

Office of Evidence Based Practice (EBP) – Critically Appraised Topic: Duration of Antibiotics after Medical NEC

Specific Care Question

For the patient in the ICN with medical necrotizing enterocolitis (mNEC) is there an optimal duration of treatment with antibiotics?

Recommendations Based on Current Literature (Best Evidence) Only

No recommendation can be made for or against changing the duration of antibiotics after mNEC, based on review of current literature of the by the Department of EBP. The overall certainty in the evidence is very low^d. There reports were identified, of which two reported duration of antibiotics as a secondary outcome. The third report used a guideline to decrease the duration of antibiotics and decreased the duration of antibiotic by 21% over a 15-month time frame.

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, it causes severe inflammation and necrosis of the intestinal mucosa (Kim, 2019, Shenk 2019). It also presents in less severe forms. 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 body temperature regulation (Hock et al., 2018). The Surgical Infection Society and the Infectious Disease Society of America recommends ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem for Stage II NEC (Downard et al., 2012). Length of antibiotic therapy to prevent the recurrence of NEC is not addressed in the recommendation.

Bell stage II NEC can be treated medically or surgically depending on the symptoms. It is unknown if length of antibiotic therapy plays a role in mNEC recurrence, time to full feeds, growth, or hospital length of stay (Downard et al., 2012). Conference abstracts suggest no difference in mortality, intestinal stricture, parenteral nutrition complications, or reinstitution of antibiotic therapy when the duration of antibiotics for Bell Stage IIa and IIb is reduced (Lance et al., 2016; Shenk et al., 2019).

The goal of the NICU is to standardize the length of treatment with antibiotics after mNEC to decrease patient important outcomes such as NEC recurrence, time to full feeds and hospital length of stay. In the calendar year 2017-2018, the NICU at Children's Mercy Kansas City cared for 13 patients with a discharge diagnosis of mNEC (Younger, 2019). This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on December 11, 2019. Ayman Khmour, MD and Denise Smith, RN, NNP-BC reviewed the 78 titles and/or abstracts found in the search and identified^a. A conference presentation was added to the studies for a total of 79 papers. Thirteen single studies believed to answer the question were identified. After an in-depth review of the remaining articles^b, three answered the question (see Figure 1).

Duration of antibiotics after mNEC. Both Albert et al. (2018) and Lance et al. (2016) are abstract reports of QI projects, while Shenk et al. (2019) is a conference presentation of a QI project. Increasing the number of neonates who had appropriate selection of antibiotics for the treatment of NEC was the goal of (Albert et al., 2018). Lance et al. (2016) reports the de-escalation of antibiotic treatment time and the occurrence of parenteral nutrition complications, neurodevelopmental disability, and mortality. Shenk et al. (2019) is a report of a quality improvement project

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where a consensus guideline was used to decrease length of antibiotic therapy for patients with Bell stage IIa and IIb NEC.

Summary by Outcome

Duration of antibiotics after mNEC. Three studies assessed duration of antibiotics after mNEC (Albert et al., 2018; Lance et al., 2016; Shenk et al., 2019). Albert et al. (2018) created a guideline to standardize the selection of antibiotics for NEC and the duration of treatment with antibiotics. Duration of therapy before guideline implementation equated to vancomycin 155 days of therapy/1000 patient days, and meropenem 55 days of therapy/1000 patient days. After the guideline, days of therapy decreased to vancomycin 101 days of therapy/1000 patient days and meropenem 12 days of therapy/1000 patient days. Significance was not reported. An algorithm for antibiotic selection and length of therapy was included in this report and can be found in the Appendix.

Lance et al. (2016) compared the number of patients with both mNEC and surgical NEC (sNEC) who either had antibiotics for 8 to 10 days, 11 to 14 day, or greater than 14 days following the outcomes of parenteral nutrition complications, intestinal stricture, neurodevelopmental disabilities and mortality in either the mNEC or sNEC groups. Empiric antibiotic regimens were de-escalated in 77/142(54%) and there were no differences in the outcomes.

Finally, Shenk et al. (2019) is a QI initiative where a guideline was developed that recommended length of antibiotic therapy of 7 days for Bell stage IIa NEC, and 14 days for Bell stage IIb NEC. For the seven-month baseline period prior to the guideline, the average length of therapy for stage IIa and IIb was 9.8 days. For the 15 months after the guideline was instantiated, the average length of therapy decreased to 7.7 days. No patient required antibiotics restarted for NEC, however a few patients (not quantified by the authors) required extended therapy because pneumatosis persisted.

Certainty of the evidence for duration of antibiotics after mNEC. The certainty of the body of evidence was very low due to none of the included reports have been published in a peer review journal. All are quality projects which are open to biases such as lack of randomization, unable to blind the providers or outcome assessors. Two of the papers provide indirect evidence. In Albert et al. (2018), the primary goal was to guide antibiotic selection, length of therapy was reported as a secondary finding. The primary goal of Lance et al. (2016) was to compare medical and surgical NEC, length of therapy was reported as a secondary finding. Imprecision very serious across all three reports. Imprecision is present when there is a low number of studies that include low number of subjects; both are present.

Identification of Studies

Search Strategy and Results (see Figure 1)

PubMed

Search: (mNEC 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 ("Anti-Bacterial Agents"[Majr] OR ((antibiotic OR "Anti-Bacterial Agents"[mesh]) AND (duration OR standard OR length)))

Embase

Step#	Query	Results
14	#13 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	68
13	#12 AND ([infant]/lim OR [newborn]/lim OR 'newborn'/exp OR newborn OR 'neonate'/exp OR neonate OR 'infant'/exp OR infant OR 'neonatal intensive care unit'/exp OR 'neonatal intensive care unit' OR 'newborn intensive care'/exp OR 'newborn intensive care')	320
12	#5 AND #11	749,333
11	#6 OR #10	199,248
10	#8 AND #9	199,248
9	#7 AND #8	3,415,902

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8	'treatment duration'/exp OR 'treatment duration' OR 'duration'/exp OR duration OR 'standard'/exp OR standard OR 'length'/exp OR length	1,656,779
7	'antibiotic agent'/exp OR 'antibiotic agent' OR 'antibiotic'/exp OR antibiotic OR nonsurgical	603,709
6	'antibiotic agent'/exp/mj	7,166
5	#1 OR #4	7,148
4	#2 AND #3	13,407
3	'necrotizing enterocolitis'/exp OR 'necrotizing enterocolitis'	9507984
2	nonoperative* OR medical OR nonsurgical	20
1	mnec:ti,ab	

Records identified through database searching $n = 78$
Additional records identified through other sources $n = 1$

Studies Included in this Review

Citation	Study Type
Albert et al. (2018)	Quality Improvement
Lance et al. (2016)	Quality Improvement
Shenk et al. (2019)	Quality Improvement

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Afjeh et al. (2016)	Does not address length of antibiotic treatment after NEC
Carter (2007)	Does not address length of antibiotic treatment after NEC
Chakkarapani and Russell (2019)	Narrative review
Kosloske and Musemeche (1989)	Narrative review
Lang, Hickey, King, and Curley (2019)	Does not address length of antibiotic treatment after NEC
Manzoni et al. (2018)	Does not address length of antibiotic treatment after NEC
Panigrahi (2006)	Narrative review
Thompson and Bizzarro (2008)	Narrative review
Wojkowska-Mach, Rózańska, and Heczko (2013)	Does not address length of antibiotic treatment after NEC

Methods Used for Appraisal and Synthesis

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

^bReview Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics.

^cThe 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).

^aOuzzani, 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

^bHiggins, 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.

^cMoher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA*

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Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit www.prisma-statement.org.

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Acronyms Used in this Document

Acronym	Explanation
CAT	Critically Appraised Topic
EBP	Evidence Based Practice
mNEC	Medical necrotizing enterocolitis
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QI	Quality Improvement
sNEC	Surgical necrotizing enterocolitis

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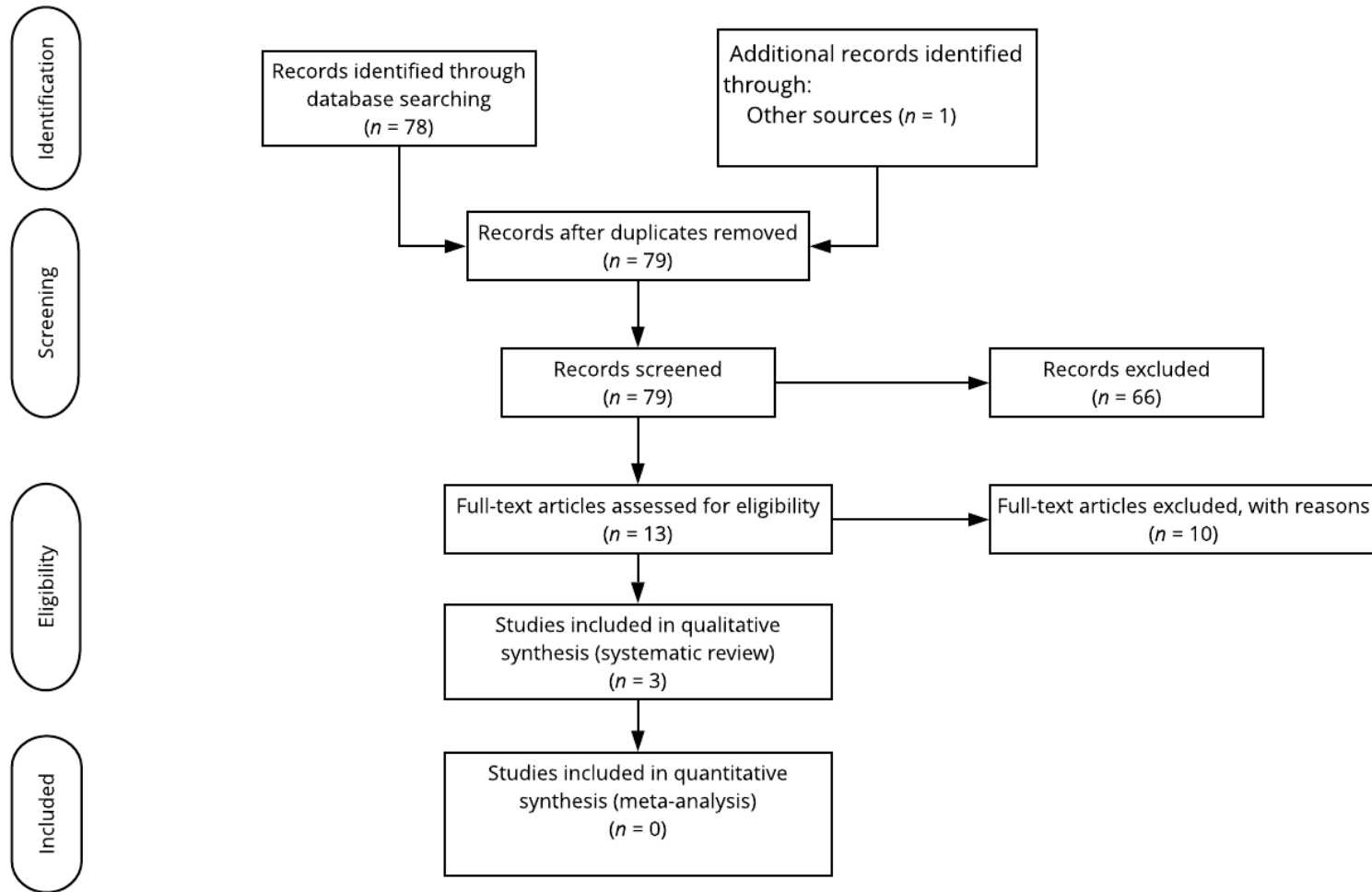


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^c

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Albert et al. (2018)

<i>Characteristics of Study^c</i>	
Methods	QI Project- Abstract only
Participants	<p>Participants: Patients who received vancomycin and meropenem in the NICU for NEC between January 2015 and December 2015</p> <p>Setting: Philadelphia, Pennsylvania</p> <p>Number enrolled into study: <i>N</i> = 118</p> <ul style="list-style-type: none"> • Group 1, Vancomycin <i>n</i> = 91 • Group 2, Meropenem, <i>n</i> = 27 <p>Number completed: <i>N</i> = 88</p> <ul style="list-style-type: none"> • Group 1: <i>n</i> = 91 • Group 2: <i>n</i> = 27 <p>Gender, males: (as defined by researchers)</p> <ul style="list-style-type: none"> • Not reported <p>Race / ethnicity or nationality (as defined by researchers):</p> <ul style="list-style-type: none"> • The study occurred at St. Christopher’s Hospital for Children, Philadelphia, Pennsylvania. The authors did not identify race or ethnicity of the participants. <p>Age</p> <ul style="list-style-type: none"> • At the start of antibiotics, the mean gestation and chronological age was 28.8 weeks and 26.9 days <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Use of vancomycin or meropenem <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • No stated <p>Covariates identified:</p> <ul style="list-style-type: none"> • Not reported
Interventions	Both: Compared the use of vancomycin and meropenem before and after the implementation of a guideline that directed treatment with antibiotics
Outcomes	<p>Primary outcome(s):</p> <ul style="list-style-type: none"> • Days of therapy before and after guideline implementation <p>Secondary outcome(s)</p> <ul style="list-style-type: none"> • For each course of vancomycin or meropenem was the use <ul style="list-style-type: none"> ○ Clearly indicated ○ Likely indicated ○ Clearly not indicated ○ Unclear if indicated <p>Safety outcome(s):</p> <ul style="list-style-type: none"> • Not reported <p>*Outcomes of interest to the CMH CPG or CAT development team</p>

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Notes	Results:
	Days of therapy before guideline- Vancomycin, 155/1,000 patient days Meropenem. 56/1,000 patient days Days of therapy after guideline Vancomycin, 101/1,000 patient days Meropenem, 12/ 1,000

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Lance et al. (2016)

<i>Characteristics of Study</i>	
Methods	QI Project- Abstract only
Participants	<p>Participants: Patients diagnosed with NEC (Bell Stage 2 or higher) from 2007-2014 Setting: Arkansas Children’s Hospital Number enrolled into study: <i>N</i> = 142</p> <ul style="list-style-type: none"> • Group 1, non-surgical NEC: <i>n</i> = 65 • Group 2, surgical NEC: <i>n</i> = 77 <p>Number completed: <i>N</i> = 142</p> <ul style="list-style-type: none"> • Group 1: <i>n</i> = 65 • Group 2: <i>n</i> = 77 <p>Gender, males: (as defined by researchers)</p> <ul style="list-style-type: none"> • Not reported <p>Race / ethnicity or nationality (as defined by researchers):</p> <ul style="list-style-type: none"> • The study occurred at Arkansas Children’s Hospital. The authors did not identify race or ethnicity of the participants. <p>Age</p> <ul style="list-style-type: none"> • Not reported <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Diagnosis of NEC (Bell stage 2 or higher) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Patients with gastroschisis, encephalocele, congenital heart defects, and/or < 7 days of antibiotic therapy <p>Covariates identified:</p> <ul style="list-style-type: none"> • Not reported
Interventions	<p>Both: Separated care out by length of therapy</p> <ul style="list-style-type: none"> • 8-10 days • 11-14 days • > 14 days
Outcomes	<p>Primary outcome(s):</p> <ul style="list-style-type: none"> • *Parenteral nutrition complications • *Intestinal stricture • Neurodevelopmental disabilities • Mortality <p>Secondary outcome:</p> <ul style="list-style-type: none"> • Not reported <p>Safety outcome:</p> <ul style="list-style-type: none"> • Not reported <p>*Outcomes of interest to the CMH CPG or CAT development team</p>

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Notes	Results:
	<ul style="list-style-type: none">• Empiric regimens were not de-escalated (not defined)<ul style="list-style-type: none">○ Total = 95/113 (57%)• No differences were seen between de-escalated and usual care antibiotic delivery in:<ul style="list-style-type: none">○ Parenteral nutrition complications○ Intestinal stricture○ Neurodevelopmental disabilities○ Mortality

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Shenk et al. (2019)

<i>Characteristics of study</i>	
Methods	QI Project- Slide from presentation only
Participants	<p>Participants: None</p> <p>Setting: University of Pittsburg Medical Center</p> <ul style="list-style-type: none"> • Diagnosis of NEC Bell stage II <ul style="list-style-type: none"> ○ Temp instability ○ Apnea and bradycardia <ul style="list-style-type: none"> ▪ Stage IIa - abdominal tenderness and no bowel sounds, definite pneumatosis on abdominal x-ray ▪ Stage IIb – abdominal tenderness and no bowel sounds with abdominal cellulitis, definite pneumatosis plus portal venous gas on abdominal x-ray
Interventions	<ul style="list-style-type: none"> • Both <ul style="list-style-type: none"> ○ For the first 48 hours, empiric antibiotics <ul style="list-style-type: none"> ▪ Ampicillin or vancomycin ▪ Cefepime ▪ Metronidazole ○ If isolated NEC after 48 hours <ul style="list-style-type: none"> ▪ Piperacillin-tazobactam monotherapy • Length of therapy <ul style="list-style-type: none"> ○ Stage IIa – 7 days of antibiotics, ○ Stage IIb – 14 days of antibiotics
Outcomes	<p>Primary outcome(s):</p> <ul style="list-style-type: none"> • *Duration of antibiotics <p>Secondary outcome:</p> <ul style="list-style-type: none"> • Not reported <p>Safety outcome:</p> <ul style="list-style-type: none"> • Not reported <p>*Outcomes of interest to the CMH CPG or CAT development team</p>
Notes	<p>Results:</p> <ul style="list-style-type: none"> • During the 7-month baseline period, length of antibiotic treatment of IIa and IIb NEC was 9.8 days • For the 15 months following the initiation of the guideline, length of antibiotic treatment decreased to 7.7 days. • “A few patients required extended therapy due to persistence of pneumatosis” – not quantified • No patient required re-institution of therapy

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Appendix

Algorithm for Bell Stage II NEC, from Albert et al. (2018)

