Australasian Society of Infectious Diseases updated guidelines for the management of Clostridium difficile infection in adults and children in Australia and New Zealand

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Australasian Society of Infectious Diseases updated guidelines for the management of *Clostridium difficile* infection in adults and children in Australia and New Zealand

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Abstract

The incidence of *Clostridium difficile* infection (CDI) continues to rise, whilst treatment remains problematic due to recurrent, refractory and potentially severe nature of disease. The treatment of *C. difficile* is a challenge for community and hospital-based clinicians. With the advent of an expanding therapeutic arsenal against *C. difficile* since the last published Australasian guidelines, an update on CDI treatment recommendations for Australasian clinicians was required. On behalf of the Australasian Society of Infectious Diseases, we present the updated guidelines for the management of CDI in adults and children.

Introduction

The reported incidence of *Clostridium difficile* infection (CDI) continues to rise and treatment remains problematic due to the recurrent, refractory and potentially severe nature of disease. In addition to curative intent, CDI treatment is aimed at preventing severe and recurrent disease.[1,2] Despite being classically regarded as a nosocomial infection, community acquired CDI (CA-CDI) is now being increasingly recognised.[3] *C. difficile* as a pathogen proves a therapeutic challenge for a range of community and hospital-based clinicians. With the advent of an expanding therapeutic arsenal against *C. difficile* since the last published Australasian guidelines, an update on CDI treatment recommendations for Australasian clinicians is provided within. A summary of recommendations is provided in Box 1.

The objective of this guideline is to provide Australasian physicians with guidance regarding the management of CDI in adults and children.

Methods

These guidelines are an update of the 2011 Australasian Society of Infectious Diseases (ASID) guidelines.[5] A working group was formed and the primary author reviewed all literature published since the last guidelines were developed, utilising a PubMed search for keywords '*Clostridium difficile*' AND ('treatment' OR 'trial'). The primary author (JAT) drafted an updated manuscript,

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Box 1 Key points in the new ASID *Clostridium difficile* infection (CDI) management guidelines.

1. Oral metronidazole 400 mg (child: 10 mg/kg/dose up to 400 mg) three times daily (TDS) for 10 days is recommended as first-line therapy for first episode mild CDI.
2. Oral vancomycin 125 mg (child: 10 mg/kg/dose up to 125 mg) four times daily (QID) is recommended as therapy for first or subsequent CDI recurrence.
3. Oral vancomycin 125 mg (child: 10 mg/kg/dose up to 125 mg) QID is recommended as first-line therapy for severe CDI.
4. Oral fidaxomicin 200 mg twice daily (BD) is a treatment alternative in recurrent CDI (adults).
   a. Especially in those with a high risk of relapse
5. Faecal microbiota transplantation (FMT) is a treatment alternative in recurrent CDI for the appropriately selected patient (adults).
6. A rifaximin 'chaser' regimen is a treatment alternative in recurrent CDI not amenable to first-line therapies (adults).
7. Oral nitazoxanide: (child 1–3 years) 100 mg; (child 4–11 years) 200 mg; 12 hourly for 7–10 days is a treatment alternative in recurrent CDI (children).

Recommendations 1 and 3 are identical to those within Therapeutic Guidelines: Antibiotic Edition 15, 2014.[4]

Box 2 Clinical features suggestive of severe disease.

Any of the following features are suggestive of severe CDI if no other explanation can be provided

Clinical	• Fever (>38.5°C), rigors
	• Haemodynamic instability
	• Peritonitis or evidence of bowel perforation
	• Ileus or toxic megacolon
Laboratory	• White blood cell count $>15 \times 10^9$/L and <20% neutrophils
	• Elevated lactate level
	• Rise in creatinine level (>50% above baseline)
	• Albumin level <25 mg/L
Other	• Large intestine distension, colonic wall thickening, fat stranding, unexplained ascites (imaging)
	• Pseudomembranous colitis (colonoscopy)

Clinical, laboratory and other signs of severe disease. Require >1 of the listed factors with NO other clinical explanation.[5–7]

There is no consensus definition of severe disease for CDI for children. Caution should be used in directly applying adult criteria to children with CDI as this can overestimate severity.[8]

which was circulated to other members of the working group for critical appraisal. Proposed changes and areas of controversy were presented at the ASID Annual Scientific Meeting for discussion, and a consensus response was achieved by discussion within the working group. These were reviewed by a working group from the paediatric special interest group of ASID (ANZPID) who proposed additions specific for children. Following this consensus was then obtained from ANZPID and the working group, resulting in a final version.

Definitions

- CDI: A + (B or C).
  - A. Clinical features suggestive of CDI (diarrhoea, ileus, toxic megacolon)
  - B. Microbiological evidence of toxin producing *C. difficile*
  - C. Pseudomembranous colitis demonstrated on colonoscopy
- Recurrent CDI
  - ○ When CDI reoccurs within 8 weeks of the onset of a previous episode, after resolution of symptoms from the previous episode.
- Refractory CDI
  - ○ When CDI fails to demonstrate clinical improvement following 3–4 days of recommended therapy.
- Severe CDI
  - ○ In adults, this is defined as an episode of CDI with one or more signs/symptoms demonstrated in Box 2.[5] There is no consensus definition of disease severity for CDI for children.
- Complicated CDI
  - ○ An episode of CDI complicated by toxic megacolon, admission to intensive care for severe sepsis, requirement for surgery or death due to CDI.

What are the principles of CDI diagnosis?

CDI cannot be distinguished clinically from other causes of acute diarrhoea without laboratory testing. Conversely asymptomatic carriage of toxigenic *C. difficile* is not infrequent. Patients continue to excrete *C. difficile* for weeks following recovery. The previously published ASID recommendations concerning laboratory diagnosis of CDI remain relevant.[9] A more recent discussion of diagnostic pitfalls is provided by Wilcox *et al.*[10] Important considerations include:

- Diagnostic testing should not be performed on patients who are asymptomatic, or are minimally

symptomatic or who have laxative-associated diarrhoea.
- Diagnostic strategies that test on physician request underestimate the prevalence of *C. difficile* and it is recommended that regardless of request, laboratories automatically test unformed stools from patients hospitalised for >72 h for toxigenic *C. difficile*.[9,10]
- Laboratories should reject formed or soft stools for *C. difficile* testing; test only watery or loose stools that adopt the shape of the container. If testing inadvertently occurs (e.g. multiplex faecal polymerase chain reaction assay that includes *C. difficile*), the laboratory should add a result comment that downplays the significance of the positive result, recommending careful clinical evaluation of the patient's current status.
- Laboratories should use a screening test that is of adequate sensitivity (>90%) and adopt a testing algorithm that ensures specificity of the final result.
- Retesting of recovered patients as a test of cure is not indicated.

Specific paediatric considerations regarding CDI diagnosis and testing

Asymptomatic colonisation in children <1 year is common, particularly in neonates. Acquisition of *C. difficile* appears to be from the environment rather than maternal sources.[11] Reported *C. difficile* colonisation rates vary, and may be as high as 50% in neonates and 70% in infants <1 year of age.[12] By the age of 2 years, reported colonisation rates are more consistent (35–46%).[13] Thus, it remains controversial whether CDI can even be diagnosed in children <1 year of age. The Infectious Diseases Society of America recently published an official opinion that CDI probably does not exist or is very rare in children <2 years of age.[14] While this expert opinion remains controversial,[15,16] most paediatric infectious diseases physicians would consider the diagnosis of CDI in an infant <2 years as one of exclusion. It is unclear why asymptomatic colonisation (often with demonstrably toxigenic strains of *C. difficile*) is so common in infancy; host factors rather than differences in *C. difficile* strain types are thought to be responsible.[13]

True hospital-acquired CDI (HA-CDI) in older children usually occurs in the context of traditional risk factors, such as chronic hospitalisation, extensive antibiotic use and multiple co-morbidities; these include primary or secondary immunodeficiency, Hirschsprung disease, inflammatory bowel disease, cystic fibrosis and structural or postoperative intestinal disorders.[17–20] Other possible risk factors include proton pump inhibitor use and the presence of a gastrostomy tube.[17,21,22] The role of CDI (if any) in necrotising enterocolitis (NEC) remains uncertain.[23]

Recommendations

1. Testing of asymptomatic children is not indicated.
2. For children <2 years of age:
   - testing for investigation of mild diarrhoea, failure to thrive or NEC is not indicated
   - HA-CDI should be a diagnosis of exclusion in significantly symptomatic children with predisposing risk factors
3. For children >2 years of age:
   - testing should only be performed in significantly symptomatic children with predisposing risk factors

What are the general principles for CDI prevention and management?

Antibiotic exposure remains the central risk factor for both community and HA-CDI, the greatest risk with cephalosporins and lincosamides, although all antibiotic classes, including fluoroquinolones, are potentially implicated.[24,25] Longer antibiotic course duration is associated with CDI, cessation of the instigating antimicrobial therapy is the cornerstone of CDI prevention and treatment.[26] Anti-motility agents should be avoided if possible due to the potential of worsening CDI.[27] Acid suppression therapy should be avoided post-diagnosis due to associations with increased disease severity of CDI, mortality and recurrence (Fig. 1).[28,43] The success of therapy should not be based on repeat stool testing, as asymptomatic carriage of *C. difficile* at 30 days post-treatment has been estimated at 25–30%. In various studies, 4–15% of asymptomatic healthy volunteers and hospitalised inpatients carry toxigenic *C. difficile*.[44–46]

Implementation of effective infection control measures, including hand hygiene with soap and water or alcohol based rubs, patient isolation and environmental cleaning are essential to avoid nosocomial spread.[47] Antimicrobial stewardship programmes targeting high-risk antibiotics (particularly cephalosporins, quinolones, beta-lactam/beta-lactamase inhibitors and clindamycin) have been shown to reduce the incidence of CDI.[24,48–51]

In a patient with CDI and concurrent need for ongoing-directed antibacterial therapy, we recommend using the most narrow spectrum therapeutic for the shortest possible duration. Evidence to suggest a particular class of antibacterial is superior over another in this situation is absent. Primary or secondary CDI 'prophylaxis' where antibacterial therapy cannot be ceased is not recommended as routine practice.

Probiotic therapy was not recommended for prevention of or adjunctive treatment option for CDI in the previous Australian guidelines. A Cochrane review and isolated reports of invasive fungaemia following therapy did not

<table>
<tr><th colspan="3">General measures</th></tr>
<tr><td colspan="3">• Stop all non-essential antibiotic therapy or use narrow spectrum at minimum
• Avoid proton pump inhibitors after CDI diagnosis
• Avoid anti-motility medications
• Ongoing clinical (fevers/abdominal pain/bowel chart) and biochemical assessment (white cell count, lactate, electrolytes) required</td></tr>
<tr><th colspan="3">Suggested medical therapies</th></tr>
<tr><th colspan="3">Non-severe episode</th></tr>
<tr><th colspan="2">Adults</th><th>Children</th></tr>
<tr><td>First episode</td><td>Metronidazole 400mg TDS orally for 10d</td><td>Metronidazole (Child:10mg/kg/dose up to 400mg)TDS orally for 10d</td></tr>
<tr><td>First recurrence</td><td>Vancomycin 125mg QID orally for 10d</td><td>Vancomycin (Child:10mg/kg/dose up to 125mg)QID orally for 10d</td></tr>
<tr><td>2nd or subsequent recurrence</td><td>Vancomycin 125mg QID orally for 14d +/- taper[a]

<u>OR</u>

Fidaxomicin 200mg BD orally for 10d

<u>OR</u>

Faecal Microbiota Transplantation (FMT) (See Table 1)

<u>OR</u>
Rifaximin “chaser”[c]</td><td>Vancomycin (Child:10mg/kg/dose up to 125mg) QID orally for 14d +/-taper[a]

<u>OR</u>

Nitazoxanide 100mg (Child 1-3 years) or 200mg (Child 4-11 years) BD orally for 7-10d.</td></tr>
<tr><td>Refractory Disease</td><td><u>1st Line therapy</u>
Vancomycin 125mg QID for 14d

<u>2nd Line therapy</u>

FMT

<u>OR</u>
Fidaxomicin 200mg BD for 10d[b]</td><td><u>1st Line therapy</u>
Vancomycin (Child: 10mg/kg/dose up to 125mg) QID for 14d

<u>2nd Line therapy</u>
Nitazoxanide 100mg (Child 1-3 years) or 200mg (Child 4-11 years) BD orally for 7-10d.</td></tr>
<tr><th colspan="3">Severe disease</th></tr>
<tr><th colspan="2">Adults</th><th>Children</th></tr>
<tr><td colspan="2"><u>1st Line therapy</u>
Vancomycin 125mgQID orally for 10d

<u>2nd Line therapy</u>
If unable to tolerate oral therapy: NG vancomycin 125mg QID AND IV metronidazole 500mg TDS +/ rectal tube vancomycin 500mg in 100ml N. saline TDS-QID.</td><td><u>1st Line therapy</u>
Vancomycin (Child: 10mg/kg/dose up to 125mg) QID orally for 10d

<u>2nd Line therapy</u>
If unable to tolerate oral therapy: NG vancomycin (Child: 10mg/kg/dose up to 125mg) QID AND IV metronidazole (Child: 12.5mg/kg up to 500mg) TDS</td></tr>
<tr><td colspan="2"><u>3rd line therapy</u>
In ‘2nd or > recurrent’ or ‘refractory disease’ severe CDI consider recommendations as per non-severe disease

In cases were oral therapy not possible and refractory to combination therapy consider tigecycline (100mg IV as a single dose then 50mg TDS for 14d)</td><td>If unable to tolerate oral or nasogastric vancomycin consider rectal instillation of vancomycin (500mg in 100ml N. Saline) BD-QID. The optimal doses have not been established, suggested volumes for children: 1-3 years- 50ml; 4-9 years -75ml; > 10 years -100ml <u>AND</u> IV metronidazole (12.5mg/kg up to 500mg) TDS

<u>3rd line therapy</u>
In ‘2nd or > recurrent’ or ‘refractory disease’ severe CDI consider recommendations as per non-severe disease

In cases where oral therapy not possible and refractory to combination therapy consider IV tigecycline in children over the age of 8. (Child aged 8-11 years: 1.2mg/kg up to 50mg BD and child aged 12 years and over 100mg as a single dose then 50mg TDS for 14d)</td></tr>
<tr><th colspan="3">Indications for surgical intervention</th></tr>
<tr><td colspan="3">1. Toxic megacolon or bowel perforation
2. Severe deterioration despite 1st and 2nd line medical therapy</td></tr>
</table>

Figure 1 Summary recommendations for *Clostridium difficile* infection (CDI) management.[27–42] [a]Vancomycin taper can be considered: 125 mg BD oral for 7 days, 125 mg oral every second day for 2–8 weeks (other regimens described). Not required prior to fidaxomicin or FMT use; [b]Fidaxomicin not studied in patients with multiple relapses therefore use with caution. Reasonable to consider prior to more invasive FMT; [c]400 mg TDS for 7–10 days OR 400 mg TDS 14–20 days post initial therapy. Rifaximin ‘chaser’ used in patients with multiple recurrences and in case reports for recurrent and refractory disease. Used in a small randomised control trial, not extensively in severe or recurrent disease. BD, twice daily; FMT, faecal microbiota transplantation; IV, intravenous; IVIG, intravenous immunoglobulin; NG, nasogastric; O, oral; TDS, three times daily; QID, four times daily.

support its use.[5,52–54] A revised Cochrane review and two recent randomised control trials (RCT) examined the prevention effects of probiotic therapy in CDI and antibiotic associated diarrhoea.[55–57] While probiotics may be of some value in limited studies, we do not recommend probiotic therapy use in prevention or adjunctive treatment in CDI. In the largest RCT of lactobacilli and bifidobacteria (probiotic therapy), there was no demonstrable benefit of this probiotic mixture preventing CDI.[55]

What antibiotics should be used for treatment of an initial CDI episode?

Initial CDI episode therapy

Since the Australasian *C. difficile* treatment guidelines were published in 2011, no significant studies have become available to modify the current local and international guidelines recommending metronidazole therapy for mild to moderate CDI.[5,29,58–61] The mainstay of therapy remains ceasing the causative antibiotic(s). Metronidazole remains cost effective and readily available. In systematic reviews, there appears to be no difference between metronidazole and vancomycin therapy for initial episodes of CDI.[62–64] There are concerns regarding possible generation of vancomycin-resistant enterococci with vancomycin use. Therefore, vancomycin should be reserved for recurrent or severe disease or those that do not respond to metronidazole after 3–4 days of therapy.[65]

In general, CDI in children is less severe than in adults. It is recommended that only children with moderate to severe disease should be treated. In children with mild disease, stopping antibiotic therapy is usually sufficient to resolve symptoms. Current experience in the USA suggests that CA-CDI may be more severe than HA-CDI in children.[66] There are no equivalent data from Australia. There is also no consensus definition of severe disease for CDI in children. Determination of disease severity should be guided by adult criteria combined with clinical judgement until paediatric definitions are established. Caution should be used in directly applying adult criteria to children with CDI as this can overestimate severity.[8] While immunodeficiency predisposes to CDI, there are no consistent data in children to suggest that more aggressive therapy is warranted in the presence of immunodeficiency.[8,67]

Dosing and administration

Metronidazole administration is preferred through the oral route compared with intravenous administration.[29] Vancomycin should be administered orally at 125 mg four times daily. Hospital compounded oral solution is not inferior to commercially available vancomycin capsules.[68] Vancomycin dose above 125 mg four times daily is not routinely recommended, recent reports suggesting no improvement in clinical cure, mortality or complications with increasing dose in severe disease.[69] Reports of high serum vancomycin levels with 500 mg four times day dosing have also been noted in patients.[70–72] Intravenous vancomycin therapy is not effective in CDI, however, colonic administration through an enema may be effective as an adjunctive therapy (uncertain dosing) if oral therapy is unable to be tolerated (500 mg in 100 mL normal saline, rectally 6 hourly).[4,73–75]

Recommendations

1. Oral metronidazole is recommended for initial episode CDI without clinical features of severe disease at 400 mg three times daily for 10 days. Paediatric dosing: oral metronidazole 10 mg/kg up to 400 mg orally or through a nasogastric (NG) tube three times daily for 10 days.
2. Oral vancomycin is recommended for initial episode refractory CDI or if severe disease features are present. Vancomycin is recommended at 125 mg four times daily for 10 days. Paediatric dosing: vancomycin 10 mg/kg up to 125 mg orally or through a NG tube four times daily for 10 days.

Newer therapies

Fidaxomicin, a first-in-class 18-membered macrocyclic bactericidal antibiotic, has targeted bactericidal activity against *C. difficile* through inhibiting clostridial RNA polymerase.[76,77] Fidaxomicin demonstrates minimal impact on normal gut flora and spares *Bacteroides* spp., a major 'protective' constituent of faecal flora.[78] Fidaxomcin has minimal oral absorption like vancomycin and a prolonged post-antibiotic effect and has recently been approved by the Therapeutic Drug Administration (TGA) for use in CDI.[79] In the two large concurrently run double-blind randomised non-inferiority trials and recent meta-analyses, fidaxomicin was non-inferior to vancomycin in resolving symptoms in the treatment of new onset or first recurrence CDI. Fidaxomicin is associated with reduced recurrences in patients on concurrent antibiotics and sustained clinical cure, and therefore might be considered in this setting.[30,80–82] However, due to uncertain cost effectiveness relative to existing treatment, fidaxomicin is not recommended as first-line therapy for CDI.

The use of fidaxomicin in children younger than 18 years of age is restricted by the lack of approval by the TGA and the limited paediatric studies that are currently available. A randomised controlled trial comparing oral vancomycin and fidaxomicin in children is currently

in progress and early data suggests that it is safe in children.[83–85]

Faecal microbiota transplantation (FMT), although described as initial therapy for CDI, has primarily been investigated for recurrent disease and therefore is only recommended in recurrent or refractory disease.[86] FMT is further discussed in the 'recurrent CDI' section. Although fusidic acid, teicoplanin and tigecycline have been used for the treatment of CDI, evidence to support first-line therapy is unavailable and therefore they are not recommended.

Rifaximin has been primarily used for refractory CDI, and with some success as a 2-week 'chaser therapy' course following vancomycin therapy.[31–33,87] In a small RCT of rifaximin versus placebo following CDI therapy, there was a non-statistically significant reduction in disease recurrence.[34] Concerns remain regarding increasing *C. difficile* rifaximin resistance, especially in patients previously exposed to a rifamycin.[32,88] Rifaximin is not recommended for first-line therapy. Monoclonal antibodies have gathered interest as an adjunctive therapy. Although a phase II RCT found a single intravenous infusion of monoclonal antibodies did not affect initial cure, it was associated with reduced recurrence.[89]

What agents should be used for recurrent disease?

The recommended agents for recurrent disease are outlined in Figure 1. In the setting of a recent systematic review and RCT demonstrating superiority of vancomycin to metronidazole in recurrent disease, we recommend vancomycin in the setting of recurrent disease, a change from the previous guideline.[90,91] For a second or further recurrence, vancomycin therapy is recommended. The previous guidelines recommended a vancomycin taper following a second CDI recurrence. The use of a vancomycin taper is however only supported by an observational study demonstrating reduced recurrence.[60,92] No data exist comparing the safety, acceptability and effectiveness of FMT, fidaxomicin and oral vancomycin for multiple CDI recurrences. There are recent RCT data to support FMT and fidaxomicin for recurrent CDI, although a vancomycin taper remains a recommended therapy, it does not need to be used before considering an alternative treatment option.

FMT has gained interest as a therapy for CDI. Failure to preserve normal bowel flora is a factor in severe, recurrent and prolonged CDI.[93] FMT aims to reconstitute the normal flora with a transplant from a healthy donor. A small open-label RCT of duodenal infusion was terminated early after interim analysis demonstrated superiority of FMT given through nasoduodenal tube over vancomycin therapy for patients with recurrent disease.[86] A further RCT of vancomycin versus FMT (rectal administration) also demonstrated superiority of FMT for recurrent CDI, although multiple FMT infusions were used in patients with pseudomembranous colitis.[94] These RCT data follow a series of large reviews and meta-analyses demonstrating 80–90% first instillation FMT effectiveness.[95–98] The utility of pre-screened frozen donor faeces banks has potentially removed many of the practical issues of requiring 'fresh' donor faeces.[99,100] Frozen stool retains viable bacteria for up to 6 months following storage in −80°C.[101] Costello *et al.* recently described the process of establishing a frozen donor stool bank.[102]

There are practical safety concerns that have been reported for FMT (e.g. aspiration, bowel perforation) and the long-term impacts of the donor microbiota remain unknown.[103,104] Regulation of FMT has not been fully addressed nationally, whilst safety and ethical considerations are currently managed at an institutional level. FMT can be an alternative therapy in the setting of recurrent CDI following failure of less-invasive options and local institutional approval (Fig. 1). The logistical requirements of FMT are outlined in Table 1. The donor screening processes are not well validated; our recommendations are consistent with the RCT protocols. The use of FMT in subgroups, such as the immunosuppressed, is ill defined, with only case series/cohort data to support similar efficacy.[105,111,112]

A 'pill' administration of donor faeces was demonstrated in an open-label single cohort study and in the near future could potentially expand debate over mode of delivery.[99,100] Future therapies may include the development of synthetic microbiota, selecting desired anaerobes and eliminating risks associated with donor disease transmission. Despite a small open-label pilot RCT trial of NG versus colonoscopic administration and data from systematic reviews, an optimal mode of delivery has not been determined.[95,96,98,100]

Six reports since 2001 describe FMT for CDI in children.[113–117] This represents a total of 32 children, in comparison with data on >1000 adult patients.[114] This may in part reflect that severe disease in children is not as common as adults. Logistical, ethical and safety issues and success rate appear to be the same as in adult cases.[115] Long-term effects (if any) on the microbiome are not known, and exact mechanism of action remains unclear. Some preliminary data from a case series of eight children post-FMT suggest the microbiome normalises within 6 months.[114] Screening requirements for donors currently remain the same as those recommended for adults. There have been no published reports of adverse events in children receiving FMT.

Fidaxomicin was compared with vancomycin in the two concurrently run double blind non-inferiority RCT including recurrent CDI, demonstrating similar time to resolution of diarrhoea and clinical responses at the end of therapy, with reduced recurrence at 28 days follow-up.[81,118,119] In those patients with a previous episode of CDI (15%), clinical cure was unchanged, although less recurrence was noted with fidaxomicin.[119] In sub-group analysis, patients at high risk of recurrence, oncology patients and those on concurrent antibiotic therapy had improved outcomes and reduced recurrence, however patients on vancomycin had more severe disease.[81,120] These studies did not investigate patients with multiple relapsed CDI, severe disease or previous fidaxomicin failure.[121] Fidaxomicin has been used as a 'vancomycin chaser' for small cohorts with multiple relapsed CDI.[122] Therefore, despite a higher cost fidaxomicin can be considered in early recurrent disease in high-risk populations or if FMT is contraindicated/unavailable. The cost effectiveness of fidaxomicin has been demonstrated for severe CDI and first CDI recurrence in international studies although this has not been addressed in an Australasian setting.[123]

Nitazoxanide is a thiazoline-class antibiotic, with activity against *C. difficile*, that is currently used to treat other parasitic gastrointestinal infections in children.[124,125] In two randomised controlled trials conducted in adults, nitazoxanide had similar efficacy to vancomycin and metronidazole for the initial treatment of CDI.[126,127] A prospective study found that adult patients who were unresponsive to metronidazole treatment had a 66% response rate to one or more courses of nitazoxanide.[128] Given the paucity of data available in children for the use of newer alternative therapies for CDI, nitazoxanide is a safe and reasonable second-line agent to consider.[126]

Recommendations

1. Oral vancomycin is recommended for first CDI recurrence (adults + children).
2. Oral vancomycin, including a vancomycin taper, is suggested for second or subsequent CDI recurrence (adults + children).
3. Fidaxomicin is a therapeutic option for second or subsequent CDI recurrence, especially in high risk of relapse populations (i.e. concurrent antibiotic therapy) (adults).
4. FMT is a therapeutic option for second or subsequent CDI recurrence if above therapy has failed and no contraindications (adults).
5. Rifaximin 'chaser therapy' is a therapeutic option in the setting of metronidazole, vancomycin or fidaxomicin failure or where FMT may not be available or contraindicated (adults).
6. Nitazoxanide can be considered for subsequent CDI recurrence (children only).[126] Nitazoxanide (child 1–3 years) 100 mg; (child 4–11 years) 200 mg; orally 12 hourly for 7–10 days.

What agents should be used for refractory or severe CDI?

Patients should be investigated for signs of severe disease (i.e. renal impairment, rising lactate, white cell count, toxic megacolon) as outlined in Box 2. Vancomycin is superior to metronidazole in cases of severe CDI and therefore remains the treatment of choice.[65,90,129] The choice of agent for refractory CDI is unclear, with evidence primarily extrapolated from cohort data rather than prospective or RCT (Fig. 1). Older therapies, such as bacitracin and fusidic acid, have no current role in CDI therapy.[35,36,130]

Fidaxomicin has not been extensively studied in severe or refractory disease. There are no data on the efficacy in severe life-threatening/fulminant disease and/or toxic megacolon (excluded from both RCT).[81,118] In patients with severe disease from the RCT data, there was no difference in clinical cure rates between vancomycin and fidaxomicin.[119] Fidaxomicin should therefore be used with caution in fulminant, life-threatening or toxic megacolon disease.

Refractory and severe CDI were excluded also from the RCT of FMT and therefore limited data exist for its use in this context. The recent FMT 'capsule' single cohort study by Youngster *et al*. included refractory and severe patients.[99] Numerous case reports exist for its successful FMT use in refractory and severe disease;[103,106,112,131–134] however, like fidaxomicin FMT can only be recommended following failure of the standard of care outlined in Figure 1.

Combination therapy (oral/NG vancomycin and intravenous metronidazole) is commonly recommended for severe CDI not responding to single agent vancomycin therapy.[5] Recent reports limited by retrospective design have demonstrated mixed results. Bass *et al*. indicate no improved outcomes with vancomycin combination therapy.[68] Conversely, Rokas *et al*. demonstrated improved mortality in patients treated with combination therapy in the intensive care unit.[135] Nonetheless, in severe disease combination therapy with intravenous metronidazole and oral vancomycin with or without the addition of rectally administered vancomycin is recommended.[136] In patients unable to take oral therapy and/or failure of combination therapy, treatment options for severe CDI are limited. Intravenous tigecycline has been demonstrated in case series/cohort data to be successful in some patients with recurrent and severe disease.[137–140]

Surgery remains an important consideration in cases of severe disease. In severe disease associated with toxic megacolon, surgery may be required. Besides traditional colectomy, a recent case series highlights the benefit of loop ileostomy and vancomycin instillation

Table 1 Faecal microbiota transplantation (FMT) for *Clostridium difficile* infection (CDI)

FMT	Suggested approaches	Comments
General	• Ensure local hospital governance and/or ethics approval • Ensure informed patient and donor consent • Only perform in specialised centres or in consultation with an infectious diseases physician and gastroenterologist	• A standardised approach for FMT is absent and the long-term effects of FMT are ill defined. • Consider less-invasive medical therapies prior to FMT
Donor selection	• Related or non-related donor • Avoid donor if ○ Recent antibiotic exposure (3–6 months) ○ Loose stools ○ Recent gastrointestinal illness ○ Recent overseas travel (3–6 months) ○ Medical co-morbidities or ongoing, including BBV risk factors	• RCT used as non-related donors • Unless donor bank available, related donor FMT may prove more practical • Frozen inoculum from unrelated donors used with similar effectiveness in pilot study • Ensuring donors are free of medical co-morbidities is important, considering the transference of donor medical co-morbidities has been demonstrated in animal studies and a single case report
Donor screening	• BBV • Hepatitis A, B, C; HIV, *Treponema pallidum* Enteric pathogens Enteric bacterial pathogens VRE & ESBL Cysts, ova, parasites *Heliocobacter pylori* Ag Giardia ICT Cryptosporidium/microsporidium Strongyloides serology *Clostridium difficile* culture and toxin	• Screening within 7 days of donation • No reported cases of transmitted infectious diseases from FMT • There are no standardised screening processes across trials and cohort studies
Donor faeces	• Prepare faeces close to time of FMT† • Donor faeces (50–100 g) emulsified with N. saline for administration‡ • Donor suspensions of 100–500 mL recommended – greater volume required with lower GI method • Frozen donor faeces may be considered if frequent use	• Preparation of faeces is preferred in anaerobic conditions within a microbiology department anaerobic chamber, a faecal suspension generated with N. saline and mixed through hazardous materials blender or through manual agitation inside sterile container. Considering an anaerobic chamber offers only a theoretical advantage of protecting obligate anaerobic bacteria and FMT produced in aerobic conditions has been effective, the absence of an anaerobic chamber is not a contraindication to FMT. • Specimens should be processed using appropriate precautions to protect staff, including the use of personal protective equipment
Pre-FMT	• Pre-treatment with vancomycin or fidaxomicin is recommended for 3–5 days before FMT • Cease CDI antibiotics 24–48 h prior • Fast for 4–6 h prior to FMT	• A low-dose bowel prep can be considered prior to FMT‡ • A single PPI dose is used in many centres if administration is through upper GI method.
Mode of delivery	• Upper GI§ Nasoduodenal tube (NDT) Nasogastric tube (NG) Gastroscopy • Lower GI¶ Colonoscopy Rectal tube • Capsule†† Post-treatment • Avoid antibacterial therapy, including CDI agents. Consider repeat FMT if first episode FMT failure. • Anti-motility agents (e.g. loperamide) can be considered for lower GI delivery methods to aid FMT retention.	• Pilot study demonstrated similar effectiveness of NG versus colonoscopy administration • No evidence of superiority of one mode of delivery, NDT method used in RCT • Tailor delivery to patient population and availability • Episodes of fatal aspiration have been reported with gastroscopy administration • At home, faecal enema is discouraged • Capsule administration not yet widely validated

†RCT and other trials used FMT suspension within 6 h of FMT. ‡Bowel lavage as a therapy was demonstrated to be ineffective in RCT FMT trial. Low-dose may be considered, especially if lower GI method. §Avoid upper GI modality if history or concerns of aspiration. ¶Avoid colonoscopy administration if severe disease or toxic megacolon due to concerns of perforation. ††Capsule administration evaluated in single cohort open-label study administering 15 capsule over 2 consecutive days, contained a centrifuged mean of 48 g of faecal matter.[99] Ag, antigen; BBV, blood-borne viruses; ESBL, extended spectrum beta-lactamase; GI; gastrointestinal; HIV, human immunodeficiency virus; N. saline, normal saline 0.9% solution; NDT, nasoduodenal tube; PPI, proton pump inhibitor; RCT, randomised control trial; VRE, vancomycin-resistant *Enterococcus faecium*.[86,94,95,99,100,102,106–111]

through the ileostomy created. This requires further evaluation.[141,142]

Alternative therapies that have been used for recurrent and refractory CDI are listed in Figure 1. None of these therapies has been explored in prospective studies and therefore are not recommended for routine management.

Recommendations

1. Vancomycin is recommended as first-line therapy in severe disease (adults + children).
2. Combination therapy including oral/NG vancomycin and intravenous metronidazole is recommended in non-responsive severe disease (adults + children).
3. FMT, tigecycline and fidaxomicin are only suggested as second-line therapy if oral vancomycin and combination therapy have failed, due to limited evidence in severe CDI (adults).
4. Surgery is indicated for life threatening severely refractory CDI or cases of toxic megacolon (adults + children).
5. In children, FMT may be considered as salvage therapy on a case-by-case basis in severe, refractory or relapsing CDI with ≥3 episodes of disease until further experience in children is collated.

New agents on the horizon?

The use of intravenous immunoglobulin has been investigated: a prior case–control study and systematic review, illustrating no difference in patient outcomes.[37,143] A more recent systematic review demonstrated an 80% initial response rate when intravenous immunoglobulin was used alone or in combination.[144] In a phase II RCT, a single monoclonal antibody infusion against *C. difficile* was administered as an adjunct to standard CDI therapy, demonstrating no effect on clinical cure however there was a reduction of CDI recurrence; phase III clinical trials have just completed (ClinicalTrials.gov identifiers NCT01241552 and NCT01512239).[89] Recent reports from the unpublished phase III trial found that the use of bezlotoxumab, a monoclonal antibody against toxin B, was associated with a lower risk of recurrence.[145]

Cadazolid (formerly ACT-179811), a new oxazolidinone-type antibiotic that primarily inhibits protein synthesis and is in development for use in CDI, demonstrated activity *in vitro* and in CDI mouse models.[146–148] Cadazolid is currently undergoing a phase III CDI study. MCB3681 has demonstrated intro activity against *C. difficile* although no clinical trials are currently available.[149] Ramoplanin is a glycolipodepsipeptide that targets bacterial cell walls like vancomycin, although at a distinct site, displays potent antimicrobial activity against *C. difficile* in animal CDI models.[150,151] Surotomycin an orally available cyclic liopeptide, reduces *C. difficile* counts and toxin in an *in vitro* gut model whilst sparing *B. fragilis*, and is undergoing a phase III trial.[111] Thuricin CD is an antibiotic (a novel class of post-translationally modified bacteriocins) that exhibits narrow-spectrum antimicrobial activity against *C. difficile*.[152,153] Auranofin (2,3,4,6-tetra-*o*-acetyl-L-thio-β-D-glycopyranp-sato-S-(triethyl-phosphine)-gold) was approved for the treatment of rheumatoid arthritis in 1985 and inhibits *C. difficile in vitro* at low-micromolar concentrations. Auranofin is excreted in the faeces (85%), has a half-life of 15–25 days and after oral administration 15–25% of the dose can be detected in the plasma, peaking at a concentration of 6–9 μg/100 mL within 2 h.[154] Auranofin is able to disrupt selenium metabolism in *C. difficile* by forming a stable bond with inorganic selenium.[155] Without selenium, *C. difficile* cannot synthesise selenoproteins essential for energy production. Auranofin does not have an inhibitory effect on *Clostridium* species that do not utilise selenoproteins such as *C. perfringens* and *C. tetani*.[155] Despite promising *in vitro* or animal studies, no published clinical trials are available for auranofin, ramoplanin or thuricin CD.

Recommendation

1. Cadazolid, auranofin, ramoplanin, thuricin CD, surotomycin or monoclonal antibody therapy cannot be recommended currently for clinical use for CDI (adults + children).

References

1 Kelly CP, LaMont JT. *Clostridium difficile* – more difficult than ever. *N Engl J Med* 2008; **359**: 1932–40.

2 Kelly CP. Can we identify patients at high risk of recurrent *Clostridium difficile* infection? *Clin Microbiol Infect* 2012; **18**: 21–7.

3 Slimings C, Armstrong P, Beckingham WD, Bull AL, Hall L, Kennedy KJ *et al.* Increasing incidence of *Clostridium difficile* infection, Australia, 2011-2012. *Med J Aust* 2014; **200**: 272–6.

4 Antibiotic Expert Groups. *Therapeutic Guidelines: Antibiotic. Version 15*. Melbourne: Therapeutic Guidelines Limited; 2014.

5 Cheng AC, Ferguson JK, Richards MJ, Robson JM, Gilbert GL, McGregor A *et al.* Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of *Clostridium difficile* infection. *Med J Aust* 2011; **194**: 353–8.

6 Debast SB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases.

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect* 2014; **20**: 1–26.
7 Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M *et al.* Fulminant *Clostridium difficile* colitis: patterns of care and predictors of mortality. *Arch Surg* 2009; **144**: 433–9; discussion 439–40.
8 Pai S, Aliyu SH, Enoch DA, Karas JA. Five years experience of *Clostridium difficile* infection in children at a UK tertiary hospital: proposed criteria for diagnosis and management. *PLoS One* 2012; **7**: e51728.
9 Ferguson JK, Cheng AC, Gilbert GL, Gottlieb T, Korman T, McGregor A *et al. Clostridium difficile* laboratory testing in Australia and New Zealand: national survey results and Australasian Society for Infectious Diseases recommendations for best practice. *Pathology* 2011; **43**: 482–7.
10 Wilcox MH. Preface: *Clostridium difficile* Infection. *Infect Dis Clin North Am* 2015; **29**: xiii–xiv.
11 Rousseau C, Poilane I, De Pontual L, Maherault AC, Le Monnier A, Collignon A. *Clostridium difficile* carriage in healthy infants in the community: a potential reservoir for pathogenic strains. *Clin Infect Dis* 2012; **55**: 1209–15.
12 Libby JM, Donta ST, Wilkins TD. *Clostridium difficile* toxin A in infants. *J Infect Dis* 1983; **148**: 606.
13 Rousseau C, Lemée L, Le Monnier A, Poilane I, Pons JL, Collignon A. Prevalence and diversity of *Clostridium difficile* strains in infants. *J Med Microbiol* 2011; **60**: 1112–8.
14 Faust SN, Wilcox MH, Banaszkiewicz A, Bouza E, Raymond J, Gerding DN. Lack of evidence for an unmet need to treat *Clostridium difficile* infection in infants aged <2 years: expert recommendations on how to address this issue. *Clin Infect Dis* 2015; **60**: 912–8.
15 Sammons JS, Toltzis P. Pitfalls in diagnosis of pediatric *Clostridium difficile* infection. *Infect Dis Clin North Am* 2015; **29**: 465–76.
16 Kim J, Shaklee JF, Smathers S, Prasad P, Asti L, Zoltanski J *et al.* Risk factors and outcomes associated with severe *clostridium difficile* infection in children. *Pediatr Infect Dis J* 2012; **31**: 134–8.
17 Sandora TJ, Fung M, Flaherty K, Helsing L, Scanlon P, Potter-Bynoe G *et al.* Epidemiology and risk factors for *Clostridium difficile* infection in children. *Pediatr Infect Dis J* 2011; **30**: 580–4.
18 Pascarella F, Martinelli M, Miele E, Del Pezzo M, Roscetto E, Staiano A. Impact of *Clostridium difficile* infection on pediatric inflammatory bowel disease. *J Pediatr* 2009; **154**: 854–8.
19 Rivlin J, Lerner A, Augarten A, Wilschanski M, Kerem E, Ephros MA. Severe *Clostridium difficile*-associated colitis in young patients with cystic fibrosis. *J Pediatr* 1998; **132**: 177–9.
20 Thomas DF, Fernie DS, Bayston R, Spitz L, Nixon HH. Enterocolitis in Hirschsprung's disease: a controlled study of the etiologic role of *Clostridium difficile*. *J Pediatr Surg* 1986; **21**: 22–5.
21 Furuichi M, Imajo E, Sato Y, Tanno S, Kawada M, Sato S. Characteristics of *Clostridium difficile* colonization in Japanese children. *J Infect Chemother* 2014; **20**: 307–11.
22 Brown KE, Knoderer CA, Nichols KR, Crumby AS. Acid-suppressing agents and risk for *Clostridium difficile* infection in pediatric patients. *Clin Pediatr (Phila)* 2015; **54**: 1102–6.
23 Grishin A, Papillon S, Bell B, Wang J, Ford HR. The role of the intestinal microbiota in the pathogenesis of necrotizing enterocolitis. *Semin Pediatr Surg* 2013; **22**: 69–75.
24 Slimings C, Riley TV. Antibiotics and hospital-acquired *Clostridium difficile* infection: update of systematic review and meta-analysis. *J Antimicrob Chemother* 2014; **69**: 881–91.
25 Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ *et al.* Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimicrob Chemother* 2013; **68**: 1951–61.
26 Brown KA, Fisman DN, Moineddin R, Daneman N. The magnitude and duration of *Clostridium difficile* infection risk associated with antibiotic therapy: a hospital cohort study. *PLoS One* 2014; **9**: e105454.
27 Kato H, Kato H, Iwashima Y, Nakamura M, Nakamura A, Ueda R. Inappropriate use of loperamide worsens *Clostridium difficile*-associated diarrhoea. *J Hosp Infect* 2008; **70**: 194–5.
28 Abou Chakra CN, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in *Clostridium difficile* infection: a systematic review. *PLoS One* 2014; **9**: e98400.
29 Wenisch JM, Schmid D, Kuo HW, Allerberger F, Michl V, Tesik P *et al.* Prospective observational study comparing three different treatment regimes in patients with *Clostridium difficile* infection. *Antimicrob Agents Chemother* 2012; **56**: 1974–8.
30 Berman AL. Efficacy of rifaximin and vancomycin combination therapy in a patient with refractory *Clostridium difficile*-associated diarrhoea. *J Clin Gastroenterol* 2007; **41**: 932–3.
31 Johnson S, Schriever C, Patel U, Patel T, Hecht DW, Gerding DN. Rifaximin Redux: treatment of recurrent *Clostridium difficile* infections with rifaximin immediately post-vancomycin treatment. *Anaerobe* 2009; **15**: 290–1.
32 Rubin DT, Sohi S, Glathar M, Thomas T, Yadron N, Surma BL. Rifaximin is effective for the treatment of *Clostridium difficile*-associated diarrhoea: results of an open-label pilot study. *Gastroenterol Res Pract* 2011; **2011**: 106978.
33 Mattila E, Arkkila P, Mattila PS, Tarkka E, Tissari P, Anttila VJ. Rifaximin in the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2013; **37**: 122–8.
34 Garey KW, Ghantoji SS, Shah DN, Habib M, Arora V, Jiang ZD *et al.* A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with *Clostridium difficile* infection. *J Antimicrob Chemother* 2011; **66**: 2850–5.
35 Dudley MN, McLaughlin JC, Carrington G, Frick J, Nightingale CH, Quintiliani R. Oral bacitracin vs vancomycin therapy for *Clostridium difficile*-induced diarrhoea. A randomized double-blind trial. *Arch Intern Med* 1986; **146**: 1101–4.
36 Young GP, Ward PB, Bayley N, Gordon D, Higgins G, Trapani JA *et al.* Antibiotic-associated colitis due to *Clostridium difficile*: double-blind comparison of vancomycin with

bacitracin. *Gastroenterology* 1985; **89**: 1038–45.
37 Aldeyab MA, McElnay JC, Scott MG, Davies E, Edwards C, Darwish Elhajji FW *et al.* An evaluation of the impact of a single-dose intravenous immunoglobulin regimen in the treatment of *Clostridium difficile* infections. *Infect Control Hosp Epidemiol* 2011; **32**: 631–3.
38 de Lalla F, Nicolin R, Rinaldi E, Scarpellini P, Rigoli R, Manfrin V *et al.* Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea. *Antimicrob Agents Chemother* 1992; **36**: 2192–6.
39 Bektas M, Toruner M, Cetinkaya H, Soykan I, Ozden A. Fucidic acid use in metronidazole nonresponders with *Clostridium difficile* infection. *Digestion* 2007; **75**: 177–8.
40 Garey KW, Salazar M, Shah D, Rodrigue R, DuPont HL. Rifamycin antibiotics for treatment of *Clostridium difficile*-associated diarrhoea. *Ann Pharmacother* 2008; **42**: 827–35.
41 Rodriguez-Pardo D, Almirante B, Bartolomé RM, Pomar V, Mirelis B, Navarro F *et al.* Epidemiology of *Clostridium difficile* infection and risk factors for unfavorable clinical outcomes: results of a hospital-based study in Barcelona, Spain. *J Clin Microbiol* 2013; **51**: 1465–73.
42 DuPont HL, Haake R, Taylor DN, Ericsson CD, Jiang ZD, Okhuysen PC *et al.* Rifaximin treatment of pathogen-negative travelers' diarrhoea. *J Travel Med* 2007; **14**: 16–9.
43 Morrison RH, Hall NS, Said M, Rice T, Groff H, Brodine SK *et al.* Risk factors associated with complications and mortality in patients with *Clostridium difficile* infection. *Clin Infect Dis* 2011; **53**: 1173–8.
44 Galdys AL, Nelson JS, Shutt KA, Schlackman JL, Pakstis DL, Pasculle AW *et al.* Prevalence and duration of asymptomatic *Clostridium difficile* carriage among healthy subjects in Pittsburgh, Pennsylvania. *J Clin Microbiol* 2014; **52**: 2406–9.
45 Zacharioudakis IM, Zervou FN, Pliakos EE, Ziakas PD, Mylonakis E. Colonization with toxinogenic *C. difficile* upon hospital admission, and risk of infection: a systematic review and meta-analysis. *Am J Gastroenterol* 2015; **110**: 381–90.
46 Kong LY, Dendukuri N, Schiller I, Bourgault AM, Brassard P, Poirier L *et al.* Predictors of asymptomatic *Clostridium difficile* colonization on hospital admission. *Am J Infect Control* 2015; **43**: 248–53.
47 Oughton MT, Loo VG, Dendukuri N, Fenn S, Libman MD. Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of *Clostridium difficile*. *Infect Control Hosp Epidemiol* 2009; **30**: 939–44.
48 Wenisch JM, Equiluz-Bruck S, Fudel M, Reiter I, Schmid A, Singer E *et al.* Decreasing *Clostridium difficile* infections by an antimicrobial stewardship program that reduces moxifloxacin use. *Antimicrob Agents Chemother* 2014; **58**: 5079–83.
49 Aldeyab MA, Kearney MP, Scott MG, Aldiab MA, Alahmadi YM, Darwish Elhajji FW *et al.* An evaluation of the impact of antibiotic stewardship on reducing the use of high-risk antibiotics and its effect on the incidence of *Clostridium difficile* infection in hospital settings. *J Antimicrob Chemother* 2012; **67**: 2988–96.
50 Talpaert MJ, Gopal Rao G, Cooper BS, Wade P. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of *Clostridium difficile* infection. J Antimicrob Chemother 2011; 66: 2168–74.
51 Furuya-Kanamori L, Stone JC, Clark J, McKenzie SJ, Yakob L, Paterson DL *et al.* Comorbidities, exposure to medications, and the risk of community-acquired *Clostridium difficile* infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2015; **36**: 132–41.
52 Enache-Angoulvant A, Hennequin C. Invasive *Saccharomyces* infection: a comprehensive review. *Clin Infect Dis* 2005; **41**: 1559–68.
53 Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. *Cochrane Database Syst Rev* 2008; **1**: CD004611.
54 Santino I, Alari A, Bono S, Teti E, Marangi M, Bernardini A *et al.* *Saccharomyces cerevisiae* fungemia, a possible consequence of the treatment of *Clostridium difficile* colitis with a probioticum. *Int J Immunopathol Pharmacol* 2014; **27**: 143–6.
55 Allen SJ, Wareham K, Wang D, Bradley C, Hutchings H, Harris W *et al.* Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2013; **382**: 1249–57.
56 Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K *et al.* Probiotics for the prevention of *Clostridium difficile*-associated diarrhoea in adults and children. *Cochrane Database Syst Rev* 2013; CD006095.
57 Pozzoni P, Riva A, Bellatorre AG, Amigoni M, Redaelli E, Ronchetti A *et al.* Saccharomyces boulardii for the prevention of antibiotic-associated diarrhoea in adult hospitalized patients: a single-center, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2012; **107**: 922–31.
58 Teasley DG, Gerding DN, Olson MM, Peterson LR, Gebhard RL, Schwartz MJ *et al.* Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. *Lancet* 1983; **2**: 1043–6.
59 Wenisch C, Parschalk B, Hasenhündl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhoea. *Clin Infect Dis* 1996; **22**: 813–8.
60 Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC *et al.* 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). *Infect Control Hosp Epidemiol* 2010; **31**: 431–55.
61 Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH *et al.* Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol* 2013; **108**: 478–98.

62 Drekonja DM, Butler M, MacDonald R, Bliss D, Filice GA, Rector TS *et al.* Comparative effectiveness of *Clostridium difficile* treatments: a systematic review. *Ann Intern Med* 2011; **155**: 839–47.

63 Nelson RL, Kelsey P, Leeman H, Meardon N, Patel H, Paul K *et al.* Antibiotic treatment for *Clostridium difficile*-associated diarrhoea in adults. *Cochrane Database Syst Rev* 2011; CD004610.

64 Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. *JAMA* 2015; **313**: 398–408.

65 Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhoea, stratified by disease severity. *Clin Infect Dis* 2007; **45**: 302–7.

66 Tschudin-Sutter S, Tamma PD, Naegeli AN, Speck KA, Milstone AM, Perl TM. Distinguishing community-associated from hospital-associated *Clostridium difficile* infections in children: implications for public health surveillance. *Clin Infect Dis* 2013; **57**: 1665–72.

67 Tamma PD, Sandora TJ. *Clostridium difficile* infection in children: current state and unanswered questions. *J Ped Infect Dis* 2012; **1**: 230–43.

68 Bass SN, Bauer SR, Neuner EA, Lam SW. Comparison of treatment outcomes with vancomycin alone versus combination therapy in severe *Clostridium difficile* infection. *J Hosp Infect* 2013; **85**: 22–7.

69 Lam SW, Bass SN, Neuner EA, Bauer SR. Effect of vancomycin dose on treatment outcomes in severe *Clostridium difficile* infection. *Int J Antimicrob Agents* 2013; **42**: 553–8.

70 Chihara S, Shimizu R, Furukata S, Hoshino K. Oral vancomycin may have significant absorption in patients with *Clostridium difficile* colitis. *Scand J Infect Dis* 2011; **43**: 149–50.

71 Thompson CM Jr, Gilligan PH, Fisher MC, Long SS. *Clostridium difficile* cytotoxin in a pediatric population. *Am J Dis Child* 1983; **137**: 271–4.

72 Pettit NN, DePestel DD, Fohl AL, Eyler R, Carver PL. Risk factors for systemic vancomycin exposure following administration of oral vancomycin for the treatment of *Clostridium difficile* infection. *Pharmacotherapy* 2015; **35**: 119–26.

73 Tedesco F, Markham R, Gurwith M, Christie D, Bartlett JG. Oral vancomycin for antibiotic-associated pseudomembranous colitis. *Lancet* 1978; **2**: 226–8.

74 Apisarnthanarak A, Khoury H, Reinus WR, Crippin JS, Mundy LM. Severe *Clostridium difficile* colitis: the role of intracolonic vancomycin? *Am J Med* 2002; **112**: 328–9.

75 Saffouri G, Khanna S, Estes L, Pardi D. Outcomes from rectal vancomycin therapy in patients with *Clostridium difficile* infection. *Am J Gastroenterol* 2014; **109**: 924–5.

76 Tannock GW, Munro K, Taylor C, Lawley B, Young W, Byrne B *et al.* A new macrocyclic antibiotic, fidaxomicin (OPT-80), causes less alteration to the bowel microbiota of *Clostridium difficile*-infected patients than does vancomycin. *Microbiology* 2010; **156**: 3354–9.

77 Babakhani F, Bouillaut L, Gomez A, Sears P, Nguyen L, Sonenshein AL. Fidaxomicin inhibits spore production in *Clostridium difficile*. *Clin Infect Dis* 2012; **55**: S162–9.

78 Louie TJ, Cannon K, Byrne B, Emery J, Ward L, Eyben M *et al.* Fidaxomicin preserves the intestinal microbiome during and after treatment of *Clostridium difficile* infection (CDI) and reduces both toxin reexpression and recurrence of CDI. *Clin Infect Dis* 2012; **55**: S132–42.

79 Mullane K. Fidaxomicin in *Clostridium difficile* infection: latest evidence and clinical guidance. *Ther Adv Chronic Dis* 2014; **5**: 69–84.

80 Mullane KM, Miller MA, Weiss K, Lentnek A, Golan Y, Sears PS *et al.* Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. *Clin Infect Dis* 2011; **53**: 440–7.

81 Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y *et al.* Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; **364**: 422–31.

82 Cornely OA, Nathwani D, Ivanescu C, Odufowora-Sita O, Retsa P, Odeyemi IA. Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in *Clostridium difficile* infections: a meta-analysis and indirect treatment comparison. *J Antimicrob Chemother* 2014; **69**: 2892–900.

83 Smeltzer S, Hassoun A. Successful use of fidaxomicin in recurrent *Clostridium difficile* infection in a child. *J Antimicrob Chemother* 2013; **68**: 1688–9.

84 Sears P. *Safety and Pharmacokinetic Study of Fidaxomicin in children with* Clostridium difficile-*associated diarrhoea, in ID week*. Philadelphia, PA; 2014.

85 ClinicalTrials.gov. A study to investigate the safety and efficacy of fidaxomicin (oral suspension or tablets) and vancomycin (oral liquid or capsules) in pediatric subjects with *Clostridium difficile* associated diarrhoea (CDAD) [cited 2015 August 3]. Available from URL: https://clinicaltrials.gov/ct2/show/NCT

86 van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM *et al.* Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; **368**: 407–15.

87 Johnson S, Schriever C, Galang M, Kelly CP, Gerding DN. Interruption of recurrent *Clostridium difficile*-associated diarrhoea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis* 2007; **44**: 846–8.

88 Curry SR, Marsh JW, Shutt KA, Muto CA, O'Leary MM, Saul MI *et al.* High frequency of rifampin resistance identified in an epidemic *Clostridium difficile* clone from a large teaching hospital. *Clin Infect Dis* 2009; **48**: 425–9.

89 Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN *et al.* Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *N Engl J Med* 2010; **362**: 197–205.

90 Johnson S, Louie TJ, Gerding DN, Cornely OA, Chasan-Taber S, Fitts D *et al.* Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis* 2014; **59**: 345–54.

91 Vardakas KZ, Polyzos KA, Patouni K, Rafailidis PI, Samonis G, Falagas ME. Treatment failure and recurrence of *Clostridium difficile* infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *Int J Antimicrob Agents* 2012; **40**: 1–8.

92 McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle:

treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol* 2002; **97**: 1769–75.
93 Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM *et al.* Decreased diversity of the fecal microbiome in recurrent *Clostridium difficile*-associated diarrhoea. *J Infect Dis* 2008; **197**: 435–8.
94 Cammarota G, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G *et al.* Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2015; **41**: 835–43.
95 Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2011; **53**: 994–1002.
96 Guo B, Harstall C, Louie T, Veldhuyzen van Zanten S, Dieleman LA. Systematic review: faecal transplantation for the treatment of *Clostridium difficile*-associated disease. *Aliment Pharmacol Ther* 2012; **35**: 865–75.
97 Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. *Am J Gastroenterol* 2013; **108**: 500–8.
98 Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection: a systematic review. *J Clin Gastroenterol* 2014; **48**: 693–702.
99 Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA* 2014; **312**: 1772–8.
100 Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB *et al.* Fecal microbiota transplant for relapsing *Clostridium difficile* infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. *Clin Infect Dis* 2014; **58**: 1515–22.
101 Costello SP, Conlon MA, Vuaran MS, Roberts-Thomson IC, Andrews JM. Faecal microbiota transplant for recurrent *Clostridium difficile* infection using long-term frozen stool is effective: clinical efficacy and bacterial viability data. *Aliment Pharmacol Ther* 2015; **42**: 1011–8.
102 Costello SP, Tucker EC, La Brooy J, Schoeman MN, Andrews JM. Establishing a fecal microbiota transplant service for the treatment of *Clostridium difficile* infection. *Clin Infect Dis* 2015. doi:10.1093/cid/civ994
103 Baxter M, Ahmad T, Colville A, Sheridan R. Fatal aspiration pneumonia as a complication of fecal microbiota transplant. *Clin Infect Dis* 2015; **61**: 136–7.
104 Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. *Open Forum Infect Dis* 2015; **2**: ofv004.
105 Trubiano JA, George A, Barnett J, Siwan M, Heriot A, Prince HM *et al.* A different kind of 'allogeneic transplant': successful fecal microbiota transplant for recurrent and refractory *Clostridium difficile* infection in a patient with relapsed aggressive B-cell lymphoma. *Leuk Lymphoma* 2015; **56**: 512–4.
106 Trubiano JA, Gardiner B, Kwong JC, Ward P, Testro AG, Charles PG. Faecal microbiota transplantation for severe *Clostridium difficile* infection in the intensive care unit. *Eur J Gastroenterol Hepatol* 2013; **25**: 255–7.
107 Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. *Am J Gastroenterol* 2012; **107**: 761–7.
108 Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL *et al.* Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 2013; **341**: 1241214.
109 Satokari R, Mattila E, Kainulainen V, Arkkila PE. Simple faecal preparation and efficacy of frozen inoculum in faecal microbiota transplantation for recurrent *Clostridium difficile* infection – an observational cohort study. *Aliment Pharmacol Ther* 2015; **41**: 46–53.
110 Tauxe WM, Dhere T, Ward A, Racsa LD, Varkey JB, Kraft CS. Fecal microbiota transplant protocol for *clostridium difficile* infection. *Lab Med* 2015; **46**: e19–23.
111 Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A *et al.* Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol* 2014; **109**: 1065–71.
112 Neemann K, Eichele DD, Smith PW, Bociek R, Akhtari M, Freifeld A. Fecal microbiota transplantation for fulminant *Clostridium difficile* infection in an allogeneic stem cell transplant patient. *Transpl Infect Dis* 2012; **14**: E161–5.
113 Hourigan SK, Chen LA, Grigoryan Z, Laroche G, Weidner M, Sears CL *et al.* Microbiome changes associated with sustained eradication of *Clostridium difficile* after single faecal microbiota transplantation in children with and without inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **42**: 741–52.
114 Rossen NG, MacDonald JK, de Vries EM, D'Haens GR, de Vos WM, Zoetendal EW *et al.* Fecal microbiota transplantation as novel therapy in gastroenterology: a systematic review. *World J Gastroenterol* 2015; **21**: 5359–71.
115 Walia R, Kunde S, Mahajan L. Fecal microbiota transplantation in the treatment of refractory *Clostridium difficile* infection in children: an update. *Curr Opin Pediatr* 2014; **26**: 573–8.
116 Walia R, Garg S, Song Y, Girotra M, Cuffari C, Fricke WF *et al.* Efficacy of fecal microbiota transplantation in 2 children with recurrent *Clostridium difficile* infection and its impact on their growth and gut microbiome. *J Pediatr Gastroenterol Nutr* 2014; **59**: 565–70.
117 Pierog A, Mencin A, Reilly NR. Fecal microbiota transplantation in children with recurrent *Clostridium difficile* infection. *Pediatr Infect Dis J* 2014; **33**: 1198–200.
118 Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K *et al.* Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis* 2012; **12**: 281–9.
119 Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of *Clostridium difficile* infection: fidaxomicin versus vancomycin. *Clin Infect Dis* 2012; **55**: S154–61.
120 Cornely OA, Miller MA, Fantin B, Mullane K, Kean Y, Gorbach S. Resolution of *Clostridium difficile*-associated diarrhoea in patients with

cancer treated with fidaxomicin or vancomycin. *J Clin Oncol* 2013; **31**: 2493–9.
121 Crook DW, Walker AS, Kean Y, Weiss K, Cornely OA, Miller MA *et al.* Fidaxomicin versus vancomycin for *Clostridium difficile* infection: meta-analysis of pivotal randomized controlled trials. *Clin Infect Dis* 2012; **55**: S93–103.
122 Johnson S, Gerding DN. Fidaxomicin "chaser" regimen following vancomycin for patients with multiple *Clostridium difficile* recurrences. *Clin Infect Dis* 2013; **56**: 309–10.
123 Nathwani D, Cornely OA, Van Engen AK, Odufowora-Sita O, Retsa P, Odeyemi IA. Cost-effectiveness analysis of fidaxomicin versus vancomycin in *Clostridium difficile* infection. *J Antimicrob Chemother* 2014; **69**: 2901–12.
124 Freeman J, Baines SD, Todhunter SL, Huscroft GS, Wilcox MH. Nitazoxanide is active against *Clostridium difficile* strains with reduced susceptibility to metronidazole. *J Antimicrob Chemother* 2011; **66**: 1407–8.
125 Aslam S, Musher DM. Nitazoxanide: clinical studies of a broad-spectrum anti-infective agent. *Future Microbiol* 2007; **2**: 583–90.
126 Musher DM, Logan N, Bressler AM, Johnson DP, Rossignol JF. Nitazoxanide versus vancomycin in *Clostridium difficile* infection: a randomized, double-blind study. *Clin Infect Dis* 2009; **48**: e41–6.
127 Musher DM, Logan N, Hamill RJ, Dupont HL, Lentnek A, Gupta A *et al.* Nitazoxanide for the treatment of *Clostridium difficile* colitis. *Clin Infect Dis* 2006; **43**: 421–7.
128 Musher DM, Logan N, Mehendiratta V, Melgarejo NA, Garud S, Hamill RJ. *Clostridium difficile* colitis that fails conventional metronidazole therapy: response to nitazoxanide. *J Antimicrob Chemother* 2007; **59**: 705–10.
129 Louie TJ, Peppe J, Watt CK, Johnson D, Mohammed R, Dow G *et al.* Tolevamer, a novel nonantibiotic polymer, compared with vancomycin in the treatment of mild to moderately severe *Clostridium difficile*-associated diarrhoea. *Clin Infect Dis* 2006; **43**: 411–20.
130 Wullt M, Odenholt I. A double-blind randomized controlled trial of fusidic acid and metronidazole for treatment of an initial episode of *Clostridium difficile*-associated diarrhoea. *J Antimicrob Chemother* 2004; **54**: 211–6.
131 Weingarden AR, Hamilton MJ, Sadowsky MJ, Khoruts A. Resolution of severe *Clostridium difficile* infection following sequential fecal microbiota transplantation. *J Clin Gastroenterol* 2013; **47**: 735–7.
132 Nagy GG, Varvolgyi C, Paragh G. Successful treatment of life-threatening, treatment resistant *Clostridium difficile* infection associated pseudomembranous colitis with faecal transplantation. *Orv Hetil* 2012; **153**: 2077–83.
133 Gallegos-Orozco JF, Paskvan-Gawryletz CD, Gurudu SR, Orenstein R. Successful colonoscopic fecal transplant for severe acute *Clostridium difficile* pseudomembranous colitis. *Rev Gastroenterol Mex* 2012; **77**: 40–2.
134 Brandt LJ, Borody TJ, Campbell J. Endoscopic fecal microbiota transplantation: "first-line" treatment for severe *clostridium difficile* infection? *J Clin Gastroenterol* 2011; **45**: 655–7.
135 Rokas KE, Johnson JW, Beardsley JR, Ohl CA, Luther VP, Williamson JC. The addition of intravenous metronidazole to oral vancomycin is associated with improved mortality in critically ill patients with *Clostridium difficile* infection. *Clin Infect Dis* 2015; **61**: 934–41.
136 Apisarnthanarak A, Razavi B, Mundy LM. Adjunctive intracolonic vancomycin for severe *Clostridium difficile* colitis: case series and review of the literature. *Clin Infect Dis* 2002; **35**: 690–6.
137 Metan G, Türe Z, Kaynar L, Berk E, Gürsoy Ş, Alp E *et al.* Tigecycline for the treatment of *Clostridium difficile* infection refractory to metronidazole in haematopoietic stem cell transplant recipients. *J Chemother* 2014; **27**: 354–7.
138 Thomas A, Khan F, Uddin N, Wallace MR. Tigecycline for severe *Clostridium difficile* infection. *Int J Infect Dis* 2014; **26**: 171–2.
139 Cheong EY, Gottlieb T. Intravenous tigecycline in the treatment of severe recurrent *Clostridium difficile* colitis. *Med J Aust* 2011; **194**: 374–5.
140 Larson KC, Belliveau PP, Spooner LM. Tigecycline for the treatment of severe *Clostridium difficile* infection. *Ann Pharmacother* 2011; **45**: 1005–10.
141 Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated *Clostridium difficile* associated disease. *Ann Surg* 2011; **254**: 423–7; discussion 427–9.
142 Brown CJ, Boutros M, Morris A, Divino CM; CAGS/ACS Evidence Based Reviews in Surgery Group. CAGS and ACS evidence based reviews in surgery. Is a diverting loop ileostomy and colonic lavage an alternative to colectomy for the treatment of severe *Clostridium difficile*-associated disease? *Can J Surg* 2014; **57**: 214–6.
143 O'Horo J, Safdar N. The role of immunoglobulin for the treatment of *Clostridium difficile* infection: a systematic review. *Int J Infect Dis* 2009; **13**: 663–7.
144 O'Horo JC, Jindai K, Kunzer B, Safdar N. Treatment of recurrent *Clostridium difficile* infection: a systematic review. *Infection* 2014; **42**: 43–59.
145 Wilcox MH, Gerding D, Poxton I, Kelly C, Nathan R, Cornely O *et al. Bezlotoxumab (BEZ) Alone and With Actoxumab (ACT) for Prevention of Recurrent* C. difficile *Infection (rCDI) in Patients on Standard of Care (SoC) Antibiotics: Integrated Results of 2 Phase 3 Studies (MODIFY I and MODIFY II). in ID Week*. San Diego, CA; 2015.
146 Locher HH, Caspers P, Bruyére T, Schroeder S, Pfaff P, Knezevic A *et al.* Investigations of the mode of action and resistance development of cadazolid, a new antibiotic for treatment of *Clostridium difficile* infections. *Antimicrob Agents Chemother* 2014; **58**: 901–8.
147 Locher HH, Seiler P, Chen X, Schroeder S, Pfaff P, Enderlin M *et al. In vitro* and *in vivo* antibacterial evaluation of cadazolid, a new antibiotic for treatment of *Clostridium difficile* infections. *Antimicrob Agents Chemother* 2014; **58**: 892–900.
148 Baldoni D, Gutierrez M, Timmer W, Dingemanse J. Cadazolid, a novel antibiotic with potent activity against *Clostridium difficile*: safety, tolerability and pharmacokinetics in healthy

subjects following single and multiple oral doses. *J Antimicrob Chemother* 2014; **69**: 706–14.
149 Rashid MU, Dalhoff A, Weintraub A, Nord CE. *In vitro* activity of MCB3681 against *Clostridium difficile* strains. *Anaerobe* 2014; **28**: 216–9.
150 Freeman J, Baines SD, Jabes D, Wilcox MH. Comparison of the efficacy of ramoplanin and vancomycin in both *in vitro* and *in vivo* models of clindamycin-induced *Clostridium difficile* infection. *J Antimicrob Chemother* 2005; **56**: 717–25.
151 Mathur H, O'Connor PM, Hill C, Cotter PD, Ross RP. Analysis of anti-*Clostridium difficile* activity of thuricin CD, vancomycin, metronidazole, ramoplanin, and actagardine, both singly and in paired combinations. *Antimicrob Agents Chemother* 2013; **57**: 2882–6.
152 Rea MC, Dobson A, O'Sullivan O, Crispie F, Fouhy F, Cotter PD *et al.* Effect of broad- and narrow-spectrum antimicrobials on *Clostridium difficile* and microbial diversity in a model of the distal colon. *Proc Natl Acad Sci U S A* 2011; **108**: 4639–44.
153 Rea MC, Sit CS, Clayton E, O'Connor PM, Whittal RM, Zheng J *et al.* Thuricin CD, a posttranslationally modified bacteriocin with a narrow spectrum of activity against *Clostridium difficile*. *Proc Natl Acad Sci U S A* 2010; **107**: 9352–7.
154 Walz DT, DiMartino MJ, Griswold DE, Intoccia AP, Flanagan TL. Biologic actions and pharmacokinetic studies of auranofin. *Am J Med* 1983; **75**: 90–108.
155 Jackson-Rosario S, Cowart D, Myers A, Tarrien R, Levine RL, Scott RA *et al.* Auranofin disrupts selenium metabolism in *Clostridium difficile* by forming a stable Au-Se adduct. *J Biol Inorg Chem* 2009; **14**: 507–19.

BRIEF COMMUNICATIONS

Discontinuation of statins in a population of older New Zealanders with limited life expectancy

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Abstract

Discontinuation of statins may be considered for older individuals with a cancer, multimorbidity, approaching end-of-life and in primary prevention. The aim of this study is to investigate the relationship between the rates of statin discontinuation in the last 12 months of life and a diagnosis of cancer, and in individuals using statins for primary or secondary prevention. A case–control study of matched cases and controls. Matching was based on age, Charlson comorbidity index scores and socioeconomic status. Prescription and diagnostic data for 20 482 individuals who were aged over 75 years, were in their last 12 months of life and were receiving statins during the study period (1 January 2007 to 31 December 2012). After propensity score matching, we identified 4832 cases with a diagnosis of cancer and 4809 matched controls. We used Cox regression to test the relationship between the relative risk of statin discontinuation and a diagnosis of cancer, and in individuals using statins for primary or secondary prevention. Statins were discontinued in 70.4% of older adults with a diagnosis of cancer and 55.8% of those without cancer ($P < 0.05$). The Cox regression analysis supports that a diagnosis of cancer can increase the rate of statin discontinuation compared with individuals without a diagnosis of cancer regardless of whether statins were used for primary or secondary prevention ($P < 0.05$). The findings from this study support that statins are likely to be discontinued in the last year of life in older people with limited life expectancy from cancer, even if statins were indicated for secondary prevention of cardiovascular disease.

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