

SAFER MEDICATION USE

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Drug-induced *Clostridium difficile* infection

Clostridium difficile is often present in the lower gastrointestinal tract, but can proliferate, produce cytotoxins and cause profuse watery diarrhoea. Several risk factors have been identified for *C.difficile* infection. These include age over 65 years, exposure to certain antibiotics - particularly long courses and possibly the use of acid-suppressing medications such as proton pump inhibitors. Prudent use of antibiotics is an essential component of controlling *C.difficile* infection. An effective antimicrobial control programme should include avoiding broad spectrum antibiotics, only prescribing antibiotics when necessary, and then for as short a duration as practicable.

What is *Clostridium difficile*?

C.difficile is an anaerobic gram positive bacterium,¹ estimated to be present in the lower gastrointestinal tract of between 3% asymptomatic healthy adults and 20% hospitalised or elderly patients in long-term care.^{2,3} In the normal healthy state *C.difficile* proliferation is kept to a minimum by the immune system and the presence of other gastrointestinal bacteria.^{3,4} In patients with risk factors, *C.difficile* can proliferate and cause *C.difficile* infection (CDI), the principal symptom of which is profuse watery diarrhoea, sometimes progressing to pseudomembranous colitis.^{1,3,4} A formal diagnosis of CDI is made following the demonstration of toxins A and / or B in the stool samples.¹

C.difficile is more commonly a hospital-acquired infection, although there are increasing reports of community-acquired CDI, the exact incidence of which is not clear, but appears to be under-diagnosed.^{5,6} A Swedish study reported 28% of all CDI cases to be community-acquired, whereas data from one UK acute hospital trust quoted 10% of cases.⁶ Recently published national guidelines recommend that all cases of diarrhoea among people in the community aged two years and above should be investigated for CDI unless there are good clinical or epidemiological reasons not to.⁶ Drug related causes of diarrhoea are discussed in a later section. There are ongoing national and local initiatives to reduce the incidence of CDI.

Which patients are at a higher risk of developing *C.difficile*?

Several risk factors have been identified for CDI. Patients over the age of 65 years are particularly at risk and the occurrence of CDI in this age group is increasing.^{1,2} Patients who are suffering from severe underlying diseases, e.g. cancer, and those who are immunocompromised, are also particularly susceptible.^{1,2,4,7} Other factors that may increase the risk of CDI include close contact with other patients e.g. in care homes, recent gastrointestinal procedures and the presence of nasogastric tubes.^{2,4,7} Antibiotic use is the most

significant and frequently reported predisposing risk factor for CDI in hospital and community settings.^{1,5} This and other drug related causes, including acid suppressant medication are discussed in later sections.

For community-acquired CDI, hospitalisation in the preceding six months is significantly associated with detection of *C.difficile*, as reported in a recent prospective case control study which found prior hospitalisation in 45% cases versus 23% controls (p=0.022).⁵ A significant association with exposure to antibiotics in the four weeks before symptom onset was demonstrated compared with controls (52% vs 18%, p=0.001). Aminopenicillins (p=0.02) and oral cephalosporins (p=0.045) were the most commonly implicated antibiotics, along with multiple antimicrobials (p=0.0006). However, approximately one-third of CDI cases had not received antibiotic therapy in the month before the *C.difficile* detection, nor been admitted to hospital.⁵

Table 1: Relative risk of antibiotics and their association with CDI¹

High risk antibiotics for CDI
Second-generation cephalosporins e.g. cefaclor, cefuroxime
Third-generation cephalosporins e.g. cefixime, cefotaxime, ceftazidime, ceftriaxone
Clindamycin
Quinolones e.g. ciprofloxacin, levofloxacin, ofloxacin, norfloxacin
Intermediate risk antibiotics for CDI
Macrolides e.g. erythromycin, clarithromycin
Aminopenicillins* e.g. co-amoxiclav, amoxicillin, ampicillin
* risk increases with prolonged courses ^{6,7}
Low risk antibiotics for CDI
Trimethoprim
Tetracyclines e.g. tetracycline, oxytetracycline, doxycycline, minocycline
Benzylpenicillin / Phenoxymethylpenicillin
Aminoglycosides e.g. gentamicin
Vancomycin
Piperacillin with tazobactam

Which antimicrobials are implicated?

Nearly all antibiotics may predispose towards *C.difficile*, but some appear to have a much higher propensity to cause CDI than others (see table 1).^{1,2,6} Use of broad spectrum antibiotics has been strongly associated with CDI, especially third-generation cephalosporins given to the elderly, clindamycin and prolonged courses of amniopenicillins.⁶

There is a lack of easily comparable data on rates of CDI between different antibiotics.⁶ A meta-analysis of 49 published studies ranked antibiotics in relation to the risk of CDI.⁷ There was an overall statistically significant correlation between antimicrobial use and CDI (pooled OR 5.9 [95% CI 4.0 to 8.5]).⁷ The odds ratios were, highest for broad spectrum cephalosporins; 36.2 [95% CI 19 to 68.9] for cefotaxime and 28.8 [95% CI 12.7 to 65.1] for ceftazidime; followed by amoxicillin / beta-lactamase inhibitor 22.1 [95% CI 6.5 to 75.4] and lowest for tetracyclines 1.3 [95% CI 0.1 to 19.6], although confidence intervals are wide and overlapping.⁷

The risks related to specific antimicrobials can change over time; quinolones which had previously not been associated with CDI have been strongly implicated in recent outbreaks caused by the hypervirulent 027 strain.^{1,6} Other factors associated with an increased risk of CDI are long duration of treatment and the use of multiple courses and combinations of antimicrobials.⁷ There is evidence to suggest that restricting the use of broad spectrum antibiotics, specifically cephalosporins and clindamycin can reduce *C.difficile*.⁶ Other measures which can help to reduce the incidence of CDI are discussed in the *Practice Point*. If you suspect that CDI is related to antimicrobial use this should be reported via the Yellow Card scheme. www.yellowcard.gov.uk

Are acid suppressant medicines a risk factor?

There is conflicting evidence suggesting that proton pump inhibitors (PPI) and possibly H₂-receptor antagonists increase risk of CDI.^{5,8-11} The available evidence has limitations and

as yet a causal link has not been established. It has been postulated that the survival of *C.difficile* through the stomach and into the lower intestines is increased as a result of reduced acidity of the gastric environment.¹² National guidelines for the prevention and management of CDI advise that PPIs should be used only when there is a clear indication.⁶

Are any other drugs implicated in CDI?

Other drugs which have been suggested to be associated with the development of CDI, mainly via case reports, include anti-fungal agents, antiviral agents, antineoplastic agents, non-steroidal anti-inflammatory drugs (NSAIDs) and gold salts.² The reason why these drugs may induce CDI is not fully understood.² A review of 59 patients on an oncology unit who developed diarrhoea found chemotherapy to be a risk factor for CDI and antibiotic consumption significantly increased this risk. There was no difference reported in the type or dose of chemotherapy received, although the numbers analysed were small.¹³

Which drugs cause diarrhoea?

Diarrhoea is a common adverse reaction which has been reported with most drugs (see table 2).⁶ Antimicrobials account for 25% of drug induced diarrhoea, although most cases are benign.⁶ Alternative diagnoses for diarrhoea are important, therefore the timing of when the medicine was first taken and when diarrhoea first appears is important.⁶

Table 2: Drugs commonly causing diarrhoea⁶

Acarbose	Laxatives
Antimicrobials	Leflunamide
Biguanides	Magnesium preparations (e.g.antacids)
Bile salts	Metoclopramide
Colchicine	Misoprostol
Cytotoxics	NSAIDs (e.g. aspirin, ibuprofen)
Dipyridamole	Olisalazine
Gold preparations	Orlistat
Iron salts	Proton pump inhibitors

Practice Point - Components of an effective antimicrobial control programme include^{1,6}

- Only prescribe antibiotics when necessary, e.g. avoidance of use for sore throat, coughs and colds etc.
- Prescribe short durations of antibiotics including single-dose prophylaxis.
- Avoid broad spectrum antibiotics. Use narrow spectrum agents when clinically appropriate and according to sensitivity testing.
- Consult local guidance.

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G-guideline, R-review, SR - systematic review

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