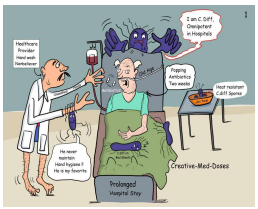
Clostridioides difficile infection



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FN MOTOL

Clostridium difficile ([klos-trid′e-əm di-fi -sil′]

*„**Clostridium**“* comes from Greek klóstēr (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.

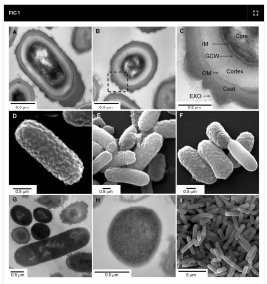
Clostridium difficile* nebo *Clostridioides difficile?

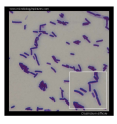
Both names are still valid

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*.

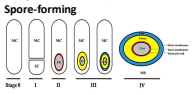
Etymologia: *Clostridium difficile*. Emerg Infect Dis. 2010;16(4):674. doi: 10.3201/eid1604.ET1604; Oren and Rupnik , 2018; Lawson et al., 2016.

Dormant spore vs metabolically active cell





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

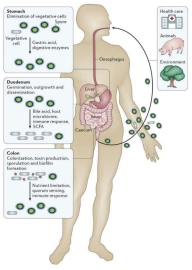


Spore formation by *C. difficile* is crucial for the survival and dissemination of the bacterium in the environment.

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)

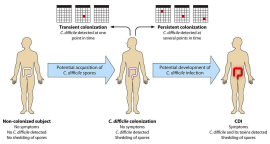


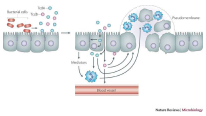
Fecal-oral route of transmission.

Asymptomatic colonization or infection.

Recurrence of CDI (25%, 50%).

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

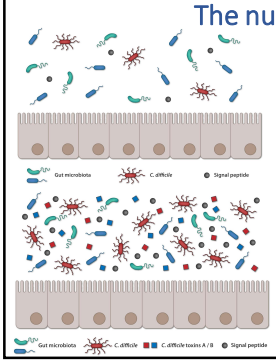




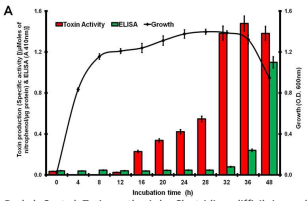
Toxins=disruption of cytoskeletal structure and tight junctions with subsequent cell rounding, detachment and cell death.

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

The number matters!

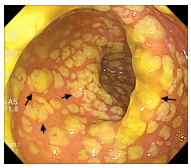


***C. difficile* toxin synthesis is regulated** using "Quorum Signaling", which is mediated by a small (<1,000 Da) thiolactone.



Darkoh C, et al. Toxin synthesis by *Clostridium difficile* is regulated through quorum signalling. mBio. 2015;6(2):e02569. doi: 10.1128/mBio.02569-14.

Severe forms of CDI



Pseudomembranous colitis

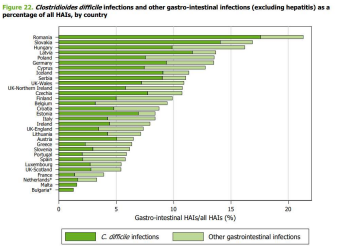
Paralytic ileus = toxic megacolon, surgical intervention,high mortality

How common is CDI?

The CDC lists 4 antibiotic-resistant bacteria as **URGENT THREATS** in the U.S.

Carbapenem-resistant *Acinetobacter*	8,500 EST. CASES	700 EST. DEATHS
Carbapenem-resistant Enterobacteriaceae (CRE)	13,100 EST. CASES	1,100 EST. DEATHS
Drug-resistant Neisseria gonorrhoeae (N. gonorrhoeae)	550,000 EST. CASES	-- EST. DEATHS
***Clostridioides difficile* (*C. difficile*)**	**223,900** EST. CASES	**12,800** EST. DEATHS

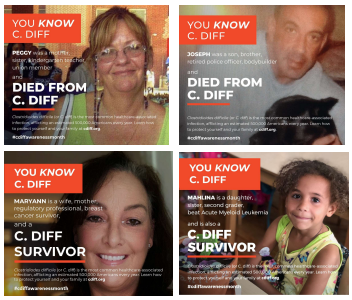
C. diff is currently the *only threat* that is **NOT** nationally notifiable, even though it has the **2ND HIGHEST** number of cases and the **HIGHEST** number of deaths.



124 000 CDI cases a year
Approx. 17% died; 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).

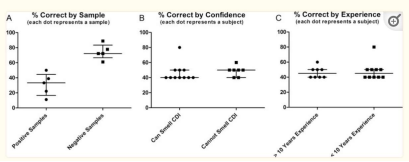
EVERYTHING WHICH AFFECTS MICROBIOTA and IMMUNE SYSTEM.

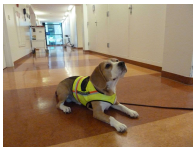
Laboratory diagnostics–odor?

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]

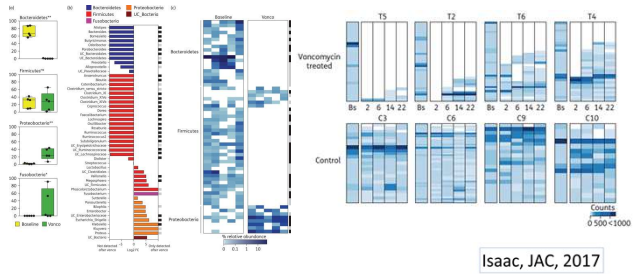




The dog correctly identified 25 of the 30 cases (sensitivity 83%, 65% to 94%) and 265 of the 270 controls (specificity 98%, 95% to 99%).

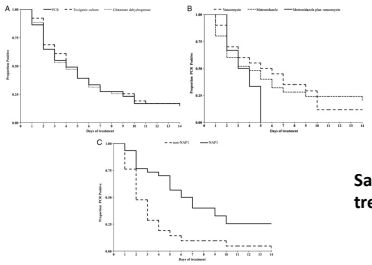
Better to send the sample to the laboratory!!!

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 *et al.*, 2014; Crobach *et al.*, 2016; Krůtová *et al.*, 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.

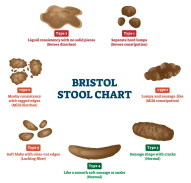
If we test all diarrheal stools delivered to the laboratory.

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

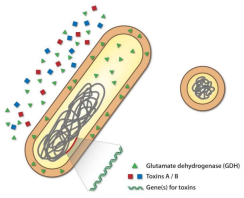


Unformed stool sample
(taking the shape of a container)

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 three-step algorithm is recommended**

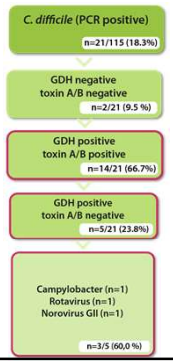
Crobach et al., CMI, 2016

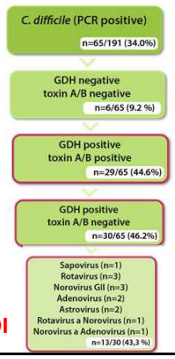
PCR alone is not enough for CDI diagnostics

March-August 2022

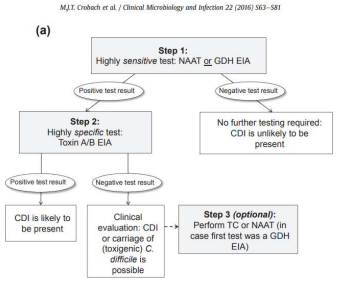
Children = 191
Adults =115

If you use PCR, you can treat patient without CDI





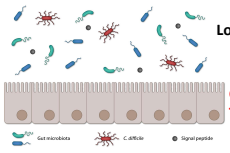
Laboratory diagnostics of CDI



Reasons for toxin negative-test
-insufficient sensitivity
-non-toxigenic strain
-low number of toxigenic cells
-old stool sample/patient already on treatment

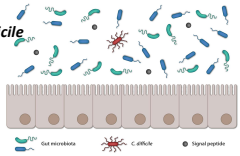
Crobach *et al.*, CMI, 2016

Let's not let *C. difficile* multiply (produce toxins)!



Low density of *C. difficile*
≠infection

GDH: positive
Toxin A/B: negative



Should I start antibiotic therapy?

How do I support the gut microbiota?
-Is de-escalation of antibiotics and antifungals possible?
-Do we need proton pump inhibitors?
-Is the patient moving?
-Solid food and a good mood are important.

Another pathogen testing?
-diarrhoea at the time of admission or at the day 1 of hospitalisation

Stool testing: Dept. Med. Mic. FNM

- **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

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!

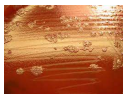
de Graaf H, Pai S, Burns DA, Karas JA, Enoch DA, Faust SN. Co-infection as a confounder for the role of *Clostridium difficile* infection in children with diarrhoea: a summary of the literature. Eur J Clin Microbiol Infect Dis. 2015;34(7):1281-7.

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

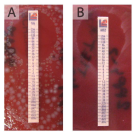
Pathogen	Number of co-infection reports (%)
Viruses	164 (73.9)
Rotavirus	97 (43.7)
Adenovirus	32 (14.4)
Norovirus	17 (7.7)
Astrovirus	9 (4.1)
Sapovirus	5 (2.3)
Others[a]	4 (1.8)
Bacteria	53 (23.9)
E. coli	17 (7.7)
Enteropathogenic	8 (47.1)
Enterotoxigenic	3 (17.6)
Verocytotoxin-producing	4 (23.5)
O18	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)

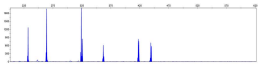
Culture of *C. difficile*-why?



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.



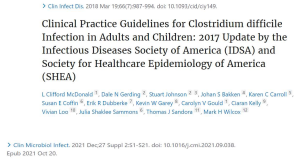
Antimicrobial susceptibility testing and characterisation of strain for epidemiologic purposes.



Not for diagnostics of intestinal forms of CDI

Questions *C. difficile* and diagnostics?

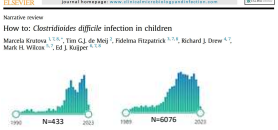
Guidance documents USA/Europe



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)

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

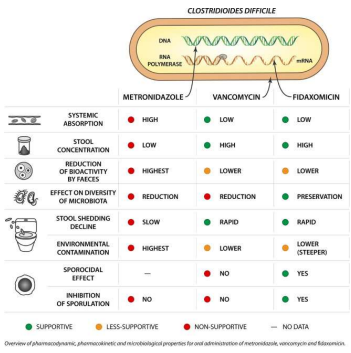
Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults



How to: *Clostridioides difficile* infection in children

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.

Krutova *et al.*, 2022

Passive immunisation

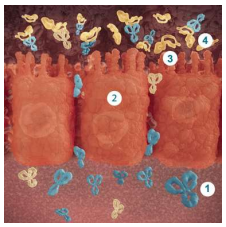
Bezlotoxumab (ZINPLAVA™) is a human monoclonal antibody that binds to *Clostridioides difficile* toxin B indicated to reduce the recurrence of CDI.

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)

NOT ON THE MARKET: discontinued by manufacturer in 2025



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

FMT: Feacal microbiota transplantation

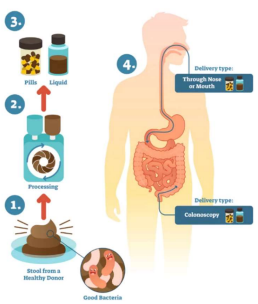


Table 2
Donor screening by laboratory screening of faeces and serum

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) • *Strongyloides* (IgG1/IgG4)[3]	• *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*, *Entomoeba histolytica*, *Cryptosporidium parvum* and *C. hominis*, *Microsporidium* spp, *Strongyloides*[3] • Microscopy for ova, cysts, and larvae (88): e.g. *Blastocystis hominis*

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

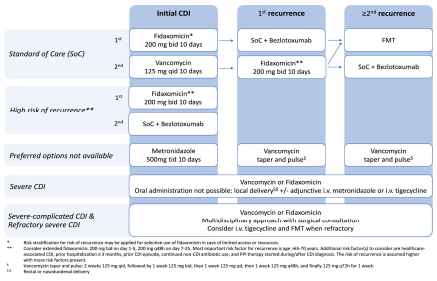
Terveer et al., 2017

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



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

Resistance to the drugs of choice-Europe

Intestinal infections

Isolates	MET	VAN	FDX
Human	0.29	0.52	0.03
Animal	0.18	0.71	0.02
All	0.25	0.58	0.03

RT	MET	VAN	FDX
001	0.29	0.44	0.01
002	0.20	0.79	0.04
003	0.17	0.50	0.04
005	0.30	0.30	0.03
009	0.16	0.63	0.04
010	0.61	0.41	0.04
014	0.18	0.41	0.03
015	0.14	0.50	0.03
018	0.19	0.21	0.01
020	0.19	0.64	0.03
027	1.87	0.79	0.03
039	0.29	0.55	0.04
046	0.19	0.57	0.02
078	0.18	0.69	0.05
106	0.21	0.65	0.05
181	1.03	0.51	0.03

Freeman J, et al. JAC Antimicrob Resist. 2024;6(4):dlae112.

Vancomycin resistance

Houston, we have a problem!

- ✓ 34% [102/300]) of *C. difficile* isolates showed reduced susceptibility to vancomycin (0.5-16 µg/ml; MIC50/90 = 2/4 µg/ml).
- ✓ VANR was associated with more recurrences and prolongation of time to clinical response.
- ✓ The prevalence increased with time (P = 0.0163).
- ✓ Reduced sensitivity was associated with ribotypes 027 and 255.

Eubank TA, et al. Clin Infect Dis. 2024;79(1):15-21. Eubank TA, et al. Open Forum Infect Dis. 2024;11(11):ofae588. Kolte B, Nübel U. J Antimicrob Chemother. 2024;79(6):1320-1328.

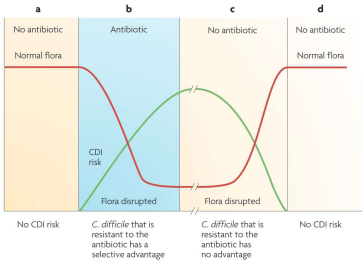
And fidaxomicin?

114/535 (21.3%) isolates showed reduced susceptibility to fidaxomicin (MIC_{50} = 0.5 mg/l, MIC_{90} = 1.0 mg/l).
Reduced sensitivity was more common in RT 027 (49.4%, 41/83) compared to other ribotypes (16%, 68/425; P < 0.001).
New mutations in the *rpo*B gene have been demonstrated, resistance is not associated with time.

	Fidaxomicin				
rpoB-p.V1143D[a]	>64/>64	[10]/this study	8	3×10^{-4}	2 (RT002), 1 (RT078), 4 (RT027)
rpoB-p.V1143G[a]	16	9,10	4	2×10^{-4}	178 (RT018), 209, 3628
rpoB-p.V1143L	8	6	2	8×10^{-5}	17 (RT017), 178 (RT018)
rpoB-p.V1143F	2	10	0	0	—
rpoB-p.Q1074R[e,f]	4	46	0	0	—
rpoB-p.Q1074H	ND	47	0	0	—
rpoB-p.Q1074K	1	11	0	0	—
rpoB-p.Q1149P (suspected)	0.25	8	1	4×10^{-5}	178 (RT018)
rpoC-p.R89G	ND	47	1	4×10^{-5}	178 (RT018)
rpoC-p.D233Y	ND	47	0	0	—
rpoC-p.D781R	2–4	11	0	0	—
rpoC-p.D1127E	2–4	11	0	0	—
marR-g.349delT	1	46	8	3×10^{-4}	178 (RT018)

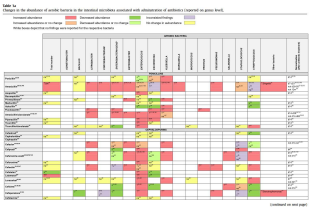
Anne J Gonzales-Luna et al., *Open Forum Infectious Diseases*, Volume 10, Issue Supplement_2, ofad500.744,https://doi.org/10.1093/ofid/ofad500.744. Kolte B, Nübel U. J Antimicrob Chemother. 2024;79(6):1320-1328.
Kolte B, Nübel U. J Antimicrob Chemother. 2024;79(6):1320-1328.

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



Rupnik et al., 2009

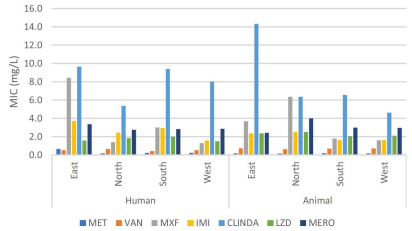
Safe antibiotics for patients at risk of CDI? The effect of antibiotics on the composition of the gut microbiota



- ✓ 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, JID, 2019)

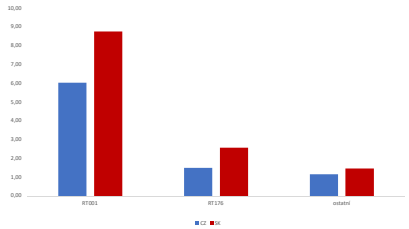
Accumulation of antimicrobial resistance



Geometric mean MICs for all antibiotics tested against human clinical and animal isolates by European regions. MET, metronidazole; VAN, vancomycin; MXF, moxifloxacin; IMI, imipenem; CLINDA, clindamycin; LZD, linezolid; MERO, meropenem; FDX, fidaxomicin; TIGE, tigecycline; RIF, rifampicin.

Freeman *et al.*, 2024

Linezolid at risk!!

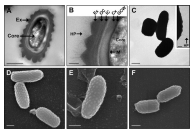


Presence of *cfr*B gene, which also causes resistance to clindamycin and erythromycin!

Zíková J., diploma thesis

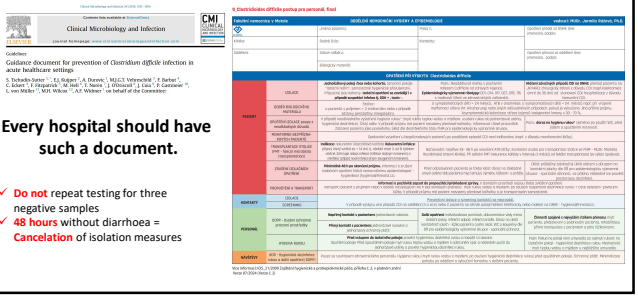
Questions for CDI treatment?

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

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

Every hospital should have such a document.

- ✓ **Do not** repeat testing for three negative samples
- ✓ **48 hours** without diarrhoea = **Cancelation** of isolation measures

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

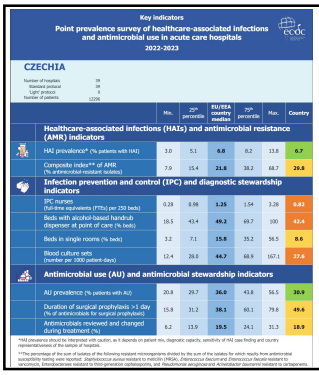
Everyone has to follow them; otherwise, they don't work!

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.



Key indicators
Point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals
2022-2023

CZECHIA

Number of hospitals: 39
Point prevalence: 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	20.8
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	69.2	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.

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

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

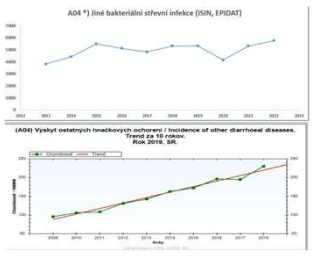
What should I do if I don't have a single room?
-Priority - patient with faecal incontinence
-Patient cohorting
-Fellow patients without ATBs and immunosuppression

Anti-epidemic measures/contact precautions

Frequent cleaning and disinfection of the area (Terminal room cleaning)!
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



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

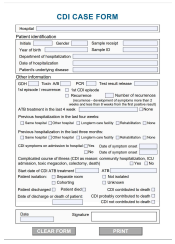
CDI is one of the mandatory notifiable infectious diseases

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

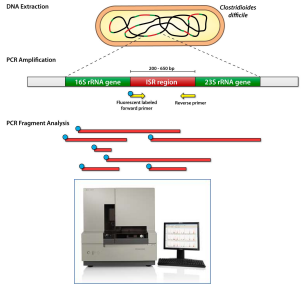


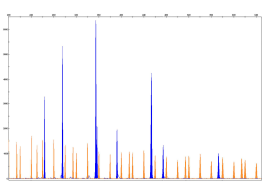
Krutova M. - Faculty Hospital Motol

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

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

C. difficile - antigen
GDH: POZITIVNÍ
Toxiny A/B: POZITIVNÍ

Kultivace cílená na C. difficile
Nález 1: **Clostridium difficile**
ANTIBIOGRAM - MIC = mg/l (stolice)
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

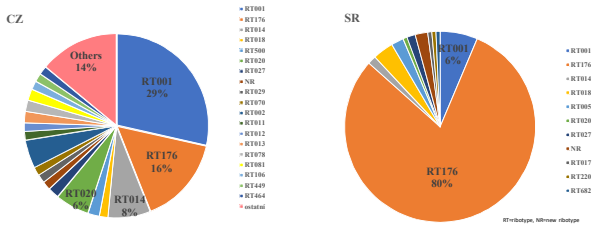
Kódy pro pojišťovnu: 82031(1), 82058(1), 82067(3), 82117(2)

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

Strana 1/1 UNIS-STEINER, © 1991-2024, rev. 01-01-24/MIC 03.11.2024-05:33

FN MOTOL

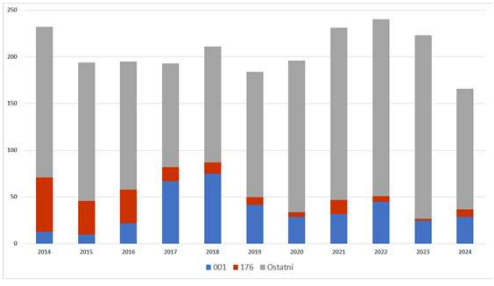
PCR ribotyping national data



Europe, RT 027 instead of 176

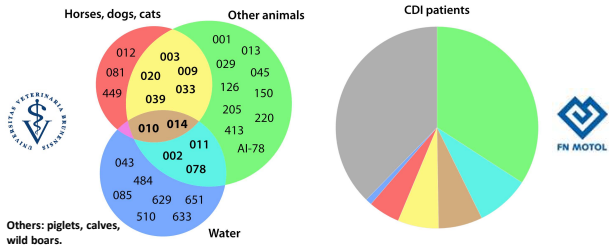
Zíková J., diploma thesis

C. difficile – ribotyping – FN Motol



FN MOTOL

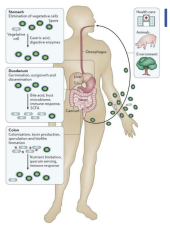
PCR ribotyping – Patients vs. Other sources



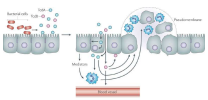
Krutova et al., 2018; Kecerova et al., 2019; Masarikova et al., 2020; Cizek et al., 2022

Question for hospital hygiene and epidemiology?

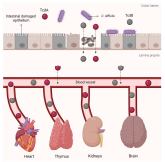
Infections caused by *C. difficile* Intestinal and extraintestinal



Faecal-oral transmission
Contamination of the wound from the environment
Hematogenous spread



Toxins disrupt the structures of the cytoskeleton and tight junctions with subsequent rounding, separation and cell death.
Immune response, cytokine production.



During CDI, *C. difficile* TcdA and TcdB toxins can penetrate the intestinal barrier and enter the bloodstream, leading to systemic **toxemia**.
In vitro studies show that the pro-inflammatory cytokines TNF-alpha and IFN-gamma strongly potentiate the toxic activity of low doses of TcdB.
In addition to toxins, *C. difficile* can also penetrate and spread.

Smits WK, et al. *Clostridium difficile* infection. Nat Rev Dis Primers. 2016;2:16020. doi: 10.1038/nrdp.2016.20; Cheng JKJ, Unnikrishnan M. *Clostridioides difficile* infection: traversing host-pathogen interactions in the gut. Microbiology (Reading). 2023;169(2):001306. doi: 10.1099/mic.0.001306. Pourliotopoulou E, et al. Exploring the Toxin-Mediated Mechanisms in *Clostridioides difficile* Infection. Microorganisms. 2024;12(5):1004. doi: 10.3390/microorganisms12051004. Fettucciari K, et al. Proinflammatory Cytokines: Possible Accomplices for the Systemic Effects of *Clostridioides difficile* Toxin B. J Inflamm Res. 2021;14:57-62. doi: 10.2147/JIR.S287096.

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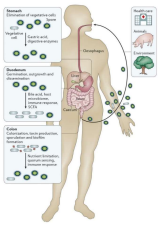

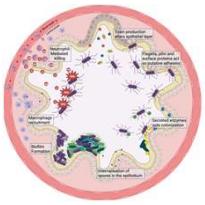

Surface-expressed proteins allow adherence, invasion into tissues and induce an immune inflammatory response of the host.

Sporulation, biofilm formation and internalization of spores into macrophages and epithelial cells

Faecal-oral transmission
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Extraintestinal *C. difficile* infections

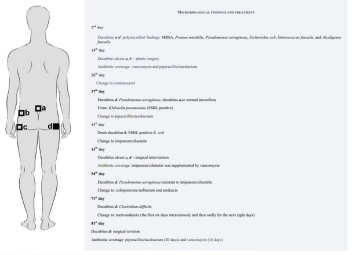

Fig. 1 Localization of decubitus ulcers (a–d) and timeline of microbiological findings and antibiotic treatment

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

Antibiotics of Choice in Extraintestinal *C. difficile* Infections

NO guidance document for extraintestinal infections

Literary research will NOT help. NO clinical trials, only case reports.

Antibiotic therapy should be preceded by surgical removal of pus or necrotic tissue.

Antibiotic	Bloodstream	Tissue	Joint fluid	Abdominal abcess	Brain abcess/CNS
Tigecycline	low serum levels	Excellent	weaker	Excellent	Bad
Linezolid	Decent	Excellent	good	Excellent	Excellent
Metronidazole	Decent	Excellent	good	Excellent	Excellent

*Polymicrobial infections: tigecycline yes; linezolid for G+ only; metronidazole yes for anaerobes.
However, linezolid, clindamycin and metronidazole (ribotypes 027 and 176) should be expected to be at a higher risk of resistance.

Duration of antibiotic therapy individual, according to clinical, laboratory and radiological response.

Štefan M. Antibiotika v klinické praxi. Galén. 2024. Rodvold KA, Gotfried MH, Cwik M, Korth-Bradley JM, Dukart G, Ellis-Grosse EJ. Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. J Antimicrob Chemother. 2006;58(6):1221-9. 5(M). (www.sukl.cz).

Resistance to the drugs of choice- Europe

Extraintestinal infections

Isolates	MET	CLINDA	TIGE	LZD
Human	0.29	7.84	0.04	1.76
Animal	0.18	6.35	0.04	2.15
All	0.25	7.34	0.04	1.87

RT	MET	CLINDA	TIGE	LZD
001	0.29	14.81	0.05	1.41
002	0.20	7.55	0.04	1.59
003	0.17	4.88	0.05	2.00
005	0.30	6.56	0.04	2.00
009	0.16	8.98	0.04	1.41
010	0.61	23.78	0.04	1.90
014	0.18	8.00	0.05	2.00
015	0.14	3.56	0.04	2.00
018	0.19	9.19	0.03	1.52
020	0.19	7.05	0.05	2.00
027	1.87	7.46	0.05	1.54
039	0.29	26.25	0.03	1.81
046	0.19	36.76	0.06	2.00
078	0.18	4.81	0.04	1.72
106	0.21	6.17	0.05	1.83
181	1.03	9.14	0.03	1.70

Freeman J, et al. JAC Antimicrob Resist. 2024;6(4):dlae112.

QUESTIONS FOR EXTRAINTESTINAL INFECTIONS

Thank you for your attention!

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