Appendix K. Rapid Evidence Review

Treatments for *Clostridium Difficile* Colitis

A Rapid Review From the ECRI-Penn Evidence-based Practice Center

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Summary

- All guidelines and published clinical pathways for the treatment of *Clostridium difficile* infection (CDI) in the hospital setting provide recommendations for antibiotic treatments (i.e., vancomycin, fidaxomicin, metronidazole) as first-line therapy in mild-moderate disease.
- There does not appear to be relevant new evidence since 2014 in the area of antibiotic treatment for *Clostridium difficile*.
- Consideration of fecal microbiota transplantation (FMT) in refractory disease is supported by moderate-quality evidence.
- One small randomized controlled trial for adjunct use of probiotics had some positive results. More research is needed.

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Introduction

Clostridium difficile infection (CDI) is a significant healthcare-associated infection that often occurs in the setting of antibiotic use, particularly in hospitals and long-term care facilities. CDI is associated with significant morbidity and mortality, causing longer hospital stays, greater readmission rates, higher mortality, and higher costs compared with similar patients without CDI.[1-3] Timely, evidence-based, and effective management of CDI will help contain the burden of CDI on the healthcare system.

The purpose of this rapid review is to identify recent guidelines, systematic reviews, randomized controlled trials (RCTs), and pathways addressing the treatment of acute CDI to help inform the development of a clinical pathway for the treatment of acute CDI. We examine both antibiotic and other treatment modalities.

Current UPHS Policy

Table K-1 lists relevant policy documents in effect at University of Pennsylvania Health System (UPHS) hospitals.

Table K-1. Links to relevant UPHS documents (available to UPHS staff only)

Entity	Link
HUP	**Recommendations for diagnosis and treatment of *Clostridium difficile* Associated Diarrhea:** http://www.uphs.upenn.edu/antibiotics/Gastroenteritis.html
PPMC	**Recommendations for diagnosis and treatment of *Clostridium difficile* Associated Diarrhea:** http://www.uphs.upenn.edu/antibiotics/Gastroenteritis.html
PAH	**Algorithm for Management of *Clostridium difficile* Associated Diarrhea (CDAD) Infection – (PH-DG5, last reviewed 2014):** http://uphsxnet.uphs.upenn.edu/pahhome/pharmacy/policies/dosingguidelines/ph-dg5.pdf **ANTIMICROBIAL STEWARDSHIP POLICY (PAH PP PH.616.MEDMGT (PAH Intranet #: PH-P4**): http://uphsxnet.uphs.upenn.edu/pahhome/pharmacy/policies/general/ph-p4.pdf

HUP: Hospital of the University of Pennsylvania; PAH: Pennsylvania Hospital; PPMC: Penn Presbyterian Medical Center

Methods

Penn Center for Evidence-based Practice Protocol for Systematic Review

Specific aim: A rapid synthesis of recent guidelines, reviews, RCTs, and pathways, including a focused update of the treatment-focused portions of Key Question (KQ) 3 and KQ4 of the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) report Early Diagnosis, Prevention, and Treatment of *Clostridium difficile* for the management of patients with acute *Clostridium difficile* (*C. difficile*) colitis. [KQ3: What are the comparative effectiveness and harms of different antibiotic treatments? KQ4: What are the effectiveness and harms of other interventions?]

Study designs: Any recent guidelines, systematic reviews, RCTs, or pathways reporting specific management approaches for these patients. For guidelines, priority given to evidence-based clinical practice guidelines issued by professional societies and national health systems.

Inclusion and exclusion criteria:

- **Participants:** Adult patients (age > 18yo) with acute *C. difficile* colitis in the inpatient setting, including initial, recurrent, relapsed, or refractory infection. *Exclude* outpatient and extended care setting.
- **Interventions:** Drug therapy, fecal microbiota transplantation, probiotics, and other approaches to the treatment of acute *C. difficile* colitis in the inpatient setting. *Exclude* prevention and therapies not likely to be available on U.S. market within 1 year.
- **Comparisons:** Any, including antibiotic treatments or placebo, usual care, active care, or none.
- **Outcomes:** Mortality, recurrence (study defined), clearance or cure (study defined), complications, symptom resolution (study defined), CDI-related colectomy rate, harms (e.g., delayed treatment response).

Timing: Acute or recurrent infection.

Setting: Acute inpatient setting. *Exclude* outpatient and extended care setting.

Other: Published in English, developed in Organisation for Economic Co-operation and Development (OECD) countries, April 2015-present for original studies, January 2010-present for guidelines and pathways.

Data collection: We will search Embase.com (Medline®/Embase® combined) and PubMed® (In Process/Publisher subsets). Our gray literature search will include targeted searches using Google as well as the National Guideline Clearinghouse, Web sites of professional organizations, UpToDate, Dynamed, and Clinical Key.

Study quality assessment: Guidelines assessed using Penn Medicine's Center for Evidence-based Practice (CEP) Trustworthy Guideline scale, systematic reviews assessed using modified AMSTAR (Assessing the Methodological Quality of Systematic Reviews) scale. (www.uphs.upenn.edu/cep/methods)

Data synthesis (calculation of relative risks and confidence intervals, meta-analyses, exploration of heterogeneity): Qualitative, including descriptive evidence tables with applicable relative risks from studies, but not de novo calculations.

NOTE: CEP standard review methods, including scales for quality assessment of guidelines, systematic reviews, and primary studies, can be found in the Methods section of the CEP website at (www.uphs.upenn.edu/cep/methods).

Literature Search

ECRI Institute information specialists searched the following databases and other resources for relevant information. Search terms and strategies for each resource appear in tables K-2 through K-8 below.

Table K-2. Guideline search

Database or organization	Keywords or syntax	Hits	Marked for retrieval	Included
National Guideline Clearinghouse	'clostridium difficile'	29	2	
Guidelines International Network	'clostridium difficile'	2	0	

Table K-3. National Institute for Health and Care Excellence (NICE) evidence search

Search keywords	Hits	Marked for retrieval	Included
'clostridium difficile'	20	2	1

Table K-4. Cochrane Review search

Database	Keywords or syntax	Hits	Marked for retrieval	Included
Cochrane Database of Systematic Reviews	'c diff' OR difficile OR 'clostridium difficile' OR 'c-diff' OR 'c dif*'	38104		
	antibiotic* OR vancomycin OR metronidazole OR 'fecal microbiotia' OR fidaxomicin OR clindamycin OR probiotic* OR ciprofloxacin OR rifaximin OR cotrimoxazole OR ceftriaxone OR piperacillin OR quinolone* OR penicillin* OR levofloxacin OR gentamicin OR cephalosporin OR amoxicillin OR carbapenem* OR tigecycline OR cefaxolin OR linezolid OR meropenem* OR cefepime OR sultamicillin OR axomicillin OR ceftazidime OR macrolide OR carbapenem OR rifampicin OR azithromycin OR 'beta lactam' OR bezlotoxumab OR cephalexin OR daptomycin OR moxifloxacin OR clarithromycin OR doxycycline OR ampicillin OR cadazolid OR prebiotic* OR tetracycline OR aztreonam OR cefuroxime OR ertapenem OR nitazoxanide OR infliximab OR 'beta lactamase inhibitor' OR colistin OR 'fmt' OR 'fecal transplant' OR 'fecal transplantation'	47462		
	'lactobacillus acidophilus' OR 'lactobacillus' OR 's. boulardii' OR probiotic* OR 'lactobacilli'	4589		
	1 AND (2 OR 3)	124	6	

Table K-5. Pre-Medline search (National Library of Medicine)

Search	Syntax	Hits	Retrieved	Included
1	Difficile OR c-dif* c-diff* OR "c diff*"	6494		
2	Antibiotic* OR vancomycin OR metronidazole OR "fecal microbiotia" OR fidaxomicin OR clindamycin OR probiotic* OR ciprofloxacin OR rifaximin OR cotrimoxazole OR ceftriaxone OR piperacillin OR quinolone* OR penicillin* OR levofloxacin OR gentamicin OR cephalosporin OR amoxicillin OR carbapenem* OR tigecycline OR cefaxolin OR linezolid OR meropenem* OR cefepime OR sultamicillin OR axomicillin OR ceftazidime OR macrolide OR carbapenem OR rifampicin OR azithromycin OR "beta lactam" OR bezlotoxumab OR cephalexin OR daptomycin OR moxifloxacin OR clarithromycin OR doxycycline OR ampicillin OR cadazolid OR prebiotic* OR tetracycline OR aztreonam OR cefuroxime OR ertapenem OR nitazoxanide OR infliximab OR "beta lactamase inhibitor" OR colistin OR "fmt" OR "fecal transplant" OR "fecal transplantation"	659314		
3	'lactobacillus acidophilus' OR lactobacillus OR 's. boulardii' OR probiotic* OR lactobacilli	46132		
4	2 OR 3	682797		
5	1 AND 4	3175		
6	5 AND (inprocess[sb] OR pubmednotmedline[sb]	365		

Table K-6. Embase/Medline search (Embase.com syntax)

Search	Syntax	Hits	Retrieved	Included
1	'peptoclostridium difficile'/exp OR 'c diff' OR difficile OR 'clostridium difficile' OR 'c-diff'	25198		
2	'antibiotic agent'/exp OR antibiotic* OR vancomycin OR metronidazole OR 'fecal microbiotia' OR fidaxomicin OR clindamycin OR probiotic* OR ciprofloxacin OR rifaximin OR cotrimoxazole OR ceftriaxone OR piperacillin OR quinolone* OR penicillin* OR levofloxacin OR gentamicin OR cephalosporin OR amoxicillin OR carbapenem* OR tigecycline OR cefaxolin OR linezolid OR meropenem* OR cefepime OR sultamicillin OR axomicillin OR ceftazidime OR macrolide OR carbapenem OR rifampicin OR azithromycin OR 'beta lactam' OR bezlotoxumab OR cephalexin OR daptomycin OR moxifloxacin OR clarithromycin OR doxycycline OR ampicillin OR cadazolid OR prebiotic* OR tetracycline OR aztreonam OR cefuroxime OR ertapenem OR nitazoxanide OR infliximab OR 'beta lactamase inhibitor' OR colistin OR 'fmt' OR 'fecal transplant' OR 'fecal transplantation'	1558898		
3	'probiotic agent'/exp OR 'lactobacillus acidophilus' OR 'lactobacillus' OR 's. boulardii' OR probiotic* OR 'probiotic agent'/exp OR 'lactobacilli'	61052		
4	2 OR 3	1586169		
5	1 AND 4	15114		
6	5 AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim)	4408		
7	6 AND English:la AND [2010-2018]/py	2992		
8	7 AND 'clinical pathway'/exp OR 'clinical protocol'/exp OR 'practice guideline'/exp OR 'nursing protocol'/exp OR 'nursing care plan'/exp OR algorithm*:ti,ab OR protocol*:ti,ab OR protocol* OR pathway* OR guide* OR plan OR process* OR map*	552		
9	7 AND ('practice guideline'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)	273		
10	7 AND (rct OR random* OR meta* OR systematic* OR 'evidence base*')	578		
11	8 OR 9 OR 10	979		
12	11 AND [embase]/lim NOT ([embase]/lim AND [medline]/li	473		
13	11 AND [medline]/lim NOT ([medline]/lim AND [embase]/lim)	43		

Abbreviations: de = publication type; lim = limiter; ti,ab = title or abstract

Table K-7. Clinical resources

Database or organization	Keywords or syntax	Hits	Marked for retrieval	Included
Clinical Key	Search results were filtered by source type = "Guideline" 1. 'clostridium difficile treatment' 2. 'c difficile treatment' 3. 'c diff treatment' Dates: no limit Search results were filtered by source type = "Image" 1. 'clostridium difficile algorithm 2. 'c difficile algorithm' 3. 'c diff algorithm'5	 1. 36 2. 39 3. 23	 1. 36 2. 39 3. 23 1. 7 2. 8 3. 1	 All marked All marked
Dynamed	Searching for 'c diff' OR 'c difficile' OR 'clostridium difficile' pointed to the same page for 'clostridium difficile infection'. 1. clostridium difficile infection. Search results were filtered by source type = "Guidelines and Resources" 2. clostridium difficile infection. Search results were filtered by source type = "Treatment" 3. clostridium difficile infection. Search results were filtered by source type = "References" Content for 'clostridium difficile infection' was last updated on Updated 2017 Dec 18 12:53 PM (ET) 1. GEIH-CDI score may predict risk for recurrent C. difficile infection (Int J Antimicrob Agents 2017 Sep 19) view update 2. oral delivery of fecal microbial transplantation is as effective as infusion by colonoscopy for preventing recurrence of C. difficile infection in patients with recurrent infections (JAMA 2017 Nov 28) 3. fecal microbiota transplantation reported to have high rate of clinical resolution in patients with recurrent C. difficile infection (Aliment Pharmacol Ther 2017 Sep)	 1 1 1	 1 1 1	 0
UptoDate	'clostridium difficile'		4	

Table K-8. Professional organization website searches

Organization	Keywords or syntax	Hits	Retrieved	Included
American College of Gastroenterology	'clostridium difficile' OR 'c diff'; browsed		0	
American Gastroenterological Association	'clostridium difficile' OR 'c diff'; browsed practice guidelines		0	
Health Canada	Browsed c. difficile treatment guidelines		0	
Infectious Disease Society of America	'clostridium difficile' OR 'c diff'; browsed	2	0	
Kaiser Permanente	'clostridium difficile' OR 'c diff'; browsed		0	
Veterans Health Administration, including HSRD	'clostridium difficile' OR 'c diff'; browsed practice guidelines		1	0

HSRD: Health Services Research and Development

NOTE: If results were not unique, guidelines were not retrieved from these sites. Most guidelines were captured in the bibliographic and clinical searches.

Results

Guidelines

Guidelines categorize recommendations according to occurrence (initial vs. recurrent) and severity of illness (mild-moderate vs. severe). Listed in Appendix K-A are definitions of severity by guideline for those that provided a definition. For an initial and first recurrence of mild-moderate CDI in a hospital setting, the mainstay treatment recommended by guidelines is antibiotics (e.g., vancomycin, fidaxomicin, metronidazole). In severe disease, consideration of surgical treatment is recommended in addition to or after failed antibiotic therapy. For refractory illness, consideration of fecal microbiota transplantation (FMT) is also recommended. However, probiotic use is not recommended by guidelines. Guidelines provided little specific guidance on the role of imaging modalities in the management of CDI, citing a lack of direct evidence. In Table K-9 through Table K-13, we highlight eight fair-to-good quality guidelines[4-11] from major national societies in North America, Europe, Australia and New Zealand that provide recommendations for antibiotic treatment, surgical treatment, FMT, and probiotic treatment. We provide appraisals of the eight guidelines in Table K-14. In Table K-15, we list and describe four additional guidelines we identified that were deemed of less immediate relevance to this rapid review. Definitions for grading the strength of the recommendations and evidence are provided in Appendix K-B.

Table K-9. Guideline recommendations for treatment of initial CDI

Organization	Recommendations
Infectious Diseases Society of America and Society for Healthcare Epidemiology of America [IDSA/SHEA] 2017[8]	• 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*). • 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*). • For fulminant CDI (previously referred to as severe, complicated 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 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. • 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*).
Australasian Society of Infectious Diseases 2016[4]	**Oral antibiotic treatment – nonsevere disease** Oral metronidazole is recommended for initial episode CDI without clinical features of severe disease at 400 mg three times daily for 10 days. **Oral antibiotic treatment – severe disease** Oral vancomycin is recommended for initial episode refractory CDI or if severe disease features are present. Vancomycin is recommended at 125 mg four times daily for 10 days. If unable to tolerate oral therapy: nasogastric vancomycin 125mg four times daily AND intravenous metronidazole 500mg three times daily +/ - rectal tube vancomycin 500mg in 100ml normal saline three to four times daily.
American Society of Colon and Rectal Surgeons 2015[5]	Metronidazole and vancomycin are acceptable first-line agents for an initial bout of CDI, with selection normally based on disease severity. *Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.*

Organization	Recommendations
European Society of Clinical Microbiology and Infectious Disease [ESCMID] 2014[6]	**Non-antibiotic treatment – non-severe disease** In non-epidemic situations and with (non-severe) CDI clearly induced by the use of antibiotics, it may be acceptable to stop the inducing antibiotic and observe the clinical response for 48 h, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. (C-II).**refer to tables 1 and 2 of original guideline for definitions* **Oral antibiotic treatment – non-severe disease** Metronidazole orally 500 mg three times daily for 10 days (A-I). Vancomycin orally 125 mg four times daily for 10 days (B-I). Fidaxomicin orally 200 mg twice daily for 10 days (B-I). **Treatment of non-severe CDI when oral administration is not possible:** intravenous metronidazole 500 mg three times daily for 10 days (A-II). **Oral antibiotic treatment – severe CDI infection** Vancomycin orally 125 mg four times daily for 10 days (A-I) Fidaxomicin orally 200 mg twice daily for 10 days (B-I) <u>Notes for oral antibiotic treatment of severe infection:</u> • It can be considered to increase the vancomycin dosage to 500 mg four times daily for 10 days (B-III). • There is no evidence that supports the use of fidaxomicin in life-threatening CDI (D-III). • The use of oral metronidazole in severe CDI or life-threatening disease is strongly discouraged (D-I). **Treatment of severe CDI when oral administration is not possible:** intravenous metronidazole 500 mg three times daily for 10 days (A-II) combined with vancomycin retention enema 500 mg in 100 mL normal saline four times daily intracolonic, or combined with vancomycin 500 mg four times daily by oral/nasogastric tube for 10 days (B-III).

Organization	Recommendations
American College of Gastroenterology [ACG] 2013[7]	**Management of mild, moderate, and severe CDI:** • Patients with mild-to-moderate CDI should be treated with metronidazole 500 mg orally 3 times per day for 10 days. *(Strong recommendation, high-quality evidence)* • Patients with severe CDI should be treated with vancomycin 125 mg 4 times daily for 10 days *(Conditional recommendation, moderate-quality evidence)* • Failure to respond to metronidazole therapy within 5–7 days should prompt consideration of a change in. therapy to vancomycin at standard dosing. *(Strong recommendation, moderate-quality evidence)* • For mild-to-moderate CDI in patients who are intolerant/allergic to metronidazole and for pregnant/breastfeeding women, vancomycin should be used at standard dosing. *(Strong recommendation, high-quality evidence)* • In patients in whom oral antibiotics cannot reach a segment of the colon, such as with Hartman's pouch, ileostomy, or colon diversion, vancomycin therapy delivered via enema should be added to treatments above until the patient improves. *(Conditional recommendation, low-quality evidence)* • The use of anti-peristaltic agents to control diarrhea from confirmed or suspected CDI should be limited or avoided, as they may obscure symptoms and precipitate complicated disease. Use of anti-peristaltic agents in the setting of CDI must always be accompanied by medical therapy for CDI. *(Strong recommendation, low-quality evidence)* **Management of severe and complicated CDI:** • Supportive care should be delivered to all patients and includes intravenous fluid resuscitation, electrolyte replacement, and pharmacological venous thromboembolism prophylaxis. Furthermore, in the absence of ileus or significant abdominal distention, oral or enteral feeding should be continued. *(Conditional recommendation, low-quality evidence)* • Computed Tomography (CT) scanning of the abdomen and pelvis is recommended in patients with complicated CDI. *(Conditional recommendation, low-quality evidence)* • Vancomycin delivered orally (125 mg 4 times per day) plus intravenous metronidazole (500 mg 3 times a day) is the treatment of choice in patients with severe and complicated CDI who have no significant abdominal distention. *(Strong recommendation, low-quality evidence)* • Vancomycin delivered orally (500 mg 4 times per day) and per rectum (500 mg in a volume of 500 ml 4 times a day) plus intravenous metronidazole (500 mg 3 times a day) is the treatment of choice for patients with complicated CDI with ileus or toxic colon and/or significant abdominal distention. *(Strong recommendation, low-quality evidence)* • Surgical consult should be obtained in all patients with complicated CDI. Surgical therapy should be considered in patients with any one of the following attributed to CDI: hypotension requiring vasopressor therapy; clinical signs of sepsis and organ dysfunction (renal and pulmonary); mental status changes; white blood cell count ≥ 50,000 cells/µ l, lactate ≥ 5 mmol/l; or failure to improve on medical therapy after 5 days. (*Strong recommendation, moderate-quality evidence)*

Table K-10. Guideline recommendations for treatment of first recurrence of CDI

Organization	Recommendation
Infectious Diseases Society of America and Society for Healthcare Epidemiology of America [IDSA/SHEA] 2017[8]	• 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)* [Taper regimen: 125mg 4 times per day for 10-14 days, then 125mg 2 times per day for 7 days, then 125mg once per day for a week, and then 125mg every 2 or 3 days for 2-8 weeks] **OR** • 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** • 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)*.
Australasian Society of Infectious Diseases 2016[4]	Oral vancomycin is recommended for first CDI recurrence, 125mg 4 times daily for 10 days.

Organization	Recommendation
European Society of Clinical Microbiology and Infectious Disease [ESCMID] 2014[6]	**Oral antibiotic treatment** Fidaxomicin orally 200 mg twice daily for 10 days (B-I) Vancomycin orally 125 mg 4 times daily for 10 days (B-I) Metronidazole orally 500 mg 3 times daily for 10 days (C-I) Note: Fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027 ribotypes.
American College of Gastroenterology [ACG] 2013[7]	The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. *(Conditional recommendation, low-quality evidence)* [Taper/pulsed regimen: 125 mg 4 times daily x10 days, then 125 mg daily pulsed every 3 days for 10 doses]

PCR: polymerase chain reaction

Table K-11. Guideline recommendations for treatment of multiple recurrences of CDI*

Organization	Recommendation
Infectious Diseases Society of America and Society for Healthcare Epidemiology of America [IDSA/SHEA] 2017[8]	• 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)*. [Taper regimen: 125mg 4 times per day for 10-14 days, then 125mg 2 times per day for 7 days, then 125mg once per day for a week, and then 125mg every 2 or 3 days for 2-8 weeks] • Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI when appropriate antibiotic treatments have failed *(strong recommendation, moderate quality of evidence)*. • 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)*.
Australasian Society of Infectious Diseases 2016[4]	• Oral vancomycin, including a vancomycin taper, is suggested for second or subsequent CDI recurrence, 125mg 4 times daily for 14 days +/- taper. [Taper: 125mg twice daily for 7 days, then 125mg every second day for 2-8 weeks] • Fidaxomicin is a therapeutic option for second or subsequent CDI recurrence, especially in populations with high risk of relapse (i.e., concurrent antibiotic therapy), 200mg twice daily orally for 10 days. • FMT is a therapeutic option for second or subsequent CDI recurrence if above therapy has failed and no contraindications. • Rifaximin 'chaser therapy' is a therapeutic option in the setting of metronidazole, vancomycin, or fidaxomicin failure or where FMT may be unavailable or contraindicated. • FMT, tigecycline, and fidaxomicin are only suggested as second-line therapy if oral vancomycin and combination therapy have failed, due to limited evidence in severe CDI. • Surgery is indicated for life threatening severely refractory CDI or cases of toxic megacolon.
American Society of Colon and Rectal Surgeons 2015[5]	• Adjunctive agents, including toxin binders, probiotics, and/or other antibiotics, may be considered in recurrent or recalcitrant CDI. *Grade of Recommendation: Strong recommendation based on low-quality evidence, 2C.* • A prolonged course of oral antibiotics is acceptable therapy for recurrent or resistant disease in stable patients. *Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.* • Patients with refractory CDI may be considered for fecal bacteriotherapy (intestinal microbiota transplantation) if conventional measures have failed. *Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.*

Organization	Recommendation
European Society of Clinical Microbiology and Infectious Disease [ESCMID] 2014[6]	**Oral antibiotic treatment** Fidaxomicin orally 200 mg twice daily for 10 days (B-II) Vancomycin orally 125 mg 4 times daily for 10 days followed by pulse strategy (B-II) or Vancomycin orally 125 mg 4 times daily for 10 days followed by taper strategy (B-II) **Non-antibiotic treatment in combination with oral antibiotic treatment** For multiple recurrent CDI unresponsive to repeated antibiotic treatment, fecal transplantation in combination with oral antibiotic treatment is strongly recommended (A-I).
National Institute for Health and Care Excellence [NICE] 2014[9]	In patients with recurrent CDI who have failed to respond to antibiotics and other treatments, use of FMT is adequately supported by the current evidence on safety and efficacy.
American College of Gastroenterology [ACG] 2013[7]	• If there is a third recurrence after a pulsed vancomycin regimen, FMT should be considered. *(Conditional recommendation, moderate-quality evidence)* [Taper/pulsed regimen: 125 mg 4 times daily x10 days, then 125 mg daily pulsed every 3 days for 10 doses] • No effective immunotherapy is currently available. Intravenous immune globulin (IVIG) does not have a role as sole therapy in treatment of RCDI. However, it may be helpful in patients with hypogammaglobulinemia*. (Strong recommendation, low-quality evidence)*

*Also includes recommendations for refractory CDI infection where applicable CDI: Clostridium difficile infection; FMT: Fecal microbiota transplantation

Table K-12. Guideline recommendations for adjunct probiotic treatment in CDI

Organization	Recommendation
Asociación Mexicana de Gastroenterología 2016[10]	In accordance with the moderate-to-low level of evidence observed and taking the benefits and risks into account, we suggest that probiotics are not effective in the treatment of CDI in the adult population.
American Society of Colon and Rectal Surgeons 2015[5]	Probiotics may be useful in the prevention and treatment of *C difficile*-associated diarrhea. *Grade of Recommendation: Weak recommendation based on high-quality evidence, 2A.*
American College of Gastroenterology [ACG] 2013[7]	There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI. *(Moderate recommendation, moderate-quality evidence)*

CDI: Clostridium difficile infection; RCDI: refractory Clostridium difficile infection

Table K-13. Guideline recommendations for surgical treatment of CDI

Organization	Recommendation
Infectious Diseases Society of America and Society for Healthcare Epidemiology of America [IDSA/SHEA] 2017[8]	• 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*).
American Society of Colon and Rectal Surgeons 2015[5]	• Surgery for *C difficile* colitis should typically be reserved for patients with severe colitis that fails to improve with medical therapy, for generalized peritonitis, or for rare cases of colonic perforation. *Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.* • Subtotal colectomy with ileostomy is typically the operative procedure of choice for *C difficile* colitis. *Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.* • Diverting loop ileostomy with colonic lavage may be an alternative to total abdominal colectomy for the treatment of severe *C difficile* colitis. *Grade of Recommendation: Weak recommendation based on low-quality evidence, 2C.*

Organization	Recommendation
Eastern Association for the Surgery of Trauma [EAST] 2014[11]	• In adult patients with *Clostridium difficile*-associated disease (CDAD), we strongly recommend that patients undergo surgery early, that is, before the development of shock or the need for vasopressors. This recommendation is based on very low quality evidence but considers that individual patients will place a high value on the overall benefit (reduced mortality rates). • In adult patients with CDAD undergoing surgery, we conditionally recommend total or subtotal colectomy (vs. partial colectomy or other surgery). This recommendation is based on very low-quality evidence but places a high value on patient preferences for a definitive surgical intervention that may more effectively reduce mortality rates.
European Society of Clinical Microbiology and Infectious Disease [ESCMID] 2014[6]	**Surgical treatment – severe CDI infection** Total abdominal colectomy with ileostomy should be performed in case of: • Perforation of the colon • Systemic inflammation and deteriorating clinical condition not responding to antibiotic therapy; including toxic megacolon, an acute abdomen, and severe ileus. Surgical treatment should preferably be performed before colitis becomes very severe. Serum lactate may, inter alia, serve as a marker for severity (operate before lactate exceeds 5.0 mM). A future alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with antibiotic treatment (intracolonic antegrade vancomycin and intravenous metronidazole).

Table K-14. Guideline appraisal

Guideline issuer		IDSA/ SHEA 2017	ASID 2016	Mexican consensus 2016 (probiotics)	ASCRS 2015	ESCMID 2014	EAST 2014 (surgical management)	NICE 2014 (FMT)	ACG 2012
1. Transparency		B	B	A	B	A	A	B	A
2. Conflict of interest		C	B	A	NR	A	A	NR	A
3. Development group		B	B	B	NR	B	B	NR	B
4. Systematic review		A	C	A	B	A	A	C	A
5. Supporting evidence		A	B	A	A	A	A	B	A
6. Recommendations		A	C	B	B	A	A	B	A
7. External review		NR	NR	NR	NR	B	B	NR	NR
8. Currency and updates		B	B	B	B	B	B	B	A

Abbreviations: A = guideline development methods are fully disclosed; B = guideline development methods are partially disclosed; C = guideline development methods are not disclosed; NR = not reported

Note: Penn Center for Evidence-based Practice (CEP) Trustworthy Guideline Appraisal Scale available at www.uphs.upenn.edu/cep/methods

Table K-15. Other related guidelines

Organization	Notes
Health Canada 2016[12]	Interim policy that provides guidance for implementation of FMT for treatment of CDI not responsive to conventional therapies.
World Society of Emergency Surgery [WSES] 2015[13]	Guideline on management of CDI in surgical patients.
National Clinical Effectiveness Committee (Ireland) 2014[14]	Includes treatment of CDI, new section on patients/residents with Irritable Bowel Disease (IBD), surgical management of CDI, and new drugs/non-pharmacological options.
Public Health England 2013[15]	Includes management and treatment strategies for mild, moderate, and severe CDI and treatment algorithms.

CDI: Clostridium difficile infection; FMT: Fecal microbiota transplantation

Systematic Reviews and Individual Studies

Antibiotic Therapy

No systematic reviews or completed RCTs on antibiotic treatment for CDI published since 2014 were identified in our searches. There does not appear to be strong new evidence in the area of antibiotic treatments that are currently available in the United States.

FMT and Other Therapies

Moayyedi et al.[16] conducted a systematic review (SR) on FMT for the treatment of *Clostridium difficile*-associated diarrhea (CDAD), focusing on evidence from RCTs. It is a good quality SR that we appraise using a modified AMSTAR scale (see Table K-16). The review incorporated a total of 657 patients with CDAD from five RCTs comparing FMT with vancomycin or placebo (4 of which were published since 2014) and five RCTs comparing different FMT preparations and routes of delivery (4 of which were published since 2014). The authors found moderate-quality evidence that FMT is more effective than placebo or vancomycin treatment for treating CDAD that is not responsive to or has recurred after antibiotic treatment (risk ratio (RR) 0.41; 95% confidence interval ([CI], 0.22-0.74). The authors also report evidence from one RCT that frozen/thawed transplants may be as effective as fresh FMT, but further studies are needed in this area. The authors suggest that further investigation into the best route of administration for FMT is also needed. They report that naso-duodenal and colonoscopic transplantation may be more effective than retention enemas, however there are greater risks associated with these procedures: aspiration and perforation, respectively.

Table K-16. Systematic review appraisal

Review	Moayyedi, P., et. al.
1. Search terms described	Yes
2. Two or more databases	Yes
3. Inclusion/exclusion criteria	Yes
4. Number of included/excluded	Yes
5. Two independent screeners	Yes
6. Two independent reviewers	Yes
7. Study quality assessed	Yes
8. Heterogeneity assessed	Yes
9. Publication bias assessed	Yes
10. Studies described in evidence table	Yes
11. Funding described, no conflict	Yes

We identified a single small RCT published after 2014 on adjunct probiotic use for patients with an initial episode of mild or moderate CDI conducted by Barker et al.[17] Participants who were receiving either vancomycin or metronidazole for treatment of CDI additionally received either a once-daily dose of a four-strain oral probiotic or a control placebo. The authors reported a significant improvement in diarrhea outcomes compared to placebo: duration (0.0 vs 1.0 days, p=0.039) and rate (0.1 vs 0.3 days of diarrhea/stool diary days submitted, p=0.009). However, they reported no significant between-group difference in CDI recurrence or functional improvement. Since this was a small trial (n=33), the authors concluded that probiotic therapy shows promise for treatment of an initial mild or moderate CDI but additional studies in a larger population are needed to confirm this finding. No new studies on surgical treatments were identified.

Algorithms and Pathways

We identified 13 algorithms and pathways. Most of them focused primarily on antibiotic treatment of CDI and are listed in Table K-17. Two pathways[18,19] were focused on FMT and are listed in Table K-18.

Table K-17. Algorithms and pathways focused primarily on antibiotic therapy

Source	Components	Notes
Hitchcock 2017[20] Stanford Health Care	Presents treatment guidelines by severity: mild/moderate, severe, severe/complicated, first recurrence, multiple recurrence. Includes first line and alternate regimens with dose specifics.	References cited for each recommendation.
MD Anderson 2017[21] Texas	Provides flowchart from first presentation of symptoms through treatment and reassessment. Includes separate pathways for mild and severe/complicated disease. Mentions consideration of FMT at multiple recurrence but no protocol for that treatment.	References listed but not specifically cited for each recommendation.
Bagdasarian 2015[22]	Lists possible antibiotic treatments according to CDI severity and occurrence. Also includes consideration for surgical and FMT consultation.	Included within narrative review (p. 404).
Yeung 2015[23] Vancouver General Hospital	Provides flowchart from suspected or confirmed CDI through multiple recurrence. Includes criteria for severity assessment and pharmacological treatment. Provides specific dosing for first episode, first recurrence and subsequent recurrence.	Pre-post evaluation of new management policy.
Debast 2014[6] Netherlands	Provides schematic overview of therapeutic regimens for CDI.	Included in ESCMID guideline.
National Clinical Effectiveness Committee 2014[14] Ireland	Includes CDI disease severity stratification and general and specific treatments, including dosing for initial episode, first recurrence, and multiple recurrences.	Included in updated version of guideline (pp. 25, 28).
Knight 2013[24] University of Washington School of Medicine	Provides treatment algorithm for initial and first recurrence, stratified by disease severity (mild/moderate, severe, complicated). General guidelines for treatment of recurrence are mentioned but few specifics given.	References cited in text for most recommendations.
Raman 2013[25] Tufts	Includes recommended antibiotic dosing according to severity but no flowchart. No specific protocol for recurrence other than ID consult.	Reports that algorithm is based on consensus guidelines with potentially antiquated data and heavy dependence on expert opinion. A few recent references cited.
Wilcox 2013[15]	Includes treatment plans for first episode and recurrent CDI. Provides protocol for daily assessment and dosing specifics for both severe and non-severe symptoms. Cites references to support microbiology consult for multiple recurrences.	Included in Public Health England guidance (pp. 17-18).
Nassour 2012[26] University of Pittsburgh	Provides treatment algorithm which uses SHEA/IDSA guidelines for mild, moderate and severe disease. Also includes operative management strategy for CDI.	Some references cited for recommendations.
Efron 2009[27] Washington University School of Medicine	Includes flowchart of treatment of initial or primary CDI. Probiotics, alternate antimicrobial regimens and surgical therapies summarized in text but no specific recommendations provided.	

CDI: Clostridium difficile infection; ESCMID: European Society of Clinical Microbiology and Infectious Disease; FMT: Fecal microbiota transplantation; ID: infectious disease; SHEA/IDSA: Infectious Diseases Society of America and Society for Healthcare Epidemiology of America

Table K-18. Algorithms and pathways specific to fecal microbiota transplantation or other therapies

Source	Components	Notes
Costello 2016[19] Australia	Includes flowchart for route of delivery of FMT, from patient preparation through followup.	Summarizes references in text.
Fischer 2015[18]	Algorithm used in study at Indiana University Hospital that incorporates presence or absence of pseudomembranes on colonoscopy in decision making regarding FMT treatment of severe/complicated C. difficile infection.	p. 473

Conclusions

This rapid review identified no new relevant evidence in the area of antibiotic treatment for CDI. We did identify one systematic review with moderate-quality evidence in support of FMT in the setting of refractory CDI. One small RCT was identified on the adjunct use of probiotics, which reported some positive results; however, more research is needed. No new studies on surgical treatments were identified.

We identified several guidelines and pathways. Management approaches vary, but decision points focus around disease severity and number of episodes. Antibiotics remain the mainstay of treatment recommendations for mild-moderate CDI, with consideration of surgery and FMT in severe or recurrent disease. Evidence is insufficient to recommend use of probiotics for primary treatment.

Conflict of Interest Disclosures

None of the authors have any relevant financial relationships with commercial interests associated with the subject of this review. The CEP conflict of interest disclosure policy is found at www.uphs.upenn.edu/cep/methods.

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Butler M, Olson A, Drekonja D, Shaukat A, Schwehr N, Shippee N, Wilt TJ. Early Diagnosis, Prevention, and Treatment of Clostridium difficile: Update. Comparative Effectiveness Review No. 172. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 16-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Appendix K-A. Definitions of Disease Severity by Guideline

Organization	Definitions
Infectious Diseases Society of America and Society for Healthcare Epidemiology of America [IDSA/SHEA] 2017[8]	Clinical definition with supportive clinical data: **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. **Initial episode, severe:** Leukocytosis with a white blood cell count of ≥15,000 cells/mL or higher or a serum creatinine level >1.5 mg/dL. **Initial episode, severe, complicated:** Hypotension or shock, ileus, megacolon.
Asociación Mexicana de Gastroenterología 2016[10]	Consensus statement for probiotic use in gastroenterology, covers a range of diseases including CDI. Does not provide specific definitions for severity of CDI.
Australasian Society of Infectious Diseases 2016[4]	**CDI: A + (B or C)** A. Clinical features suggestive of CDI (diarrhea, ileus, toxic megacolon) B. Microbiological evidence of toxin producing *C. difficile* C. Pseudomembranous colitis demonstrated on colonoscopy **Severe CDI** In adults, this is defined as an episode of CDI with one or more clinical, laboratory and other signs of severe disease signs/symptoms demonstrated below: *Clinical* • Fever (>38.5_C), rigors • Hemodynamic instability • Peritonitis or evidence of bowel perforation • Ileus or toxic megacolon *Laboratory* • White blood cell count >15 × 109/L and <20% neutrophils • Elevated lactate level • Rise in creatinine level (>50% above baseline) • Albumin level <25 mg/L *Other* • Large intestine distension, colonic wall thickening, fat stranding, unexplained ascites (imaging) • Pseudomembranous colitis (colonoscopy) Require >1 of the listed factors with NO other clinical explanation. There is no consensus definition of severe disease for CDI for children. Caution should be used in directly applying adult criteria to children with CDI as this can overestimate severity. **Complicated CDI** An episode of CDI complicated by toxic megacolon, admission to intensive care for severe sepsis, requirement for surgery, or death due to CDI.
American Society of Colon and Rectal Surgeons 2015[5]	Does not provide specific definitions of mild or moderate CDI. **Severe CDI** is defined by a leukocytosis (>15,000 cells/μL) or an elevated serum creatinine (>1.5 mg/dL). Additional risk factors to identify severe disease and increased mortality risk include leukopenia (<4000 cells/μL), bandemia (>10% bands), cardiorespiratory failure, shock, megacolon, and perforation.
Eastern Association for the Surgery of Trauma [EAST] 2014[11]	Does not provide specific definitions of mild or moderate CDI. *Clostridium difficile*-associated disease (CDAD), was defined as **severe CDI** resulting in clinical deterioration, such as multiorgan system failure, peritonitis, and/or sepsis as a consequence of the disease.
European Society of Clinical Microbiology and Infectious Disease [ESCMID] 2014[6]	Does not provide specific definitions of mild or moderate CDI. **Definition of severe *Clostridium difficile* infection**. • Severe CDI is defined as an episode of CDI with (1 or more specific signs and symptoms of) severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for intensive care unit (ICU) admission, colectomy, or death.

Organization	Definitions
	• *Clostridium difficile* infection without signs of severe colitis in patients with greater age (≥65 years), serious comorbidity, ICU admission, or immunodeficiency may also be considered at increased risk of severe CDI.
National Institute for Health and Care Excellence [NICE] 2014[9]	• Symptoms of **mild** *C. difficile* infections include purulent watery diarrhea, abdominal cramps, nausea, and dehydration. • In more **severe** cases the infection can cause bloody diarrhea and fever. In a few people *C. difficile* infection can lead to pseudomembranous colitis, sepsis, toxic megacolon, colonic rupture, and death. The risk of death increases in patients with multiple comorbidities.

American College of Gastroenterology [ACG] 2013[7]	<u>CDI Severity Scoring System</u>
	• **Mild-to-moderate disease:** Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria.
	• **Severe disease:** Serum albumin < 3 g / dl plus ONE of the following:
	  • WBC ≥ 15,000 cells / mm 3
	  • Abdominal tenderness
	• **Severe and complicated disease:** Any of the following attributable to CDI:
	  • Admission to ICU for CDI
	  • Hypotension with or without required use of vasopressors
	  • Fever ≥ 38.5 ° C
	  • Ileus or significant abdominal distention
	  • Mental status changes
	  • WBC ≥ 35,000 cells/mm 3 or < 2,000 cells/mm 3
	  • Serum lactate levels >2.2 mmol/l
	  • End organ failure (mechanical ventilation, renal failure, etc.)

CDI: Clostridium difficile infection; WBC: white blood cells

Appendix K-B. Guideline Evidence and Recommendation Rating Schemes

1. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America (IDSA/SHEA) 2017 [8]
   Evidence rating: Grading of Recommendations Assessment, Development and Evaluation (GRADE) system
   Recommendation rating: GRADE system
2. Australasian Society of Infectious Diseases (ASID) 2016[4]
   Evidence rating: None described or presented
   Recommendation rating: None described or presented
3. Mexican consensus[10]
   Evidence rating: "The level of evidence was evaluated (very high, high, moderate, or low) for each specific statement based on the GRADE system."
   Recommendation rating: "For the recommendation grades the words 'we recommend' were used for a strong recommendation grade and 'we suggest' for a weak recommendation grade."
4. American Society of Colon and Rectal Surgeons (ASCRS) 2015[5]
   Evidence rating: GRADE system
   Recommendation rating: GRADE system
5. European Society of Clinical Microbiology and Infectious Disease (ESCMID) 2014[6]
   Evidence rating: ESCMID developed (evidence hierarchy)
   Recommendation rating: ESCMID developed
6. Eastern Association for the Surgery of Trauma (EAST) 2015[11]
   Evidence rating: GRADE system
   Recommendation rating: GRADE system: "Strong recommendations are prefaced by the statement 'we strongly recommend,' while weak recommendations are prefaced by the statement 'we suggest' or 'we conditionally recommend' as per the GRADE methodology."
7. NICE[9]
   Evidence rating: None described or presented
   Recommendation rating: None described or presented
8. American College of Gastroenterology (ACG) 2013[7]
   Evidence rating: GRADE system, "The quality of the evidence is graded as follows: 'high', if further research is unlikely to change our confidence in the estimate of the effect; 'moderate', if further research is likely to have an important impact and may change the estimate; and 'low', if further research is very likely to change the estimate."
   Recommendation rating: "The strength of a recommendation is graded as 'strong', when the evidence shows the benefit of the intervention or treatment clearly outweighs any risk, and as 'conditional', when uncertainty exists about the risk – benefit ratio."