



***Clostridioides difficile* in Neonatal Intensive Care Unit Patients: A Systematic Review**

**Centers for Disease Control and Prevention
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Suggested citation:

Centers for Disease Control and Prevention. *Clostridioides difficile* in Neonatal Intensive Care Unit Patients: A Systematic Review Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality and Promotion, Atlanta, GA. August 30, 2018. (<https://www.cdc.gov/ncezid/dhqp/index.html>)

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1. Introduction

Clostridioides difficile (*C. difficile*), a frequently identified healthcare-associated pathogen in the United States, causes considerable morbidity and mortality.¹ Many uncertainties persist regarding the epidemiology of *C. difficile* in neonates, but despite these uncertainties, development of guidance for the prevention and control of *C. difficile* in the neonatal intensive care unit (NICU) setting is warranted.

The pathogenicity of *C. difficile* in neonates and infants has long been debated. More than four decades after investigators identified a link between toxin-producing *C. difficile* and pseudomembranous colitis in adults, most experts regard this organism as a harmless commensal in neonates and infants.² Up to 70% of healthy newborns may become colonized in the first months of life, and most remain asymptomatic, even in the presence of large numbers of toxin-producing bacteria.²⁻⁵ It has been proposed that the immature intestinal mucosa of the neonate might lack receptors for *C. difficile* toxin, although other factors such as an immature immune response may also play a role.⁶⁻⁹ Despite these theories, it remains unknown why most colonized infants do not develop clinically relevant *C. difficile* infection (CDI).¹⁰ Cases of CDI have been confirmed in neonates, but there is a lack of consensus on a definition for this disease in this population. Because of this issue and the difficulty in discriminating between *C. difficile* colonization and CDI, guidelines and expert guidance from professional societies, including the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the American Academy of Pediatrics (AAP) do not recommend routine *C. difficile* testing in neonates and young children.^{11,12}

While clinically relevant CDI remains rare in neonates, several studies provide indirect evidence suggesting that CDI is an increasingly common diarrheal pathogen in infants and young children.¹³⁻¹⁵ The increase in rates could be due to the availability of more sensitive testing techniques;¹⁴ nevertheless, the issue of *C. difficile* in the NICU is an important area to examine.

NICU stays can be prolonged, and it is difficult to predict when a given infant may develop susceptibility to CDI. While risk factors for clinically significant CDI are not well understood in young infants, NICU patients have frequent exposures that have been identified as CDI risk factors in older children and adults, including exposures to antibiotics and gastric acid suppression medication.¹⁶⁻¹⁸ Further, compelling evidence demonstrates *C. difficile* transmission to neonates in healthcare settings, often within the first days of life.^{19,20} *C. difficile* spores have been isolated from baby scales, baths, incubators, and refrigerators in NICUs, and *C. difficile* strains known to cause disease in adults have been isolated from asymptomatic neonates.²¹⁻²⁵

The epidemiology of *C. difficile* is changing, rates of pediatric CDI are rising in hospital settings as well as in the community, and evidence points to transmission in healthcare environments, including the NICU. Clinically relevant guidance is needed to inform the care of infants in NICU settings.

2. Scope and Purpose

This systematic review aimed to evaluate available evidence on three topics related to the prevention and control of *C. difficile* in NICUs. The topics included:

- How to identify NICU patients at high risk for clinically relevant CDI who may warrant *C. difficile* testing,
- The optimal tests for diagnosing clinically relevant CDI, and
- Interventions that can prevent adverse clinical consequences in neonates with CDI, including transmission to other NICU patients, healthcare personnel, or caregivers.

The topics were determined by the workgroup, vetted at national infectious disease society meetings, and refined based on input received from the Healthcare Infection Control Practices Advisory Committee (HICPAC) at public meetings occurring from November 2010 to December 2016.

3. Methods

3.1 Development of Key Questions

Three questions were developed to identify the best available evidence and were finalized after vetting with HICPAC. The questions formulated to guide the literature review are:

Question A: What clinical, demographic, or other criteria have been shown to prompt diagnostic testing for *C. difficile* that results in identifying symptomatic *C. difficile*-infected NICU patients?

Question B: What tests or sequence of tests for *C. difficile* perform best in detecting CDI among NICU patients?

Question C: What is the significance of a positive *C. difficile* test in a NICU patient?

3.2 Systematic Literature Search

The Workgroup selected key words and medical subject heading (MeSH) terms to search four electronic databases through July 5, 2016: MEDLINE®, EMBASE®, CINAHL®, and the Cochrane Library (Appendix, Section 1.2). These terms were relevant to the key questions and aligned with terms used in reviews and studies on this subject.

3.3 Study Selection and Data Extraction

One subject matter expert (AE or MI) screened titles and abstracts from articles published through December 2012, and the other reviewed a random sample of 20% of titles and abstracts to assess and resolve any differences in screening decisions. Titles and abstracts from articles published between January 2012 and July 5, 2016, were screened by two independent reviewers (MD, AE, ADO, or ECS). Articles were retrieved for full text review if they were:

- Relevant to a key question;
- Primary research, a systematic review, or meta-analysis; and
- Written in English.

Two independent reviewers (MD, AE, MI, ADO, or ECS) reviewed each full-text article for inclusion and exclusion criteria (Appendix, Section 2). A third reviewer (AE or MI) resolved differences of opinion. However, no studies were retrieved that answered the key questions for NICU patients.

4. Conclusions

This systematic review identified several studies related to the key questions, but none directly addressed the questions for NICU patients. Thus, the evidence was not sufficient to make evidence-based recommendations about the following issues:

- Characteristics of NICU patients at high risk for clinically relevant CDI who would warrant diagnostic testing for *C. difficile*;
- The optimal assay or series of assays for detecting CDI among NICU patients; or
- The significance of a positive *C. difficile* test in a NICU patient.

The literature review revealed substantial gaps in the available data regarding risk factors for CDI in neonates cared for in NICUs and interventions to prevent *C. difficile* transmission in this setting. The unanswered questions include:

- What is the potential for toxigenic *C. difficile* to cause diarrhea in young infants?
- If *C. difficile* can cause diarrhea in young infants, are there any biomarkers or clinical or laboratory factors that can differentiate diarrhea due to another cause from diarrhea due to *C. difficile*?
- If CDI occurs in neonates, what is a valid definition of CDI in this population?
- If it is possible to clearly identify diarrhea from *C. difficile*, what are the risk factors for *C. difficile* based on a valid definition of CDI in these infants, including risk factors associated with changes in the microbiome?
- Which traditional interventions that enhance the protective effects of the normal microbiome, prevent infection (e.g., antimicrobial stewardship and reduced H2 blockers), and decrease transmission (e.g., treating to decrease volume of diarrhea, mitigating environmental contamination, and implementing contact precautions) are also effective in the NICU?

Young infants colonized with toxigenic *C. difficile* rarely develop clinical disease, and it is not known why. Additionally, the consequences of colonization with *C. difficile* in the first year of life remain unknown, and it is not understood whether colonized infants are more or less likely than non-colonized infants to develop clinically relevant CDI later in life. Further, high-quality evidence is not available to support a non-invasive test or series of tests that can reliably identify infants with CDI.

The actual burden of CDI in NICU patients is not clear. Further, it is not known how this burden might be affected by other factors, such as prematurity, breastmilk versus formula feeding, hospital versus community acquisition, and previous treatment with antibiotics or medications to prevent gastric acid secretion. Additionally, the effect of the infant microbiome, both in health and illness, in facilitating *C. difficile* colonization, symptomatic disease, and recurrence remains uncertain. A central multi-center registry of infants with strictly defined CDI would advance knowledge regarding these risk factors. Similar databases have helped to build clinicians' understanding of relevant risk factors and findings for other diseases.^{26,27}

The systematic review also revealed a lack of high-quality evidence about the impact of *C. difficile* in the NICU. For instance, it is not clear whether infants colonized with toxigenic *C. difficile* contribute to the transmission of *C. difficile* to other hospitalized patients, or whether certain infection prevention practices may decrease the risk of *C. difficile* transmission from symptomatic *C. difficile*-infected NICU patients to others in the NICU. Certainly, evidence suggests the possibility of environmental contamination leading to transmission.²¹⁻²⁵ But while this evidence is important to highlight, it is insufficient to make a definitive statement about *C. difficile*-colonized or -infected NICU patients and transmission of the pathogen.^{26,27}

Many questions remain in the consideration of *C. difficile* and CDI in the NICU; the paucity of evidence points to larger gaps in our understanding of this challenging pathogen in these vulnerable patients. Until these questions are answered, interim guidance is available to inform the delivery of healthcare in NICUs.

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Acknowledgements

The Centers for Disease Control and Prevention thanks the many individuals and organizations who provided valuable feedback on and support of this document during the development process: Sonya Arundar, MS; Wanda Barfield, MD, MPH; Wendy Bruening, PhD, Meredith Noble Calloway, MS; Kendra Cox, MA; Susan Dolan, RN, MS, CIC; Yvonne Florence; Joann Fontanarosa, PhD; Suzanne Frey, BSN, RN; Rachel Gorwitz MD, MPH; David Kaufman, MD; Anne McCarthy; Amanda Paschke, MD, MSCE; Richard Polin, MD; Kristin Tansil Roberts, MSW; Lisa Saiman, MD; Pablo Sanchez, MD; Karen Schoelles, MD, SM; Srila Sen, MA; and Gautham Suresh, MD.

Additionally, Michael Bell, MD, and L. Clifford McDonald, MD, Centers for Disease Control and Prevention, and Jeffrey Hageman, MHS, formerly Centers for Disease Control and Prevention, provided technical advice during various stages of document development.

Declarations of Interest

None of the workgroup members reported financial or intellectual interests related to the topics in this review except for the following:

- Dr. Bryant: Reports receiving research support from Pfizer
- Dr. Milstone: Reports receiving research support from Sage Products and MITRE Corporation

Abbreviations

Abbreviation	Definition
<i>C. difficile</i>	<i>Clostridioides difficile</i>
CDI	<i>Clostridioides difficile</i> infection
NICU	Neonatal intensive care unit