Stato dell'arte sull'infezione da C. difficile: consensus italiana

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Disclosures
(past 2 years)

- Advisor/consultant/speaker bureau
  - Angelini, Biomerieux, Cidara, Ecdc,Gilead, Menarini, Medscape, Mundipharma, MSD, Pfizer, Shionogi

Key facts about *C. difficile*

C. difficile

- Gram-positive, anaerobic, motile, spore-forming bacillus[1,2]
- Found throughout the environment including hospital and healthcare settings[3]
- **Most common cause of infectious nosocomial diarrhoea[1]**
- Not generally found in healthy adults[4]
- Produces toxins[1]
- Transmitted by spores[5]
- Potential for hypervirulent strains – ribotypes[6]
- Harboured in bacterial biofilms that allow surface persistence[7]
- CDI is associated with increased hospital stays, increased costs and increased mortality[8]

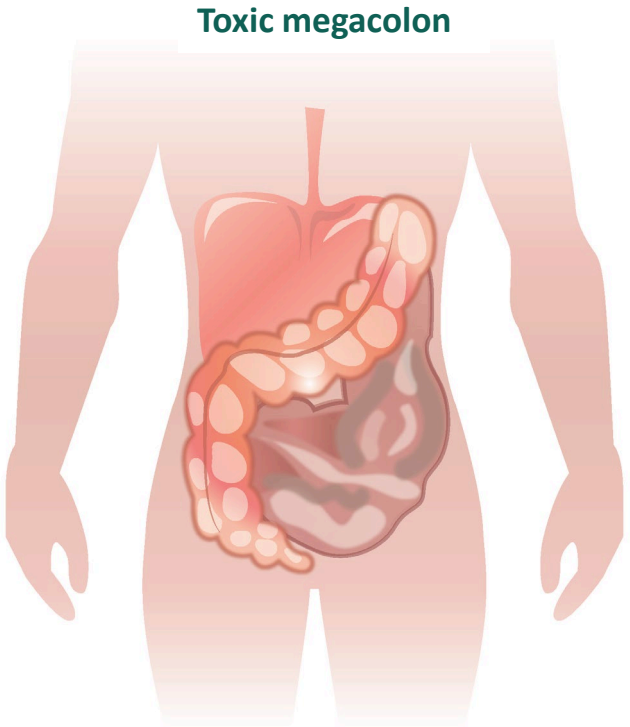
Gram stain of *C. difficile*

C. difficile in spore and vegetative forms

C. difficile, *Clostridioides difficile*; CDI, *C. difficile* infection.

1. Vindigni S & Surawicz C, Clin Translat Gastroenterol 2015;6:e99; 2. Barer. Medical Microbiology, 2019 (19th Edition), Chapter 29, p201. Elsevier Ltd; 3. Bauer M, et al. Lancet 2011;377:63–73;
4. NICE. Clostridium difficile infection: risk with broad-spectrum antibiotics. 2015; 5. NHS UK. Clostridium Difficile Infection (CDI) Medicines Management Fact File. December 2011;
6. Huber CA, et al. J Clin Microbiol 2013;51:2810-14; 7. Normington C, et al. Biofilms Microbiomes 2021;7:16; 8. Eberly MD, et al. Mil Med 2021;usab116.

CDI contributes to increased mortality



Mortality risks include:
Increased age, immunocompromised state, patients with IBD, significant co-morbidities, relapsing CDI[1,2]

CDI:
Mortality of all CDI patients is 2.5-fold higher than matched controls at Day 30[3]

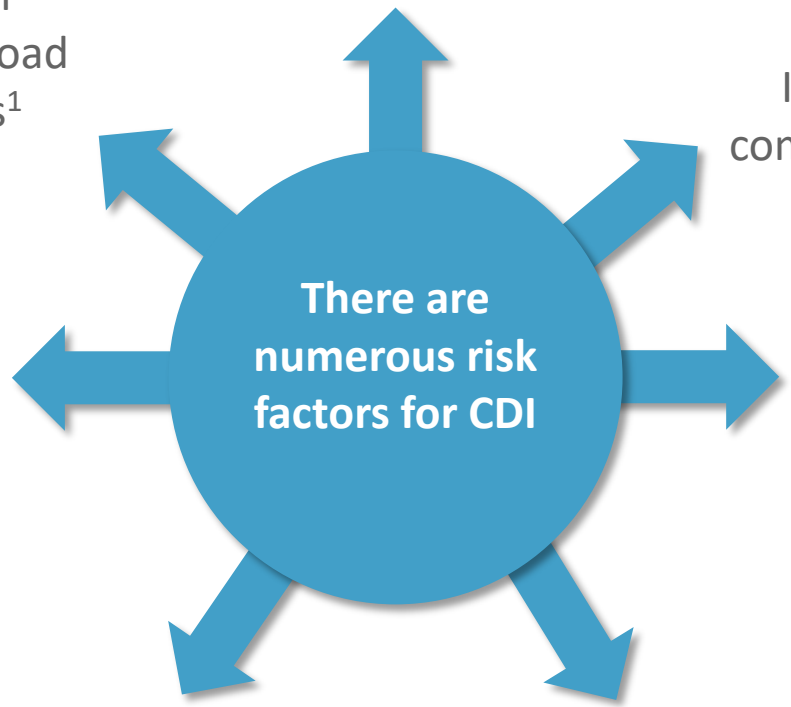
Recurrent CDI:
Mortality was significantly higher in patients with recurrent CDI at Days 90 ($p=0.002$) and 180 ($p<0.001$) compared with patients with no recurrent infection[2]

Fulminant CDI:
Up to 8% of patients develop fulminant CDI, including toxic megacolon[4]
Fulminant CDI mortality is up to 80%, despite surgery[4]

CDI, *C. difficile* infection; IBD, inflammatory bowel disease.

1. Vindigni S & Surawicz C, Clin Translat Gastroenterol 2015;6:e99; 2. Olsen M, et al. Clin Microbiol Infect 2015;21:164-170; 3. Hensgens MPM, et al. Clin Infect Dis 2013;56:1108-16; 4. Farooq P, et al. Dis Mon 2015;65:181-206.

Risk factors for CDI



Proton pump inhibitors[1]

Inappropriate use of antibiotics[4,5]/use of broad spectrum antibiotics[1]

Immuno-compromised[2]

Nasogastric tube/ GI surgery[2,3]

Severity of underlying diseases[2]

Prolonged stay in hospital/ care home[2]

Older age (>65)[1]

Most important risk factors in patients aged >65 years[6]

- Hospitalisation/residential nursing home
- History of IBD or chronic liver disease

Predictors of mortality[7]

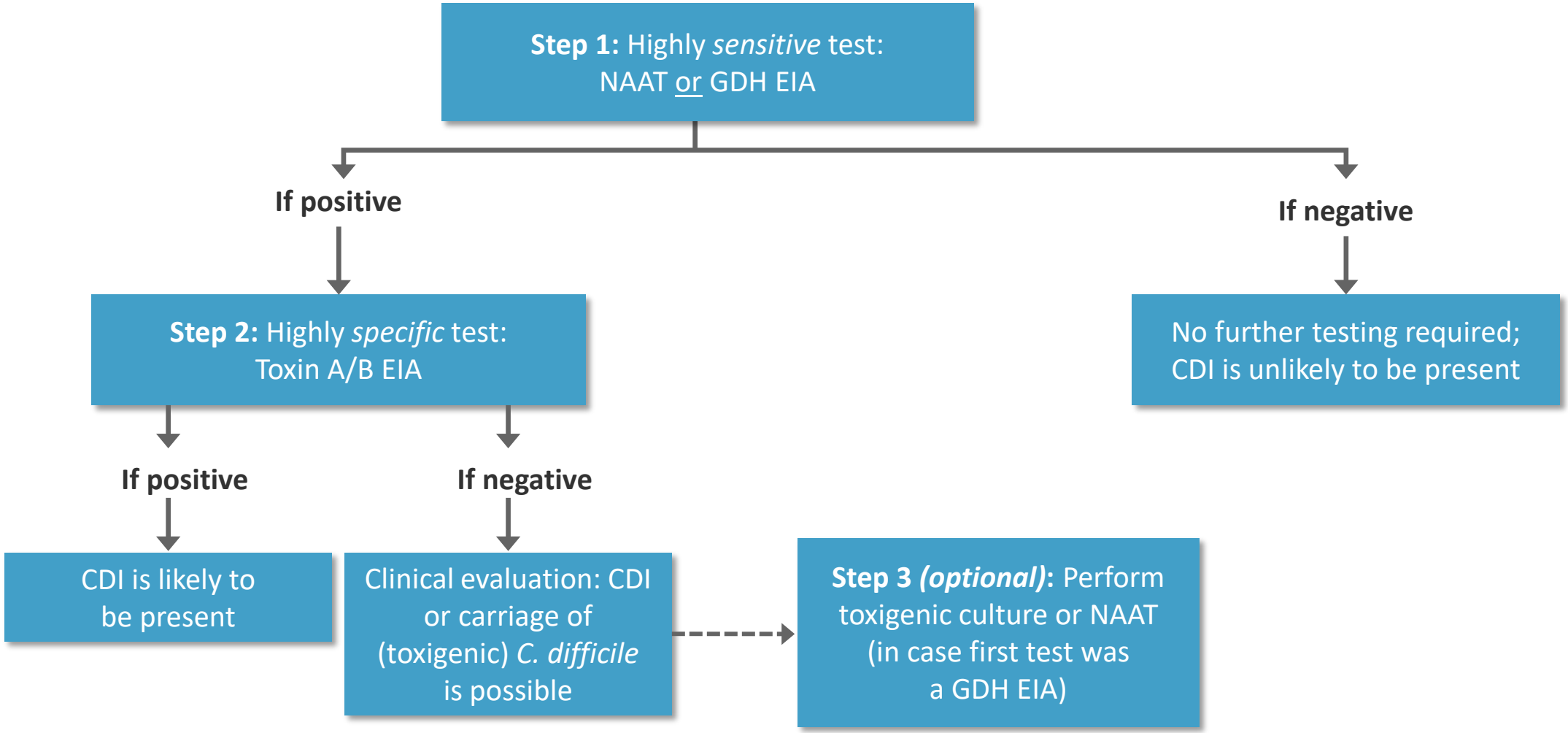
- High leucocyte count
- Elevated creatinine levels
- Elevated lactate levels

CDI, *C. Difficile* infection; GI, gastrointestinal; IBD, inflammatory bowel disease.

1. Tawam D, et al. Pharm Pract & Pract Based Res 2021;12:21; 2. Cole et al. Clin Colon Rectal Surg 2015; 28: 65-69; 3. Predrag. Braz J Microbiol 2016; 47: 902-910; 4. Bye M, et al. Open Forum Infect Dis 2017;4:ofx162.001; 5. Thompson W, et al. Infect Cont Hosp Epidemiol 2021;1-8; 6. Zilberberg MD, et al. JAGS 2016;64:1690-95; 7. Mahida YR. Br Med Bull 2019;131:109-18.

Diagnosis of CDI

ESCMID updated diagnostic guidance document for CDI (2016) recommends a 2-step process for diagnosis of CDI

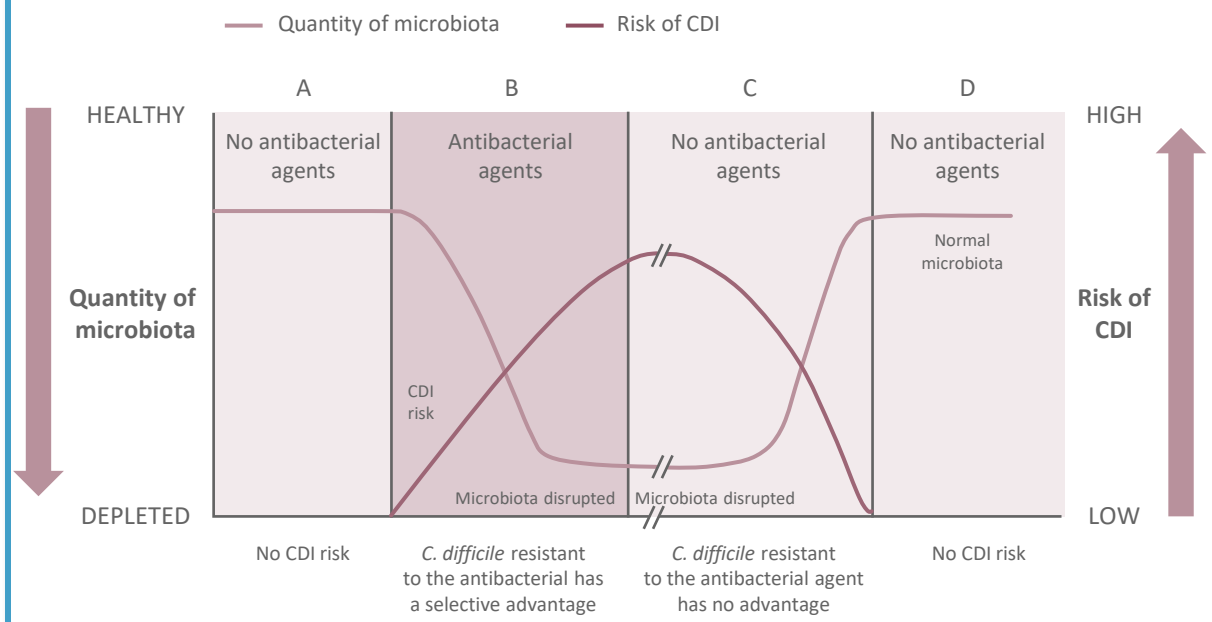


C. difficile, *Clostridioides difficile*; CDI, *C. difficile* infection; ESCMID, European Society for Clinical Microbiology and Infectious Disease; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification tests.

Crobach MJT, et al. Clin Microbiol Infect 2016;22:S63-S81.

Antibiotic exposure and CDI

Antibacterial therapy depletes the colonic microbiota and increases the risk of infection[1]



Adapted from: Rupnik M et al. 2009

Different antibiotics are associated with different levels of CDI risk

Reducing risk of CDI

Lincosamides e.g. clindamycin[2,3] – the first antibiotic to be associated with CDI[4]	OR 16.8–20.43
Fluoroquinolones[2,3]	OR 5.5–5.65
Cephalosporins[2,3]	OR 4.47–5.68
Macrolides, e.g. erythromycin[2,3]	OR 2.55–2.65
Penicillins[2,3] (widely used, in medicine and dentistry)[5]	OR 2.71–3.25
Sulphonamides/trimethoprim[2,3]	OR 1.81–1.84

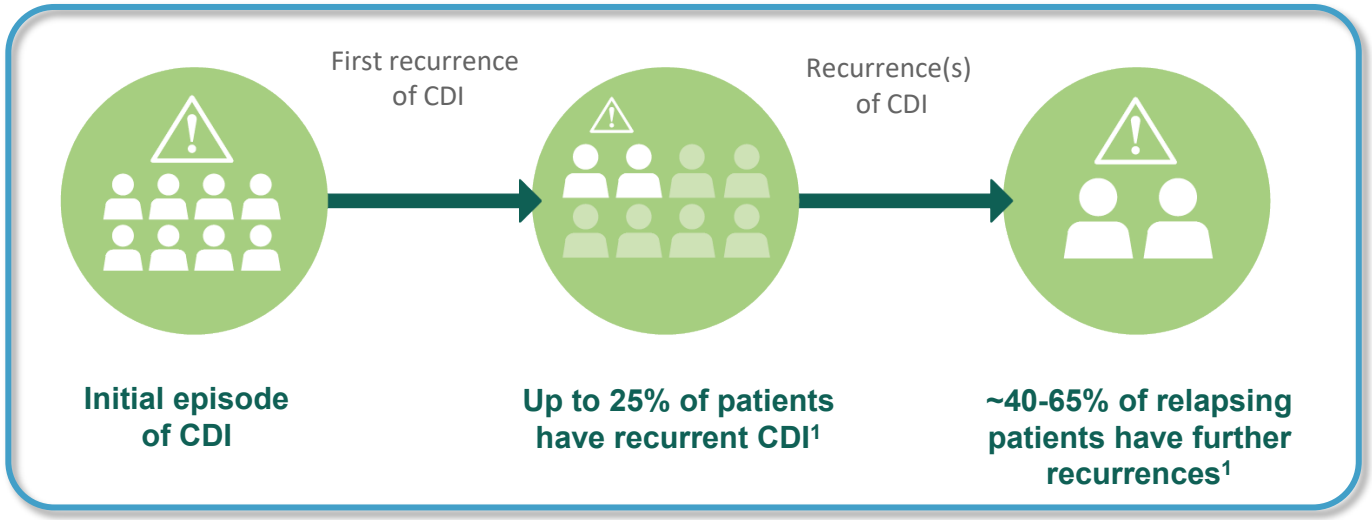
C. difficile, *Clostridioides difficile*; CDI, *C. difficile* infection; OR, odds ratio.

1. Rupnik M, et al. Nat Rev Microbiol 2009;7:526–36; 2. Brown KA, et al. Antimicrob Agents Chemother 2013;57:2326-32; 3. Deshpande A, et al. J Antimicrob Chemother 2013;68:1951-61;
4. Barlett JG, et al. NEJM 1978;298:531-34; 5. Beacher N, et al. Br Dent J 2015;219:275-79.

CDI recurrence

CDI has a high likelihood of recurrence,[1] with a range of contributing factors

- Up to 25% of patients treated for CDI will have a recurrence[1,2]



Recurrence may be a **new infection** or **relapse of the original infection** due to the persistence of spores[3]

Community acquired CDI is on the rise[4]

Effective agents **that treat CDI** and **reduce the likelihood of recurrence** are needed[4]

Main reasons for recurrence[3,5]

- Disruption of the colonic microbiota
- Failure to clear spores
- Inadequate immune response
- Failure to clear the initial infection

CDI, *C. difficile* infection.

1. Meehan AM, et al. World J Clin Infect Dis 2016;6:28-36; 2. Asempa TE, et al. Clin Interv Aging 2017;12:1799–1809; 3. Gomez S, et al. Clin Anaerobe 2017;48:147-151; 4. Fu Y, et al. Ther Adv Gastroenterol 2021;14:1-11; 5. Deshpande A, et al. Infect Control Hosp Epidemiol 2015;36(4):452-460

ESCMID and IDSA/SHEA guidelines recommend fidaxomicin as first-line therapy

	Europe ESCMID[1]	USA IDSA/SHEA[2]
Initial CDI	**PO 200 mg fidaxomicin bd for 10 days** Alternative: PO vancomycin qd 125 mg for 10 days	**PO 200 mg fidaxomicin bd for 10 days** Alternative: PO vancomycin qd 125 mg for 10 days
Recurrence #1/ risk of recurrence	**PO 200 mg fidaxomicin bd for 10 days** (if initial treatment vancomycin) SoC antibiotics *plus* bezlotoxumab (if initial treatment fidaxomicin)	**PO 200 mg fidaxomicin bd for 10 days** *OR* 200 mg fidaxomicin bd for 5 days followed by od dosing every other day for 20 days Alternative: pulsed tapered vancomycin 125 mg qd for 10 days
Recurrent	FMT SoC antibiotic *plus* bezlotoxumab	**PO 200 mg fidaxomicin bd for 10 days** *OR* 200 mg fidaxomicin bd for 5 days followed by od dosing every other day for 20 days Pulsed tapered vancomycin 125 mg qd for 10 days Vancomycin 125 mg qd for 10 days followed by rifaximin 400g td for 20 days FMT

CDI, *C. difficile* infection; bd, twice daily dosing; ESCMID, European Society for Clinical Microbiology and Infectious Disease; FMT, faecal microbiota transplantation; IDSA, Infectious Disease Society of America; od, once daily dosing; PO per oros (oral dosing); qd, four times daily dosing; SHEA, Society for Healthcare Epidemiology of America; SoC, standard of care.

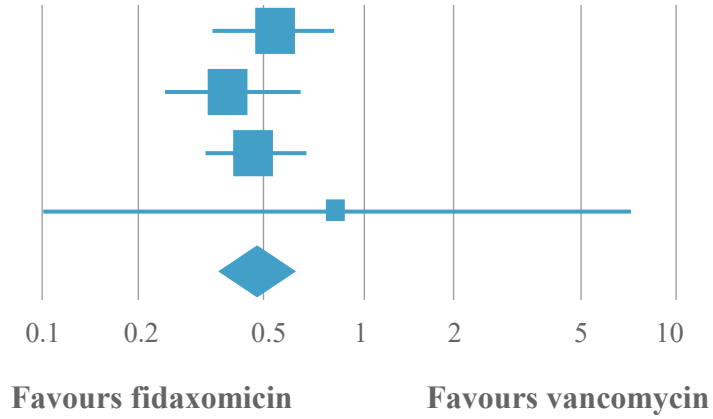
1. Van Prehn J, et al. Clin Microbiol Infect 2021, https://doi.org/10.1016/; 2. Johnson S, et al. Clin Infect Dis 2021;73:e1029-e1044.

Evidence for fidaxomicin as first-line therapy

Evidence for fidaxomicin as first-line therapy comes from the registration studies,[1,2] post-hoc analyses[3,4] and additional studies (EXTEND study,[5] Japanese data[6]). Meta-analyses show significant differences favouring fidaxomicin with respect to sustained clinical cure[7,8]

Recurrence rate[9]

Study name	Outcome	Statistics for each study			
		Odds ratio	Lower limit	Upper limit	p-value
Louie et al. 2011[1]	Recurrence	0.54	0.35	0.84	0.01
Cornely et al. 2012[2]	Recurrence	0.39	0.24	0.64	0.00
Louie et al. 2013[10]	Recurrence	0.46	0.32	0.67	0.00
Housman et al. 2016[11]	Recurrence	0.85	0.10	7.04	0.88
Pooled data[9]		**0.47**	**0.37**	**0.60**	**0.00**



Meta-analysis: CDI recurrence with fidaxomicin was significantly better than vancomycin[9]

CDI, *C. difficile* infection; CI, confidence interval.

1. Louie TJ, et al. N Engl J Med 2011;364:422-31; 2. Cornely OA, et al. Lancet Infect Dis 2012;12:281-9; 3. Goldstein EJ, et al. Clin Infect Dis 2012;55(Suppl 2):S143-8; 4. Louie TJ, et al. Clin Infect Dis 2012;55(Suppl 2):S132-42; 5. Guery B, et al. Lancet Infect Dis 2018;18:296-307; 6. Mikamo H, et al. J Infect Chemother 2018;24:744-52; 7. Beinortas T, et al. Lancet Infect Dis 2018;18:1035-44; 8. Cornely OA, et al. J Antimicrob Chemother 2014;69:2892-900; 9. Al Momani L, et al. Cureus 2018;10:e2778; 10. Louie TJ, et al. J Am Geriatr Soc 2013;62:22-30; 11. Housman ST, et al. Infect Control Hosp Epidemiol 2016;37:215-8.

History of antibiotic therapy in CDI

Metronidazole was the early standard of care for CDI, but was superseded by **vancomycin** due to the latter's superior cure rates[1,2]

	Metronidazole	Vancomycin
Dosing / administration	Three times daily dosing 10-14 days[3]	Four times daily dosing 10-14 days[3]
Cure rates	Mild CDI: 79%; severe CDI 66%[2*]	Mild CDI: 83%; severe CDI 79%[2]
CDI recurrence	Up to 23% of cases[2]	Up to 25% of cases[4]
Treatment failure	Up to 22% of cases[2*]	Between 14% and 20% of cases[2,5]
Use	First line (pre-2021) and mild/moderate CDI[3]	May be reserved for severe cases[3]
VRE	May promote overgrowth of VRE[6]	
Other	Rapid systemic absorption, variable pharmacokinetics[6]	

Fidaxomicin is now the first-line therapy for CDI recommended in the ESCMID and IDSA/SHEA guidelines[7,8]

*Figure rounded up

CDI, *C. difficile* infection; bd, twice daily dosing; ESCMID, European Society for Clinical Microbiology and Infectious Disease; IDSA, Infectious Disease Society of America; SHEA, Society for Healthcare Epidemiology of America; VRE, vancomycin-resistant enterococci.

1. Zar FA, et al. Clin Infect Dis 2007;45:302–7; 2. Johnson S, et al. Clin Infect Dis 2014;59:345–54; 3. PHE. Clostridium difficile infection: guidance on management and treatment. June 2013;
4. Louie TJ, et al. N Engl J Med 2011;364:422–31; 5. Vardakas KZ, et al. Int J Antimicrob Agents 2012;40:1–8; 6. Li R, et al. PLOS ONE 2015;10;e0137252;
7. Van Prehn J, et al. Clin Microbiol Infect 2021, https://doi.org/10.1016/; 8. Johnson S, et al. Clin Infect Dis 2021;73:e1029-e1044.

Limitations of metronidazole and vancomycin in the treatment of CDI

Metronidazole

- Frequent dosing (3x daily) needed[1]
- Low concentrations in the colon[2,3]
- High levels of systemic absorption[1]
- Not selective for *C. diff*icile and may disrupt microbiota[1,4]
- In patients pre-colonised with VRE, metronidazole promotes overgrowth of VRE[5]
- Does not reduce spore production or sporulation[6]
- CDI ribotype 001 has shown reduced susceptibility to metronidazole[7]
- Increasing rates of treatment failure – estimated to be >20%[8]
- CDI recurrence of up to 47% reported since 2004[9]
- Use not in keeping with antimicrobial stewardship due to its broad-spectrum of activity[10]

Vancomycin

- Frequent dosing (4 × daily) needed[11]
- Risk of overgrowth with VRE in the colon[5]
- Does not reduce spore production or sporulation[6]
- Not selective for *C. difficile* and may disrupt microbiota[4,11]
- CDI recurrence rates of up to 25% reported[12]
- Use not in keeping with antimicrobial stewardship due to its broad-spectrum of activity[10]

C. difficile, *Clostridioides difficile*; CDI, *C. difficile* infection; VRE, vancomycin-resistant enterococci.

1. Sanofi. Flagyl® (metronidazole) SmPC; 2. Bauer MP, et al. Clin Microbiol Infect 2009;15:1067–79; 3. DuPont HL. N Engl J Med 2011;364:473–5; 4. Finegold SM, et al. Antimicrob Agents Chemother 2004;48:4898–902; 5. Al-Nassir WN, et al. Antimicrob Agents Chemother 2008;52:2403–6; 6. Chen C, et al. Bioorg Med Chem Lett 2014;24: 595-600; 7. Baines SD, et al. J Antimicrob Chemother 2008;62:1046–52; 8. Mullish BH, et al. Clin Med 2018;18:237-41; 9. McFarland LV, et al. Curr Opin Gastroenterol 2009;25:24–35; 10. Public Health England. UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018. https://www.gov.uk/government/ publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018. (Accessed February 2022); 11. Bowmed Ibisqus Limited. Vancomycin SmPC; 12. Asempa TE & DP Nicolau. Clin Interv Aging 2017;12:1799-1809.

Post-registration trials of fidaxomicin in adults: EXTEND

Randomised, controlled, open-label, superiority study to compare clinical outcomes of extended-pulsed fidaxomicin with standard vancomycin

Rationale: an extended-pulsed fidaxomicin regimen might facilitate sustained clinical cure by prolonging *C. difficile* suppression to support gut microbiota recovery

Hospitalised patients >60 years with confirmed CDI randomised 1:1

Extended-pulsed fidaxomicin
200 mg bd Days 1–5
200 mg od alternate Days 7–25

Vancomycin
125 mg qd Days 1–10

Day 55

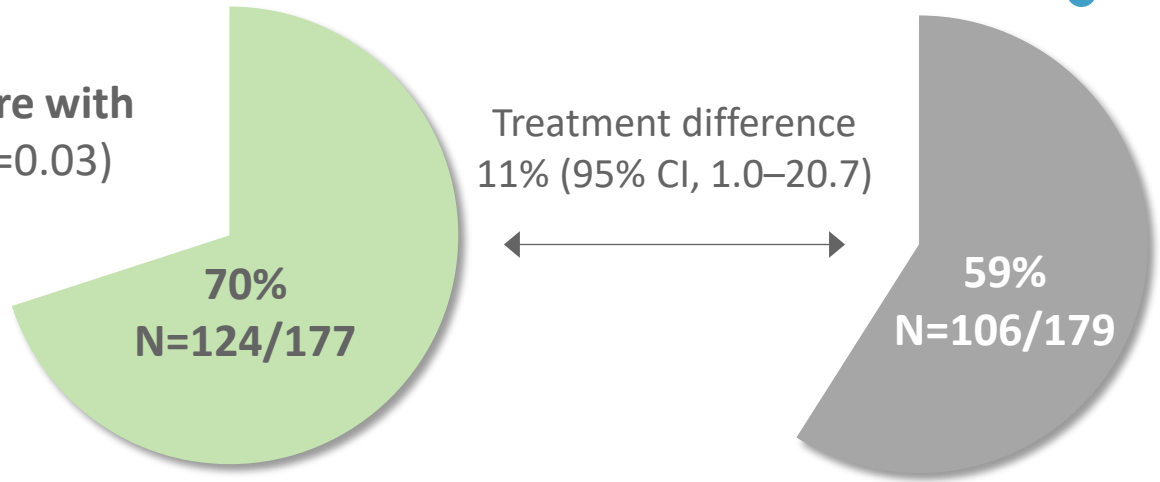
Day 40

Primary endpoint: Sustained clinical cure at 30 days after EOT

Patients were stratified by CDI severity, cancer, age and number of previous CDI episodes – a third had severe CDI

Significantly more patients had sustained clinical cure with fidaxomicin than vancomycin at 30 days post-EOT (p=0.03)

Emergence of **TEAEs** was **comparable** between treatment arms**: fidaxomicin 67%; vancomycin 71%**



bd, twice daily dosing; *C. difficile*, *Clostridioides difficile*; CDI, *C. difficile* infection; CI, confidence interval; EOT, end of treatment; od once daily dosing; qd, four times daily dosing; TEAEs, treatment emergent adverse events.

Guery B, et al. Lancet Infect Dis 2018;18:296-307.

Management of *Clostridioides difficile* infection: an Italian Delphi consensus

Matteo Bassetti ✉, Antonio Cascio, Francesco Giuseppe De Rosa, Marianna Meschiari, Roberto Parrella, Nicola Petrosillo, Alessandro Armuzzi, Flavio Caprioli, Francesco Dentali, Marcello Pani, Alberto Pilotto, Umberto Restelli, Maurizio Sanguinetti

National consensus document on:

– Management and treatment of CDI and rCDI,

– Identification of high risk patients or patients with higher for severe and severe-complicated infection

– Best use of fdx according to European guidelines,

Through Delphi methodology based on guidelines and clinical practice

The Delphi Panel method

- Questionnaires output
- Local Laws/protocols…

- Kick-off meeting
- Research materials validation

Literature review

1° ROUND
- Individual email voting
- 2° round email voting preparation

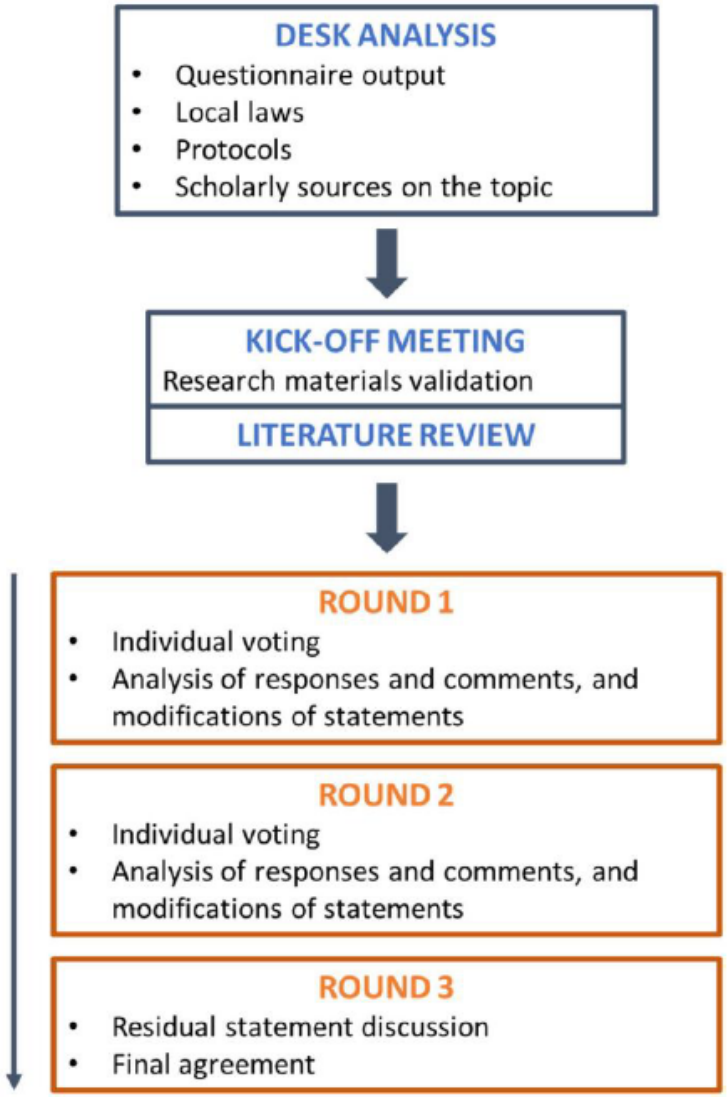
2° ROUND
- Individual email voting
- 3° voting preparation

3° ROUND
- Residual statement web-discussion
- Final agreement

Consensus paper

Eubank, et at. Using the modified Delphi method to establish clinical consensus for the diagnosis and treatment of patients with rotator cuff pathology, BMC Medical Research Methodology, 2016; Loblaw et al. American Society of Clinical Oncology Clinical Practice Guidelines: Formal Systematic Review–Based Consensus Methodology, Journal Of Clinical Oncology, 2012

Delphi panel: Jun 2023-March 2024



Likert Scale

Voting was undertaken by email using a 5-point Likert scale to indicate the level of agreement on each statement:

1 = absolutely disagree,

2 = disagree,

3 = neither agree nor disagree,

4 = agree,

5 = totally agree.

The collected answers were expressed as a percentage response for each item. A total cumulative agreement was defined as the sum of response percentages in items 4 (‘agree’) and 5 (‘absolutely agree’).

For the purpose of this consensus, a **total cumulative agreement ≥75%** was considered a priori to represent consensus for each statement.

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024

Outcomes

23 statements were drafted after the kick-off meeting and spanned the following areas:

- diagnosis, including definition of severe infection, frail patient, and patients at risk of recurrences;
- management of CDIs in patients at high risk;
- benefits of fidaxomicin therapy compared with treatment with broader spectrum antibiotics;
- management of CDI and cost monitoring.

Diagnosi, isolation measures and stewardship

The convenience in adhering to the current ESCMID guidelines on the diagnostic process and on the management of patients with CDI was confirmed

CDI diagnosis Diagnosis of CDI should be made according to the recommended algorithms for CDI testing described in ESCMID diagnostic guidance document[31]	Agreement reached—final statement
Patient management before and after confirmation of CDI Isolation measures for patients with (or suspected to have) CDI should be implemented in a timely way in agreement with ESCMID prevention guidance document[32] and with 2017 IDSA/SHEA guidelines[33]	Agreement reached—final statement

Implementation of antimicrobial stewardship and infection prevention and control programmes in persons at risk of developing bacterial infection, including CDI, would result in reductions in healthcare-associated infections caused by MDR organisms and *C. difficile*, infection-related deaths, and related therapy and management costs[52]	Agreement reached—final statement

Particular attention should be given to monitoring for CDI in high-risk subjects living in long-term care facilities/nursing homes	Agreement reached—final statement
Patients, caregivers and/or family members should be consistently informed about the risk of transmission and recurrence and about the significance of promptly reporting any recurrence or infection in vulnerable contacts to healthcare professionals	Agreement reached—final statement
Patients at risk of low compliance should be identified and closely monitored	

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024
Van Prehn et al., CMI 2021

Severe infection

According to the ESCMID guidelines, severe CDI is characterized by one of the following factors at presentation:

- fever (i.e. core body temperature >38.5°C),
- marked leucocytosis (i.e. leucocyte count >15 × 109/L)
- rise in serum creatinine (i.e. >50% above the baseline).

Additional supporting factors are distension of the large intestine, peri-colonic fat stranding or colonic wall thickening (including low-attenuation mural thickening) at imaging.

The prompt consideration of severe infection should be undertaken in conjunction with its principal risk factors:	Agreement reached—final statement
• older age (>65 y old)[17,18,34] • hypoalbuminaemia prior to infection <2.5 g/dL[1,34–37] • presence of comorbidities or conditions: IBD, chronic kidney failure, liver failure, diabetes, cardiovascular/pulmonary disease[34] • Zar score ≥2[38,39]	

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024
Van Prehn et al., CMI 2021

Patients at risk of recurrence

Identification of patients at risk of recurrences holds significant importance in establishing the therapeutic approach. The foremost risk factors for rCDI with strong evidence are:

- Older age (>65 y old)[17,18,34]
- IBD[34,40]
- Immunocompromised patients: transplanted,[14] on oncological/ oncohaematological treatments,[41] on immunosuppressive therapies,[42] HIV-positive/AIDS, other immunodeficiencies[17,18]

Agreement reached—final statement

- Healthcare-associated CDI[18,34]
- Prior hospitalization in the last 3 mo[34]
- Recent use of PPIs[18,34]
- Recent exposure to fluoroquinolones, cephalosporins, carbapenems, clindamycin[9,18]
- and (a) prior CDI episode(s)[18,34]

Other established risk factors are:

- Severe form of infection[17]
- Chronic kidney failure, liver failure, diabetes, cardiovascular/ pulmonary disease, parenteral nutrition[34]
- And use of concomitant antibiotics started during/after CDI diagnosis[18,34]

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024

IBD and frail patients

- IBD is identified as a risk factor for both severe and recurrent infections
- In terms of predictability of negative outcomes, frailty condition emerged as the most significant risk factor, stronger than the chronological age of the patient

In IBD patients, it must be considered that: • Since CDI is the most important cause of an IBD flare, all IBD patients with worsening of underlying diarrhoea or symptoms of colitis, should be tested for CD[43] • Recurrences are more likely in correspondence with: recent antibiotic therapy, steroid use, infliximab and adalimumab.[40,43] Evidence is conflicting on other immunosuppressive drugs[40]	Agreement reached—final statement

Frailty condition should be taken into proper account in the management of CDI, because of higher risks of negative outcomes reported in frail patients.[44] In persons >65 y with CDI, multidimensional frailty level predicts mortality (at 90 d) more accurately than chronological age and disease severity[44]	Agreement reached—final statement

In hospitalized older patients with CDI, multidimensional frailty should be accurately assessed through validated frailty tools such as the Multidimensional Prognostic Index (MPI)[44–46] or its screening short version BRIEF-MPI[47]	Agreement reached—final statement

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024

Treatment: fidaxomicin place in therapy

Fidaxomicin is a CD narrow spectrum agent,[8] not systemically absorbed, with limited or no activity against other enteric bacteria[51]	Agreement reached—final statement	
Resistance to fidaxomicin has rarely been reported in *C. difficile* without any effect on selection of cross-resistance with other antibiotics due to its limited activity against other enteric commensal bacteria[51]		

Extended-pulsed fidaxomicin regimen (200 mg oral tablets, twice daily on Days 1–5, then once daily on alternate days on Days 7–25) was superior to standard-dose vancomycin for sustained cure of CDI and to reduce recurrence rates without additional costs[8,49]	Agreement reached—final statement	92%

In patients at first CDI episode with high risk of recurrence, fidaxomicin is recommended, since it is associated with significantly higher sustained response[11,12]		100%
Considering that recurrent CDI is associated with significantly higher risks of complications or death within 12 mo of the initial CDI episode,[11] in patients with recurrent CDI fidaxomicin is recommended since it is associated with a significantly lower rate of recurrence of CDI[18,34]	Agreement reached—final statement	100%

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024

Treatment: FMT

- FMT in combination with standard-of-care (SoC) antibiotics was the preferred treatment option of second or further recurrence of CDI

- The main drawback of FMT lies in its current availability in a very limited number of hospitals in Italy.

When available, faecal microbiota transplantation (FMT) is recommended for recurrent CDI and for patients with severe complicated CDI that have deteriorated despite CDI antibiotic treatment and for whom surgery is not feasible.[18,34] FMT, in addition to standard of care antibiotics, is preferred for treatment of a second or further recurrence of CDI[18]	Agreement reached—final statement
The risk-benefit analysis of FMT and/or surgical management should be taken on a case-by-case basis and discussed by the multidisciplinary team[32,33] in accordance with the centre's availability	Agreement reached—final statement

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024

Treatment: bezlotoxumab

Bezlotoxumab should be considered for:	Agreement reached—final statement
• Patients with multiple (≥3) rCDI risk factors, in addition to SoC, regardless of the severity of previous episodes	
• Patients at first CDI recurrence in addition to vancomycin or fidaxomicin, when fidaxomicin was used to manage the initial CDI episode, independently of rCDI risk factors	Agreement reached—final statement
• Patients with second or multiple CDI recurrences, in centres where FMT is not available[50]	Agreement reached—final statement

To balance risks/costs and benefits of its use, bezlotoxumab use should be limited in the first CDI episode only to high-risk patients and considered in patients with second or multiple CDI recurrences especially in centres where FMT is not available or contraindicated	Agreement reached—final statement

This suggestion comes from an Italian RW multicentric cohort study, confirming greater efficacy of bezlotoxumab + SoC versus SoC alone for the prevention of rCDI. Although not reaching statistical significance, the benefit of bezlotoxumab + SoC on the composite outcome appeared to be attenuated in participants aged <70 years and in those who received fidaxomicin as first-line treatment.

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024
Meschiari et al., Int J Infect Dis 2023

Treatment: vancomycin

Clinically, vancomycin high-dose use (250 mg or higher 4 times a day) is discouraged due to possible side effects such as abdominal pain and nausea, whereas no benefit is observed[18]	Agreement reached—final statement	83%

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024

Cost monitoring

Cost monitoring of CDI treatment should be performed considering the global assessment of patient pathway related to CDI, including testing and other exam costs, hospital readmission rates, inpatients' and outpatients' costs	Agreement reached—final statement	77%

Studies have demonstrated that initial CDI treatment with fidaxomicin results in reduced healthcare costs compared with vancomycin/metronidazole. Despite higher drug acquisition costs for fidaxomicin, these are offset by lower hospitalization expenses resulting from fewer recurrences, reduced complication costs and fewer GP visits compared with vancomycin.

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024

Recurrences

According to the preparatory analysis of this consensus, one of the issues limiting appropriate management of CDI is the complexity in recurrence identification when the patient is hospitalized in different clinics without a comprehensive medical record.

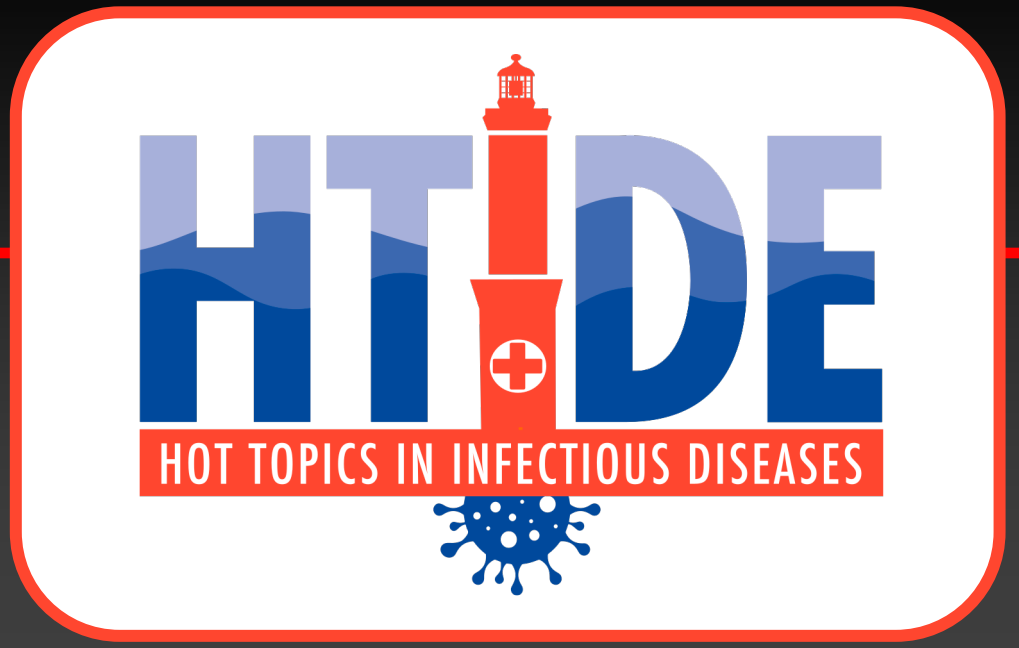
Considering recurrence as a pivotal factor in addressing the infection, when feasible, the anamnesis should identify earlier CDI and the information flow should facilitate both retrospective and prospective patient's history	Agreement reached—final statement	
The information flow should ensure that there is a seamless transfer of information when a patient is discharged from the hospital. Infection details should be consistently and clearly recorded using specialized software for managing patient information	Agreement reached—final statement	92%
An 8-wk follow-up call is recommended to promptly detect any potential recurrences		

Excluded statements

Table 2. Excluded statements

#	Round 1 statements	Results	Round 2 statements	Results
Ex 12	Prophylaxis of CDAD with fidaxomicin can reduce the incidence of confirmed CDAD in the HSCT population. Patients with a history of CDAD or *C. difficile* colonization prior to transplantation or at risk of recurrent CDAD after transplantation should be considered candidates for fidaxomicin prophylaxis[40]	Agreement failed—statement excluded		
Ex 13	Prophylaxis with fidaxomicin should be considered in other transplanted patients	Agreement failed—statement excluded		
Ex 16	It is suggested to always have a minimum supply of fidaxomicin available, calibrated to the different needs of hospitals, to allow for initiation of therapy when appropriate	Agreement failed—statement to be amended and voted again	In order to have equal antimicrobial stewardship programmes in different hospitals, it is desirable that, based on local and hospital epidemiology, a minimum availability of fidaxomicin is considered	Agreement failed—statement excluded
Ex 23	It is advisable to implement patient empowerment initiatives to enhance their involvement and engagement in managing the condition	Agreement failed—statement excluded		

Bassetti et al., Journal of Antimicrobial Chemotherapy, 2024



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