Infezioni da Clostridioides difficile

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DISCLOSURE

In qualità di RELATORE, ai sensi dell'art.76 sul Conflitto di Interessi dell'Accordo Stato-Regioni del 2 febbraio 2017,

dichiara

per l'evento in oggetto l'esistenza negli ultimi due anni di rapporti di natura finanziaria e/o lavorativa con le seguenti imprese commerciali operanti in ambito sanitario: MSD, Pfizer, B&D, Tillots, Termofisher, ImmuneMed, Qiagen, Takeda.

Dichiaro, inoltre, che i contenuti formativi esposti sono indipendenti da interessi commerciali.

- **Clostridium difficile was first described in 1935 in the resident flora of healthy neonates.**

- **Corresponding to the difficulty of cultivating the bacteria, it was initially termed Bacillus difficilis.**

- **More than 3 decades later, the relation between pseudomembranous colitis and C difficile was revealed, especially after clindamycin treatment.**

- **During the past 20 years this gram-positive and spore-forming bacterium has been identified as the most common cause of antibiotic-associated diarrhea in industrialized countries.**

Hall IC and O'Toole ER. Am J Dis Chil 1935; 49:390-42
Cohen E et al. JAMA 1973; 223:1379-80

Anaerobe 40 (2016) 95–99

Contents lists available at ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe

Clostridium difficile

Reclassification of *Clostridium difficile* as *Clostridioides difficile* (Hall and O'Toole 1935) Prévot 1938

Paul A. Lawson [a, *], Diane M. Citron [b], Kerin L. Tyrrell [b], Sydney M. Finegold [c, d, e]

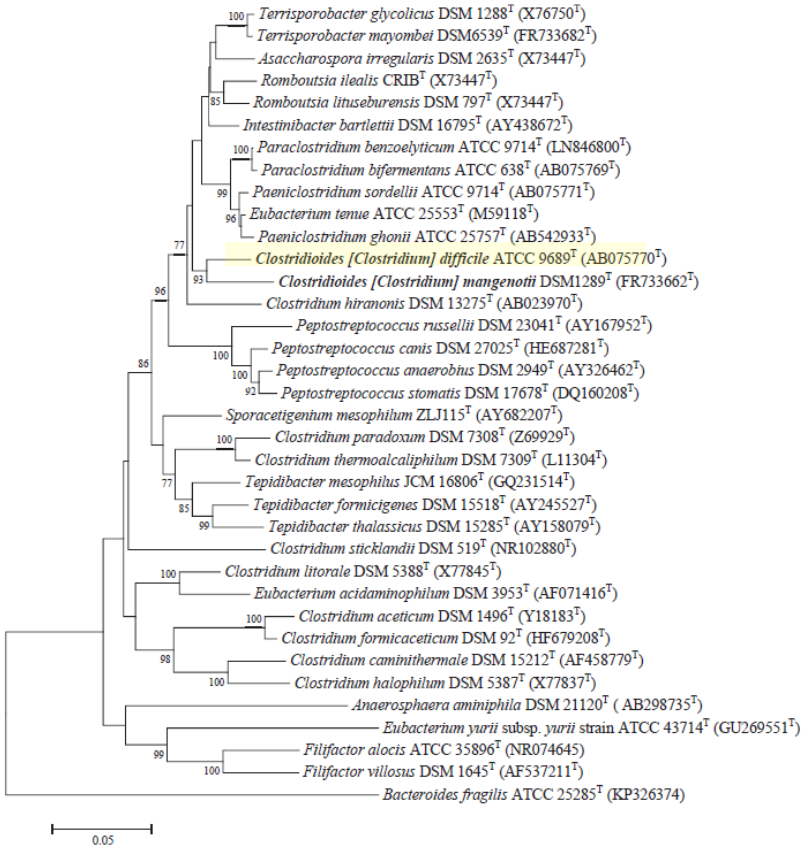


Fig. 1. Evolutionary relationships of taxa. Neighbor-Joining tree based on 16S rRNA gene sequence data, showing the phylogenetic position of members fo the family Peptostreptococcaceae. The tree was constructed using the Neighbor-Joining method [27] using the Kimura 2-parameter method [29] and are in the units of the number of base substitutions per site. All ambiguous positions were removed for each sequence pair. There were a total of 1425 positions in the final dataset. Evolutionary analyses were conducted in MEGA7 [30]. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches [28]. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The outgroup used was *Bacteroides fragilis*.

Introduction

Most common cause of infectious diarrhea in hospitalized patients

Symptoms of diarrhea that can progress to life-threatening inflammation of the colon

Associated with substantial morbidity and mortality

Community-acquired CDI has also become epidemiologically and clinically relevant

Recurrence is common

Presents a substantial challenge

CDI, *Clostridioides difficile* infection.
Finn E, et al. BMC Infect Dis. 2021;21:456.

Burden of CDI in Europe and the US

US[a,b]

- 223,900 cases of CDI/y (2017)
- 12,800 deaths (2017)
- Most common agent responsible for HAIs (12.1%)[b]
- Classed by the CDC as an urgent threat

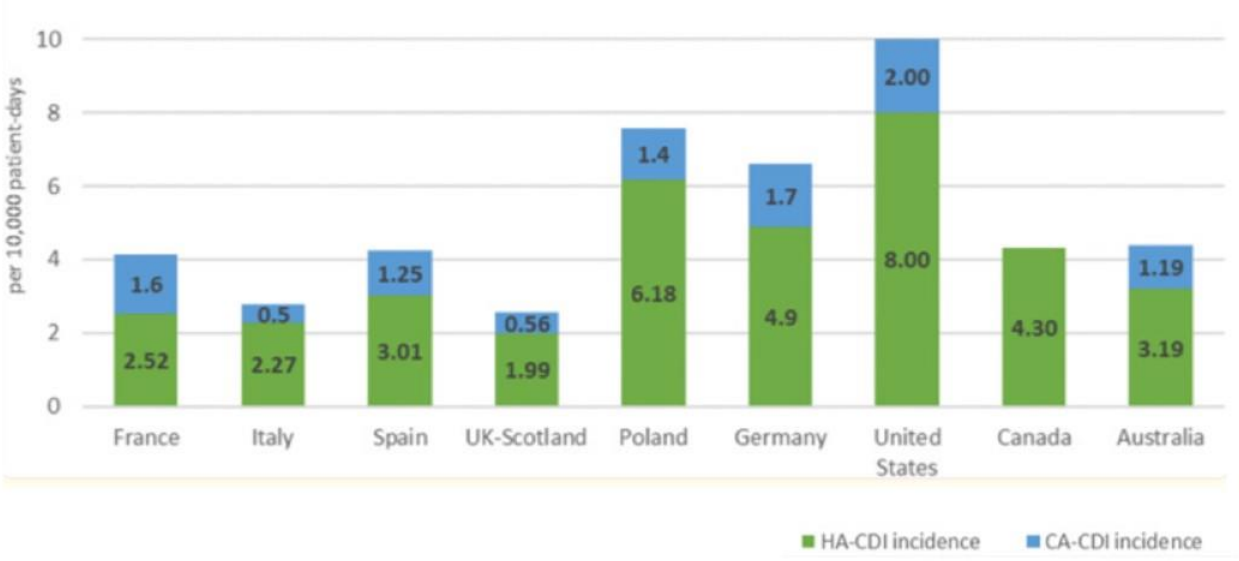
Europe[c]

- ~124,000 cases of CDI/y
- 3700 deaths
- Eighth most common agent responsible for HAIs (5.4%)

CDC, Centers for Disease Control and Prevention; HAI, healthcare-associated infection.
a. CDC. Accessed February 9, 2023. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf; b. Magill SS, et al. N Engl J Med. 2014;370:1198-1208; c. ECDC. Accessed February 15, 2023. https://www.ecdc.europa.eu/en/clostridium-difficile-infections/facts

Overall CDI Incidence per 10,000 Patient-Days
*Systematic Literature Review of Epidemiology Studies, 2009-2019**

CDI Incidence Rate/10,000 Patient-Days[a]



Study Findings[a]

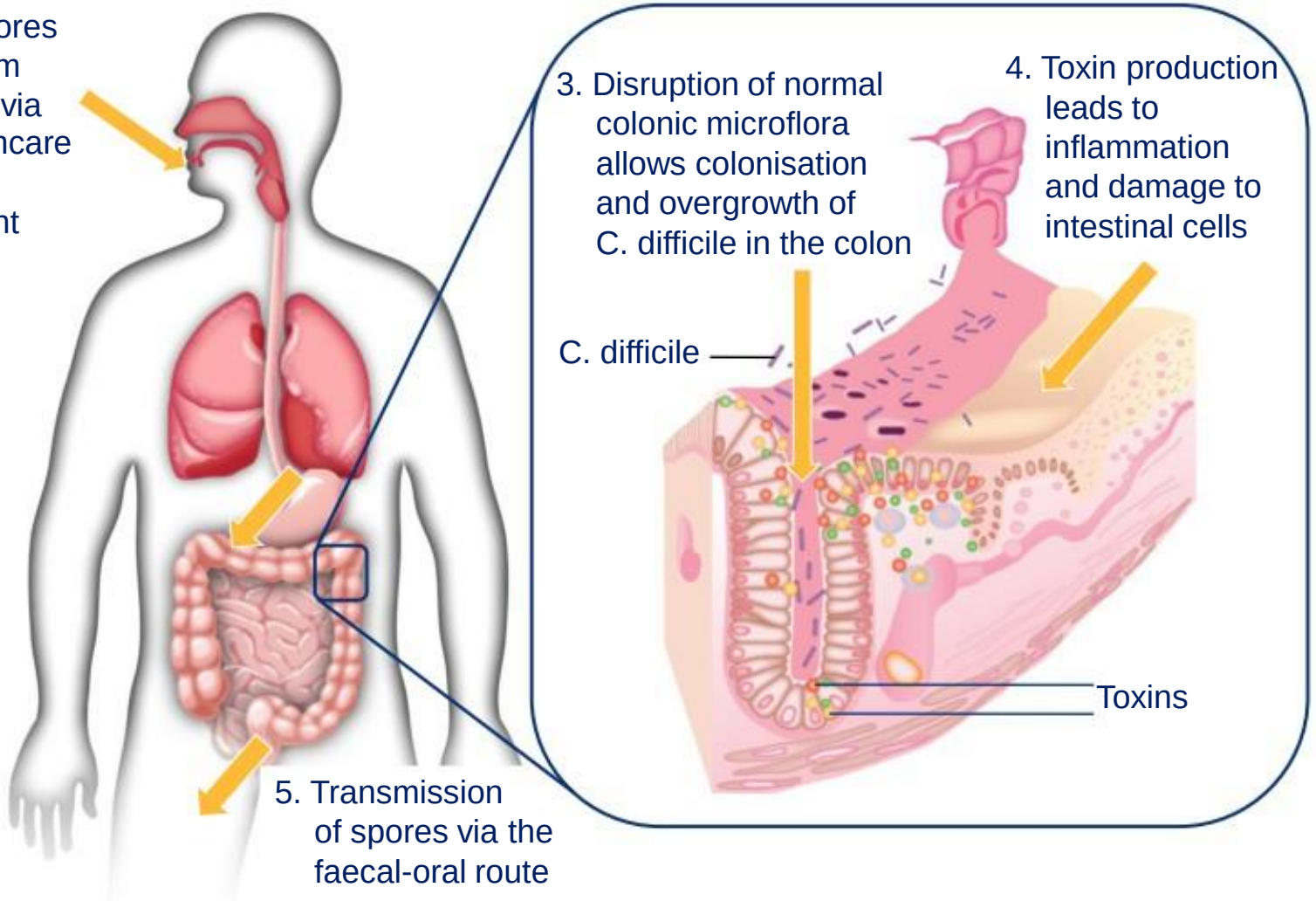
- Incidence rates vary widely between countries, which reflects differences in:
  - Incidence
  - Who gets tested
  - Diagnostic methods
- **Almost 70% of cases were HA-CDI, > 30% were CA-CDI[b]**

*185 included records, most focused on the US.
CA-CDI, community-associated CDI; HA-CDI, healthcare-associated CDI.
a. Finn E, et al. BMC Infect Dis. 2021;21:456; b. Ofori E, et al. J Hosp Infect. 2018;99:436-442.

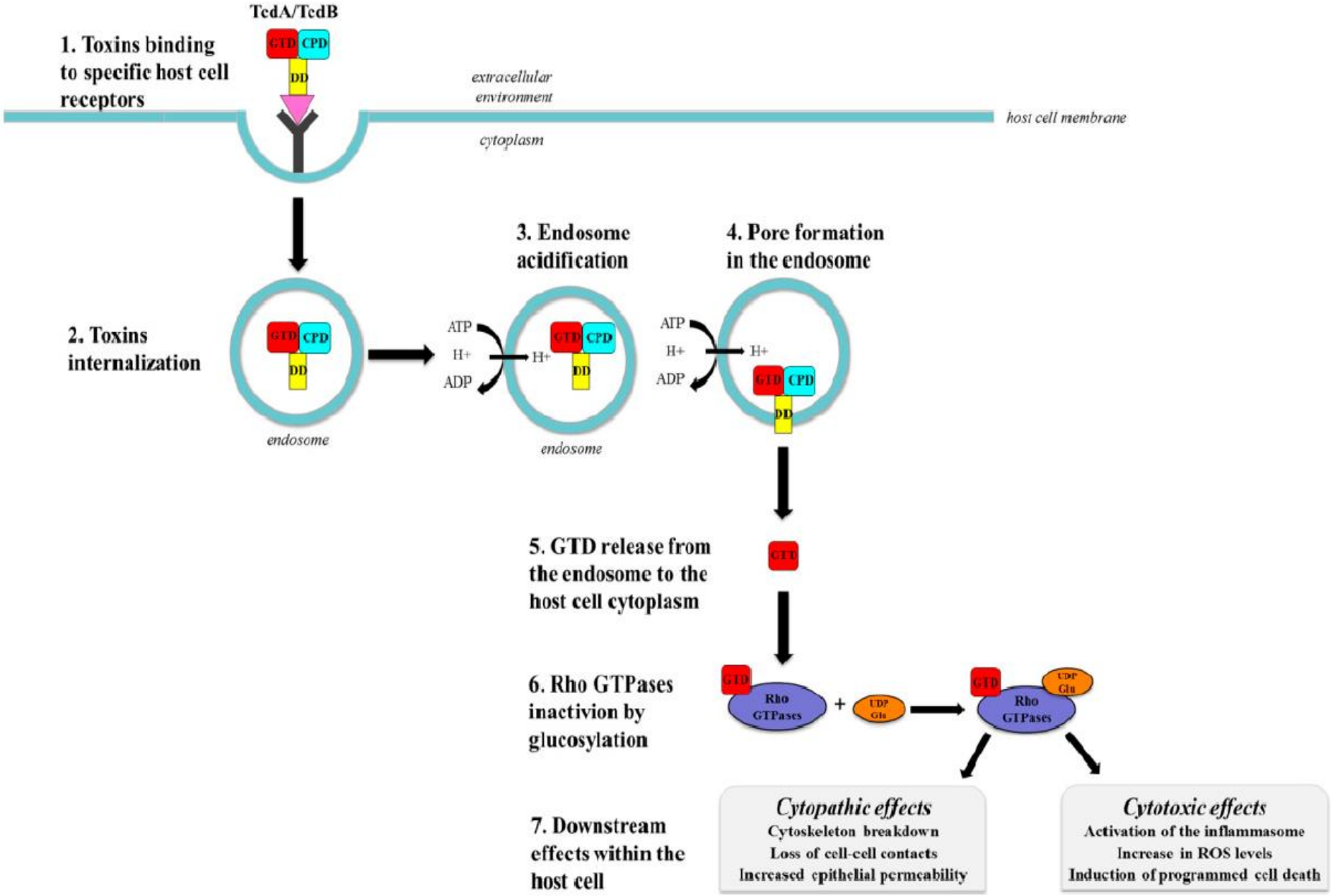
The infectious cycle of transmission and recurrence of CDI

1. Ingestion of spores transmitted from other patients, via hands of healthcare personnel and the environment

2. Germination into growing (vegetative) cells

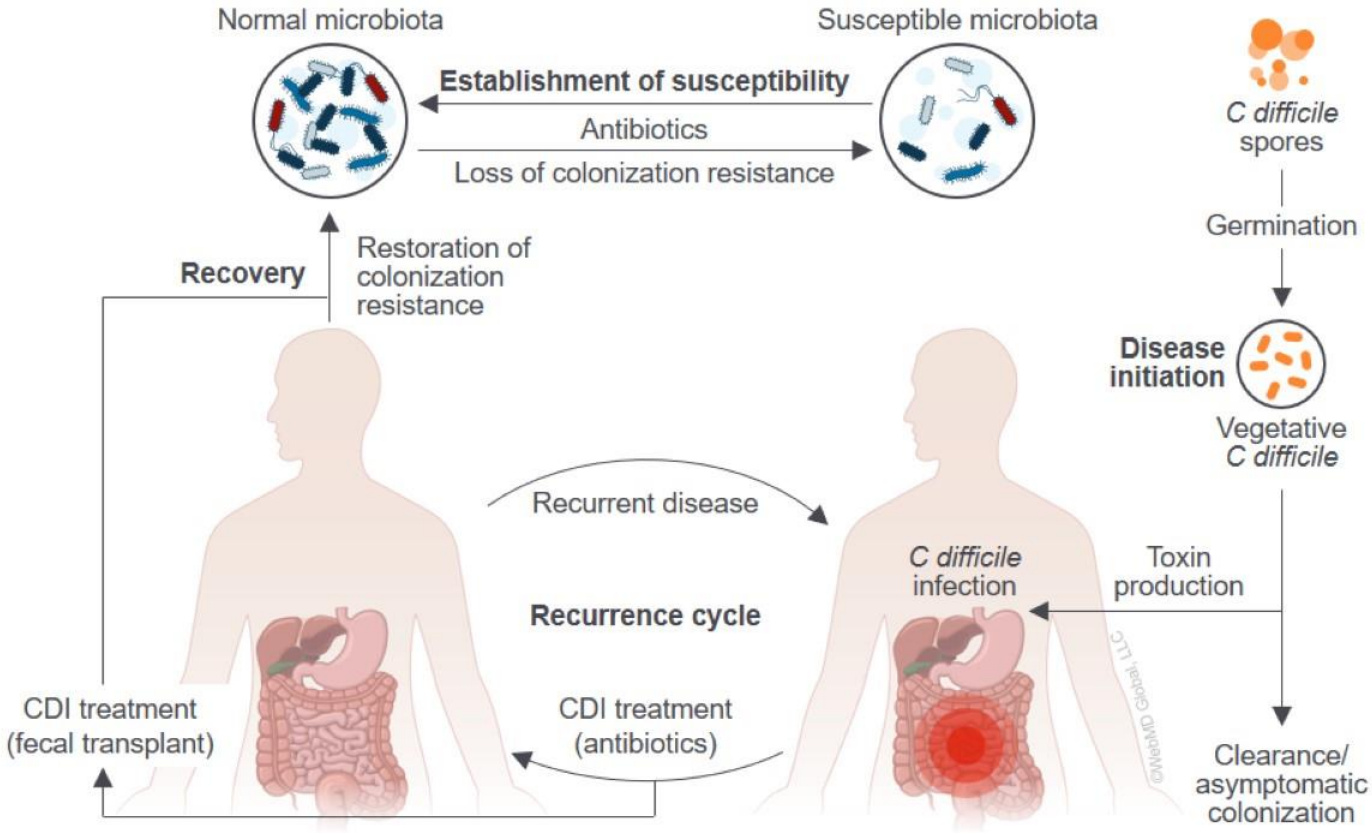


Adapted from Sunenshine RH, et al. Cleve Clin J Med 2006;73:187-97.



Di Bella S et al. Toxins 2016; 8: 134

Recurrence of CDI



Britton RA, et al. Gastroenterology. 2014;146:1547-1553.

Burden of Recurrent CDI

Prevalence is common[a]

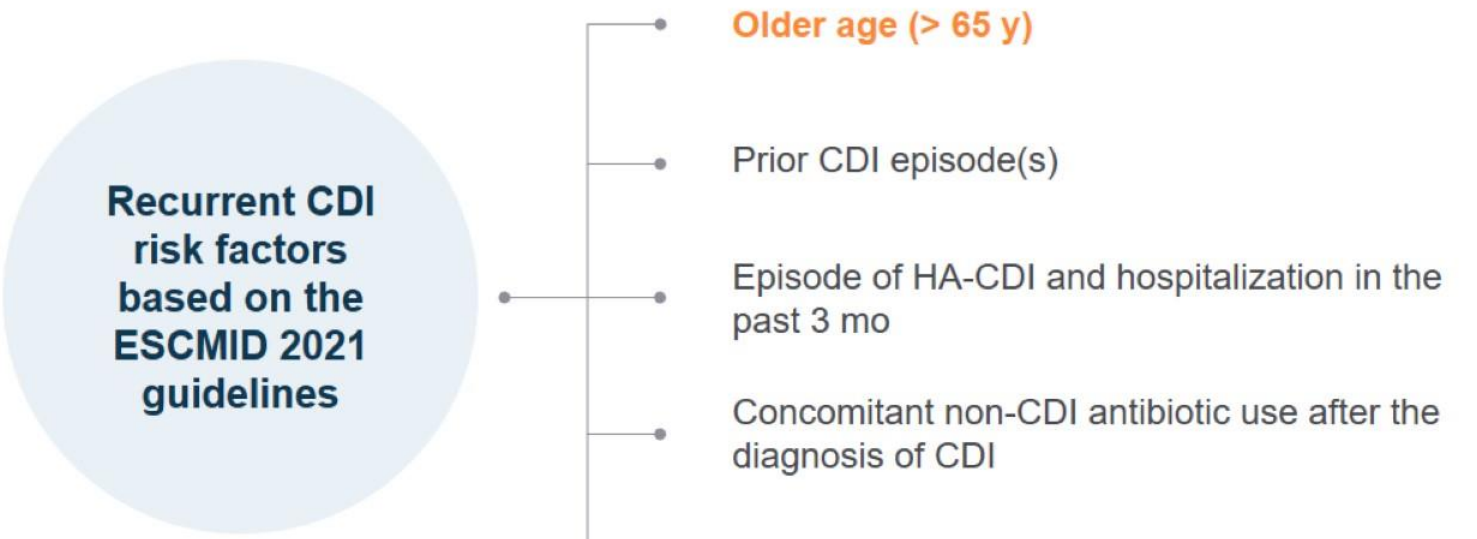
- Occurs in ~25% of patients
- ~40% of first recurrence patients experience a second recurrence
- ~One-third of second recurrence patients experience a third recurrence
- ~One-quarter of those patients will experience a fourth or additional recurrence

Consequences of recurrence

- Significant morbidity and healthcare costs[a]
- Higher risk of mortality and complications in patients hospitalized with a first CDI episode than for those with no evidence of CDI[b,c]
- Mortality and complications increase significantly in patients with recurrent CDI vs nonrecurrent CDI[b,c]

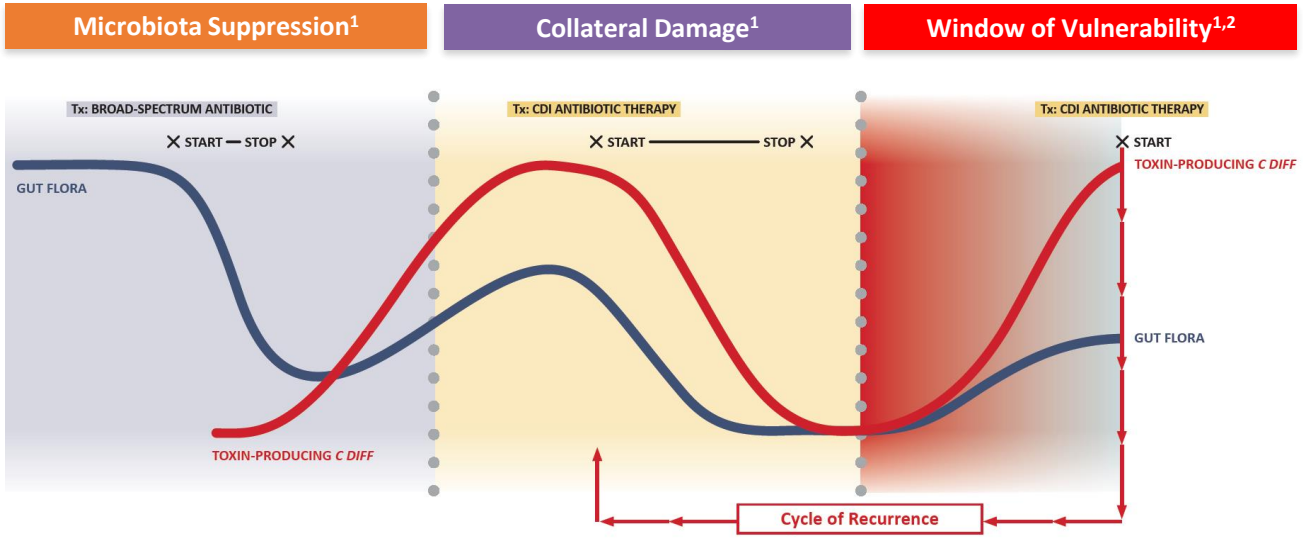
a. Finn E, et al. BMC Infect Dis. 2021;21:456; b. Enoch DA, et al. J Hosp Infect. 2020;106:286-289; c. Olsen MA, et al. Clin Microbiol Infect. 2015;21:164-170.

Risk Factors for Recurrent CDI



ESCMID, European Society of Clinical Microbiology and Infectious Diseases; PPI, proton pump inhibitor.
van Prehn J, et al. Clin Microbiol Infect. 2021;27(suppl 2):S1-S21.

Triphasic Pathogenesis of CDI and the Role of *Clostridium difficile* Toxins

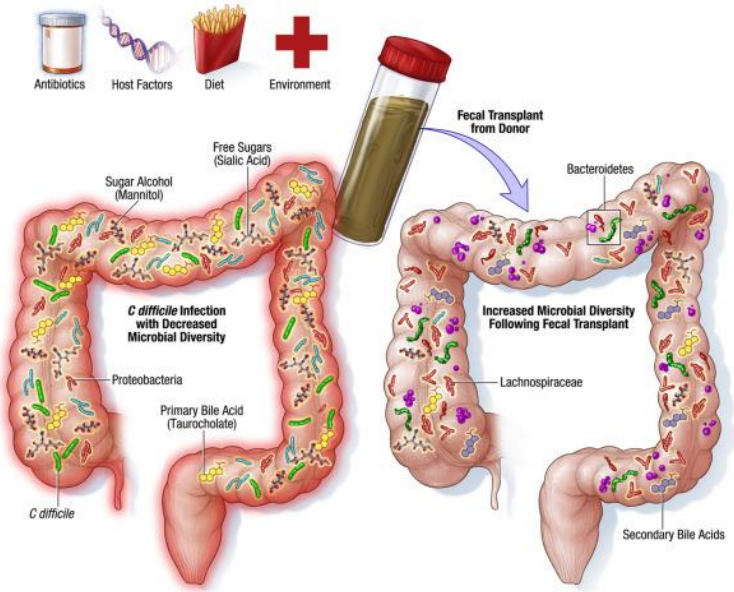


- Toxins, particularly toxin B, are the cause of CDI symptoms through damaging the GI epithelium and invoking an inflammatory response[3]

GI=gastrointestinal.

1. Bagdasarian N et al. *JAMA*. 2015;313(4):398–408. **2.** Abujamel T et al. *PLoS One*. 2013;8(10):e76269. doi:10.137/journal.pone.0076296. **3.** Carter GP et al. *Trends Microbiol*. 2012;20(1):21-29.

CDI
- Not only a matter of antimicrobials and non-antimicrobials -

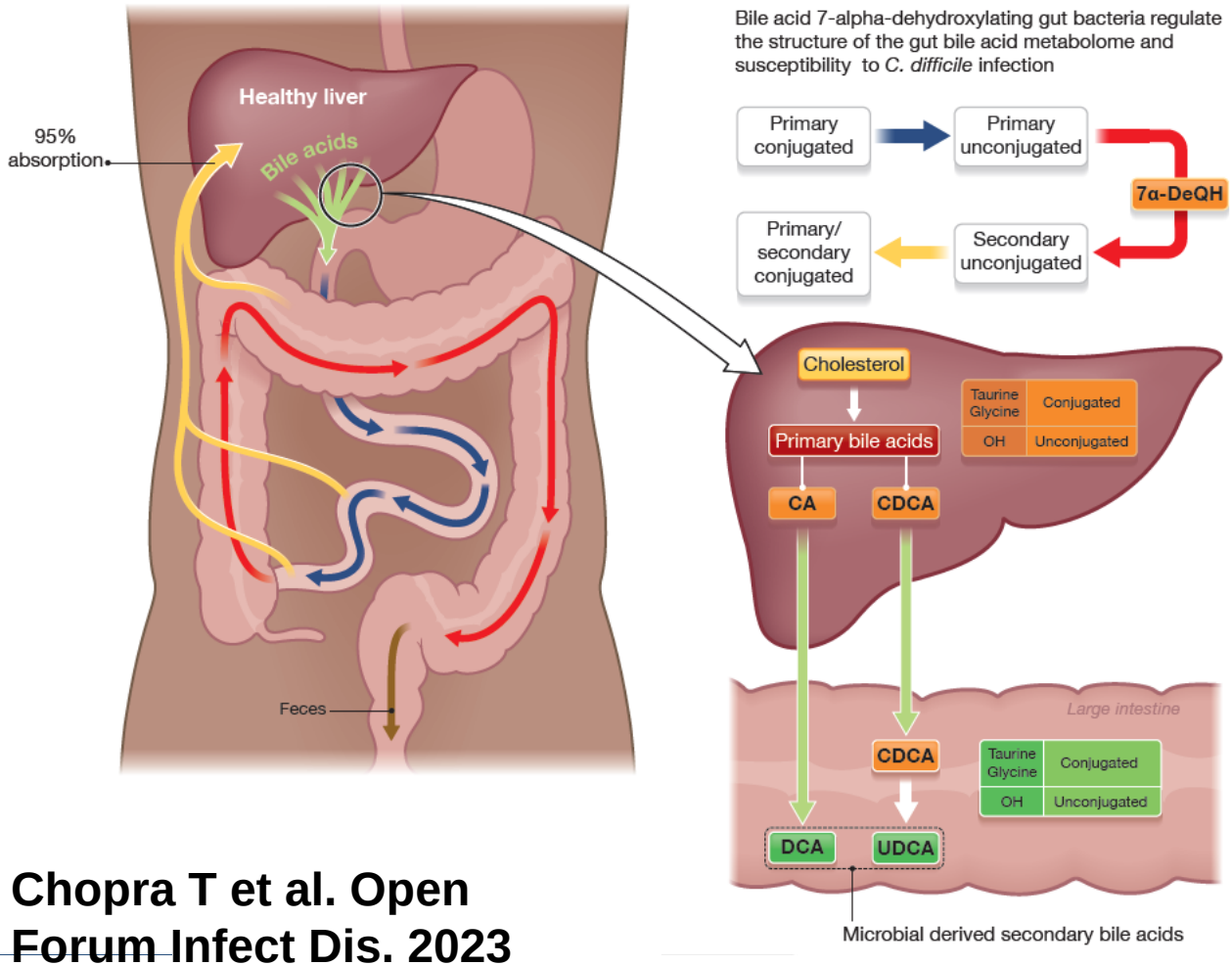


Functions of the gut microbiota and colonization resistance

A rich and diverse gut microbiome provides resistance to colonization of the gut by exogenous organisms and prevents expansion of potential pathogenic organisms within the gut through a variety of mechanisms:

- ✓ **Competition for key nutrients**
- ✓ **Production of inhibitory bile acids**
- ✓ **Production of short-chain fatty acids**
- ✓ **Lowering the luminal pH**
- ✓ **Production of bacteriocins**
- ✓ **Maintenance and enhancement of intestinal barrier function**

Role of the microbiome in the life cycle of *Clostridioides difficile*



Chopra T et al. Open Forum Infect Dis. 2023 Sep 1;10(9):ofad447.

Clostridioides difficile ferrosome organelles combat nutritional immunity

- **Iron is indispensable for almost all forms of life but toxic at elevated levels.**
- **To survive within their hosts, bacterial pathogens have evolved iron uptake, storage and detoxifcation strategies to maintain iron homeostasis.**
- **Recent studies showed that three Gram-negative environmental anaerobes produce iron-containing ferrosome granules.**
- **However, it remains unclear whether ferrosomes are generated exclusively by Gram-negative bacteria.**
- **C. difficile undergoes an intracellular iron biomineralization process and stores iron in membrane-bound ferrosome organelles containing non-crystalline iron phosphate biominerals.**

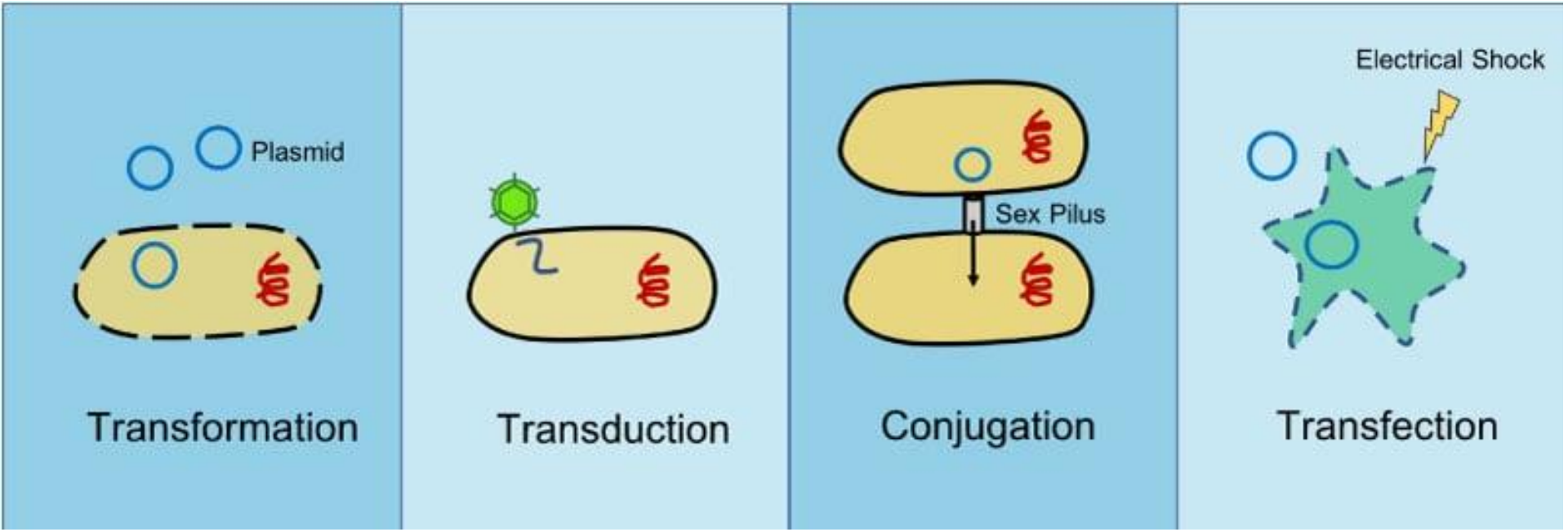
Pi H et al. Nature 2023 Nov;623(7989):1009-1016.

Prophage Carriage and Genetic Diversity within Environmental Isolates of *Clostridioides difficile*

Khald Blau and Claudia Gallert *

- **In this study, the whole genomes of 166 environmental C. difficile isolates from diverse environmental samples were sequenced**
- **Prophages were predicated in varying numbers in all genomes of 166 environmental C. difficile isolates tested,**
- **Among 372 intact prophages, the predominant prophages were phiCDHM1, phiCDHM19, phiMMP01, phiCD506, phiCD27, phiCD211, phiMMP03, and phiC2, followed by phiMMP02, phiCDKM9, phiCD6356, phiCDKM15, and phiCD505.**
- **Two newly discovered siphoviruses, phiSM101- and phivB_CpeS-CP51-like Clostridium phages, were identified in two C. difficile genomes.**

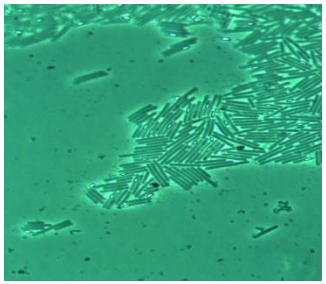
Int J Mol Sci 2023 Dec 19;25(1):2.


Plasmid
Transformation
Transduction
Sex Pilus
Conjugation
Electrical Shock
Transfection

"All disease begins in the gut"

Hippocrates, circa 340 BC

Diagnosis…it's complicated



Bug

- Grow the organism (culture)
- Cell surface protein (GDH)

More sensitive C. difficile carriage

Its Toxins

- Toxin activity
- Toxin protein

More specific Lack of sensitivity

Its DNA

- Toxin genes (NAAT)

More sensitive C. difficile carriage

Table 3. Summary of Available Tests for *Clostridium difficile* Infection, in Decreasing Order of Sensitivity

Test	Sensitivity	Specificity	Substance Detected
Toxigenic culture	High	Low[a]	*Clostridium difficile* vegetative cells or spores
Nucleic acid amplification tests	High	Low/moderate	*C. difficile* nucleic acid (toxin genes)
Glutamate dehydrogenase	High	Low[a]	*C. difficile* common antigen
Cell culture cytotoxicity neutralization assay	High	High	Free toxins
Toxin A and B enzyme immunoassays	Low	Moderate	Free toxins

McDonald LC et al. Clin Infect Dis 2018; 66: e1-e47

Bristol Stool Chart

Tipo 1		Grumi duri separati tra loro, come noci (difficili da espellere)
Tipo 2		A forma di salsiccia, ma formata da grumi uniti tra loro
Tipo 3		Come un salame, ma con crepe sulla sua superficie
Tipo 4		Come una salsiccia o un serpente, liscia e morbida
Tipo 5		Pezzi separati morbidi con bordi come tagliati/spezzati; chiara (facile da evacuare)
Tipo 6		Pezzi soffici/flocculari con bordi frastagliati, feci pastose
Tipo 7		Acquosa, nessun pezzo solido **Completamente liquida**

STIPSIS

NORMAL

DIARRHEA

Ask for CD test

Clostridium difficile Infection Control and Prevention

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[2,3] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

Clinical Infectious Diseases® 2018;66(7):987–94

Isolation Measures for Patients With CDI

XIII. Should private rooms and/or dedicated toilet facilities be used for isolated patients with CDI?

Recommendations

1. Accommodate patients with CDI in a private room with a dedicated toilet to decrease transmission to other patients. If there is a limited number of private single rooms, prioritize patients with stool incontinence for placement in private rooms *(strong recommendation, moderate quality of evidence).*
2. If cohorting is required, it is recommended to cohort patients infected or colonized with the same organism(s)—that is, do not cohort patients with CDI who are discordant for other multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus (strong recommendation, moderate quality of evidence).*

XIV. Should gloves and gowns be worn while caring for isolated CDI patients?

Recommendation

1. Healthcare personnel must use gloves *(strong recommendation, high quality of evidence)* and gowns *(strong recommendation, moderate quality of evidence)* on entry to a room of a patient with CDI and while caring for patients with CDI.

XV. When should isolation be implemented?

Recommendation

1. Patients with suspected CDI should be placed on preemptive contact precautions pending the *C. difficile* test results if test results cannot be obtained on the same day *(strong recommendation, moderate quality of evidence)*.

XVI. How long should isolation be continued?

Recommendations

1. Continue contact precautions for at least 48 hours after diarrhea has resolved *(weak recommendation, low quality of evidence)*.
2. Prolong contact precautions until discharge if CDI rates remain high despite implementation of standard infection control measures against CDI *(weak recommendation, low quality of evidence)*.

XIX. Should noncritical devices or equipment be dedicated to or specially cleaned after being used on the isolated patient with CDI?

Recommendation

1. Use disposable patient equipment when possible and ensure that reusable equipment is thoroughly cleaned and disinfected, preferentially with a sporicidal disinfectant that is equipment compatible *(strong recommendation, moderate quality of evidence)*.

XXIV. Should asymptomatic carriers of *C. difficile* be identified and isolated if positive?

Recommendation

1. There are insufficient data to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions *(no recommendation)*.

XXV. What is the role of antibiotic stewardship in controlling CDI rates?

Recommendations

1. Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk *(strong recommendation, moderate quality of evidence).*
2. Implement an antibiotic stewardship program *(good practice recommendation).*
3. Antibiotics to be targeted should be based on the local epidemiology and the *C. difficile* strains present. Restriction of fluoroquinolones, clindamycin, and cephalosporins (except for surgical antibiotic prophylaxis) should be considered *(strong recommendation, moderate quality of evidence).*

European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults

Van Prehn J et al. Clin Microbiol Infect 2021;27 Suppl 2:S1-S21.

I. What is the best treatment for an initial episode of CDI?

- **In case of non-severe CDI, we recommend to discontinue antibiotic therapy if possible with the inciting antibiotic and closely monitor the patient for 48 hours. (Good practice statement)**

- **For the initial episode of CDI we recommend fidaxomicin 200 mg twice daily for 10 days. [Strong (recommendation), Moderate(level of evidence)]**

- **When access to fidaxomicin is limited, it is reasonable to make a risk stratification for selected use. [Good practice statement]**

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In this case, fidaxomicin is recommended whenever the clinicians deems the risk of recurrence high.

This can be supported by

- **an older age of the patient (>65 years)**

plus the presence of one or more additional risk factor(s), i.e.

- **healthcare-associated CDI,**
- **prior hospitalization in the last 3 months,**
- **use of concomitant antibiotics,**
- **PPIs started during/after CDI diagnosis and**
- **a prior CDI episode.**

The risk of recurrence is assumed to be higher with more risk factors present.

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I. What is the best treatment for an initial episode of CDI?

- **When fidaxomicin is not available or feasible, oral vancomycin 125 mg four times daily for 10 days is a suitable alternative. (Strong, High)**
- **Oral metronidazole 500 mg three times daily for 10 days should be used only when vancomycin and fidaxomicin are not available or feasible. (Strong, Moderate)**
- **The use of vancomycin 500 mg four times daily is not recommended. (Strong, very low)**

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II. What is the best treatment for severe and severe complicated CDI?

- **Options for treatment of any severe and severe-complicated CDI episode include vancomycin 125 mg four times daily for 10 days or fidaxomicin 200 mg twice daily for 10 days.**

- **There is no data supporting the superiority of one over the other. (Good practice statement)**

- **For severe CDI, routine addition of iv metronidazole to oral SoC therapy is not recommended. (Weak, Very Low)**

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Van Prehn J et al. Clin Microbiol Infect 2021;27 Suppl 2:S1-S21.

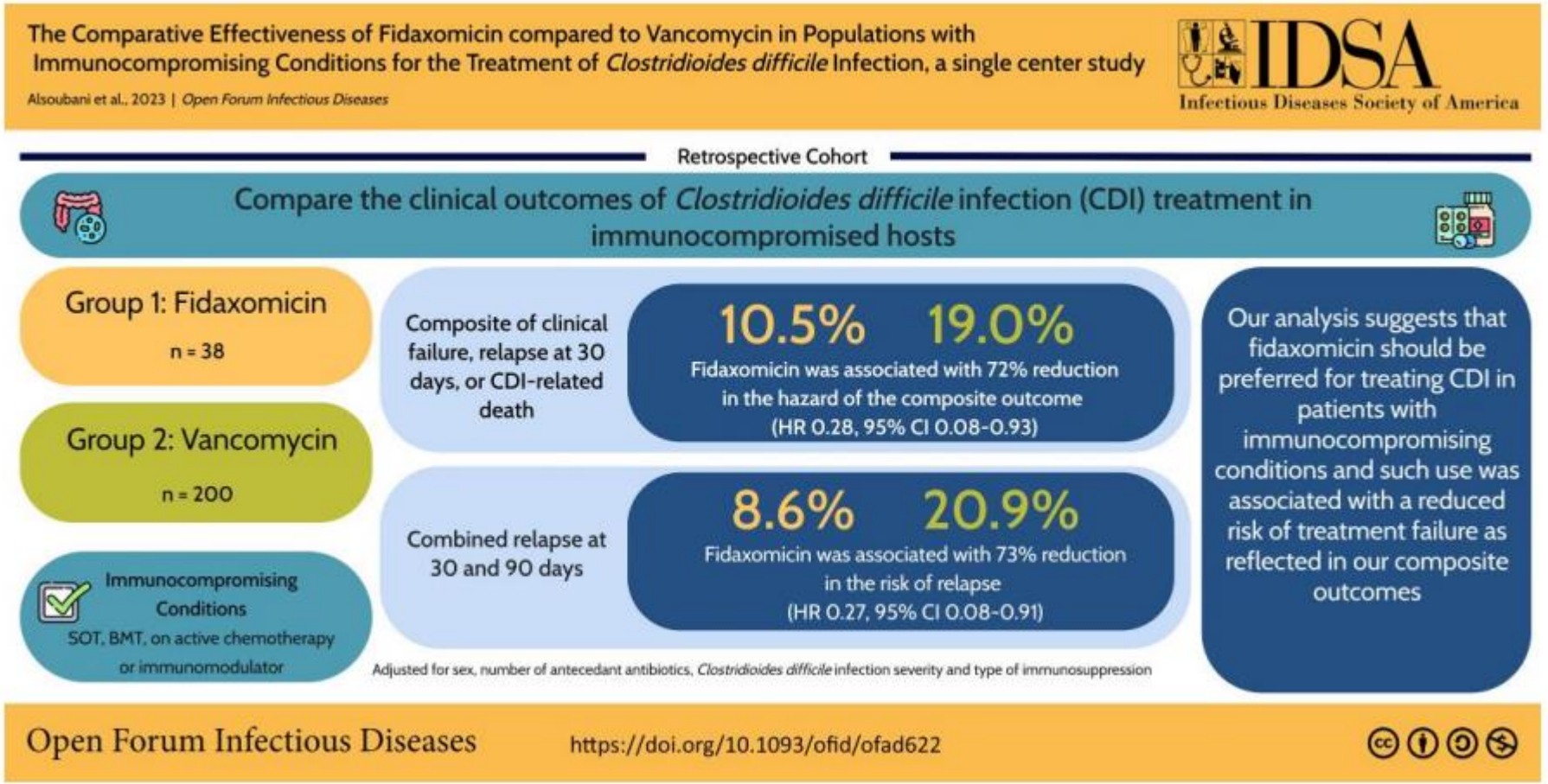
II. What is the best treatment for severe and severe complicated CDI?

- **When a patient is deteriorating or progressing to severe complicated CDI while on anti-CDI antibiotic therapy, addition of iv tigecycline 50 mg twice daily (100 mg loading dose) may be considered on a case-by-case basis. (Weak, Very Low)**

- **Consult a surgeon for any severe-complicated case. (Good practice statement)**

- **Total abdominal colectomy might be prevented by partial colectomy or loop ileostomy. (Weak, Very Low)**

Comparative Effectiveness of Fidaxomicin vs Vancomycin in Populations With Immunocompromising Conditions for the Treatment of *Clostridioides difficile* Infection: A Single-Center Study



Alsoubani M et alOpen Forum Infect Dis 2023 Dec 8;11(1):ofad622.

European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults

Van Prehn J et al. Clin Microbiol Infect 2021;27 Suppl 2:S1-S21.

III. What is the best treatment for CDI when no oral treatment is possible?

- **When oral therapy is not possible, attempt intraluminal (gastroduodenal or coloscopic) delivery of vancomycin or fidaxomicin. (Good practice statement)**

- **and consider adjunctive treatment with iv metronidazole 500 mg three times daily or iv tigecycline 50 mg two times daily (100 mg loading dose). (Weak, Very Low)**

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IV. What is the best treatment for refractory CDI?

- **When non-complicated CDI is not responding to CDI treatment and the patient is not deteriorating or progressing to complicated CDI, carefully re-evaluate the diagnosis of CDI and consider an alternative diagnosis. (Good practice statement)**

- **Consult a surgeon as soon as a patient's condition is deteriorating and the patient is not responding to CDI treatment. (Good practice statement)**

- **FMT may be a rescue therapy for patients with severe complicated CDI that have deteriorated despite CDI antibiotic treatment and for whom surgery is not feasible. 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. (Weak, Very Low)**

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Van Prehn J et al. Clin Microbiol Infect 2021;27 Suppl 2:S1-S21.

V. What is the best treatment for recurrent CDI?

- **If the initial CDI episode was treated with vancomycin or metronidazole, then fidaxomicin 200 mg twice daily for 10 days is the preferred agent to treat a first CDI recurrence. (Strong, Low)**

- **If the initial CDI episode was treated with fidaxomicin, consider addition of bezlotoxumab (when available and feasible) to an oral SoC antibiotic treatment, i.e. vancomycin or fidaxomicin. Addition to vancomycin: Weak, Moderate / Addition to fidaxomicin: good practice statement**

- **Consider a vancomycin tapering and pulse scheme for recurrent CDI when fidaxomicin or bezlotoxumab are not available or feasible. (Weak, Very low)**

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VI. What is the best treatment for multiple recurrent CDI?

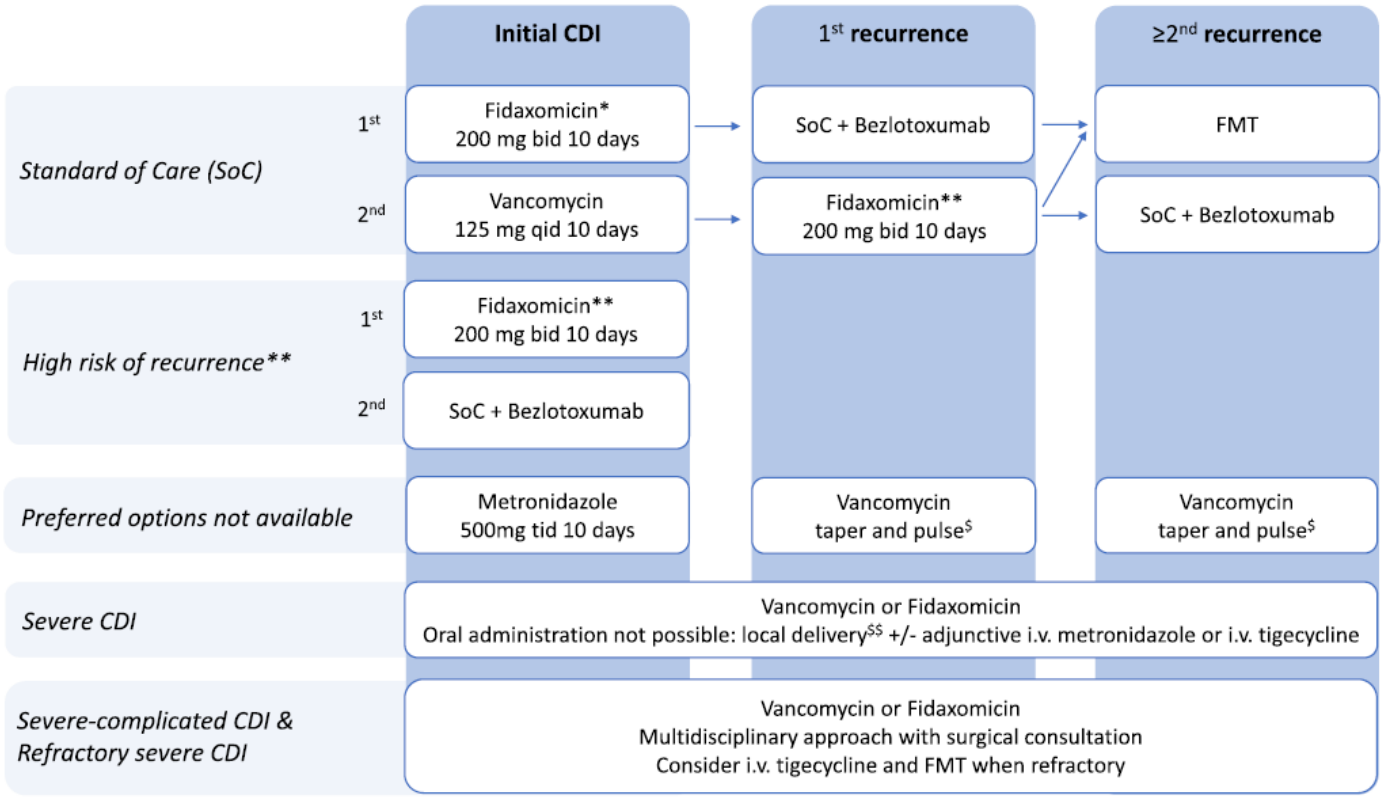
- **Treatment options for a second or further CDI recurrence include FMT after SoC antibiotic pre-treatment or bezlotoxumab in addition to SoC antibiotic treatment.**

- **The choice between either depends on patients' characteristics, previous treatment, local regulations, availability and feasibility.**

- **For FMT an adequate multidisciplinary risk assessment is mandatory and FMT products should be available with standardized preparation and screening. Weak, Moderate (FMT) / Low (bezlotoxumab)**

ESCMID-Suggested treatment algorithm

Van Prehn J et al. Clin Microbiol Infect 2021;27 Suppl 2:S1-S21.



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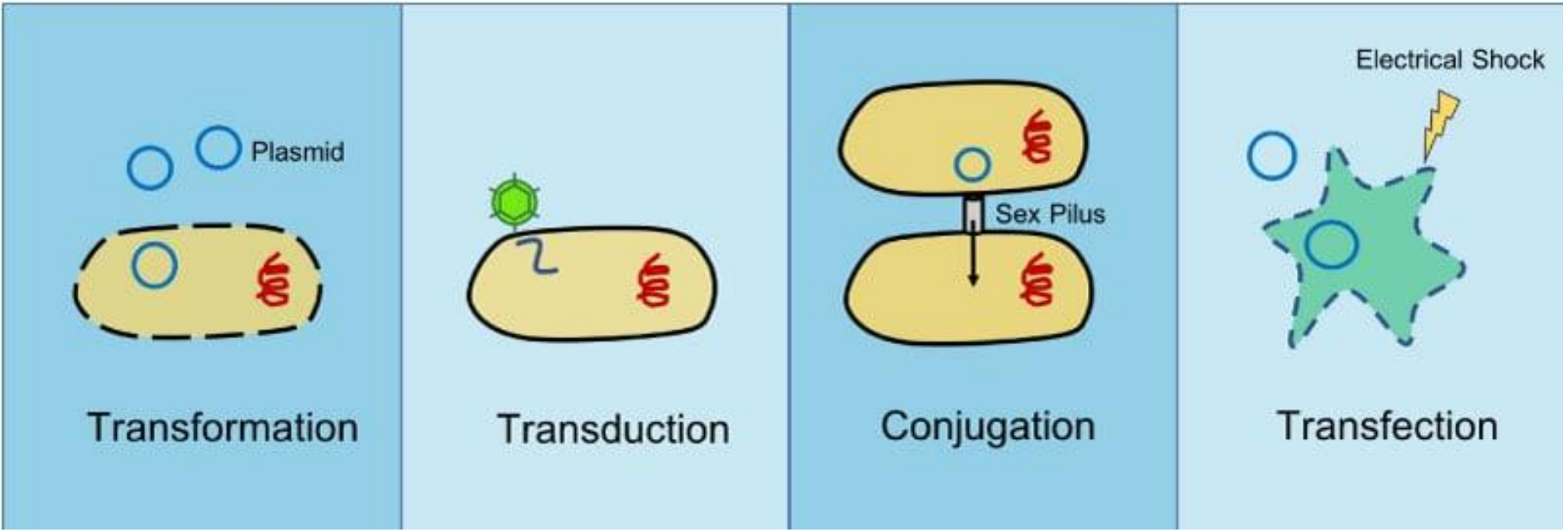
- Two newly discovered siphoviruses, phiSM101- and phivB_CpeS-CP51-like Clostridium phages, were identified in two C. difficile genomes.

Int J Mol Sci 2023 Dec 19;25(1):2.


Plasmid
Transformation
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Conjugation
Electrical Shock
Transfection

"All disease begins in the gut"

Hippocrates, circa 340 BC