Clostridium difficile: prevention and treatment strategies.

Nicola Petrosillo

National Institute for Infectious Diseases «L. Spallanzani», IRCCS, Rome
<table>
<thead>
<tr>
<th>(Potential) conflict of interest</th>
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<tbody>
<tr>
<td><strong>Potentially relevant company relationships in connection with event</strong> ¹</td>
</tr>
<tr>
<td>• Sponsorship or research funding²</td>
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<td>• Fee or other (financial) payment³</td>
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<td>• Shareholder⁴</td>
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<td>• Other relationship, i.e. …⁵</td>
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| Speaker’s/advisory board’s fees from Pfizer, MSD, Zambon, Angelini, Accelerate, Cepheid, Takeda, Shionogi, Johnson & Johnson, 3M, Becton & Dickinson |
| President, IC MJC, UEMS Chairperson, IPC CdiFoundation |
• Clostridium difficile was first described in 1935 in the resident flora of healthy neonates.

• Corresponding to the difficulty of cultivating the bacteria, it was initially termed Bacillus difficilis.

• More than 3 decades later, the relation between pseudomembranous colitis and C difficile was revealed, especially after clindamycin treatment.

• During the past 20 years this gram-positive and spore-forming bacterium has been identified as the most common cause of antibiotic-associated diarrhea in industrialized countries.

Hall IC and O’Toole ER. Am J Dis Chil 1935; 49:390-42
Cohen E et al. JAMA 1973; 223:1379-80
In 2011–2012, 29 EU/EEA Member States and Croatia participated in the first EU-wide, ECDC-coordinated point prevalence survey (PPS) of healthcare-associated infections (HAIs) and antimicrobial use in acute care hospitals.

231,459 patients from 947 hospitals were included in the final European sample for analysis.
• The prevalence of patients with at least one HAI in acute care hospitals in the PPS sample was 6.0% (country range 2.3%–10.8%).

• Of a total of 15 000 reported HAIs, the most frequently reported HAI types were - respiratory tract infections (pneumonia 19.4% and lower respiratory tract 4.1%), - surgical site infections (19.6%), - urinary tract infections (19.0%), - bloodstream infections (10.7%) and - gastro-intestinal infections (7.7%), with Clostridium difficile infections accounting for 48% of the latter.
Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017

• HAI PPS and antimicrobial use in the European Union and European Economic Area (EU/EEA) from 2016 to 2017 included 310,755 patients from 1,209 acute care hospitals (ACH) in 28 countries and 117,138 residents from 2,221 long-term care facilities (LTCF) in 23 countries.

• 6.5% patients in ACH and 3.9% residents in LTCF had at least one HAI.

• On any given day, 98,166 patients in ACH and 129,940 residents in LTCF had an HAI.

• HAI episodes per year were estimated at 8.9 million, including 4.5 million in ACH and 4.4 million in LTCF; 3.8 million patients acquired an HAI each year in ACH.

• Antimicrobial resistance (AMR) to selected AMR markers was 31.6% in ACH and 28.0% in LTCF.

The most frequently reported types of HAI were

- respiratory tract infections (21.4% pneumonia and 4.3% other lower respiratory tract infections),
- urinary tract infections (18.9%),
- surgical site infections (18.4%),
- bloodstream infections (10.8%) and
- gastro-intestinal infections (8.9%), with *C. difficile* infections accounting for 44.6% of the latter or 4.9% of all HAI.

Twenty-three per cent of HAI were present on admission. One third of HAI on admission were surgical site infections.
Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,1 Dale N. Gerding,2 Stuart Johnson,2,3 Johan S. Bakken,4 Karen C. Carroll,5 Susan E. Coffin,6 Erik R. Dubberke,7 Kevin W. Garey,8 Carolyn V. Gould,1 Ciaran Kelly,9 Vivian Loo,10 Julia Shaklee Sammons,6 Thomas J. Sandora,11 and Mark H. Wilcox12
Isolation Measures for Patients With CDI

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

Recommendations

1. Accommodate patients with CDI in a private room with a dedicated toilet to decrease transmission to other patients. If there is a limited number of private single rooms, prioritize patients with stool incontinence for placement in private rooms (strong recommendation, moderate quality of evidence).

2. If cohabiting is required, it is recommended to cohort patients infected or colonized with the same organism(s)—that is, do not cohort patients with CDI who are discordant for other multidrug-resistant organisms such as methicillin-resistant Staphylococcus aureus or vancomycin-resistant Enterococcus (strong recommendation, moderate quality of evidence).
XIV. Should gloves and gowns be worn while caring for isolated CDI patients?

**Recommendation**

1. Healthcare personnel must use gloves (*strong recommendation, high quality of evidence*) and gowns (*strong recommendation, moderate quality of evidence*) on entry to a room of a patient with CDI and while caring for patients with CDI.
XIX. Should noncritical devices or equipment be dedicated to or specially cleaned after being used on the isolated patient with CDI?

**Recommendation**

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

**Recommendation**

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

Recommendations

1. Continue contact precautions for at least 48 hours after diarrhea has resolved (weak recommendation, low quality of evidence).

2. Prolong contact precautions until discharge if CDI rates remain high despite implementation of standard infection control measures against CDI (weak recommendation, low quality of evidence).
XXIV. Should asymptomatic carriers of *C. difficile* be identified and isolated if positive?

**Recommendation**

1. There are insufficient data to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions (*no recommendation*).
Does screening for *C. difficile* identify colonised/carerrier patients at increased or decreased risk of developing *C. difficile* infection?

**Recommendation for outbreak and endemic settings**

4. We do not recommend screening for *C. difficile* to identify colonised/carerrier patients as a way of altering the risk of developing CDI in either colonized subjects or other patients and thus reducing CDI-rates (conditional recommendation, low level of evidence in the endemic setting).
XXV. What is the role of antibiotic stewardship in controlling CDI rates?

**Recommendations**

1. Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk (*strong recommendation, moderate quality of evidence*).

2. Implement an antibiotic stewardship program (*good practice recommendation*).

3. Antibiotics to be targeted should be based on the local epidemiology and the *C. difficile* strains present. Restriction of fluoroquinolones, clindamycin, and cephalosporins (except for surgical antibiotic prophylaxis) should be considered (*strong recommendation, moderate quality of evidence*).
Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis

David Baur*, Beryl Primrose Gladstone*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli

Lancet Infect Dis 2017; 17: 990-1001

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/patient-days</th>
<th>Incidence ratio (95% CI)</th>
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<tbody>
<tr>
<td>Cruz-Rodriguez et al37</td>
<td>8/7026, 2/16507</td>
<td>0.11 (0.02-0.50)</td>
</tr>
<tr>
<td>Leung et al22</td>
<td>8/1373, 1/1202</td>
<td>0.14 (0.02-1.14)</td>
</tr>
<tr>
<td>McNulty et al46</td>
<td>37/26144, 16/30467</td>
<td>0.37 (0.21-0.67)</td>
</tr>
<tr>
<td>Price et al27</td>
<td>353/271538, 258/373913</td>
<td>0.53 (0.45-0.62)</td>
</tr>
<tr>
<td>Malani et al26</td>
<td>46/2976, 20/2408</td>
<td>0.54 (0.32-0.91)</td>
</tr>
<tr>
<td>Borde et al46</td>
<td>71/127596, 20/55156</td>
<td>0.65 (0.40-1.07)</td>
</tr>
<tr>
<td>Lübbert et al39</td>
<td>156/310857, 115/313060</td>
<td>0.73 (0.58-0.93)</td>
</tr>
<tr>
<td>Dubrovskaya et al21</td>
<td>8/2551, 7/2489</td>
<td>0.90 (0.33-2.47)</td>
</tr>
<tr>
<td>Cook and Gooch37</td>
<td>134/220474, 149/261318</td>
<td>0.94 (0.74-1.18)</td>
</tr>
<tr>
<td>Schön et al38</td>
<td>182/169886, 191/170541</td>
<td>1.05 (0.85-1.28)</td>
</tr>
<tr>
<td>Frank et al37</td>
<td>50/103573, 48/91965</td>
<td>1.08 (0.73-1.61)</td>
</tr>
<tr>
<td>Overall</td>
<td>874/163249, 266/27773</td>
<td>0.68 (0.53-0.88)</td>
</tr>
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I²=80.2%, p=0.000

Figure 4: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of Clostridium difficile infections
### Effect of FQ ASP on CDI incidence

<table>
<thead>
<tr>
<th>Wenisch JM, 2014 [33]</th>
<th>Austria</th>
<th>Before-after</th>
<th>2013-2014</th>
<th>Fluoroquinolone</th>
<th>Yes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>A large tertiary care community hospital with 1,081 beds and 357,892 patient days in 2013</td>
<td></td>
<td>p= 0.0044</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluoroquinolone</td>
<td>From 59 to 32 CDI cases per month</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Four hospitals</td>
<td></td>
<td>p= 0.044</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluoroquinolone</td>
<td>From 4.0 to 2.2 monthly CDI cases per 10,000 patient days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sarma JB, 2015 [34]</th>
<th>UK</th>
<th>Interrupted time series</th>
<th>2007-2012</th>
<th>Fluoroquinolone</th>
<th>Yes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nine hospitals and a number of long-term care facilities</td>
<td></td>
<td>Decrease in CDI rate of 60% RR: 0.394 (95% CI: 0.199-0.781)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluoroquinolone</td>
<td>From &gt;280 cases per year in 2007-2008 to 72 cases in 2011-2012</td>
</tr>
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</table>
To screen or not to screen?
They prospectively recruited consecutive IBD patients presenting to their outpatient clinic between April 2015 and February 2016.

A rectal swab was performed from which toxigenic culture and PCR analysis for the presence of toxin and fluorescent PCR ribotyping were performed. The primary outcome of interest was isolation of toxigenic C. difficile.
• 190 patients including 137 (72%) with Crohn's disease and 53 (28%) with ulcerative colitis. At the time of enrollment, 69 (36%) had clinically active disease.

• Sixteen (8.4%) patients had toxigenic C. difficile isolated on rectal swab at enrollment and four (2.1%) patients had non-toxigenic C. difficile cultured.

• Mixed infection with more than one toxigenic isolate was present in 5/16 (31.3%) individuals.

• C. difficile isolation at the time of presentation was not associated with a subsequent disease relapse over a 6-month period in CD ($p = 0.557$) or UC ($p = 0.131$).
Aim: evaluate the clinical effectiveness of CD screening at admission on the rate of hospital-onset CDI.
Before-and-after trial

All 5,357 patients admitted to the BMT and general medicine wards from January 2014 to February 2017 were included in the study. All BMT patients were screened within 48 hours of admission. Colonized patients, as defined by a C. difficile-positive PCR stool result, were placed under contact precautions for the duration of their hospital stay.
Interventions to Reduce the Incidence of Hospital-Onset *Clostridium difficile* Infection: An Agent-Based Modeling Approach to Evaluate Clinical Effectiveness in Adult Acute Care Hospitals

Anna K. Barker,^1^ Oguzhan Alagoz,^1,2^ and Nasia Safdar^3,4^

- Agent-based model of *C. difficile* transmission in a 200-bed adult hospital.
- Model→ environmental component and 4 distinct agent types: patients, visitors, nurses and physicians.
- 9 single interventions and 8 multiple-intervention bundles→ effectiveness to reduce HO-CDI and asymptomatics *C. difficile* colonization.
Daily cleaning with sporicidal disinfectant and *C. difficile* screening at admission were the most effective single-intervention strategies, reducing HO-CDI by 68.9% and 35.7%, respectively (both $P < .001$).

Combining these interventions into a 2-intervention bundle reduced HO-CDI by 82.3% and asymptomatic hospital-onset colonization by 90.6% (both, $P < .001$).

Adding patient hand hygiene to healthcare worker hand hygiene reduced HO-CDI rates an additional 7.9%.

Visitor hand hygiene and contact precaution interventions did not reduce HO-CDI, compared with baseline.

Excluding those strategies, healthcare worker contact precautions were the least effective intervention at reducing hospital-onset colonization and infection.
Asymptomatic Carriers Contribute to Nosocomial Clostridium difficile Infection: A Cohort Study of 4508 Patients


- Screening results were blinded to patients, staff, and researchers.

- Patients were followed during their hospital stay by daily registration of wards and patient rooms.

- The primary outcomes were rate of C difficile infection in exposed and unexposed patients and factors associated with transmission.
Asymptomatic Carriers Contribute to Nosocomial Clostridium difficile Infection: A Cohort Study of 4508 Patients

- C difficile infection was found in 2.6% of the unexposed and 4.6% of the exposed patients in the room, and the odds of C difficile infection were higher in patients sharing a room with an asymptomatic carrier than in patients without this exposure (OR, 1.79; 95% CI, 1.162.76).

- Amount of exposure correlated with risk of C difficile infection, from 2.2% in the lowest quartile to 4.2% in the highest quartile of exposed patients (P = .026).
Screening for *Clostridium difficile* colonization on admission to a hematopoietic stem cell transplant unit may reduce hospital-acquired *C difficile* infection

- Patients admitted to the Mayo Clinic unit for HSCT or chemotherapy for hematologic malignancy were screened for CDI starting in 2010 as part of an infection control surveillance program.
- Stools collected within 3 days of admission were tested for toxigenic *C difficile* by polymerase chain reaction (GeneXpert).
- 1,090 total admissions to the HSCT unit from December 2012-December 2013.
- A total of 470 patients (43%) met criteria for screening (HSCT patients or receiving chemotherapy for hematologic malignancy) and did not have diarrhea and were able to provide a formed stool sample for *C difficile* testing.

Colonized patients were placed in contact isolation.
Aim: To test the hypothesis that LTCF residents with CDI or asymptomatic carriage of toxigenic strains are an important source of transmission in the LTCF and in the hospital during acute-care admissions.

A 6-month cohort study with identification of transmission events was conducted based on tracking of patient movement combined with restriction endonuclease analysis (REA) and whole-genome sequencing (WGS).
Transmission of *Clostridium difficile* from asymptptomatically colonized or infected long-term care facility residents

29 LTCF residents identified as asymptomatic carriers of toxigenic C. difficile based on every other week perirectal screening and 37 healthcare facility-associated CDI cases

Of the 37 CDI cases, 7 (18.9%) were linked to LTCF residents with LTCF-associated CDI or asymptomatic carriage, including 3 of 26 hospital-associated CDI cases (11.5%) and 4 of 11 LTCF-associated cases (36.4%).

Of the 7 transmissions linked to LTCF residents, 5 (71.4%) were linked to asymptomatic carriers versus 2 (28.6%) to CDI cases, and all involved transmission of epidemic BI/NAP1/027 strains.
LTCF residents with asymptomatic carriage of *Clostridium difficile* or CDI contribute to transmission both in the LTCF and in the affiliated hospital during acute-care admissions.

Donskey CJ et al. Infect Control Hosp Epidemiol 2018; 39: 909-16
In response to frequent *C. difficile* outbreaks on the surgical service, a quality improvement initiative identifying and isolating *C. difficile* carriers was implemented to:

(1) compare rates of HA-CDI before and after implementation of isolation for asymptomatic carriers,

(2) evaluate the prevalence of and risk factors for *C. difficile* carriage, and

(3) determine the association between carriage and subsequent development of symptomatic CDI.
• 773 patients → 24 (3.1%) were asymptomatic C. difficile carriers.

• Symptomatic CDI within 90 days of admission occurred in 15 of 773 patients (1.9%): 7 (29%) of 24 asymptomatic C. difficile carriers compared with 8 (1%) of 749 with negative results at admission (P < .05).

• In the multivariate analysis controlling for antimicrobial use, C. difficile carriage was the only factor independently associated with the development of HA-CDI, with a >25-fold increased risk among patients who were carriers at admission (OR, 26.1; 95% CI, 7.4–92.1).
Asymptomatic carriers were then placed on contact isolation, similar to standard precautions for symptomatic patients with CDI.

**Figure 1.** Observed versus forecasted hospital-acquired *Clostridium difficile* (HA-CDI) incidence rates (per 10 000 bed-days of care), with forecasts based on an autoregressive integrated moving average (ARIMA) model. Abbreviations: Jan, January; Sept, September.
When to discontinue isolation?
• IDSA/SHEA guidelines → with Solomon wisdom, they suggest to continue precautions for at least 48 after diarrhea ends, or prolong contact precautions until discharge in settings with high CDI rates despite implementation on infection control measures against CDI. (McDonald LC et al. Clin Infect Dis. 2018 Feb 15)

• However, Clostridium difficile stool detection is high up to 4 weeks post-treatment (Sethi AK et al. Infect Control Hosp Epidemiol 2010; 31:21–7).
Healthcare worker contact precautions were the least effective intervention at reducing hospital-onset colonization and infection.

In this study, paradoxically, daily cleaning with sporicidal disinfectant significantly reduced hospital onset-CDI by 68.9%.

Can we hypothesize that the failure of contact precautions as single intervention depended on its duration?
I'll tell you my opinion.
Take home messages

• Asymptomatic CD carriage is a topic of relevant interest and perspective

• CD screening is currently not recommended routinely, mainly due to uncertainty with regards to the appropriate management of asymptomatic carriers.

• However data are accumulating in certain settings and epidemiological conditions on its value.

• Discontinuing isolation should not be based only on the resolution of diarrhea, but also on the setting and infection control practices.
TREATMENT STRATEGIES
Recurrence Is a Major Healthcare Concern, Especially in High-Risk Subgroups


HSCT=Hematopoietic Stem Cell Transplant
CDAD= C. difficile Associated Disease
Tackling the recurrence of *Clostridium difficile* infection

*Clostridium difficile* recurrence definitions in studies assessing prediction scores of recurrences.

Définition d’une récide d’infection à *Clostridium difficile* dans les études ayant évalué les scores de prédiction clinique des récidives.

<table>
<thead>
<tr>
<th>Year/First author/Ref.</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009/Hu MY/34</td>
<td>A new episode of diarrhea confirmed by a positive stool <em>C. difficile</em> toxin assay, after resolution of the initial <em>C. difficile</em> infection (CDI) episode for at least 2 days and after discontinuation of therapy with metronidazole or vancomycin.</td>
</tr>
<tr>
<td>2012/Eyre DW/2</td>
<td>Definition not given.</td>
</tr>
<tr>
<td>2014/Zilberberg MD/35</td>
<td>A repeat positive toxin within 42 days following the end of the initial CDI treatment.</td>
</tr>
<tr>
<td>2014/D’Agostino RB/37</td>
<td>Definition not given. Patients who were cured were subsequently followed for 28 days for an assessment of recurrence.</td>
</tr>
<tr>
<td>2015/LaBarbera FD/38</td>
<td>Confirmed presence of <em>C. difficile</em> toxin via polymerase chain reaction after complete resolution of diarrhea for a minimum of 6 months and the completion of antibiotic therapy.</td>
</tr>
<tr>
<td>2017/Viswesh V/39</td>
<td>Recurrence was defined as (1) a documented positive result on an enzyme immunoassay or PCR test for <em>C. difficile</em> antigen and toxin or (2) a documented return of CDAD symptoms and subsequent CDAD treatment.</td>
</tr>
</tbody>
</table>

CDAD: *Clostridium difficile*-associated diarrhea.
• From January to December 2014, 717 episodes of CDI were observed.

• CDI incidence was 4.2 cases/10,000 patient-days during the study period.
Risk factors for recurrence in patients with *Clostridium difficile* infection due to 027 and non-027 ribotypes


![Flowchart diagram](https://example.com/flowchart.png)
European Society of Clinical Microbiology and Infectious Diseases (ESCMID): update of the treatment guidance document for Clostridium difficile infection (CDI)

Figure 1. Schematic overview of therapeutic regimens for CDI.
Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment</th>
<th>Strength of Recommendation/Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level ≤1.5 mg/dL</td>
<td>• VAN 125 mg given 4 times daily for 10 days, OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days&lt;br&gt;• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days</td>
<td>Strong/High&lt;br&gt;Strong/High&lt;br&gt;Weak/High</td>
</tr>
<tr>
<td>Initial episode, severe&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level &gt;1.5 mg/dL</td>
<td>• VAN, 125 mg 4 times per day by mouth for 10 days, OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days</td>
<td>Strong/High&lt;br&gt;Strong/High</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.</td>
<td>Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)</td>
</tr>
<tr>
<td>First recurrence</td>
<td>...</td>
<td>• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR&lt;br&gt;• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (e.g., 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode</td>
<td>Weak/Low&lt;br&gt;Weak/Low&lt;br&gt;Weak/Moderate</td>
</tr>
<tr>
<td>Second or subsequent recurrence</td>
<td>...</td>
<td>• VAN in a tapered and pulsed regimen, OR&lt;br&gt;• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days, OR&lt;br&gt;• Fecal microbiota transplantation&lt;sup&gt;h&lt;/sup&gt;</td>
<td>Weak/Low&lt;br&gt;Weak/Low&lt;br&gt;Weak/Low&lt;br&gt;Strong/Moderate</td>
</tr>
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Comparative efficacy of treatments for *Clostridium difficile* infection: a systematic review and network meta-analysis

Tumas Beinortas*, Nicholas E Burr*, Mark H Wilcox, Venkataraman Subramanian

*Lancet Infect Dis* 2018; 18: 1035-44

**Figure 3:** Network of eligible comparisons for efficacy of treatments of *Clostridium difficile*

Line width is proportional to the number of trials comparing every pair of treatments. The size of the circle is proportional to the number of patients assigned to receive the treatment.
Comparative efficacy of treatments for *Clostridium difficile* infection: a systematic review and network meta-analysis

Tumas Beinortas*, Nicholas E Burr*, Mark H Wilcox, Venkataraman Subramanian

- Of 23,004 studies screened, 24 trials, which comprised 5,361 patients and 13 different treatments, were included in the analysis.

- The overall quality of evidence was rated as moderate to low.

- For sustained symptomatic cure, fidaxomicin (odds ratio 0·67, 95% CI 0·55–0·82) and teicoplanin (0·37, 0·14–0·94) were significantly better than vancomycin.

- Teicoplanin (0·27, 0·10–0·70), ridinilazole (0·41, 0·19–0·88), fidaxomicin (0·49, 0·35–0·68), surotomycin (0·66, 0·45–0·97), and vancomycin (0·73, 0·56–0·95) were better than metronidazole.

- Bacitracin was inferior to teicoplanin (0·22, 0·06–0·77) and fidaxomicin (0·40, 0·17–0·94), and tolevamer was inferior to all drugs except for LF571 (0·50, 0·18–1·39) and bacitracin (0·67, 0·28–1·58).
Triphasic Pathogenesis of CDI and the Role of Clostridium difficile Toxins

- Toxins, particularly toxin B, are the cause of CDI symptoms through damaging the GI epithelium and invoking an inflammatory response.\(^3\)

GI=gastrointestinal.

**Phase 1: Microbiota Suppression**

Initiation of an antibiotic disrupts the protective intestinal microbiota.\(^1,2\)

*Clostridium difficile* spores germinate into vegetative, toxin-producing *C. difficile*.\(^1\)

Phase 2: Collateral Damage

Microbiota Suppression

Administration of CDI antibiotics leads to suppression of *Clostridium difficile*, along with collateral damage of the protective intestinal microbiota.\(^2,\)^\(^3\)

Collateral Damage

*C difficile* toxins induce symptoms by damaging the GI epithelium and invoking an inflammatory response.\(^1\)

---

Phase 3: Window of Vulnerability

Spore survival in the GI tract despite treatment with CDI antibiotics leads to recurrent CDI upon spore germination.\(^2\)

Toxin production from vegetative cells restarts the cycle of CDI symptoms and treatment with CDI antibiotics.\(^1\)

1. Toxins binding to specific host cell receptors

2. Toxins internalization

3. Endosome acidification

4. Pore formation in the endosome

5. GTD release from the endosome to the host cell cytoplasm

6. Rho GTPases inactivation by glucosylation

7. Downstream effects within the host cell

Cytopathic effects
- Cytoskeleton breakdown
- Loss of cell-cell contacts
- Increased epithelial permeability

Cytotoxic effects
- Activation of the inflammasome
- Increase in ROS levels
- Induction of programmed cell death
Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection


![Graph showing the percentage of participants with infection recurrence through Wk 12 (%) for MODIFY I, MODIFY II, and Pooled Data. The graph includes bars for Actoxumab–bezlotoxumab, Bezlotoxumab, Placebo, and Actoxumab. The p-values are marked as P<0.001 for all comparisons.](image)
Novel Antimicrobials for the Treatment of Clostridium difficile Infection

Nicola Petrosillo*, Guido Granata and Maria Adriana Cataldo

TABLE 1 | Main characteristics and activity on CD spore and toxins production of the novel antimicrobials in development for CD.

<table>
<thead>
<tr>
<th>Antimicrobials in development</th>
<th>Chemical structure description</th>
<th>Mode of action</th>
<th>Gut availability and effect on gut microbiota</th>
<th>Activity on CD sporulation and CD toxin inhibition</th>
<th>Selectivity against CD or narrow spectrum activity</th>
<th>MIC ranges against CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadazolid</td>
<td>Oxazolidinone antimicrobial, containing a quinoline pharmacophore incorporated in an oxazolidinone ring</td>
<td>Bacterial DNA and protein synthesis inhibition</td>
<td>Minimum observed fecal concentration following a single 3,000 mg oral dose from 24 h up to day 7 was 311 μg/g. Maximum daily individual fecal concentration after up to 7 days was 1,419 μg/g</td>
<td>Inhibited CD sporulation even at sub-growth-inhibitory concentrations</td>
<td>Narrow spectrum</td>
<td>Baseline MIC\textsubscript{50}, MIC\textsubscript{90} and MIC ranges were 0.125 mg/L, 0.25 mg/L, and 0.06–0.25 mg/L, respectively</td>
</tr>
</tbody>
</table>

Cadazolid for the treatment of Clostridium difficile infection: results of two double-blind, placebo-controlled, non-inferiority, randomised phase 3 trials

Dale N Gerding, Oliver A Cornely, Simon Grill, Hilke Kracker, Anne Claire Marrast, Carl Erik Nord, George H Talbot, Martha Buitrago, Iulian Gheorghe Diaconescu, Claudia Murta de Oliveira, Liliana Preotescu, John Pullman, Thomas J Louie, Mark H Wilcox

Interpretation Cadazolid was safe and well tolerated but did not achieve its primary endpoint of non-inferiority to vancomycin for clinical cure in one of two phase 3 C difficile infection trials. Therefore, further commercial development of cadazolid for C difficile infection is unlikely.
Surotomycin failed to demonstrate a significant benefit over the existing vancomycin therapy; although surotomycin was generally well tolerated during the conduction of the phase III trials, the published results make doubtful that surotomycin will be introduced for the treatment of CDI (Daley P et al. J Antimicrob Chemother 2017; 72(12):3462–70).

The trial results demonstrated ridinilazole superiority in achieving response rates at the end of treatment (77.8% and 69.7% for ridinilazole and vancomycin, respectively), in reducing rates of recurrent CDI (14.3% and 34.8% for ridinilazole and vancomycin, respectively) and in obtaining sustained clinical responses (66.7% and 42.4% for ridinilazole and vancomycin, respectively). These results sound promising and support larger phase III clinical trials. (Vickers RJ et al. Lancet Infect Dis 2017; 17(7):735–44)
LFF571 is a novel semi-synthetic cyclic lipopeptide antibiotic derived from a natural metabolite produced by the actinomycete *Planobisporarosea*. In 2015, a phase II trial has been carried out to compare LFF571 and vancomycin safety and efficacy. The trial results showed higher clinical response rates at the end of treatment with LFF571 (90.6% vs. 78.3%), unfortunately also higher recurrence rates were reported with LFF571 (37% vs 31%). (Mullane K et al. *Antimicrob Agents Chemother* 2015; 59(3):1435–40.)

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>LFF571</td>
<td>Thiopeptide antibiotic</td>
<td>Bacterial protein synthesis disruption by inhibition of the elongation factor Tu</td>
<td>Low oral bioavailability, high colonic concentrations after oral administration</td>
<td>Reduce CD toxin production</td>
<td>activity against other Gram-positive anaerobes and Gram-positive aerobes, including lactobacilli and enterococci</td>
<td>MIC range of 0.08–0.5 mg/L</td>
</tr>
</tbody>
</table>

Ramoplanin is a glycolipodepsipeptide antimicrobial that exerts its mechanism of action preventing cell wall peptidoglycan biosynthesis. A phase III trial on ramoplanin against CDI has been planned and has been recently approved by the FDA (Bassères E et al. *Curr Opin Gastroenterol* 2017; 33(1):1–7).
<table>
<thead>
<tr>
<th>Antimicrobial in development</th>
<th>Phase of the latest clinical trials</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadazolid</td>
<td>II</td>
<td>(24)</td>
</tr>
<tr>
<td>Surotomycin</td>
<td>III</td>
<td>(26, 27)</td>
</tr>
<tr>
<td>Ridinilazole</td>
<td>II</td>
<td>(32)</td>
</tr>
<tr>
<td>LFF571</td>
<td>II</td>
<td>(34, 35)</td>
</tr>
<tr>
<td>Ramoplanin</td>
<td>II</td>
<td>(92)</td>
</tr>
<tr>
<td>CRS3123</td>
<td>I</td>
<td>(37)</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>III</td>
<td>(38, 39)</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>III</td>
<td>(40, 42)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>II</td>
<td>(43)</td>
</tr>
<tr>
<td>NVB302</td>
<td>I</td>
<td>Unpublished</td>
</tr>
<tr>
<td>Thuricin CD</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Lacticin 3147</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Auranofin</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Acyldepsipeptide-1</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>II</td>
<td>(44)</td>
</tr>
</tbody>
</table>
Ribaxamase

- It is a recombinant beta-lactamase which has been formulated as an oral accompaniment to beta-lactam antibiotics.

- This agent degrades unmetabolized antibiotic in the host intestine in order to protect the gut microbiota from dysbiosis and is well tolerated.

Connelly S et al. Gastroenterology 2015; 148: S1195
Ribaxamase

• 412 patients (mean age 70 years) at higher risk for CDI, hospitalized for ≥5 days and received IV ceftriaxone for treatment lower respiratory tract infections.

• Patients were randomly assigned 1:1 to receive oral ribaxamase 150mg four times daily or placebo during IV ceftriaxone treatment and for an additional 72 hours.

• There was a 71% relative risk reduction in CDI \( (P=0.045) \) and a statistically significant 44% relative risk reduction in new colonization by vancomycin-resistant enterococci \( (P=0.0002) \).

• Moreover, the respiratory infection was cleared in ~99% of cases demonstrating that concomitant ribaxamase did not impact the cure rate of ceftriaxone.

Kokai-Kun J et al. IDWeek 2017, San Diego CA
DAV132

- Another novel approach to CDI prophylaxis is DAV132, which is an activated charcoal based product in an enteric-coated pill.

- This adsorbent product irreversibly captures antibiotics in the intestine whilst hopefully avoiding interruption of antibiotic absorption.

- In-vitro human gut model and in-vivo hamster models also have positive findings but clinical efficacy data are awaited.

# Microbiome-Based Therapeutics

## FMT

### Table 2. A summary of benefits and risks/challenges associated with FMT

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks/challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provides a therapeutic option for patients with (multiply) recurrent CDI who have failed standard therapy</td>
<td>Patient eligibility criteria, donor/recipient screening tests and FMT procedures, including priming with antibiotics, are nonstandardized</td>
</tr>
<tr>
<td>High clinical response rates (~80%) in patients with multiply recurrent CDI</td>
<td>Risks associated with method of administration</td>
</tr>
<tr>
<td>Rapid resolution of symptoms in the majority of FMT recipients</td>
<td>Recruitment of willing faecal donors who pass screening tests can be challenging</td>
</tr>
<tr>
<td>Rapid to administer</td>
<td>Acquisition of known/unknown pathogens (donor screening for common faecal/blood-borne pathogens is common practice)</td>
</tr>
<tr>
<td>Can be organized as day-case procedure</td>
<td>Long-term safety profile of FMT currently unclear</td>
</tr>
<tr>
<td>Generally reported to have high patient acceptability</td>
<td>Patient’s pretreatment attitudes/experience may limit acceptability</td>
</tr>
<tr>
<td>Short-term safety profile mostly favourable</td>
<td>Logistics of stool preparation without losing microbial viability</td>
</tr>
<tr>
<td>Cost-benefit may be favourable (e.g. if admission/complications avoided)</td>
<td>Repeat FMT may be required for long-term symptom resolution</td>
</tr>
<tr>
<td>Possible expansion of ‘indications’ for FMT</td>
<td>Short-term symptoms of irritable colon can occur posttreatment (constipation, bloating, cramping)</td>
</tr>
<tr>
<td>Option to use stool banks if faeces sourcing is problematic</td>
<td>FMT is considered as an investigational procedure by some regulatory authorities</td>
</tr>
<tr>
<td>Maybe replaced by (regulated) live biotherapeutic options</td>
<td>Limited information about true costs of FMT</td>
</tr>
</tbody>
</table>
RBX2660 is a live biotherapeutic microbiota suspension that aims to harness the effectiveness of FMT, but within a standardized, regulated product for the treatment of recurrent CDI.

In a phase II study, given as enema (twice), the success rate was 87.1%.

Results From a Randomized, Placebo-Controlled Clinical Trial of a RBX2660—A Microbiota-Based Drug for the Prevention of Recurrent *Clostridium difficile* Infection

Erik R. Dubberke,¹ Christine H. Lee,²,³,⁴ Robert Orenstein,⁵ Sahil Khanna,⁶ Gail Hecht,⁷ and Dale N. Gerding⁶

**Figure 2.** Efficacy of microbiota-based drug RBX2660 or placebo following blinded treatment. The proportions of participants in the blinded phase who responded to treatment with 2 doses of RBX2660 (group A); 2 doses of placebo (group B); and 1 dose of RBX2660 followed by 1 dose of placebo (group C).
• It is also a live biotherapeutic that comprises an encapsulated mixture of purified *Firmicutes* spores, derived from human faeces.

• Ethanol treatment for eliminate the risk of transmissible agents contaminating the therapeutic product.

• 2 phase II studies→ in one of them (ECOSPORE) it was not effective overall at reducing CDI recurrence, but was efficacious in older than 65 years. Small numbers.

http://ir.serestherapeutics.com/phoenix.zhtml?c=254006&p=irolf-newsArticle&ID=2190006
Take home messages

• *C. difficile* remains a significant cause of morbidity and mortality worldwide. Current approaches to reduce CDI using ASP and ICP have not led to a consistent marked decline in disease rates.

• Historically, two antibiotics (metro & vanco) have been used routinely for CDI treatment.

• Novel antimicrobial agents are being evaluated in phase III trials; it is not yet clear what will be the roles of these agents in future CDI treatment.

• The study of pathogenesis of CDI remains the key for the best CDI management.
• Prophylaxis is an optimum approach to reduce the impact of CDI especially in high-risk populations; monoclonal antibodies, antibiotic blocking approaches and multiple vaccines are currently in advanced clinical trials, and some are on the market.

• The treatment of rCDI is particularly troublesome, and several different live biotherapeutics are being developed, in addition to FMT.