 95% CI
Abra 2018	2	40	12	98	56.3%	0.38 [0.08, 1.77]
Bohnhorst 2003	2	26	1	18	21.9%	1.42 [0.12, 16.91]
Brotschi 2009	1	30	2	17	21.8%	0.26 [0.02, 3.09]
Total (95% CI)		**96**		**133**	**100.0%**	**0.46 [0.15, 1.48]**
Total events	5		15			

Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)

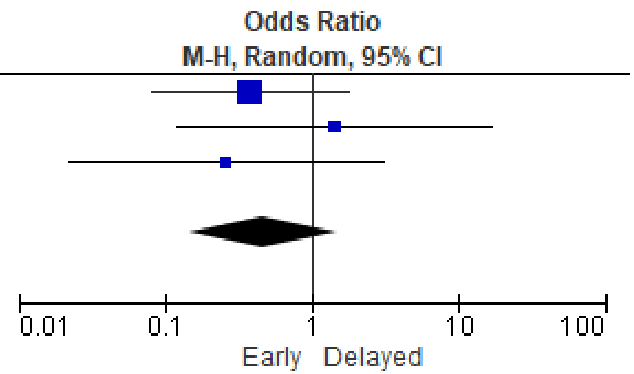

Figure 2. Comparison: Early re-initiation of enteral feeds after mNEC versus Delayed initiation of enteral feeds, Outcome: NEC recurrence, lower is better

Study or Subgroup	Early Events	Early Total	Delayed Events	Delayed Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bohnhorst 2003	5	26	5	18	41.1%	0.62 [0.15, 2.56]
Brotschi 2009	0	30	5	17	58.9%	0.04 [0.00, 0.73]
Total (95% CI)		**56**		**35**	**100.0%**	**0.28 [0.09, 0.86]**
Total events	5		10			

Heterogeneity: Chi² = 2.99, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 2.22 (P = 0.03)

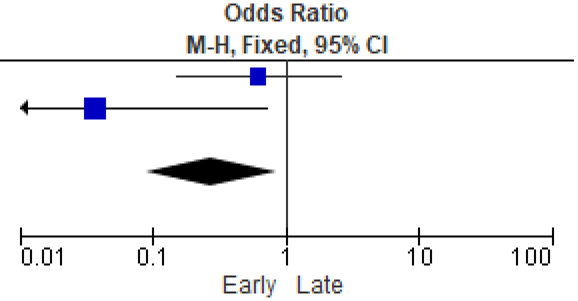

Figure 3. Comparison: Early re-initiation of enteral feeds after mNEC versus Delayed initiation of enteral feeds, Outcome: Catheter related sepsis, lower is better

Study or Subgroup	Early Events	Early Total	Delayed Events	Delayed Total	Weight	Odds Ratio M-H, Random, 95% CI
Abra 2018	0	40	4	98	25.9%	0.26 [0.01, 4.93]
Bohnhorst 2003	2	26	2	18	52.9%	0.67 [0.09, 5.23]
Brotschi 2009	1	30	0	17	21.2%	1.78 [0.07, 46.12]
Total (95% CI)		**96**		**133**	**100.0%**	**0.64 [0.14, 2.88]**
Total events	3		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

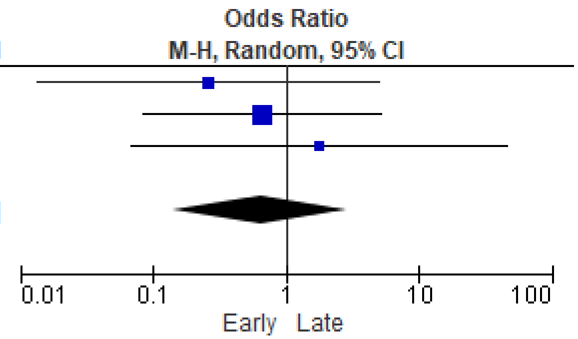

Figure 4. Comparison: Early re-initiation of enteral feeds after mNEC versus Delayed initiation of enteral feeds, Outcome: Intestinal Stricture

If you have questions regarding this Specific Care Question – please contact Ayman Khmour, MD or Denise Smith, RN, NNP-BC

Arbra et al. (2018)

<table>
<tr><td colspan="2">Characteristics of Study</td></tr>
<tr><td>Methods</td><td>Cohort</td></tr>
<tr><td>Participants</td><td>Participants: NICU patients discharged between 0 and 6 months of age with a discharge diagnosis of NEC over a 10-year study period (July 2006-June 2016)
Setting: Tertiary care children’s hospital with a 64-bed level IV NICU at the Medical University of South Carolina
Number enrolled into study: N = 138
• Group 1, Early feeding (<7 days after NEC diagnosis): n = 40
• Group 2, Late feeding (≥ 7 days after NEC diagnosis): n = 98
Number completed: N = 138
• Group 1: n = 40
• Group 2: n = 98
Gender, males:
• Group 1: n = 20 (50%)
• Group 2: n = 49 (50%)
Ethnicity:
<table><tr><th></th><th>Group 1</th><th>Group 2</th></tr><tr><td>African American</td><td>26 (65%)</td><td>54 (55.1%)</td></tr><tr><td>Caucasian</td><td>12 (30%)</td><td>37 (37.8%)</td></tr><tr><td>Hispanic</td><td>1 (2.5%)</td><td>6 (6.1%)</td></tr><tr><td>Other</td><td>1 (2.5%)</td><td>1 (1.0%)</td></tr></table>Age at NEC diagnosis, mean in days:
• Group 1: 19
• Group 2: 22.6
Inclusion criteria:
• NICU patients discharged between 0 and 6 months of age
• Discharge diagnosis of NEC over a 10-year study period (July 2006-June 2016)
Exclusion criteria:
• Feeds never restarted after NEC diagnosis
• Death
Covariates identified:
• Not reported</td></tr>
<tr><td>Interventions</td><td>Both:
• Group 1: feeds restarted <7 days after NEC diagnosis</td></tr>
</table>

	• **Group 2:** feeds restarted ≥7 days after NEC diagnosis
Outcomes	**Primary outcome(s):** • NEC recurrence* **Secondary outcome(s)** • Intestinal stricture • Mortality **Safety outcome(s):** not reported *Outcomes of interest to the Children's Mercy Hospital (CMH) Critically Appraised Topic (CAT) Development team
Notes	**Results:** **Length of Stay** In patients without cardiac disease, length of stay (adjusted for Bell's Stage) was significantly shorter (p<0.01) for Group 1 on linear regression analysis by 30.5 days [95% CI 9.8-51.2] *Note*: sample size is small.

Bohnhorst et al. (2003)

Characteristics of Study	
Methods	**Cohort**
Participants	**Participants:** Infants born at <36 weeks gestational age and admitted to NICU. **Setting:** Hannover Medical School between January 1, 1998 and December 31, 2001 for group 1; data from retrospective cohort with NEC admitted between April 1, 1993 and March 31, 1997 for group 2. **Number enrolled into study:** *N* = 44 • **Group 1, Early feeding re-initiation:** *n* = 26 • **Group 2, Historic feeding re-initiation:** *n* = 18 **Number completed:** *N* = 44 • **Group 1:** *n* = 26 • **Group 2:** *n* = 18 **Gender, males: (as defined by researchers)** • Not reported. **Race / ethnicity or nationality (as defined by researchers):** • The study occurred in Germany. The authors did not identify race or ethnicity of the participants. **Age, mean/median in months/years, range/IQR** • Not reported **Inclusion criteria:** • At least one clinical sign (gastric residuals, abdominal distension, blood in stool) plus gas bubbles in the portal vein or liver parenchyma, pneumatosis intestinalis, and/or free air on ultrasound or radiograph. • This definition corresponds to the Bell stage II or higher. **Exclusion criteria:** • Not reported **Covariates identified:** • Not reported
Interventions	**Both:** Complete cessation of enteral feedings, nasogastric drainage, total parenteral nutrition, and appropriate antibiotic treatment. • **Group 1:** Enteral feedings were reinitiated after 3 consecutive days without evidence of gas bubbles via ultrasound. • **Group 2:** Enteral feedings and advancement performed at the discretion of the attending; usually began at 14 days after onset.

Outcomes	**Primary outcome(s):** • Early feedings would shorten duration of central venous access **Secondary outcome(s)** • *Enteral feedings restarted at a median of 4 days versus 10 days **Safety outcome(s):** • Not reported *Outcomes of interest to the CMH CAT development team
Notes	**Results:** • Complete enteral feedings were established after 10 days in group 1 compared with 19 days in group 2 ($p < .001$). • Reduction of central line duration (13.5 days vs 26 days; $p < .001$). • In group 1, catheter related septicemia occurred in 18% episodes of NEC compared with 29% in group 2 ($P<.01$). • Time to hospital discharge was 63 vs 69 days ($p < .05$).

Brotschi et al. (2009)

Characteristics of Study	
Methods	**Retrospective Cohort**
Participants	**Participants:** term and preterm neonates with NEC, Bell stage II **Setting:** Five tertiary NICUs, over a 7-year, January 2000 to Dec 2006 **Number enrolled into study:** *N* = 47 • **Group 1:** Early feedings, *n* = 30 • **Group 2: Late feedings,** *n* =17 **Number completed:** *N* = 47 • **Group 1:** *n* = 30 • **Group 2:** *n* = 17 **Gender, males: (as defined by researchers)** • *n* = 28 (60%) **Race / ethnicity or nationality (as defined by researchers):** • The study occurred in Switzerland. The authors did not identify race or ethnicity of the participants. **Gestational age, mean in weeks ±SD** • **Group 1:** 32 ±2.8 • **Group 2:** 31.7 ±3.0 **Inclusion criteria:** Bell stage II **Exclusion criteria:** • Bell stage I – definition is vague • Bell stage III- required surgery **Covariates identified:** • Not reported
Interventions	**Both:** The same feeding algorithm was used for all subjects • **Group 1:** Fasted < 5-days to feed re-initiation • **Group 2:** Fasted >5 days to feed re-initiation
Outcomes	**Primary outcome(s):** • *NEC recurrence **Secondary outcome(s)** • *Intestinal stricture **Safety outcome** • *Catheter related sepsis *Outcomes of interest to the CMH CAT development team

Notes	Results:
	(see table below)

	Fasting period		
	< 5days	>5 days	*p* value
NEC recurrence	1	2	.27
Catheter related sepsis	0	5	.004
Intestinal stricture	1	4	.05

If you have questions regarding this Specific Care Question – please contact Ayman Khmour, MD or Denise Smith, RN, NNP-BC

Hock et al. (2018)

Characteristics of Study	
Design	**Quantitative Synthesis (meta-analysis)**
Objective	Determine if timing of the initiation of enteral feedings after an episode of Bell stage II NEC influenced the recurrence of NEC

Methods	**Protocol and registration.**
	• Not reported
	Eligibility Criteria.
	• Human studies
	• Assessed the timing of feeds after medical NEC
	  ○ Early – starting feeds < 5 days (median)
	  ○ Late – starting feeds > 5 days (median)
	• Primary outcome was recurrence of NEC
	Exclusion criteria
	• Feeding protocol was unclear
	• Timing of starting feeds after mNEC was unclear
	• Overlap of data form a study in the same center
	Information sources.
	• MEDLINE 1966 to November 2016
	• EMBASE 1947 to November2016
	• Google Scholar
	• Cochrane database
	Search
	• feed OR feeding AND necrotizing enterocolitis
	Study Selection.
	• Two authors independently screened, extracted, and analyzed the studies and gave reasons for excluding studies.
	• All authors achieved consensus when faced with disagreements
	Data collection process.
	• A spreadsheet was designed to collect the following information: study characteristics, criteria for diagnosing NEC, study design, feeding protocols, and outcomes.
	Risk of bias (RoB) across studies.
	• The Newcastle-Ottawa scale was employed
	Summary measures.
	•
	Synthesis of results.
	RevMan 5.3 to calculate pooled odds ratios with 95% confidence intervals. If the I^2 was < 25% a random effects model was used, if ≥ 25% a random effects model was employed.

Results	**Study Selection.** **Number of articles identified:** *N* = 4377 **Full-text articles assessed for eligibility:** *n* = 47 ○ **Studies included in qualitative synthesis:** *n* = 2 **Synthesis of results.** • There was no significant difference in the recurrence rate of NEC between early and delayed enteral feeding, *OR* = .61, 95% CI [0.12, 3.16], *p* = .56 • There was no significant difference in the occurrence of catheter related sepsis, *OR* = .2, 95% CI [0.01, 3.29], *p* = .26 • There was not significant difference in the occurrence of post NEC strictures, *OR* = .28, 95% CI [.07, 1.18], *p* = .08. **Risk of bias across studies.** • Risk of bias was assessed as low on the Newcastle Ottawa scale
Discussion	**Summary of evidence.** • Starting enteral feeding within 5 days did not increase the incident of recurrent NEC, catheter related sepsis, or occurrence of intestinal stricture. • When feedings were started post mNEC, early low volume feedings are suggested • It is not known the optimal time to increase to full volume enteral feeds. **Limitations.** • Different definitions for early and late re-initiation of feedings • One study included only medical NEC, and the other included mNEC and surgical NEC (sNEC). In the latter study, findings were not reported separately for mNEC and sNEC.
Funding	**Funding.:** Conflict of interest was reported as None

References

*Included in the meta-analysis

Arbra, C. A., Oprisan, A., Wilson, D. A., Ryan, R. M., & Lesher, A. P. (2018). Time to reintroduction of feeding in infants with nonsurgical necrotizing enterocolitis. *J Pediatr Surg, 53*(6), 1187-1191. doi:10.1016/j.jpedsurg.2018.02.082

Downard, C. D., Renaud, E., St Peter, S. D., Abdullah, F., Islam, S., Saito, J. M., . . . Aspelund, G. (2012). Treatment of necrotizing enterocolitis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. *J Pediatr Surg, 47*(11), 2111-2122. doi:10.1016/j.jpedsurg.2012.08.011

Hock, A. M., Chen, Y., Miyake, H., Koike, Y., Seo, S., & Pierro, A. (2018). Initiation of Enteral Feeding After Necrotizing Enterocolitis. *Eur J Pediatr Surg, 28*(1), 44-50. doi:10.1055/s-0037-1604436

*Bohnhorst, B., Muller, S., Dordelmann, M., Peter, C. S., Petersen, C., & Poets, C. F. (2003). Early feeding after necrotizing enterocolitis in preterm infants. *J Pediatr, 143*(4), 484-487. doi:10.1067/S0022-3476(03)00443-8

*Brotschi, B., Baenziger, O., Frey, B., Bucher, H., & Ersch, J. (2009). Early enteral feeding in conservatively managed stage II necrotizing enterocolitis is associated with a reduced risk of catheter-related sepsis. *J Perinat. Med, 37*, 701-705. doi:10.1515/JPM.2009.129

Jayanthi, S., Seymour, P., Puntis, J. W., & Stringer, M. D. (1998). Necrotizing enterocolitis after gastroschisis repair: a preventable complication? *J Pediatr Surg, 33*(5), 705-707. doi:10.1016/s0022-3468(98)90191-9

Kasivajjula, H., & Maheshwari, A. (2014). Pathophysiology and current management of necrotizing enterocolitis. *Indian J Pediatr, 81*(5), 489-497. doi:10.1007/s12098-014-1388-5

Kosloske, A. M., & Musemeche, C. A. (1989). Necrotizing enterocolitis of the neonate. *Clin Perinatol, 16*(1), 97-111.

O'Donnell, B., Brozanski, B. S., Azzuqa, A., Schmidt, H., Maieilo, A., Konnikova, L., . . . Yanowitz, T. D. (2019, November 4-6, 2019). *A QI journey to standardize refeeding after treatment for medical necrotizing enterocolitis across a large health system UPMC Division of Newborn Medicine.* Paper presented at the CHNC Annual Symposium, Atlanta, GA, USA.

Panigrahi, P. (2006). Necrotizing enterocolitis: a practical guide to its prevention and management. *Paediatr Drugs, 8*(3), 151-165. doi:10.2165/00148581-200608030-00002

Sisk, P. M., Lovelady, C. A., Dillard, R. G., Gruber, K. J., & O'Shea, T. M. (2007). Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *J Perinatol, 27*(7), 428-433. doi:10.1038/sj.jp.7211758

Sterne, J. A. C., Higgins, J. P. T., & Reeves, B. C. (2014). A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI). 1.0.0. Retrieved from http://www.riskofbias.info

Stringer, M. D., Brereton, R. J., Drake, D. P., Kiely, E. M., Capps, S. N., & Spitz, L. (1993). Recurrent necrotizing enterocolitis. *J Pediatr Surg, 28*(8), 979-981. doi:10.1016/0022-3468(93)90496-8

Thompson, A. M., & Bizzarro, M. J. (2008). Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. *Drugs, 68*(9), 1227-1238. doi:10.2165/00003495-200868090-00004

Wu, S. F., Caplan, M., & Lin, H. C. (2012). Necrotizing enterocolitis: old problem with new hope. *Pediatr Neonatol, 53*(3), 158-163. doi:10.1016/j.pedneo.2012.04.001

Younger, D. (2019). *ICN Discharge of infants with mNEC 2017-2018*. Dataset. Accessed Dec. 6, 2019.