Clostridioides difficile infection: antimicrobial prescribing

NICE guideline

Draft for consultation, January 2021

This guideline sets out an antimicrobial prescribing strategy for *Clostridioides difficile* infection. It aims to optimise antibiotic use and reduce antibiotic resistance.

The recommendations in this guideline are for managing *C. difficile* infection in adults, young people and children aged 72 hours and over in both community and hospital settings. It does not cover diagnosis.

The recommendations do not cover children in the first 72 hours of life. Seek specialist advice for this population.

We have also produced associated NICE guidelines on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use, antimicrobial stewardship: changing risk-related behaviours in the general population, healthcare-associated infections: prevention and control in primary and community care and healthcare-associated infections: prevention and control.

See a 2-page visual summary of the recommendations, including tables to support prescribing decisions.

Who is it for?

- Healthcare professionals
- People with *C. difficile* infection, their families and carers

The guideline contains:

- the draft recommendations
- the rationales

- summary of the evidence.

Information about how the guideline was developed is on the guideline's page on the NICE website. This includes the full evidence review, details of the committee and any declarations of interest.

Recommendations

1.1 Managing suspected or confirmed *Clostridioides difficile* infection

Assessment

1.1.1 For people with suspected or confirmed *C. difficile* infection, follow Public Health England's guidance on diagnosis and reporting, and on how to deal with the problem.

1.1.2 For people with suspected or confirmed *C. difficile* infection, assess:

- whether it is a first or recurrent episode of *C. difficile* infection
- the severity of infection
- individual factors such as age, frailty or comorbidities, which may affect the risk of complications or recurrence.

1.1.3 For people with suspected or confirmed *C. difficile* infection, review the need to continue any treatment with:

- antibiotics
- proton pump inhibitors.

For a short explanation of why the committee made these recommendations, see the rationale section on assessment.

For more details, see the evidence review.

Treating suspected or confirmed *C. difficile* infection

1.1.4 For children and young people with suspected or confirmed *C. difficile* infection, seek specialist advice.

1.1.5 For adults, offer an oral antibiotic to treat suspected or confirmed *C. difficile* infection (see the recommendations on choice of antibiotic).

1.1.6 If the person cannot take oral medicines, seek specialist advice about alternative enteral routes for administering antibiotics, such as a nasogastric tube or rectal catheter.

1.1.7 Do not offer bezlotoxumab to prevent recurrence of *C. difficile* infection because it is not cost effective.

1.1.8 Consider a faecal microbiota transplant alongside antibiotic treatment for recurrent *C. difficile* infection in adults who have had 2 or more previous episodes that have not responded to antibiotics (see NICE's interventional procedure guidance on faecal microbiota transplant for recurrent *C. difficile* infection).

1.1.9 Manage fluid loss and symptoms associated with suspected or confirmed *C. difficile* infection as for acute gastroenteritis. Avoid using antimotility medicines such as loperamide.

For a short explanation of why the committee made these recommendations, see the rationale section on treating suspected or confirmed C. difficile infection.

For more details, see the summary of evidence.

Advice

1.1.10 Advise people with suspected or confirmed *C. difficile* infection about:

- drinking enough fluids to avoid dehydration
- preventing the spread of infection
- seeking medical help if symptoms worsen rapidly or significantly at any time.

For a short explanation of why the committee made these recommendations, see the rationale section on advice.

For more details, see the evidence review.

Reassessment

1.1.11 In people with suspected or confirmed *C. difficile* infection, reassess during antibiotic treatment (for example, between days 3 to 5 after starting antibiotics for *C. difficile* infection).

1.1.12 If antibiotics have been started for suspected *C. difficile* infection, and subsequent stool sample tests do not confirm *C. difficile* infection, consider stopping these antibiotics (see Public Health England's guidance on diagnosis and reporting for recommendations on stool sample tests).

For a short explanation of why the committee made these recommendations, see the rationale section on reassessment.

For more details, see the evidence review.

Referral or seeking specialist advice

1.1.13 Refer people in the community with suspected or confirmed *C. difficile* infection to hospital if symptoms are severe, or worsen rapidly or significantly at any time.

1.1.14 Consider referral or seeking specialist advice for people who may be at high risk of complications or recurrence because of individual factors such as age, frailty or comorbidities.

1.1.15 Refer people in hospital with suspected or confirmed *C. difficile* infection to a microbiologist or infectious diseases specialist if symptoms worsen rapidly or significantly at any time.

For a short explanation of why the committee made these recommendations, see the rationale section on referral or seeking specialist advice.

For more details, see the evidence review.

1.2 Choice of antibiotic

1.2.1 When prescribing antibiotics for suspected or confirmed *C. difficile* infection in adults, follow table 1.

1.2.2 When prescribing antibiotics for suspected or confirmed *C. difficile* infection in children and young people, take account of the licensed indications in this group. Specialists might want to consider basing their choice of antibiotic on what is recommended for *C. difficile* infection in adults.

Table 1 Antibiotics for adults aged 18 years and over

Treatment	Antibiotic, dosage and course length
Antibiotic for life-threatening *Clostridioides difficile* infection	Seek specialist advice
First-line antibiotic for a first episode of mild, moderate or severe *C. difficile* infection	**Vancomycin**: 125 mg orally four times a day (using either powder for solution given orally or capsules) for 10 days

Second-line antibiotic for a first episode of *C. difficile* infection if vancomycin is ineffective	**Fidaxomicin**: 200 mg orally twice a day for 10 days
Antibiotic for *C. difficile* infection not responding to first- or second-line antibiotic	Seek specialist advice
Antibiotic for a further episode of *C. difficile* infection within 12 weeks of symptom resolution (relapse)	**Fidaxomicin**: 200 mg orally twice a day for 10 days
Antibiotic for a further episode of *C. difficile* infection more than 12 weeks after symptom resolution (recurrence)	**Vancomycin**: 125 mg orally four times a day (using either powder for solution given orally or capsules) for 10 days **Fidaxomicin** (for severe infection): 200 mg orally twice a day for 10 days

See the BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

For a short explanation of why the committee made these recommendations, see the rationale section on choice of antibiotic.

For more details, see the summary of the evidence.

1.3 Preventing *C. difficile* infection

1.3.1 Do not offer antibiotics to prevent *C. difficile* infection.

1.3.2 Do not offer prebiotics to prevent *C. difficile* infection in people taking antibiotics.

1.3.3 Do not routinely offer probiotics to prevent *C. difficile* infection in people taking antibiotics.

For a short explanation of why the committee made these recommendations, see the rationale section on preventing *C. difficile* infection.

For more details, see the summary of the evidence.

Terms used in the guideline

C. difficile infection

This is defined as (Public Health England, 2013) diarrhoea and:

- a positive *C. difficile* toxin test **or**
- results of a *C. difficile* toxin test pending **and** clinical suspicion of *C. difficile* infection.

Severity of *C. difficile* infection

This is defined as (Public Health England, 2013):

Mild: not associated with an increased white cell count (WCC). Typically associated with fewer than 3 episodes of loose stools (defined as loose enough to take the shape of the container used to sample them) per day.

Moderate: associated with an increased WCC (but less than $15x10^9$ per litre). Typically associated with 3 to 5 loose stools per day.

Severe: associated with a WCC greater than $15x10^9$ per litre, or an acutely increased serum creatinine concentration (greater than 50% increase above baseline), or a temperature higher than 38.5°C, or evidence of severe colitis (abdominal or radiological signs). The number of stools may be a less reliable indicator of severity.

Life threatening: signs and symptoms include hypotension, partial or complete ileus, or toxic megacolon, or CT evidence of severe disease.

Recommendations for research

The guideline committee has made the following recommendation for research.

Oral teicoplanin compared with oral vancomycin for treating *Clostridioides difficile* infection

What is the clinical effectiveness, cost effectiveness and safety of oral teicoplanin 100 mg to 200 mg twice a day for 7 to 14 days compared with oral vancomycin or oral fidaxomicin for treating *C. difficile* infection in adults?

To find out why the committee made the research recommendation on oral teicoplanin in adults with *C. difficile* infection, see the rationales.

Rationales

The recommendations in this guideline are based on the evidence identified and the experience of the committee.

Assessment

Why the committee made the recommendations

Recommendations 1.1.1 to 1.1.3

The committee discussed and agreed that although diagnostics and reporting, and good infection control and environmental hygiene, were out-of-scope for this guideline, a recommendation should be included on where to find such information. The committee concluded from its experience that people should be directed to Public Health England's updated guidance on the diagnosis and reporting of *C. difficile* and on *C. difficile* infection: how to deal with the problem).

The committee discussed that, in practice, there has been a change in the definition of severity currently in use by Public Health England from 4 categories (mild, moderate, severe and life threatening) to 3 categories (non-severe, severe and life threatening). However, the Public Health England categories still apply because this is current national guidance.

The committee discussed the findings of the economic model, which took into account severity by adjusting for older age, increased risk of recurrence, increased hospitalisation and higher risk of fulminant colitis (see the economic analysis for full details; there was a lack of useful direct evidence for severity that could be used in

the economic model). The economic model found that severity did not cause a substantial change in which antibiotic was the most cost effective. Therefore, the committee agreed that the main reason to assess severity was to identify the appropriate place of care and overall management. The committee agreed that the recommendation should have included an assessment of whether the current infection was a first or subsequent (recurrent) episode. This was because it was a driver in the economic model and determines the antibiotic choice (see also choice of antibiotic).

The committee recognised that *C. difficile* infection most commonly affects people who are taking or have recently taken antibiotics. They discussed that, even though the antibiotics being taken may be associated with the *C. difficile* infection, the person may still need antibiotics for the original infection. They agreed that, in line with good antimicrobial stewardship, prescribers should review the need for antibiotic treatment, and stop antibiotic treatment that is no longer needed or de-escalate antibiotic treatment when a person's condition improves.

The committee discussed and agreed that it is good prescribing practice to review the continuing need for any existing proton pump inhibitor (PPI) treatment in people with suspected or confirmed *C. difficile* infection, in line with NICE's guideline on medicines optimisation. They were aware that, although some associations have been made between PPI use and the risk of *C. difficile* infection or recurrence, there is no definitive evidence of a causal or exacerbator effect. No evidence from systematic reviews or randomised controlled trials (RCTs) was found to support stopping current PPI treatment. The committee discussed that suddenly stopping a PPI during an acute episode of infection may cause additional gastric symptoms. Additionally, some people will need ongoing gastroprotection for a clinical indication. However, they were aware that many people may be taking a PPI without a clear indication, so concluded that the use and need for a PPI should be reviewed.

Return to the recommendations.

Treating suspected or confirmed *C. difficile* infection

Why the committee made the recommendations

Recommendations 1.1.4 to 1.1.9

The committee discussed the lack of evidence on treating *C. difficile* infection in children and young people. They were aware that, in practice, only a very small number of children have *C. difficile* infection. The committee agreed that a positive test for *C. difficile* in young children (2 years and under) test is often because of high carriage rates of the bacteria rather than because of actual infection (which is very uncommon in children). The committee considered that this may lead to overprescribing of antibiotics. They concluded that prescribers should seek specialist advice for managing suspected or confirmed *C. difficile* infection in a child or young person, including for antibiotic choice.

The committee agreed that an oral antibiotic should be given for suspected or confirmed *C. difficile* infection and discussed the most appropriate route of administration. They agreed that the enteral route is best because sufficient concentrations within the intestinal lumen need to be reached. The committee concluded that it is preferable to give antibiotics via the oral route or, if this is not possible, enterally in some other way (such as a nasogastric or enteral feeding tube, or rectally). They advised seeking specialist advice on administration if the oral or another enteral route is not available.

Bezlotoxumab was not recommended as adjunctive therapy to antibiotics to prevent recurrent *C. difficile* infection. The committee discussed the clinical evidence, which showed that bezlotoxumab was more effective than placebo at preventing recurrence. However, they also reviewed the health-economic evidence and agreed that adding bezlotoxumab to either vancomycin or fidaxomicin was not a cost-effective option (with a 0% probability of it being cost effective at £30,000 per quality-adjusted life years [QALY] gained). The committee agreed that this finding was robust, even in people with a higher risk of recurrence, and were confident in making a recommendation for bezlotoxumab not to be used.

The committee noted that faecal microbiota transplantation (FMT; a procedure done in a small number of specialist centres) was not effective as a first-line treatment for *C. difficile* infection compared with vancomycin. They were aware that long-term safety data on, and regulations about the use of, FMT are minimal compared with medicines. They were aware of variation in mortality rates associated with FMT use, and that there is almost no evidence for its use in children. NICE's interventional procedure guidance on FMT for recurrent *C. difficile* infection states that 'current evidence on the efficacy and safety of FMT for recurrent *Clostridium difficile* infection is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. This procedure should only be considered for patients with recurrent *C. difficile* infections that have failed to respond to antibiotics and other treatments'. The committee agreed that, as an adjunct to antibiotic treatment to prevent recurrence of *C. difficile* infection, FMT may be useful in a very small group of adults who have had 2 or more previous episodes of *C. difficile* infection in addition to the current episode. In the economic model, FMT was placed as a third-line treatment (for people with continuing symptoms after first- and second-line antibiotics) that may help prevent serious complications. The committee were aware of ongoing developments around the screening of faecal microbiota donors to identify multidrug resistant organisms.

The committee agreed that, in line with the general management of gastroenteritis (see the NICE Clinical Knowledge Summary on adult gastroenteritis and NICE's guideline on diarrhoea and vomiting caused by gastroenteritis in under 5s), prescribers and other care staff should monitor and manage fluid loss and gastroenteritis symptoms. Antimotility drugs such as loperamide should be avoided because they slow down the action of the gut. This can lead to *C. difficile* toxins being retained for longer, which may make a person more unwell.

For more details, see the summary of evidence on treating initial or recurrent *C. difficile* infection.

Return to the recommendations.

Advice

Why the committee made the recommendations

Recommendation 1.1.10

The committee discussed what advice on self-care people with a *C. difficile* infection would need. They agreed that, from their experience, there were 3 key areas of advice needed, on:

- maintaining fluid intake to avoid dehydration (and on the symptoms or signs of dehydration that the person should be aware of)
- the need to help reduce the spread of *C. difficile* infection, which is contagious (that is, people should follow the advice in the NICE Clinical Knowledge Summary on adult gastroenteritis and in NICE's guideline on diarrhoea and vomiting caused by gastroenteritis in under 5s)
- when to seek medical help.

Return to the recommendations.

Reassessment

Why the committee made the recommendations

Recommendations 1.1.11 to 1.1.12

The committee were aware that *C. difficile* infection should be managed as a diagnosis in its own right. They agreed that the management and progress of suspected or confirmed *C. difficile* infection should be monitored during treatment. This could include assessing the severity of the infection and symptoms, and the need for hydration. The committee concluded that, from their experience, it would be good practice to review midway through the expected course of antibiotic treatment. This is because laboratory diagnosis should be available at this time, which would allow clinicians to consider stopping antibiotics for *C. difficile* infection if this is not confirmed.

Return to the recommendations.

Referral or seeking specialist advice

Why the committee made the recommendations

Recommendations 1.1.13 to 1.1.15

The committee discussed that people who develop *C. difficile* infection while in hospital are unlikely to be having care from a microbiologist or infectious diseases specialist at diagnosis. The committee agreed that referral to these specialisms may be necessary if symptoms worsen rapidly or significantly at any time. Additionally, people with suspected or confirmed *C. difficile* infection in the community should be referred to hospital if their symptoms are severe or worsen rapidly or significantly at any time. The committee recognised that there are some individual factors (such as age, frailty and comorbidities) for which it may be appropriate to consider referral or seeking specialist advice. This was because they are associated with a higher risk of complications or recurrence.

Return to the recommendations.

Choice of antibiotic

Recommendation 1.2.1 to 1.2.2

Why the committee made the recommendations

The committee discussed the evidence for the effectiveness and cost effectiveness of the different antibiotic options for treating *C. difficile* infection. They were aware that antibiotic resistance is not a major concern when treating *C. difficile* infection.

Vancomycin and fidaxomicin for first episode of *C. difficile* infection

Oral vancomycin was recommended by the committee as the first-line antibiotic for a first episode of *C. difficile* infection of any severity. Fidaxomicin was recommended as the second-line antibiotic for a first episode of *C. difficile* infection of any severity when treatment with vancomycin is not effective (treatment failure). The committee noted that, while fidaxomicin was more clinically effective than vancomycin in the network meta-analysis, the cost of fidaxomicin is substantially higher.

The committee agreed that, when teicoplanin and second-line metronidazole were excluded from the health-economic model, the remaining results clearly showed that vancomycin was the most cost-effective first-line antibiotic across a range of scenarios. This was the case when results from people at both higher and lower risks of recurrence were included (in particular, it was more cost effective as a first-line option than either metronidazole or fidaxomicin). They also agreed that fidaxomicin was the appropriate second-line option. In the base-case analysis, there was only an 2% probability of first-line fidaxomicin being cost effective compared with first-line vancomycin (at £30,000 per QALY gained).

The committee discussed that, from its experience, some hospital trusts use fidaxomicin for first-line treatment of *C. difficile* infection in people who are older or frailer as a strategy to reduce recurrence and readmission. The aim is to offset the cost of using fidaxomicin by reducing future costs. The committee were made aware of a real-world evaluation of fidaxomicin (data not included in the economic model) in which its use first line had a greater effect on reducing mortality than its use second line after treatment with vancomycin. However, they heard that the economic model considered a range of benefits and harms (including deaths), as well as the costs of each strategy. Even then, vancomycin (not fidaxomicin) was still the most cost-effective first-line option in people at higher risk of recurrence. The committee concluded that a recommendation to use fidaxomicin first line would incur unreasonably large opportunity costs that are not appropriate in the wider context of overall healthcare resource allocation. There are possible rare exceptions when vancomycin may not be acceptable, such as for people with an infection that is vancomycin resistant.

The committee discussed that, when given orally, vancomycin is not well absorbed from the gut into the circulation (unless the gut is damaged). So, the likelihood of side effects (such as ototoxicity) is lower with oral than with intravenous administration, although there is still a need to monitor in some people (see medicines safety).

In pregnancy, vancomycin is only advised by the manufacturer if the potential benefit outweighs the risk. For fidaxomicin, the manufacturer advises it is preferable to avoid use during pregnancy as a precaution.

The committee agreed that specialist advice should be sought about the choice of antibiotics for people with a life-threatening infection. However, they recognised that antibiotic choices for a first episode were likely to be the same as for less severe infections.

Vancomycin and fidaxomicin for a further episode of *C. difficile* infection

Fidaxomicin was recommended by the committee for people with a further episode of *C. difficile* infection of any severity occurring within 12 weeks of symptom resolution. They defined this as a relapse. Vancomycin was recommended by the committee for most people with a further episode of *C. difficile* infection occurring more than 12 weeks after symptom resolution. They defined this as recurrence. However, the committee recommended fidaxomicin for severe recurrent infections.

The committee noted there was no clinical evidence comparing vancomycin with fidaxomicin in a population having a further episode of *C. difficile* infection after initial cure. Their decisions were therefore heavily influenced by the threshold analyses around risks of future recurrence. This was because they agreed that 1 key difference with a further episode of infection is the higher risk of subsequent additional recurrences. The committee noted that the risk of future recurrence needed to be around 30% to 40% for fidaxomicin to be cost effective as a first-line option compared with vancomycin (at £30,000 per QALY gained). While they did not believe that this would be the case for all people with a recurrent infection, they did agree that there would be people with a risk of recurrence that high. They therefore agreed that it was appropriate for both vancomycin and fidaxomicin to be first-line options for further episodes, with the choice coming down to the severity of the infection and the associated risk of additional recurrences.

The committee were aware that there is poor agreement on the definition of relapse or recurrence in *C. difficile* infection, both nationally and internationally. They discussed different time periods and agreed, based on expert opinion, that 30 days was too short a time period to define recurrence. They thought that further symptoms within this time period after initial symptom resolution were more likely to represent relapse. The committee heard that, in practice, further symptoms within 12 to 24 months may be considered a recurrence. However, evidence that the committee

were aware of suggested that recurrence generally relates to a further episode within 20 weeks. Defining relapse or recurrence is outside of the remit of the committee, and evidence on this issue was not searched for. So, the committee agreed that it could not be certain about the time period but thought that 12 weeks was a reasonable cut-off point between relapse and recurrence.

Teicoplanin

Teicoplanin was not recommended by the committee for use in treating *C. difficile* infection. It was ranked first in the network meta-analysis results. However, the committee were concerned about the extensive limitations of the 2 small studies of teicoplanin included in the network meta-analysis, both of which were at considerable risk of bias. The committee noted that the point estimate of effect was important. However, the 95% confidence intervals were wide, revealing much uncertainty in the estimate. This meant that there was little difference from, and overlap with, the estimate of effect for vancomycin. The committee were also aware of the limited clinical experience with using teicoplanin in the UK for *C. difficile* infection. They concluded that further research was needed on teicoplanin for treating *C. difficile* infection.

The committee had an initial discussion about the findings from the economic model. They noted that if the results from the studies of teicoplanin were considered robust, it would come out as clearly the most cost-effective first-line treatment. However, they were not convinced by either the sample size or quality of the studies on teicoplanin and agreed there was not enough clinical evidence to recommend it. They therefore focused on the economic model results excluding teicoplanin.

Metronidazole

Metronidazole was not recommended by the committee for treating *C. difficile* infection. The committee noted that there is some evidence that metronidazole is effective, but also evidence that other antibiotic choices are more effective. They heard that metronidazole is comparatively inexpensive compared with other antibiotic treatments. However, they discussed that, from experience, many hospital trusts have moved away from using metronidazole. This has been prompted by lower efficacy compared with other antibiotics and potential side effects. The

committee also heard expert testimony that cure or improvement may take longer with metronidazole compared with other antibiotic treatments. A longer period before treatment becomes effective is concerning because this may lead to increased transmission of the infection, particularly in hospital or residential care settings. Neither of these issues were addressed in the economic model.

When considering the economic model, the committee agreed that it was appropriate to exclude strategies in which metronidazole was used as a second-line intervention. They noted that 1 limitation of the analysis was that interventions were assumed to be equally effective as second-line options compared with first-line options. This was because there were no data to test this assumption. They agreed that when *C. difficile* is not clinically cured using first-line vancomycin or fidaxomicin it is likely to represent infection that is harder to treat. So, it would be less likely to respond to metronidazole, meaning it would not be effective as a second-line agent. As discussed in more detail in the section on vancomycin and fidaxomicin, first-line metronidazole was found to be less cost effective than first-line vancomycin, so the committee were confident in not recommending it.

The committee recognised that intravenous metronidazole may be a treatment option in the rare event that *C. difficile* infection fails to respond to either vancomycin or fidaxomicin, or in people with a life-threatening infection. The committee noted that, from its experience, intravenous metronidazole (as an adjunct to vancomycin via the enteral route) is used in practice for some people in these circumstances. However, they were not able to make a recommendation because of the lack of evidence, and agreed that specialist advice should be sought.

Course length, dosage, and route of administration

The committee noted the evidence showing no statistically significant difference in clinical effectiveness with low-dose (125 mg four times a day) compared with high-dose (500 mg four times a day) vancomycin. The committee concluded that the standard licensed dose of oral vancomycin 125 mg four times a day for 10 days was sufficient to treat *C. difficile* infection. Oral vancomycin can be given as either capsules or the powder for solution given orally. A tapered or pulsed regimen of vancomycin was not recommended because its use was limited in the evidence

review to studies in which there was co-administration of FMT. The committee were aware that there are ongoing trials, which might provide evidence for wider use of pulsed or tapered vancomycin.

The committee noted the evidence suggesting that fidaxomicin 400 mg daily was more clinically effective than 100 mg or 200 mg daily. They concluded that the standard licensed dose of oral fidaxomicin 200 mg twice a day for 10 days was sufficient to treat *C. difficile* infection.

The committee considered the comparison of the standard and extended-pulsed regimens of fidaxomicin in the economic model. The unlicensed extended-pulsed regimen of fidaxomicin is 200 mg twice a day on days 1 to 5, then 200 mg once a day on alternate days from days 7 to 25. The committee noted that the point estimates were in favour of extended-pulsed fidaxomicin being the better option. However, there was considerable uncertainty in this conclusion (with a 36% chance of standard fidaxomicin being more cost effective than extended-pulsed fidaxomicin at £30,000 per QALY gained). Also, the absolute magnitude of the differences was small. The committee agreed that there was insufficient evidence of benefits from the extended-pulsed regimen to justify recommending an unlicensed treatment regimen over a licensed one.

Antibiotics for children

The committee agreed that specialists may want to base antibiotic choice for children and young people on recommendations for adults, taking into account the varying licensed indications for children.

Vancomycin capsules are only licensed to treat *C. difficile* infection in people aged 12 years and over. Vancomycin powder for solution given orally is licensed to treat *C. difficile* infection in all age groups.

Fidaxomicin tablets are licensed to treat *C. difficile* infection in children with a body weight of at least 12.5 kg. Fidaxomicin granules for oral suspension have a European licence (import required because no UK supplier) to treat *C. difficile* infection from birth. However, there is a caution for use in babies less than 6 months and in babies with body weight less than 4 kg.

For more detail see the summary of the evidence on Antibiotic dose.

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Preventing *C. difficile* infection

Why the committee made the recommendations

Recommendation 1.3.1 to 1.3.3

The committee noted the lack of evidence of clinical or cost effectiveness to prevent *C. difficile* infection with antibiotics. They recognised that there was some evidence for rifaximin preventing further recurrences from a single study in people who already had recurrent infection. However, the intensive way in which antibiotics were used in the study has raised concerns about the possible emergence of rifamycin resistance, which has been reported in *C. difficile* infection cases, and prolonged flora disturbance.

The committee also recognised the limited evidence of benefit for:

- fidaxomicin in preventing *C. difficile* infection in people having a haematopoietic stem cell transplant who had fluoroquinolone prophylaxis
- vancomycin in preventing *C. difficile* infection in people who are hospitalised.

The NICE economic model only included treatment options, including adjunctive treatment with bezlotoxumab (which is used to prevent recurrent infection) and FMT to determine sequencing of treatments. It did not include comparisons for preventing a first episode of *C. difficile* infection with antibiotics, prebiotics or probiotics. The committee concluded that, because of the lack of evidence and concerns about antimicrobial resistance, antibiotics should not be offered for preventing *C. difficile* infection.

The committee noted the lack of convincing evidence of effect for prebiotics (oligofructose), which showed little difference in preventing *C. difficile* associated outcomes in the included studies. They concluded that prebiotics conferred no benefit and should not be used to prevent *C. difficile* infection.

The committee agreed that there is some evidence of a small effect with probiotics in preventing *C. difficile* infection. However, there were many limitations in the evidence and the number needed to treat was high. Limitations included aggregating the results of different types of probiotics in meta-analyses, and the lack of effectiveness when using confirmed cases only (in adults and particularly in children). The committee also noted concerns from expert testimony about the high prevalence of *C. difficile* infection in the placebo arms of some studies, which does not reflect clinical practice in the UK. The single study conducted in a UK setting found no evidence of effect for probiotics in people aged over 65 years. The committee also noted that NHS England guidance on conditions for which over the counter items should not routinely be prescribed in primary care states that probiotics should not routinely be prescribed.

The committee concluded that, because of concerns about the evidence base (including cost effectiveness), probiotics should not be used routinely for preventing *C. difficile* infection.

Return to the recommendations

Context

Clostridioides difficile is a bacterium that can infect the bowel and cause diarrhoea. Certain groups, such as older people, are at higher risk of *C. difficile* infection. The infection most commonly affects people who are taking, or have recently taken antibiotics, and it can be transmitted very easily. It can be mild, moderate, severe or life threatening, and is treated with antibiotics.

Summary of the evidence

This is a summary of the evidence, for full details see the evidence review.

The evidence for treating *C. difficile* infection in adults specifically included antibiotic efficacy, choice, dose and dose frequency, faecal microbiota transplantation (FMT), bezlotoxumab and prebiotics. The evidence for treating *C. difficile* infection in children included antibiotic choice and probiotics.

For *C. difficile* infection in adults, young people or children, no evidence from systematic reviews or randomised controlled trials (RCTs) was identified for antibiotic prescribing strategies, course length or route of administration. There was also no evidence found for probiotics for *C. difficile* infection in adults, nor for antibiotic efficacy, dose or dose frequency, FMT, bezlotoxumab or prebiotics for infection in children.

There was evidence found for prophylactic antibiotics (in adults having a stem cell transplant or in hospital), prebiotics and probiotics to prevent *C. difficile* infection in adults. There was evidence for probiotics to prevent *C. difficile* infection in children.

Interventions included in the search were antimicrobial interventions, non-antimicrobial interventions (bezlotoxumab and intravenous immunoglobulin), and non-pharmacological interventions (probiotics, prebiotics, FMT, and stopping current antibiotics or proton pump inhibitors). No evidence from systematic reviews or RCTs was found for intravenous immunoglobulin or stopping current antibiotics or proton pump inhibitors. In addition, the following interventions were outside the scope of this guideline because there is no UK licensed product available: ridinilazole, cadazolid, surotomycin, nitazoxanide, tolevamer, LFF517, bacitracin and tolevamer.

Treating initial or recurrent *C. difficile* infection in adults

Antibiotics

Antibiotic efficacy

A statistically significant improvement was seen in symptomatic and bacteriological cure with vancomycin 125 mg four times daily for 5 days compared with placebo in adults with first-episode pseudomembranous colitis (some associated with evidence of *C. difficile* infection) (Nelson et al. 2017).

Antibiotic choice

In 1 network meta-analysis, different antibiotic treatments were compared for treating the initial or first recurrent episode of *C. difficile* infection. Vancomycin was used as the reference treatment (Beinortas et al. 2018), and the treatments were ranked using P scores. Of the antibiotics available in the UK, sustained symptomatic cure

was most effective with teicoplanin (P score=0.9386), followed by fidaxomicin (P score=0.7922), vancomycin (P score=0.4850), rifaximin (P score=0.4296), fusidic acid (P score=0.3794) and metronidazole (P score=0.2411). P scores are calculated as the average p value for superiority for that intervention compared with all the other interventions in the network. They take account of the magnitude of the difference and the level of uncertainty. Higher P scores (on a 0 to 1 scale) represent treatments where there is more confidence that they are better than the other alternatives in the network.

A sensitivity analysis was done in which the effect was explored of removing studies with fewer than 50 people per arm, studies that were published before 2000, and unblinded studies. When non-blinded studies or studies with fewer than 50 people per arm were removed, fidaxomicin was the highest ranked treatment available in the UK. When studies published before the year 2000 were removed, teicoplanin was the highest ranked treatment available in the UK, followed by fidaxomicin.

Subgroup analysis was done for severe *C. difficile* infection, non-severe *C. difficile* infection, initial *C. difficile* infection, non-initial *C. difficile* infection, people aged 65 years and over and people aged under 65 years. For all subgroups, fidaxomicin was the highest ranked treatment available in the UK, and metronidazole was the least effective (being ranked either the fifth, sixth or seventh most effective option in the different subgroups).

There were no statistically significant differences in clinical effectiveness (recurrence of *C. difficile* infection, clinical resolution of *C. difficile* infection, relapse of *C. difficile* infection at 5 weeks and adverse events) for oral vancomycin compared with fidaxomicin (Hvas et al. 2019).

Antibiotic dose

There was no statistically significant difference in clinical effectiveness (symptomatic cure) with low-dose (125 mg four times a day) compared with high-dose (500 mg four times a day) vancomycin, both taken for 5 to 15 days (Nelson et al. 2017).

There was a statistically significant improvement in clinical effectiveness (symptomatic cure) with fidaxomicin 400 mg daily compared with fidaxomicin 100 mg or 200 mg daily, all taken for 10 days.

Antibiotic dose frequency

There was no statistically significant difference in clinical effectiveness (symptomatic cure) with 100 mg of teicoplanin twice daily compared with 50 mg of teicoplanin four times daily (Nelson et al. 2017).

FMT for treating initial *C. difficile* infection

There were no statistically significant differences in clinical effectiveness (resolution of *C. difficile* infection, treatment failure, all-cause and *C. difficile* infection attributable mortality or length of stay) of:

- the first dose of FMT compared with vancomycin
- the second dose of FMT compared with vancomycin (Camacho-Ortiz et al. 2017).

FMT for treating recurrent *C. difficile* infection

There were statistically significant increases in clinical effectiveness (resolution of symptoms, resolution of diarrhoea, relapse of diarrhoea) with:

- a 4- to 10-day course of vancomycin followed by FMT compared with 10 days of vancomycin at 1- and 8-week follow up (Hvas et al. 2019)
- a 4- to 10-day course of vancomycin followed by FMT compared with 10 days of fidaxomicin at 8-week follow up (Hvas et al. 2019)
- a 4- to 5-day course of vancomycin plus bowel lavage followed by FMT compared with either 14 days of vancomycin (with or without bowel lavage) at 10-week follow up, and at 5 weeks follow up for relapse (van Nood et al. 2013)
- a 3-day course of vancomycin followed by FMT compared with a standard then a pulsed course of vancomycin at 10-week follow up (Cammarota et al. 2015).

There were no statistically significant differences in all-cause or *C. difficile* infection-related mortality for a short course of vancomycin plus bowel lavage followed by FMT compared with 14 days of vancomycin or 14 days of vancomycin plus bowel lavage (van Nood et al. 2013).

There were no statistically significant differences in adverse events for:

- a short course of oral vancomycin followed by FMT compared with either 10 days of vancomycin or fidaxomicin (Hvas et al. 2019)
- a short course of vancomycin followed by FMT compared with vancomycin, either with or without bowel lavage (van Nood et al. 2013).

There was a statistically significant lower mean number of days of diarrhoea compared with a course of vancomycin followed by FMT compared with tapered vancomycin (Hota et al. 2017). However, a short course of vancomycin followed by FMT or bowel lavage plus FMT statistically significantly increased treatment-related diarrhoea, bloating or cramping (Cammarota et al. 2015; van Nood et al. 2013).

Serious adverse events were reported in 2 RCTs. In 1 RCT, a sepsis-like response occurred (possibly related to FMT) but resolved without admission or treatment (Hvas et al. 2019). In the other RCT, 3 serious adverse events were noted but none were thought to be treatment related (Hota et al. 2017).

Preventing recurrence in people with *C. difficile* infection in adults

Antibiotics

In adults who had an initial or first recurrent episode of *C. difficile* infection treated with vancomycin or metronidazole, immediate rifaximin for 20 days was statistically significantly more effective than placebo at reducing recurrence of both *C. difficile* infection-confirmed diarrhoea and self-reported diarrhoea. However, when the outcomes of recurrent *C. difficile* infection-confirmed diarrhoea and recurrent self-reported diarrhoea were analysed separately, there was no statistically significant difference between rifaximin and placebo in either group (Garey et al. 2011).

In adults who had an initial, first recurrent, or second or later recurrent episode of *C. difficile* infection treated with vancomycin or metronidazole, there was no statistically significant difference between immediate rifaximin for 28 days and placebo for recurrent *C. difficile* infection at 12 weeks or 6 months, or for rehospitalisation for *C. difficile* infection within 6 months. When subgroup analysis was done for standard care antibiotic treatment with metronidazole or vancomycin,

there was no statistically significant difference between rifaximin and placebo for *C. difficile* infection recurrence. There was also no statistically significant difference in effect between rifaximin and placebo on *C. difficile* infection recurrence when post-hoc analyses were done for *C. difficile* infection history (Major et al. 2019).

A Kaplan–Meier analysis showed that rifaximin led to a statistically significant increased time to both recurrent *C. difficile* infection-confirmed diarrhoea and recurrent self-reported diarrhoea) compared with placebo (Garey et al. 2011). However, when the time to *C. difficile* infection-confirmed diarrhoea and time to self-reported diarrhoea were analysed separately, there was no statistically significant difference between rifaximin and placebo.

There were no statistically significant differences between rifaximin and placebo for mortality, serious and non-serious adverse events (Major et al. 2019).

Monoclonal antibodies

In adults with an initial or recurrent episode of *C. difficile* infection treated with standard care antibiotic treatment (that is, metronidazole, vancomycin or fidaxomicin), bezlotoxumab was statistically significantly more effective than placebo for recurrent *C. difficile* infection, 12 weeks of sustained cure and recurrence of diarrhoea (regardless of whether it was associated with a positive toxin test) (Wilcox et al. 2017). A Kaplan–Meier analysis suggested that bezlotoxumab increased time to recurrence of *C. difficile* infection compared with placebo, but it was unclear if the differences were statistically significant.

Various subgroup analyses for *C. difficile* infection risk factors and stratification variables were done. Bezlotoxumab was statistically significantly more effective than placebo for recurrence of *C. difficile* infection for the stratification variables of inpatients and outpatients, and whether people had vancomycin or metronidazole as their standard care antibiotic treatment. However, there was no statistically significant difference between bezlotoxumab and placebo for the outcome of recurrence of *C. difficile* infection for the stratification variable of people having fidaxomicin as their standard care antibiotic treatment.

There were no statistically significant differences between bezlotoxumab and placebo for the outcomes of initial clinical cure at 2 days and mortality.

There was no statistically significant difference between bezlotoxumab and placebo for infusion-specific adverse events or adverse events leading to treatment being stopped at 24-hour follow up. There was also no statistically significant difference between bezlotoxumab and placebo for drug-related adverse events, other adverse events (most commonly abdominal pain, diarrhoea, nausea, vomiting, fatigue, pyrexia, serious *C. difficile*, urinary tract infection or headache), serious adverse events or for drug-related serious adverse events, occurring during the 4 weeks after the bezlotoxumab infusion.

FMT for preventing *C. difficile* infection recurrence

In NICE analyses, there were no statistically significant differences in the clinical effectiveness (recurrence) of the following doses of FMT given after antibiotic treatment for a current episode of *C. difficile* infection in adults with multiple recurrent infections:

- a single dose of FMT compared with placebo
- 2 doses of FMT compared with placebo
- 2 doses of FMT compared with a single dose of FMT
- 1 or 2 doses of FMT (pooled) compared with placebo (Dubberke et al. 2018).

There was no statistically significant difference in adverse events. However, 3 severe adverse events were reported and thought to be related to FMT in the '2 doses of FMT' group. There were 6 deaths (3 in the '2 doses of FMT' group and 3 in the '1 dose of FMT' group) in the FMT arms of the trial and none in the placebo group.

Prebiotics for relapse of diarrhoea

There was a statistically significant decrease in relapse of diarrhoea with metronidazole or vancomycin plus the prebiotic oligofructose compared with metronidazole or vancomycin plus placebo for diarrhoea associated with *C. difficile* infection in adults aged over 65 years (Lewis et al. 2005a). No statistically significant difference was noted for *C. difficile* culture positivity at 30- or 60-day follow up.

Treating initial or recurrent *C. difficile* infection in children and young people

Antibiotics choice

Oral metronidazole compared with oral rifaximin

There was no statistically significant difference in clinical effectiveness (*C. difficile* infection cure rate or recurrent *C. difficile* infection) with oral metronidazole compared with oral rifaximin for a first episode of *C. difficile* infection in children with inflammatory bowel disease (Gawronska et al. 2017).

Oral fidaxomicin compared with oral vancomycin

There was no statistically significant difference in confirmed clinical response or resolution of diarrhoea with oral fidaxomicin compared with oral vancomycin for confirmed *C. difficile* infection in children and young people aged under 18 years (Wolf et al. 2019).

In the total study population and subgroup of children aged under 2 years, there was no statistically significant difference between oral fidaxomicin and oral vancomycin for the outcome of global cure. However, in other subgroups (those aged 2 years and over and those with a positive toxin test aged 2 years and over), fidaxomicin was statically significantly more effective than vancomycin for global cure.

Oral fidaxomicin statistically significantly reduced *C. difficile* infection recurrence compared with oral vancomycin in children and young people aged under 18 years. When results were stratified by age, fidaxomicin was statistically significantly more effective than vancomycin in children aged 2 years and over and in children with a positive toxin test aged 2 years and, but the effect was no longer statistically significant in those aged under 2 years.

There was no statistically significant difference for treatment-emergent adverse events (including serious events, drug-related events, those leading to death or withdrawal from treatment).

Probiotics for persistent diarrhoea

There was a statistically significant reduction in the mean number of days of diarrhoea with oral rehydration solution plus the probiotic *Lactobacillus rhamnosus GG* compared with oral rehydration solution alone in children with a positive *C. difficile* stool culture (Basu et al. 2007). However, there was no statistically significant difference in the mean number of days of vomiting.

Preventing *C. difficile* infection in adults without infection

Antibiotics

In people without *C. difficile* infection having a haematopoietic stem cell transplant and fluoroquinolone prophylaxis during neutropenia, there was no statistically significant difference between fidaxomicin and placebo for reducing prophylaxis failure at 30, 60 or 70 days (Mullane et al. 2019). There was also no statistically significant difference between fidaxomicin and placebo for any adverse events reported in the study.

Fidaxomicin was statistically significantly more effective than placebo at reducing confirmed diarrhoea associated with *C. difficile* infection at 30, 60 and 70 days. A Kaplan–Meier analysis showed a statistically significantly increased time to recurrence of *C. difficile* infection with fidaxomicin compared with placebo.

In people without *C. difficile* infection who were hospitalised for up to 30 days before their current hospitalisation, there was no statistically significant difference between oral vancomycin and placebo for:

- healthcare facility-onset (symptomatic infection more than 72 hours after hospital admission) *C. difficile* infection, or
- community-onset healthcare facility-associated (symptomatic infection up to 3 months after hospital discharge) *C. difficile* infection after hospital discharge (Johnson et al. 2019).

Prebiotics

In inpatients aged over 65 years without *C. difficile* infection who were prescribed a broad-spectrum antibiotic, the prebiotic oligofructose did not have a statistically

significantly different effect to placebo at end of follow up for all-cause mortality or for incidence of diarrhoea, significant diarrhoea (3 loose stools or more in a 24-hour period), non-significant diarrhoea (1 or 2 loose stools in a 24 hour period), *C. difficile* associated diarrhoea or *C. difficile* associated significant diarrhoea (Lewis et al 2005b).

In the oligofructose group, the median (interquartile range) length of hospital stay was 17 days (13 to 22) compared with 15 days (11 to 18) in the placebo group.

Probiotics

The evidence for probiotics in the prevention of *C. difficile* infection in adults comes from 1 systematic review (Goldenberg et al. 2017). The population in the included studies was people aged over 18 years having antibiotic treatment for any reason.

Probiotics statistically significantly reduced the incidence of *C. difficile* infection compared with any comparator (follow-up time point not reported) in studies in inpatients, but not in studies in outpatients or patients in mixed settings.

Probiotics were not statistically significantly different compared with any comparator for the outcome of incidence of *C. difficile* infection determined by detection of *C. difficile* in stools, either overall or in any setting (inpatients, outpatients, or mixed settings; follow-up time points not reported).

Probiotics statistically significantly reduced the number of adverse events compared with any comparator (follow-up time point not reported). Details of the adverse events were not reported.

Preventing *C. difficile* infection in children and young people without infection

Probiotics

The evidence for probiotics in preventing *C. difficile* infection in children and young people comes from 1 systematic review (Goldenberg et al. 2017) and 1 RCT (Kolodziej and Szajewska 2019). The population in the included studies was children

and young people aged under 18 years who were having antibiotic treatment for any reason.

Probiotics statistically significantly reduced the incidence of *C. difficile* infection compared with any comparator (follow-up time point not reported) in the inpatient and mixed settings studies.

Probiotics were not statistically significantly different compared with any comparator in inpatient studies for the outcome of incidence of *C. difficile* infection determined by detection of *C. difficile* in stool (follow-up time point not reported).

Probiotics were not statistically significantly different compared with any comparator for adverse events.

Other considerations

Medicines safety

Vancomycin is a glycopeptide that is given orally to treat *C. difficile* infection. With oral use, the company advises monitoring serum vancomycin concentration in people with inflammatory intestinal disorders. It also advises that serial auditory function tests may help to minimise the risk of ototoxicity in people with an underlying hearing loss, or who are having concomitant therapy with other ototoxic drugs. In renal impairment or in people having concomitant treatment with an aminoglycoside or other nephrotoxic drug, the manufacturer advises serial monitoring of renal function (BNF information on vancomycin, vancomycin summary of product characteristics).

Fidaxomicin is a macrocyclic antibacterial that is poorly absorbed from the gastrointestinal tract, so not used to treat systemic *C. difficile* infections. Common side effects when given orally for *C. difficile* infection include constipation, nausea and vomiting (BNF information on fidaxomicin).

In NICE's interventional procedure guidance on faecal microbiota transplant for recurrent C. difficile infection, it states that 'The US Food and Drug Administration has advised that stool donors for faecal microbiota transplantation should be screened with questions that specifically address risk factors for colonization with

Multi Drug Resistant Organisms (MDROs), and individuals at higher risk of colonization with MDROs should be excluded as donors. In addition, donor stool should be specifically tested for MDROs and not used if positive'. While short-term safety and adverse events with a faecal microbiota transplant were reported in the included studies for this guidance, the committee identified that longer-term safety of the procedure is not yet known.

Medicines adherence

Medicines adherence may be a problem for some people taking antibiotics that need frequent dosing or longer treatment duration (see NICE's guideline on medicines adherence).

Resource implications

See the economic model for detailed costs, including estimated costs of a faecal microbiota transplant. Vancomycin capsules and powder for solution are available as generic formulations. Fidaxomicin tablets are a proprietary product.

See the evidence review for more information.

Finding more information and committee details

You can see everything NICE says on this topic in the NICE Pathway on *Clostridioides difficile* – antimicrobial prescribing.

To find NICE guidance on related topics, including guidance in development, see the NICE webpages on healthcare associated infections and on digestive tract conditions.

For full details of the evidence and the guideline committee's discussions, see the evidence review. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.