METHODOLOGICAL APPENDIX
Guideline for Inpatient *Clostridium difficile* Infection in Adults and Children, 2016
Literature Review Methods and Results

Contents	Page

Section 1. Overview

This document details the methods and results of the systematic literature review performed for the 2016 UMHS clinical guideline for Inpatient *Clostridium difficile* Infection in Adults and Children.

A systematic search for best evidence was provided by the informationists at the Taubman Health Sciences Library, University of Michigan, which reviewed evidence from July 2013 to May 2014. The search included publications:

- Indexed in the Medline (Ovid) database and the Cochrane Database of Systematic Reviews
- Addressing humans, all ages, pediatric (separate) and in the English language
- Categorized as clinical guidelines, controlled trials or meta-analyses, and cohort studies
- From 7/2013 – 5/2014

The searched addressed 21 topics. The topics are listed in Section II. The detailed search specifications are listed in Section III. This search was supplemented by the literature review results included in the European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect 2014, which covered literature up to 7/2013.

Section IV lists the number of publications identified by topic and type of publication. The search identified a total of 279 potentially relevant publications.

Members of the guideline team reviewed these publications, excluding those found not to be relevant to our population or topic (e.g., study population, measures/outcomes) or not to be the best evidence (e.g., studies with better methodology already available). This process is summarized in Section V.

Additional articles were identified by searching references in retrieved publications. Very recent publications known to expert members of the guideline team were also considered.

The review process resulted in 163 studies identified as presenting best evidence on a topic. For each topic for which "best evidence" was identified, the evidence was synthesized in an evidence table that describes for each article the key aspects of methods, results, and issues (e.g., benefits and harms). The 23 evidence tables are presented in Section VI.

Section II. Search Framework and Topics

Presented below is the outline for a systematic search on specific topics relevant to the diagnosis and treatment of *Clostridium difficile* Infection in Adults and Children in the inpatient care setting. For each topic, searches were performed for (a) guidelines, (b) controlled trials and meta-analyses, and (c) cohort studies. The topic searches are not mutually exclusive. This approach assumes that each topic will be reviewed independently and that the search on a topic must include all references relevant to it.

Recent Systematic Search and Review

We performed a systematic search and review of literature concerning the diagnosis and treatment of *Clostridium difficile* Infection in Adults and Children in an inpatient setting in preparing the Clinical Practice Guideline for the Inpatient *Clostridium difficile* Infection in Adults and Children. Inclusion/exclusion criteria are listed below.

Inclusion and Exclusion Criteria for Systematic Search of More Recent Literature

To search perform a search of relevant literature published we developed the following framework of inclusion and exclusion criteria.

Domain	**Inclusion**	**Exclusion**
Language:	English	Not written in English
Time frame	Literature search included articles published from July 2013 – May 2014.	Studies published previous to or following these dates unless within categories noted in section (2) below
Study type/design	Meta-analyses, controlled trials, cohort studies, guidelines	Opinion, letter, commentary
Study population	Adult, pediatric, inpatient	Not inpatient, non-human
Medical condition	Clostridium *difficile* infection	
Setting	Inpatient	Ambulatory care, population health
Interventions/ indicators	<u>A. Preventive and Risk Factors</u> 1. Proton Pump inhibitor, immunosuppression, inflammatory bowel disease, Chronic Carriage and Treatment (Prophylaxis) 2. Probiotics and Prevention 3. Antibiotic risk factors 4. Pediatric risk factors, Hirschsprung's disease, cystic fibrosis 5. Infection control <u>B. Diagnosis</u> 1. History, physical exam, signs, symptoms: Diarrhea, leukocytosis, Ileus, bowel thickening, toxic megacolon, pseudomembranes, post-infectious Irritable bowel disease 2. Laboratory tests/culture: PCR, Cell cytotoxicity assay, Glutamate dehydrogenase, Enzyme immunoassay 3. Imaging: abdominal X-ray, computerized tomography 4. Endoscopy, colonoscopy, flexible sigmoidoscopy, pseudomembranes 5. Clostridium Difficile and Inflammatory bowel disease, Clostridium Difficile and Crohn's, Clostridium Difficile and Ulcerative colitis 6. Neonates and Clostridium Difficile	Interventions/indications that are out of scope for guideline.

	7. Differential Diagnosis: Diarrhea etiology; Nosocomial diarrhea other than clostridium difficile C. Disease Classification 1. Risk scoring system and Clostridium difficile, severe clostridium difficile, recurrent clostridium difficile, clostridium difficile small-bowel enteritis, complicated Clostridium difficile D. Treatment 1. Proton pump inhibitor therapy and recurrent clostridium difficile, antimotility agents 2. Antibiotic Treatment, vancomycin pulse, vancomycin taper, vancomycin enemas, metronidazole, probiotics, fidaxomicin, nitazoxanide, Rifaximin, tolevamer 3.Probiotics, toxin binders, immunotherapy 4. Fecal bacteriotherapy, donor stool, fecal microbiota transplant, stool substitute 5. Pediatrics and treatment 6. Surgical management of clostridium difficile, colectomy, loop ileostomy, toxic megacolon, fulminant colitis, risk scoring system for surgery, antegrade lavage	
Outcomes	• For diagnosis test, studies that report sensitivity / specificity of diagnostic test or procedure • For treatment, studies that report cure rate, infection rate, or time to improvement • For other studies: Any quantitative outcomes reported in studies meeting our other inclusion criteria	
Relative quality of evidence available		Articles are excluded if other articles within retrieved literature are deemed methodologically superior, e.g. have more representative relevant population; larger sample size; stronger methodological design, superior execution of study.

Additional sources considered to supplement our search were:

- References cited in articles identified by the literature search from July 2013 – May 2014 (section 1, described above).
- Publications (meta-analyses, controlled trials, cohort studies, and guidelines) published since the literature search was completed, though December 2016, known to members to the guideline team.

Search of Literature from July 1, 2013 – May 29, 2014

An initial search was performed for the time period from 7/2013 – 5/2014.

The general specifications for the search are outlined below. The detailed search terms and specifications are reproduced in Section III.

Within the Medline (Ovid) database, clostridium difficile, pseudomembraneous colitis, enterocolitis, Hirschsprung (for pediatric only) were searched as major topics. The MEDLINE In-Process database was also searched, using a keyword search. The strategy is available in Section III.

The Cochrane Database of Systematic Reviews was searched using the terms listed in Section III.

Overall specification terms

- Major topic area: clostridium difficile, pseudomembraneous colitis, enterocolitis, Hirschsprung (for pediatric only)
- Time frame: 7/1/2013-5/29/2014
- Population: human, all ages, pediatric (separate)
- Language: English

Specific searches

A. Preventive and Risk Factors

1. Risk Factors, Proton Pump inhibitor, immunosuppression, inflammatory bowel disease, Chronic Carriage and Treatment (Prophylaxis)
2. Probiotics and Prevention
3. Antibiotic risk factors
4. Pediatric risk factors, Hirschsprung's disease, cystic fibrosis
5. Infection control

B. Diagnosis

1. History, physical exam, signs, symptoms: Diarrhea, leukocytosis, Ileus, bowel thickening, toxic megacolon, pseudomembranes, post-infectious Irritable bowel disease,
2. Laboratory tests/culture: PCR, Cell cytotoxicity assay, Glutamate dehydrogenase, Enzyme immunoassay
3. Imaging: abdominal X-ray, computerized tomography
4. Endoscopy, colonoscopy, flexible sigmoidoscopy, pseudomembranes
5. Clostridium Difficile and Inflammatory bowel disease, Clostridium Difficile and Crohn's, Clostridium Difficile and Ulcerative colitis
6. Neonates and Clostridium Difficile
7. Differential Diagnosis: Diarrhea etiology; Nosocomial diarrhea other than clostridium difficile
8. Diagnosis: other references not included in 1-7

C. Disease Classification

1. Risk scoring system and Clostridium difficile, severe clostridium difficile, recurrent clostridium difficile, clostridium difficile small-bowel enteritis, complicated Clostridium difficile

D. Treatment

1. Proton pump inhibitor therapy and recurrent clostridium difficile, antimotility agents
2. Antibiotic Treatment, vancomycin pulse, vancomycin taper, vancomycin enemas, metronidazole, probiotics, fidaxomicin, nitazoxanide, Rifaximin, tolevamer
3. Probiotics, toxin binders, immunotherapy
4. Fecal bacteriotherapy, donor stool, fecal microbiota transplant, stool substitute
5. Pediatrics and treatment
6. Surgical management of clostridium difficile, colectomy, loop ileostomy, toxic megacolon, fulminant colitis, risk scoring system for surgery, antegrade lavage
7. Treatment or management, other references not included in …

E. Other

1. Other articles not in A-D above

Section III. Detailed Search Terms and Strategy

The searches were performed by informationists at the Taubman Health Sciences Library, University of Michigan.

Overall searches were performed on the date 5/29/2014 for the period from 7/2013 – 5/2014.

The search strategies are listed below.

Clostridium difficile Main Search (NOTE: Referred to throughout strategies as Main)
1. exp *Clostridium difficile/ or exp *enterocolitis/ or exp *Clostridium Infections/
2. exp *Hirschsprung Disease/
3. limit 2 to "all child (0 to 18 years)"
4. 1 or 3
5. exp animals/ not (exp animals/ and humans/)
6. 4 not 5
7. limit 6 to (english language and yr="2013 -Current")
8. remove duplicates from 7

Clinical Trials Search Hedge
1. randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or meta-analysis/ or clinical trial, phase iv/
2. clinical trial/
3. limit 2 to humans
4. 1 or 3

Cohort Studies Search Hedge
1. randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or meta-analysis/ or clinical trial, phase iv/
2. clinical trial/
3. limit 2 to humans
4. 1 or 3
5. exp cohort studies/ not 4

Guideline Search Hedge
1. clinical protocols/ or physician's practice patterns/ or algorithms/ or "Outcome and Process Assessment (Health Care)"/ or consensus development conference, nih/ or consensus development conference/ or practice guideline/ or guideline/
2. randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or meta-analysis/ or clinical trial, phase iv/
3. clinical trial/
4. limit 3 to humans
5. 2 or 4 or exp cohort studies/
6. 1 not 5

A. Preventive and Risk Factors
1. Risk Factors, Proton Pump inhibitor, immunosuppression, inflammatory bowel disease, Chronic Carriage and Treatment (Prophylaxis)
2. exp Risk Factors/ or exp *Proton Pump Inhibitors/ or exp *Immunosuppression/ or exp *Immunosuppressive Agents/ or exp *Inflammatory Bowel Diseases/ or chronic carriage.mp. or carrier state/
3. 1 and Main

B. Probiotics and Prevention
1. probiotics/ and pc.fs.
2. 1 and Main

C. Antibiotic risk factors
1. exp *anti-bacterial agents/
2. exp Risk Factors/ or Risk/ or exp Risk Assessment/
3. 1 and 2

4. exp *Anti-Bacterial Agents/ae, ct [Adverse Effects, Contraindications]
5. 3 or 4
6. 5 and Main

D. Pediatric risk factors, Hirschsprung's disease, cystic fibrosis
1. Risk Factors/ or Hirschsprung Disease/ or Cystic Fibrosis/
2. limit 1 to "all child (0 to 18 years)"
3. 2 and Main

E. Infection control
1. exp *Communicable Disease Control/
2. pc.fs.
3. 1 or 2
4. 3 and Main

F. Diagnosis
1. History, physical exam, signs, symptoms: Diarrhea, leukocytosis, Ileus, bowel thickening, toxic megacolon, pseudomembranes, post-infectious Irritable bowel disease
2. exp medical history taking/ or exp physical examination/ or exp "signs and symptoms"/
3. exp Irritable Bowel Syndrome/ and exp Bacterial Infections/
4. exp Diarrhea/ or exp Leukocytosis/ or exp Ileus/ or exp Intestinal Obstruction/ or exp Intestine, Small/ or Megacolon, Toxic/
4. (bowel and thicken*).ti. or (bowel and thicken*).ab. or pseudomembrane$1.ti,ab.
5. or/1-4
6. 5 and Main

G. Laboratory tests/culture: PCR, Cell cytotoxicity assay, Glutamate dehydrogenase, Enzyme immunoassay
1. clinical laboratory techniques/ or exp clinical chemistry tests/ or exp cytological techniques/ or exp genetic testing/ or exp hematologic tests/ or exp histological techniques/ or exp immunologic tests/ or metabolic clearance rate/ or exp microbiological techniques/ or exp molecular diagnostic techniques/ or exp parasite load/ or exp parasitic sensitivity tests/ or exp radioligand assay/ or exp specimen handling/
2. (bl or cy or mi or cf or im or ur or pa or pp).fs.
3. exp Polymerase Chain Reaction/ or exp Cytotoxicity Tests, Immunologic/ or Glutamate Dehydrogenase/ or exp Immunoenzyme Techniques/
4. or/1-3
5. 4 and Main

H. Imaging: abdominal X-ray, computerized tomography
1. (ra or ri).fs. or exp Diagnostic Imaging/
2. 1 and Main

I. Endoscopy, colonoscopy, flexible sigmoidoscopy, pseudomembranes
1. exp Endoscopy/
2. 1 and Main

J. Clostridium Difficile and Inflammatory bowel disease, Clostridium Difficile and Crohn's, Clostridium Difficile and Ulcerative colitis
1. exp Inflammatory Bowel Diseases/
2. 1 and Main

K. Neonates and Clostridium Difficile
1. limit Main to "newborn infant (birth to 1 month)"

L. Differential Diagnosis: Diarrhea etiology; Nosocomial diarrhea other than clostridium difficile
1. exp *Diarrhea/et
2. (exp *Diarrhea/ and Cross Infection/) not exp Clostridium difficile/
3. exp Diagnosis, Differential/
4. or/1-3
5. 4 and Main

M. Diagnosis: other references not included in 1-7

1. exp medical history taking/ or exp physical examination/ or exp "signs and symptoms"/
2. exp Irritable Bowel Syndrome/ and exp Bacterial Infections/
3. exp Diarrhea/ or exp Leukocytosis/ or exp Ileus/ or exp Intestinal Obstruction/ or exp Intestine, Small/ or Megacolon, Toxic/
4. (bowel and thicken*).ti. or (bowel and thicken*).ab. or pseudomembrane$1.ti,ab.
5. or/1-4
6. clinical laboratory techniques/ or exp clinical chemistry tests/ or exp cytological techniques/ or exp genetic testing/ or exp hematologic tests/ or exp histological techniques/ or exp immunologic tests/ or metabolic clearance rate/ or exp microbiological techniques/ or exp molecular diagnostic techniques/ or exp parasite load/ or exp parasitic sensitivity tests/ or exp radioligand assay/ or exp specimen handling/
7. (bl or cy or mi or cf or im or ur or pa or pp).fs.
8. exp Polymerase Chain Reaction/ or exp Cytotoxicity Tests, Immunologic/ or Glutamate Dehydrogenase/ or exp Immunoenzyme Techniques/
9. or/6-8
10. (ra or ri).fs. or exp Diagnostic Imaging/
11. exp Endoscopy/
12. exp Inflammatory Bowel Diseases/
13. exp *Clostridium difficile/ or exp *enterocolitis/ or exp *Clostridium Infections/
14. exp *Hirschsprung Disease/
15. limit 14 to "all child (0 to 18 years)"
16. 13 or 15
17. exp animals/ not (exp animals/ and humans/)
18. 16 not 17
19. limit 18 to (english language and yr="2013 -Current" and "all infant (birth to 23 months)")
20. (exp *Diarrhea/ and Cross Infection/) not exp Clostridium difficile/
21. exp *Diarrhea/et or exp Diagnosis, Differential/
22. 20 or 21
23. 5 or 9 or 10 or 11 or 12 or 19 or 22
24. false negative reactions/ or false positive reactions/
25. likelihood functions/ or exp "sensitivity and specificity"/
26. exp diagnosis/ or di.xs. or du.fs.
27. (sensitivity or specificity or predictive value).af.
28. or/24-27
29. 28 not 23
30. 29 and Main

N. Disease Classification

1. (severe* or recurren* or complicat*).mp.
2. (risk and scor*).ti. or (risk and scor*).ab.
3. exp risk/ or exp Recurrence/ or exp "Predictive Value of Tests"/ or cl.fs. or exp Intestine, Small/
4. or/1-3
5. 4 and Main

O. Treatment

1. Proton pump inhibitor therapy and recurrent clostridium difficile, antimotility agents
2. exp Proton Pump Inhibitors/ or exp antidiarrheals/ or exp antiemetics/ or antimotility.ti,ab.
3. 1 and Main

P. Antibiotic Treatment, vancomycin pulse, vancomycin taper, vancomycin enemas, metronidazole, probiotics, fidaxomicin, nitazoxanide, Rifaximin, tolevamer

1. exp Anti-Bacterial Agents/ or Vancomycin/ or Metronidazole/ or exp Rifamycins/
2. (fidaxomicin or nitazoxanide or rifaximin or tolevamer).mp.
3. 1 or 2
4. 3 and Main

Q. Probiotics, toxin binders, immunotherapy

1. (toxin*1 and bind*).ti. or (toxin*1 and bind*).ab.

2. exp Probiotics/ or exp Lactobacillus/ or exp Immunotherapy/
3. 1 or 2
4. 3 and Main

R. Fecal bacteriotherapy, donor stool, fecal microbiota transplant, stool substitute
1. ((donor or substitute) and stool*).mp.
2. (fecal or faecal).mp. or feces/
3. (bacteriotherap* or microbiota or transplant*).mp. or biological therapy/
4. 2 and 3
5. 1 or 4
6. 5 and Main

S. Pediatrics and treatment
1. (tu or th).xs. or exp therapeutics/
2. limit 1 to "all child (0 to 18 years)"
3. 2 and Main

T. Surgical management of clostridium difficile, colectomy, loop ileostomy, toxic megacolon, fulminant colitis, risk scoring system for surgery, antegrade lavage
1. exp *Digestive System Surgical Procedures/ or su.fs.
2. Megacolon, Toxic/ or Therapeutic Irrigation/ or fulminant colitis.mp.
3. (risk and scor*).ti. or (risk and scor*).ab.
4. Severity of Illness Index/ or exp risk/ or exp "Predictive Value of Tests"/
5. or/2-4
6. 1 and 5
7. 6 and Main

U. Treatment or management, other references not included in D.1-6
1. exp Proton Pump Inhibitors/ or exp antidiarrheals/ or exp antiemetics/ or antimotility.ti,ab.
2. exp Anti-Bacterial Agents/ or Vancomycin/ or Metronidazole/ or exp Rifamycins/ or (fidaxomicin or nitazoxanide or rifaximin or tolevamer).mp.
3. exp Probiotics/ or exp Lactobacillus/ or exp Immunotherapy/ or (toxin*1 and bind*).ti. or (toxin*1 and bind*).ab.
4. ((donor or substitute) and stool*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. ((fecal or faecal).mp. or feces/) and ((bacteriotherap* or microbiota or transplant*).mp. or biological therapy/)
6. (tu or th).xs. or exp therapeutics/
7. limit 6 to "all child (0 to 18 years)"
8. exp *Digestive System Surgical Procedures/ or su.fs.
9. Megacolon, Toxic/ or Therapeutic Irrigation/ or fulminant colitis.mp.
10. (risk and scor*).ti. or (risk and scor*).ab.
11. Severity of Illness Index/ or exp risk/ or exp "Predictive Value of Tests"/
12. or/9-11
13. 8 and 12
14. 1 or 2 or 3 or 4 or 5 or 7 or 13
15. (tu or th).xs. or exp therapeutics/
16. 15 not 14
17. 16 and Main

V. Other references not in A-D
1. exp Risk Factors/ or exp *Proton Pump Inhibitors/ or exp *Immunosuppression/ or exp *Immunosuppressive Agents/ or exp *Inflammatory Bowel Diseases/ or chronic carriage.mp. or carrier state/
2. probiotics/ and pc.fs.
3. exp *anti-bacterial agents/
4. exp Risk Factors/ or Risk/ or exp Risk Assessment/
5. 3 and 4
6. exp *Anti-Bacterial Agents/ae, ct [Adverse Effects, Contraindications]
7. 5 or 6
8. Risk Factors/ or Hirschsprung Disease/ or Cystic Fibrosis/

9. limit 8 to "all child (0 to 18 years)"
10. exp *Communicable Disease Control/ or pc.fs.
11. 1 or 2 or 7 or 9 or 10
12. exp medical history taking/ or exp physical examination/ or exp "signs and symptoms"/
13. exp Irritable Bowel Syndrome/ and exp Bacterial Infections/
14. exp Diarrhea/ or exp Leukocytosis/ or exp Ileus/ or exp Intestinal Obstruction/ or exp Intestine, Small/ or Megacolon, Toxic/
15. (bowel and thicken*).ti. or (bowel and thicken*).ab. or pseudomembrane$1.ti,ab.
16. or/12-15
17. clinical laboratory techniques/ or exp clinical chemistry tests/ or exp cytological techniques/ or exp genetic testing/ or exp hematologic tests/ or exp histological techniques/ or exp immunologic tests/ or metabolic clearance rate/ or exp microbiological techniques/ or exp molecular diagnostic techniques/ or exp parasite load/ or exp parasitic sensitivity tests/ or exp radioligand assay/ or exp specimen handling/
18. (bl or cy or mi or cf or im or ur or pa or pp).fs.
19. exp Polymerase Chain Reaction/ or exp Cytotoxicity Tests, Immunologic/ or Glutamate Dehydrogenase/ or exp Immunoenzyme Techniques/
20. or/17-19
21. (ra or ri).fs. or exp Diagnostic Imaging/
22. exp Endoscopy/
23. exp Inflammatory Bowel Diseases/
24. exp *Clostridium difficile/ or exp *enterocolitis/ or exp *Clostridium Infections/
25. exp *Hirschsprung Disease/
26. limit 25 to "all child (0 to 18 years)"
27. 24 or 26
28. exp animals/ not (exp animals/ and humans/)
29. 27 not 28
30. limit 29 to (english language and yr="2013 -Current" and "all infant (birth to 23 months)")
31. (exp *Diarrhea/ and Cross Infection/) not exp Clostridium difficile/
32. exp *Diarrhea/et or exp Diagnosis, Differential/
33. 31 or 32
34. 16 or 20 or 21 or 22 or 23 or 30 or 33
35. false negative reactions/ or false positive reactions/
36. likelihood functions/ or exp "sensitivity and specificity"/
37. exp diagnosis/ or di.xs. or du.fs.
38. (sensitivity or specificity or predictive value).af.
39. or/35-38
40. 34 or 39
41. (severe* or recurren* or complicat*).mp.
42. (risk and scor*).ti. or (risk and scor*).ab.
43. exp risk/ or exp Recurrence/ or exp "Predictive Value of Tests"/ or cl.fs. or exp Intestine, Small/
44. or/41-43
45. exp Proton Pump Inhibitors/ or exp antidiarrheals/ or exp antiemetics/ or antimotility.ti,ab.
46. exp Anti-Bacterial Agents/ or Vancomycin/ or Metronidazole/ or exp Rifamycins/ or (fidaxomicin or nitazoxanide or rifaximin or tolevamer).mp.
47. exp Probiotics/ or exp Lactobacillus/ or exp Immunotherapy/ or (toxin*1 and bind*).ti. or (toxin*1 and bind*).ab.
48. ((donor or substitute) and stool*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
49. ((fecal or faecal).mp. or feces/) and ((bacteriotherap* or microbiota or transplant*).mp. or biological therapy/)
50. (tu or th).xs. or exp therapeutics/
51. limit 50 to "all child (0 to 18 years)"
52. exp *Digestive System Surgical Procedures/ or su.fs.
53. Megacolon, Toxic/ or Therapeutic Irrigation/ or fulminant colitis.mp.
54. (risk and scor*).ti. or (risk and scor*).ab.
55. Severity of Illness Index/ or exp risk/ or exp "Predictive Value of Tests"/
56. or/53-55
57. 52 and 56
58. 45 or 46 or 47 or 48 or 49 or 51 or 57

59. (tu or th).xs. or exp therapeutics/
60. 58 or 59
61. 11 or 40 or 44 or 60
62. Main not 61

MEDLINE In-Process

1. (clostridium difficile or c difficile or cdifficile or c diff or cdiff or CDI or CDAD).ti.
2. (clostridium difficile or c difficile or cdifficile or c diff or cdiff or CDI or CDAD or enterocolitis or pseudomembraneous).mp.
3. (microbiome or microbiota or bacteriotherapy).ti,ab.
4. 2 and 3
5. 1 or 4
6. limit 5 to (english language and yr="2013 -Current")

Search hedges used for MEDLINE In-Process

Clinical Trials

1. ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab.

Cohort Studies

1. (cohort or longitudinal or prospective or retrospective).ti,ab.

Practice Guidelines

1. guideline*.ti. or ((practice adj3 parameter*) or guidance or care pathway* or (clinical adj3 pathway*)).ti,ab.

Cochrane

ID	Search
#1	MeSH descriptor: [Clostridium difficile] explode all trees
#2	#1 Publication Date from 2013 to 2014

Section IV. Number of Search Results by Topic and Type of Publication

The search (literature published 7/2013 – 5/2014) identified 279 unique indexed publications in Medline, listed as the "Base Search" and 1 Cochrane review.

The results by topic and type of publication are drawn from this base search, and summarized below. Note that a publication may be relevant to more than one topic, so the sum of entries by topic is greater than the number of unique publications overall.

Results for Search, 7/2013 – 5/2014

	Guidelines (-GDL)	Clinical Trials (-Trials)	Cohort Studies (-Cohort)
Base Search Numbers:	8	50	129
A. Preventive and Risk Factors			
A1. Risk factors, Proton Pump inhibitor, immunosuppression, inflammatory bowel disease, Chronic Carriage and Treatment (Prophylaxis)	1	7	33
A2. Probiotics and Prevention	0	7	2
A3. Antibiotic risk factors	0	8	6
A4. Pediatric risk factors, Hirschsprung's disease, cystic fibrosis	0	4	6
A5. Infection control	1	13	13
B. Diagnosis			
B.1. History, physical exam, signs, symptoms: Diarrhea, leukocytosis, Ileus, bowel thickening, toxic megacolon, pseudomembranes, post-infectious Irritable Bowel Disease	2	12	20
B2. Laboratory tests/culture: PCR, Cell cytotoxicity, Glutamate dehydrogenase, Enzyme immunoassay	6	22	72
B3. Imaging: abdominal X-ray, computerized tomography	0	0	3
B4. Endoscopy, colonoscopy, flexible sigmoidoscopy, pseudomembranes	0	0	6
B5. Clostridium Difficile and Inflammatory bowel disease, Clostridium Difficile and Crohn's, Clostridium Difficile and Ulcerative colitis	0	1	6
B6. Neonates and Clostridium Difficile	1	4	5
B7. Differential Diagnosis: Diarrhea etiology; Nosocomial diarrhea other than clostridium difficile	0	0	2
B8. Diagnosis: other references not included in 1-7	0	2	6
C. Disease Classification			
C1. Risk scoring system and Clostridium difficile, severe clostridium difficile, recurrent clostridium difficile, clostridium difficile small-bowel enteritis, complicated Clostridium	3	24	63

difficile			
D. Treatment			
D1. Proton pump inhibitor therapy and recurrent clostridium difficile, antimotility agents	0	0	5
D2. Antibiotic treatment, vancomycin pulse, vancomycin taper, vancomycin enemas, metronidazole, probiotics, fidaxomicin, nitazoxanide, Rifaximin, tolevamer	3	12	26
D3. Probiotics, toxin binders, immunotherapy	1	8	2
D4. Fecal bacteriotherapy, donor stool, fecal microbiota transplant, stool substitute	0	2	7
D5. Pediatrics and treatment	0	25	13
D6. Surgical management of clostridium difficile, colectomy, loop ileostomy, toxic megacolon, fulminant colitis, risk scoring system for surgery, antegrade lavage	0	4	4
D7. Treatment or management, other references not included in 1-6	1	5	16
E. Other articles not included in A-D	0	0	1
Medline-in-Process	8	26	57
Cochrane	1		

Section V. Evidence Review and Identification of Best Evidence

Criteria for Best Evidence

In order to identify best evidence, team members were assigned topics, then team members reviewed publications to identify studies that had the overall best methods ("best evidence") taking into consideration:

Study setting: reflects care and care settings that are similar to inpatient care in the U.S.

Study population and sample(s): represents adult patients typically seen related to *Clostridium difficile* Infection in Adults and Children care seen inpatient in the U.S.

Study design: strength of design in the ability to identify causal relationships using the following categories.

A = systematic reviews of randomized controlled trials with or without meta-analysis,
B = randomized controlled trials,
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
D = individual observation studies (case study/case series),
E = expert opinion regarding benefits and harm

Size of study sample: larger size generally reflecting more stable results

Variables: Extent to which the variables studied matched topics of interest in the inclusion criteria

Measures: Extent to which the measures likely reflected the conceptual variables

Data collection: Extent to which data collection procedures were likely to collect data appropriate for the measures

Intervention appropriateness: Extent to which an intervention was likely to produce the desired condition

Intervention execution: Extent to which interventions were carried out as planned

Analysis appropriateness: Appropriateness of analyses to address the questions of interest

Clarity of description: Extent to which the above information was communicated to readers

Best Evidence Identified and Organized into Evidence Tables

The best evidence for the current guideline is synthesized into 23 evidence tables reflecting the primary questions posed in the literature review. These tables include a total of 127 publications. The tables themselves are contained in Section VI, and present the synthesis of the best evidence identified.

Section VI. Evidence Synthesis: Tables Describing Best Evidence

The best evidence for the current guideline is synthesized into 23 evidence tables reflecting the primary questions posed in the literature review. These tables include a total of 127 publications.

*For all evidence tables, level of evidence rating is noted as follows:

A = systematic reviews of randomized controlled trials with or without meta-analysis,
B = randomized controlled trials,
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
D = individual observation studies (case study/case series),
E = expert opinion regarding benefits and harm

Topic A. Risk Factors for Clostridium *difficile* Infection

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Bliss, D. Z., Johnson, S., Savik, K., Clabots, C. R., Willard, K., & Gerding, D. N. (1998). Acquisition of clostridium difficile and clostridium difficile-associated diarrhea in hospitalized patients receiving tube feeding. *Annals of Internal Medicine, 129*(12), 1012-1019. PMID: 9867755	C	Comparing tube-fed (n=76) vs non tube fed (n=76) patients for C. difficile acquisition and diarrhea in hospitalized patients	76 consecutive hospitalized, tube-fed patients 76 hospitalized, non-tube-fed patients	More tube-fed patients than non-tube-fed patients acquired *C. difficile* (15 of 76 patients [20%] compared with 6 of 76 patients and developed *C. difficile*-associated diarrhea.	NA
Issa, M., Vijayapal, A., Graham, M. B., Beaulieu, D. B., Otterson, M. F., Lundeen, S., et al. (2007). Impact of clostridium difficile on inflammatory bowel disease. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association, 5*(3), 345-351. PMID: 17368234	C	IBD patients followed in a referral center (n=999)	IBD (Crohn's disease, ulcerative colitis) n=46 c-diff positive patients n=953 c-diff negative patients	Infection increased to 1.8% of IBD patients in 2005 (P < .01). Proportion of IBD patients within the total number of C difficile infections increased to 16% in 2005 (P < .01). IBD colonic involvement was found in the majority of C difficile-infected patients in 2005 (91%), and the majority contracted infection as an outpatient (76%). Antibiotic exposure was identified in 61% of IBD patients with C difficile infection in 2005. Pseudomembranes and fibrinopurulent eruptions were not seen endoscopically or histologically. During 2004-2005 more than half of the infected IBD patients required hospitalization, and 20% required colectomy.	Univariate and multivariate analysis identified maintenance immunomodulator use and colonic involvement as independent risk factors for C difficile infection in IBD.
Khanna, S., Baddour, L. M., Huskins, W. C., Kammer, P. P., Faubion, W. A., Zinsmeister, A. R., et al. (2013). The epidemiology of clostridium difficile infection in children: A population-based study. *Clinical Infectious Diseases, 56*(10), 1401-1406. PMID: 23408679	C	n=92 children with clostridium difficile infection	Case series	Initial treatment in 82% of patients was metronidazole, and 18% experienced treatment failure. The initial treatment in 8% of patients was vancomycin and none of them failed therapy. Majority of cases (75%) were community-acquired.	NA
Kim, J., Smathers, S. A., Prasad, P., Leckerman, K. H., Coffin, S., & Zaoutis, T. (2008). Epidemiological features of clostridium difficile-associated disease among inpatients at	C	n=4895 patients with C-diff	Hospitalized children with C difficile infection from 2001 to 2006	C difficile-associated disease increased to 4.0 cases per 1000 admissions and to 6.5 cases per 10000 patient-days. Median age of children with C difficile-	Examined change of infection rates over time.

children's hospitals in the united states, 2001-2006. *Pediatrics, 122*(6), 1266-1270. PMID: 19047244				associated disease was 4 years. Twenty-six percent of patients were <1 year of age. The majority of patients (67%) had underlying chronic medical conditions. The colectomy and all-cause mortality rates among children with C difficile-associated disease did not increase during the study period.	
Pepin, J., Valiquette, L., Alary, M. E., Villemure, P., Pelletier, A., Forget, K., et al. (2004). Clostridium difficile-associated diarrhea in a region of quebec from 1991 to 2003: A changing pattern of disease severity. *CMAJ: Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne, 171*(5), 466-472. PMID: 15337727	B	n=1721 cases of Clostridium difficile-associated diarrhea in Quebec	Case series	Increased from 35.6 per 100,000 populations in 1991 to 156.3 per 100,000 in 2003. Among patients aged 65 years or more, it increased from 102.0 to 866.5 per 100,000.	Examined changes over time in prevalence
Sanchez, T. H., Brooks, J. T., Sullivan, P. S., Juhasz, M., Mintz, E., Dworkin, M. S., et al. (2005). Bacterial diarrhea in persons with HIV infection, united states, 1992-2002. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 41*(11), 1621-1627 PMID: 16267735	C	n=44,778 people with bacterial diarrhea infection and HIV infection	Persons with HIV infection who were receiving medical care in >100 medical facilities in 9 major United States cities	C. difficile is the most common recognized cause of bacterial diarrhea among persons infected with HIV. The risk for bacterial diarrhea increases with increased severity of HIV disease.	Patients with AIDS are at increased risk for bacterial diarrhea, and they should reinforce recommendations for decreasing the chances of acquiring bacterial diarrhea.
Haines CF, Moore RD, Bartlett JG, et al. Clostridium difficile in a HIV-infected cohort: Incidence, risk factors, and clinical outcomes. *AIDS*. 2013;27(17):2799-2807. PMID: 23842125	C	n=154 cases of people with C-diff diarrhea infection and HIV infection	Cohort	Data show that compromised cellular immunity, as defined by CD4 cell count of 50 cells/μl or less, is a risk factor for CDI. Increased CDI risk, particularly in those with severe CD4 cell count suppression.	NA
McFarland LV, Ozen M, Dinleyici EC, Goh S. Comparison of pediatric and adult antibiotic-associated diarrhea and clostridium difficile infections. *World J Gastroenterol*. 2016;22(11):3078-3104. PMID: 27003987	C	Literature review to examine differences between adults and childeren in C. difficile infections.	Systematic review of literature published between June 1978 and 2015. Search strategies were not specified.	NA	Compare AAD and CDI in pediatric and adult populations and determine significant differences and similarities that might impact clinical decisions. Because search methodology was not specified. We were unable to determine the content of the search we classified this as C review of nonrandom trials.

Topic B. Contraindications to Testing for Clostridium *difficile*

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Fekety R, Silva J, Kauffman C, Buggy B, Deery HG. Treatment of antibiotic-associated clostridium difficile colitis with oral vancomycin: Comparison of two dosage regimens. *Am J Med*. 1989;86(1):15-19. PMID: 2910090.	A	n=46 patients with antibiotic-associated clostridium difficile colitis, receiving oral vancomycin	Compared two vancomycin dosage regimens in a randomized trial: High-dose (500 mg orally four times daily) vancomycin. (n=22) A lower dosage of 125 or 150 mg given three or four times a day. (n=24)	No significant differences in measurable responses to the two regimens were noted. Duration of diarrhea after initiation of therapy was about four days, and almost all patients had no diarrhea after one week. The organism continued in the stools of about 50 percent of patients for the first few weeks after completion of therapy, and nine (20 percent) patients developed a recurrence of their diarrheal illness. Vancomycin was well tolerated by all patients.	Patients who have finished treatment for CDI and have experienced clinical improvement in symptoms can have persistent shedding of toxin for up to 6 weeks after completing treatment.

Topic C. Optimal Testing Strategy

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Bagdasarian, N., Rao, K., & Malani, P. N. (2015). Diagnosis and treatment of clostridium difficile in adults: A systematic review. *Jama*, *313*(4), 398-408. PMID: 25626036	A	n=116 articles on best practices for treatment of C-diff	Systematic review in adults	Laboratory testing cannot distinguish between asymptomatic colonization and symptomatic infection with C difficile. Multistep algorithms using polymerase chain reaction (PCR) for the toxin gene(s) or single-step PCR on liquid stool samples have the best test performance characteristics (for multistep: sensitivity was 0.68-1.00 and specificity was 0.92-1.00; and for single step: sensitivity was 0.86-0.92 and specificity was 0.94-0.97). Clinical success rates of 66.3% for metronidazole vs 78.5% for vancomycin for severe CDI. Newer therapies show promising results, including fidaxomicin (similar clinical cure rates to vancomycin, with lower recurrence rates for fidaxomicin, 15.4% vs vancomycin, 25.3%; P = .005) and fecal microbiota transplantation (response rates of 83%-94% for recurrent CDI).	Some meta-analytic techniques used, but not formally identified as meta-analysis.
Bignardi, G. E., Hill, K., Berrington, A., & Settle, C. D. (2013). Two-stage algorithm for clostridium difficile: Glutamate-dehydrogenase-positive toxin-negative enzyme immunoassay results may require further testing. *Journal of Hospital Infection*, *83*(4), 347-349. PMID: 23399483	C	n=102 episodes in which a glutamate dehydrogenase-positive enzyme immunoassay (EIA)-toxin-negative result was	One group: 102 toxin neg Longitudal study for 32 days Polymerase chain reaction (PCR) testing was also used	Forty-six percent were culture positive with a toxigenic strain Nine GDH-positive EIA-toxin-negative stools were followed by a GDH-positive EIA-toxin-positive result in repeat samples: the interval between the initial EIA-toxin-negative and the subsequent EIA-toxin-positive result was 2–32 days (median: 17 days). Forty-seven episodes in which the stool was found to be culture positive with a toxigenic strain, 32 related to	NA

		obtained with a C. difficile testing protocol		inpatients, and, on checking the prescribing records, we found that *C. difficile* treatment had been started within seven days of the result in 18 of these episodes. Detection of a GDH-positive EIA-toxin-positive result in a subsequent stool did occur in two out of 18 treated patients (11%) and in four out of 14 (29%) untreated patients. Thirty randomly selected patients with diarrhoeal stools giving a GDH-negative result, a subsequent GDH-positive EIA-toxin-positive result did not occur in any patient.	
Brown, N. A., Lebar, W. D., Young, C. L., Hankerd, R. E., & Newton, D. W. (2011). Diagnosis of clostridium difficile infection: Comparison of four methods on specimens collected in cary-blair transport medium and tcdB PCR on fresh versus frozen samples. *Infectious Disease Reports, 3*(1), e5. PMID: 24470904	C	n=357 stool specimens	Enzyme immunoassay for the antigen glutamate dehydrogenase (Wampole C. DIFF CHEK-60 Assay, GDH) Toxin A and B enzyme immunoassay (Remel ProSpecT C. difficile Toxin A/B Microplate Assay, Toxin EIA) Cell culture cytotoxicity neutralization assay (Bartels Cytotoxicity Assay, CT) Real-time PCR targeting the toxin B gene (BD GeneOhm Cdiff Assay, PCR)	GDH, 100% and 93.2%; Toxin EIA, 82.9% and 82.9%; CT, 100% and 100%; PCR (performed on frozen specimens) 74.3% and 96.6%; respectively. The sensitivity and specificity of PCR improved to 100% when performed on 50 fresh stool samples.	NA
Debast, S. B., Bauer, M. P., Kuijper, E. J., & Committee. (2014). European society of clinical microbiology and infectious diseases: Update of the treatment guidance document for clostridium difficile infection. *Clinical Microbiology & Infection, 20*(Suppl 2), 1-26. PMID: 24118601	Guideline	NA	NA	NA	Systematic review/guideline, see evidence tables in source.
Finch, L. S., & Duncan, C. M. (2013). Molecular test to determine toxigenic capabilities in GDH-positive, toxin-negative samples: Evaluation of the portrait toxigenic C. difficile assay. *British Journal of Biomedical Science, 70*(2), 62-66. PMID: 23888607	C	n=40 stool specimens	The Portrait toxigenic *C. difficile* assay was used to examine GDH-positive, toxin A/B-negative stool samples for tcbB	GDH-positive, toxin A/B-negative stool samples (*n*=37), 40% were positive for *tcdB*. CDI were detected in two patients with positive *tcdB* stools; none were detected in patients with negative *tcdB* stools.	Examined the financial cost of various testing modalities

					and their benefits. There was a financial benefit.
Sunkesula, V. C., Kundrapu, S., Muganda, C., Sethi, A. K., & Donskey, C. J. (2013). Does empirical clostridium difficile infection (CDI) therapy result in false-negative CDI diagnostic test results? *Clinical Infectious Diseases, 57*(4), 494-500. PMID: 23645849	C	n=51 stool samples from CDI patients	Determine the time to conversion of CDI test results, including polymerase chain reaction (PCR) for toxin B genes, glutamate dehydrogenase, and toxigenic culture, from positive to negative during CDI therapy Evaluated the frequency of and risk factors for persistence of positive CDI tests	PCR, glutamate dehydrogenase, and toxigenic culture results converted to negative at similar rates. For PCR, 14%, 35%, and 45% of positive CDI tests converted to negative after 1, 2, and 3 days of treatment. Increased age and infection with North American pulsed-field gel electrophoresis strains were associated with persistent positive PCR results. CDI patients diagnosed at the time of the test order, conversion to negative PCR results by the time clinical stool specimens were collected occurred in 4 of 9 (44%) patients who were prescribed empirical CDI therapy versus 0 of 23 (0%) who were not (P = .004).	NA
Walkty, A., Lagace-Wiens, P. R., Manickam, K., Adam, H., Pieroni, P., Hoban, D., et al. (2013). Evaluation of an algorithmic approach in comparison with the illumigene assay for laboratory diagnosis of clostridium difficile infection. *Journal of Clinical Microbiology, 51*(4), 1152-1157. PMID: 23363829	C	n=428 stool specimens	Three diagnostic algorithms were evaluated in comparison with the Illumigene assay as a stand-alone test for Clostridium difficile detection: 1. glutamate dehydrogenase antigen screen (GDH) followed by toxin A/B antigen testing (Tox A/B) with the cell cytotoxicity assay for discordant specimens 2. GDH followed by the Illumigene 3. GDH followed by Tox A/B with the Illumigene for discordant specimens	C. difficile in the stool specimens was 14.7% (63/428). The sensitivity and specificity of the Illumigene for C. difficile detection were 73.0% and 99.7%. Corresponding sensitivities and specificities were 65.1% and 100.0% for algorithm 1, 68.3% and 100.0% for algorithm 2, and 69.8% and 100.0% for algorithm 3. Using algorithm 1, a cell cytotoxicity assay was required for toxin detection in 37% of positive tests.	NA

Topic D. Pediatric Testing

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Jangi, S., & Lamont, J. T. (2010). Asymptomatic colonization by clostridium difficile in infants: Implications for disease in later life. *Journal of Pediatric Gastroenterology and Nutrition, 51*(1), 2-7. PMID: 20512057	C	Literature review of PubMed for C. difficile in infants,	No search strategies or quantitative analysis of literature results provided	NA	No primary data. No meta analysis. No reporting of search strategies.
Kim, J., Smathers, S. A., Prasad, P., Leckerman, K. H., Coffin, S., & Zaoutis, T. (2008). Epidemiological features of clostridium difficile-associated disease among inpatients at children's hospitals in the united states, 2001-2006. *Pediatrics, 122*(6), 1266-1270. PMID: 19047244	C	n=4895 patients with C-diff	Hospitalized child with C difficile infection from 2001 to 2006	C difficile-associated disease increased to 4.0 cases per 1000 admissions and to 6.5 cases per 10 000 patient-days. Median age of children with C difficile-associated disease was 4 years. Twenty-six percent of patients were <1 year of age. The majority of patients (67%) had underlying chronic medical conditions. The colectomy and all-cause mortality rates among children with C difficile-associated disease did not increase during the study period.	Examined change of infection rates over time.
Leibowitz, J., Soma, V. L., Rosen, L., Ginocchio, C. C., & Rubin, L. G. (2015). Similar proportions of stool specimens from hospitalized children with and without diarrhea test positive for clostridium difficile. *The Pediatric Infectious Disease Journal, 34*(3), 261-266. PMID: 25247582	C	n=262 stool samples from patients age 1-18 years	Symptomatic patients (n=188 samples) Asymptomatic patients: (n=74 samples)	Thirty-five of 188 (19%) stool samples from symptomatic patients and 18 of 74 (24%) samples from asymptomatic patients were positive by PCR (P = 0.31). Among PCR-positive patients, symptomatic patients had a significantly higher proportion of subjects who received antimicrobials in the preceding 30 days (P = 0.04) and a greater number of preceding antimicrobial days than did asymptomatic patients (P = 0.02) but were comparable with respect to the other variables analyzed.	NA

Topic E. Other Diagnostic Modalities

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Ash, L., Baker, M. E., O'Malley, C. M.,Jr, Gordon, S. M., Delaney, C. P., & Obuchowski, N. A. (2006). Colonic abnormalities on CT in adult hospitalized patients with clostridium difficile colitis: Prevalence and significance of findings. *AJR.American Journal of Roentgenology, 186*(5), 1393-1400. PMID: 16632736	C	n=152 C-diff positive patients	152 inpatients with C. difficile colitis who had CT scans performed within 2 weeks of the diagnosis	Seventy-six (50%) of 152 scanned hospitalized patients with C. difficile colitis were CT-positive. These patients most often had segmental involvement (50 [66%] of 76 patients), with the rectum (60 [82%] of 73 patients) and sigmoid colon (61 [82%] of 74 patients) most often affected. Positive scans were associated with increased WBC, abdominal pain, and diarrhea. No statistical correlation was found between specific CT findings and clinical parameters or clinical parameters and patients requiring surgery. There was no predictive value of specific CT findings for surgical treatment.	NA
Gerding, D. N., Olson, M. M., Peterson, L. R., Teasley, D. G., Gebhard, R. L., Schwartz, M. L., et al. (1986). Clostridium difficile-associated diarrhea and colitis in adults. A prospective case-controlled epidemiologic study. Archives of Internal Medicine, 146(1), 95-100. PMID: 3942469	C	n=149 adult cases of Clostridium difficile n=148 diarrhea-free controls.	149 cases of c-diff-associated diarrhea 148 diarrhea-free (control)	Eighty-seven percent were nosocomial and 75% were on surgical services. Endoscopy revealed pseudomembranes in 51% of the 109 cases in which stool cytotoxin was present, compared with 11% of the 40 cases that were culture-positive but cytotoxin-negative. Cases diagnosed only by stool culture showed essentially no differences from controls, 21% of whom had asymptomatic stool colonization. Only 20% of these cases had	NA

				diarrhea due to C difficile.	
Kirkpatrick, I. D., & Greenberg, H. M. (2001). Evaluating the CT diagnosis of clostridium difficile colitis: Should CT guide therapy? AJR.American Journal of Roentgenology, 176(3), 635-639. PMID: 11222194	C	n=54 symptomatic patients C. dificile positive patients n=56 patients with antibiotic associated diarrhea and negative C. difficile test	A retrospective review covering a 4-year period was performed of the charts and CT scans of 54 symptomatic patients with stool test results positive for C. difficile and of a control group of 56 patients with antibiotic-associated diarrhea with stool test results negative for C. difficile	C. difficile colitis was explicitly diagnosed at CT in these patients with a sensitivity of 52%, specificity of 93%, positive predictive value of 88%, and negative predictive value of 67%. The sensitivity can be raised to 70% with no change in specificity with more rigid adherence to diagnostic criteria of colon wall thickening of greater than 4 mm combined with any one or more findings of pericolonic stranding, colon wall nodularity, the "accordion" sign, or otherwise unexplained ascites.	NA
Macari, M., Balthazar, E. J., & Megibow, A. J. (1999). The accordion sign at CT: A nonspecific finding in patients with colonic edema. *Radiology, 211*(3), 743-746. PMID: 10352600	C	n=57 patients with evidence of colitis	57 patients with CT evidence of severe colitis, as judged by colonic wall thickening, an abnormal haustral pattern, the target sign, and stranding of the pericolic fat, were identified from a computerized CT database for 25 months	The images in 15 of these patients demonstrated the accordion sign, and those in 20 patients did not. C difficile colitis was documented in four of the 15 cases displaying the accordion sign. In the remaining 11 patients, a different cause was documented. Oral contrast material had not reached the colon in the remaining 22 patients. Within this group with findings similar to the accordion sign, five patients had documented C difficile colitis, and four had colitis from other causes.	NA
Surawicz, C. M., Brandt, L. J., Binion, D. G., Ananthakrishnan, A. N., Curry, S. R., Gilligan, P. H., et al. (2013). Guidelines for diagnosis, treatment, and prevention of clostridium difficile infections. *The American Journal of Gastroenterology, 108*(4), 478-98; quiz 499. PMID: 23439232	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Tedesco, F. J. (1979). Antibiotic associated pseudomembranous colitis with negative proctosigmoidoscopy examination. *Gastroenterology, 77*(2), 295-297. PMID:	D	n=6 patients with tissue culture evidence of a clostridial toxin	Case series to show diagnositic antibiotic associated pseudomembranous colitis	Five of six patients demonstrated pseudomembranes located in various areas of the colon at a time when the rectosigmoid area	NA

447043		in stools and either normal or only edematous rectal mucosa		was uninvolved. This demonstrates the occurrence of antibiotic associated pseudomembranous colitis which can be missed by routine proctosigmoidoscopy.	
To, K. B., & Napolitano, L. M. (2014). Clostridium difficile infection: Update on diagnosis, epidemiology, and treatment strategies. *Surgical Infections, 15*(5), 490-502. PMID: 25314344	E	Literature review	Review of the pertinent English-language medical literature on C. difficile	Clostridium difficile infection can range from benign diarrhea to severe disease associated with substantial morbidity and mortality. Treatment modalities vary based on disease severity and timing of onset. The mainstay of medical treatment remains metronidazole and oral/rectal vancomycin. New management strategies are evolving, including adjunctive treatments such as monoclonal antibodies, vaccination, and fecal transplant. In patients with severe disease or clinical deterioration, early surgical consultation for total colectomy or loop ileostomy may be life-saving. Infection control measures are vital to mitigating the spread of CDI.	NA

Topic F. Classification

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Abou Chakra, C. N., Pepin, J., Sirard, S., & Valiquette, L. (2014). Risk factors for recurrence, complications and mortality in clostridium difficile infection: A systematic review. *PloS One, 9*(6), e98400. PMID 24897375	A	n=68 studies targeting *C. difficile* as the main pathogen; ii) measuring at least one relevant outcome; iii) identifying risk factors for the main outcome(s) using risk assessment	Systematic review was completed according to PRISMA guidelines. An electronic search in five databases was performed. Studies published until October 2013 were included if risk factors for at least one CDI outcome were assessed with multivariate analyses	Of the 68 studies analyzed: 24 assessed for recurrence 18 for complicated CDI 8 for treatment failure 30 for mortality Older age, use of antibiotics after diagnosis, use of proton pump inhibitors, and strain type were the most frequent risk factors for recurrence. Older age, leucocytosis, renal failure and co-morbidities were frequent risk factors for complicated CDI Laboratory parameters currently used in European and American guidelines to define patients at risk of a complicated CDI are adequate. Strategies for the management of CDI should be tailored according to the age of the patient, biological markers of severity, and underlying co-morbidities.	Substantial heterogeneity and methodological limitations were noted, mainly in the sample size, the definition of the outcomes and periods of follow-up, precluding a meta-analysis..
Cohen, S. H., Gerding, D. N., Johnson, S., Kelly, C. P., Loo, V. G., McDonald, L. C., et al. (2010). Clinical practice guidelines for clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of america (SHEA) and the infectious diseases society of america (IDSA). *Infection Control and Hospital Epidemiology, 31*(5), 431-455. PMID: 20307191	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Debast, S. B., Bauer, M. P., Kuijper, E. J., & European Society of Clinical Microbiology and Infectious Diseases. (2014). European society of clinical microbiology and infectious diseases: Update of the treatment guidance document for clostridium difficile infection. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases,*	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.

20 Suppl 2, 1-26. PMID: 24118601					
Fujitani, S., George, W. L., & Murthy, A. R. (2011). Comparison of clinical severity score indices for clostridium difficile infection. *Infection Control and Hospital Epidemiology, 32*(3), 220-228. PMID: 21460506	C	n=184 patients with CDI	Comparing 8 severity score indices for Clostridium difficile infection. Within sample of n=184, 19 had severe cases of CDI and 165 had non-severe	Sensitivities of the 8 severity score indices studied ranged from 63.2% to 84.2%. Specificities ranged from 59.4% to 93.9%. Hines VA index had the highest kappa score (0.69 [95% confidence interval, 0.54-0.83]). Independent risk factors for severe CDI determined by multivariate analysis were abdominal distention (P = .007), fever (temperature, 38.0 degrees C or above; P = .042), white blood cell count of at least 20,000 cells/mm (3) (P = .035), and hypoalbuminemia (serum albumin level less than 3 mg/dL; P = .029).	NA
Kuijper, E. J., Coignard, B., Tull, P., ESCMID Study Group for Clostridium difficile, EU Member States, & European Centre for Disease Prevention and Control. (2006). Emergence of clostridium difficile-associated disease in north america and europe. *Clinical Microbiology and Infection : The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 12 Suppl 6*, 2-18. PMID: 16965399	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies
Lessa, F. C., Gould, C. V., & McDonald, L. C. (2012). Current status of clostridium difficile infection epidemiology. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 55 Suppl 2*, S65-70. PMID: 22752867	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies
McDonald, L. C., Coignard, B., Dubberke, E., Song, X., Horan, T., Kutty, P. K., et al. (2007). Recommendations for surveillance of clostridium difficile-associated disease. *Infection Control and Hospital Epidemiology, 28*(2), 140-145. PMID: 17265394	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies
Surawicz, C. M., Brandt, L. J., Binion, D. G., Ananthakrishnan, A. N., Curry, S. R., Gilligan, P. H., et al. (2013). Guidelines for diagnosis, treatment, and prevention of clostridium difficile infections. *The American Journal of Gastroenterology, 108*(4), 478-98; quiz 499. PMID: 23439232	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.

Topic G. Inflammatory Bowel Disease and Clostridium *difficile*

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Ananthakrishnan, A. N., Issa, M., & Binion, D. G. (2009). Clostridium difficile and inflammatory bowel disease. *Gastroenterology Clinics of North America, 38*(4), 711-728. PMID: 19913210	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies.
Ananthakrishnan, A. N., McGinley, E. L., Saeian, K., & Binion, D. G. (2011). Temporal trends in disease outcomes related to clostridium difficile infection in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases, 17*(4), 976-983. PMID: 20824818	C	Nationwide Inpatient Sample, identified all IBD-related hospitalizations 2007 and examined hospitalizations with a coexisting diagnosis of C. difficile	Compared the absolute outcomes of in-hospital mortality and colectomy in the C. difficile-IBD cohort Examined these outcomes relative to non-C. difficile IBD controls	During 2007, approximately 2.9% of all IBD hospitalizations nationwide were complicated by CDI ($P < 0.001$). The absolute mortality in the C. difficile-IBD in 2007 was 7.2%. Total colectomy odds from 2007 (OR 2.51, 95% CI: 1.90-3.34).	This is a time trend from 1998-2007. Current prevalence is reported relevant to current search.
Causey, M. W., Spencer, M. P., & Steele, S. R. (2009). Clostridium difficile enteritis after colectomy. *The American Surgeon, 75*(12), 1203-1206. PMID: 19999913	Case review	n=3 cases of isolated C. difficile enteritis after colectomy	Case series of patients with C. difficile infection in the small bowel following colectomy.	Early recognition of antibiotic-associated enteritis, medical management may be effective in limiting the severity, duration, and complications of C. difficile. Most important initial intervention, just like that of colonic disease, is to stop the inciting antibiotic or switch to alternative antibiotics with a similar spectrum of antimicrobial properties. Effective antibiotics against C. difficile are metronidazole and vancomycin with cure rates of 76 and 97 per cent and recurrence in 14 and 15 per cent.	NA
Issa, M., Ananthakrishnan, A. N., & Binion, D. G. (2008). Clostridium difficile and inflammatory bowel disease. *Inflammatory Bowel Diseases, 14*(10), 1432-1442. PMID: 18484669	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies.
Issa, M., Vijayapal, A., Graham, M. B., Beaulieu, D. B., Otterson, M. F., Lundeen, S., et al. (2007). Impact of clostridium difficile on inflammatory bowel disease. *Clinical*	C	n=46 c-diff positive patients n=953 c-diff negative patients IBD patients	IBD (Crohn's disease, ulcerative colitis)	Infection increased to 1.8% of IBD patients in 2005 ($P < .01$). Proportion of IBD patients within the total number of C difficile infections increased to 16% in 2005 ($P < .01$). IBD colonic involvement was found in the majority of C	Univariate and multivariate analysis identified maintenance

Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association, 5(3), 345-351. PMID: 17368234		followed in a referral center		difficile-infected patients in 2005 (91%), and the majority contracted infection as an outpatient (76%). Antibiotic exposure was identified in 61% of IBD patients with C difficile infection in 2005. Pseudomembranes and fibrinopurulent eruptions were not seen endoscopically or histologically. During 2004-2005 more than half of the infected IBD patients required hospitalization, and 20% required colectomy.	immunomodulator use and colonic involvement as independent risk factors for C difficile infection in IBD.
Jen, M. H., Saxena, S., Bottle, A., Aylin, P., & Pollok, R. C. (2011). Increased health burden associated with clostridium difficile diarrhoea in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics, 33*(12), 1322-1331. PMID: 21517920	C	n=2185 patients with c-diff	IBD inpatients with co-existing *C. difficile* infection with inpatients that had IBD alone Compared the relative risk of death and of having GI surgery for patients with and without healthcare associated *C. difficile* Separated the two main clinical subgroups of patients with IBD: Crohn's disease (IBD-CD) and ulcerative colitis (IBD-UC)	IBD-CDAD-HAI group were more likely to die in hospital (adjusted OR 6.32), had 27.9 days longer in-patient stays and higher gastrointestinal surgery rates (adjusted OR 1.87) than patients admitted for inflammatory bowel disease alone.	NA
Jodorkovsky, D., Young, Y., & Abreu, M. T. (2010). Clinical outcomes of patients with ulcerative colitis and co-existing clostridium difficile infection. *Digestive Diseases and Sciences, 55*(2), 415-420. PMID: 19255850	C	n=99 patient charts were reviewed	Fifty-two patients were C. difficile-negative and 47 were positive Demographic data and laboratory values upon admission did not differ between the two groups	Patients who were C. difficile-positive had significantly more UC-related hospitalizations and emergency room visits in the year following initial admission (58 visits vs. 27, P = 0.001 and eight visits vs. 1 visit (P = 0.012). One year following the index admission, C. difficile patients had significantly higher rates of colectomy compared to C. difficile-negative patients (44.6% vs. 25%, P = 0.04). Length of hospitalization (11.7 vs. 11 days), use of cyclosporine therapy during index admission (48% vs. 47% of patients), and percentage requiring colectomy at initial admission (23.4% vs. 13.5%) did not reach statistical significance.	NA
Kelsen, J. R., Kim, J., Latta, D., Smathers, S., McGowan, K. L., Zaoutis, T., et al. (2011). Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflammatory Bowel Diseases, 17*(1), 50-55. PMID: 20722068	C	n=111 patients with IBD and CDI n=77 control patients with CDI Second control population of 127 IBD patients without CD	Patients with CD but without IBD Patients with IBD but without CD	Recurrence of CD in the IBD population was 34% compared to 7.5% in the control population (P < 0.0001). Fifty-seven percent of IBD-CD patients were readmitted with an exacerbation of disease within 6 months of infection with CD and 67% required escalation of therapy following CD infection, compared to 30% of IBD patients without CD (P < 0.001). Of the patients with IBD and CD, 44% of the cases were	NA

				new-onset IBD, 63% were on immunosuppression therapy, and 33% were on gastric acid suppression prior to infection. In comparing the IBD-CD and control CD populations, there was no significant difference in antibiotic exposure: 33% of IBD patients and 26% of control patients were on antibiotics (P < 0.2). With regard to prior hospitalization, 10% of patients with IBD were hospitalized in the 30 days prior to infection in comparison to 27% of the control CD patients (P < 0.002).	
Kostic, A. D., Xavier, R. J., & Gevers, D. (2014). The microbiome in inflammatory bowel disease: Current status and the future ahead. *Gastroenterology, 146*(6), 1489-1499. PMID: 24560869	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies.
Li, Y., Qian, J., Queener, E., & Shen, B. (2013). Risk factors and outcome of PCR-detected clostridium difficile infection in ileal pouch patients. *Inflammatory Bowel Diseases, 19*(2), 397-403. PMID: 23328770	C	n=21 patients with CDI	Patients with CDI (n = 21) were treated with oral vancomycin (500 - 1000 mg/day) for 2-4 weeks	Univariate analysis, patients with CDI had more stool frequency (P = 0.014) and significant current weight loss (P = 0.003) than patients with no CDI. In logistic regression analysis, there was a trend that recent hospitalization (odds ratio [OR] = 4.00, 95% confidence interval [CI], 0.95-16.84) might be associated with CDI. Of the 14 CDI patients with follow-up data, eight (57.1%) had either recurrent (n = 5) or refractory (n = 3) CDI after oral vancomycin therapy.	NA
Lundeen, S. J., Otterson, M. F., Binion, D. G., Carman, E. T., & Peppard, W. J. (2007). Clostridium difficile enteritis: An early postoperative complication in inflammatory bowel disease patients after colectomy. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract, 11*(2), 138-142. PMID: 17390162	D	n=14 reported cases of C. diff Three with no prior history of surgery Eleven underwent gastrointestinal surgery	Case series	Five of the six developed complications requiring further surgery or prolonged hospitalization. Patients were treated with intravenous hydration and metronidazole then converted to oral metronidazole and/or vancomycin. None of the patients died. A high suspicion of C. difficile enteritis in patients with inflammatory bowel disease and history of C. difficile colitis may lead to more rapid diagnosis, aggressive treatment, and improved outcomes for patients with C. difficile enteritis.	NA
Rodemann, J. F., Dubberke, E. R., Reske, K. A., Seo da, H., & Stone, C. D. (2007). Incidence of clostridium difficile infection in inflammatory bowel disease. *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association, 5*(3), 339-344. PMID: 17368233	C	n=44 patients hospitalized with the primary diagnoses of CD and U	Compared CDAD incidence between non-IBD and all IBD admissions All IBD was further subanalyzed as CD and UC versus the non-IBD group	CDAD incidence increased in each group and was higher in all IBD than non-IBD groups. CDAD rates approximately doubled in CD (9.5 to 22.3/1000 admissions) and tripled in UC (18.4 to 57.6/1000). Length of stay was similar among the groups. For all years combined, the adjusted odds ratios for CDAD in all IBD, CD, and UC admissions were 2.9 (95% confidence interval, 2.1-4.1), 2.1 (1.3-3.4), and 4.0 (2.4-6.6), respectively.	NA

				The median times from admission to a positive C difficile test result for non-IBD, CD, and UC were 4.0, 0.8, and 0.5 days, respectively.	
Schneeweiss, S., Korzenik, J., Solomon, D. H., Canning, C., Lee, J., & Bressler, B. (2009). Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Alimentary Pharmacology & Therapeutics, 30*(3), 253-264. PMID: 19438424	C	n=10,662 IBD patient	Compared CDAD incidence between non-IBD and all IBD admissions. All IBD was further subanalyzed as CD and UC versus the non-IBD group Patients initiating an immunomodulating drug were identified Exposure of interest was initiation of infliximab or corticosteroids compared with initiation of other immunosuppressive agents, including azathioprine, mercaptopurine (MP) and methotrexate (MTX)	Among 10,662 IBD patients, the incidence rate of bacteriaemia ranged from 3.8 per 1000 person-years (95% confidence interval 2.1-6.2) for other immunosuppressive agents to 7.4 (3.3-19.3) for infliximab with slightly higher rate for serious bacterial infections resulting in an adjusted relative risk 1.4 (0.47-4.24). Clostridium difficile infections occurred in 0/1000 (0-5.4) among 521 infliximab initiations and 14/1000 (10.6-18.2) for corticosteroids. Corticosteroid initiation tripled the risk of C. difficile infections (RR = 3.4; 1.9-6.1) compared with other immunosuppressant agents. Corticosteroid effect was neither dose-dependent nor duration-dependent. Bacteriaemia and other serious bacterial infections were not increased by corticosteroids or infliximab (5 events).	NA
Shen, B., Goldblum, J. R., Hull, T. L., Remzi, F. H., Bennett, A. E., & Fazio, V. W. (2006). Clostridium difficile-associated pouchitis. *Digestive Diseases and Sciences, 51*(12), 2361-2364. PMID: 17103037	D	n=1 Clostridium difficile-associated pouchitis	Case Report	While on the antibiotic therapy, pouch endoscopy was performed and showed severe pouchitis. Assays for Clostridium difficile toxins in stool specimens were positive. Treated with a 4-week course of ciprofloxacin 500 mg BID and tinidazole 500 mg TID. Symptoms resolved within several days from the initiation of therapy. A repeat pouch endoscopy at week 5 showed a complete resolution of mucosal inflammation of the pouch, while tests for Clostridium difficile toxins became negative.	NA

Topic H. Inflammatory Bowel Disease

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Ananthakrishnan, A. N., McGinley, E. L., Saeian, K., & Binion, D. G. (2011). Temporal trends in disease outcomes related to clostridium difficile infection in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases, 17*(4), 976-983. PMID: 20824818	C	Nationwide Inpatient Sample, identified all IBD-related hospitalizations 2007 and examined hospitalizations with a coexisting diagnosis of C. difficile	Compared the absolute outcomes of in-hospital mortality and colectomy in the C. difficile-IBD cohort Examined these outcomes relative to non-C. difficile IBD controls	During 2007, approximately 2.9% of all IBD hospitalizations nationwide were complicated by CDI ($P < 0.001$). The absolute mortality in the C. difficile-IBD in 2007 was 7.2%. Total colectomy odds from 2007 (OR 2.51, 95% CI: 1.90-3.34).	This is a time trend from 1998-2007. Current prevalence is reported relevant to current search.
Cammarota, G., Masucci, L., Ianiro, G., Bibbo, S., Dinoi, G., Costamagna, G., et al. (2015). Randomised clinical trial: Faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent clostridium difficile infection. *Alimentary Pharmacology & Therapeutics, 41*(9), 835-843. PMID: 25728808	A	n=20 patients undergoing FMT	vancomycin (25 mg four times a day for 3 day followed by one or more infusions of faeces via colonoscopy or vancomycin vancomycin 125 mg four times daily for 10 days, followed by 125-500 mg/day every 2-3 days for at least 3 weeks	Eighteen of the 20 patients (90%) treated by FMT exhibited resolution of C. difficile-associated diarrhoea. Five of the seven patients with pseudomembranous colitis reported a resolution of diarrhoea. Resolution of C. difficile infection occurred in 5 of the 19 (26%) patients in vancomycin ($P < 0.0001$). No significant adverse events were observed in either of the study groups.	NA
He, M., Miyajima, F., Roberts, P., Ellison, L., Pickard, D. J., Martin, M. J., et al. (2013). Emergence and global spread of epidemic healthcare-associated clostridium difficile. *Nature Genetics, 45*(1), 109-113. PMID: 23222960	C	n=151 isolates from a global collection of c. difficile 027/BI/NAP1 n=188 isolates from the UK	*C. difficile* isolates chosen for this study were characterized as PCR-ribotype 027 or 176, REA type BI or PFGE type NAP1	Two distinct epidemic lineages, FQR1 and FQR2. Two epidemic lineages showed distinct patterns of global spread. FQR2 lineage spread more widely.	NA
Lagier, J. C., Delord, M., Million, M., Parola, P., Stein, A., Brouqui, P., et al. (2015). Dramatic reduction in clostridium difficile ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: A preliminary report. *European Journal of*	C	n=61 patients hospitalized for CD027 infection	Sixteen patients were treated during the primary infection with fecal transplantation combined with antibiotics (26.2 %)	Global mortality rate was 3/16 (18.75 %) patients treated by early transplantation. 29/45 (64.4 %) patients only treated by antibiotics or by tardive transplantation ($p < 0.01$). Among these 45 patients, 23 (51 %) died at day 31, including 17 who died	NA

Clinical Microbiology & Infectious Diseases : Official Publication of the European Society of Clinical Microbiology. PMID: 25947205			Three patients were treated by fecal transplantation after at least two relapses (4.9 %) Forty-two patients were treated only by antibiotics (68.8 %)	at day 7. Early fecal transplantation was associated with a significantly reduced mortality rate, with only one patient dead at day 31 (6.25 %).	
Sha, S., Liang, J., Chen, M., Xu, B., Liang, C., Wei, N., et al. (2014). Systematic review: Faecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children. *Alimentary Pharmacology & Therapeutics, 39*(10), 1003-1032. PMID: 24641570	A	n=844 patients who had undergone FMT	Available articles were identified using three electronic databases in addition to hand searching and contacting experts Inclusion criteria were any reports of FMT therapy written in English	There has been only one placebo-controlled trial, a successful trial in 43 patients with recurrent CDI. Seven publications report FMT in paediatric patients with a total of 11 treated, 3 with chronic constipation and the remainder with recurrent CDI or ulcerative colitis (UC). 90.7% of patients with refractory/relapsing CDI were cured and 78.4% of patients with IBD were in remission after FMT.	NA
Youngster, I., Sauk, J., Pindar, C., Wilson, R. G., Kaplan, J. L., Smith, M. B., et al. (2014). Fecal microbiota transplant for relapsing clostridium difficile infection using a frozen inoculum from unrelated donors: A randomized, open-label, controlled pilot study. *Clinical Infectious Diseases, 58*(11), 1515-1522. PMID: 24762631	A	n=20 Patients with relapsing/refractory CDI	Fecal microbiota transplant (FMT) using a frozen suspension from unrelated donors, comparing colonoscopic and nasogastric tube (NGT) administration	Resolution of diarrhea was achieved in 14 patients (70%) after a single FMT (8 of 10 in the colonoscopy group and 6 of 10 in the NGT group). Five patients were retreated, with 4 obtaining cure, resulting in an overall cure rate of 90%. Daily number of bowel movements changed from a median of 7 (interquartile range [IQR], 5-10) the day prior to FMT to 2 (IQR, 1-2) after the infusion. Self-ranked health score improved significantly, from a median of 4 (IQR, 2-6) before transplant to 8 (IQR, 5-9) after transplant.	NA

Topic I. Antibiotics and Prevention

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Drekonja, D. M., Amundson, W. H., Decarolis, D. D., Kuskowski, M. A., Lederle, F. A., & Johnson, J. R. (2011). Antimicrobial use and risk for recurrent clostridium difficile infection. *The American Journal of Medicine, 124*(11), 1081.e1-1081.e7. PMID: 21944159	C	n=246 patients with c-diff	Case series followed for 30 days	One hundred forty-one patients (57%) received non-CDI antimicrobials, including 61 (25%) who received non-CDI antimicrobials during CDI treatmen.t Eighty patients (33%) who received non-CDI antimicrobial therapy after CDI treatment. With adjustment for age, disease severity, duration of CDI treatment, and recent hospital or intensive-care unit stay, receipt of non-CDI antimicrobials after CDI treatment was significantly associated with recurrent CDI (odds ratio [OR] 3.02; 95% confidence interval [CI], 1.66-5.52), compared with no antimicrobial use. Antimicrobial use during CDI treatment was not associated with recurrent CDI (OR 0.79; 95% CI, 0.40-1.52). Neither number of antimicrobial courses nor antimicrobial days was associated with recurrence.	NA
Goorhuis, A., Debast, S. B., Dutilh, J. C., van Kinschot, C. M., Harmanus, C., Cannegieter, S. C., et al. (2011). Type-specific risk factors and outcome in an outbreak with 2 different clostridium difficile types simultaneously in 1 hospital. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 53*(9), 860-869. PMID: 21914851	C	n=168 CDI patients	Investigated general and type-specific risk factors as well as outcome parameters for CDI due to type 027 or 017	At day 30 of follow-up, the overall mortality among patients with types 017, 027, other types, non-CDI diarrheal patients, and nondiarrheal patients was 23%, 26%, 3%, 2%, and 6%, respectively. MLVA showed persistent clonal dissemination of types 017 and 027, despite appropriate infection control measures.	NA
Hensgens, M. P., Goorhuis, A., Dekkers, O. M., & Kuijper, E. J. (2012). Time interval of increased risk for clostridium difficile infection after exposure to antibiotics. *The Journal of Antimicrobial Chemotherapy, 67*(3), 742-748. PMID: 22146873	C	n=337 patients with diarrhoea n=337 patients without diarrhoea n=227 patients with diarrhoea due to a	Case study	All antibiotic classes, except first-generation cephalosporins and macrolides, were associated with CDI. Second- and third-generation cephalosporins (OR 3.3 and 5.3, respectively) and carbapenems (OR 4.7)	NA

		cause other than CDI		were the strongest risk factors for CDI. Patients with CDI used more antibiotic classes and more defined daily doses, compared with non-diarrhoeal patients.	
Modena, S., Gollamudi, S., & Friedenberg, F. (2006). Continuation of antibiotics is associated with failure of metronidazole for clostridium difficile-associated diarrhea. *Journal of Clinical Gastroenterology, 40*(1), 49-54. PMID: 16340634	C	n=27 patients with C. difficile-associated diarrhea	Patients had symptomatic *C. difficile*-associated diarrhea, either mild or severe Received <=24 hours of treatment with oral metronidazole. Oral metronidazole had to be their sole treatment; Patients were included if they were switched to another antibiotic after day 5.	Response by day 5 did not predict treatment success by day 14 ($P = 0.76$). Seven patients had an additional identifiable risk factor for *C. difficile*-associated disease besides exposure to antibiotics. Fifty-nine percent of patients who remained on antibiotics during treatment of CDAD had resolution of symptoms by day 14 of treatment ($P = 0.02$). CDAD severity was predictive of response by day 5 ($P = 0.01$), it was not predictive of response by day 14. CDAD severity was not different between patients who remained on antibiotics and those who were taken off antibiotics ($P = 0.66$). Response by day 5 was not associated with response at day 14, and was also not associated with frequency of CDAD relapse ($P = 0.64$).	NA
Owens, R. C.,Jr, Donskey, C. J., Gaynes, R. P., Loo, V. G., & Muto, C. A. (2008). Antimicrobial-associated risk factors for clostridium difficile infection. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 46 Suppl 1*, S19-31. PMID: 18177218	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies.
Pop-Vicas, A., Shaban, E., Letourneau, C., & Pechie, A. (2012). Empirical antimicrobial prescriptions in patients with clostridium difficile infection at hospital admission and impact on clinical outcome. *Infection Control and Hospital Epidemiology, 33*(11), 1101-1106. PMID: 23041807	C	n=94 patients with CDI at hospital admission during a 24-month period	Retrospective cohort of all patients with CDI, examining treatment patterns	62% received at least one non-CDI-related antimicrobial during their hospitalization for CDI. Severe complicated CDI (odds ratio [OR], 7.1 [95% confidence interval {CI}, 1.8-28.5]. Duration of non-CDI-related antimicrobial exposure (OR, 1.2 [95% CI, 1.03-1.36 and age (OR, 1.1 [95% CI, 1.0-1.1]; were independent risk factors for adverse clinical outcomes. One-third of the patients received unnecessary antimicrobial therapy. Sepsis at hospital admission (OR, 5.3 [95% CI, 1.8-15.8]; and clinical suspicion of urinary tract infection (OR, 9.7 [95% CI,	NA

				2.9-32.3]; were independently associated with unnecessary antimicrobial prescriptions.	
Slimings, C., & Riley, T. V. (2014). Antibiotics and hospital-acquired clostridium difficile infection: Update of systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy*, *69*(4), 881-891. PMID: 24324224	A	n=569 citations, 13 case-control, 1 cohort study, 15,938 patients	Associations between antibiotic classes and hospital-acquired Clostridium difficile infection	Strongest associations were found for third-generation cephalosporins (OR = 3.20, 95% CI = 1.80-5.71; n = 6 studies; I(2) = 79.2%), clindamycin (2.86, 2.04-4.02; n = 6; I(2) = 28.5%). Second-generation cephalosporins (2.23, 1.47-3.37; n = 6; I(2) = 48.4%). Fourth-generation cephalosporins (2.14, 1.30-3.52; n = 2; I(2) = 0.0%), carbapenems (1.84, 1.26-2.68; n = 6; I(2) = 0.0%), trimethoprim/sulphonamides (1.78, 1.04-3.05; n = 5; I(2) = 70%), fluoroquinolones (1.66, 1.17-2.35; n = 10; I(2) = 64%) and penicillin combinations (1.45, 1.05-2.02; n = 6; I(2) = 54%). Study population and the timing of measurement of antibiotic exposure were the most common sources of heterogeneity. Study quality scored high for seven studies, moderate for six studies and low for one study.	NA
Stevens, V., Dumyati, G., Fine, L. S., Fisher, S. G., & van Wijngaarden, E. (2011). Cumulative antibiotic exposures over time and the risk of clostridium difficile infection. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *53*(1), 42-48. PMID: 21653301	C	n=10,154 hospitalizations for 7,792 patients and 241 cases of CDI	CDI in patients over 18 years of age prescribed 2 or more consecutive days of antibiotics Patients who received only 1 antibiotic	Dose-dependent increases in the risk of CDI associated with increasing cumulative dose, number of antibiotics, and days of antibiotic exposure. Compared to patients who received only 1 antibiotic, the adjusted hazard ratios (HRs) for those who received 2, 3 or 4, or 5 or more antibiotics were 2.5 (95% confidence interval [CI] 1.6-4.0), 3.3 (CI 2.2-5.2), and 9.6 (CI 6.1-15.1), respectively. The receipt of fluoroquinolones was associated with an increased risk of CDI, while metronidazole was associated with reduced risk.	NA

Topic J. Infection Control

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Pepin, J., Saheb, N., Coulombe, M. A., Alary, M. E., Corriveau, M. P., Authier, S., et al. (2005). Emergence of fluoroquinolones as the predominant risk factor for clostridium difficile-associated diarrhea: A cohort study during an epidemic in quebec. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 41*(9), 1254-1260. PMID: 16206099	C	Chart review of all adult patients in internal medicine, family medicine, or gastroenterology wards in a single hospital. n=7,421 episodes of care 5,619 individuals	Patients hospitalized during the period of January 2003 through June 2004 were observed until they either: • developed CDAD • Died • Passed 60 days post discharge from the hospital	CDAD occurred in 293 patients. Fluoroquinolones were the antibiotics most strongly associated with CDAD (AHR, 3.44; 95% confidence interval [CI], 2.65-4.47). Almost one-fourth of all inpatients received quinolones, for which the population-attributable fraction of CDAD was 35.9%. All 3 generations of cephalosporins, macrolides, clindamycin, and intravenous beta-lactam/beta-lactamase inhibitors were intermediate-risk antibiotics, with similar AHRs (1.56-1.89). Proton pump inhibitors (AHR, 1.00, 95% CI, 0.79-1.28) were not associated with CDAD.	NA

Topic K. Probiotics for Prevention

Reference Citation	**Study Design ***	**Patient Population** • Description • Total N of patients • If systematic review, N of studies	**Description of Groups** For Main Outcome(s), • Study group (n) • Comparison group (n)	**Summary of Results for Relevant Main Outcome(s)** • Effect size • Statistical significance)	**Reviewer notes** • Methodological issues, • Noteworthy harms • Other
Besselink, M. G., van Santvoort, H. C., Buskens, E., Boermeester, M. A., van Goor, H., Timmerman, H. M., et al. (2008). Probiotic prophylaxis in predicted severe acute pancreatitis: A randomized, double-blind, placebo-controlled trial. *Lancet, 371*(9613), 651-659. PMID: 18438065	B	n=298 patients with predicted severe acute pancreatitis	Patients were randomly assigned within 72 h of onset of symptoms to receive a multispecies probiotic preparation (n=153) or placebo (n=145), administered enterally twice daily for 28 days	Infectious complications occurred in 46 (30%) patients in the probiotics group and 41 (28%) of those in the placebo group (relative risk 1.06, 95% CI 0.75-1.51). Twenty-four (16%) patients in the probiotics group died, compared with nine (6%) in the placebo group (relative risk 2.53, 95% CI 1.22-5.25). Nine patients in the probiotics group developed bowel ischaemia (eight with fatal outcome), compared with none in the placebo group (p=0.004).	NA
Luong, M. L., Sareyyupoglu, B., Nguyen, M. H., Silveira, F. P., Shields, R. K., Potoski, B. A., et al. (2010). Lactobacillus probiotic use in cardiothoracic transplant recipients: A link to invasive lactobacillus infection? *Transplant Infectious Disease: An Official Journal of the Transplantation Society, 12*(6), 561-564. PMID: 21040283	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies.

Topic L. Proton Pump Inhibitor

Reference Citation	**Study Design ***	**Patient Population** • Description • Total N of patients • If systematic review, N of studies	**For Main Outcome(s), Description of** • Study group (n) • Comparison group (n)	**Summary of Results for Relevant Main Outcome(s)** • Effect size • Statistical significance)	**Reviewer notes** • Methodological issues, • Noteworthy harms • Other
Deshpande A, Pant C, Pasupuleti V, Rolston DD, Jain A, Deshpande N, Thota P, Sferra TJ, Hernandez AV. Association between proton pump inhibitor therapy and Clostridium difficile infection in a meta-analysis. Clin Gastroenterol Hepatol. 2012 Mar;10(3):225-33. doi: 10.1016/j.cgh.2011.09.030. Epub 2011 Oct 20. PubMed. PMID: 22019794.	A	Evaluated the association between PPI therapy and the risk of CDI by performing a meta-analysis Thirty studies (n= 25 case-control and n= 5 cohort) reported in 29 articles met the inclusion criteria (n = 202,965 patients in meta-analysis)	All observational studies that investigated the risk of CDI associated with PPI therapy and used CDI as an end point	PPI therapy increased the risk for CDI (odds ratio, 2.15, 95% confidence interval, 1.81-2.55). PPI therapy is associated with a 2-fold increase in risk for CDI. There was significant heterogeneity in results among studies (P < .00001).	This association remained after subgroup and sensitivity analyses, although significant heterogeneity persisted among studies. Because of the observational nature of the analyzed studies, they were not able to study the causes of this association.

Topic M. Inflammatory Bowel Disease

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Ananthakrishnan, A. N., Issa, M., & Binion, D. G. (2009). Clostridium difficile and inflammatory bowel disease. *Gastroenterology Clinics of North America, 38*(4), 711-728. PMID: 19913210	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies.
Ananthakrishnan, A. N., McGinley, E. L., Saeian, K., & Binion, D. G. (2011). Temporal trends in disease outcomes related to Clostridium difficile infection in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases, 17*(4), 976-983. PMID: 20824818	C	Nationwide Inpatient Sample, identified all IBD-related hospitalizations 2007 and examined hospitalizations with a coexisting diagnosis of C. difficile	Compared the absolute outcomes of in-hospital mortality and colectomy in the C. difficile-IBD cohort Examined these outcomes relative to non-C. difficile IBD controls	During 2007, approximately 2.9% of all IBD hospitalizations nationwide were complicated by CDI ($P < 0.001$). The absolute mortality in the C. difficile-IBD in 2007 was 7.2%. Total colectomy odds from 2007 (OR 2.51, 95% CI: 1.90-3.34).	This is a time trend from 1998-2007. Current prevalence is reported relevant to current search.
Causey, M. W., Spencer, M. P., & Steele, S. R. (2009). Clostridium difficile enteritis after colectomy. *The American Surgeon, 75*(12), 1203-1206. PMID: 19999913	Case review	n=3 cases of isolated C. difficile enteritis after colectomy	cefotetan perioperatively	Early recognition of antibiotic-associated enteritis, medical management may be effective in limiting the severity, duration, and complications of C. difficile. Most important initial intervention, just like that of colonic disease, is to stop the inciting antibiotic or switch to alternative antibiotics with a similar spectrum of antimicrobial properties. Effective antibiotics against C. difficile are metronidazole and vancomycin with cure rates of 76 and 97 per cent and recurrence in 14 and 15 per cent.	NA
Issa, M., Ananthakrishnan, A. N., & Binion, D. G. (2008). Clostridium difficile and inflammatory bowel disease. *Inflammatory Bowel Diseases, 14*(10), 1432-1442. PMID: 18484669	Review	NA	NA	NA	No primary data. No meta analysis. No reporting of search strategies
Issa, M., Vijayapal, A., Graham, M. B.,	C	n=46 c-diff	IBD (Crohn's disease,	Infection increased to 1.8% of IBD patients in 2005 (P	Univariate and

Beaulieu, D. B., Otterson, M. F., Lundeen, S., et al. (2007). Impact of clostridium difficile on inflammatory bowel disease. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association, 5*(3), 345-351. PMID: 17368234		positive patients n=953 c-diff negative patients IBD patients followed in a referral center	ulcerative colitis)	< .01). Proportion of IBD patients within the total number of C difficile infections increased to 16% in 2005 (P < .01). IBD colonic involvement was found in the majority of C difficile-infected patients in 2005 (91%), and the majority contracted infection as an outpatient (76%). Antibiotic exposure was identified in 61% of IBD patients with C difficile infection in 2005. Pseudomembranes and fibrinopurulent eruptions were not seen endoscopically or histologically. During 2004-2005 more than half of the infected IBD patients required hospitalization, and 20% required colectomy.	multivariate analysis identified maintenance immunomodulator use and colonic involvement as independent risk factors for C difficile infection in IBD.
Jen, M. H., Saxena, S., Bottle, A., Aylin, P., & Pollok, R. C. (2011). Increased health burden associated with clostridium difficile diarrhoea in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics, 33*(12), 1322-1331. PMID: 21517920	C	n=2185 patients with c-diff	IBD inpatients with co-existing *C. difficile* infection with inpatients that had IBD alone Compared the relative risk of death and of having GI surgery for patients with and without healthcare associated *C. difficile* Separated the two main clinical subgroups of patients with IBD: Crohn's disease (IBD-CD) and ulcerative colitis (IBD-UC)	IBD-CDAD-HAI group were more likely to die in hospital (adjusted OR 6.32), had 27.9 days longer in-patient stays and higher gastrointestinal surgery rates (adjusted OR 1.87) than patients admitted for inflammatory bowel disease alone.	NA
Jodorkovsky, D., Young, Y., & Abreu, M. T. (2010). Clinical outcomes of patients with ulcerative colitis and co-existing clostridium difficile infection. *Digestive Diseases and Sciences, 55*(2), 415-420. PMID: 19255850	C	n=99 patient charts were reviewed	Fifty-two patients were C. difficile-negative and 47 were positive Demographic data and laboratory values upon admission did not differ between the two groups	Patients who were C. difficile-positive had significantly more UC-related hospitalizations and emergency room visits in the year following initial admission (58 visits vs. 27, P = 0.001 and eight visits vs. 1 visit (P = 0.012). One year following the index admission, C. difficile patients had significantly higher rates of colectomy compared to C. difficile-negative patients (44.6% vs. 25%, P = 0.04). Length of hospitalization (11.7 vs. 11 days), use of cyclosporine therapy during index admission (48% vs. 47% of patients), and percentage requiring colectomy at initial admission (23.4% vs. 13.5%) did not reach statistical significance.	NA

Topic N. Prophylactic Therapy

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Johnson S, Homann SR, Bettin KM, et al. Treatment of asymptomatic clostridium difficile carriers (fecal excretors) with vancomycin or metronidazole. A randomized, placebo-controlled trial. *Ann Intern Med*. 1992;117(4):297-302. PMID: 1322075	B	n=30 patients excreting C. difficile without diarrhea or abdominal symptoms	Patients were randomized to receive 10 days of oral treatment: n=10: vancomycin, 125 mg four times daily; n=10: metronidazole, 500 mg twice daily and n=10: placebo, three times daily	Clostridium difficile organisms were not detected during treatment in 9 of 10 patients treated with vancomycin compared with 3 of 10 patients treated with metronidazole (P = 0.02) and 2 of 10 patients in the placebo group (P = 0.005). The fecal vancomycin concentration was 1406 +/- 1164 micrograms/g feces. Metronidazole was not detectable in 9 of 10 patients. Eight of the nine evaluable patients who had negative stool cultures after treatment with vancomycin began to excrete C. difficile again 20 +/- 8 days after completing treatment. Three of these patients received additional antibiotics before C. difficile excretion recurred, and five acquired new C. difficile REA strains. Four of six patients who received only vancomycin before C. difficile excretion recurred were culture-positive at the end of the study compared with one of nine patients who received only placebo (P = 0.047).	NA
Curry SR, Muto CA, Schlackman JL, et al. Use of multilocus variable number of tandem repeats analysis genotyping to determine the role of asymptomatic carriers in clostridium difficile transmission. *Clin Infect Dis*. 2013;57(8):1094-1102. PMID: 23881150	D	n=3006 patients screened for c-diff	Case series	Sixteen (29%) cases were associated with carriers. Transmission events from prior bed occupants with CDI (n = 2) or carriers (n = 2) were identified in 4 of 56 cases.	NA

Topic O. Antimicrobial Treatment Based on Disease Severity

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Cohen, S. H., Gerding, D. N., Johnson, S., Kelly, C. P., Loo, V. G., McDonald, L. C., et al. (2010). Clinical practice guidelines for clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of america (SHEA) and the infectious diseases society of america (IDSA). *Infection Control and Hospital Epidemiology, 31*(5), 431-455. PMID: 20307191	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Debast, S. B., Bauer, M. P., Kuijper, E. J., & European Society of Clinical Microbiology and Infectious Diseases. (2014). European society of clinical microbiology and infectious diseases: Update of the treatment guidance document for clostridium difficile infection. *Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases, 20 Suppl 2,* 1-26. PMID: 24118601	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Johnson, S., Louie, T. J., Gerding, D. N., Cornely, O. A., Chasan-Taber, S., Fitts, D., et al. (2014). Vancomycin, metronidazole, or tolevamer for clostridium difficile infection: Results from two multinational, randomized, controlled trials. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 59*(3), 345-354. PMID: 24799326	A	n=1118 patients with CDiff	CDI patients were randomly assigned in a 2:1:1 ratio to oral tolevamer 9 g (loading dose) followed by 3 g every 8 hours for 14 days, vancomycin 125 mg every 6 hours for 10 days, or metronidazole 375 mg every 6 hours for 10 days 563 patients received tolevamer, 289 received metronidazole, and 266 received vancomycin	Clinical success of tolevamer was inferior to both metronidazole and vancomycin ($P < .001$), and metronidazole was inferior to vancomycin ($P = .02$; 44.2% [n = 534], 72.7% [n = 278], and 81.1% [n = 259], respectively). Clinical success in patients with severe CDI who received metronidazole was 66.3% compared with vancomycin, which was 78.5%. ($P = .059$). A post-hoc multivariate analysis that excluded tolevamer found 3 factors that were strongly associated with clinical	NA

				success: vancomycin treatment, treatment-naive status, and mild or moderate CDI severity. Adverse events were similar among the treatment groups.	
Surawicz, C. M., Brandt, L. J., Binion, D. G., Ananthakrishnan, A. N., Curry, S. R., Gilligan, P. H., et al. (2013). Guidelines for diagnosis, treatment, and prevention of clostridium difficile infections. *The American Journal of Gastroenterology, 108*(4), 478-98; quiz 499. PMID: 23439232	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Zar, F. A., Bakkanagari, S. R., Moorthi, K. M., & Davis, M. B. (2007). A comparison of vancomycin and metronidazole for the treatment of clostridium difficile-associated diarrhea, stratified by disease severity. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 45*(3), 302-307. PMID: 17599306	A	n=172 patients with mild or severe CDAD 150 of these patients successfully completed the trial	Patients with mild (n=81) or severe (n=69) disease based on clinical criteria and were randomly assigned to receive: n=79: oral metronidazole (250 mg 4 times per day) n=71: oral vancomycin (125 mg 4 times per day) for 10 days Both groups received an oral placebo in addition to the study drug	Patients with mild CDAD, treatment with metronidazole or vancomycin resulted in clinical cure in 90% and 98% of the patients, respectively (p=.36). Patients with severe CDAD, treatment with metronidazole or vancomycin resulted in clinical cure in 76% and 97% of the patients, respectively (p=.02). Clinical symptoms recurred in 15% of the patients treated with metronidazole and 14% of those treated with vancomycin.	NA

Topic P. Recurrent Treatment

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Bagdasarian, N., Rao, K., & Malani, P. N. (2015). Diagnosis and treatment of clostridium difficile in adults: A systematic review. *Jama, 313*(4), 398-408. PMID: 25626036	A	n=116 articles on best practices for treatment of C-diff	Systematic review in adults	Laboratory testing cannot distinguish between asymptomatic colonization and symptomatic infection with C difficile. Multistep algorithms using polymerase chain reaction (PCR) for the toxin gene(s) or single-step PCR on liquid stool samples have the best test performance characteristics (for multistep: sensitivity was 0.68-1.00 and specificity was 0.92-1.00; and for single step: sensitivity was 0.86-0.92 and specificity was 0.94-0.97). Clinical success rates of 66.3% for metronidazole vs 78.5% for vancomycin for severe CDI. Newer therapies show promising results, including fidaxomicin (similar clinical cure rates to vancomycin, with lower recurrence rates for fidaxomicin, 15.4% vs vancomycin, 25.3%; P = .005) and fecal microbiota transplantation (response rates of 83%-94% for recurrent CDI).	Some meta-analytic techniques used, but not formally identified as meta-analysis.
Bartsch, S. M., Umscheid, C. A., Fishman, N., & Lee, B. Y. (2013). Is fidaxomicin worth the cost? an economic analysis. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 57*(4), 555-561. PMID: 23704121	C	Developed decision analytic simulation model using 3 use-cases to determine economic impact of Fidaxomicin n=1000 simulated patients, run through simulation 1000 times, (total 1,000,000 simulated encounters)	(1) no fidaxomicin (2) only fidaxomicin (3) fidaxomicin based on strain typing results	Cost-effectiveness ratio for fidaxomicin based on screening given current conditions was >$43.7 million per quality-adjusted life-year and using only fidaxomicin was dominated (ie, more costly and less effective) by the other 2 treatment strategies explored. The fidaxomicin strategy tended to remain dominated, even at lower costs. With approximately 50% of CDI due to the NAP1/BI/027 strain, a course of fidaxomicin would need to cost </=$150 to be cost-effective in the treatment of all CDI cases and between $160 and $400 to be cost-effective for those with a non-NAP1/BI/027 strain (ie, treatment based on strain typing).	NA
Cohen, S. H., Gerding, D. N., Johnson, S., Kelly, C. P., Loo, V. G., McDonald, L. C., et al. (2010). Clinical practice guidelines for clostridium difficile infection in adults: 2010 update by the	Guideline	NA	NA	NA	Systematic review/guideline, see evidence

society for healthcare epidemiology of america (SHEA) and the infectious diseases society of america (IDSA). *Infection Control and Hospital Epidemiology, 31*(5), 431-455. PMID: 20307191					in tables in source
Cornely, O. A., Crook, D. W., Esposito, R., Poirier, A., Somero, M. S., Weiss, K., et al. (2012). Fidaxomicin versus vancomycin for infection with clostridium difficile in europe, canada, and the USA: A double-blind, non-inferiority, randomised controlled trial. *The Lancet.Infectious Diseases, 12*(4), 281-289. PMID: 22321770	A	n=535 patients positive for c-diff	270 patients were assigned oral fidaxomicin (200 mg every 12 h) 265 patients were assigned oral vancomycin (125 mg every 6 h) for 10 days	Twenty-six patients were excluded, 509 were included in the modified intention-to-treat (mITT) population. 198 (91.7%) of 216 patients in the per-protocol population given fidaxomicin achieved clinical cure, compared with 213 (90.6%) of 235 given vancomycin, meeting the criterion for non-inferiority (one-sided 97.5% CI -4.3%). Non-inferiority was also shown for clinical cure in the mITT population, with 221 (87.7%) of 252 patients given fidaxomicin and 223 (86.8%) of 257 given vancomycin cured (one-sided 97.5% CI -4.9%). Subgroup analyses of the primary endpoint in the mITT population, outcomes in the two treatment groups did not differ significantly; although patients receiving concomitant antibiotics for other infections had a higher cure rate with fidaxomicin (46 [90.2%] of 51) than with vancomycin (33 [73.3%] of 45; p=0.031). Occurrence of treatment-emergent adverse events did not differ between groups. 20 (7.6%) of 264 patients given at least one dose of fidaxomicin and 17 (6.5%) of 260 given vancomycin died.	NA
Debast, S. B., Bauer, M. P., Kuijper, E. J., & Committee. (2014). European society of clinical microbiology and infectious diseases: Update of the treatment guidance document for clostridium difficile infection. *Clinical Microbiology & Infection, 20*(Suppl 2), 1-26. PMID: 24118601	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Drekonja, D. M., Amundson, W. H., Decarolis, D. D., Kuskowski, M. A., Lederle, F. A., & Johnson, J. R. (2011). Antimicrobial use and risk for recurrent clostridium difficile infection. *The American Journal of Medicine, 124*(11), 1081.e1-1081.e7. PMID: 21944159	C	n=246 patients with c-diff	Case series followed for 30 days	One hundred forty-one patients (57%) received non-CDI antimicrobials, including 61 (25%) who received non-CDI antimicrobials during CDI treatmen.t Eighty patients (33%) who received non-CDI antimicrobial therapy after CDI treatment. With adjustment for age, disease severity, duration of CDI treatment, and recent hospital or intensive-care unit stay, receipt of non-CDI antimicrobials after CDI treatment was significantly associated with recurrent CDI (odds ratio [OR] 3.02; 95% confidence interval [CI], 1.66-5.52), compared with no antimicrobial use. Antimicrobial use during CDI treatment was not associated with recurrent CDI (OR 0.79; 95% CI, 0.40-1.52). Neither	NA

				number of antimicrobial courses nor antimicrobial days was associated with recurrence.	
Herpers, B. L., Vlaminckx, B., Burkhardt, O., Blom, H., Biemond-Moeniralam, H. S., Hornef, M., et al. (2009). Intravenous tigecycline as adjunctive or alternative therapy for severe refractory clostridium difficile infection. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 48*(12), 1732-1735. PMID: 19435431	D	n=4 patients with severe CDI	Severe CDI patients treated with tigecycline	Patients had >4 of the following severity markers: leukocytosis, elevated creatinine level, elevated lactate level, hypoalbuminemia, fever and signs of severe colitis. Standard therapy failed for 3 of 4 patients. 4 patients symptoms of CDI subsided within 1 week after initiation of treatment with tigecycline.	NA
Johnson, S., & Gerding, D. N. (2013). Fidaxomicin "chaser" regimen following vancomycin for patients with multiple clostridium difficile recurrences. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 56*(2), 309-310. PMID: 23024296	D	n=3 patients with multiple CDI recurrences	Initially treated with metronidazole followed by vancomycin and a tapering/pulsed vancomycin	Fidaxomicin was offered based on published reports of the phase 3 randomized treatment trials and the product insert for fidaxomicin. Following the vancomycin “maintenance” therapy, vancomycin was stopped and a10-day course of oral fidaxomicin, 200 mg twice daily, was administered. Two patients have had no CDI recurrences to date (9- and 10-month follow-ups) andone patient had no recurrence for 3 months but then had a symptomatic recurrence 1 week after a 3-day course of levofloxacin was given for a urinary tract infection.	NA
Johnson, S., Schriever, C., Galang, M., Kelly, C. P., & Gerding, D. N. (2007). Interruption of recurrent clostridium difficile-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 44*(6), 846-848. PMID: 17304459	D	n=8 women experiencing C-Diff episodes	All experienced at least 4 episodes of CDAD and multiple other approaches had been employed to treat the recurrent episodes	Rifaximin as a follow-up therapy, or “chaser,” after vancomycin treatment was remarkably effective for interrupting recurrent CDAD episodes in this very challenging group of patients. All patients had at least 1.5 months of symptom free follow up after completion of rifaximin therapy. Patient who had a symptomatic relapse after completion of rifaximin therapy responded to a second course of rifaximin therapy without subsequent symptoms.	NA
Louie, T. J., Miller, M. A., Mullane, K. M., Weiss, K., Lentnek, A., Golan, Y., et al. (2011). Fidaxomicin versus vancomycin for clostridium difficile infection. *The New England Journal of Medicine, 364*(5), 422-431. PMID: 21288078	B	n=629 patients were enrolled n=548 (87.1%) could be evaluated	Randomly assigned patients to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days End point was clinical cure Secondary end points were recurrence of C. difficile infection (diarrhea and a positive result on a stool toxin test within 4 weeks after	Rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% vs. 25.3%, P=0.005) and the per-protocol analysis (13.3% vs. 24.0%, P=0.004). The lower rate of recurrence was seen in patients with non-North American Pulsed Field type 1 strains. The adverse-event profile was similar for the two therapies.	NA

			treatment) and global cure (i.e., cure with no recurrence)		
McFarland, L. V., Elmer, G. W., & Surawicz, C. M. (2002). Breaking the cycle: Treatment strategies for 163 cases of recurrent clostridium difficile disease. *The American Journal of Gastroenterology*, *97*(7), 1769-1775. PMID: 12135033	C	n=163 cases of recurrent C-Diff	Patients with active RCCD were enrolled, prescribed either vancomycin or metronidazole, and randomized to either the investigational biological or a placebo	163 cases, 44.8% recurred. A tapering course of vancomycin resulted in significantly fewer recurrences (31%, p = 0.01), as did pulsed dosing of vancomycin (14.3%, p = 0.02). A trend (p = 0.09) for a lower recurrence frequency was observed for high-dose (> or =2 g/day) vancomycin and low-dose (< or =1 g/day) metronidazole. Vancomycin was significantly more effective in clearing C. difficile culture and/or toxin by the end of therapy than metronidazole (89% vs 59%, respectively; p < 0.001).	NA
Modena, S., Gollamudi, S., & Friedenberg, F. (2006). Continuation of antibiotics is associated with failure of metronidazole for clostridium difficile-associated diarrhea. *Journal of Clinical Gastroenterology*, *40*(1), 49-54. PMID: 16340634	C	n=27 patients with C. difficile-associated diarrhea	Patients had symptomatic *C. difficile*-associated diarrhea, either mild or severe Received <=24 hours of treatment with oral metronidazole. Oral metronidazole had to be their sole treatment; Patients were included if they were switched to another antibiotic after day 5.	Response by day 5 did not predict treatment success by day 14 (*P* = 0.76). Seven patients had an additional identifiable risk factor for *C. difficile*-associated disease besides exposure to antibiotics. Fifty-nine percent of patients who remained on antibiotics during treatment of CDAD had resolution of symptoms by day 14 of treatment (*P* = 0.02). CDAD severity was predictive of response by day 5 (*P* = 0.01), it was not predictive of response by day 14. CDAD severity was not different between patients who remained on antibiotics and those who were taken off antibiotics (*P* = 0.66). Response by day 5 was not associated with response at day 14, and was also not associated with frequency of CDAD relapse (*P* = 0.64).	NA
Mullane, K. M., Miller, M. A., Weiss, K., Lentnek, A., Golan, Y., Sears, P. S., et al. (2011). Efficacy of fidaxomicin versus vancomycin as therapy for clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *53*(5), 440-447. PMID: 21844027	A	n=564 subjects in the fidaxomicin treatment group n=583 subjects in the vancomycin group (safety population)	To study effects of CAs on response to fidaxomicin or vancomycin. Subjects with CDI were treated for 10 days with either: • fidaxomicin 200 mg every 12 hours • vancomycin 125 mg every 6 hours, Rates of cure, recurrence, and global cure (cure without recurrence) were determined for subgroups of subjects	CAs were prescribed for 27.5% of subjects during study participation. The use of CAs concurrent with CDI treatment was associated with a lower cure rate (84.4% vs 92.6%; P < .001) and an extended time to resolution of diarrhea (97 vs 54 hours; P < .001). CA use during the follow-up was associated with more recurrences (24.8% vs 17.7%; not significant), and CA administration at any time was associated with a lower global cure rate (65.8% vs 74.7%; P = .005). When subjects received CAs concurrent with CDI treatment, the cure rate was 90.0% for fidaxomicin and 79.4% for vancomycin (P = .04). In subjects receiving CAs during treatment and/or follow-up, treatment with fidaxomicin compared with vancomycin was associated with 12.3% fewer recurrences (16.9% vs 29.2%; P = .048).	NA

			defined by CA use and treatment group		
Musher, D. M., Logan, N., Mehendiratta, V., Melgarejo, N. A., Garud, S., & Hamill, R. J. (2007). Clostridium difficile colitis that fails conventional metronidazole therapy: Response to nitazoxanide. *The Journal of Antimicrobial Chemotherapy, 59*(4), 705-710. PMID: 17337513	C	n=35 patients who failed treatment with metronidazole for C. difficile colitis	Treatment was: Nitazoxanide, 500 mg twice daily, for 10 days	Twenty-six (74%) of 35 patients responded to nitazoxanide. Seven later had recurrent disease, yielding a cure rate of 19 of 35 (54%) from initial therapy. Three who initially failed and one who had recurrent disease were re-treated with, and responded to, nitazoxanide. Aggregate cure with nitazoxanide in this difficult-to-treat population was 23 of 35 (66%).	NA
Nathwani, D., Cornely, O. A., Van Engen, A. K., Odufowora-Sita, O., Retsa, P., & Odeyemi, I. A. (2014). Cost-effectiveness analysis of fidaxomicin versus vancomycin in clostridium difficile infection. *The Journal of Antimicrobial Chemotherapy, 69*(11), 2901-2912. PMID: 25096079	C	Markov model (simulation) of CDI treatment adults (aged ≥18 years) with severe CDI adults with a first CDI recurrence	Treated either with oral fidaxomicin or oral vancomycin for 10 days (i) index CDI episode; (ii) first non-severe recurrence; (iii) first severe recurrence; (iv) second or more non-severe recurrence; and (v) second or more severe recurrence	Total costs were similar with fidaxomicin and vancomycin in patients with severe CDI (pound14,515 and pound14,344, respectively) and in patients with a first recurrence (pound16,535 and pound 16,926, respectively). Improvements in clinical outcomes with fidaxomicin resulted in small QALY gains versus vancomycin (severe CDI, +0.010; patients with first recurrence, +0.019). Fidaxomicin was cost-effective in severe CDI (ICER pound16,529/QALY) and dominant (i.e. more effective and less costly) in patients with a first recurrence. The probability that fidaxomicin was cost-effective at a willingness-to-pay threshold of pound 30,000/QALY was 60% for severe CDI and 68% in a first recurrence.	Simulation data for cost-effectiveness
Pop-Vicas, A., Shaban, E., Letourneau, C., & Pechie, A. (2012). Empirical antimicrobial prescriptions in patients with clostridium difficile infection at hospital admission and impact on clinical outcome. *Infection Control and Hospital Epidemiology, 33*(11), 1101-1106. PMID: 23041807	C	n=94 patients with CDI at hospital admission during a 24-month period	Retrospective cohort of all patients with CDI, examining treatment patterns	62% received at least one non-CDI-related antimicrobial during their hospitalization for CDI. Severe complicated CDI (odds ratio [OR], 7.1 [95% confidence interval {CI}, 1.8-28.5]. Duration of non-CDI-related antimicrobial exposure (OR, 1.2 [95% CI, 1.03-1.36 and age (OR, 1.1 [95% CI, 1.0-1.1]; were independent risk factors for adverse clinical outcomes. One-third of the patients received unnecessary antimicrobial therapy. Sepsis at hospital admission (OR, 5.3 [95% CI, 1.8-15.8]; and clinical suspicion of urinary tract infection (OR, 9.7 [95% CI, 2.9-32.3]; were independently associated with unnecessary antimicrobial prescriptions.	NA
Surawicz, C. M., Brandt, L. J., Binion, D. G., Ananthakrishnan, A. N., Curry, S. R., Gilligan, P. H., et al. (2013). Guidelines for diagnosis, treatment, and prevention of clostridium difficile infections. *The American Journal of Gastroenterology, 108*(4), 478-98; quiz 499. PMID: 23439232	Guideline	NA	NA	NA	Systematic review/guideline, see evidence in tables in source.

Topic Q. Probiotics for Treatment

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	Description of Groups (For main outcomes) • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Bakken, J. S. (2014). Staggered and tapered antibiotic withdrawal with administration of kefir for recurrent clostridium difficile infection. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *59*(6), 858-861. PMID: 24917658	D	n=25 evaluable patients with recurrent CDI	Case series: Treatment: Drink a 5-oz glass of Lifeway kefir with each meal (at least 3 glasses per day) while tapering ongoing therapy with either metronidazole or vancomycin	25 patients had reestablished normal bowel function with formed bowel movements at the start and completion of STAW. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. Twenty patients have remained symptom free for >12 months. Four patients (16%) experienced diarrhea relapse with a positive stool *C. difficile* test between 24 and 45 days after completion of STAW. There was no relationship between diarrhea relapse and H2-blocker usage, active immunosuppressive therapy, comorbid conditions, or predisposing infectious illness (*P* = NS, data not shown). 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. 4 patients remained symptom-free at 12 months of follow-up.	NA
Enache-Angoulvant, A., & Hennequin, C. (2005). Invasive saccharomyces infection: A comprehensive review. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *41*(11), 1559-1568. PMID: 16267727	D	n=92 cases from published reports	Collected published case reports, through May 2005, of invasive Saccharomyces infection by use of a Medline query	92 cases of Saccharomyces invasive infection. Predisposing factors were similar to those of invasive candidiasis, with intravascular catheter and antibiotic therapy being the most frequent. Blood was the most frequent site of isolation (for 72 patients). S. boulardii accounted for 51.3% of fungemias and was exclusively isolated from blood. Compared with patients infected with S. cerevisiae, patients infected with S. boulardii were more frequently	NA

				immunocompetent and had a better prognosis. Saccharomyces invasive infection was clinically indistinguishable from an invasive candidiasis. Overall, S. cerevisiae clinical isolates exhibited low susceptibility to amphotericin B and azole derivatives. However, global outcome was favorable in 62% of the cases. Treatment with intravenous amphotericin B and fluconazole, in combination with central vascular catheter removal, were effective therapeutic options.	
McFarland, L. V., Surawicz, C. M., Greenberg, R. N., Fekety, R., Elmer, G. W., Moyer, K. A., et al. (1994). A randomized placebo-controlled trial of saccharomyces boulardii in combination with standard antibiotics for clostridium difficile disease. *Jama, 271*(24), 1913-1918. PMID: 8201735	A	n=124 patients with active CDI (CDD) n=64 initial CDI n=60 recurrent	Oral S boulardii (1 g/d for 4 weeks) n=57 Placebo in combination with a standard antibiotic n=67	History of CDD episodes dramatically increased the likelihood of further recurrences. Multivariate analysis revealed that patients treated with S boulardii and standard antibiotics had a significantly lower relative risk (RR) of CDD recurrence (RR, 0.43; 95% confidence interval, 0.20 to 0.97) compared with placebo and standard antibiotics. Efficacy of S boulardii was significant (recurrence rate 34.6%, compared with 64.7% on placebo; P = .04) in patients with recurrent CDD, but not in patients with initial CDD (recurrence rate 19.3% compared with 24.2% on placebo; P = .86). There were no serious adverse reactions associated with S boulardii.	NA
Surawicz, C. M., McFarland, L. V., Greenberg, R. N., Rubin, M., Fekety, R., Mulligan, M. E., et al. (2000). The search for a better treatment for recurrent clostridium difficile disease: Use of high-dose vancomycin combined with saccharomyces boulardii. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 31*(4), 1012-1017. PMID: 11049785	A	n=168 patients with recurrent CDI	Regimen of a standard antibiotic for 10 days and then added either • S. boulardii (1 g/day for 28 days) • placebo (32 patients had been prescribed high-dose vancomycin, 83 low dose vancomycin and 53 given metronidazole)	Significant decrease in recurrences was observed only in patients treated with high-dose vancomycin (2 g/day) and S. boulardii (16.7%), compared with those who received high-dose vancomycin and placebo (50%; P=.05). No serious adverse reactions were observed in these patients. Comparison of data from this trial with data from previous studies indicates that recurrent CDD may respond to a short course of high-dose vancomycin or to longer courses of low-dose vancomycin when either is combined with S. boulardii.	NA

Topic R. Immunotherapy

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Debast, S. B., Bauer, M. P., Kuijper, E. J., & Committee. (2014). European society of clinical microbiology and infectious diseases: Update of the treatment guidance document for clostridium difficile infection. *Clinical Microbiology & Infection, 20*(Suppl 2), 1-26. PMID: 24118601	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.
Juang, P., Skledar, S. J., Zgheib, N. K., Paterson, D. L., Vergis, E. N., Shannon, W. D., et al. (2007). Clinical outcomes of intravenous immune globulin in severe clostridium difficile-associated diarrhea. *American Journal of Infection Control, 35*(2), 131-137. PMID: 17327194	C	n=79 patients with positive C. difficile toxin titer and severe disease	patients recieving IVIG treatment (200-300 mg/kg) (n=18) patients matched to characteristics of CDAD from the available pool of 61 subjects who did not receive IVIG treatment (n=18)	No significant difference was observed in the baseline characteristics between the two groups. There were no statistical differences in clinical outcomes as measured by all-cause mortality, colectomies, and length of stay.	NA
Lowy, I., Molrine, D. C., Leav, B. A., Blair, B. M., Baxter, R., Gerding, D. N., et al. (2010). Treatment with monoclonal antibodies against clostridium difficile toxins. *The New England Journal of Medicine, 362*(3), 197-205. PMID: 20089970	B	n=200 patients with symptomatic C. difficile infection who were receiving either metronidazole or vancomycin	Test of two neutralizing, fully human monoclonal antibodies against C. difficile toxins administered together as a single infusion, each at a dose of 10 mg per kilogram of body weight • antibody (n=101) • placebo group (n=99)	Rate of recurrence of C. difficile infection was lower among patients treated with monoclonal antibodies (7% vs. 25%; 95% confidence interval, 7 to 29; P<0.001). Recurrence rates among patients with the epidemic BI/NAP1/027 strain were 8% for the antibody group and 32% for the placebo group (P=0.06). Patients with more than one previous episode of C. difficile infection, recurrence rates were 7% and 38%, respectively (P=0.006). Mean duration of the initial hospitalization for inpatients did not differ significantly between the antibody and placebo groups (9.5 and 9.4 days, respectively). At least one serious adverse event was reported by 18 patients in the antibody group and by 28 patients in the placebo group (P=0.09).	NA
Surawicz, C. M., Brandt, L. J., Binion, D. G., Ananthakrishnan, A. N., Curry, S. R., Gilligan, P. H., et al. (2013). Guidelines for diagnosis, treatment, and prevention of clostridium difficile infections. *The American Journal of Gastroenterology, 108*(4), 478-98; quiz 499. PMID: 23439232	Guideline	NA	NA	NA	Systematic review/Guideline, see evidence tables in source.

Topic S. Toxin-binding Polymers and Resins

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Johnson, S., Louie, T. J., Gerding, D. N., Cornely, O. A., Chasan-Taber, S., Fitts, D., et al. (2014). Vancomycin, metronidazole, or tolevamer for clostridium difficile infection: Results from two multinational, randomized, controlled trials. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *59*(3), 345-354. PMID: 24799326	A	n=1118 patients with CDiff	CDI patients were randomly assigned in a 2:1:1 ratio to oral tolevamer 9 g (loading dose) followed by 3 g every 8 hours for 14 days, vancomycin 125 mg every 6 hours for 10 days, or metronidazole 375 mg every 6 hours for 10 days 563 patients received tolevamer, 289 received metronidazole, and 266 received vancomycin	Clinical success of tolevamer was inferior to both metronidazole and vancomycin (P < .001), and metronidazole was inferior to vancomycin (P = .02; 44.2% [n = 534], 72.7% [n = 278], and 81.1% [n = 259], respectively). Clinical success in patients with severe CDI who received metronidazole was 66.3% compared with vancomycin, which was 78.5%. (P = .059). A post-hoc multivariate analysis that excluded tolevamer found 3 factors that were strongly associated with clinical success: vancomycin treatment, treatment-naive status, and mild or moderate CDI severity. Adverse events were similar among the treatment groups.	NA
Mogg, G. A., George, R. H., Youngs, D., Johnson, M., Thompson, H., Burdon, D. W., et al. (1982). Randomized controlled trial of colestipol in antibiotic-associated colitis. The British Journal of Surgery, 69(3), 137-139. PMID: 7039758	B	n=38 Patients with severe antibiotic-associated postoperative diarrhoea	17 colestipol 21 placebo (sherbet)	Clostridium difficile or its toxin was present before treatment in 12 of the colestipol group, compared with only 5 in the placebo group. colestipol nor placebo had any influence on the faecal excretion of Cl. difficile or its toxin. Colestipol was clinically no better than placebo. In view of the persistent faecal excretion of Cl. difficile toxin, ion exchange resins cannot be recommended for the treatment of antibiotic-associated colitis.	Because of the low incidence of Cl. difficile or its toxin, the placebo group data from 22 patients receiving placebo in a previous trial (9 of whom had Cl. difficile or toxin) were included for comparison.
Pantosti, A., Luzzi, I., Cardines, R., & Gianfrilli, P. (1985). Comparison of the in vitro activities of teicoplanin and vancomycin against clostridium difficile and their interactions with cholestyramine. *Antimicrobial Agents and Chemotherapy*, *28*(6), 847-848. PMID: 2935077	C	teicoplanin was compared with vancomycin against fecal isolates of Clostridium difficile n =75	75 strains of c-diff isolated from stool samples 75 vancomycin 75 teicoplanin (in vitro comparison)	All strains were susceptible to both antibiotics, but teicoplanin was fourfold more active than vancomycin. Cholestyramine was found to bind teicoplanin almost completely, reducing its activity to nondetectable levels.	In vitro comparison

Topic T. Fecal Microbiota Transplantation

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Cammarota, G., Masucci, L., Ianiro, G., Bibbo, S., Dinoi, G., Costamagna, G., et al. (2015). Randomised clinical trial: Faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent clostridium difficile infection. *Alimentary Pharmacology & Therapeutics, 41*(9), 835-843. PMID: 25728808	A	n=20 patients undergoing FMT	vancomycin (25 mg four times a day for 3 day followed by one or more infusions of faeces via colonoscopy or vancomycin vancomycin 125 mg four times daily for 10 days, followed by 125-500 mg/day every 2-3 days for at least 3 weeks	Eighteen of the 20 patients (90%) treated by FMT exhibited resolution of C. difficile-associated diarrhoea. Five of the seven patients with pseudomembranous colitis reported a resolution of diarrhoea. Resolution of C. difficile infection occurred in 5 of the 19 (26%) patients in vancomycin (P < 0.0001). No significant adverse events were observed in either of the study groups.	NA
Lee CH et al JAMA 2016- frozen versus Fresh FMT, PMID: 26757463	B	n=219 adults with recurrent or refractory CDI n=178 patients in the per protocol population	219 patients (n = 108 in the frozen FMT group and n = 111 in the fresh FMT group) 178 (frozen FMT: n = 91, fresh FMT: n = 87) in the per-protocol population	Per-protocol population, the proportion of patients with clinical resolution was 83.5% for the frozen FMT group and 85.1% for the fresh FMT group (difference, -1.6% [95% CI, -10.5% to infinity]; P = .01 for noninferiority). In the mITT population the clinical resolution was 75.0% for the frozen FMT group and 70.3% for the fresh FMT group (difference, 4.7% [95% CI, -5.2% to infinity]; P < .001 for noninferiority).	NA

Fecal Microbiota Transplantation for *Clostridium difficile* Infection: A Systematic Review Fecal Microbiota Transplantation for *Clostridium difficile* Infection. Dimitri, Drekonja, *Ann Intern Med.* 2015;162(9):630-638. doi:10.7326/M14-2693 PMID: 25938992	C	n=2 randomized, controlled trials (RCTs);
		n=28 case-series studies;
		n=5 case reports
		Of these, those reporting FMT use included:
		n=2 RCTs
		n=21 case-series studies
		(n=516 patients) receiving FMT
			Any study of FMT to treat adult patients with CDI
			28 case-series studies; and 5 case reports were included
			Two RCTs and 21 case-series studies (516 patients receiving FMT) reported using FMT for patients with recurrent CDI
			One RCT comparing FMT with 2 control groups. vancomycin, or vancomycin-plus-bowel lavage groups
				One RCT comparing FMT with 2 control groups (n = 43) reported resolution of symptoms in 81%, 31%, and 23% of the FMT, vancomycin, or vancomycin-plus-bowel lavage groups, respectively (P < 0.001 for both control groups vs. FMT).
				An RCT comparing FMT route (n = 20) reported no difference between groups (60% in the nasogastric tube group and 80% in the colonoscopy group; P = 0.63).
				Across all studies for recurrent CDI, symptom resolution was seen in 85% of cases. In 7 case-series studies of patients with refractory CDI, symptom resolution ranged from 0% to 100%. Among 7 patients treated with FMT for initial CDI, results were mixed.
					NA

Topic U. Avoid Anti-Motility Agents

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Koo HL, Koo DC, Musher DM, DuPont HL. Antimotility agents for the treatment of clostridium difficile diarrhea and colitis. *Clin Infect Dis*. 2009;48(5):598-605. PMID: 19191646	D	n=20 reports regarding antimotility treatment of CDI n=55 patients with CDI	Case study	Nineteen (35%) of the 55 patients with CDI described improvement and experienced clinical resolution. Nine patients (16%) died. Twenty-seven patients (49%) had unknown outcomes. Seventeen (31%) of the 55 patients with CDI treated with an antimotility agent clinically deteriorated and developed complications of toxic megacolon or colonic dilation. Five of these 17 patients had underlying conditions associated with immunosuppression, including advanced AIDS, pregnancy, uncontrolled diabetes mellitus and cancer requiring chemotherapy. Six (40%) of the 15 patients with known outcomes of complicated colonic dilation died. For 5 patients death occurred despite surgical intervention.	No primary data. No meta analysis. No reporting of search strategies.

Topic V. Surgical Treatment

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Ali, S. O., Welch, J. P., & Dring, R. J. (2008). Early surgical intervention for fulminant pseudomembranous colitis. *The American Surgeon, 74*(1), 20-26. PMID: 18274423	D	n=36 patients who underwent colectomy for fulminant PMC from 1995 to 2006 including 21 females	21 females ranged from 40 to 89 years of age (mean, 70 years) Diabetes (39%), cardiovascular disease (77%), chronic obstructive pulmonary disease (47%), and intake of immunosuppressive medications (45%) All patients underwent colectomy Patients with a confirmation of PMC on pathology specimens were included	Survival was correlated with mean white blood cell count (23,000 survivors versus 40,000 nonsurvivors, P < 0.01); multisystem organ failure (16 per cent survivors versus 47 per cent nonsurvivors, P < 0.05); and preoperative pressors (16 per cent survivors versus 47 per cent nonsurvivors, P < 0.05). Overall mortality for the study period was 47 per cent. Mortality rate analysis revealed a lower rate for the more recent years (32 per cent for 2000 to 2006 versus 65 per cent for 1995 to 1999, P < 0.05). In the more recent years, the time elapsing before colectomy was also lower (1.4 days versus 2.5 days, nonsignificant), and patients had less preoperative hemodynamic instability (70 per cent versus 31 per cent, P < 0.03).	NA
Bhangu, A., Nepogodiev, D., Gupta, A., Torrance, A., Singh, P., & West Midlands Research Collaborative. (2012). Systematic review and meta-analysis of outcomes following emergency surgery for clostridium difficile colitis. *The British Journal of Surgery, 99*(11), 1501-1513. PMID: 22972525	A	n=31 studies comparing survivors and non-survivors of emergency surgery for CDI (n = 1433 patients)	Undergoing emergency surgery for CDI Operation performed was total colectomy with end ileostomy	1.1 per cent of all patients with CDI and 29.9 per cent with severe CDI underwent emergency surgery. Rates varied between studies (0.2-7.6 and 2.2-86 percent respectively). Total colectomy with end ileostomy (89.0 percent, 1247 of 1401 detailed surgical procedures). Total colectomy with end ileostomy was not performed, reoperation to resect further bowel was needed in 15.9 per cent (20 of 126). The 30-day mortality rate was 41.3 per cent (160 of 387.	NA
Ferrada, P., Velopulos, C. G., Sultan, S., Haut, E. R., Johnson, E., Praba-Egge, A., et al. (2014). Timing and type of surgical treatment of clostridium difficile-associated disease: A practice management guideline from the eastern association for the surgery of trauma. *The Journal of Trauma and Acute*	A	Q 1: 32 studies on adult patients with CDAD and early surgery Q 2: 17 studies on adult patients with CDAD	Question 1: In adult patients with CDAD, does early surgery compared with late surgery, as defined by the need for vasopressors, decrease mortality? PICO Question 2: In adult patients	Reduction in mortality was significantly associated with early surgery, with a risk ratio (RR) of 0.5 (95% confidence interval [CI], 0.35-0.72). The quality of evidence was rated "moderate." Considering only the first procedure performed, mortality seemed to trend higher	NA

Care Surgery, 76(6), 1484-1493. PMID: 24854320		with total abdominal colectomy	with CDAD, does total abdominal colectomy (TAC) compared with other types of surgical intervention decrease mortality?	for TAC, with an RR of 1.11 (95% CI, 0.69-1.80). Considering only the actual procedure performed, the point estimate switched sides, showing a trend toward decreased mortality with TAC (RR, 0.86; 95% CI, 0.56-1.31). The quality of evidence was rated "very low."	
Fujitani, S., George, W. L., & Murthy, A. R. (2011). Comparison of clinical severity score indices for clostridium difficile infection. *Infection Control and Hospital Epidemiology, 32*(3), 220-228. PMID: 21460506	C	n=184 patients with CDI	19 had severe cases of CDI and 165 had non-severe	Sensitivities of the 8 severity score indices studied ranged from 63.2% to 84.2%. Specificities ranged from 59.4% to 93.9%. Hines VA index had the highest kappa score (0.69 [95% confidence interval, 0.54-0.83]). Independent risk factors for severe CDI determined by multivariate analysis were abdominal distention (P = .007), fever (temperature, 38.0 degrees C or above; P = .042), white blood cell count of at least 20,000 cells/mm (3) (P = .035), and hypoalbuminemia (serum albumin level less than 3 mg/dL; P = .029).	NA
Halabi, W. J., Nguyen, V. Q., Carmichael, J. C., Pigazzi, A., Stamos, M. J., & Mills, S. (2013). Clostridium difficile colitis in the united states: A decade of trends, outcomes, risk factors for colectomy, and mortality after colectomy. *Journal of the American College of Surgeons, 217*(5), 802-812. PMID: 24011436	C	n=2,773,521 discharges over a decade	LASSO algorithm for logistic regression with 10-fold cross validation to build a predictive model for colectomy requirement and mortality after colectomy Association of colectomy day with mortality was also examined on multivariable logistic regression analysis	Colectomy was required in 19,374 cases (0.7%), with an associated mortality of 30.7%. Compared with the 2001 to 2005 period, the 2006 to 2010 period witnessed a 47% increase in the rate of CDC and a 32% increase in the rate of colectomies. LASSO algorithm identified the following predictors for colectomy: coagulopathy (odds ratio [OR] 2.71), weight loss (OR 2.25), teaching hospitals (OR 1.37), fluid or electrolyte disorders (OR 1.31), and large hospitals (OR 1.18). Predictors of mortality after colectomy were: coagulopathy (OR 2.38), age greater than 60 years (OR 1.97), acute renal failure (OR 1.67), respiratory failure (OR 1.61), sepsis (OR 1.40), peripheral vascular disease (OR 1.39), and congestive heart failure (OR 1.25). Surgery more than 3 days after admission was associated with higher mortality rates (OR 1.09; 95% CI 1.05 to 1.14; $p < 0.05$).	NA
Lipsett, P. A., Samantaray, D. K., Tam, M. L., Bartlett, J. G., & Lillemoe, K. D. (1994). Pseudomembranous colitis: A surgical disease? *Surgery, 116*(3), 491-496. PMID:	C	n=3,300 positive results for c-diff 37,000 C. difficile toxin assays	Charts of adults undergoing surgical intervention for PMC during the last 6 years	Thirteen adults (0.39%) underwent surgical intervention for PMC. Surgical intervention was performed for systemic toxic effects in all patients, with	NA

8079179		13 adults who underwent surigcal intervention for PMC		physical signs of peritonitis in six patients and worsening computed tomographic scans with ongoing illness despite appropriate medical therapy in five. Overall mortality rate in the series was 38%; in those undergoing left hemicolectomy (n = 4) the mortality rate was 100% versus a mortality rate of 14% for those undergoing subtotal colectomy (n = 9).	
Neal, M. D., Alverdy, J. C., Hall, D. E., Simmons, R. L., & Zuckerbraun, B. S. (2011). Diverting loop ileostomy and colonic lavage: An alternative to total abdominal colectomy for the treatment of severe, complicated clostridium difficile associated disease. *Annals of Surgery, 254*(3), 423-7; discussion 427-9. PMID: 21865943	C	n=42 patients with severe, complicated CDAD	Patients with severe, complicated ("fulminant") CDAD Treated surgical approach involved creation of a loop ileostomy, intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy and postoperative antegrade instillation of vancomycin flushes via the ileostomy	Operation was accomplished laparoscopically in 35 patients (83%). Treatment strategy resulted in reduced mortality compared to historical population (19% vs 50%; odds ratio, 0.24; P = 0.006). Preservation of the colon was achieved in 39 of 42 patients (93%).	NA
Surawicz, C. M., Brandt, L. J., Binion, D. G., Ananthakrishnan, A. N., Curry, S. R., Gilligan, P. H., et al. (2013). Guidelines for diagnosis, treatment, and prevention of clostridium difficile infections. *The American Journal of Gastroenterology, 108*(4), 478-98; quiz 499. PMID: 23439232	Guideline	NA	NA	NA	Systemic review/guideline, see evidence tables in source.
To, K. B., & Napolitano, L. M. (2014). Clostridium difficile infection: Update on diagnosis, epidemiology, and treatment strategies. *Surgical Infections, 15*(5), 490-502. PMID: 25314344	C	n=633 case studies n=579 randomized controlled studies n=1433 systemic review	Review of the pertinent English-language medical literature	Clostridium difficile infection can range from benign diarrhea to severe disease associated with substantial morbidity and mortality. Treatment modalities vary based on disease severity and timing of onset. The mainstay of medical treatment remains metronidazole and oral/rectal vancomycin. New management strategies are evolving, including adjunctive treatments such as monoclonal antibodies, vaccination, and fecal transplant. In patients with severe disease or clinical deterioration, early surgical consultation for total colectomy or loop ileostomy may be life-saving. Infection control measures are vital to mitigating the spread of CDI.	NA

Topic W. Pediatric Treatment

Reference Citation	Study Design *	Patient Population • Description • Total N of patients • If systematic review, N of studies	For Main Outcome(s), Description of • Study group (n) • Comparison group (n)	Summary of Results for Relevant Main Outcome(s) • Effect size • Statistical significance)	Reviewer notes • Methodological issues, • Noteworthy harms • Other
Bass, S. N., Bauer, S. R., Neuner, E. A., & Lam, S. W. (2013). Comparison of treatment outcomes with vancomycin alone versus combination therapy in severe clostridium difficile infection. *Journal of Hospital Infection, 85*(1), 22-27. PMID: 23876778	C	n=78 with severe CDI	Severe patients receiving oral vancomycin alone or combination therapy for > 72h were retrospectively reviewed	No difference in the incidence of clinical cure between monotherapy and combination therapy (57.1% vs 65.1%, P = 0.49). Median time to clinical cure was 7.0 days for the monotherapy group and 8.0 days for combination therapy (P = 0.19). Adjustment for potential confounders, the hazard ratio of the time to clinical cure for combination therapy compared with monotherapy was 0.58 (P = 0.10). No difference in recurrence rate or rates of individual complications between groups. There was a significantly higher composite complication rate in the combination therapy group.	NA
Goldenberg, J. Z., Ma, S. S., Saxton, J. D., Martzen, M. R., Vandvik, P. O., Thorlund, K., et al. (2013). Probiotics for the prevention of clostridium difficile-associated diarrhea in adults and children. *Cochrane Database of Systematic Reviews, 5*, 006095. PMID: 23728658	A	n=1,871 studies were identified with 31 (4,492 participants) meeting eligibility requirements	Randomized controlled (placebo, alternative prophylaxis, or no treatment control) trials investigating probiotics (any strain, any dose) for prevention of CDAD, or C. difficile infection were considered for inclusion	Few events (154) and the calculated optimal information size (n = 8218) was more than the total sample size. Results from 13 trials (961 participants) did not show a statistically significant reduction. Incidence of C. difficile infection was 12.6% in the probiotics group compared to 12.7% in the placebo or no treatment control group (RR 0.89; 95% CI 0.64 to 1.24). Adverse events were assessed in 26 studies (3964 participants) and our pooled complete case analysis indicates probiotics reduce the risk of adverse events by 20% (RR 0.80; 95% CI 0.68 to 0.95). In both treatment and control groups the most common adverse events included abdominal cramping,	NA

				nausea, fever, soft stools, flatulence, and taste disturbance. For the short-term use of probiotics in patients that are not immunocompromised or severely debilitated, we consider the strength of this evidence to be moderate.	
Kim, J., Smathers, S. A., Prasad, P., Leckerman, K. H., Coffin, S., & Zaoutis, T. (2008). Epidemiological features of clostridium difficile-associated disease among inpatients at children's hospitals in the united states, 2001-2006. *Pediatrics*, *122*(6), 1266-1270. PMID: 19047244	C	n=4895 patients with C-diff	Hospitalized child with C difficile infection from 2001 to 2006	C difficile-associated disease increased to 4.0 cases per 1000 admissions and to 6.5 cases per 10 000 patient-days. Median age of children with C difficile-associated disease was 4 years. Twenty-six percent of patients were <1 year of age. The majority of patients (67%) had underlying chronic medical conditions. The colectomy and all-cause mortality rates among children with C difficile-associated disease did not increase during the study period.	Examined change of infection rates over time.
Sammons, J. S., Toltzis, P., & Zaoutis, T. E. (2013). Clostridium difficile infection in children. *JAMA Pediatrics*, *167*(6), 567-573. PMID: 23460123	Review	NA	NA	NA	No primary data. No meta-analysis. No reporting of search strategies.
Walia, R., Garg, S., Song, Y., Girotra, M., Cuffari, C., Fricke, W. F., et al. (2014). Efficacy of fecal microbiota transplantation in 2 children with recurrent clostridium difficile infection and its impact on their growth and gut microbiome. *Journal of Pediatric Gastroenterology and Nutrition*, *59*(5), 565-570. PMID: 25023578	D	n=2 pediatric patients positive for recurrent c-diff infections	Failed available therapeutics responded remarkably well to FMT	FMT administration led to marked improvement in their growth, along with increased microbiota diversity, especially proportion of Bacteroides. The 2 cases illustrate the efficacy of FMT in children with RCDI and its positive effect on their growth and gut microbiota.	NA
Walia, R., Kunde, S., & Mahajan, L. (2014). Fecal microbiota transplantation in the treatment of refractory clostridium difficile infection in children: An update. *Current Opinion in Pediatrics*, *26*(5), 573-578. PMID: 25046331	C	n=7 published reports documenting the successful use of FMT for the treatment of RCDI in children	Case study	Minimal pediatric data, including few case reports and series, document the successful use of FMT for treatment of RCDI in the past 2 years. No complications to date have been reported in children who have undergone FMT.	NA