Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

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A panel of experts was convened by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) to update the 2010 clinical practice guideline on *Clostridium difficile* infection (CDI) in adults. The update, which has incorporated recommendations for children (following the adult recommendations for epidemiology, diagnosis, and treatment), includes significant changes in the management of this infection and reflects the evolving controversy over best methods for diagnosis. *Clostridium difficile* remains the most important cause of healthcare-associated diarrhea and has become the most commonly identified cause of healthcare-associated infection in adults in the United States. Moreover, *C. difficile* has established itself as an important community pathogen. Although the prevalence of the epidemic and virulent ribotype 027 strain has declined markedly along with overall CDI rates in parts of Europe, it remains one of the most commonly identified strains in the United States where it causes a sizable minority of CDIs, especially healthcare-associated CDIs. This guideline updates recommendations regarding epidemiology, diagnosis, treatment, infection prevention, and environmental management.

Keywords. *Clostridium difficile*; *Clostridioides difficile*; Guidelines; CDI; CDAD.

EXECUTIVE SUMMARY

Summarized below are recommendations intended to improve the diagnosis and management of *Clostridium difficile* infection (CDI) in adults and children. CDI is defined by the presence of symptoms (usually diarrhea) and either a stool test positive for *C. difficile* toxins or detection of toxigenic *C. difficile,* or colonoscopic or histopathologic findings revealing pseudomembranous colitis. In addition to diagnosis and management, recommended methods of infection control and environmental management of the pathogen are presented. The panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (Figure 1). A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guidelines. The extent to which these guidelines can be implemented is impacted by the size of the institution and the resources, both financial and laboratory, available in the particular clinical setting.

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GUIDELINE RECOMMENDATIONS FOR *CLOSTRIDIUM DIFFICILE* INFECTION

EPIDEMIOLOGY

I. How are CDI cases best defined?

Recommendation

1. To increase comparability between clinical settings, use available standardized case definitions for surveillance of (1) healthcare facility-onset (HO) CDI; (2) community-onset, healthcare facility–associated (CO-HCFA) CDI; and (3) community-associated (CA) CDI *(good practice recommendation)*.

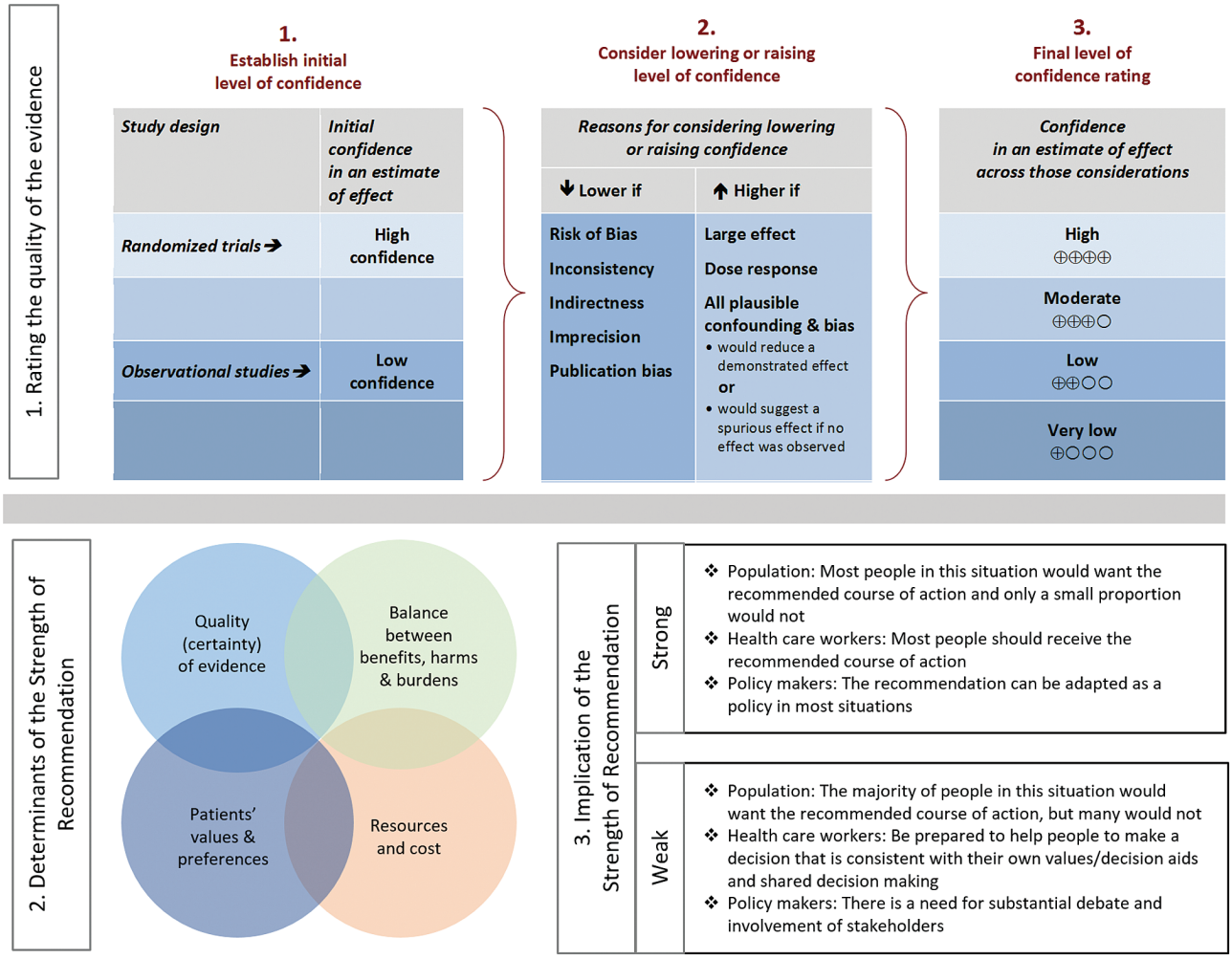

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the *Grading* of Recommendations, Assessment, Development and Evaluation (GRADE) methodology (unrestricted use of this figure granted by the US GRADE Network) [1–4].

II. What is the minimal surveillance recommendation for institutions with limited resources?

Recommendation

1. At a minimum, conduct surveillance for HO-CDI in all inpatient healthcare facilities to detect elevated rates or outbreaks of CDI within the facility *(weak recommendation, low quality of evidence)*.

III. What is the best way to express CDI incidence and rates?

Recommendation

1. Express the rate of HO-CDI as the number of cases per 10 000 patient-days. Express the CO-HCFA prevalence rate as the number of cases per 1000 patient admissions *(good practice recommendation)*.

IV. How should CDI surveillance be approached in settings of high endemic rates or outbreaks?

Recommendation

1. Stratify data by patient location to target control measures when CDI incidence is above national and/or facility reduction goals or if an outbreak is noted *(weak recommendation, low quality of evidence)*.

EPIDEMIOLOGY (PEDIATRIC CONSIDERATIONS)

V. What is the recommended CDI surveillance strategy for pediatric institutions?

Recommendations

1. Use the same standardized case definitions (HO, CO-HCFA, CA) and rate expression (cases per 10 000 patient-days for HO,

cases per 1000 patient admissions for CO-HCFA) in pediatric patients as for adults *(good practice recommendation)*.
2. Conduct surveillance for HO-CDI for inpatient pediatric facilities but do not include cases <2 years of age *(weak recommendation, low quality of evidence)*.
3. Consider surveillance for CA-CDI to detect trends in the community *(weak recommendation, low quality of evidence)*.

DIAGNOSIS

VI. What is the preferred population for *C. difficile* testing, and should efforts be made to achieve this target?

Recommendation

1. Patients with unexplained and new-onset ≥3 unformed stools in 24 hours are the preferred target population for testing for CDI *(weak recommendation, very low quality of evidence)*.

VII. What is the best-performing method (ie, in use positive and negative predictive value) for detecting patients at increased risk for clinically significant *C. difficile* infection in commonly submitted stool specimens?

Recommendation

1. Use a stool toxin test as part of a multistep algorithm (ie, glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by nucleic acid amplification test [NAAT]; or NAAT plus toxin) rather than a NAAT alone for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission (Figure 2) *(weak recommendation, low quality of evidence)*.

VIII. What is the most sensitive method of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms?

Recommendation

1. Use a NAAT alone or a multistep algorithm for testing (ie, GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission (Figure 2) *(weak recommendation, low quality of evidence)*.

IX. What is the role of repeat testing, if any? Are there asymptomatic patients in whom repeat testing should be allowed, including test of cure?

Recommendation

1. Do not perform repeat testing (within 7 days) during the same episode of diarrhea and do not test stool from asymptomatic patients, except for epidemiological studies *(strong recommendation, moderate quality of evidence)*.

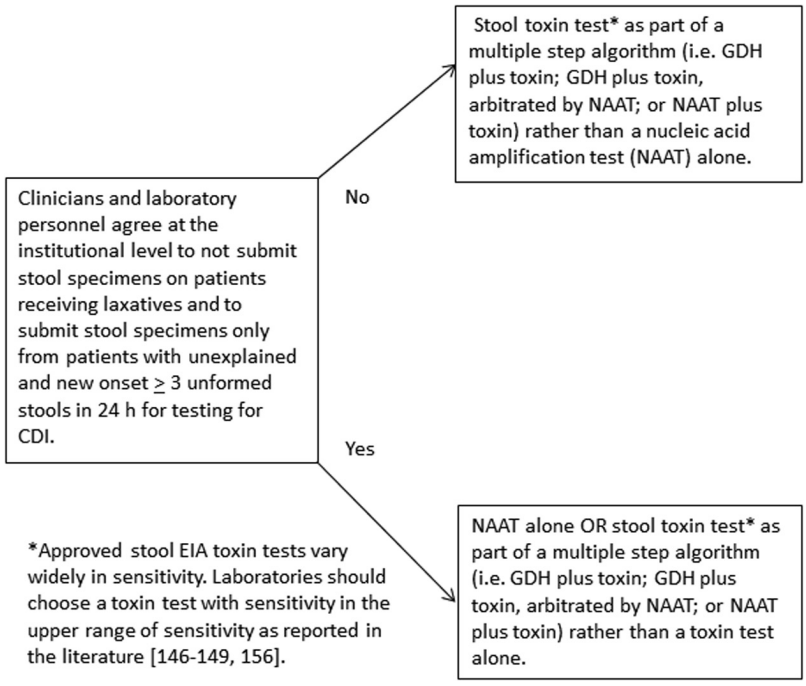

Figure 2. *Clostridium difficile* infection laboratory test recommendations based on preagreed institutional criteria for patient stool submission. Abbreviations: CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test.

X. Does detection of fecal lactoferrin or another biologic marker improve the diagnosis of CDI over and above the detection of toxigenic *C. difficile* Can such a subset predict a more ill cohort?

Recommendation

1. There are insufficient data to recommend use of biologic markers as an adjunct to diagnosis *(no recommendation)*.

DIAGNOSIS (PEDIATRIC CONSIDERATIONS)

XI. When should a neonate or infant be tested for *C. difficile*?

Recommendations

1. Because of the high prevalence of asymptomatic carriage of toxigenic *C. difficile* in infants, testing for CDI should never be routinely recommended for neonates or infants ≤12 months of age with diarrhea *(strong recommendation, moderate quality of evidence)*.

XII. When should a toddler or older child be tested for *C. difficile?*

Recommendations

1. *Clostridium difficile* testing should not be routinely performed in children with diarrhea who are 1–2 years of age unless other infectious or noninfectious causes have been excluded *(weak recommendation, low quality of evidence)*.
2. In children ≥2 years of age, *C. difficile* testing is recommended for patients with prolonged or worsening diarrhea and risk factors (eg, underlying inflammatory bowel disease or immunocompromising conditions) or relevant exposures (eg, contact with the healthcare system or recent antibiotics) *(weak recommendation, moderate quality of evidence)*.

INFECTION PREVENTION AND CONTROL

Isolation Measures for Patients With CDI

XIII. Should private rooms and/or dedicated toilet facilities be used for isolated patients with CDI?

Recommendations

1. Accommodate patients with CDI in a private room with a dedicated toilet to decrease transmission to other patients. If there is a limited number of private single rooms, prioritize patients with stool incontinence for placement in private rooms *(strong recommendation, moderate quality of evidence)*.
2. If cohorting is required, it is recommended to cohort patients infected or colonized with the same organism(s)—that is, do not cohort patients with CDI who are discordant for other multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus (strong recommendation, moderate quality of evidence)*.

XIV. Should gloves and gowns be worn while caring for isolated CDI patients?

Recommendation

1. Healthcare personnel must use gloves *(strong recommendation, high quality of evidence)* and gowns *(strong recommendation, moderate quality of evidence)* on entry to a room of a patient with CDI and while caring for patients with CDI.

XV. When should isolation be implemented?

Recommendation

1. Patients with suspected CDI should be placed on preemptive contact precautions pending the *C. difficile* test results if test results cannot be obtained on the same day *(strong recommendation, moderate quality of evidence)*.

XVI. How long should isolation be continued?

Recommendations

1. Continue contact precautions for at least 48 hours after diarrhea has resolved *(weak recommendation, low quality of evidence)*.
2. Prolong contact precautions until discharge if CDI rates remain high despite implementation of standard infection control measures against CDI *(weak recommendation, low quality of evidence)*.

XVII. What is the recommended hand hygiene method (assuming glove use) when caring for patients in isolation for CDI?

Recommendations

1. In routine or endemic settings, perform hand hygiene before and after contact of a patient with CDI and after removing gloves with either soap and water or an alcohol-based hand hygiene product *(strong recommendation, moderate quality of evidence)*.
2. In CDI outbreaks or hyperendemic (sustained high rates) settings, perform hand hygiene with soap and water preferentially instead of alcohol-based hand hygiene products before and after caring for a patient with CDI given the increased efficacy of spore removal with soap and water *(weak recommendation, low quality of evidence)*.

3. Handwashing with soap and water is preferred if there is direct contact with feces or an area where fecal contamination is likely (eg, the perineal region) *(good practice recommendation)*.

XVIII. Should patient bathing interventions be implemented to prevent CDI?

Recommendation

1. Encourage patients to wash hands and shower to reduce the burden of spores on the skin *(good practice recommendation)*.

XIX. Should noncritical devices or equipment be dedicated to or specially cleaned after being used on the isolated patient with CDI?

Recommendation

1. Use disposable patient equipment when possible and ensure that reusable equipment is thoroughly cleaned and disinfected, preferentially with a sporicidal disinfectant that is equipment compatible *(strong recommendation, moderate quality of evidence)*.

XX. What is the role of manual, terminal disinfection using a *C. difficile* sporicidal agent for patients in isolation for CDI?

Recommendation

1. Terminal room cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during endemic high rates or outbreaks, or if there is evidence of repeated cases of CDI in the same room *(weak recommendation, low quality of evidence)*.

XXI. Should cleaning adequacy be evaluated?

Recommendation

1. Incorporate measures of cleaning effectiveness to ensure quality of environmental cleaning *(good practice recommendation)*.

XXII.What is the role of automated terminal disinfection using a method that is sporicidal against *C. difficile*?

Recommendation

1. There are limited data at this time to recommend use of automated, terminal disinfection using a sporicidal method for CDI prevention *(no recommendation)*.

XXIII. What is the role of daily sporicidal disinfection?

Recommendation

1. Daily cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during outbreaks or in hyperendemic (sustained high rates) settings, or if there is evidence of repeated cases of CDI in the same room *(weak recommendation, low quality of evidence)*.

XXIV. Should asymptomatic carriers of *C. difficile* be identified and isolated if positive?

Recommendation

1. There are insufficient data to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions *(no recommendation)*.

XXV. What is the role of antibiotic stewardship in controlling CDI rates?

Recommendations

1. Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk *(strong recommendation, moderate quality of evidence)*.
2. Implement an antibiotic stewardship program *(good practice recommendation)*.
3. Antibiotics to be targeted should be based on the local epidemiology and the *C. difficile* strains present. Restriction of fluoroquinolones, clindamycin, and cephalosporins (except for surgical antibiotic prophylaxis) should be considered *(strong recommendation, moderate quality of evidence)*.

XXVI. What is the role of proton pump inhibitor restriction in controlling CDI rates?

Recommendation

1. Although there is an epidemiologic association between proton pump inhibitor (PPI) use and CDI, and unnecessary PPIs should always be discontinued, there is insufficient evidence for discontinuation of PPIs as a measure for preventing CDI *(no recommendation)*.

XXVII. What is the role of probiotics in primary prevention of CDI?

Recommendation

1. There are insufficient data at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials *(no recommendation)*.

TREATMENT

XXVIII. What are important ancillary treatment strategies for CDI?

Recommendations

1. Discontinue therapy with the inciting antibiotic agent(s) as soon as possible, as this may influence the risk of CDI recurrence *(strong recommendation, moderate quality of evidence)*.
2. Antibiotic therapy for CDI should be started empirically for situations where a substantial delay in laboratory confirmation is expected, or for fulminant CDI (described in section XXX) *(weak recommendation, low quality of evidence)*.

XXIX. What are the best treatments of an initial CDI episode to ensure resolution of symptoms and sustained resolution 1 month after treatment?

Recommendations

1. Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI. The dosage is vancomycin 125 mg orally 4 times per day or fidaxomicin 200 mg twice daily for 10 days *(strong recommendation, high quality of evidence)* (Table 1).
2. In settings where access to vancomycin or fidaxomicin is limited, we suggest using metronidazole for an initial episode of nonsevere CDI only *(weak recommendation, high quality of evidence)*. The suggested dosage is metronidazole 500 mg orally 3 times per day for 10 days. Avoid repeated or prolonged courses due to risk of cumulative and potentially irreversible neurotoxicity *(strong recommendation, moderate quality of evidence)*. (See Treatment section for definition of CDI severity.)

XXX. What are the best treatments of fulminant CDI?

Recommendations

1. For fulminant CDI*, vancomycin administered orally is the regimen of choice *(strong recommendation, moderate quality of evidence)*. If ileus is present, vancomycin can also be administered per rectum *(weak recommendation, low quality of evidence)*. The vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 hours as a retention enema. Intravenously administered metronidazole should be administered together

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

with oral or rectal vancomycin, particularly if ileus is present *(strong recommendation, moderate quality of evidence)*. The metronidazole dosage is 500 mg intravenously every 8 hours.*

*Fulminant CDI, previously referred to as severe, complicated CDI, may be characterized by hypotension or shock, ileus, or megacolon.

2. If surgical management is necessary for severely ill patients, perform subtotal colectomy with preservation of the rectum *(strong recommendation, moderate quality of evidence)*. Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes *(weak recommendation, low quality of evidence)*.

XXXI. What are the best treatments for recurrent CDI?

Recommendations

1. Treat a first recurrence of CDI with oral vancomycin as a tapered and pulsed regimen rather than a second standard 10-day course of vancomycin *(weak recommendation, low quality of evidence)*, OR
2. Treat a first recurrence of CDI with a 10-day course of fidaxomicin rather than a standard 10-day course of vancomycin *(weak recommendation, moderate quality of evidence)*, OR
3. Treat a first recurrence of CDI with a standard 10-day course of vancomycin rather than a second course of metronidazole if metronidazole was used for the primary episode *(weak recommendation, low quality of evidence)*.
4. Antibiotic treatment options for patients with >1 recurrence of CDI include oral vancomycin therapy using a tapered and pulsed regimen *(weak recommendation, low quality of evidence)*, a standard course of oral vancomycin followed by rifaximin *(weak recommendation, low quality of evidence)*, or fidaxomicin *(weak recommendation, low quality of evidence)*.
5. Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments *(strong recommendation, moderate quality of evidence)*.
6. There are insufficient data at this time to recommend extending the length of anti–*C. difficile* treatment beyond the recommended treatment course or restarting an anti–*C. difficile* agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of CDI treatment, respectively *(no recommendation)*.

TREATMENT (PEDIATRIC CONSIDERATIONS)

XXXII. What is the best treatment of an initial episode or first recurrence of nonsevere CDI in children?

Recommendation

1. Either metronidazole or vancomycin is recommended for the treatment of children with an initial episode or first recurrence of nonsevere CDI (see Pediatric treatment section for dosing) *(weak recommendation, low quality of evidence)* (Table 2).

Table 2. Recommendations for the Treatment of *Clostridium difficile* Infection in Children

Clinical Definition	Recommended Treatment	Pediatric Dose	Maximum Dose	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low Weak/Low
Initial episode, severe/ fulminant	• Vancomycin × 10 days (PO or PR) with or without metronidazole × 10 days (IV)[a]	• 10 mg/kg/dose qid • 10 mg/kg/dose tid	• 500 mg qid • 500 mg tid	Strong/Moderate Weak/Low
First recurrence, non-severe	• Metronidazole × 10 days (PO), OR • Vancomycin × 10 days (PO)	• 7.5 mg/kg/dose tid or qid • 10 mg/kg/dose qid	• 500 mg tid or qid • 125 mg qid	Weak/Low
Second or subsequent recurrence	• Vancomycin in a tapered and pulsed regimen[b], OR • Vancomycin for 10 days followed by rifaximin[c] for 20 days, OR • Fecal microbiota transplantation	• 10 mg/kg/dose qid • Vancomycin: 10 mg/kg/dose qid; rifaximin: no pediatric dosing • …	• 125 mg qid • Vancomycin: 500 mg qid; rifaximin: 400 mg tid • …	Weak/Low Weak/Low Weak/Very low

Abbreviations: IV, intravenous; PO, oral; PR, rectal; qid, 4 times daily; tid, 3 times daily.

[a]In cases of severe or fulminant *Clostridium difficile* infection associated with critical illness, consider addition of intravenous metronidazole to oral vancomycin.

[b]Tapered and pulsed regimen: vancomycin 10 mg/kg with max of 125 mg 4 times per day for 10–14 days, then 10 mg/kg with max of 125 mg 2 times per day for a week, then 10 mg/kg with max of 125 mg once per day for a week, and then 10 mg/kg with max of 125 mg every 2 or 3 days for 2–8 weeks.

[c]No pediatric dosing for rifaximin; not approved by the US Food and Drug Administration for use in children <12 years of age.

XXXIII. What is the best treatment of an initial episode of severe CDI in children?

Recommendation

1. For children with an initial episode of severe CDI, oral vancomycin is recommended over metronidazole *(strong recommendation, moderate quality of evidence)*.

XXXIV. What are the best treatments for a second or greater episode of recurrent CDI in children?

Recommendation

1. For children with a second or greater episode of recurrent CDI, oral vancomycin is recommended over metronidazole *(weak recommendation, low quality of evidence)*.

XXXV. Is there a role for fecal microbiota transplantation in children with recurrent CDI?

Recommendation

1. Consider fecal microbiota transplantation for pediatric patients with multiple recurrences of CDI following standard antibiotic treatments *(weak recommendation, very low quality of evidence)*.

Notes

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Disclaimer. The findings and conclusions in this report are those of the author(s), and do not necessarily represent the official position of the CDC or the US Department of Veterans Affairs.

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Potential conflicts of interest. The following list is a reflection of what has been reported to IDSA. To provide thorough transparency, IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest (COI) is determined by a review process that includes assessment by the Standards and Practice Guidelines Committee (SPGC) Chair, the SPGC liaison to the development Panel, the Board of Directors liaison to the SPGC, and, if necessary, the COI Task Force of the Board. This assessment of disclosed relationships for possible COI will be based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. For activities outside of the submitted work, D. G. has served as board member for Rebiotix, Merck, Actelion, Summit, and DaVolterra; has served as a consultant for Pfizer, Sanofi Pasteur, and MGB Pharma; received a grant from Seres Therapeutics; and holds patents and technology for nontoxigenic *C. difficile* for the treatment and prevention of CDI under NTCD, LLC. For activities outside of the submitted work, S. J. has served on the advisory board member for Bio-k+, Synthetic Biologics, Summit, Therapeutics, and CutisPharma; has served on Pfizer's data and safety monitoring board for vaccine study; and has received payment for lectures from Merck. For activities outside of the submitted work, K. C. has received research grants from GenePOC, Accelerate, and BD Diagnostics; has received royalties from McGraw-Hill and ASM Press; and has received travel expenses as board member with ASM. For activities outside of the submitted work, S. C. has received payment as expert testimony for medical-legal consultation; has received research grants from the Agency for Health Research and Quality, CDC, and National Institutes of Health (NIH); and has received payment for lectures from IDSA, CDC, and American Academy of Pediatrics. For activities outside of the submitted work, E. R. D. has served as a consultant for Sanofi Pasteur, Nestle, Valneva, Pfizer, Rebiotix, GSK, and Merck; has received research grants from Sanofi Pasteur, Pfizer, Merck, and Rebiotix; and has received payment for lectures from Alere and Biofire. For activities outside of the submitted work, K. G. has received research grants from Merck & Co, Summit Pharmaceuticals, and Techlab, served as a consultant for bioMérieux, Merck & Co, and Summit Pharmaceuticals; and received payment for the development of educational presentation by bioMérieux and Merck & Co. For activities outside of the submitted work, C. K. has received research grants from the NIH, Institut Mérieux, and Aptalis; has received personal fees serving as scientific advisor for Facile Therapeutics, Summit (Oxford), Synthetic Biologics, Actelion, Artugen, First Light Diagnostics, Finch, GlaxoSmithKline, Merck, Seres Therapeutics, Summit, Vedanta, Celimmune, Cour Pharma, Takeda, Innovate, Valeant, and ImmunogenX; and has received payment for the development of educational presentations by Merck and Seres. For activities outside of the submitted work, V. L. has served as a consultant for Merck, and received payment for serving on the speaker's bureau for Merck. For activities outside of the submitted work, J. S. has received grants from CDC Epicenters. For activities outside of the submitted work, M. W. has received research grants, consultancy/lecture fees from Actelion, Cubist, Astellas, Optimer, Sanofi Pasteur, Summit, Seres, bioMérieux, Da Volterra, Qiagen, and Pfizer; served as a consultant for Merck, Valneva, Alere, AstraZeneca, Durata, Nabriva, Pfizer, Roche, The Medicines Company, Abott, Basilea, and the European Tissue Symposium; and received research grants from Cerexa, Abbott, and the European Tissue Symposium. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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