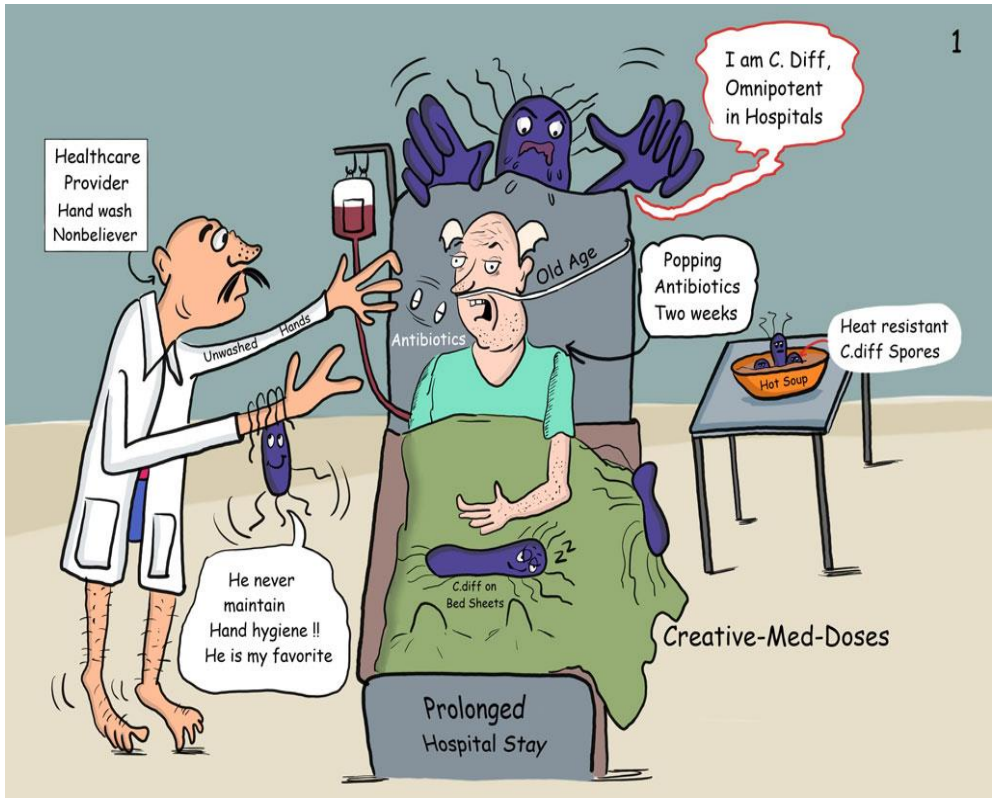
Clostridioides difficile infection



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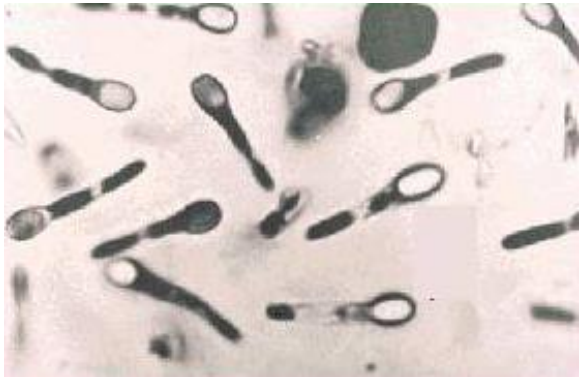
FN MOTOL

Clostridium difficile ([klos-tridʹe-əm di-fi -silʹ]

*„**Clostridium**“* pochází z řeckého klōstēr (spindle), because under the microscope, the colonies resemble spindles used in weaving fabrics and long rods with bulging ends.

Species name*„**difficile**“*is a form of the Latin adjective „difficilis“, because at first identification (Hall a O'Toole v roce 1935) the organism was difficult to isolate and grew slowly in pure culture.



Clostridium difficile nebo *Clostridioides difficile?*

Both names are still valid

Based on the analysis of the 16S rRNA gene sequence, *Clostridium difficile* is the closest relative of *Clostridium mangenotii* with a similarity of 94.7%, and both are located in the family Peptostreptococcaceae, which is phylogenetically distant from *C. butyricum* and other representatives of *Clostridium* sensu stricto.
Based on phenotypic, chemotaxonomic and phylogenetic analyses, the new genus *Clostridioides* gen. nov. is designed for *Clostridium difficile*.

Etymologia: *Clostridium difficile*. Emerg Infect Dis. 2010;16(4):674. doi: 10.3201/eid1604.ET1604; Oren and Rupnik , 2018; Lawson et al., 2016.

Dormant spore vs metabolically active cell

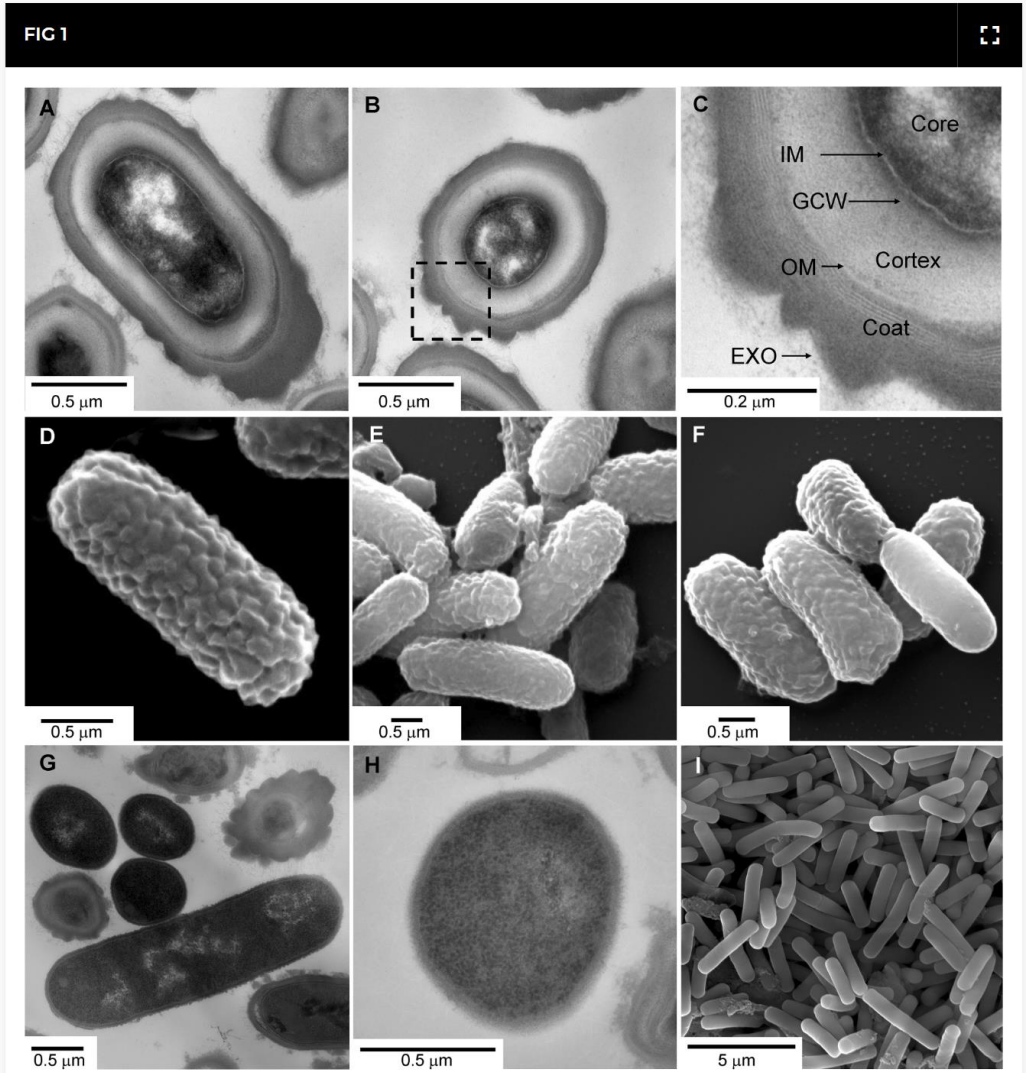
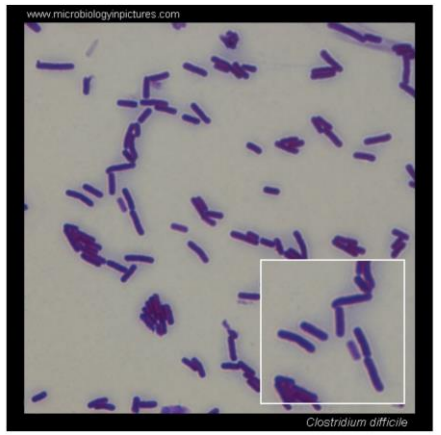
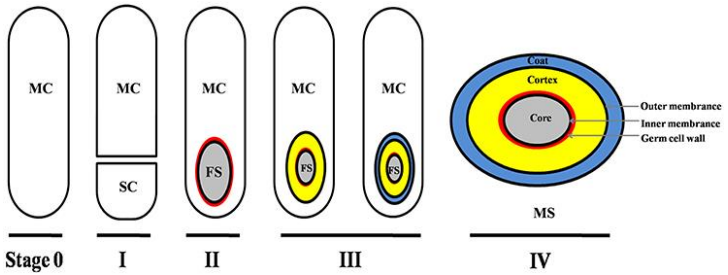


FIG 1 *C. difficile* spore structure and cell morphology visualized by TEM and SEM. Spores (A to F) and vegetative cells (G to I) derived from the *C. difficile* R20291 strain were embedded in epoxy resin, sectioned, and imaged by TEM (A, B, C, G, and H) or were chemically dried, sputter coated, and imaged by SEM (D, E, F, and I). IM, inner membrane; GCW, germ cell wall; OM, outer membrane; EXO, exosporium.



Gram-positive
Obligate anaerobe
Can produce toxins (A, B some strains Binary)
Spore-forming

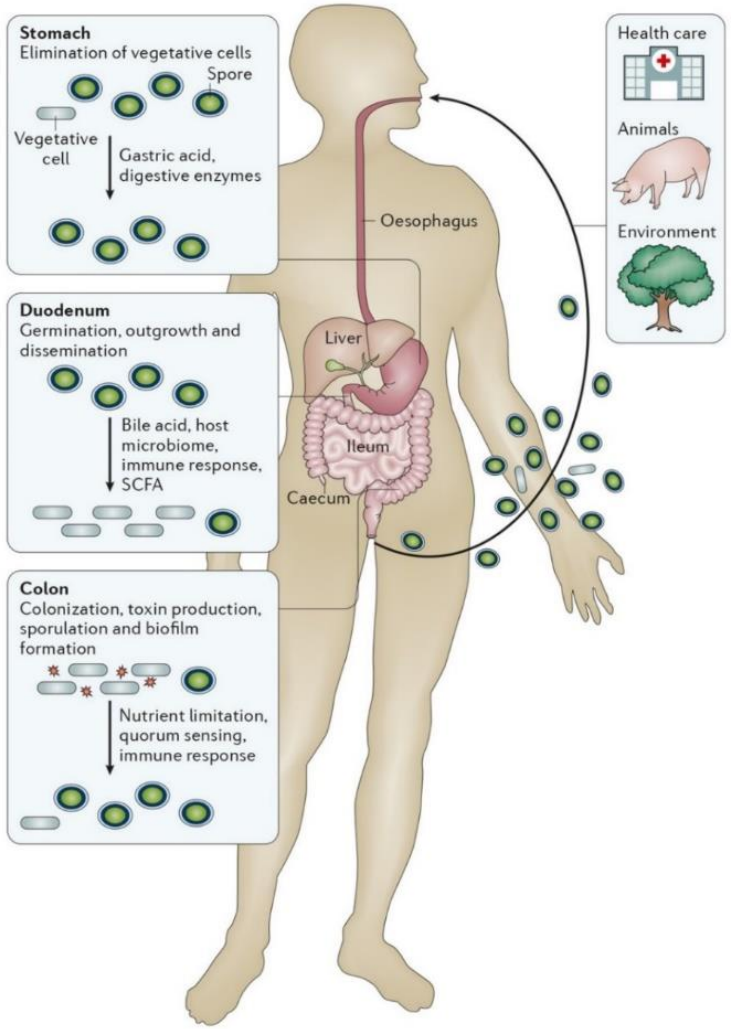


Spore formation by *C. difficile* is crucial for the survival and dissemination of the bacterium in the environment.

The dormant aerotolerant and highly resistant spore facilitates efficient transmission and persistence in the host.

Spores are resistant to different environmental conditions, antibiotics, and some disinfectants (usage of sporicidal ones).

Clostridioides difficile infection (CDI)

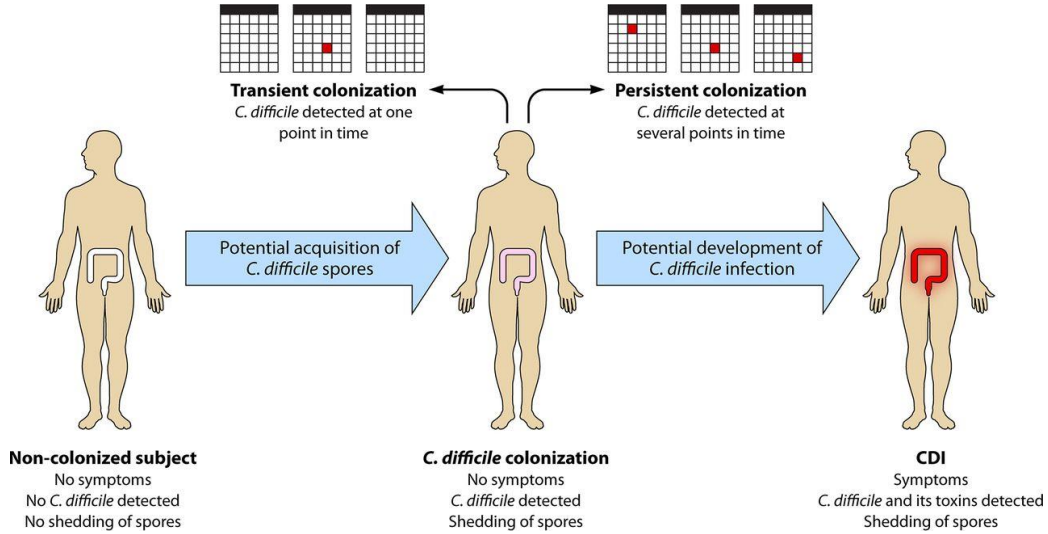


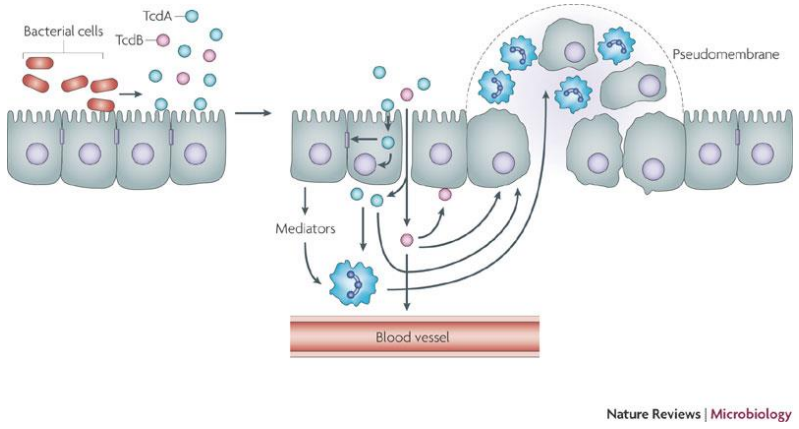
Fecal-oral route of transmission.

Asymptomatic colonization or infection.

Recurrence of CDI (25%, 50%).

Symptoms: watery diarrhoea, fever, loss of appetite, nausea and abdominal pain/tenderness.

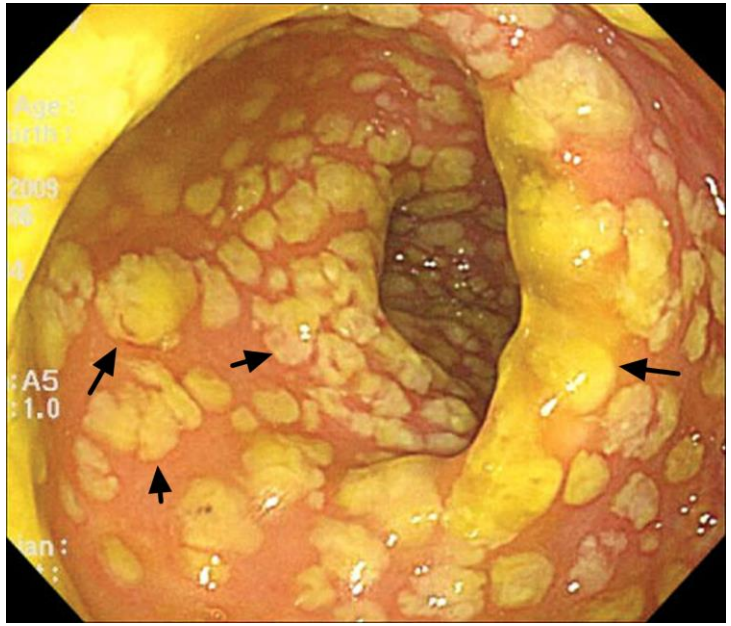




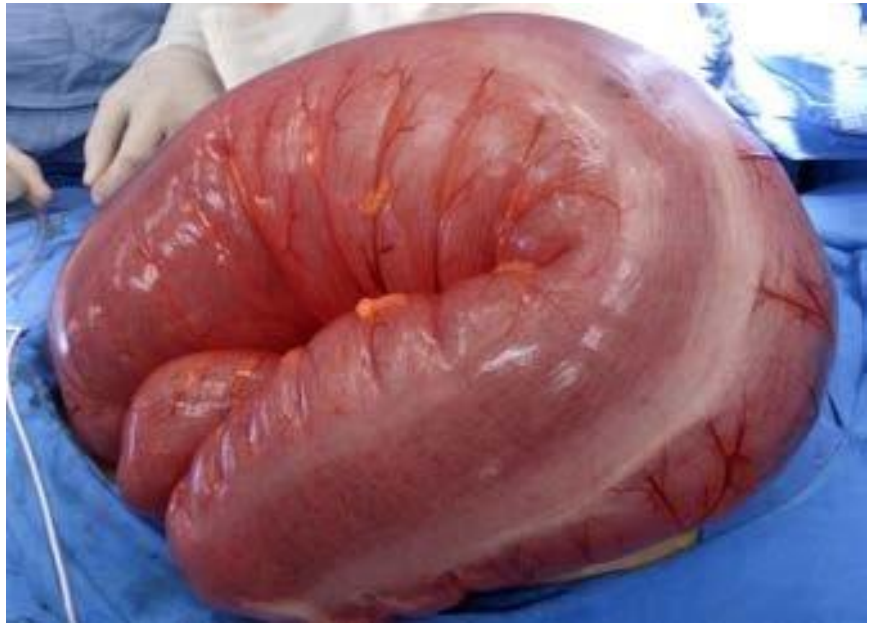
Toxins=disruption of cytoskeletal structure and tight junctions with subsequent cell rounding, detachment and cell death.

Smits et al., 2016; Crobach et al., 2018; Chilton et al., 2018

Severe forms of CDI

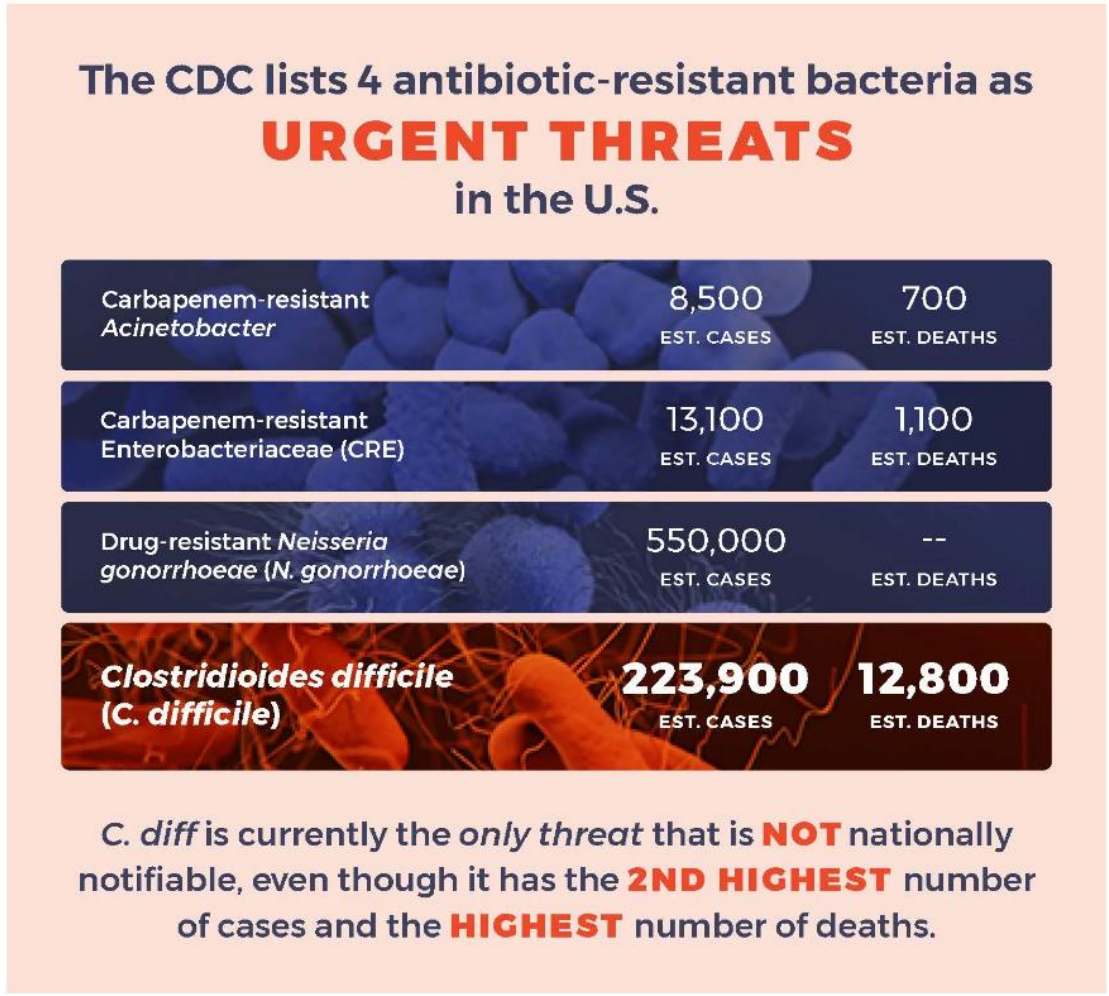


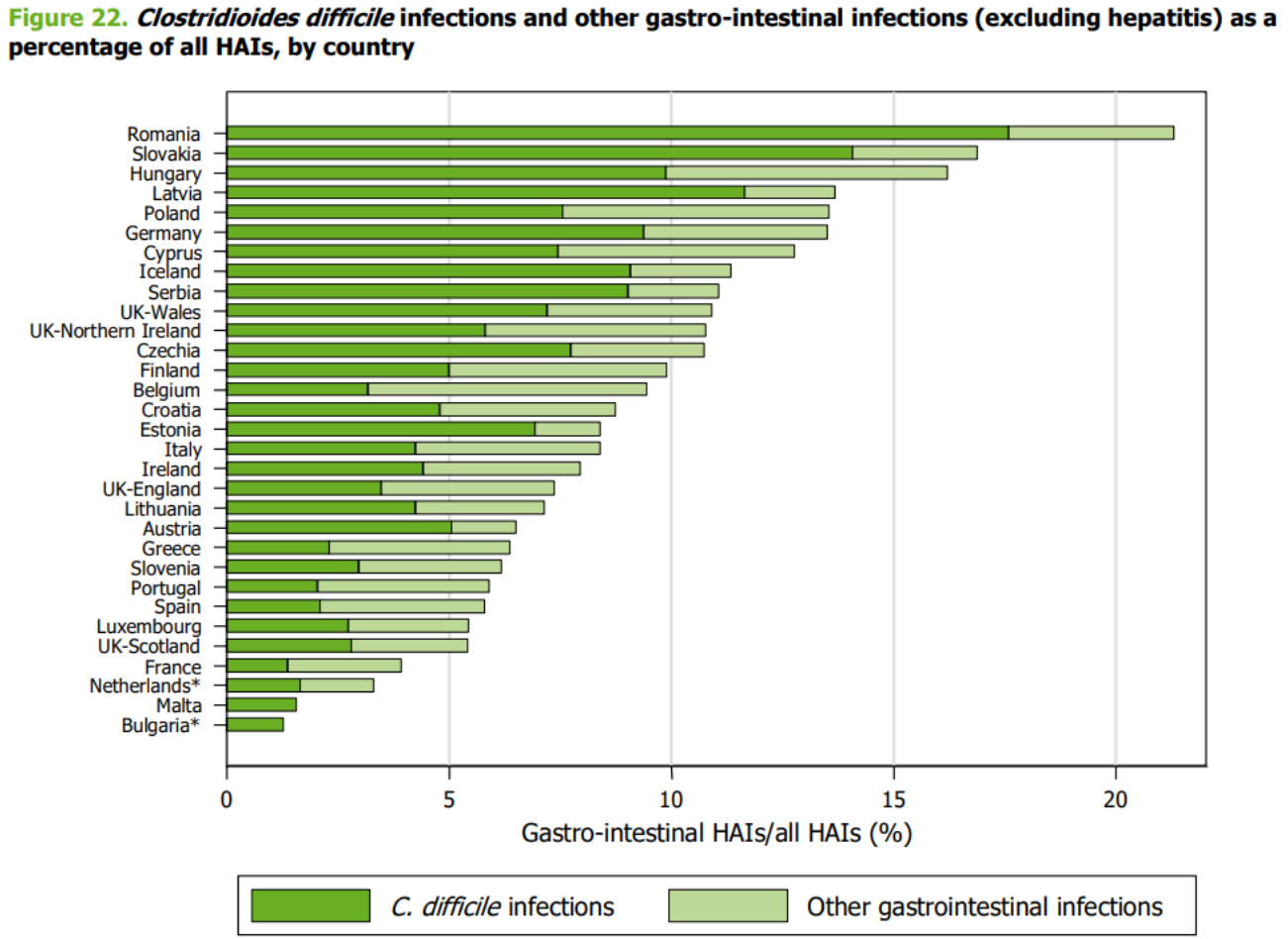
Pseudomembranous colitis



Paralytic ileus = toxic megacolon, surgical intervention, high mortality

How common is CDI?





124 000 CDI cases a year

Approx. 17% die. 4% in relation to CDI

European mean: 5 cases per 10,000 bed-days

What does a patient at risk of CDI look like?

RISK factors for CDI

Advanced age ≥ 65 years
Comorbidity conditions
Exposure to acid-suppressing agents (PPIs)
Exposure to antibiotics
Exposure to the healthcare system
Immunosuppressive conditions and agents (cancer, chemotherapy, organ transplant, HIV)
Manipulation of GI system (feeding tubes, surgery)

EVERYTHING WHICH AFFECTS MICROBIOTA and IMMUNE SYSTEM.

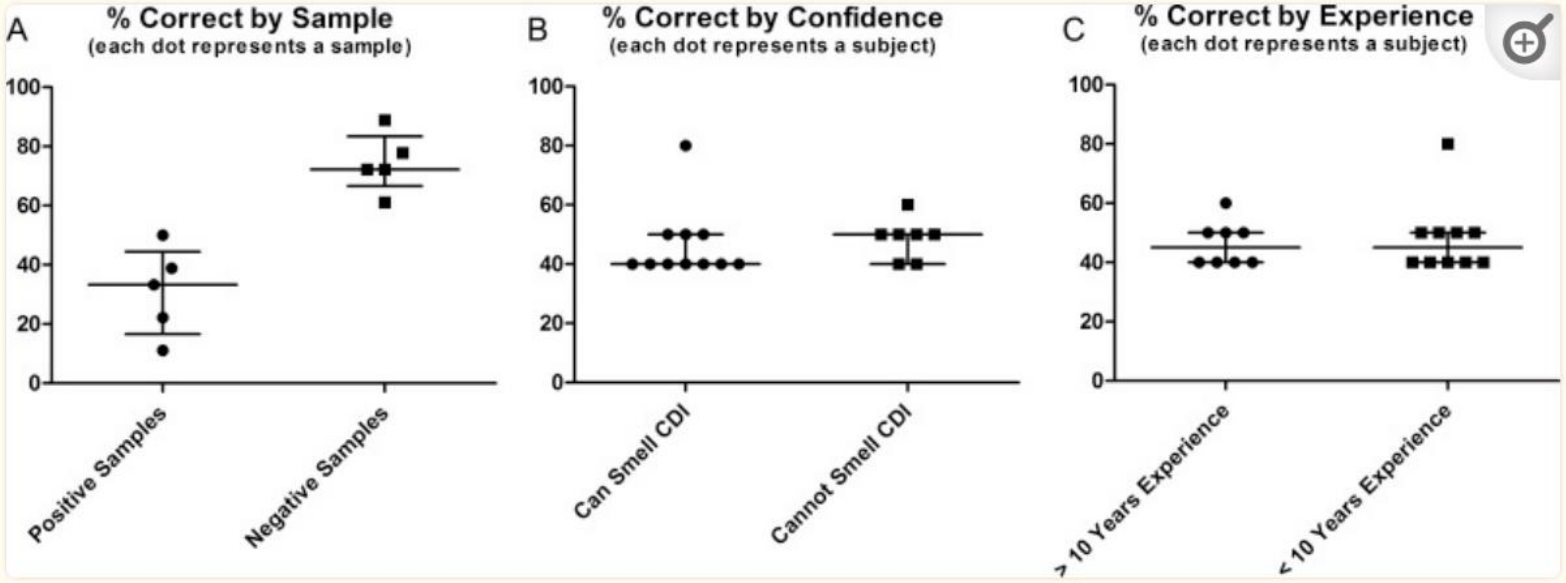
Laboratory diagnostics–odor?

Clin Infect Dis. 2013 Feb 15; 56(4): 615–616.
doi: 10.1093/cid/cis974

PMCID: PMC3571629
PMID: 23166192

The Nose Knows Not: Poor Predictive Value of Stool Sample Odor for Detection of *Clostridium difficile*

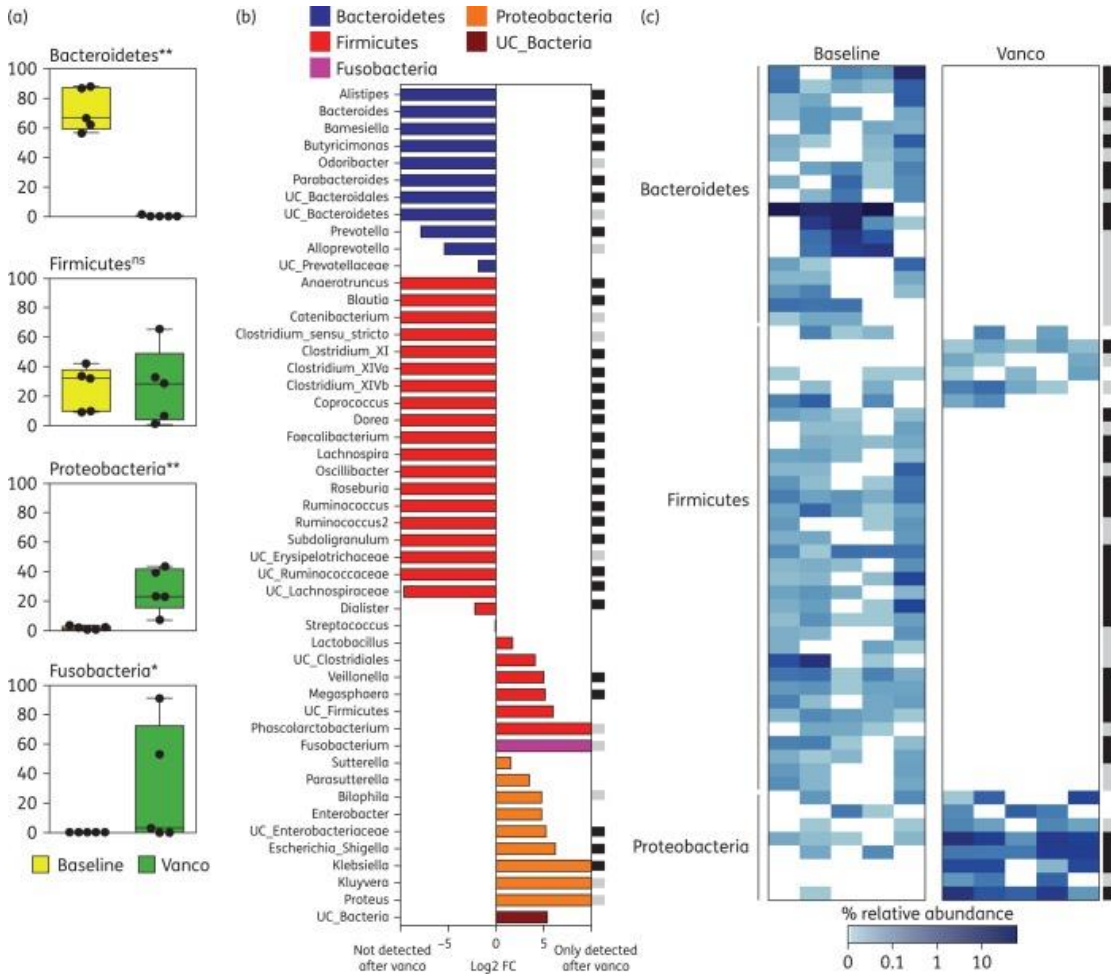
Krishna Rao,[1,2] Daniel Berland,[1,3] Carol Young,[4,5] Seth T. Walk,[1,2,6] and Duane W. Newton[4,5]

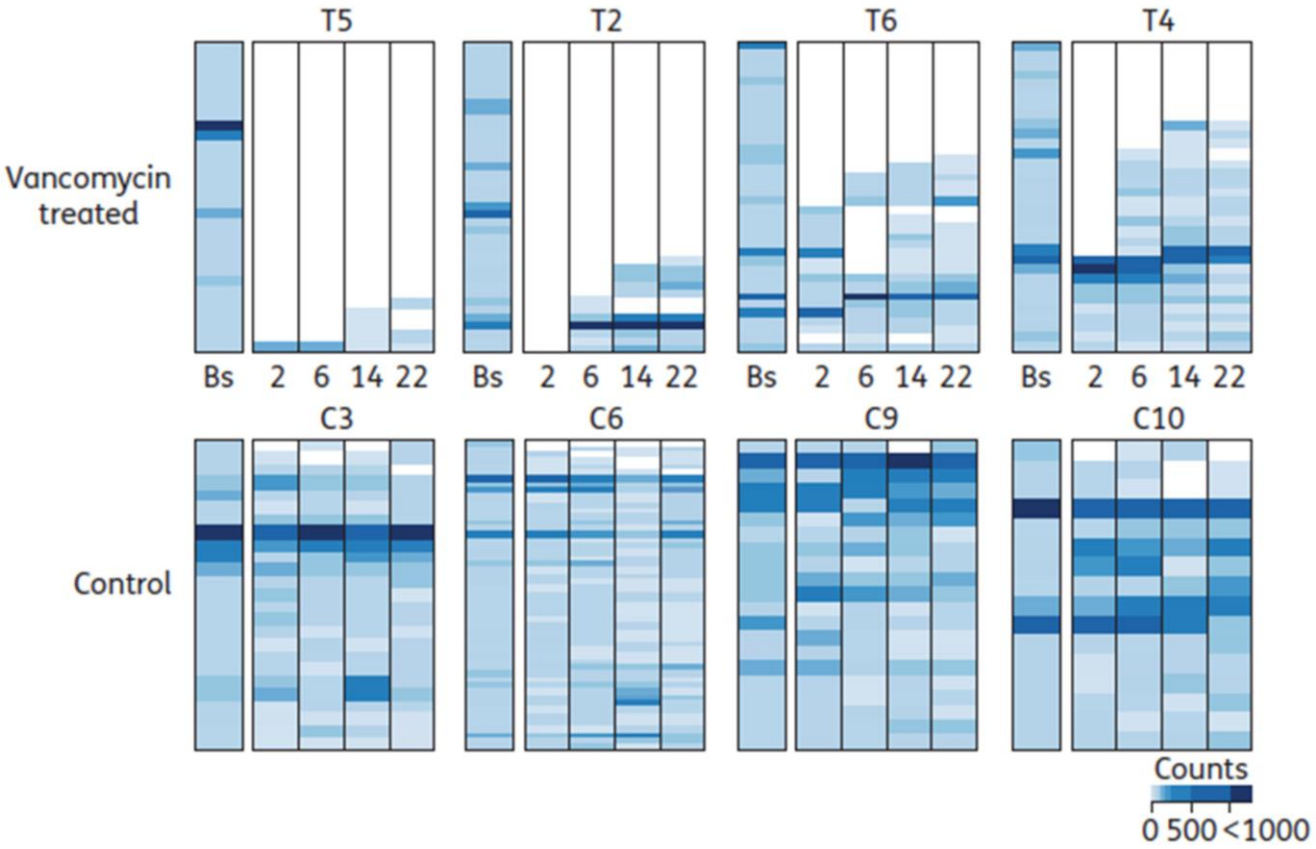


The dog correctly identified 25 of the 30 cases (sensitivity 83%, 65% to 94%) and 265 of the 270 controls (specificity 98%, 95% to 99%).

Better to send the sample to the laboratory!!!

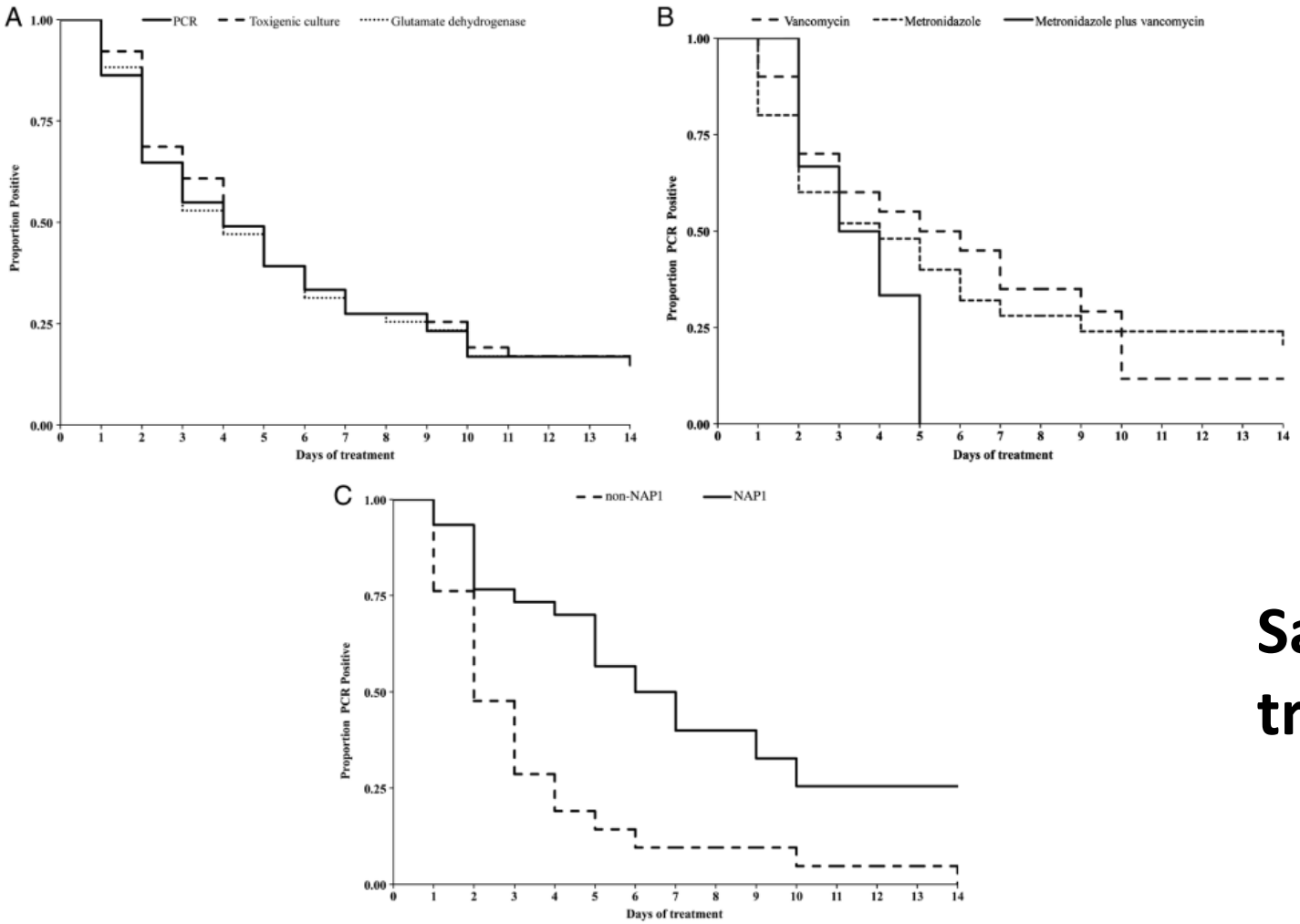
Vancomycin and its effect on the gut microbiota





Isaac, JAC, 2017

Empirical *Clostridium difficile* Infection (CDI) Therapy Result in False-Negative CDI Diagnostic Test Results



Sampling before treatment (if possible)!

Sunkesula et al., 2013

WHO should be tested?

All hospitalized patients aged ≥2 years who had three or more unformed stools within 24 hours.
*40,000 hospitalized patients a year are not diagnosed!

In primary care, patients who do not respond to oral rehydration and where antibiotic treatment is considered should be tested.

Children under 2 years of age should be tested on a case-by-case basis in consultation with a paediatrician and clinical microbiologist.
In children, the likelihood of colonization should always be considered *C. difficile* and/or co-infection with other intestinal pathogens.

Davies a kol., 2014; Crobach a kol., 2016; Krůtová a kol., 2022

Infections caused by *C. difficile* are under diagnosis

1/3 hospital CDI
Around 37,000 CDI cases per year in Europe

1/2 of community-based CDI cases
About 111,000 cases of CDI per year in Europe.

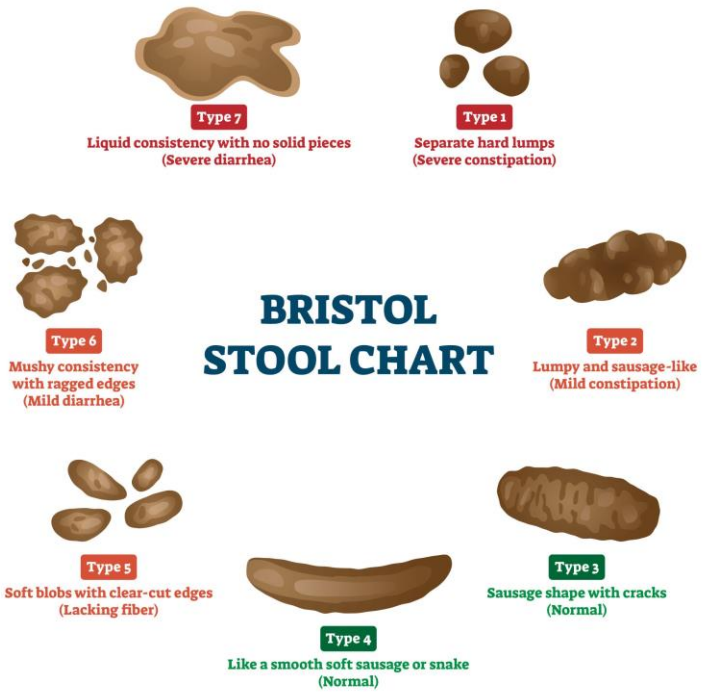
If we test all diarrheal stools delivered to the laboratory.

A patient with CDI must be detected early!!
Preventing spore spread and reducing the risk of CDI complications.

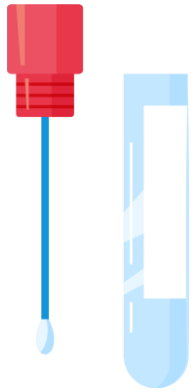
Diarrhoea=CDI?=TEST

Viprey et al., 2022

Sampling for stool testing: gastrointestinal infection



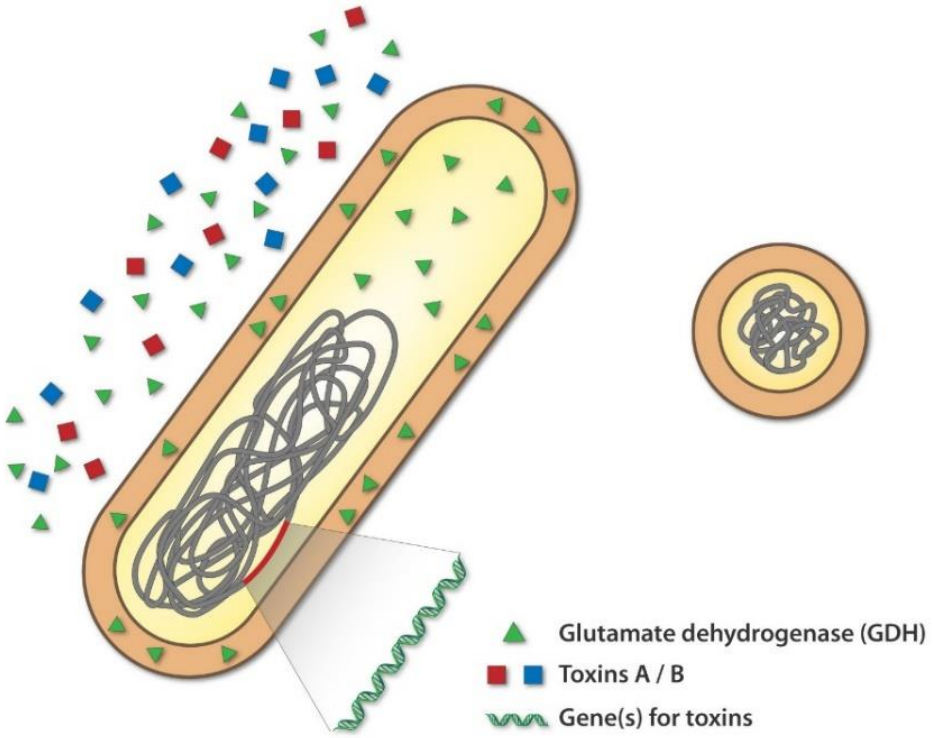
Unformed stool sample
(taking the shape of a container)



Rectal swab:
Paralytic ileus only

Bacterial culture: stool is not available

What can we test?



Glutamate dehydrogenase (GDH)
(enzyme produced by all *C. difficile*), **EIA**

Toxins A/B
(virulence factor(s)), **EIA**

Gene (s) fragment(s) for toxins, **PCR**
(not the same like toxins!)

C. difficile culture
(spores)

Recommended combination:
GDH and toxins A/B or PCR and toxins A/B

Why?

PPV and NPV for different categories of index tests at hypothetical CDI prevalences of 5, 10, 20 and 50%

Test type	CDI prevalence 5%		CDI prevalence 10%		CDI prevalence 20%		CDI prevalence 50%	
	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Well-type EIA GDH	38	100	54	99	72	98	91	94
Membrane-type EIA GDH	34	100	52	100	71	99	91	98
Well-type EIA toxins A/B	69	99	83	98	91	96	98	87
Membrane-type EIA toxins A/B	81	99	90	98	95	95	99	83
NAAT	46	100	64	100	80	99	94	96

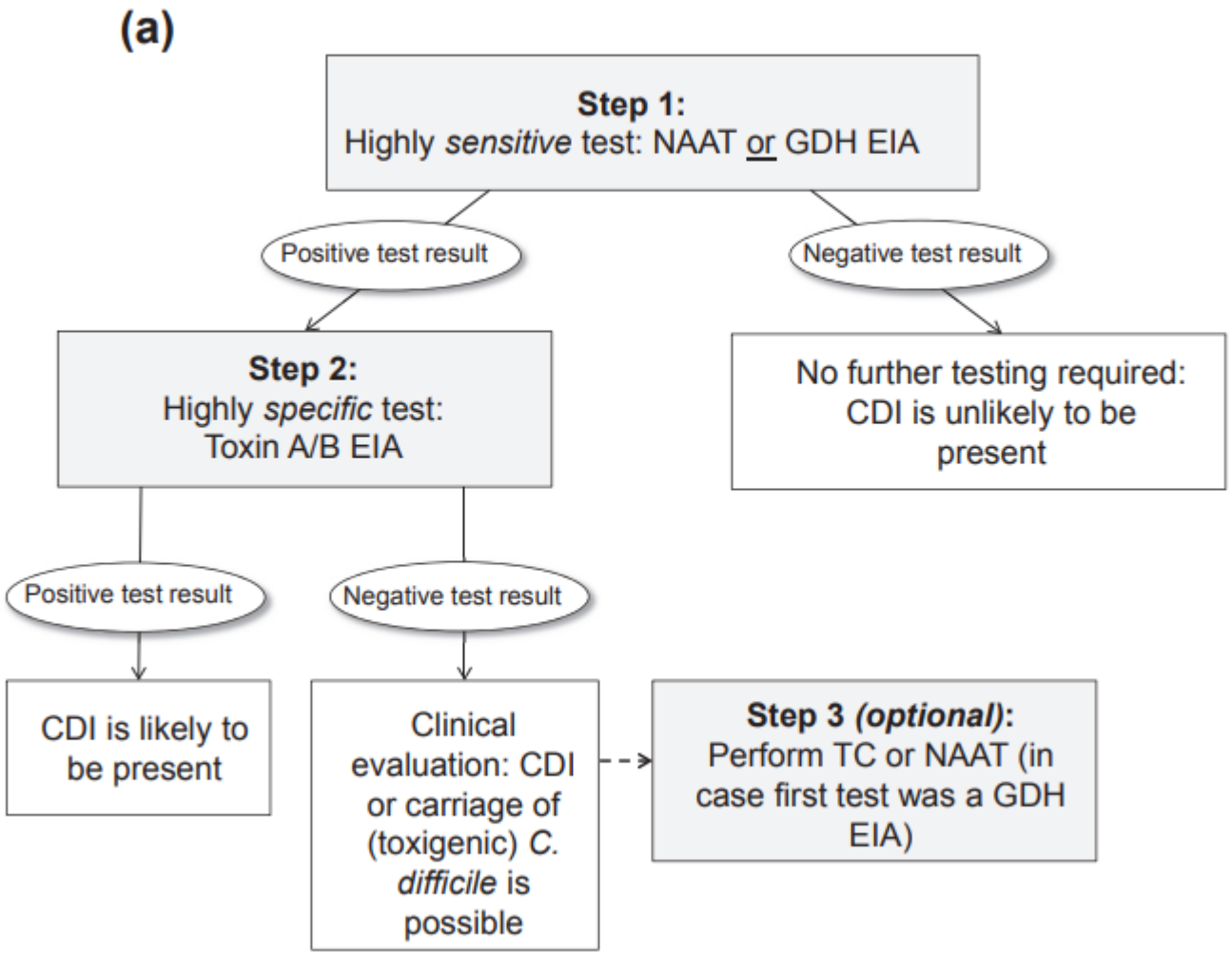
Pooled estimates of sensitivity and specificity compared to cell cytotoxicity neutralization assay were used to calculate the predictive values.
CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; NPV, negative predictive value; PPV, positive predictive value.

No single commercial test can be used as a stand-alone test for diagnosing CDI as a result of inadequate positive predictive values at low CDI prevalence.

✓ **Therefore, the use of a two-step algorithm is recommended**

Crobach et al., CMI, 2016

Laboratory diagnostics of CDI



Crobach et al., CMI, 2016

How common are co-infections in children?

In children, the likelihood of *C. difficile* colonization or co-infection with other intestinal pathogens should always be considered.

Analysis of 31 studies (1,718 patients who tested positive *C. difficile*, 20.7% (range 0-100%) had co-infection.

In children, the CDI test should not be the only test in case of diarrhoea!

Table 2 Number of reported gastrointestinal co-infections in *C. difficile*-positive patients by pathogen

Pathogen	Number of co-infection reports (%)
Viruses	164 (73.9)
Rotavirus	97 (43.7)
Adenovirus	32 (14.4)
Norovirus	17 (7.7)
Astrovirus	9 (4.1)
Sapovirus	5 (2.3)
Others[a]	4 (1.8)
Bacteria	53 (23.9)
E. coli	17 (7.7)
Enteropathogenic	8 (47.1)
Enterotoxigenic	3 (17.6)
Verocytotoxin-producing	4 (23.5)
O18	1 (5.9)
Not specified	1 (5.9)
Salmonella spp.	11 (5.0)
Campylobacter spp.	11 (5.0)
Yersinia spp.	6 (2.7)
Others[b]	8 (3.6)
Parasites	5 (2.3)
Blastocystis hominis	1 (0.45)
Entamoeba histolytica	2 (0.9)
Giardia spp.	2 (0.9)

[a] Calicivirus (n=2), coxsackievirus (n=1), enterovirus (n=1)

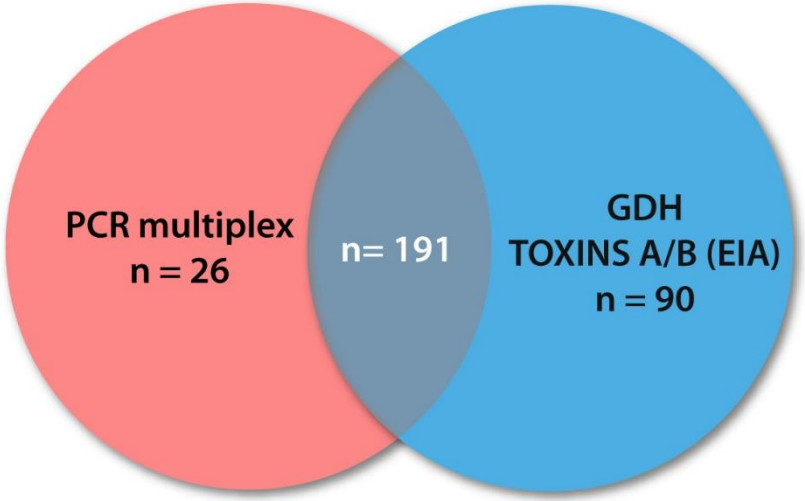
[b] *Bacillus cereus* (n=3), *Aeromonas* spp. (n=2), *Shigella* spp. (n=2), *Vibrio cholerae* (n=1)

de Graaf H, Pai S, Burns DA, Karas JA, Enoch DA, Faust SN. Co-infection as a confounder for the role of *Clostridium difficile* infection in children with diarrhoea: a summary of the literature. Eur J Clin Microbiol Infect Dis. 2015;34(7):1281-7.

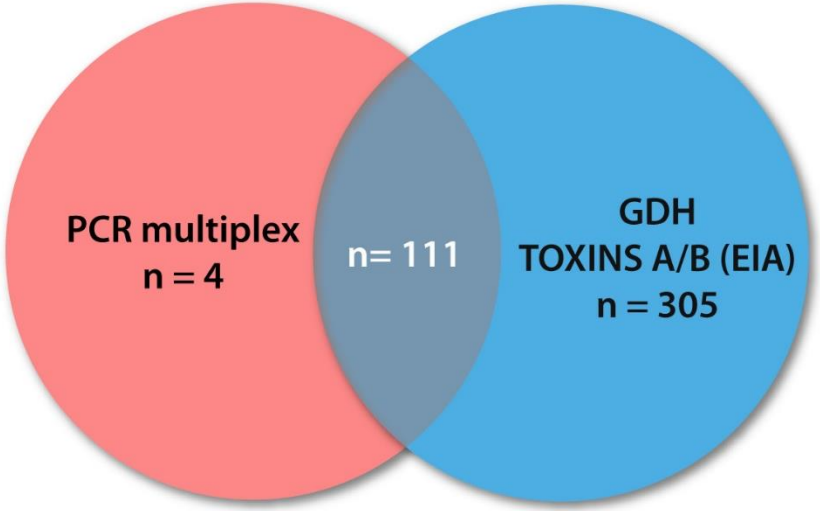
Stool testing: Dept. Med. Mic. FNM

May-August 2022

Children



Adults



- **Multiplex PCR** (daily)
- bacteria, viruses, parasites
- AusDiagnostics (panel M)
- 20 targets (AusDiagnostics (panel M)
- Community acquired diarrhoea

CDI (2 hod) - EIA

ArcDia - mariPOC CDI

- Glutamate dehydrogenase (GDH)
- *C. difficile* toxiny A/B

Internal evaluation: Krutova et al., JCM, 2019

Healthcare-assoc. and community acq. diarrhoea

PCR alone is not enough for CDI diagnostics

C. difficile (PCR positive)
n=21/115 (18.3%)

GDH negative
toxin A/B negative
n=2/21 (9.5 %)

GDH positive
toxin A/B positive
n=14/21 (66.7%)

GDH positive
toxin A/B negative
n=5/21 (23.8%)

Campylobacter (n=1)
Rotavirus (n=1)
Norovirus GII (n=1)
n=3/5 (60,0 %)

March-August 2022

Children = 191
Adults =115

C. difficile (PCR positive)
n=65/191 (34.0%)

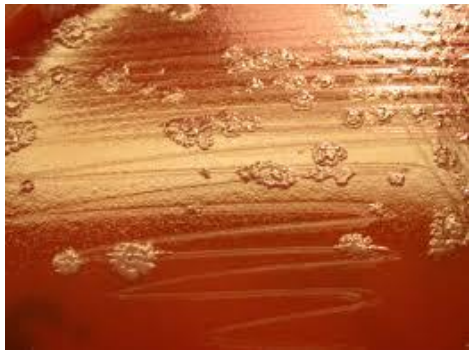
GDH negative
toxin A/B negative
n=6/65 (9.2 %)

GDH positive
toxin A/B positive
n=29/65 (44.6%)

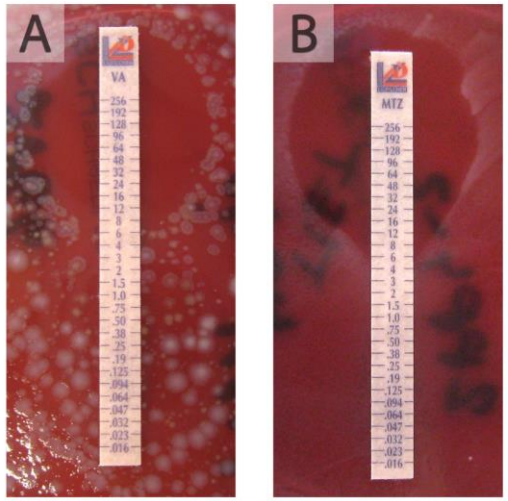
GDH positive
toxin A/B negative
n=30/65 (46.2%)

Sapovirus (n=1)
Rotavirus (n=3)
Norovirus GII (n=3)
Adenovirus (n=2)
Astrovirus (n=2)
Rotavirus a Norovirus (n=1)
Norovirus a Adenovirus (n=1)
n=13/30 (43,3 %)

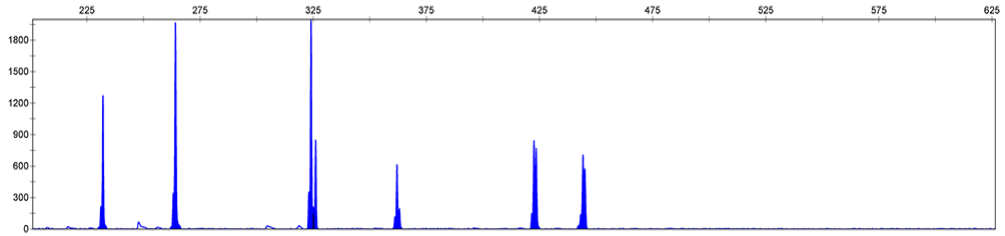
Culture of *C. difficile*-why?



Stool sample and alcohol 1:1, 30 minutes. Suppressing of other bacteria in sample, germination of spores. Culture on selective media, anaerobic atmosphere 24-48 hrs.



Antimicrobial susceptibility testing and characterisation of strain for epidemiologic purposes.



Guidance documents USA/Europe

› Clin Infect Dis. 2018 Mar 19;66(7):987-994. doi: 10.1093/cid/ciy149.

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], Mark H Wilcox [12]

Practice Guideline › Clin Infect Dis. 2021 Sep 7;73(5):755-757. doi: 10.1093/cid/ciab718.

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults

Stuart Johnson [1 2], Valéry Lavergne [3 4], Andrew M Skinner [1 2], Anne J Gonzales-Luna [5], Kevin W Garey [5], Ciaran P Kelly [6], Mark H Wilcox [7]

Clinical Microbiology and Infection 28 (2022) 1085–1090

Contents lists available at ScienceDirect

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journal homepage: www.clinicalmicrobiologyandinfection.com

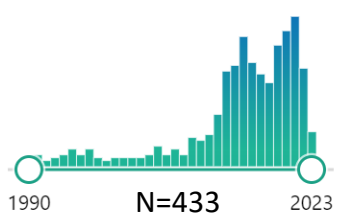
› Clin Microbiol Infect. 2021 Dec;27 Suppl 2:S1-S21. doi: 10.1016/j.cmi.2021.09.038. Epub 2021 Oct 20.

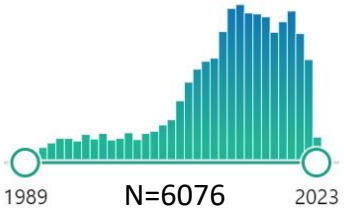
European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults

Joffrey van Prehn [1], Elena Reigadas [2], Erik H Vogelzang [3], Emilio Bouza [2], Adriana Hristea [4], Benoit Guery [5], Marcela Krutova [6], Torbjorn Norén [7], Franz Allerberger [8], John E Coia [9], Abraham Goorhuis [10], Tessel M van Rossen [3], Rogier E Ooijevaar [11], Karen Burns [12], Bente R Scharvik Olesen [13], Sarah Tschudin-Sutter [14], Mark H Wilcox [15], Maria J G T Vehreschild [16], Fidelma Fitzpatrick [17], Ed J Kuijper [18];
Guideline Committee of the European Study Group on Clostridioides difficile

How to: *Clostridioides difficile* infection in children

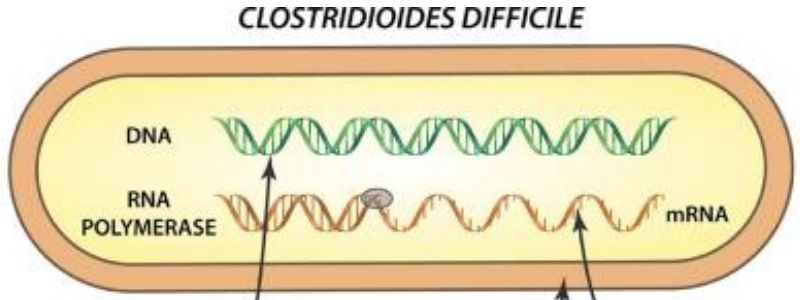
Marcela Krutova [1, 7, 8, *], Tim G.J. de Meij [2], Fidelma Fitzpatrick [3, 7, 8], Richard J. Drew [4, 7], Mark H. Wilcox [5, 7], Ed J. Kuijper [6, 7, 8]





European guidance documents do not include children, a separate document (expert opinion).

Antimicrobials approved for CDI treatment



	METRONIDAZOLE	VANCOMYCIN	FIDAXOMICIN
SYSTEMIC ABSORPTION	HIGH	LOW	LOW
STOOL CONCENTRATION	LOW	HIGH	HIGH
REDUCTION OF BIOACTIVITY BY FAECES	HIGHEST	LOWER	LOWER
EFFECT ON DIVERSITY OF MICROBIOTA	REDUCTION	REDUCTION	PRESERVATION
STOOL SHEDDING DECLINE	SLOW	RAPID	RAPID
ENVIRONMENTAL CONTAMINATION	HIGHEST	LOWER	LOWER (STEEPER)
SPOROCIDAL EFFECT	—	NO	YES
INHIBITION OF SPORULATION	NO	NO	YES

SUPPORTIVE · LESS-SUPPORTIVE · NON-SUPPORTIVE · — NO DATA

Overview of pharmacodynamic, pharmacokinetic and microbiological properties for oral administration of metronidazole, vancomycin and fidaxomicin.

Pharmacokinetic differences of metronidazole, vancomycin and fidaxomicin.

Krůtová et al., 2022

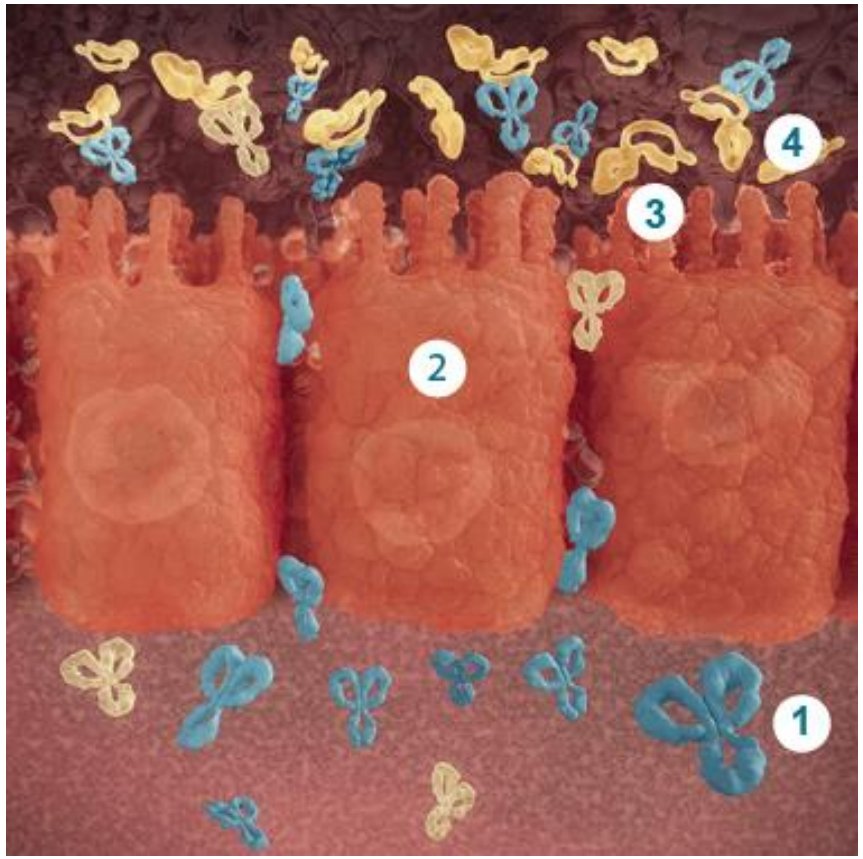
Passive immunisation

Bezlotoxumab (ZINPLAVA™) is a human monoclonal antibody that binds to *Clostridioides difficile* toxin B indicated to reduce the recurrence of CDI.

Should only be used in conjunction with antibacterial drug treatment of CDI!

Clinical Trial › N Engl J Med. 2017 Jan 26;376(4):305-317. doi: 10.1056/NEJMoa1602615.

The rate of recurrent C. difficile infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, **-10.1** percentage points; 95% confidence interval [CI], -15.9 to -4.3; P<0.001; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, -**9.9** percentage points; 95% CI, -15.5 to -4.3; P<0.001)



1.ZINPLAVA
2.Damaged gut epithelial cells
3.Toxin B
4.ZINPLAVA binding to toxin B

FMT: Feacal microbiota transplantation

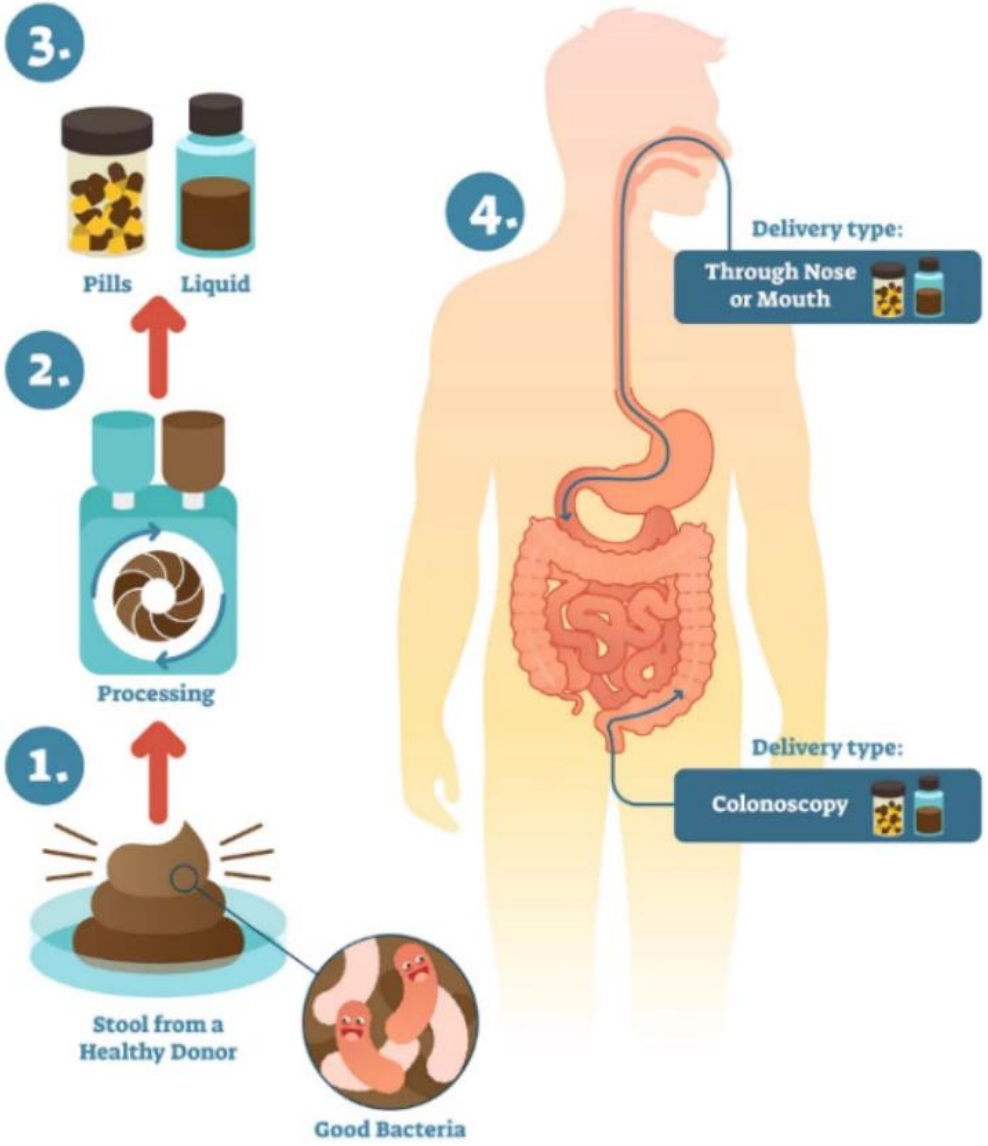


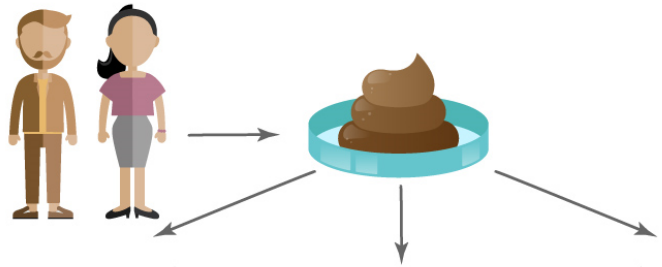
Table 2
Donor screening by laboratory screening of faeces and serum

Laboratory screening serum	Laboratory screening faeces
• Hepatitis A (IgM + IgG) • Hepatitis B (HBsAg + anti-Hbcore) • Hepatitis C (anti-HCV) • Hepatitis E (IgM + IgG) • HIV (anti-HIV, type 1 and 2) • Lues; *Treponema pallidum* (Ig) • Cytomegalovirus (IgM + IgG) • Epstein Barr Virus (IgM + IgG) • *Strongyloïdes* (IgG1/IgG4)[a]	• *Clostridium difficile* (PCR) • *Helicobacter pylori* (antigen test) • Bacterial gastroenteritis: (PCR, followed by culture) *Salmonella* spp. *Campylobacter* spp., *Campylobacter jejuni*, *C. coli*, *Shigella* spp., *Yersinia enterocolitica* and *Y. pseudotuberculosis*, *Aeromonas* spp., *Plesiomonas shigelloides*, and Shiga Toxin-producing *E. coli* • Antibiotic-resistant bacteria (culture); ESBL and/or carbapenemase-producing bacteria, vancomycin-resistant enterococci, and methicillin-resistant *Staphylococcus aureus* • Viral pathogens (PCR): Norovirus serotype I+II, Astrovirus, Sapovirus, Rotavirus, Adenovirus 40/41, Adenovirus non-40/41, Enterovirus, Parechovirus, Hepatitis E • Parasites (PCR): *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium parvum* and *C. hominis*, *Microsporidium* spp, *Strongyloïdes*[a] • Microscopy for ova, cysts, and larvae [69]: e.g. *Blastocystis hominis*

Questionnaire: 1 day before donation of faeces
Stool frequency/pattern, general health, use of antibiotics, travel history, sexual behaviour

Terveer et al., 2017

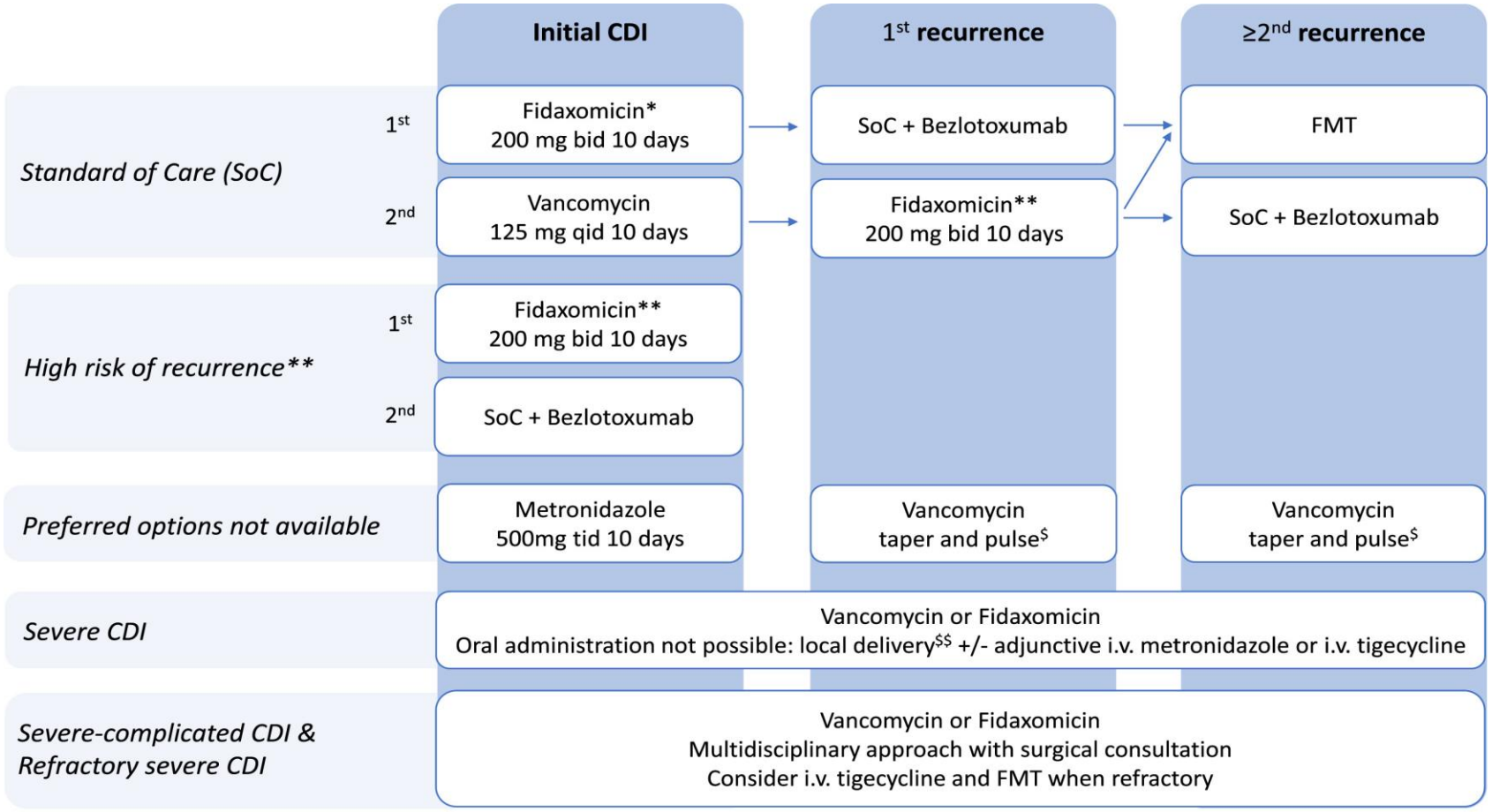
Future FMT? Live biotherapeutics



PRODUCT NAME	RBX2660	SER-109	VE303
PRODUCT TYPE	FMT-DERIVED		BACTERIAL CONSORTIA
STOOL PROCESSING	Dilution (0.9% saline/polyethylene glycol)	Spore enrichment (50 – 70% v/v EtOH 2-hrs treatment)	Bacterial culture (8 strains of Clostridiales)
FORM OF DELIVERY	Liquid enema	4x Oral capsules	2x / 10x Oral capsules Low dose / High dose
REDUCTION OF rCDI	13.1%	28.0%	8.5% / 31.7%
BATCH-TO-BATCH VARIATION	YES	YES	NO
CHARACTERIZATION OF COMPOSITION	NO	NO	YES
RISK OF PATHOGEN (AMR) TRANSMISSION	POSSIBLE	POSSIBLE	LIMITED

Benech et al., 2024

Currently valid guidance document for CDI treatment



* 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

CDI treatment should be guided order by the CDI episode.

Fidaxomicin is the drug of choice, but its price is still high.

In practice, vancomycin (p.o.) is often used.

Patients with recurrent CDI should be offered FMT!

Be careful, if peristalsis is not already preserved, the treatment will not work!

van Prehn et al., 2021

Severe (complicated) course of CDI

Severe - complicated course is defined by the presence of one of the following factors that must be assigned to CDI: hypotension, septic shock, increased serum lactate, ileus, toxic megacolon, perforation of the intestine or any fulminant course of the disease (i.e. rapid deterioration of the patient's condition).

Treatment, if CDI is suspected in a severe course, we treat immediately and at the same time take a sample for microbiology!

Consult with the surgeon.

Oral treatment: fidaxomicin or vancomycin.

After consideration: intravenous administration of tigecycline 50 mg twice daily (100 mg loading dose) or metronidazole 500 mg three times daily should be added on a case-by-case basis.

If oral treatment is not possible, intraluminal (gastroduodenal or colonoscopic) administration of vancomycin or fidaxomicin in combination with IV therapy should be attempted, see above.

Intravenous therapy alone will never reach high concentrations of the antibiotic in the stool, which is necessary to eradicate *C. difficile*!

van Prehn et al., 2021

Shortened regimens for CDI treatment?

Table 1. Comparison of study and control groups[a]

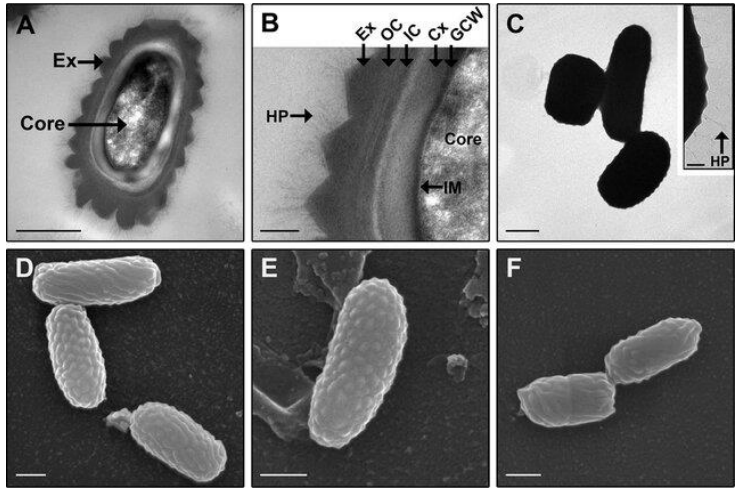
	Shortened treatment regimen ($n=25$)	Standard treatment regimen ($n=22$)	*P* value
Patient characteristics			
Gender (%)			0.58
Male	11 (44.0)	7 (31.8)	
Female	14 (56.0)	15 (68.2)	
Age, median, y (range)	76 (66.0–83.0)	74.5 (73.0–82.8)	0.20
Recurrence risk (mean)	3.3 (1.2)	2.4 (1.2)	
CDI treatment (%)			0.79
Vancomycin	21 (84.0)	20 (90.9)	
Fidaxomicin	4 (16.0)	2 (9.1)	
Blood parameters			
Leucocyte count at the beginning, cells/10^9/L	10.0 (6.2–13.2)	10.8 (8.6–14.5)[b]	0.15
Leucocyte count at the end, cells/10^9/L	7.5 (6.5–9.1)[b]	7.0 (5.6–9.4)[b]	0/76
C-reactive protein at the beginning, mg/L	78.3 (42.5–115.7)	49.9 (30.9–85.4)[b]	0.93
C-reactive protein at the end, mg/L	30.4 (13.2–54.9)[b]	11.0 (6.8–37.1)[b]	0.92
CDI characteristics and outcomes (%)			
First episode at the hospital admission	22 (88.0)	17 (77.3)	NA
Recurrent CDI at the hospital admission	3 (12.0)	3 (13.6)	
Other than first CDI episode at the hospital admission	0 (0.0)	2 (9.1)	
Recurrent CDI during follow-up	2 (8.0)	5 (22.7)	0.24

NA, not available.
[a]Data are *n* (%), median (IQR) or mean (SD).
[b]Missing data in the dataset.

An Initiated Randomized Blinded Clinical Trial at Bulovka Hospital

Duricek et al., 2023

Anti-epidemic measures/contact precautions



The patient's skin and surroundings (toilet) are contaminated with *C. difficile* spores!

You can easily transmit them (hands, shared medical devices).

Guidance document for *C. difficile* spread prevention

Clinical Microbiology and Infection 24 (2018) 1051–1054

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

Guidance document for prevention of *Clostridium difficile* infection in acute healthcare settings

S. Tschudin-Sutter [1,*], E.J. Kuijper [2], A. Durovic [1], M.J.G.T. Vehreschild [3], F. Barbut [4], C. Eckert [4], F. Fitzpatrick [5], M. Hell [6], T. Norèn [7], J. O'Driscoll [8], J. Coia [9], P. Gastmeier [10], L. von Müller [11], M.H. Wilcox [12], A.F. Widmer [1] on behalf of the Committee†

Every hospital should have such a document.

9_Clostridioides difficile postup pro personál, final

Fakultní nemocnice v Motole	ODDĚLENÍ NEMOCNIČNÍ HYGIENY A EPIDEMIOLOGIE		vedoucí: MUDr. Jarmila Rážová, Ph.D.
FN MOTOL	Jméno pacienta:	Pokoj č.:	Opatření předal za ONHE dne: jmenovka, podpis:
Klinika:	Rodné číslo:	Kontakty:	
Oddělení:	Datum odběru:		Opatření převzal za oddělení dne: jmenovka, podpis:
	Biologický materiál:		

OPATŘENÍ PŘI VÝSKYTU Clostridioides difficile				
PACIENT	IZOLACE	**Jednolůžkový pokoj /box nebo kohorta,** označení pokoje "izolační režim", samostatné hygienické příslušenství. Přípustné jsou kohorty. **Izolační opatření se zavádějí i v případě suspektní infekce tj. GDH + , toxin -.**	Pozn.: Neoddělovat matky s pozitivním nálezem C.difficile od zdravých kojenců. **Epidemiologicky významné ribotypy:** 001, 014, 017, 027, 078, 176 s možností šíření ve zdravotnických zařízeních.	**Hlášení závažných případů CDI na ONHE:** překlad pacienta na JIP/ARO; chirurgický zákrok z důvodu CDI (např.kolektomie); úmrtí do 30 dnů od stanovení CDI; hospitalizace z důvodu komunitní CDI.
	ODBĚR BIOLOGICKÉHO MATERIÁLU	Stolice: u pacientů s průjmem > 3 stolice/den nebo v případě zástavy peristaltiky (megakolon).	U symptomatických dětí > 24 měsíců. ATB v anamnéze. U symptomatických dětí < 24 měsíců např. při vrozené malformaci střeva (M. Hirschprung) nebo jiných odůvodněných případech, pokud je vyloučena jiná příčina průjmu. Asymptomatická kolonizace střeva kojenců toxigenními kmeny v 30 - 70 %.	
	OPUŠTĚNÍ IZOLACE pouze z neodkladných důvodů	V případě neodkladného vyšetření: hygiena rukou* (mytí rukou teplou vodou a mýdlem, usušení rukou do jednorázové utěrky, hygienická dezinfekce). Čistý oděv. V případě průjmu má pacient nasazeny plenkové kalhotky. Informovat cílové pracoviště. Zařazení pacienta jako posledního. Úklid dle dezinfekčního řádu FNM pro epidemiologicky významné situace.		Pozn.: **důraz na hygienu rukou*** zejména po použití WC, před jídlem a opuštěním místnosti.
	MONITORING BEZPŘÍZNAKOVÝCH PACIENTŮ	Opakování vyšetření u bezpříznakových pacientů po prodělané epizodě CDI není indikováno (např. z důvodu monitorování léčby).		
	TRANSPLANTACE STOLICE (FMT - faecal microbiota transplantation)	**Indikace:** rekurentní klostridiová kolitída **Rekurentní infekce**: případ, který vzniká za > 14 dní, tj. období mezi 3. až 8. týdnem včetně. Zahrnuje relaps infekce (infekce stejným kmenem) a reinfekci (případ nové infekce jiným exogenním kmenem).	Načasování: nejdříve 24- 48 h po ukončení ATB léčby. Kontaktní osoba pro transplantaci stolice ve FNM - MUDr. Markéta Roznětínská (Interní klinika). Při selhání FMT (rekurence kolitidy v intervalu 2 měsíců od fekální transplantace) lze výkon opakovat.	
	ZRUŠENÍ IZOLAČNÍCH OPATŘENÍ	**Minimálně 48 h po skončení průjmu.** Informaci o zrušení izolačních opatření hlásit nemocničnímu epidemiologovi – hygienikovi (hygiena@fnmotol.cz).	Před odizolováním pacienta je třeba klást důraz na důkladné omytí celého těla pacienta mycí emulzí, výměnu lůžkovin a prádla.	Úklid: průběžný závěrečný úklid otěrem s důrazem na kontaktní plochy dle DŘ pro epidemiologicky významné situace - sporicidní účinnost, viz příloha. Následně lze provést prostorovou dezinfekci.
	PROPUŠTĚNÍ A TRANSPORT	**Informaci o pozitivitě zapsat do propouštěcí/překladové zprávy.** V domácím prostředí nejsou třeba zvláštní opatření. Transport: pacient s průjmem nebo v období následujících 48 h bez klinických příznaků: mytí rukou vodou a mýdlem, po osušení hygienická dezinfekce rukou + čisté oblečení/ povlečení lůžka. V případě průjmu má pacient nasazeny plenkové kalhotky a je transportován samostatně.		
KONTAKTY	IZOLACE	Preventivní izolace a screening kontaktů se neprovádí. V případě výskytu více případů CDI na oddělení (3 a více) nebo 2 pacientů na témže pokoji hlášení telefonicky nebo mailem na ONHE - hygiena@fnmotol.cz.		
	SCREENINIG			
PERSONÁL	OOPP - Osobní ochranné pracovní prostředky	**Nepřímý kontakt s pacientem:** jednorázové rukavice.	**Další opatření:** individualizace pomůcek, dokumentace vždy mimo izolační pokoj. Infekční odpad, infekční prádlo. Důraz na úklid kontaktních ploch - lůžka pacienta a jeho okolí, WC a koupelny dle DŘ pro epidemiologicky významné situace - sporicidní účinnost.	**Činnosti spojené s nejvyšším rizikem přenosu:** mytí pacienta, přebalovaní a polohování pacienta, rehabilitace, přímá manipulace s pacientem a jeho lůžkovinami.
		Přímý kontakt s pacientem: jednorázové rukavice a jednorázový ochranný plášť.		
	HYGIENA RUKOU	**Před vstupem do izolačního pokoje:** provést hygienickou dezinfekci rukou a nasadit si rukavice. Opuštění pokoje: Před opouštěním pokoje mytí rukou teplou vodou a mýdlem k odstranění spór a následně usušit do jednorázové utěrky a provést hygienickou dezinfekci rukou.		Pozn: Pokud na pokoji není umyvadlo: po sejmutí rukavic na izolačním pokoji - hygienická dezinfekce rukou. Mechanické mytí teplou vodou a mýdlem u nejbližšího umyvadla.
NÁVŠTĚVY	HDR - Hygienická dezinfekce rukou a další opatření (OOPP)	Pouze se souhlasem zdravotnického personálu. Hygiena rukou (mytí rukou vodou a mýdlem, po osušení hygienická dezinfekce rukou) před opuštěním pokoje. Ochranný plášť. Minimalizace pohybu po oddělení a vyloučení kontaktu s dalšími pacienty.		

Více informací: IOS_21/2009 Zajištění hygienické a protiepidemické péče, příloha č. 2, v platném znění
Verze 07/2024 (Verze č. 2)

Anti-epidemic measures/contact precautions

A patient with diarrhoea should have already been isolated

Reported CDI test positivity =
Initiation of anti-epidemic measures = to prevent the spread

Everyone has to follow them, otherwise they don't work!

Patient isolation - single room/toilet

Explain to the patient and visitors what is happening

A notice should be placed on the outer door of the isolation room, advising all visitors to contact nursing staff before entering.

The door should always be closed when possible, except in the entrance and exit.
Fans must not be used as they may recirculate spores in the environment.

ECDC „School report“: Czech Republic – PPS 2022-2023

Key indicators

Point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals

2022-2023

CZECHIA

Number of hospitals	39
Standard protocol	39
'Light' protocol	0
Number of patients	12296

	Min.	25th percentile	EU/EEA country median	75th percentile	Max.	Country
Healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) indicators						
HAI prevalence* (% patients with HAI)	3.0	5.1	**6.8**	8.2	13.8	**6.7**
Composite index** of AMR (% antimicrobial-resistant isolates)	7.9	15.4	**21.8**	38.2	68.7	**29.8**
Infection prevention and control (IPC) and diagnostic stewardship indicators						
IPC nurses (full-time equivalents (FTEs) per 250 beds)	0.28	0.98	**1.25**	1.54	3.28	**0.82**
Beds with alcohol-based handrub dispenser at point of care (% beds)	18.5	43.4	**49.2**	69.7	100	**42.4**
Beds in single rooms (% beds)	3.2	7.1	**15.8**	35.2	56.5	**8.6**
Blood culture sets (number per 1000 patient-days)	12.4	28.0	**44.7**	68.9	167.1	**27.6**
Antimicrobial use (AU) and antimicrobial stewardship indicators						
AU prevalence (% patients with AU)	20.8	29.7	**36.0**	43.8	56.5	**30.9**
Duration of surgical prophylaxis >1 day (% of antimicrobials for surgical prophylaxis)	15.8	31.2	**38.1**	60.1	79.8	**49.6**
Antimicrobials reviewed and changed during treatment (%)	6.2	13.9	**19.5**	24.1	31.3	**18.9**

*HAI prevalence should be interpreted with caution, as it depends on patient mix, diagnostic capacity, sensitivity of HAI case finding and country representativeness of the sample of hospitals.

**The percentage of the sum of isolates of the following resistant microorganisms divided by the sum of the isolates for which results from antimicrobial susceptibility testing were reported: *Staphylococcus aureus* resistant to meticillin (MRSA), *Enterococcus faecium* and *Enterococcus faecalis* resistant to vancomycin, Enterobacterales resistant to third-generation cephalosporins, and *Pseudomonas aeruginosa* and *Acinetobacter baumannii* resistant to carbapenems.

Legend:

- Better than both EU/EEA country median and the 25th (or 75th) percentile
- Better than EU/EEA country median, but worse than the 25th (or 75th) percentile
- Worse than EU/EEA country median, but better than the 75th (or 25th) percentile
- Worse than both EU/EEA country median and the 75th (or 25th) percentile

What should I do if I don't have a single room?

-Priority - patient with faecal incontinence

-Patient cohorting

-Fellow patients without ATBs and immunosuppression

Anti-epidemic measures/contact precautions

Frequent cleaning and disinfection of the area (Terminal room clea

Personalised equipment

Gloves and gowns when entering the room (to the patient)

Hands must be washed before putting on gloves!

Gloves are ESSENTIAL!

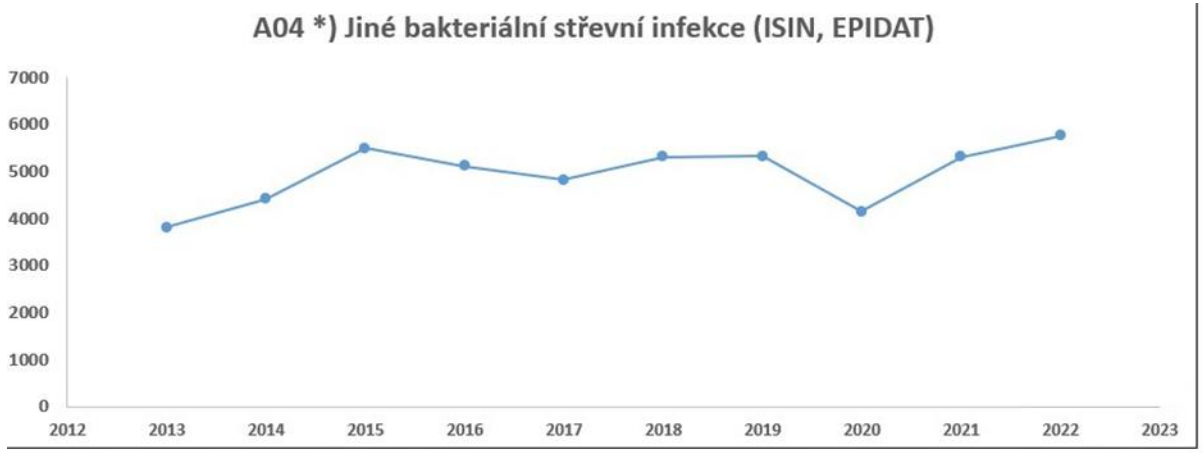
Gloves need to be changed! When?

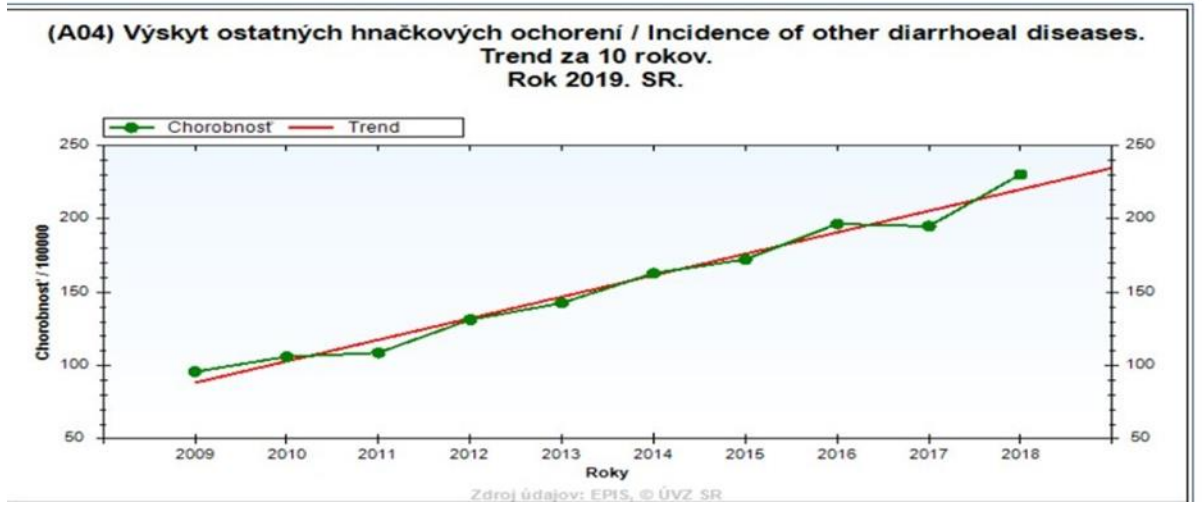
If they are visibly contaminated
If I'm moving from a dirty to a clean area of patient care

Hand hygiene!! Before putting on new gloves and after patient care

Avoid contaminating yourself and the environment with contaminated gloves!

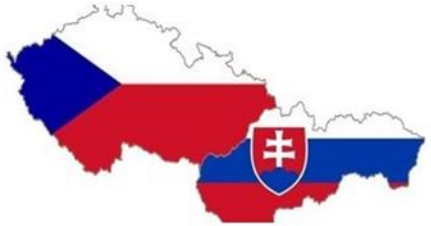
National CDI surveillance





FN MOTOL

ISIN (Informační systém infekčních nemocí)
-dříve EPIDAT



EPIS (Epidemiologický informační systém)

Czech and Slovak system for reporting infectious diseases.
Code A04: Other bacterial Intestinal infections

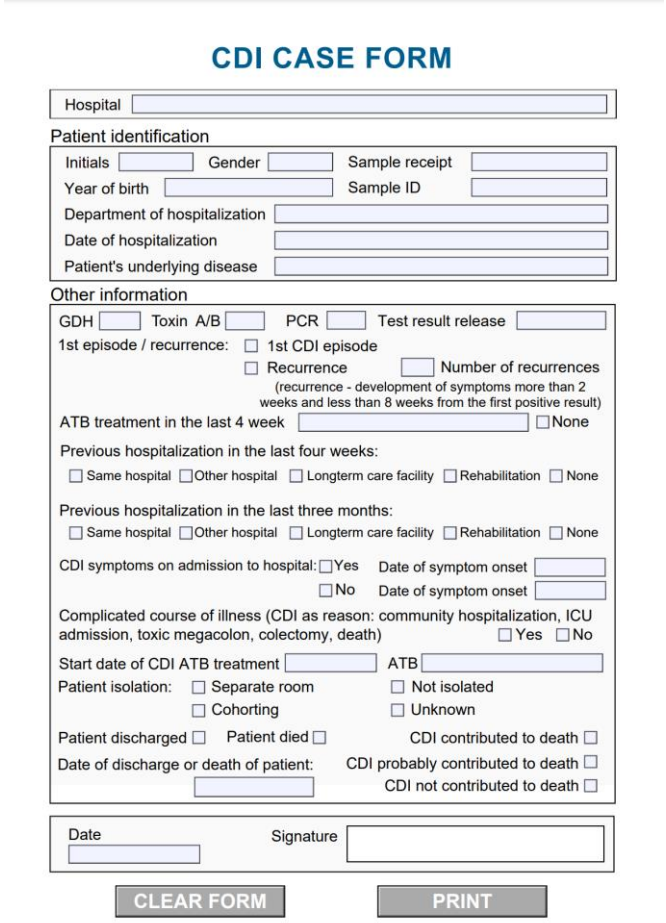
CDI is one of the mandatory notifiable infectious diseases

European CDI surveillance

Table 1. Information collected for different CDI surveillance options

	Minimal surveillance	Light surveillance	Enhanced surveillance	Form
Collected information	• **Minimum CDI surveillance for each hospital** (aggregated numerator data) • **Hospital data for each hospital** (aggregated denominator data)	• **Minimum CDI surveillance for each hospital** (aggregated numerator data) • **Hospital data for each hospital** (aggregated denominator data)	• **Minimum CDI surveillance for each hospital** (aggregated numerator data) • **Hospital data for each hospital** (aggregated denominator data)	• **Form H** (aggregated numerator and denominator data)
		• **Information on each CDI case** (case-based numerator data)	• **Information on each CDI case** (case-based numerator data)	• **Form C** (case-based numerator data)
			• **Microbiological data** (for the first 5 consecutively detected cases in each participating healthcare facility: characterisation, susceptibility testing and typing of each *C. difficile* isolate)	• **Form M** (one form for each *C. difficile* isolate)
Surveillance period	**Recommended:** continuous surveillance for 12 months, starting on the first* day of the month. The **recommended minimum** surveillance period is three consecutive months, preferably from 1 October to 31 December, or from 1 January to 31 March. The absolute minimum surveillance period is one month, starting on the first day of the month. *The pilot study demonstrated that completion of Form H is made much easier by starting surveillance on the first day of a month.			

ECDC, CDI surveillance protocol v2.4, 32 pages



CDI CASE FORM

Hospital

Patient identification

Initials Gender Sample receipt

Year of birth Sample ID

Department of hospitalization

Date of hospitalization

Patient's underlying disease

Other information

GDH Toxin A/B PCR Test result release

1st episode / recurrence: 1st CDI episode

Recurrence Number of recurrences

(recurrence - development of symptoms more than 2 weeks and less than 8 weeks from the first positive result)

ATB treatment in the last 4 week None

Previous hospitalization in the last four weeks:

Same hospital Other hospital Longterm care facility Rehabilitation None

Previous hospitalization in the last three months:

Same hospital Other hospital Longterm care facility Rehabilitation None

CDI symptoms on admission to hospital: Yes Date of symptom onset

No Date of symptom onset

Complicated course of illness (CDI as reason: community hospitalization, ICU admission, toxic megacolon, colectomy, death) Yes No

Start date of CDI ATB treatment ATB

Patient isolation: Separate room Not isolated

Cohorting Unknown

Patient discharged Patient died CDI contributed to death

Date of discharge or death of patient: CDI probably contributed to death

CDI not contributed to death

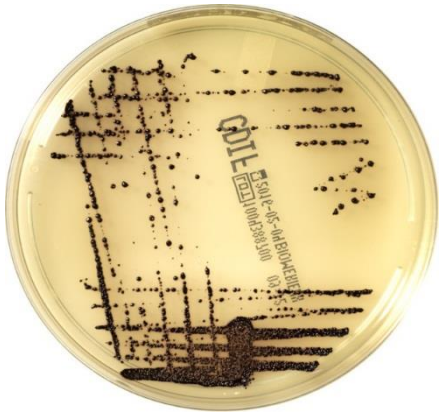
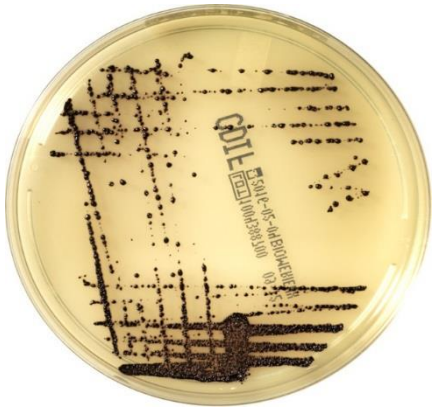
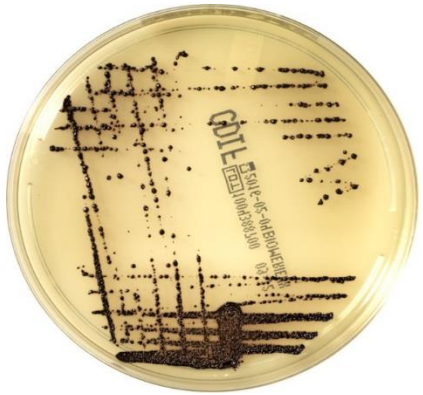
Date Signature

CLEAR FORM PRINT

Krutova M. - Faculty Hospital Motol

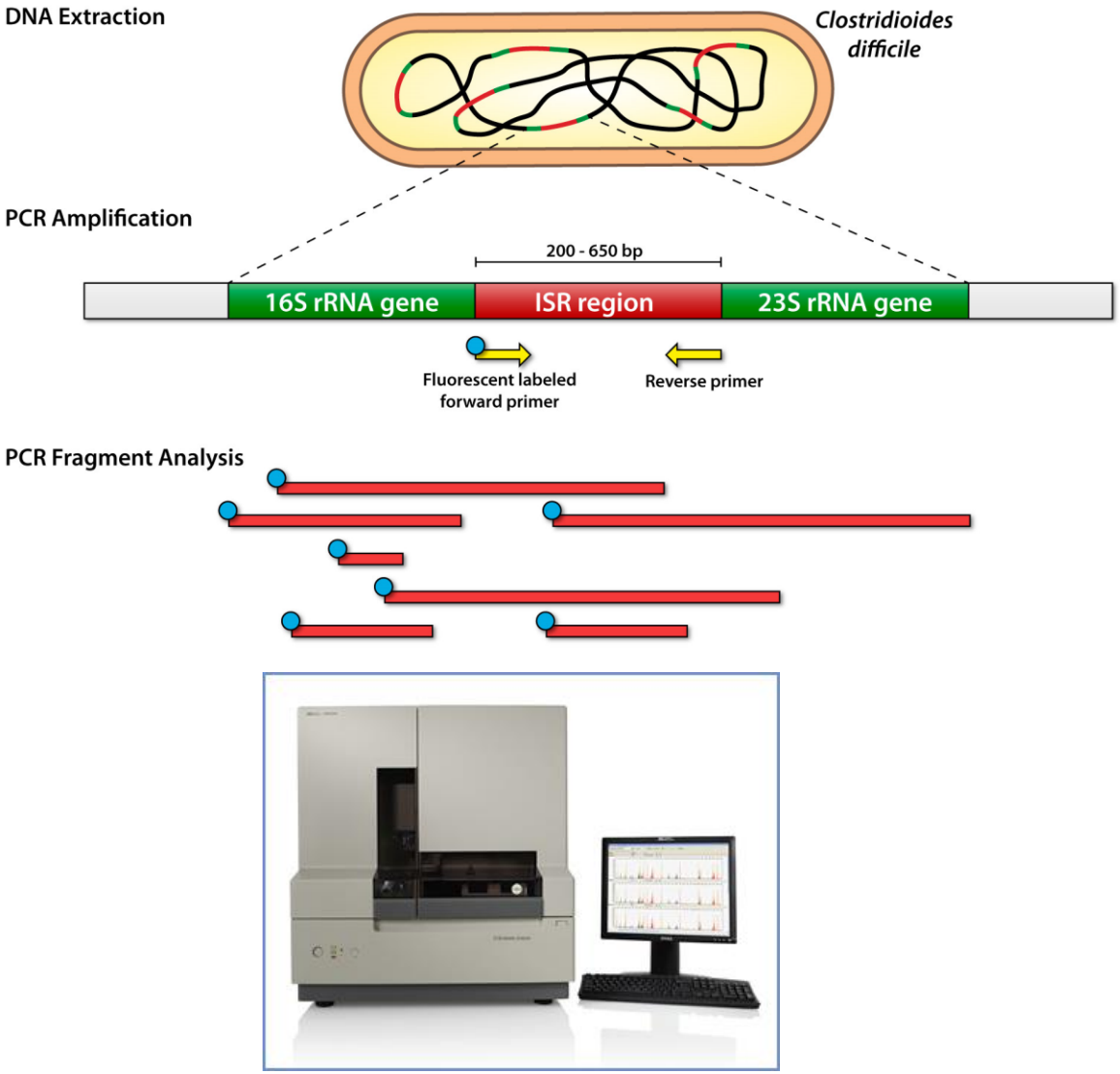
Why should we characterize *C. difficile* isolates (CDI cases)? Name the CDI case!

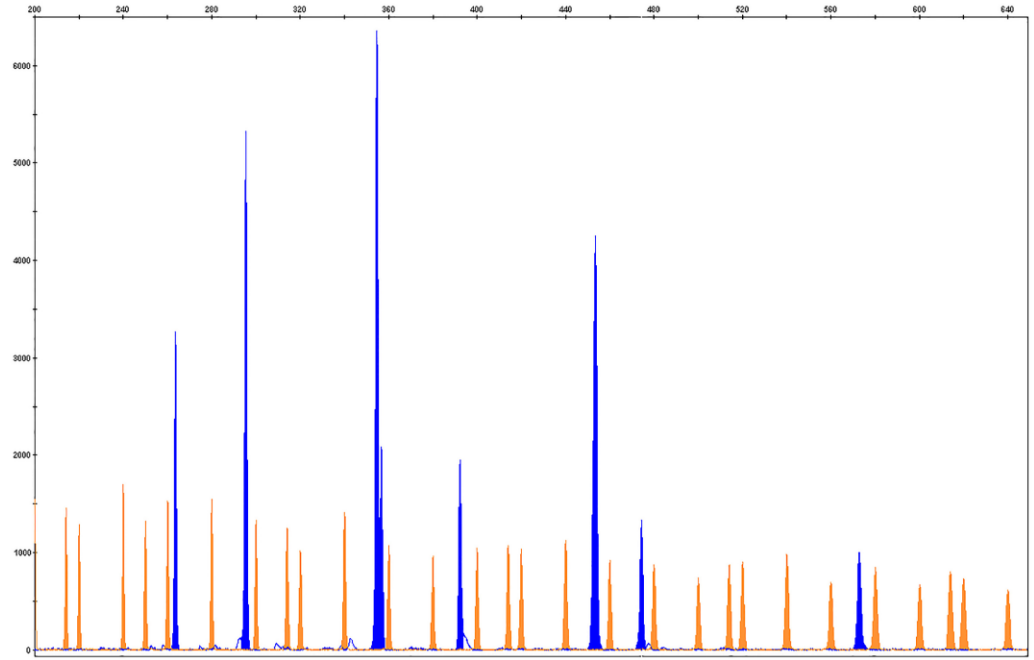


Monitoring of the occurrence and spread within healthcare facility

C. difficile PCR ribotyping





AGES
Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH

WEBRIBO

Ribotyping – Implementation into routine practice

FN MOTOL

Materiál: **Stolice**
Vyšetření: toxigenní Clostridium difficile - antigen, Cl. difficile - kultivace, PCR vyšetření toxínu C.difficile

C. difficile - antigen

GDH: POZITIVNÍ

Toxiny A/B: POZITIVNÍ

Kultivace cílená na C. difficile

Nález 1: **Clostridium difficile**

ANTIBIOGRAM - MIC v mg/l (strip)

vankomycin.....	0,5	C	metronidazol.....	0,125	C

C. difficile - charakterizace kmene

Gen toxinu A: **POZITIVNÍ**

Gen toxinu B: **POZITIVNÍ**

Gen binárního toxinu: **negativní**

Ribotyp: **001**

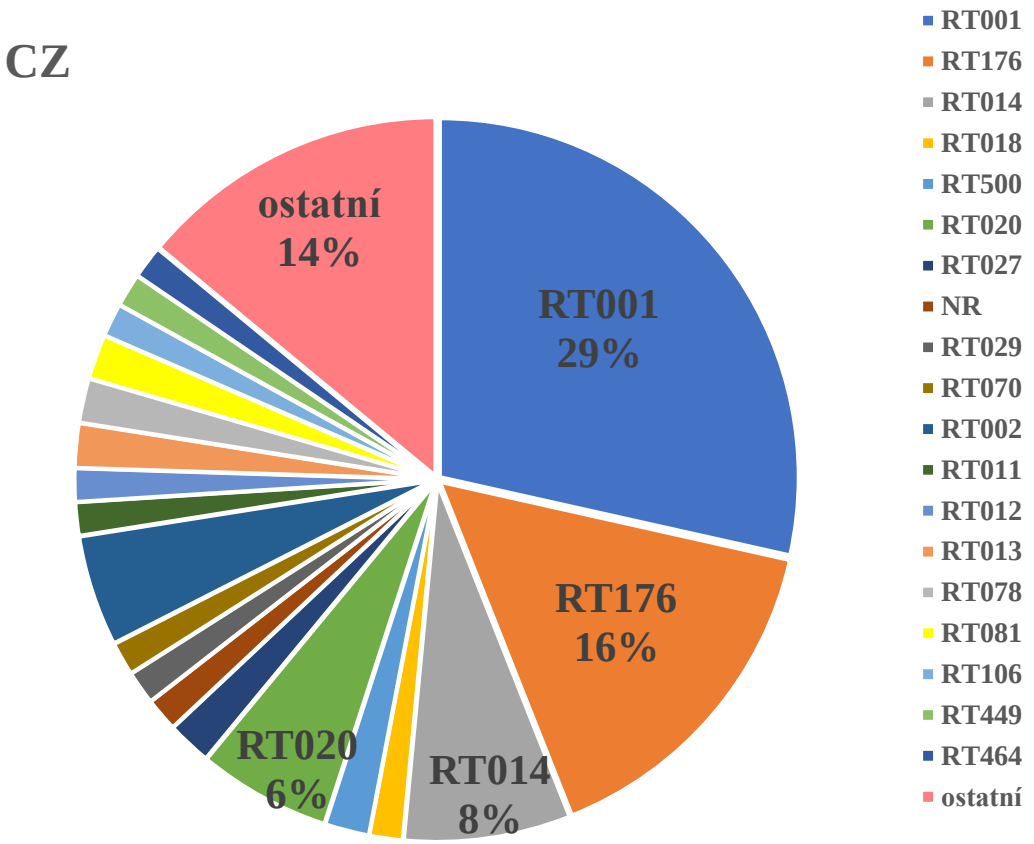
Zkratky: C = citlivý, R = rezistentní, I = intermediální, * = výsledek k dispozici po konzultaci s ATB střediskem

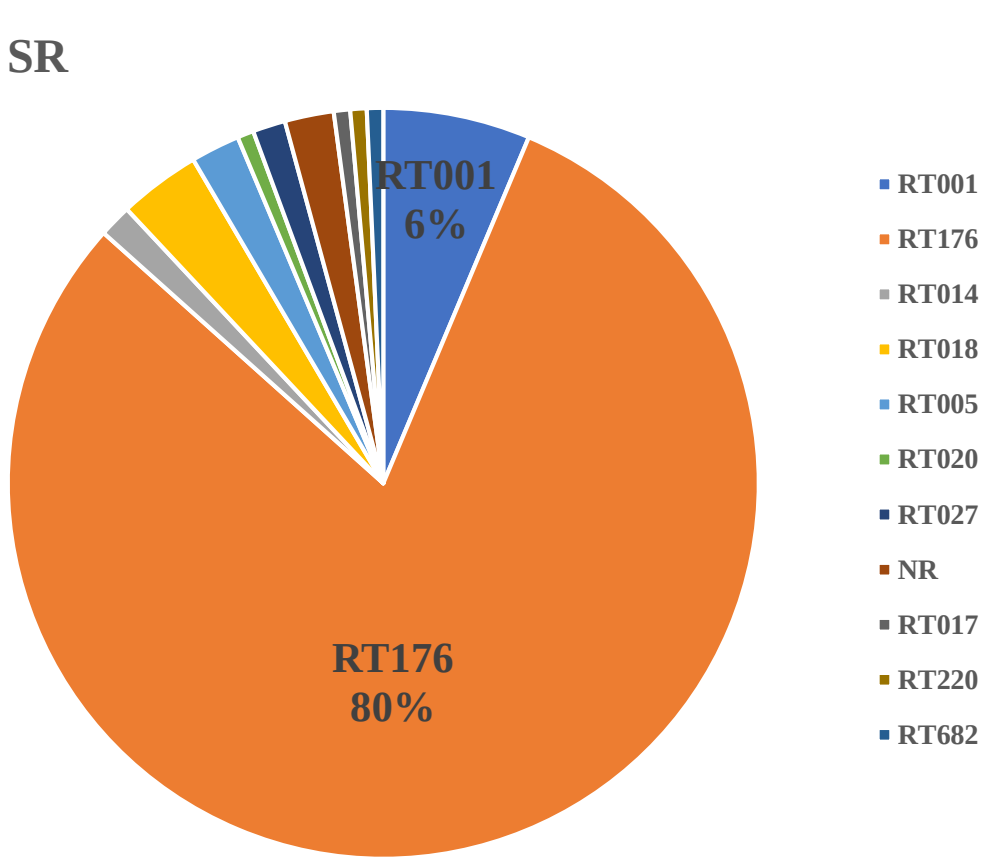
Telefonické hlášení:
25.10.2024-16:24 MUDr. Šulc Radek (Korbová Hana)
Clostridium difficile - pozitivní nález antigenu a toxinu

Kódy pro pojišťovnu: 82031(1), 82058(1), 82067(3), 82117(2)

LAB kontrola: Mgr. Krůtová Marcela, Ph.D. *VŠ kontrola: 29.10.2024-18:00 MUDr. Hurych Jakub, Ph.D.*

PCR ribotyping national data



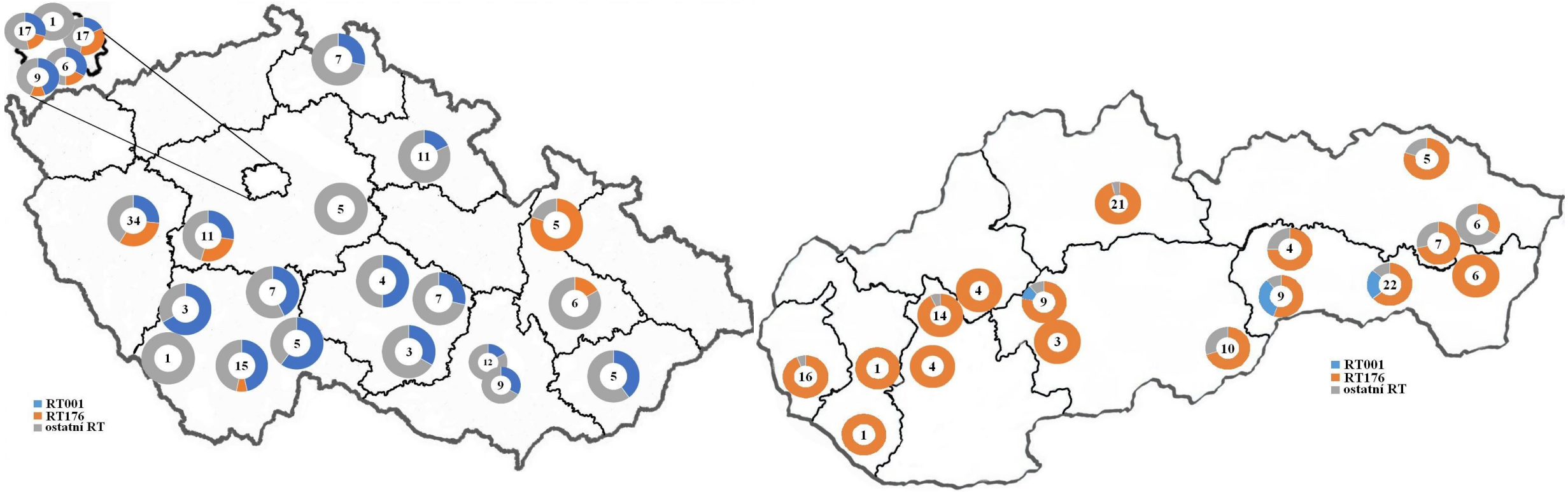


52 ribotyping profiles

Zíková J., diploma thesis

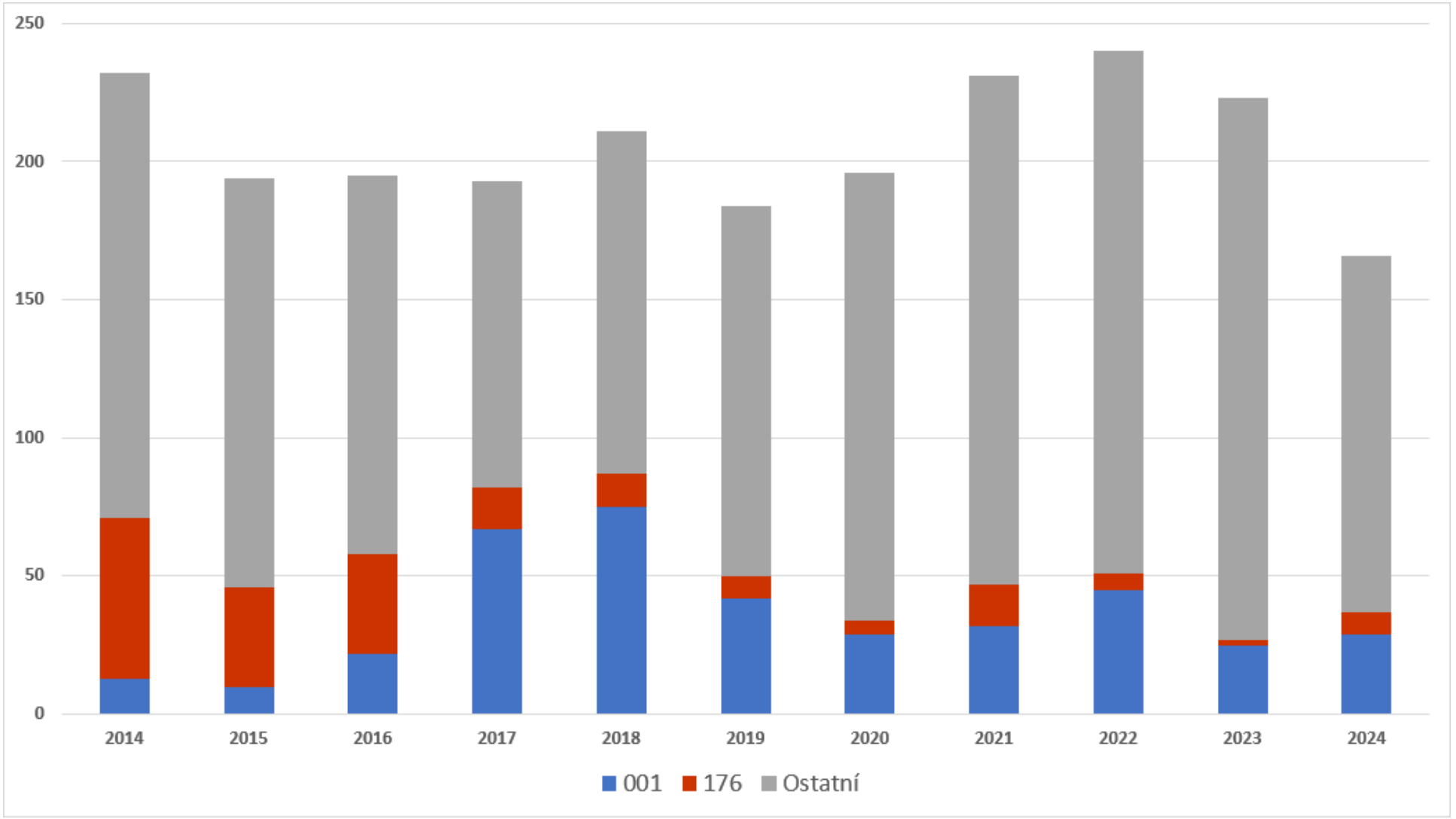
RT=ribotype, NR=new ribotype

Geographical distribution of participating hospitals



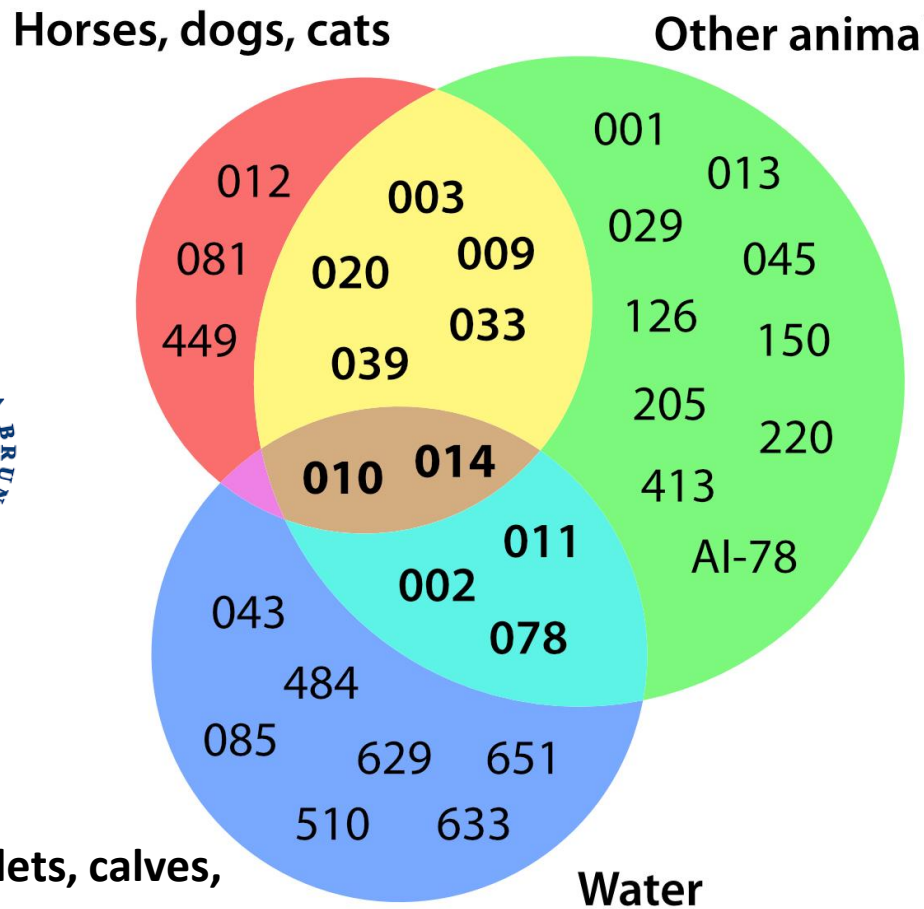
Zíková J., diploma thesis

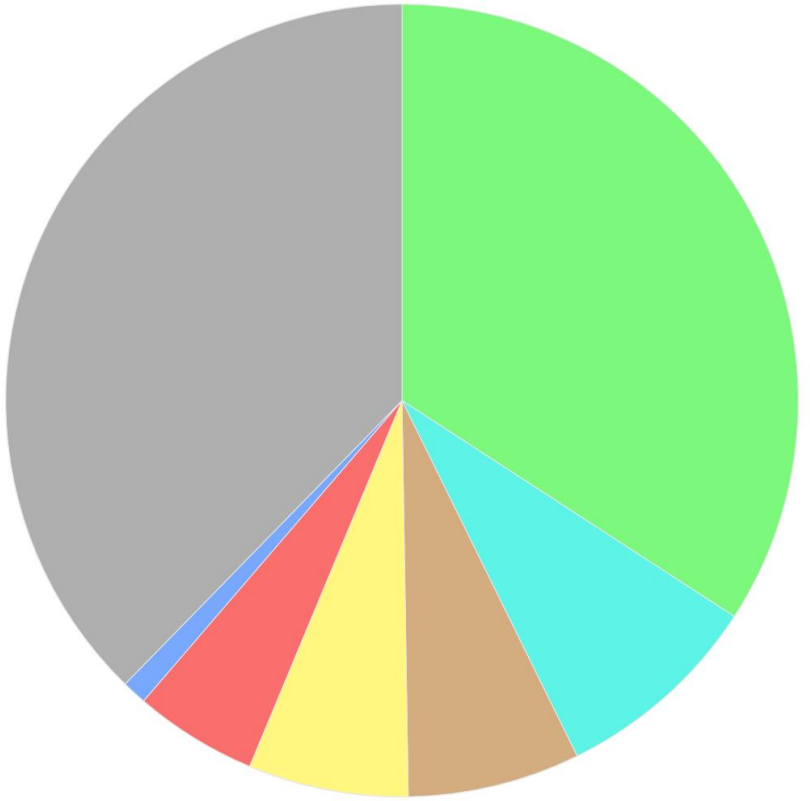
C. difficile – ribotyping – FN Motol



FN MOTOL

PCR ribotyping – Patients vs. Other sources



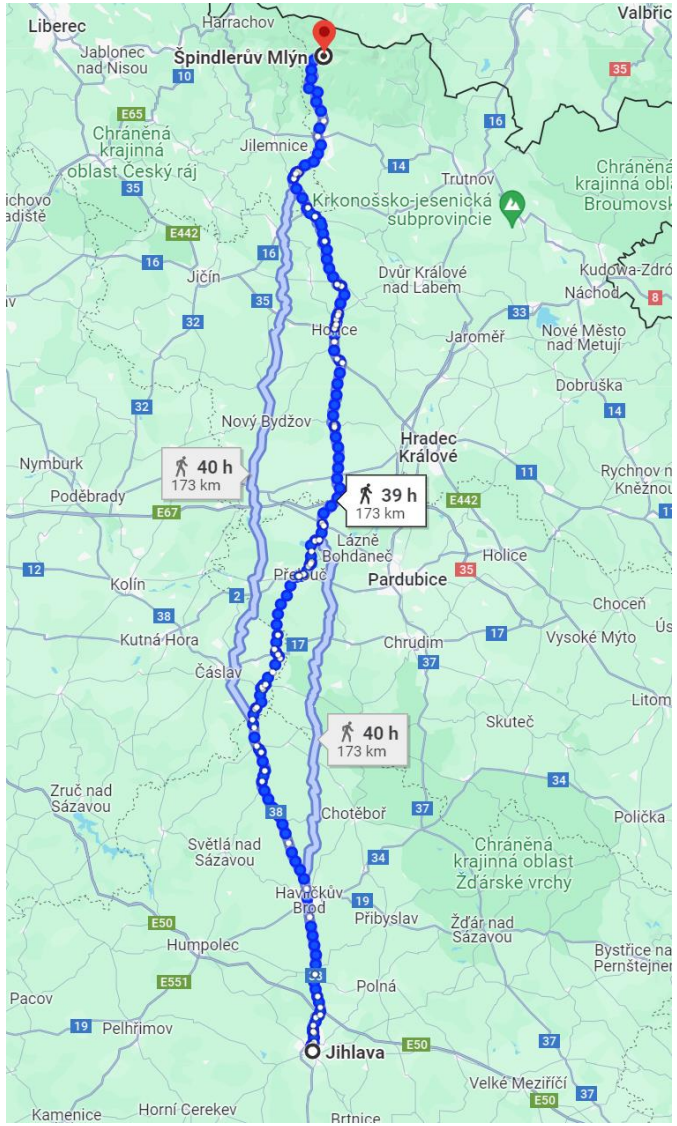


Others: piglets, calves, wild boars.

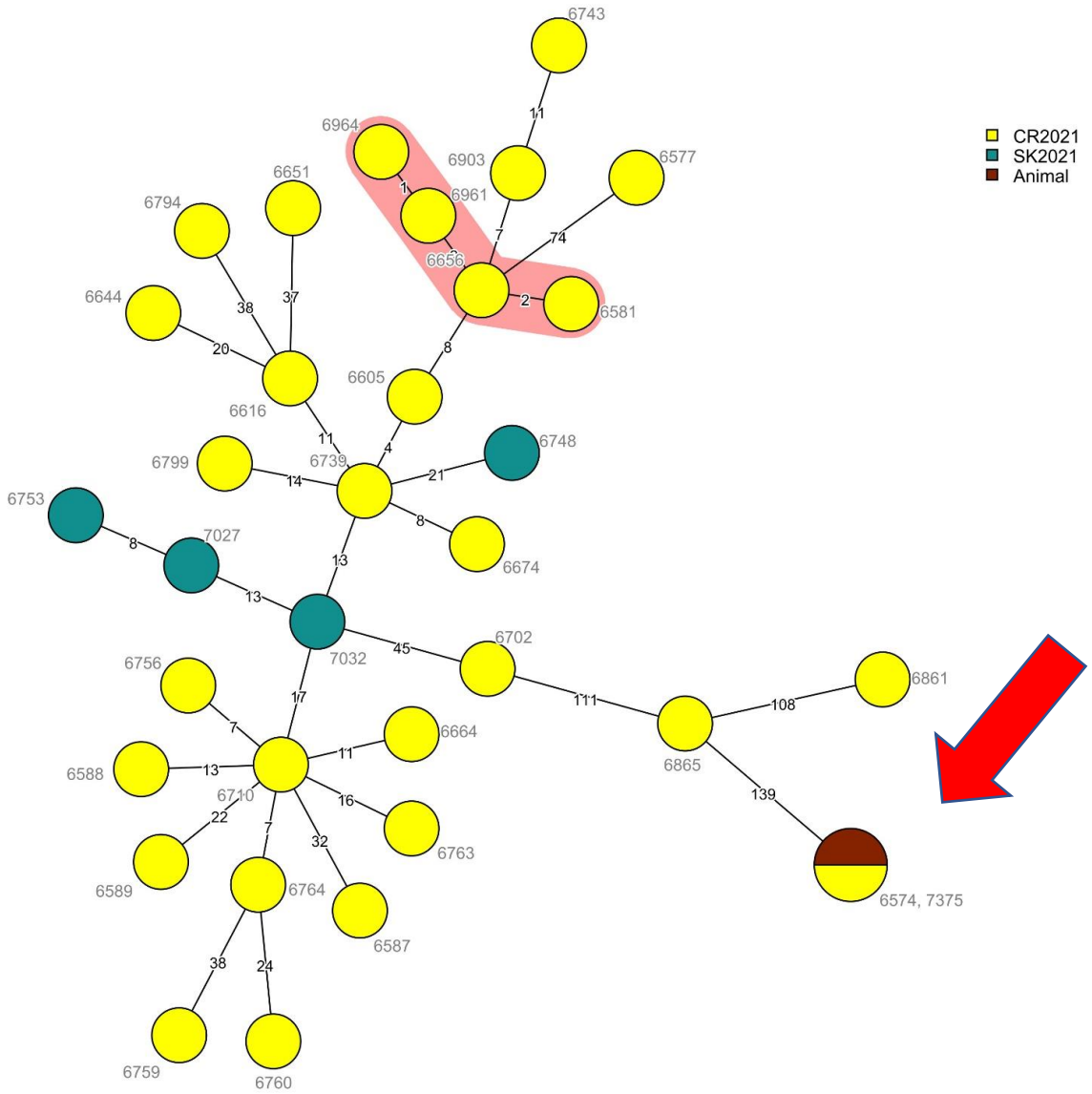
One isolate of ribotype 001 in wild boar!

Krutova et al., 2018; Kecerova et al., 2019; Masarikova et al., 2020; Cizek et al., 2022

C. difficile ribotype 001 wild boar vs. patients

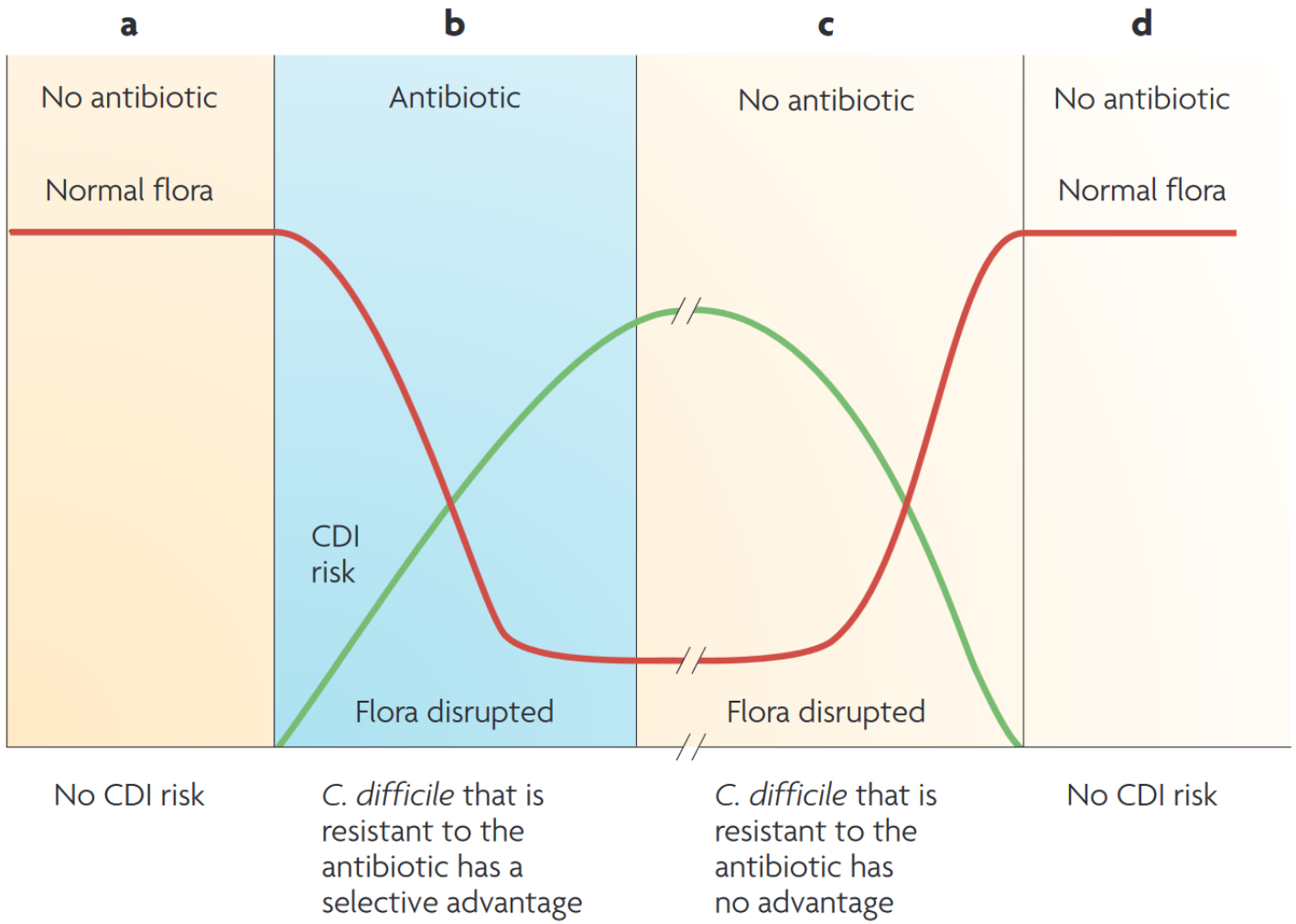


Wild boar: 30 - 55 km/h



FN MOTOL

Safe Antibiotics for Patients at Risk of CDI – *C. difficile* Colonization?

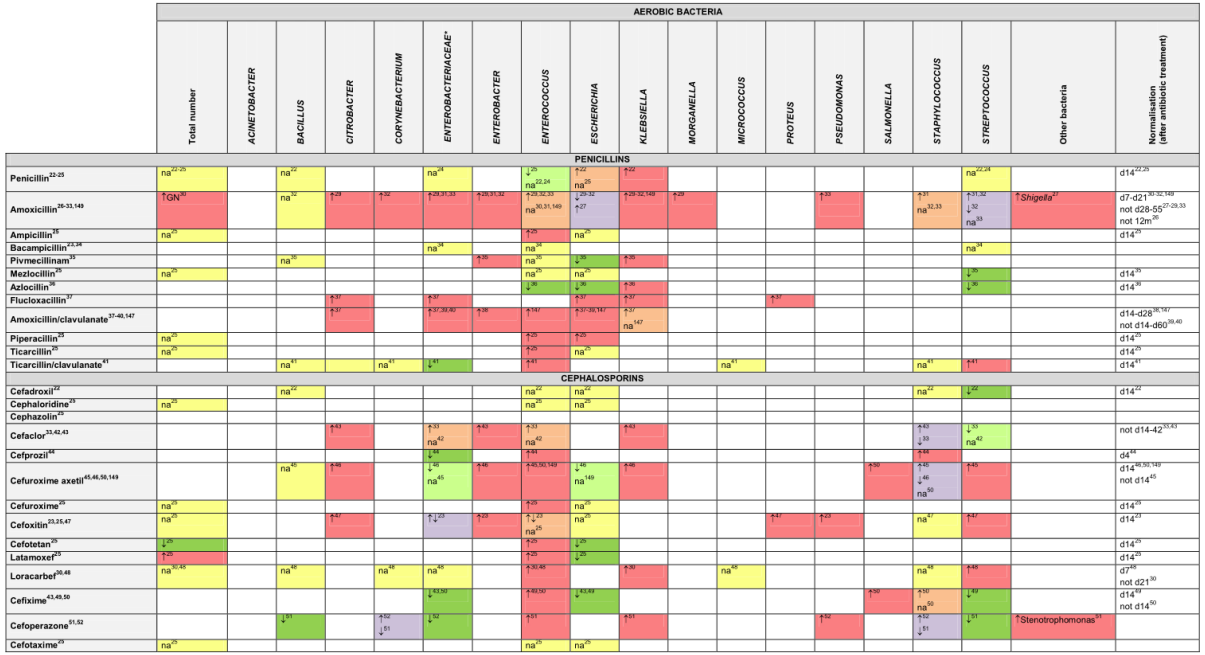


Rupnik et al., 2009

Safe antibiotics for patients at risk of CDI?
The effect of antibiotics on the composition of the gut microbiota

Table 1a
Changes in the abundance of aerobic bacteria in the intestinal microbiota associated with adminstration of antibiotics (reported on genus level).

Increased abundance | Decreased abundance | Inconsisted findings
Increased abuandance or no change | Decreased abundance or no change | No change in aubundance
White boxes depict that no finfings were reported for the respective bacteria



P. Zimmermann and N. Curtis/Journal of Infection 79 (2019) 471–489

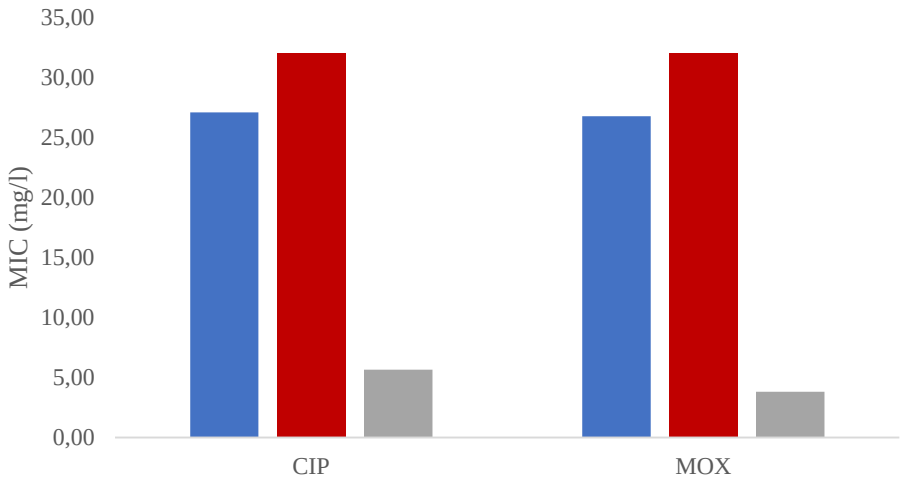
- ✓ Antibiotics cause significant changes in the intestinal microflora. These changes include a decrease in bacterial diversity,
- ✓ changes in the abundance of certain bacteria and an increase in antibiotic resistance.
- ✓ The longest duration of changes was observed after treatment with ciprofloxacin (one year), clindamycin (two years) and clarithromycin with metronidazole (four years). However, these findings are limited by the follow-up period.

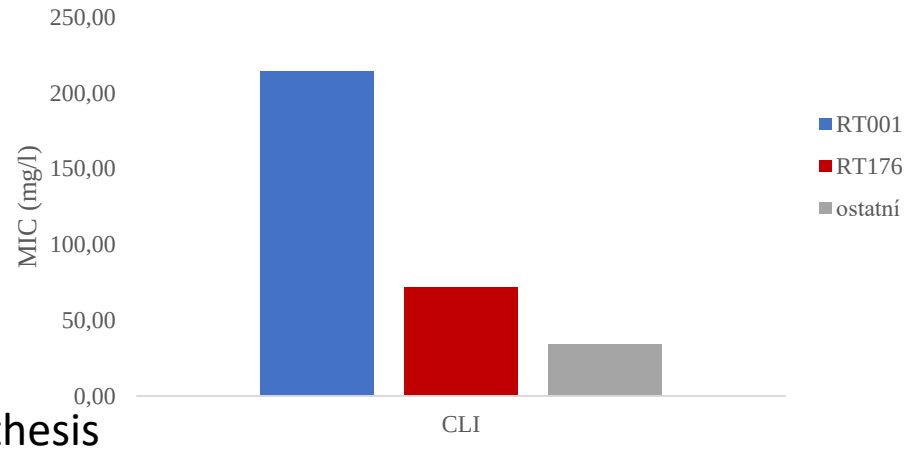
(Zimmermann and Curtis, JI, 2019)

Risky ATB
fluoroquinolones and clindamycin

- CZ

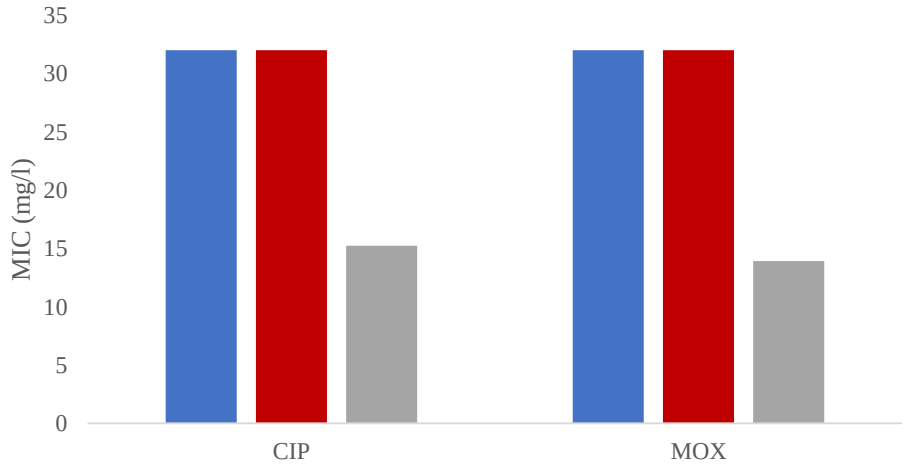
AK substitutions
T82I v GyrA

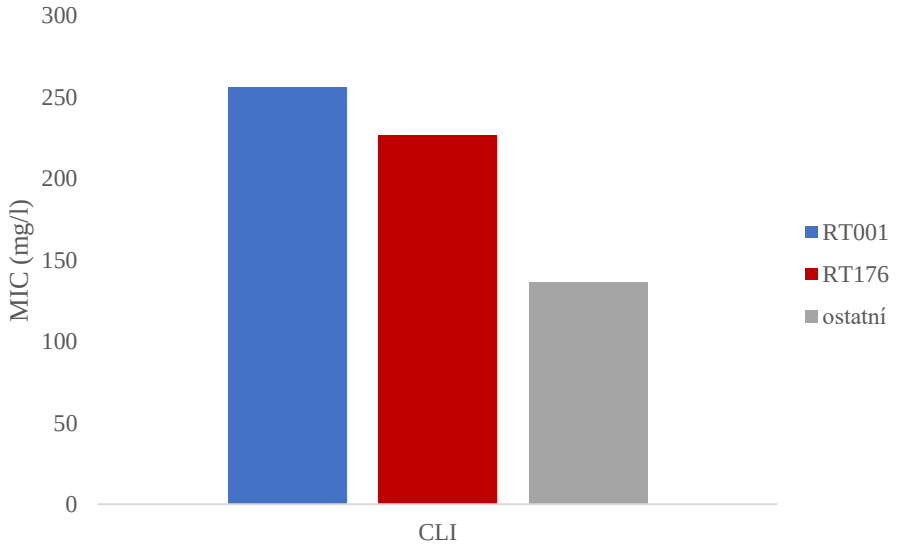




*erm*B, *cfr*B
Transmissibility!

- SR





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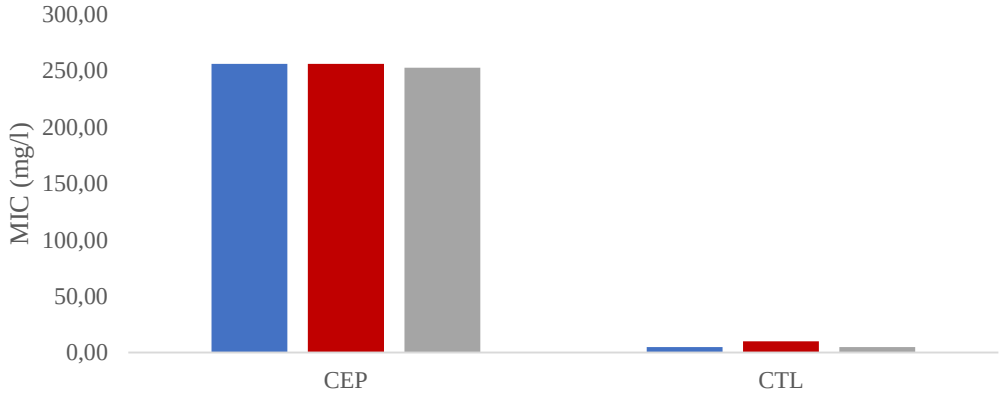
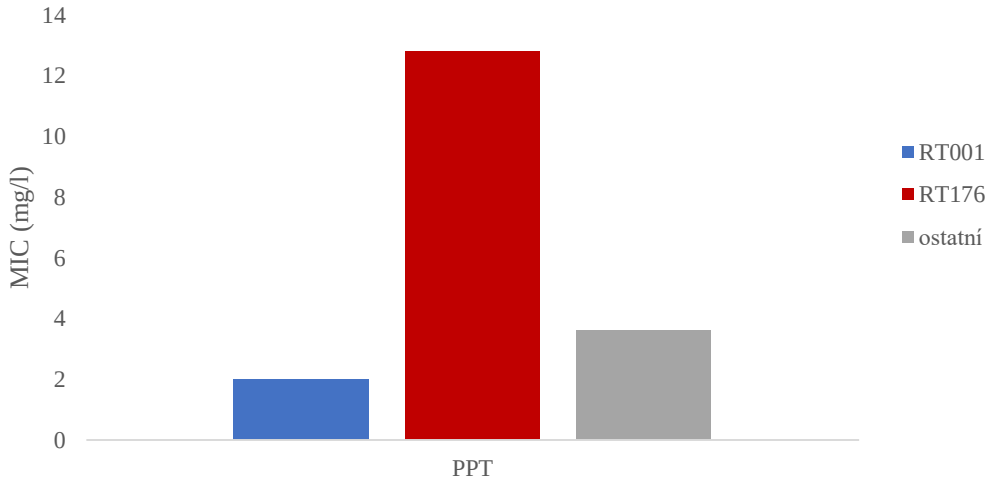
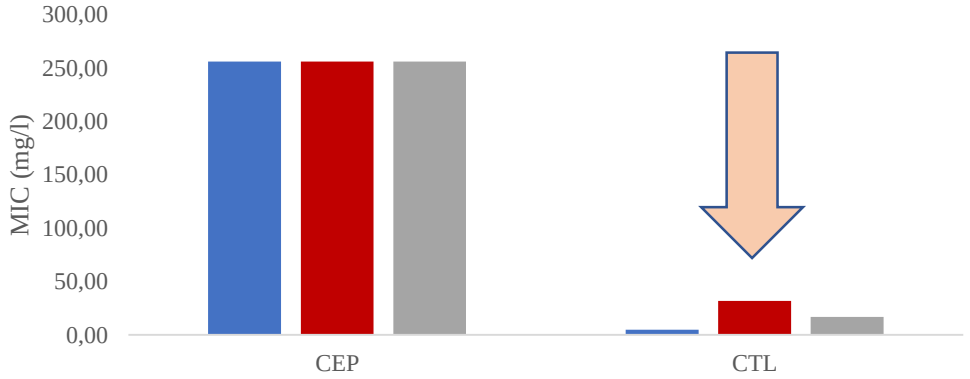
Frequently used ATB
Cephalosporins or piperacillin tazobactam?

- ČR





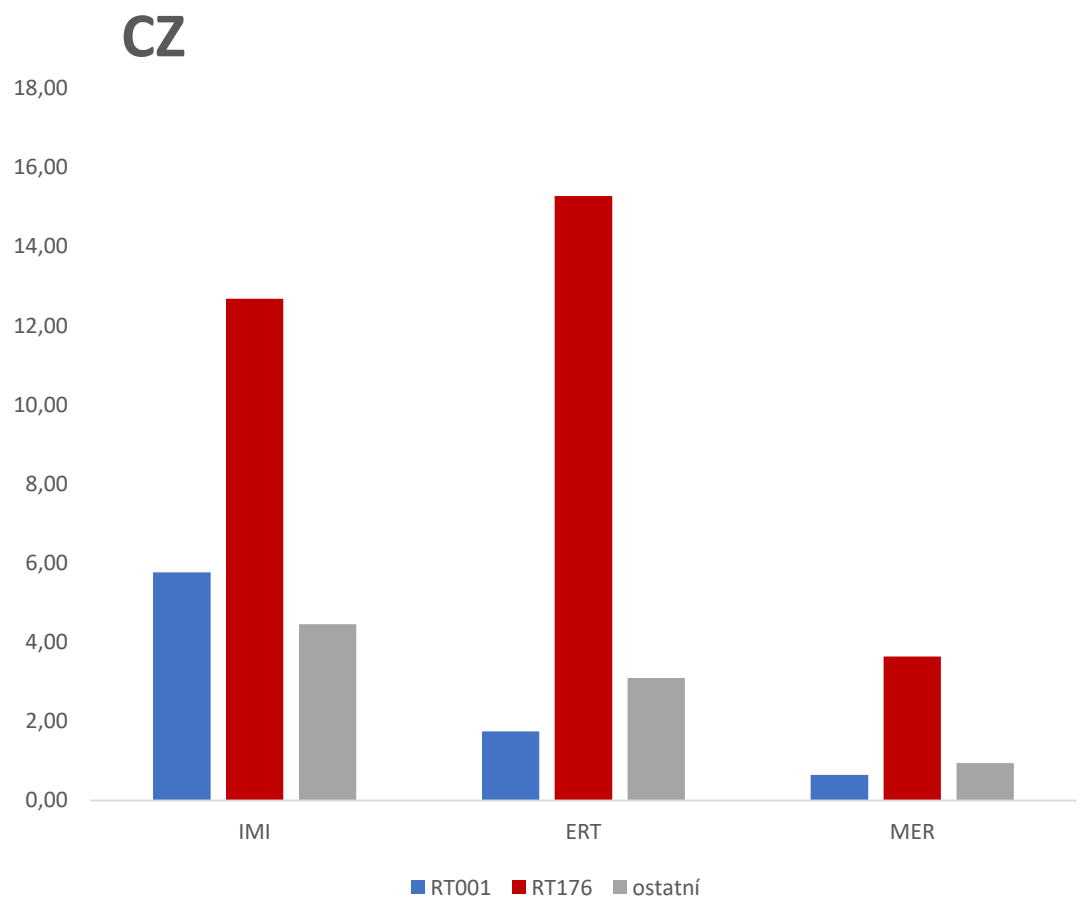
- SR

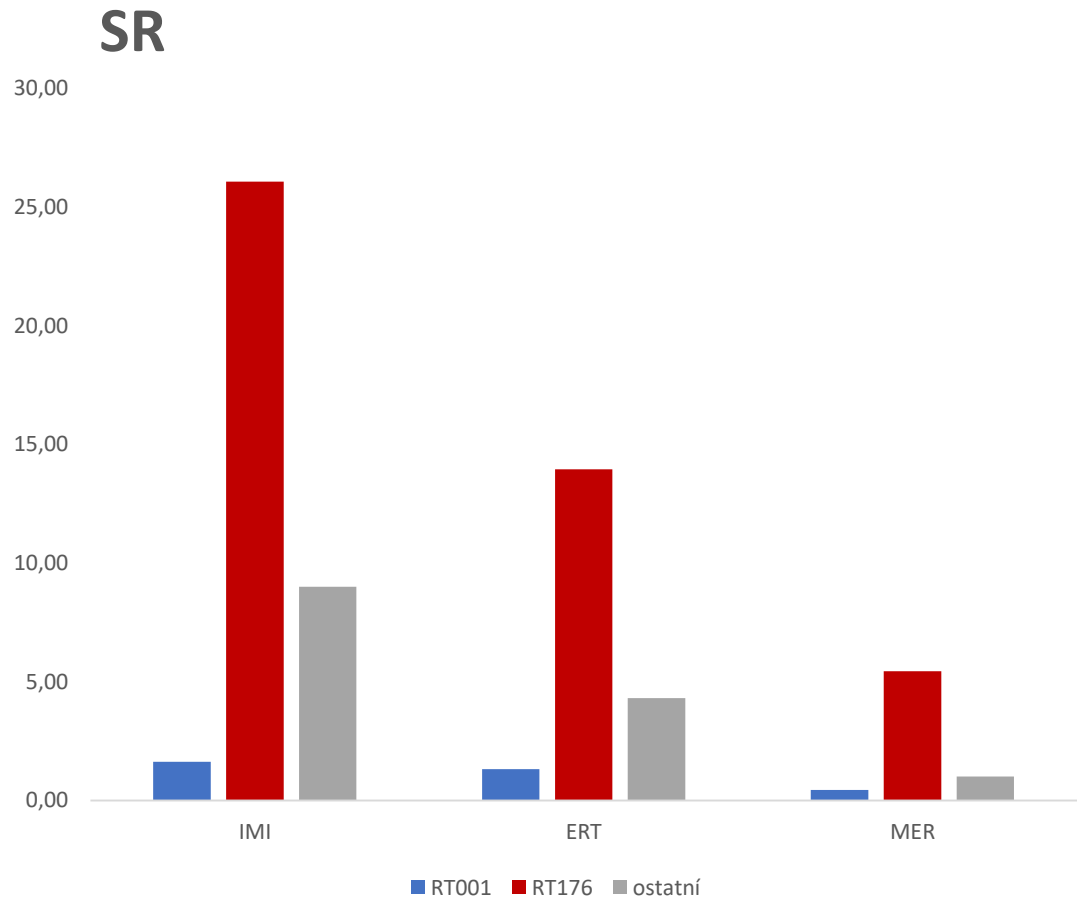


We don't know the mechanisms yet

Zíková J., diploma thesis

Carbapenems





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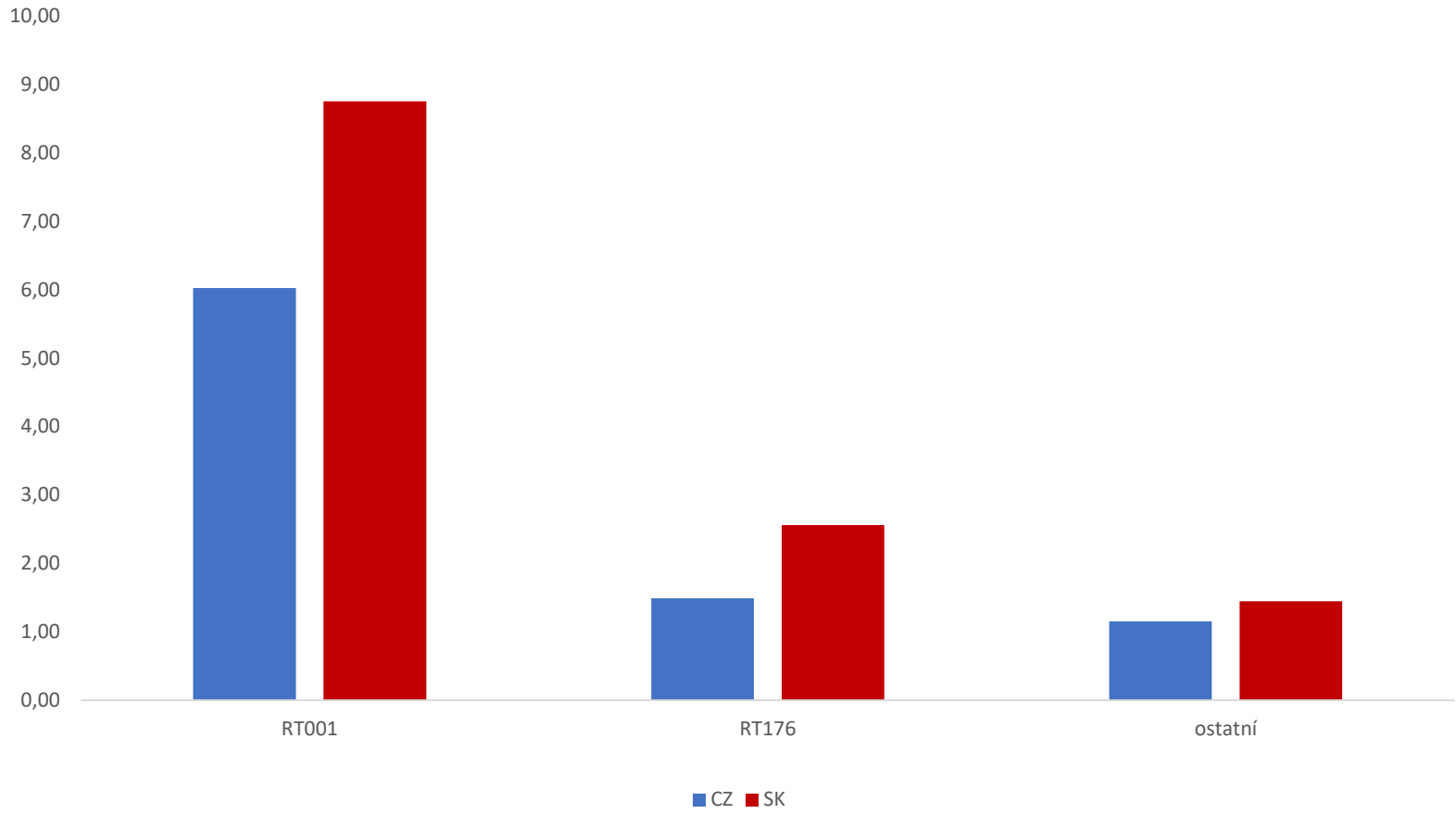
We don't know the mechanism yet.

Linezolid at risk!!



Presence of *cfr*B gene, which also causes resistance to clindamycin and erythromycin!

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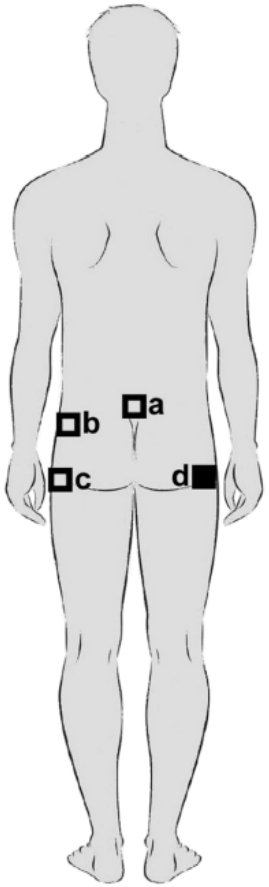
Extraintestinal *C. difficile* infections



MICROBIOLOGICAL FINDINGS AND TREATMENT

2nd day

Decubitus ***a-d***: polymicrobial findings: MRSA, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterococcus faecalis*, and *Alcaligenes faecalis*.

14th day

Decubitus ulcers ***a, b*** – plastic surgery

Antibiotic coverage: vancomycin and piperacillin/tazobactam

26th day

Change to cotrimoxazol

37th day

Decubitus ***d***: *Pseudomonas aeruginosa*, decubitus ***a-c***: normal microflora

Urine: *Klebsiella pneumoniae* (ESBL positive)

Change to piperacillin/tazobactam

41st day

Drain decubitus ***b***: ESBL-positive *E. coli*

Change to imipenem/cilastatin

43th day

Decubitus ulcers ***c, d*** – surgical intervention

Antibiotic coverage: imipenem/cilastatin was supplemented by vancomycin

54th day

Decubitus ***d***: *Pseudomonas aeruginosa* resistant to imipenem/cilastatin

Change to: cefoperazone/sulbactam and amikacin

71st day

Decubitus ***d***: *Clostridium difficile*

Change to: metronidazole (the first six days intravenously and then orally for the next eight days)

81st day

Decubitus ***d:*** surgical revision

Antibiotic coverage: piperacillin/tazobactam (20 days) and vancomycin (16 days)

Fig. 1 Localization of decubitus ulcers (a–d) and timeline of microbiological findings and antibiotic treatment

Nyč et al., 2015

Extraintestinal infections caused by *C. difficile* are rare. Examples:

- Bacteraemia with or without plaque infection
- Intra-abdominal infections, extra-abdominal infections
- abscesses (spleen, brain)
- Reactive arthritis, osteomyelitis
- Infections of prosthetic shoulder and knee joint replacements

- Non-healing wounds
- In a spore-contaminated environment
- *C. difficile* is only pathogen

Think about ANAEROBES

Thank you for your attention!

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