

CLOSTRIDIoidES DIFFICILE (C. DIFFICILE) INFECTION V2.0

Scope: Guidance on treatment of confirmed or suspected *Clostridioides difficile* (*C. difficile*) infection in adults, stratified based on disease severity, patient and disease characteristics and based on currently available treatment options in Ireland.

These treatment guidelines supersede the treatment recommendations provided in the National Clinical Effectiveness Committee guideline, Surveillance, Diagnosis and Management of *Clostridium difficile* Infection in Ireland, National Clinical Guideline No. 3 (2014).

Target Audience: Healthcare professionals in community and hospital settings involved in the care of patients diagnosed with *C. difficile* infection (CDI).

Guideline exclusions:

- Management of paediatric and pregnant patients with CDI are not included in this guideline.
- Treatment of multiple recurrent CDI and refractory CDI are beyond the scope of this guideline. Specialist advice should be sought in these instances.
- The role and use of probiotics, faecal microbiota transplantation, and surgical management of *C. difficile* are beyond the scope of this guideline.
- The use of rifaximin, tigecycline, fidaxomicin extended-pulsed regimen and vancomycin tapering and pulse regimen are not discussed in this guideline. Due to paucity of evidence associated with these therapies, recommendations cannot be made for or against the use of these agents. Use of these agents require multidisciplinary discussions and tailoring of therapy for individual patients.
- Bezlotoxumab is not included in the guidance as it is not currently approved for reimbursement by the HSE.

Comments from the Expert Advisory Group

- Clinicians should use this guidance alongside their own professional clinical judgment when assessing and managing patients with CDI.
- *C. difficile* is a spore-forming anaerobic bacterium. *C. difficile* infection (CDI) occurs when the bacterium produces toxins that causes diarrhoea and inflammation in the colon.
- The spectrum of *C. difficile* infection ranges from mild diarrhoea to potentially fatal colitis. Antibiotic use predisposes to CDI by disturbing the normal colonic microbiota permitting growth of *C. difficile*.
- When to suspect CDI?
Diarrhoea (defined as 3 or more loose stools in 24 hours) in the presence of risk factors.
Contact with the healthcare environment, advanced age (65 years or older), and antibiotic use are the biggest risk factors for developing an active infection.
- Patients/residents of a healthcare facility with potentially infectious diarrhoea (i.e. no clear alternative cause) should be isolated with Standard and Contact Precautions as soon as possible. (see Table 1 Adapted SIGHT Mnemonic)
- For those living at home, isolation is generally not appropriate. Patients should be advised to use a different bathroom in the household from others if possible, and to clean the bathroom/toilet every day with a household cleaner or disinfectant. Hand hygiene should be emphasised.

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- If you suspect CDI: Send faeces to the microbiology laboratory for *C. difficile* testing.
- Most laboratories use a 2-step testing algorithm for CDI (e.g. PCR testing followed by EIA for toxin)
 - For patients with a positive PCR result (organism present) but toxin negative (production of toxin by organism not detected), this suggests colonisation and therefore an alternative reason for diarrhoea should be sought.
 - Symptomatic patients should be treated if the probability of CDI is sufficiently high (e.g. recent antibiotic exposure, absence of alternative causes of diarrhoea).
 - *C. difficile* colonisation, defined as detection of the organism in the absence of symptoms, is common, occurring in 4%–15% of healthy adults, up to 21% of hospitalised adults, and 15%–30% of residents in long-term care facilities
- Refer patient with suspected or confirmed CDI to hospital if:
 - Severely unwell
 - Symptoms or signs worsen rapidly or significantly at any time
 - Patient is considered high risk of severe infection (i.e. age over 65 years and presence of multiple comorbidities)
- If a patient experiences a recurrence of diarrhoea after treatment response and a symptom-free period, care should be taken to exclude other potential causes of diarrhoea.
- Diarrhoea may take 1 to 2 weeks to resolve after treatment.
- Risk factors for recurrence.

A high risk of recurrence can be supported by a patient age over 65 years of age, plus the presence of one or more of the following additional risk factors:

 - Healthcare associated CDI
 - Prior hospitalisation in the last 3 months
 - Use of concomitant non-CDI antibiotic after the diagnosis of CDI
 - PPI started during/after CDI diagnosis
 - Prior CDI episode

Table 1: Adapted SIGHT Mnemonic protocol

S	Suspect that a case may be infective where there is no clear alternative cause for diarrhoea.
I	Isolate patients/residents of a healthcare facility with potentially infectious diarrhoea (i.e. no clear alternative cause) should be isolated with Standard and Contact Precautions as soon as possible. Consult with the infection prevention and control team where available while determining the cause of the diarrhoea.
G	Gloves and aprons must be used for all contacts with the patient/resident and their environment.
H	Hand Hygiene. Alcohol-based hand hygiene products are adequate if gloves are used and hands are visibly clean but otherwise hand washing with soap and water is required.
T	Test the stool for <i>Clostridioides difficile</i> toxin, by sending a specimen immediately.

Adapted from SIGHT Mnemonic UK protocol <https://www.gov.uk/government/collections/clostridium-difficile-guidance-data-and-analysis>

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Definitions

- An **episode of CDI** is defined as clinical findings compatible with CDI and microbiological evidence of *C. difficile* free toxins by enzyme immunoassay without reasonable evidence of another cause of diarrhoea **OR** a clinical picture compatible with CDI and a positive nucleic acid amplification test (NAAT) preferably with a low cycle threshold (Ct) value, or positive toxigenic *C. difficile* culture **OR** pseudomembranous colitis as diagnosed during endoscopy, after colectomy or on autopsy, in combination with a positive test for the presence of toxigenic *C. difficile*.
- **Diarrhoea** is defined as 3 or more loose stools, i.e. Bristol stool scale 6-7, in 24 hours.
- **Treatment response** is present when the patient has resolution of diarrhoea, and has had a formed or normal stool for that patient, with maintenance of resolution for the duration of therapy and at least 48 hours after the end of treatment, and no further requirement for CDI therapy, **AND** parameters of disease severity (clinical, laboratory, radiological) have improved and no new signs of severe disease have developed. In all other cases, treatment is considered a failure.
- **Refractory CDI** is CDI not responding to recommended CDI antibiotic treatment, i.e. no response after 3-5 days of therapy. Refractory CDI can be part of either non-complicated or complicated CDI, which are described below.
- **Recurrence** is present when CDI recurs within 8 weeks after a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment. It is not feasible to distinguish recurrence due to **relapse** (renewed symptoms from already present CDI) from recurrence due to reinfection in daily practice because genotyping is not readily available.
- **Sustained cure** is defined as treatment response without recurrence of CDI during follow-up
- **Severe CDI** is characterized by one of the following factors at presentation: fever, i.e. core body temperature greater than 38.5°C, marked leucocytosis, i.e. leucocyte count greater than $15 \times 10^9/L$, and rise in serum creatinine, i.e. more than 50% above the baseline. Additional supporting factors, when available are distension of the large intestine, pericolonic fat stranding or colonic wall thickening (including low-attenuation mural thickening) at imaging.
- **Severe-complicated CDI (or fulminant CD)** is defined by the presence of one of the following factors that needs to be attributed to CDI: hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or any fulminant course of disease (i.e. rapid deterioration of the patient).

Treatment

Overarching treatment principles

The following guidance applies to the treatment of patients with a clinical diagnosis of CDI and supportive microbiological evidence of CDI.

General measures advised in the treatment of patients with CDI:

- Patients/ residents of a healthcare facility with potentially infectious diarrhoea (i.e. no clear alternative cause) should be isolated with Standard and Contact Precautions as soon as possible
- Stop unnecessary antimicrobial therapy (if possible)
- Ensure adequate nutrition and replacement of fluid and electrolytes
- Avoid anti-motility medications
- Review proton pump inhibitor use

If an antibiotic is still essential, consider changing to one with a lower risk of causing CDI. It is preferable to use agents with as narrow spectrum as possible. Almost all antibiotics increase the risk of CDI but clindamycin, cephalosporins, ciprofloxacin (and other fluoroquinolones) and co-amoxiclav are well-documented as having the greatest risk.

HSE Antimicrobial Resistance and Infection Control Programme

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Treatment in community settings

TREATMENT OF C. DIFFICILE INFECTION IN COMMUNITY SETTINGS			
Drug	Dose	Duration	Notes
Non-severe CDI			
<ul style="list-style-type: none"> Mildly symptomatic patients (positive test result but less than 3 episodes of diarrhoea in 24 hours): <p>It is recommended to discontinue antibiotic therapy with the inciting antibiotic if possible and closely monitor the patient for 48 hours. <i>C. difficile</i> treatment should be initiated if any signs of clinical deterioration are observed.</p> <ul style="list-style-type: none"> Positive test result and 3 or more episodes of diarrhoea in 24 hours, follow treatment options below: 			
1st line option:			
Metronidazole oral	400 mg every 8 hours	10 days	
2nd line option:			
Vancomycin oral ¹	125 mg every 6 hours	10 days	
Severe CDI			
<ul style="list-style-type: none"> Refer to hospital 			
First recurrence of CDI			
<ul style="list-style-type: none"> If non-severe CDI: see treatment recommendation below If severe CDI: refer to hospital 			
1st line options:			
Vancomycin oral ¹	125 mg every 6 hours	10 days	Only use if metronidazole was used for treatment of the first episode
or			
Fidaxomicin oral	200 mg every 12 hours	10 days	Discuss with a clinical microbiologist or infectious diseases consultant. High Tech item, see prescribing notes* If initial CDI episode was treated with fidaxomicin, seek micro/ID advice.

¹ Vancomycin: If a person has swallowing difficulties or a nasogastric or PEG tube for enteral administration, vials of vancomycin powder for injection may be used to make an extemporaneous oral solution. [Vancomycin \(oral\) adult](#) – includes information for dispensing pharmacists on how to make extemporaneous oral solution.

*Fidaxomicin prescribing: Fidaxomicin should only be initiated on the recommendation of a Consultant Microbiologist or Infectious Diseases Physician. Fidaxomicin is only available from community pharmacies through the High Tech Arrangements. A GP may prescribe fidaxomicin, but must state the name and base hospital of the consulting Consultant Microbiologist or Infectious Diseases Physician on the prescription in order for the community pharmacy to process through the High Tech Arrangements. For hospital patients, follow the normal procedure for prescriptions of High Tech drugs. For more information, see [fidaxomicin adult safety sheet](#).

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Treatment in hospital setting

TREATMENT OF C.DIFFICILE INFECTION IN HOSPITAL SETTING (Page 1 of 2)			
Drug	Dose	Duration	Notes
Non-severe CDI :Mildly symptomatic patients (positive test result but less than 3 episodes of diarrhoea in 24 hrs)			
It is recommended to discontinue antibiotic therapy with the inciting antibiotic if possible and closely monitor the patient for 48 hours. <i>C. difficile</i> treatment should be initiated if any signs of clinical deterioration are observed.			
<ul style="list-style-type: none"> Positive test results and 3 or more episodes of diarrhoea in 24 hours, follow treatment options below: 			
1st line options:			
Metronidazole oral <i>or</i>	400 mg every 8 hours	10 days	
Vancomycin oral ¹	125 mg every 6 hours	10 days	
Treatment option for patient at high risk of recurrence supported by age over 65 years <u>plus</u> the presence of one or more of these additional risk factors (healthcare associated CDI, prior hospitalisation in the last 3 months, use of concomitant antibiotics, PPI started during/after CDI diagnosis or prior CDI episode)			
Fidaxomicin oral	200 mg every 12 hours	10 days	Discuss with a clinical microbiologist or infectious diseases consultant. High Tech item, see prescribing notes*
Severe CDI			
<ul style="list-style-type: none"> Early surgical opinion Patients with severe CDI should be managed by a multidisciplinary team to include a clinical microbiologist and/or infectious diseases physician, gastroenterologist, surgeon and pharmacist as needed 			
1st line options:			
Vancomycin oral ¹ <i>or</i>	125 mg every 6 hours	10 days	
Fidaxomicin oral	200 mg every 12 hours	10 days	Discuss with a clinical microbiologist or infectious diseases consultant. High Tech item, see prescribing notes*
Severe complicated/fulminant CDI			
<ul style="list-style-type: none"> Early surgical opinion Patients with severe CDI should be managed by a multidisciplinary team to include a clinical microbiologist and/or infectious diseases physician, gastroenterologist, surgeon and pharmacist as needed 			
1st line option:			
Vancomycin oral ¹ <i>plus</i> metronidazole intravenous	500mg every 6 hours 500mg every 8 hours	10 days	
2nd line option: Other therapeutic options may be considered on a case-by-case basis and after multidisciplinary discussions. This is beyond the scope of this guidance.			
See next page for treatment of first recurrence of <i>C. difficile</i> infection			

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TREATMENT OF C.DIFFICILE INFECTION IN HOSPITAL SETTING (Page 2 of 2)

First recurrence of CDI

1st line options:			
Vancomycin oral ¹ or	125mg every 6 hours	10 days	Only use if metronidazole was used for treatment of the first episode
Fidaxomicin oral	200mg every 12 hours	10 days	Discuss with a clinical microbiologist or infectious diseases consultant. High Tech item, see prescribing notes* If initial CDI episode was treated with fidaxomicin, seek micro/ID advice.

¹ Vancomycin: If a person has swallowing difficulties or a nasogastric or PEG tube for enteral administration, vials of vancomycin powder for injection may be used to make an extemporaneous oral solution. [Vancomycin \(oral\) adult](#) – includes information for dispensing pharmacists on how to make extemporaneous oral solution.

*Fidaxomicin prescribing: Fidaxomicin should only be initiated on the recommendation of a Consultant Microbiologist or Infectious Diseases Physician. Fidaxomicin is only available from community pharmacies through the High Tech Arrangements. A GP may prescribe fidaxomicin, but must state the name and base hospital of the consulting Consultant Microbiologist or Infectious Diseases Physician on the prescription in order for the community pharmacy to process through the High Tech Arrangements. For hospital patients, follow the normal procedure for prescriptions of High Tech drugs. For more information, see [fidaxomicin adult safety sheet](#).

Resources for healthcare professionals

Antimicrobial safety summaries for community based healthcare professionals:

- [Vancomycin \(oral\) adult](#) – includes information for dispensing pharmacists on how to make extemporaneous oral solution
- [Fidaxomicin adult safety sheet](#)

[HSELAND course](#): Clostridioides difficile infection: IPC and AMS Principles, Prevention and Management – This course is designed for all healthcare workers in all settings where healthcare is delivered. The course covers how to prevent, recognise and manage *C. difficile* infection as you implement IPC and AMS best practices in your setting,

Patient Information

[RESIST C difficile patient information leaflet](#)

[HSE A to Z C. diff](#)

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