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

Centers for Disease Control and Prevention
National Center for Zoonotic and Emerging Infectious Diseases
Division of Healthcare Quality Promotion

August 30, 2018
Updated September 2020

Alexis Elward, MD[a], Michael T. Brady, MD[b], Kristina Bryant, MD[c], Mahnaz Dasti, MPH, MTASCP[d], Loretta Fauerbach, MS, CIC[e], Kathleen L. Irwin, MD, MPH[f], Martha Iwamoto MD, MPH[g], Gretchen Kuntz, MSW, MSLIS[h], Brian Leas, MA, MS[i], Aaron Milstone, MD[j], Jason Newland, MD[a], Amanda D. Overholt, MPH[k], Craig A. Umscheid, MD, MSCE[i], and W. Charles Huskins, MD, MSc[l], for the Healthcare Infection Control Practices Advisory Committee[m]

[a]Washington University School of Medicine, St. Louis, MO; [b]Nationwide Children's Hospital, Columbus, OH; [c]University of Louisville, Louisville, KY; [d]Time Solutions, LLC, Atlanta, GA; [e]Fauerbach & Associates, LLC, Gainesville, FL; [f]formerly Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA; [g]formerly Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA (now with the New York City Department of Health and Mental Hygiene, New York, NY); [h]formerly Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA (now with the University of Florida-Jacksonville, Jacksonville, FL); [i]Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA; [j]Johns Hopkins University, Baltimore, MD; [k]formerly Northrop Grumman Corporation, Atlanta, GA; [l]Mayo Clinic, Rochester, MN; and [m]the Healthcare Infection Control Advisory Committee

Table of Contents

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 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 KI) 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: SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches to *Clostridioides difficile* prevention (DOI: 10.1017/ice.2018.209).

5. References

1. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med.* 2014;370(13):1198-1208.
2. Jangi S, Lamont JT. Asymptomatic colonization by Clostridium difficile in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr.* 2010;51(1):2-7.
3. Adlerberth I, Huang H, Lindberg E, et al. Toxin-producing Clostridium difficile strains as long-term gut colonizers in healthy infants. *J Clin Microbiol.* 2014;52(1):173-179.
4. Al-Jumaili IJ, Shibley M, Lishman AH, Record CO. Incidence and origin of Clostridium difficile in neonates. *J Clin Microbiol.* 1984;19(1):77-78.
5. Bolton RP, Tait SK, Dear PR, Losowsky MS. Asymptomatic neonatal colonisation by Clostridium difficile. *Arch Dis Child.* 1984;59(5):466-472.
6. Borriello SP. 12th C. L. Oakley lecture. Pathogenesis of Clostridium difficile infection of the gut. *J Med Microbiol.* 1990;33(4):207-215.
7. Eglow R, Pothoulakis C, Itzkowitz S, et al. Diminished Clostridium difficile toxin A sensitivity in newborn rabbit ileum is associated with decreased toxin A receptor. *J Clin Invest.* 1992;90(3):822-829.
8. Keel MK, Songer JG. The distribution and density of Clostridium difficile toxin receptors on the intestinal mucosa of neonatal pigs. *Vet Pathol.* 2007;44(6):814-822.
9. Rolfe RD, Song W. Purification of a functional receptor for Clostridium difficile toxin A from intestinal brush border membranes of infant hamsters. *Clin Infect Dis.* 1993;16 Suppl 4:S219-227.
10. Rousseau C, Lemee L, Le Monnier A, Poilane I, Pons JL, Collignon A. Prevalence and diversity of Clostridium difficile strains in infants. *J Med Microbiol.* 2011;60(Pt 8):1112-1118.
11. Schutze GE, Willoughby RE, Committee on Infectious Diseases, American Academy of Pediatrics. Clostridium difficile infection in infants and children. *Pediatrics.* 2013;131(1):196-200.
12. Dubberke ER, Carling P, Carrico R, et al. Strategies to prevent Clostridium difficile infections in acute care hospitals: 2014 Update. *Infect Control Hosp Epidemiol.* 2014;35(6):628-645.
13. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. *Pediatrics.* 2008;122(6):1266-1270.
14. Zilberberg MD, Tillotson GS, McDonald C. Clostridium difficile infections among hospitalized children, United States, 1997-2006. *Emerg Infect Dis.* 2010;16(4):604-609.
15. Benson L, Song X, Campos J, Singh N. Changing epidemiology of Clostridium difficile-associated disease in children. *Infect Control Hosp Epidemiol.* 2007;28(11):1233-1235.
16. Freedberg DE, Lamouse-Smith ES, Lightdale JR, Jin Z, Yang YX, Abrams JA. Use of Acid Suppression Medication is Associated With Risk for C. difficile Infection in Infants and Children: A Population-based Study. *Clin Infect Dis.* 2015;61(6):912-917.
17. Kim J, Shaklee JF, Smathers S, et al. Risk factors and outcomes associated with severe clostridium difficile infection in children. *Pediatr Infect Dis J.* 2012;31(2):134-138.
18. Sandora TJ, Fung M, Flaherty K, et al. Epidemiology and risk factors for Clostridium difficile infection in children. *Pediatr Infect Dis J.* 2011;30(7):580-584.

19. Delmee M, Verellen G, Avesani V, Francois G. Clostridium difficile in neonates: serogrouping and epidemiology. *Eur J Pediatr.* 1988;147(1):36-40.
20. Zwiener RJ, Belknap WM, Quan R. Severe pseudomembranous enterocolitis in a child: case report and literature review. *Pediatr Infect Dis J.* 1989;8(12):876-882.
21. Faden HS, Dryja D. Importance of asymptomatic shedding of Clostridium difficile in environmental contamination of a neonatal intensive care unit. *Am J Infect Control.* 2015;43(8):887-888.
22. Hecker MT, Riggs MM, Hoyen CK, Lancioni C, Donskey CJ. Recurrent infection with epidemic Clostridium difficile in a peripartum woman whose infant was asymptomatically colonized with the same strain. *Clin Infect Dis.* 2008;46(6):956-957.
23. Rousseau C, Poilane I, De Pontual L, Maherault AC, Le Monnier A, Collignon A. Clostridium difficile carriage in healthy infants in the community: a potential reservoir for pathogenic strains. *Clin Infect Dis.* 2012;55(9):1209-1215.
24. Stoesser N, Crook DW, Fung R, et al. Molecular epidemiology of Clostridium difficile strains in children compared with that of strains circulating in adults with Clostridium difficile-associated infection. *J Clin Microbiol.* 2011;49(11):3994-3996.
25. Larson HE, Barclay FE, Honour P, Hill ID. Epidemiology of Clostridium difficile in infants. *J Infect Dis.* 1982;146(6):727-733.
26. Congenital CMV Disease Research Clinic & Registry. Baylor College of Medicine. https://www.bcm.edu/departments/pediatrics/sections-divisions-centers/cmvregistry/. Accessed July 11, 2018.
27. St. Jude Children's Research Hospital. POND4Kids Pediatric Oncology Networked Databse. 2001-2017; https://www.pond4kids.org/pond/home/. Accessed July 11, 2018.
28. Sandora, T., Bryant, K., Cantey, J., Elward, A., Yokoe, D., & Bartlett, A. (2018). SHEA neonatal intensive care unit (NICU) white paper series: Practical approaches to Clostridioides difficile prevention. Infection Control & Hospital Epidemiology, 39(10), 1149-1153. doi:10.1017/ice.2018.209.

6. Contributors

HICPAC Infection Prevention in Neonatal Intensive Care Units Workgroup
Alexis Elward, MD, Washington University School of Medicine, St. Louis, MO; Kristina Bryant, MD, University of Louisville, Louisville, KY (Chair); Michael Brady, MD, Nationwide Children's Hospital, Columbus, OH; Loretta Fauerbach, MS, CIC, Fauerbach & Associates, LLC, Gainesville, FL; W. Charles Huskins, MD, MSc, Mayo Clinic, Rochester, MN; Gretchen Kuntz, MSW, MSLIS, Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA; Brian Leas, MA, MS, Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA; Aaron Milstone, MD, Johns Hopkins University Hospital, Baltimore, MD; Jason Newland, MD, Washington University School of Medicine, St. Louis, MO; Craig A. Umscheid, MD, MSCE, Center for Evidence-based Practice, University of Pennsylvania Health System, Philadelphia, PA

Healthcare Infection Control Practices Advisory Committee (HICPAC)
HICPAC Members: Hilary M. Babcock, MD, MPH, Washington University School of Medicine in St Louis; Judene Bartley, MS, MPH, CIC, VP Epidemiology Consulting Services, Inc.; Dale W. Bratzler, DO, MPH, The University of Oklahoma Health Sciences Center; Patrick J. Brennan, MD, University of Pennsylvania Health System; Vickie M. Brown, RN, MPH, WakeMed Health & Hospitals; Kristina Bryant, MD, University of Louisville School of Medicine; Lillian A. Burns, MT, MPH, Greenwich Hospital; Ruth M. Carrico, PhD, RN, CIC, University of Louisville School of Medicine; Sheri Chernetsky Tejedor, MD, Emory University School of Medicine; Vineet Chopra, MBBS, MD, MSc, FACP, FHM, The University of Michigan Health System; Daniel J. Diekema, MD, University of Iowa Carver College of Medicine; Alexis Elward, MD, Washington University School of Medicine in St Louis; Jeffrey Engel, MD, North Carolina State Epidemiologist; Loretta L. Fauerbach, MS, CIC, Fauerbach & Associates, LLC; Neil O. Fishman, MD, University of Pennsylvania Health System; Ralph Gonzales, MD, MSPH, University of California, San Francisco; Mary K. Hayden, MD, Rush University Medical Center; Michael D. Howell, MD, MPH, University of Chicago Medicine; Susan Huang, MD, MPH, University of California Irvine School of Medicine; W. Charles Huskins, MD, MSc, Mayo Clinic College of Medicine; Lynn Janssen, MS, CIC, CPHQ, California Department of Public Health; Tammy Lundstrom, MD, JD, Providence Hospital; Lisa Maragakis, MD, MPH, The Johns Hopkins University School of Medicine; Yvette S. McCarter, PhD, University of Florida Health Science Center; Denise M. Murphy, MPH, RN, CIC, Main Line Health System; Russell N. Olmsted, MPH, St Joseph Mercy Health System; Stephen Ostroff, MD, US Food and Drug Administration; Jan Patterson, MD, University of Texas Health Science Center, San Antonio; David A. Pegues, MD, David Geffen School of Medicine at UCLA; Peter J. Pronovost, MD, PhD, The Johns Hopkins University; Gina Pugliese, RN, MS, Premier Healthcare Alliance; Keith M. Ramsey, MD, The Brody School of Medicine at East Carolina University; Selwyn O. Rogers Jr, MD, MPH, The University of Chicago; William P. Schecter, MD, University of California, San Francisco; Barbara M. Soule, RN, MPA, CIC, The Joint Commission; Kurt Brown Stevenson, MD, MPH, The Ohio State University Medical Center; Tom Talbot, MD, MPH, Vanderbilt University Medical Center; Michael L. Tapper, MD, Lenox Hill Hospital; and Deborah S. Yokoe, MD, MPH, Brigham & Women's Hospital.

HICPAC *ex officio* Members: William B. Baine, MD, Agency for Healthcare Research and Quality; Elizabeth Claverie-Williams, MS, US Food and Drug Administration; Nicole Haynes, MD, Health Resources & Services Administration; David Henderson, MD, National Institutes of Health; Stephen Kralovic, MD, MPH, Department of Veterans Affairs; Dan Mareck, MD, Health Resources & Services Administration; Jeannie Miller, RN, MPH, Centers for Medicare & Medicaid Services; Melissa Miller,

BSN, MD, MS, Agency for Healthcare Research & Quality; Paul D. Moore, PhD, Health Resources and Services Administration; Sheila Murphey, MD, US Food and Drug Administration; Tara Palmore, MD, National Institutes of Health; Gary Roselle, MD, Department of Veterans Affairs; Daniel Schwartz, MD, MBA, Centers for Medicare & Medicaid Services; Judy Trawick, RN, BSN, Health Resources & Services Administration; Kim Willard-Jelks, MD, MPH, Health Resources & Services Administration; Rebecca Wilson, MPH, Health Resources & Services Administration.

HICPAC Liaison Representatives: Kathy Aureden, MS, MT(ASCP), SI, CIC, Association of Professionals of Infection Control and Epidemiology, Inc.; Elizabeth Bancroft, MD, Council of State and Territorial Epidemiologists; Nancy Bjerke, BSN, RN, MPH, CIC, Association of Professionals of Infection Control and Epidemiology, Inc., Joan Blanchard, RN, BSN, Association of Perioperative Registered Nurses; Debra Blog, MD, MPH, Association of State and Territorial Health Officials; William A. Brock, MD, Society of Critical Care Medicine; Michelle Cantu, MPH, National Association of County and City Health Officials; Darlene Carey, MSN RN CIC NE-BC FAPIC, Association of Professionals of Infection Control and Epidemiology, Inc., Craig Coopersmith, MD, FACS, FCCM, Society of Critical Care Medicine; Barbara DeBaun, MSN, RN, CIC, Association of Professionals of Infection Control and Epidemiology, Inc.; Elaine Dekker, RN, BSN, CDC, America's Essential Hospitals; Louise M. Dembry, MD, MS, MBA, Society for Healthcare Epidemiology of America; Kathleen Dunn, BScN, MN, RN, Public Health Agency of Canada; Beth Feldpush, PhD, American Hospital Association; Sandra Fitzler, RN, American Health Care Association; Scott Flanders, MD, Society of Hospital Medicine; Janet Franck, RN, MBA, CIC, DNV Healthcare, Inc; Diana Gaviria, MD, MPH, National Association of County and City Health Officials; Jennifer Gutowski, MPH, BSN, RN, CIC, National Association of County and City Health Officials; Lisa Grabert, MPH, American Hospital Association; Valerie Haley, PhD, Association of State and Territorial Health Officials; Lori Harmon, RRT, MBA, Society of Critical Care Medicine; Patrick Horine, MHA, DNV Healthcare, Inc.; Michael D. Howell, MD, MPH, Society of Critical Care Medicine; W. Charles Huskins, MD, MSc, Infectious Diseases Society of America; Marion Kainer, MD, MPH, Council of State and Territorial Epidemiologists; Lilly Kan, DrPH, MA, National Association of County and City Health Officials; Evelyn Knolle, American Hospital Association; Jacqueline Lawler, MPH, CIC, CPH, National Association of County and City Health Officials; Emily Lutterloh, MD, MPH, Association of State and Territorial Health Officials; Lisa Maragakis, MD, Society for Healthcare Epidemiology of America; Michael McElroy, MPH, CIC, America's Essential Hospitals; Lisa McGiffert, Consumers Union; Jennifer Meddings, MD, MSc, Society of Hospital Medicine; Richard Melchreit, MD, Council of State and Territorial Epidemiologists; Sharon Morgan, MSN, RN, NP-C, American Nurses Association; Silvia Muñoz-Price, MD, America's Essential Hospitals; Shirley Paton, RN, MN, Public Health Agency of Canada; Kelly Podgorny, DNP, MS, CPHQ, RN, Joint Commission; Michael Anne Preas, RN, CIC, Association of Professionals of Infection Control and Epidemiology, Inc; Mark E. Rupp, MD, Society for Healthcare Epidemiology of America; Mark Russi, MD, MPH, American College of Occupational and Environmental Medicine; Sanjay Saint, MD, MPH, Society of Hospital Medicine; Robert G. Sawyer, MD, Surgical Infection Society; Roslyne Schulman, MHA, MBA, American Hospital Association; Kathryn Spates, Joint Commission; Linda Spaulding, RN, CIC, DNVGL Healthcare; Lisa Spruce, RN, DNP, ACNS, ACNP, ANP, Association of Perioperative Registered Nurses; Rachel Stricof, MPH, Advisory Council for the Elimination of Tuberculosis; Sheri Chernetsky Tejedor, MD, Society of Hospital Medicine; Donna Tiberi, RN, MHA, Healthcare Facilities Accreditation Program; Margaret VanAmringe, MHS, Joint Commission; Valerie Vaughn, MD, Society of Hospital Medicine; Stephen Weber, MD, Infectious Diseases Society of America; Elizabeth Wick, MD, American College of Surgeons; Robert Wise, MD, Joint Commission; Amber Wood, MSN, RN, CNOR, CIC, CPN, Association of Perioperative Registered Nurses.

Workgroup Technical Advisors

Mahnaz Dasti, MPH; Time Solutions, LLC; Kathleen L. Irwin, MD, MPH, formerly Centers for Disease Control and Prevention; Martha Iwamoto MD, MPH, formerly Centers for Disease Control and Prevention (currently New York City Department of Health and Mental Hygiene, New York, NY); Amanda D. Overholt, MPH, formerly Northrop Grumman Corporation; and Erin Stone, MA, Centers for Disease Control and Prevention.

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

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://wwwdev.cdc.gov/hicpac/reviews/cdiff-nicu/index.html)

Abbreviations

Abbreviation	Definition
C. difficile	*Clostridioides difficile*
CDI	*Clostridioides difficile* infection
NICU	Neonatal intensive care unit