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The Therapeutic Dilemma of Antibiotic Duration in Medical Necrotizing Enterocolitis Across Neonatal Intensive Care Units: A Narrative Review

Alanoud Zaid Aljarbou[1*]
[1]Department of Pediatrics, College of Medicine, Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

Author Designation: [1]Assistant Professor

*Corresponding author: Alanoud Zaid Aljarbou (e-mail: dralanoudresearch@gmail.com).

Abstract Necrotizing enterocolitis in neonatal intensive care units was a serious gastrointestinal emergency but uncertainty over optimal antibiotic duration led to wide variability in clinical practice. This narrative review integrated clinical evidence with biological and contextual determinants of disease to examine factors contributing to heterogeneity in antibiotic prescribing and to synthesize contemporary approaches to treatment duration. Genetic susceptibility, ischemia-reperfusion injury, oxidative stress, feeding practices, microbial development and diagnostic uncertainty contributed to disease heterogeneity, shaping antibiotic strategies and their potential impact on clinical outcomes and gut microbiota. A systematic literature search of PubMed, Scopus and Web of Science revealed English-language studies published between January 2014 and December 2025 that evaluated antibiotic duration following a diagnosis of medical NEC and identified 6 studies eligible for this narrative synthesis. The available evidence demonstrated marked inter- and intra-institutional variability in antibiotic duration, with reported short courses of less than 7 days and prolonged courses of more than 14 days, even among infants with comparable disease severity. Contributing factors included institutional protocols, diagnostic uncertainty and individualized clinical risk assessment. This review observed that shortened, severity-guided antibiotic strategies were not consistently associated with increased short-term complications, whereas prolonged courses were linked to microbiome disruption, delayed feeding, longer hospitalization, higher infection risk and greater antimicrobial resistance. In individual studies, prolonged antibiotic exposure was associated with reported differences in hospital stay ranging from 8 to 12 days and odds ratios for late-onset sepsis between 1.5 and 2.0. These findings were limited by confounding factors such as disease severity, center-specific practices and heterogeneous outcome reporting, highlighting the need for a narrative review to synthesize current evidence and contextualize clinical practice rather than produce pooled quantitative estimates. Overall, current evidence remained insufficient to define an optimal treatment duration, underscoring the need for standardized clinical frameworks, improved risk stratification and prospective multicenter studies to inform antibiotic stewardship in medically managed NEC.

Key Words Necrotizing Enterocolitis, Antibiotic Duration, Neonatal Intensive Care, Practice Variation, Antibiotic Stewardship

INTRODUCTION

Medical Necrotizing Enterocolitis (NEC) presents a persistent clinical challenge in Neonatal Intensive Care Units (NICUs): antibiotics are essential to management, yet evidence guiding their optimal duration remains limited. NEC is a leading gastrointestinal emergency in preterm infants linked to high mortality, prolonged hospital stays and long-standing consequences such as intestinal failure and adverse neurodevelopmental outcomes [1,2]. Clinically, the disease is characterized by feeding intolerance, abdominal distension, systemic instability and radiographic findings including pneumatosis intestinalis, reflecting its heterogeneous and unpredictable course [3]. Despite advances in neonatal care, NEC continues to impose a substantial global burden, with marked variation in incidence, outcomes and management across institutions and regions [4,5].

Most infants with NEC are managed medically, commonly classified as Bell stage II disease, yet limited ability to predict progression or recovery remains [6]. Antibiotic therapy is a universal component of treatment, reflecting the roles of

intestinal barrier disruption, bacterial translocation and inflammation in NEC pathophysiology [7]. However, the absence of a single causative pathogen or validated biomarkers of disease resolution leaves clinicians without objective criteria to guide antibiotic discontinuation [8]. Consequently, antibiotic duration varies widely across NICUs, with reported courses ranging from fewer than seven days to more than two weeks for infants with similar clinical presentations [9,10]. Insufficient treatment raises concern for recurrence, progression to surgical NEC or systemic infection, whereas prolonged antibiotic exposure in preterm infants is associated with microbiome disruption, invasive fungal infection, late-onset sepsis, antimicrobial resistance and potentially increased NEC risk [11-13]. Current recommendations generally suggest treatment durations of 7-14 days but provide limited guidance for individualized decision-making [14]. Given that ethical and methodological challenges have constrained randomized trials, the available evidence remains heterogeneous (retrospective cohorts, practice surveys, expert opinion and single-center quality improvement initiatives) [15]. In this context, a narrative synthesis is warranted to evaluate existing evidence, explore drivers of practice variation and identify priorities for future research.

Objectives

The objectives of this review were to:

- Summarize the range of antibiotic durations reported in medically managed necrotizing enterocolitis (Bell stage II-III) and describe the associated clinical outcomes as documented in the literature
- Discuss the key determinants of practice variability across neonatal intensive care units, including institutional protocols, diagnostic uncertainty and clinician risk assessment

Etiological Contributors and Clinical Considerations Influencing Antibiotic Duration:

Necrotizing enterocolitis (NEC) is a multifactorial disorder in preterm infants and the interplay of genetic, physiological and environmental factors contributes not only to disease susceptibility but also to variability in clinical management, particularly the duration of antibiotic therapy [16]. Clinicians often adjust therapy length based on perceived disease severity, risk of progression and patient-specific vulnerabilities, leading to marked heterogeneity across Neonatal Intensive Care Units (NICUs).

Genetic Predisposition and Inflammatory Response

Genetic factors modulate susceptibility to NEC and influence the clinical course, which can affect clinicians' decisions regarding antibiotic therapy. Variants in Toll- like receptor 4 (TLR4), NFκB1, NOD2 and interleukin genes (IL-6, IL17F) have been associated with heightened inflammatory responses to bacterial colonization, while loss-of-function variants in SIGIRR amplify TLR4-mediated intestinal inflammation [17-19]. Autophagy-related genes such as ATG16L1 further contribute to mucosal vulnerability [20]. Infants with such predispositions may present with more severe or rapidly progressing disease, prompting some NICUs to extend empiric antibiotic courses despite limited evidence, thereby contributing to inter-institutional variability.

Ischemia, Hypoxia-Reperfusion Injury and Hematologic Risk Factors

Preterm neonates are uniquely susceptible to intestinal ischemia and hypoxia- reperfusion injury, compounded by immature intestinal perfusion, stasis and delayed motility [21-23]. Intrauterine growth restriction (IUGR) results in chronic fetal hypoxia and preferential blood flow to vital organs, leaving the gut vulnerable to ischemic insults [24,25]. Early-life anemia and blood transfusions further compromise mucosal oxygenation and may trigger transfusion-associated NEC (TANEC) [26-29]. These risk factors influence clinicians' risk assessment, often leading to longer empiric antibiotic regimens in infants perceived to be at higher risk for disease progression or complications. While the evidence supporting ischemia, hypoxia, anemia and transfusion exposure primarily establishes risk for NEC development rather than treatment response, these factors are frequently extrapolated by clinicians to justify prolonged antibiotic continuation in the post-diagnosis period, despite limited data demonstrating that extended duration mitigates ischemia-driven disease progression or recurrence.

Oxidative Stress and Gut Immaturity

Preterm neonates experience heightened oxidative stress due to high metabolic demand, immature antioxidant defenses and supplemental oxygen exposure [30]. Reactive Oxygen Species (ROS) destroy intestinal epithelial cells and barrier integrity, synergizing with ischemic and inflammatory pathways to exacerbate NEC vulnerability [31-33]. Infants with signs of oxidative injury or severe prematurity may trigger more conservative antibiotic strategies, reflecting clinician concern for subtle but high-risk mucosal injury.

Feeding Practices and Microbial Colonization

Enteral nutrition strategies, human milk feeding and gut microbiome stability are additional determinants of perceived NEC risk. Exclusive human milk provides trophic and immunomodulatory factors that protect the gut [34,35], while early trophic feeding and standardized advancement improve outcomes [36]. Conversely, delayed or intermittent feeding may prolong mucosal immaturity and increase bacterial translocation risk. Variability in feeding protocols and the use of probiotics (e.g., Lactobacillus rhamnosus GG, Bifidobacterium infantis BB-02, B. lactis BB-12, Streptococcus thermophilus TH-4) contribute to differing clinician assessments of disease risk, influencing decisions on antibiotic duration across centers [37,38]. In practice, decisions regarding advancement or withholding of enteral feeds are frequently coupled to antibiotic continuation, such that delayed feeding tolerance or cautious

refeeding often reinforces prolonged antimicrobial therapy, despite limited evidence that feeding readiness reliably reflects ongoing infectious risk or the need for extended antibiotic exposure.

Diagnostic Uncertainty and Staging

Accurate prompt diagnosis of NEC is challenging because of subtle clinical signs and variable radiographic findings [39]. Multiple staging systems exist for necrotizing enterocolitis, including the original Bell criteria, the Modified Bell Staging system and standardized case definitions developed by the Vermont Oxford Network (VON) [40]. Imaging modalities, including abdominal radiography and ultrasound with Doppler evaluation, provide essential information but are limited in sensitivity for early disease [41]. Diagnostic ambiguity often leads clinicians to extend empiric antibiotic therapy "to be safe," particularly in infants with equivocal signs or risk factors for rapid deterioration. The combined influence of genetic susceptibility, ischemic and hematologic stressors, oxidative injury, feeding practices, microbiome status and diagnostic uncertainty creates a spectrum of perceived risk among preterm infants with medical NEC. This heterogeneity in patient factors and clinical presentation drives the wide variability in antibiotic duration observed across NICUs, as clinicians balance the competing risks of undertreatment and prolonged therapy in the absence of validated biomarkers or standardized evidence-based guidance.

Medical Management and Antibiotic Strategies

Management of Bell Stage II NEC centers on supportive care, bowel rest and broad-spectrum antibiotics, typically ampicillin, gentamicin and either metronidazole or clindamycin for 7-14 days [42]. Empiric antibiotic initiation at diagnosis is widely accepted as necessary to address suspected infection and inflammatory translocation; however, the decision to continue antibiotics beyond the initial stabilization phase represents a distinct stewardship challenge that is less clearly supported by evidence. The absence of a definitive pathogen and validated biomarkers for disease resolution makes optimal therapy duration uncertain. Studies demonstrate substantial variability across NICUs, with some centers using shorter courses (<7 days) and others extending therapy beyond two weeks [43,44]. Institutional protocols, clinician experience, disease severity and patient factors such as prematurity or comorbidities strongly influence decisions [45]. Prolonged antibiotic exposure can disrupt the developing microbiome, promote Gram-negative overgrowth and increase risks of late-onset sepsis, fungal infection and NEC progression, while excessively short courses may inadequately control infection. Quality improvement initiatives show that protocolized pathways can safely reduce exposure and improve consistency [46]. Overall, Bell Stage II NEC management exemplifies the clinical paradox: antibiotics are essential but variability in duration reflects uncertainty, risk tolerance and institutional practices, highlighting the need for evidence-based guidance to optimize outcomes.

Impact of Antibiotic Exposure on NEC Development and Outcomes

Antibiotics in medically managed NEC protect against bacterial translocation and systemic infection but can also cause harm when overused, contributing to wide variation in duration across NICUs [47]. Observational studies show that prolonged therapy-especially without confirmed infection-may increase NEC risk, delay full enteral feeds and prolong hospitalization [48,49]. Extended courses disrupt the neonatal gut microbiome, suppressing beneficial commensals like *Bifidobacterium* and favoring pathogenic Gram-negative organisms, which exacerbate inflammation and compromise mucosal integrity [50]. Shorter or limited antibiotic exposure, including maternal intrapartum therapy, appears less harmful and does not significantly affect NEC incidence in VLBW or preterm infants [51]. The lack of validated biomarkers to guide discontinuation, combined with clinician judgment, institutional protocols and perceived disease severity, drives substantial variability in practice. These findings emphasize the delicate balance between preventing disease progression and avoiding microbial dysbiosis, explaining why antibiotic duration remains highly heterogeneous in NICUs.

Evidence Analysis

This narrative review critically synthesized contemporary evidence on antibiotic duration in medically managed necrotizing enterocolitis (NEC) to characterize current practices and associated outcomes across neonatal intensive care units (NICUs). A comprehensive search of PubMed, Scopus and Web of Science identified English-language studies published between January 2014 and December 2025, reflecting modern NICU practices and evolving NEC management, using predefined search terms including "necrotizing enterocolitis," "medical NEC," "Bell stage II NEC," "Bell stage III NEC," "antibiotic duration," "antibiotic therapy," "treatment duration," "practice variation," "NICU" and "quality improvement." Eligible studies included clinical guidelines, expert consensus statements, clinician surveys, observational cohort studies and quality improvement initiatives that reported outcomes of antibiotic therapy specifically in medically managed NEC (Bell stage II-III), addressed antibiotic duration or protocolized approaches and were published in peer-reviewed journals, while studies focused on surgical NEC, prophylactic antibiotic exposure, non-human models, case reports or reports lacking substantive synthesis were excluded. For observational studies, specific inclusion criteria required clearly defined Bell stage II-III NEC, reported antibiotic duration as a primary or secondary outcome and adjustment for at least one confounder (e.g., gestational age, birth weight or disease severity). Titles, abstracts and full texts were reviewed, with data extracted on study design, population characteristics, NEC staging, antibiotic regimens and duration, clinical outcomes and measures of practice variation. Given substantial heterogeneity across studies, findings were synthesized narratively without formal meta-analysis or

Table 1: Summary of Evidence on Antibiotic Duration in Medically Managed Necrotizing Enterocolitis

Study	Study Type/Setting	Country	Sample Size	Sample Characteristics	NEC Population	Antibiotic Duration Strategy	Outcomes Evaluated	Key Findings	Major Limitations
Blackwood *et al.* [50]	Multicenter clinician survey	USA	246 clinicians	Neonatologists and NICU providers	Bell stage II-III NEC after diagnostic confirmation	Clinician-reported duration of antibiotic therapy	Practice variation	Antibiotic duration varied widely and was primarily driven by institutional protocol rather than disease-specific evidence	Self-reported practice, no patient outcomes
Bull *et al.* [51]	Retrospective single-center cohort	USA	102 infants	Preterm infants with NEC	Bell stage II-III NEC managed non-operatively	Severity-guided duration, 5-14 days	Recurrence, progression to surgery, length of stay	Shorter antibiotic courses in less severe disease were not associated with increased recurrence or progression	Single center, retrospective
Ahmad *et al.* [52]	Multicenter observational cohort (CHNC)	USA	591 infants, 315 medical NEC	Infants treated at tertiary NICUs	Bell stage II-III NEC following diagnosis	Observed real-world duration variability	Length of stay, time to full feeds	Longer antibiotic duration was associated with longer hospitalization and delayed feeding advancement	Observational design, confounding by severity
Gill *et al.* [53]	Systematic review	International	375 infants across 5 studies	Mixed medical and surgical NEC	Bell stage II-III NEC	Variable regimens and treatment durations	Disease progression, surgery, mortality	No study provided sufficient evidence to define optimal antibiotic duration	Small studies, marked heterogeneity
Pace *et al.* [54]	Quality improvement initiative	USA	71 infants	Pre- and post-protocol implementation	Bell stage II NEC treated medically	Protocolized 5-10 vs 7-14 day courses	Antibiotic days, recurrence, mortality	Standardized shorter courses reduced antibiotic exposure without worsening outcomes	Small sample, single center
Mahmood *et al.* [55]	Quality improvement initiative	USA	64 infants	Preterm infants with culture-negative NEC	Bell stage II A medical NEC	Standardized 7-day antibiotic course	Antibiotic days, time to feeds, LOS	Reduced antibiotic exposure, faster feeding advancement, fewer central line days	Single center, QI design

NEC: Necrotizing enterocolitis, NICU: Neonatal intensive care unit, LOS: Length of stay, TPN: Total parenteral nutrition, DOT: Days of therapy, APSA: American Pediatric Surgical Association, CHNC: Children's Hospitals Neonatal Consortium, VON: Vermont Oxford Network, IDSA: Infectious Diseases Society of America, SIS: Surgical Infection Society, WSES: World Society of Emergency Surgery

risk-of-bias assessment. Table 1 summarizes key studies on antibiotic duration in medical NEC (Bell stage II-III).

DISCUSSION

Antibiotic duration in medically managed NEC varies widely across NICUs, driven by institutional protocols, diagnostic uncertainty and the absence of validated biomarkers [8,45,52]. Survey data show treatment decisions largely follow institutional norms rather than disease-specific evidence [52]. Observational studies indicate that shorter, severity-guided courses (5-14 days) are not associated with increased recurrence or progression to surgery, whereas prolonged exposure (≥14 days) correlates with delayed feeding, longer hospitalization and microbiome disruption [53-57]. However, confounding by disease severity and heterogeneous outcome definitions limit causal inference [53,54].

Practice considerations, based on the available descriptive evidence, may include exploring protocolized, severity-guided duration pathways; using diagnostic uncertainty as an opportunity for daily reevaluation rather than automatic prolongation; and incorporating antibiotic duration into local stewardship audits. Future prospective multicenter studies with standardized outcomes and biomarker validation are needed to provide more definitive guidance.

Systematic synthesis of the available literature remains limited; evidence drawn from 375 infants across five heterogeneous studies was insufficient to define an optimal antibiotic duration for medical NEC [55]. More recent quality improvement initiatives suggest that protocolized approaches can safely reduce antibiotic exposure, with reduced antibiotic days reported in cohorts of 71 and 64 infants, respectively, without increased recurrence or mortality [56,57]. Nonetheless, the potential risks of too-short therapy, including disease recurrence or sepsis, remain underexplored, requiring careful clinical judgment. Collectively, these findings indicate that although antibiotics remain central to medical NEC management, prolonged therapy has not been shown to improve outcomes and emerging evidence supports shorter, standardized and severity-informed antibiotic strategies to reduce unnecessary exposure while maintaining clinical safety.

CONCLUSIONS

Antibiotic duration in medically managed NEC varies widely due to weak evidence and diagnostic uncertainty. Observational studies suggest shorter, severity-guided regimens are feasible but prospective trials are lacking. Clinically, daily reassessment is key; stewardship should prioritize minimizing unnecessary exposure. Future research needs multicenter trials, standardized outcomes and biomarkers.

Strengths and Limitations

This narrative review comprehensively synthesizes biological, clinical and contextual drivers of antibiotic

duration variability in medically managed NEC, highlighting institutional practice differences. However, heterogeneity across study designs and outcome definitions precluded meta-analysis; reliance on observational data and quality improvement initiatives introduces potential publication bias and causal inferences are not possible.

Conflicts of Interest

The author declares no financial, commercial or other relationships that could be perceived as a conflict of interest.

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