CDI and COVID-19

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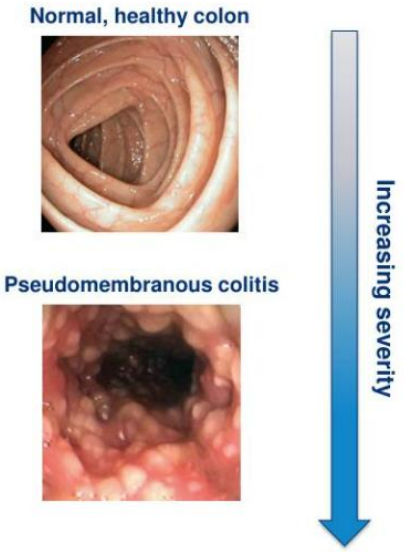
History

- 1893 first case of pseudomembraneous colitis reported as diphtheritic colitis.
- 1935 Bacillus difficile isolated.
- 1970s antibiotic-asociated colitis identified.
- 1978 C. difficile toxins identified in humans.
- 1979 therapy with vancomycin or metronidazole
- 2000 increased incidence and virulence

Clinical presentation of *C. difficile* infection (CDI)

- Asymptomatic colonisation
- Diarrhoea without colitis
  - Watery
  - Mucus but no blood
- Colitis without pseudomembrane formation
- Pseudomembranous colitis
- Fulminant colitis



Bauer MP, et al. Clin Microbiol Infect 2009;15:1067–79;
Bartlett JD, Gerding DN. Clin Infect Dis 2008;46:S12–8.

Clostridioides difficile ("C. diff") Facts

Most cases impact people **65 and older.**

223,900 estimated cases in hospitalized patients and **12,800 deaths** in the U.S. in 2017.

Nearly **500,000 C. diff infections** occur in the U.S. each year.

About **1 in 5 patients** who contract C. diff will get it again.

Complications include **dehydration, colitis and diarrhea.**

Information from Centers for Disease Control and Prevention

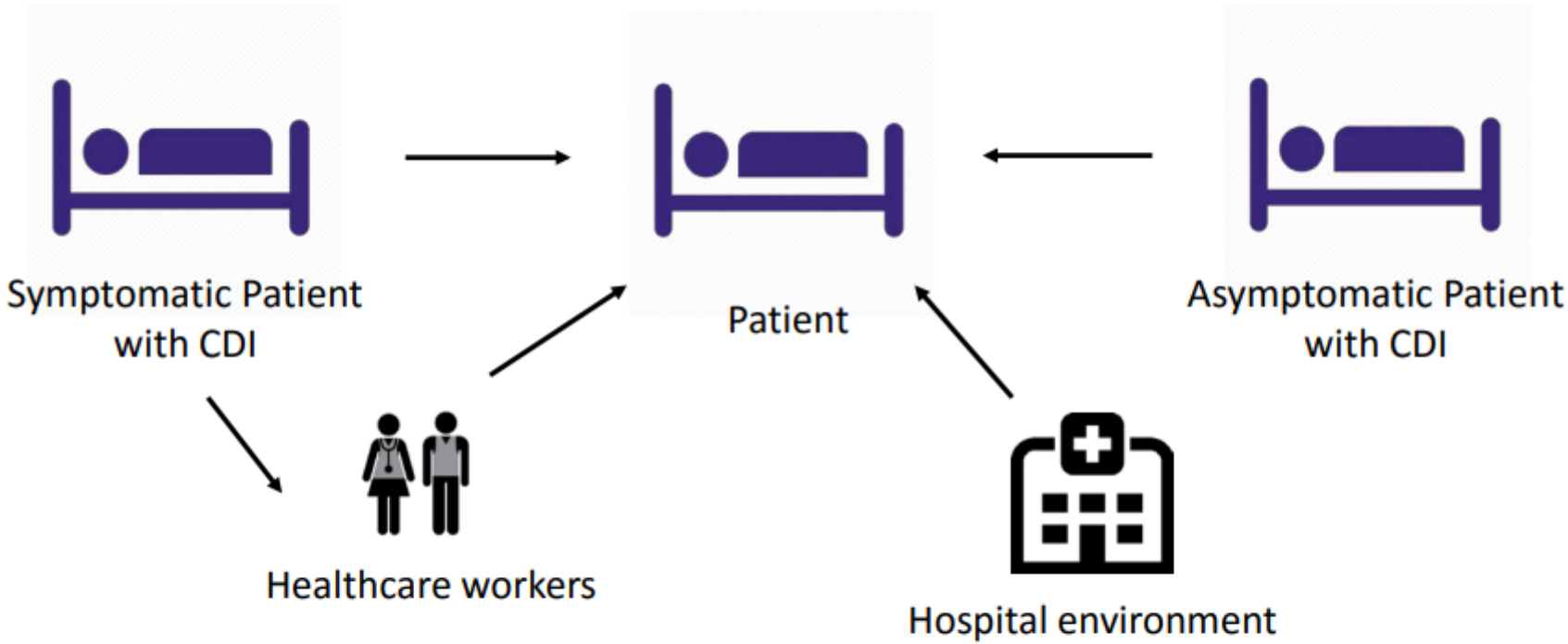
1 in 11 people over age 65 die of a health care-associated C. diff infection within **1 month of diagnosis.**

Risk Factors of CDI

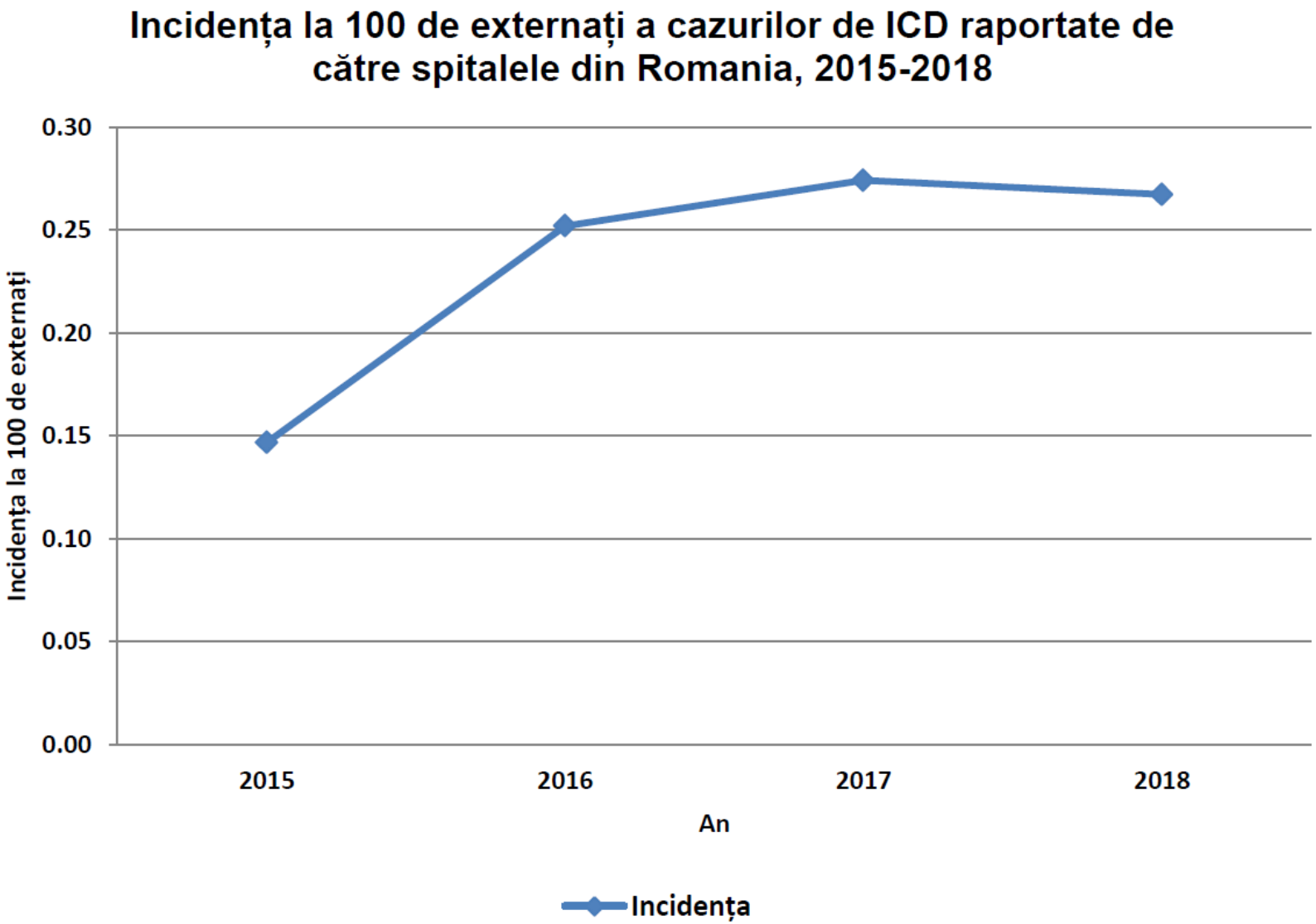
Pharmacological risk factors:
Any use of antibiotics (broad and specific)
Any use of proton pump inhibitors
Any use of histamine 2 receptor antagonists
Anti-ulcer medications (not specific)
Non-steroidal anti-inflammatory drug
Aspirin
Corticosteroids
Use of opiate during the last episode of CDI

Host-related risk factors:
Age: ≥65 years
Age: additional year or decade
Chronic kidney disease
Diabetes mellitus
Lymphoma or leukaemia
Solid cancer or malignancy
Severity of co-morbidity
Inflammatory bowel disease
Congestive heart disease
Chronic obstructive pulmonary disease
Peptic ulcer
Diverticular disease
Gastroesophageal reflux disease
Chronic obstructive pulmonary disease
Low mean concentration of 25 hydroxyvitamin D
Female sex
Previous diagnosis of CDI

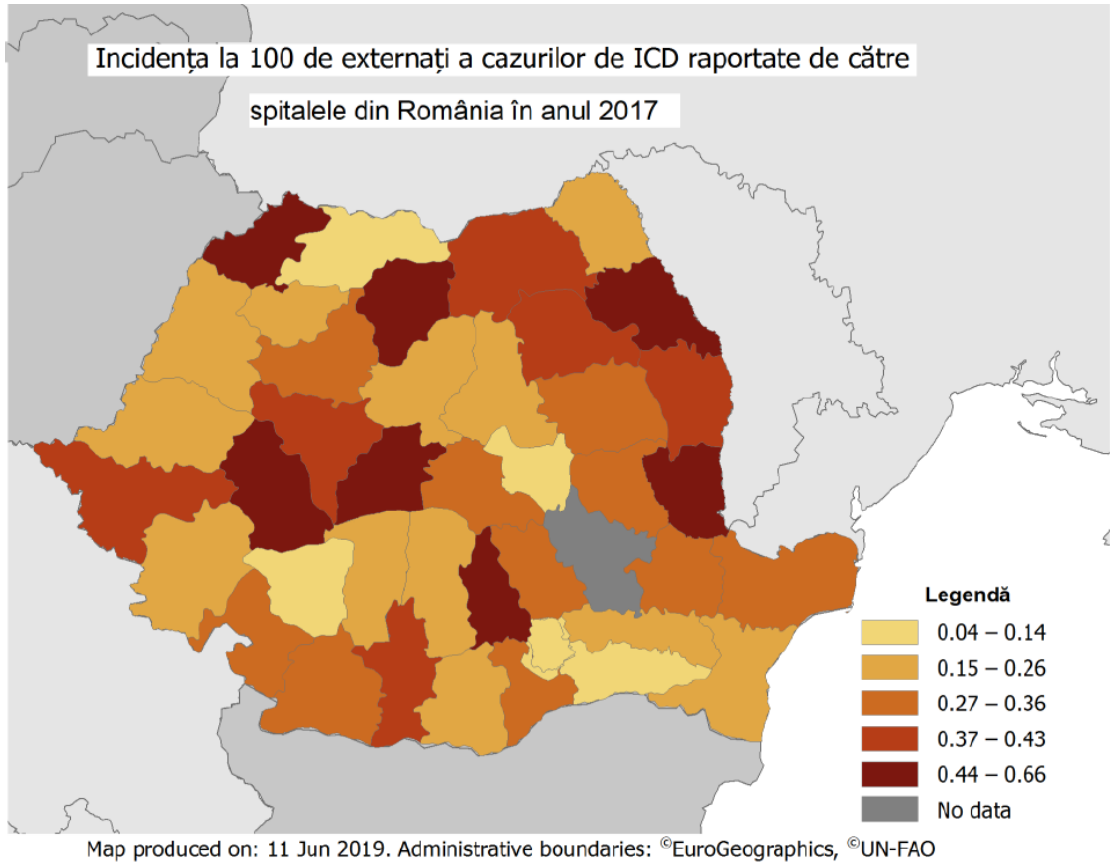
Standard view of CDI transmission

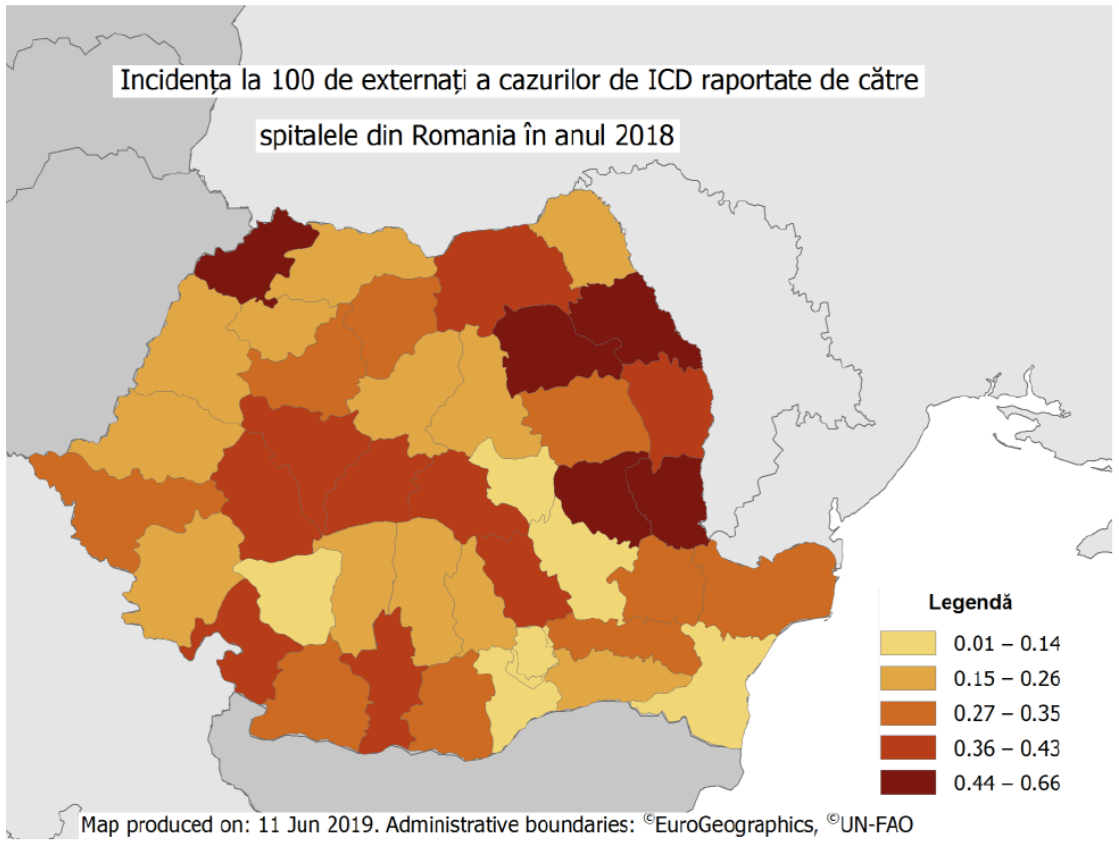


Slide courtesy of Eric Kao



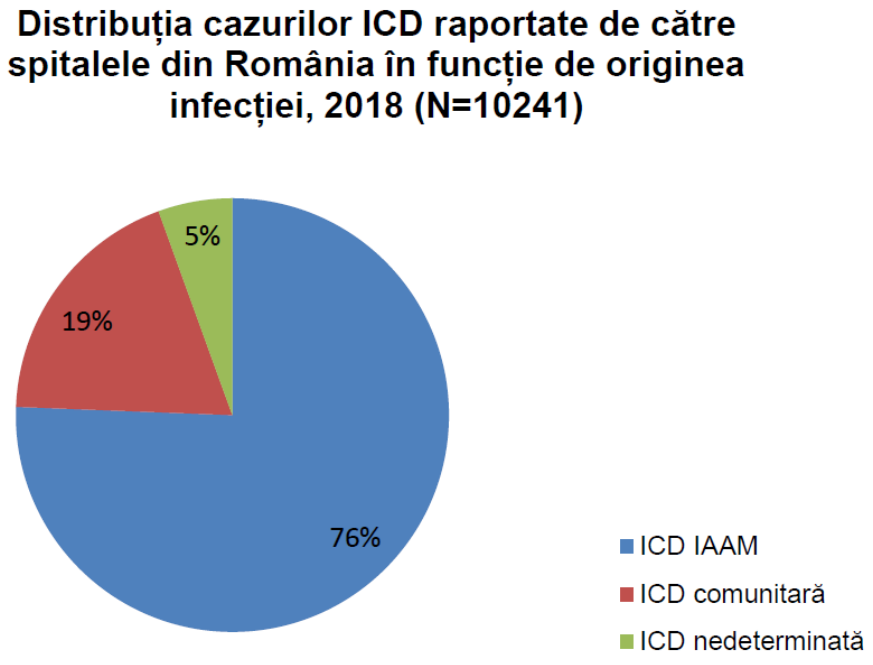
Raport INSC 2019 - Analiza evoluției infecției cu Clostridium difficile în spitalele din România, 2018





Raport INSC 2019 - Analiza evoluției infecției cu Clostridium difficile în spitalele din România, 2018

Factori de risc	Total ICD, din care		ICD IAAM		ICD comunitară		ICD nedeterminată	
	Nr. cazuri	Procent (%) *	Nr. cazuri	Procent (%) **	Nr. cazuri	Procent (%) ***	Nr. cazuri	Procent (%) ****
Administrare antisecretorii gastrice	4497	44	3760	49	585	30	152	27
Administrare citostatice	423	4	366	5	38	2	19	3
Administrare imunosupresoare	400	4	339	4	38	2	23	4
Intervenții chirurgicale în ultimele 2 saptamani	722	7	682	9	24	1	16	3
Status de imunodeprimat	2791	27	2321	30	338	18	132	23
Internare în ultimul an	5728	56	4960	64	399	21	369	65
Contact cu un caz ICD	193	2	175	2	14	1	4	1



Raport INSC 2019 - Analiza evoluției infecției cu Clostridium difficile în spitalele din România, 2018

Clasa de Antibiotice	Total ICD, din care		ICD IAAM		ICD comunitară		ICD nedeterminată	
	Nr. cazuri	Procent (%) *	Nr. cazuri	Procent (%) **	Nr. cazuri	Procent (%) ***	Nr. cazuri	Procent (%) ****
Macrolide	237	5	172	4	43	8	22	10
Aminoglicozide	385	8	351	9	22	4	12	6
Fluorochinolone	1517	31	1326	33	143	25	48	22
Cefalosporine generatia 1	41	1	22	1	11	2	8	4
Cefalosporine generatia 2	373	8	300	7	58	10	15	7
Cefalosporine generatia 3	2288	47	2054	51	143	25	91	42
Cefalosporine generatia 4	3	0.1	3	0.1	0	0	0	0
Carbapeneme	479	10	455	11	7	1	17	8
Aminopeniciline	838	17	610	15	187	33	41	19
Izoxazolilpeniciline	53	1	40	1	7	1	6	3
Tetracicline	23	1	12	0.3	7	1	4	2
Glicopeptide	413	9	348	9	44	8	21	10
Monobactame	475	10	449	11	15	3	11	5
Sulfamide	66	1	51	1	9	2	6	3
Rifampicine Fenicoli	308 5	6 0.1	278 4	7 0.1	23 0	4 0	7 1	3 1
Oxazolidinone (Linezolid)	38	1	35	1	2	0.4	1	1
Antifungice	17	0.4	12	0.3	2	0.4	3	1
Azoli (Metronidazol)	480	10	416	10	43	8	21	10
Meticilina	0	0	0	0	0	0	0	0
Colistin	61	1	59	2	0	0	2	1

Raport INSC 2019 - Analiza evoluției infecției cu Clostridium difficile în spitalele din România, 2018

Status la externare	Total ICD, din care		ICD IAAM		ICD comunitara		ICD nedeterminata	
	Nr. cazuri	Procent (%)	Nr. cazuri	Procent (%)	Nr. cazuri	Procent (%)	Nr. cazuri	Procent (%)
Vindecat	2708	26	2009	26	570	29	129	23
Ameliorat	6596	65	4907	63	1290	67	399	70
Stationar	10	0	8	0	1	0	1	0
Agravat	2	0	2	0	0	0	0	0
Decedat	925	9	817	11	70	4	38	7
Total	10241	100	7743	100	1931	100	567	100

Deces	Nr. cazuri	Procent (%)
Fara legatura cu ICD	700	76
Posibil legatura cu ICD	79	9
Din cauza ICD	17	2
Necunoscut	129	13
Total	925	100.0

Clinical Definition	Objective Evidence	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
Initial Episode, non-severe	WBC < 15,000 and SCr < 1.5mg/dL	Vancomycin 125 mg PO QID x 10 days ***OR*** Fidaxomicin 200 mg PO BID x 10 days *Alternate if above agents are unavailable: Metronidazole 500 mg PO TID x 10 days	Strong/High Strong/High Weak/High
Initial Episode, severe	WBC ≥ 15,000 or SCr ≥ 1.5 mg/dL	Vancomycin 125 mg PO QID x 10 days ***OR*** Fidaxomicin 200 mg PO BID x 10 days	Strong/High Strong/High
Initial Episode, fulminant	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg QID PO or NG (if ileus, consider adding rectal instillation) ***PLUS*** Metronidazole 500 mg IV Q8h (particularly if ileus present)	Strong/Moderate (oral vancomycin) Weak/Low (rectal vancomycin) Strong/Moderate (IV metronidazole)

[a]Adapted from McDonald et al. *Clin Microbiol Infect*. 2018; XX (00): 1–48

Clostridium difficile Infection

Concepts of Antibiotic Stewardship

- prospective audit with intervention and feedback
- formulary restriction and preauthorization for specific agents
- use of guidelines and clinical pathways
- avoidance of use of antibiotics for:
  - nonbacterial syndromes
  - asymptomatic bacteriuria
  - colonization
- shortened duration of antibiotic therapy
- combination therapy
- antimicrobial cycling and scheduled antimicrobial switch

Adopted from Wlodaver, W. & Nay, C. Antibiotic Stewardship. *Infect Dis Clin Pract* 2012; 20: 12-17.
Dellit TH, et al. Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. *Clin Infect Dis*. 2007; 44:159-77

COVID-19

- Consum crescut de antibiotice
- Consum crescut de antisecretorii
- Consum crescut de cortizon
- Pacienti imunodeprimati
- Spitalizare
- Persoane > 65 ani

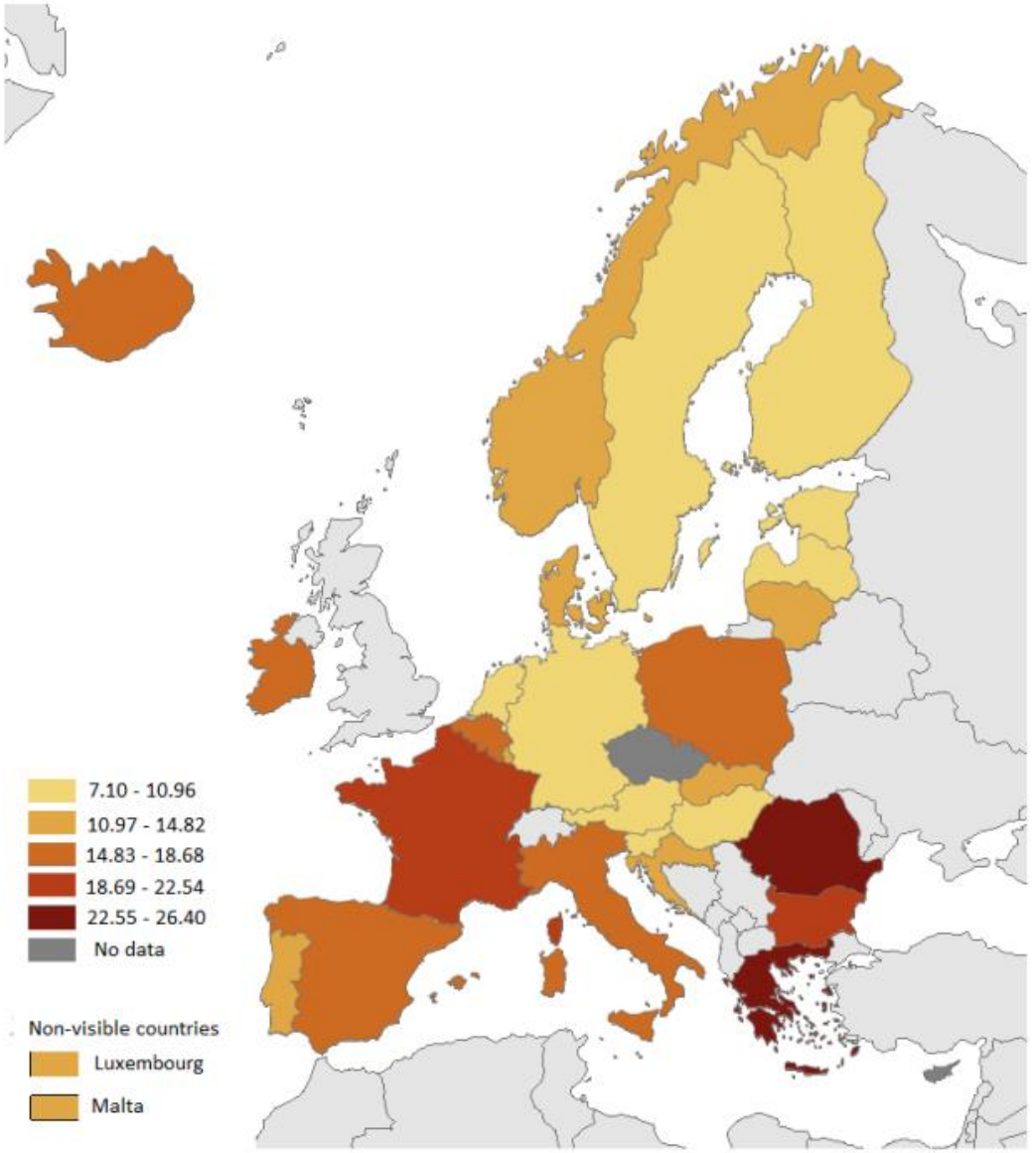
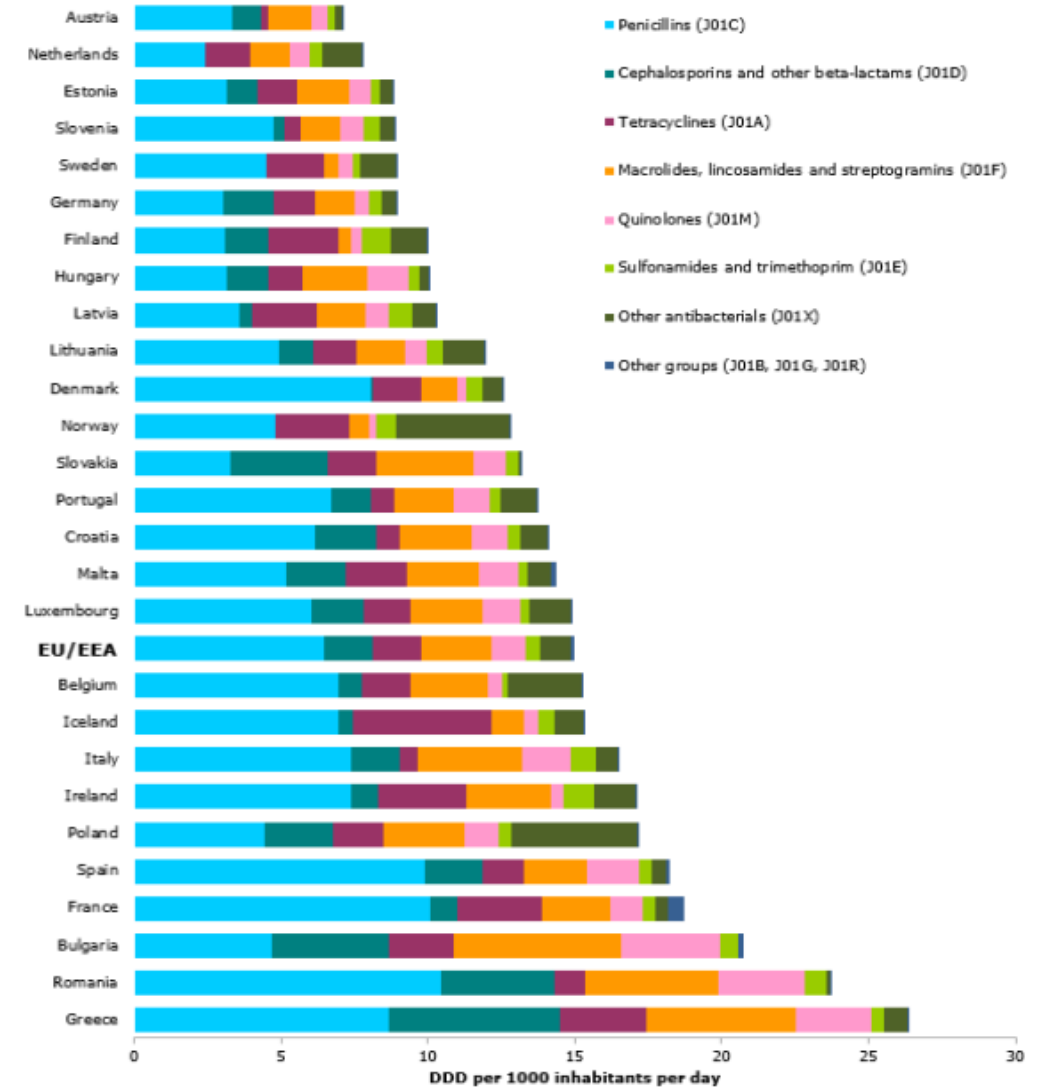


Figure 2. Community consumption of antibacterials for systemic use (ATC group J01) at ATC group level 3, by country, EU/EEA, 2020 (expressed as DDD per 1 000 inhabitants per day)



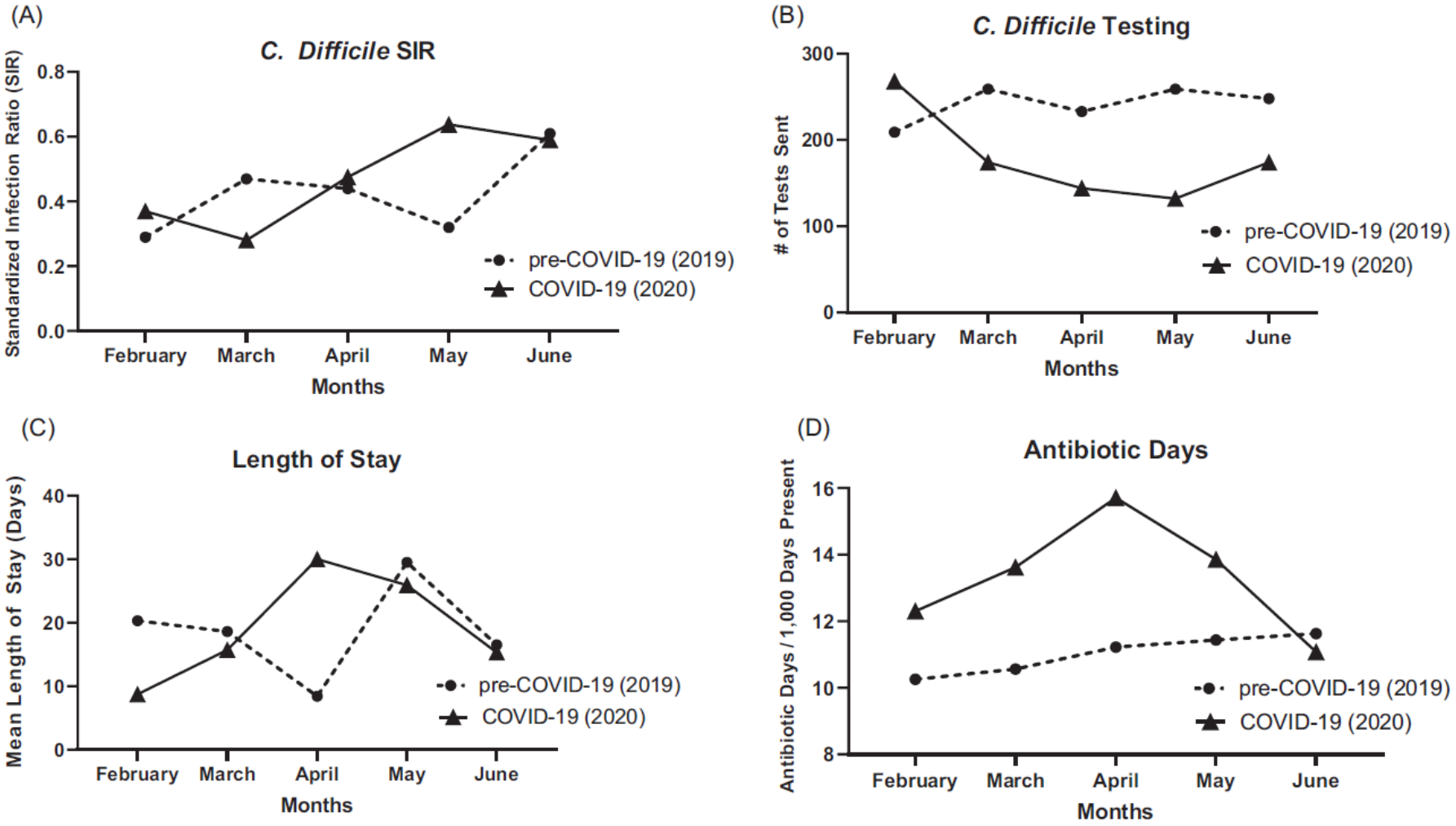


Fig. 1. Comparisons between standardized infection ratios (A), *C. difficile* testing (B), length of stay (C) and high-risk antibiotic days (D) between our COVID-19 (2020) and pre-COVID-19 (2019) cohort.

Yuying Luo , Lauren T. Grinspan , Yichun Fu, Victoria Adams-Sommer, D. Kyle Willey, Gopi Patel, Ari M. Grinspan. Hospital-onset Clostridioides difficile infections during the COVID-19 pandemic. Infection Control & Hospital Epidemiology.

- Utilizarea excesivă a antibioticelor raportată în pandemie a stârnit mai multe îngrijorări cu privire la selecția și creșterea ulterioară rezistentei bacteriile patogene, cu o selecție consecutivă a tulpinilor rezistente de C. difficile.
- Aproximativ 60% dintre tulpinile de C. difficile au fost raportate ca MDR în spitalele europene, dar tulpinile MDR au fost frecvent detectate și în afara spitalelor, la animale, alimente și mediu.
- Animalele reprezintă un rezervor important al acestui agent patogen

Patrizia Spigaglia. Clostridioides difficile infection (CDI) during the COVID-19 pandemic. Anaerobe. Jan. 2022

Pol Arch Intern Med. 2021 Feb 26;131(2):121-127. doi: 10.20452/pamw.15715. Epub 2020 Dec 14.

Clostridioides difficile infection in coronavirus disease 2019 (COVID-19): an underestimated problem?

Konrad Lewandowski [1], Mariusz Rosołowski [2], Magdalena Kaniewska [1], Piotr Kucha [1], Anna Meler [3], Waldemar Wierzba [4 5], Grażyna Rydzewska [1 6]

- Results: A significant increase in the incidence of CDI was noted during the COVID-19 pandemic compared with the prepandemic period: 10.9% versus 2.6%, P <0.001. Risk factors for CDI in patients with COVID-19 included: age, length of hospital stay, occurrence of diarrhea during hospitalization, use of antibiotics other than azithromycin, and coexistence of nervous system disease or chronic kidney disease-all of these factos had a weak association with CDI development.
- Conclusions: We observed a higher incidence of CDI in patients with COVID-19. Antibiotic therapy was a relevant risk factor for CDI, although its effect was weak. Other drugs used during the pandemic were not found to have an impact on disease development.
  - Possible causes of CDI may include fecal microbiota disruption by SARS-CoV-2 infection, but further research is needed to validate this hypothesis.

medicina

MDPI

Article

Clostridium Difficile and COVID-19: General Data, Ribotype, Clinical Form, Treatment-Our Experience from the Largest Infectious Diseases Hospital in Western Romania

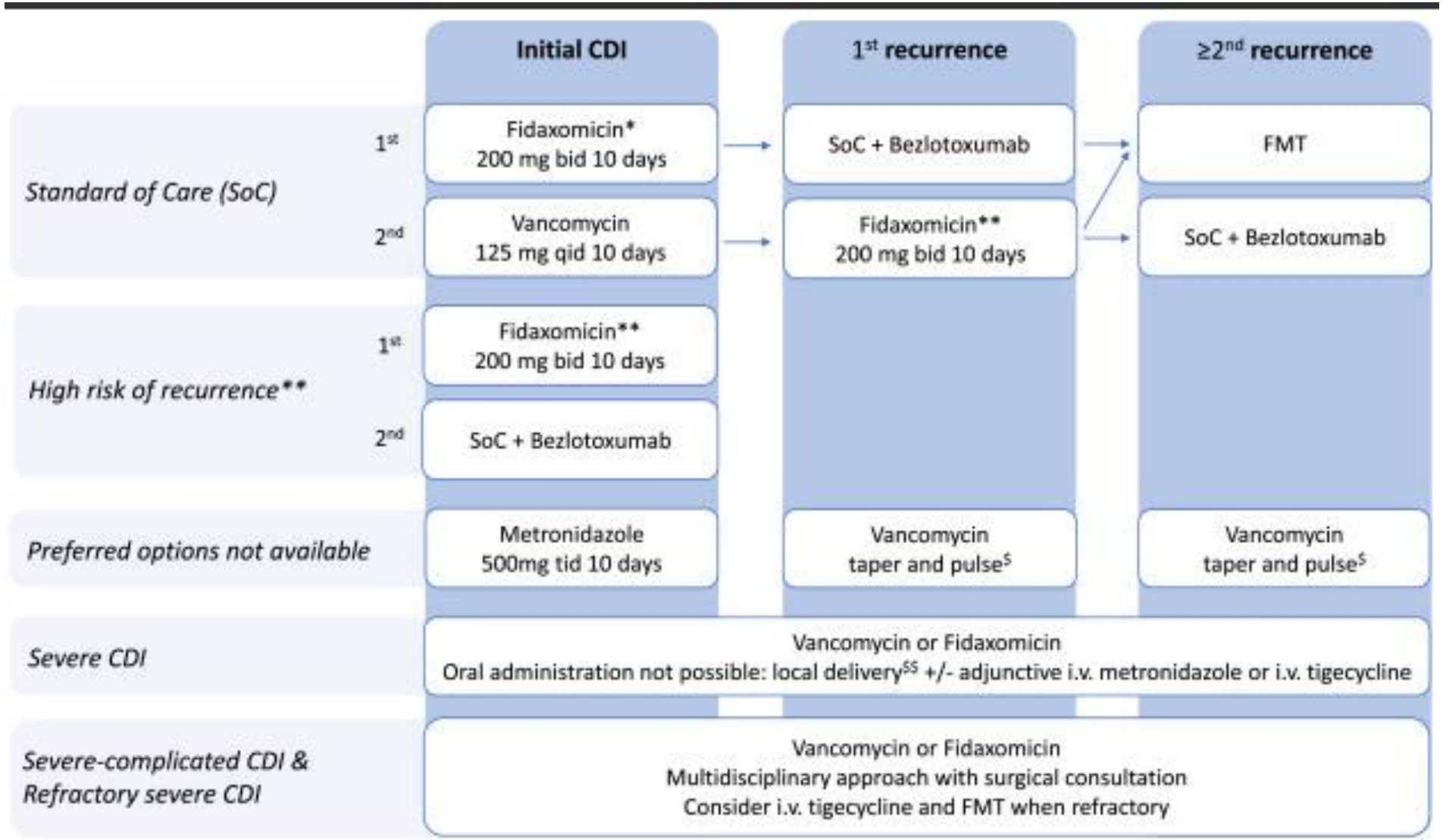
Adelina Raluca Marinescu [1,2,3], Ruxandra Laza [1,2,†], Virgil Filaret Musta [1,2,†], Talida Georgiana Cut [1,2,3,4,*], Raluca Dumache [4,5,†], Anca Tudor [6,†], Mirela Porosnicu [2,3,†], Voichita Elena Lazureanu [1,2,†] and Monica Licker [7,8]

Rom J Intern Med. 2021 Nov 20;59(4):409-415. doi: 10.2478/rjim-2021-0020. Print 2021 Dec 1.

Healthcare-associated *Clostridioides difficile* infection during the COVID-19 pandemic in a tertiary care hospital in Romania

Eliza Manea [1 2], Raluca Jipa [1 2], Alexandru Milea [1], Antonia Roman [1], Georgiana Neagu [1], Adriana Hristea [1 2]

- patients received antimicrobial treatment –
  - mainly cephalosporins (34,1%), quinolones (22,3%) and glycopeptides (21,1%) in pre-COVID-19 group and
  - mainly cephalosporins and macrolides (63,6% each) in COVID-19 group.
- The HA-CDI incidence in COVID-19 group did not change versus the same period of time during 2017-2018.
- The antibiotic use was the most important factor associated with HA-CDI.
- We identified a high use of broad-spectrum antibiotics despite the lack of empirical antimicrobial recommendations in COVID-19.



* Risk stratification for risk of recurrence may be applied for selective use of fidaxomicin in case of limited access or resources.

** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65–70 years. Additional risk factor(s) to consider are healthcare-associated CDI, prior hospitalization ≤ 3 months, prior CDI episode, continued non-CDI antibiotic use, and PPI therapy started during/after CDI diagnosis. The risk of recurrence is assumed higher with more risk factors present.

$ Vancomycin taper and pulse: 2 weeks 125 mg qid, followed by 1 week 125 mg bid, then 1 week 125 mg qd, then 1 week 125 mg q48h, and finally 125 mg q72h for 1 week.

$$ Rectal or nasoduodenal delivery

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

Immunization

- Active immunization
  - Discouraging results were reported from a recent phase III multicentre C. difficile toxoid (TcdA and TcdB) vaccine trial
- Passive immunization
  - Bezlotoxumab human monoclonal antibody against C. difficile toxin Bdwas recently approved for the prevention of R-CDI in combination with antibiotics for treatment of CDI
    - reduction in risk (25%) was observed in patients with at least three concomitant risk factors (age 65 years, history of CDI, compromised immunity, severe CDI, and ribotype 027/078/244)
    - safety profile similar to that of placebo, although heart failure was more common in patients with a history of congestive heart failure than in the placebo group

Faecal microbiota transplantation (FMT), live biotherapeutic products (LBPs), probiotics

- have been proposed as methods to restore gut microbiota and inhibit pathogenic bacterial colonization.
- LBPs are defined as biological products that contain live organisms,such as bacteria,
  - are used for the prevention, treatment, and cure of a disease or condition of human beings.
  - LBPs are under investigation for secondary prevention of CDI in phase II and phase III studies, and include SER-109 (Seres Therapeutics,Boston; NCT03183128) and VE303 (Vedanta Biosciences, Boston; NCT03788434).

Probiotics

- recent meta-analysis showed probiotics to be efficacious, albeit with a moderate quality of evidence, when administered to patients with a high baseline risk (>5%)
- However, these results were not confirmed in subsequent randomized clinical trials and other large-scale studies including ‘real-life’ patients.
- Of all the probiotics studied for preventing CDI in a hospital setting, Saccharomyces boulardii and Lactobacillus species
  - are the most frequently reported to have positive effects
  - bloodstream infection is a serious adverse event
  - the use of probiotics should be assessed carefully, especially in immunosuppressed or critically ill patients.

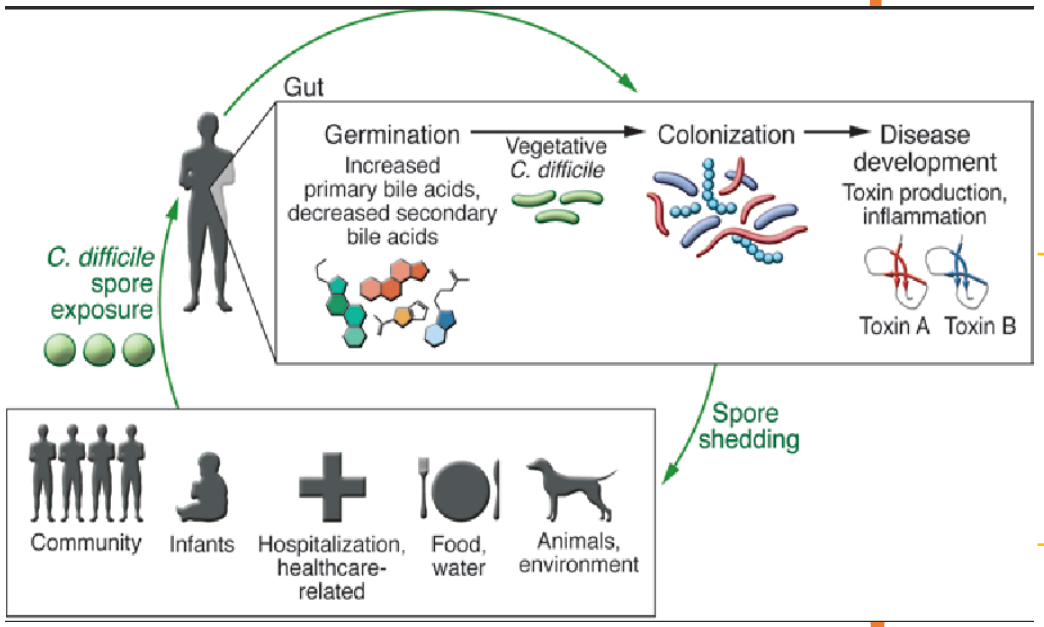
Microbiota-targeted therapy: dysbiosis prevention

- Coadministration of poorly absorbed b-lactamase enzymes when administering antibiotics to degrade these in the gastrointestinal tract.
  - In this sense, SYN-004 (ribaxamase) is a first-in-class oral class A serine enzyme designed to protect the colonic microbiota from the disruption caused by commonly used intravenous b-lactamanatibiotics.

Antibiotic prophylaxis

- Primary prophylaxis with antibiotics for prevention of CDI is problematic because of its impact on the microbiome, with an associated increased risk for R-CDI and selection of antimicrobial resistance.
  - Haematological malignancy receiving broad-spectrum antibiotics
  - Transplant (lung, kidney)
  - Patients who achieved cure with FMT for R-CDI at 8 weeks and presented afterwards with diarrhoea

Concluzii



Pandemia de COVID-19 a evidențiat dramatic interacțiunile complexe dintre infecțiile bacteriene și virale.

În era provocatoare a COVID-19, natura multifactorială a CDI a devenit și mai evidentă,

necesitând urgent includerea programelor de supraveghere globale și locale CDI într-o abordare integrată One Health,

cu o interconexiune mai puternică între autoritățile de sănătate publică, medicina veterinară, și agricultura pentru a îmbunătăți strategiile de prevenire și a reduce amenințarea pentru sănătatea publică reprezentată de această infecție.