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Klinik I für Innere Medizin
Klinisches Studienzentrum 2 für Infektiologie
AG Klinische Mikrobiomforschung

Update Leitlinie abdominelle Komplikationen

UNIKLINIK KÖLN

Offenlegung potentieller Interessenkonflikte

1. Anstellungsverhältnis oder Führungsposition

keine

2. Beratungs- bzw. Gutachtertätigkeit

Astellas Pharma, Berlin Chemie, DaVolterra und Merck/MSD

3. Besitz von Geschäftsanteilen, Aktien oder Fonds

keine

4. Patent, Urheberrecht, Verkaufslizenz

keine

5. Honorare

Astellas Pharma, Basilea, Gilead Sciences, Merck/MSD, Organobalance, Pfizer

6. Finanzierung wissenschaftlicher Untersuchungen

3M, Astellas Pharma, DaVolterra, Gilead Sciences, Merck/MSD, Morphochem, Organobalance, Seres Therapeutics

7. Andere finanzielle Beziehungen

keine

8. Immaterielle Interessenkonflikte

keine

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Categories and Grading

Category, Grade	Definition
Strength of recommendation	
A	AGIHO strongly supports a recommendation for use
B	AGIHO moderately supports a recommendation for use
C	AGIHO marginally supports a recommendation for use
D	AGIHO supports a recommendation against use
Quality of Evidence	
I	Evidence from at least one properly designed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-control analytic studies (preferably from more than one centre); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees
Index (for level II quality of evidence, only)	
R	Meta-analysis or systematic review of randomized controlled trials
T	Transferred evidence, i.e. results from different patient cohorts, or similar immune-status situation
H	Comparator group is a historical control
U	Uncontrolled trial
A	Abstract published at an international meeting

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Gliederung

Abdominelle Komplikationen:

- Nicht Infektions-assoziiert
  - ➢ Paraneoplastisch
  - ➢ Therapie-assoziiert

- Infektions-assoziiert
  - ➢ Neutropenische Kolitis
  - ➢ *Clostridium difficile* Infektion
  - ➢ SSYC (Salmonellen, Shigellen, Yersinien, Campylobacter)
  - ➢ Virale Infektionen
  - ➢ Parasitäre Infektionen

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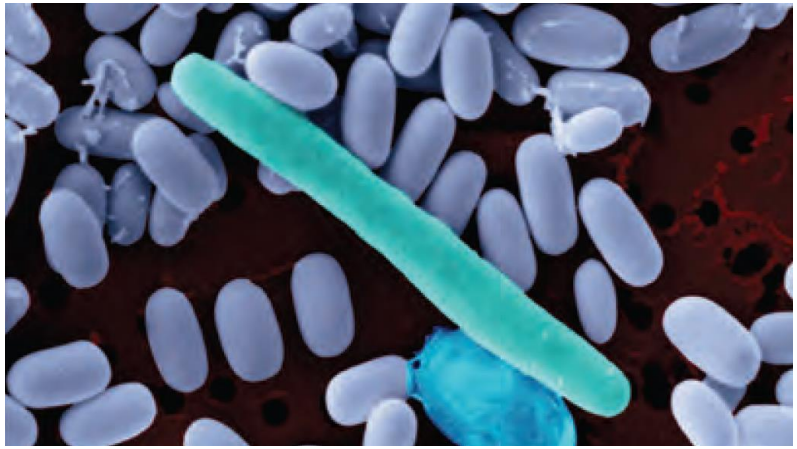
Clostridium difficile Infektion



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Definition *Clostridium difficile* Infektion

Klinisches Bild (≥3 ungeformte Stuhlgänge/24h, Kolitis, Ileus und/oder toxisches Megakolon)

+

Nachweis von *C. difficile*

+

Nachweis von freien Toxinen

+

kein anderer plausibler Grund für die Symptomatik

ODER

Endoskopisch oder histologisch nachgewiesene pseudomembranöse Kolitis

Debast Clin Microbiol Infect. 2014; 20 Suppl 2:1-26.

UNIKLINIK KÖLN

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Debast Clin Microbiol Infect. 2014; 20 Suppl 2:1-26.

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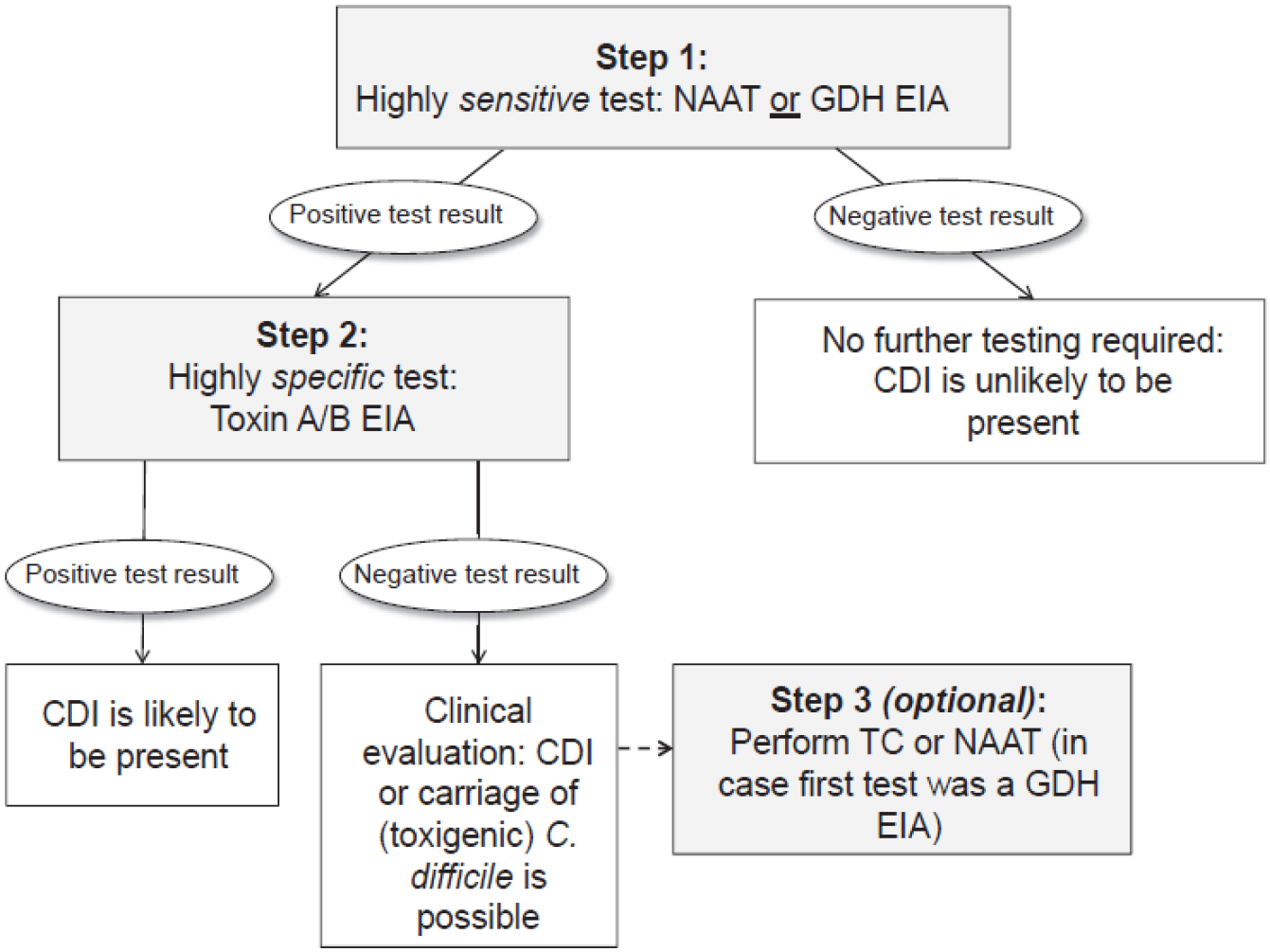
Clostridium difficile – Diagnostik



Crobach et al. Clin Microbiol Infect. 2016 Aug;22 Suppl 4:S63-81.

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Definition severe=schwer

Klinische Zeichen oder Hinweise in der Bildgebung auf einer ausgeprägten Inflammation:

- Darmwandverdickung, Darmüberdehnung über 6 cm transversal
- Fieber, Blut im Stuhl, Ileus, Peritonitis, septischer Schock, Aszites

Laborwerte:

- Leukozytose (Leukozyten>15x10E9/L) und/oder Linksverschiebung (stabförmige Leukozyten >20%)
- Serumkreatininanstieg (>50% über Baseline)
- Laktatanstieg (≥5 mM).
- Abfall des Serumalbumins (<30 g/L)

Nur ein Kriterium notwendig!

Debast Clin Microbiol Infect. 2014; 20 Suppl 2:1-26.

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Definition severe=schwer

Patienten mit einem hohen Risiko für eine schwere *Clostridium difficile* Infektion, auf Basis EINES folgender Kriterien:

- Alter ≥65 Jahre
- Schwere Komorbidität
- Aufnahme Intensivstation
- Immunschwäche

→ Ebenfalls als schwer klassifizierbar

Debast Clin Microbiol Infect. 2014; 20 Suppl 2:1-26.

UNIKLINIK KÖLN

Definition *Clostridium difficile* Infektion

- Die *Clostridium difficile* Infektion wird in non-severe und severe eingeteilt
- Pat. mit hämtologischen oder onkologischen Erkrankungen werden grundsätzlich als severe klassifiziert, außer es besteht keine Immunsuppression und keine relevante andere Komorbidität

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Clostridium difficile Infektion

Prävention

Clinical situation	Intention	Intervention	SoR	QoE	Reference	Comments
Increased risk of CDI during antimicrobial treatment	Primary prevention	Probiotic prophylaxis	C	$II_{r,t}$	Redman Ann Onc 2014	Insufficient data in immunocompromised patients
Increased risk of CDI during antimicrobial treatment	Secondary prevention	Antimicrobial prophylaxis	C	$II_{r,t}$	Splinter Ann Pharmacother 2017 Carignan Am J Gastroenterol 2016	
CDI – first episode or first recurrence	Secondary prevention	Bezlotoxumab 10 mg/kg qd iv	B	II_t	Wilcox NEJM 2017	
CDI – multiple recurrences	Secondary prevention	Bezlotoxumab 10 mg/kg qd iv	A	II_t	Wilcox NEJM 2017	
		Fecal microbiota transfer	A	II_t	Kelly Am J Gastroenterol 2014 Quraishi Aliment Pharmacol Ther 2017	Only in case of recurrence after treatment with vancomycin and fidaxomicin

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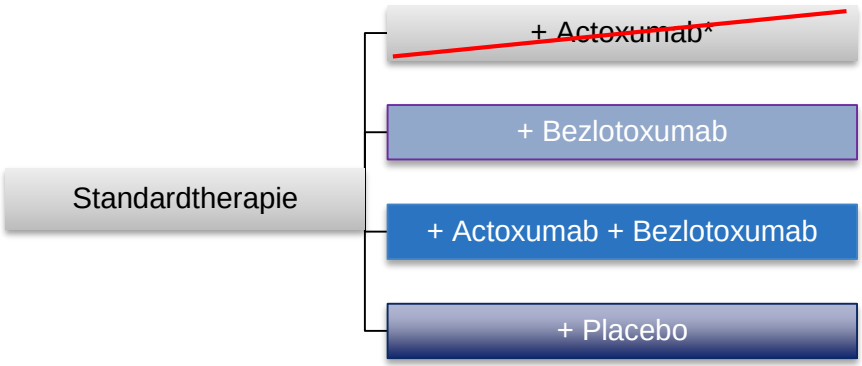
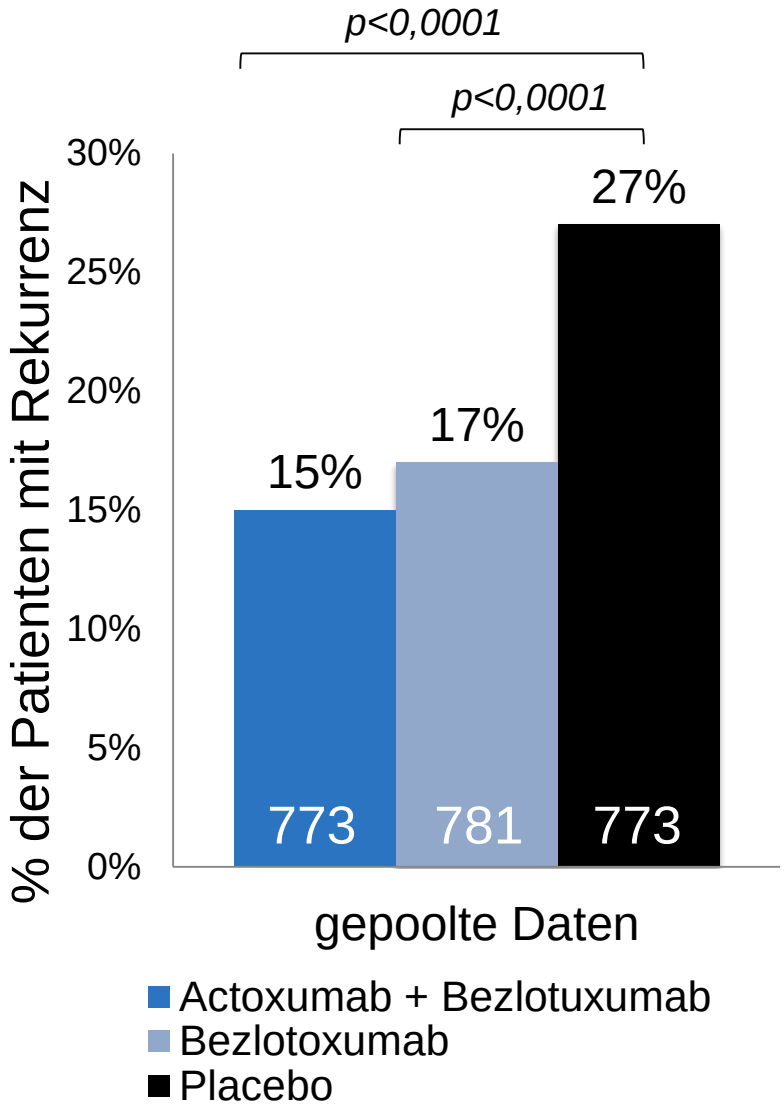
Antitoxin Antikörper

MODIFY I und II:

- zwei, doppelblinde, randomisierte, plazebokontrollierte Phase III Studien bei Patienten mit CDI
- Actoxumab (Anti-Toxin-A) bzw. Bezlotoxumab (Anti-Toxin-B) oder beide **zusätzlich** zur antibiotischen Standardtherapie





* Studienarm nur bei MODIFY I
ClinicalTrials.gov Identifier: NCT01241552 und NCT01513239
Standardtherapie = Metronidazol, Vancomycin, Fidaxomicin

Wilcox et al. N Engl J Med. 2017 Jan 26;376(4):305-317.

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Bezlotoxumab

FDA Approves Merck's ZINPLAVA™ (bezlotoxumab) to Reduce Recurrence of Clostridium difficile Infection (CDI) in Adult Patients Receiving Antibacterial Drug Treatment for CDI Who Are at High Risk of CDI Recurrence

Friday, October 21, 2016 9:57 pm EDT

- Indikation in den USA: In Gabe in Kombination mit einer Standardtherapie bei Patienten ≥18 Jahre und mit einem hohen Risiko für ein CDI Rezidiv
- Deutschland: Zulassung erfolgt, GBA steht aus

Wilcox et al. N Engl J Med. 2017 Jan 26;376(4):305-317.

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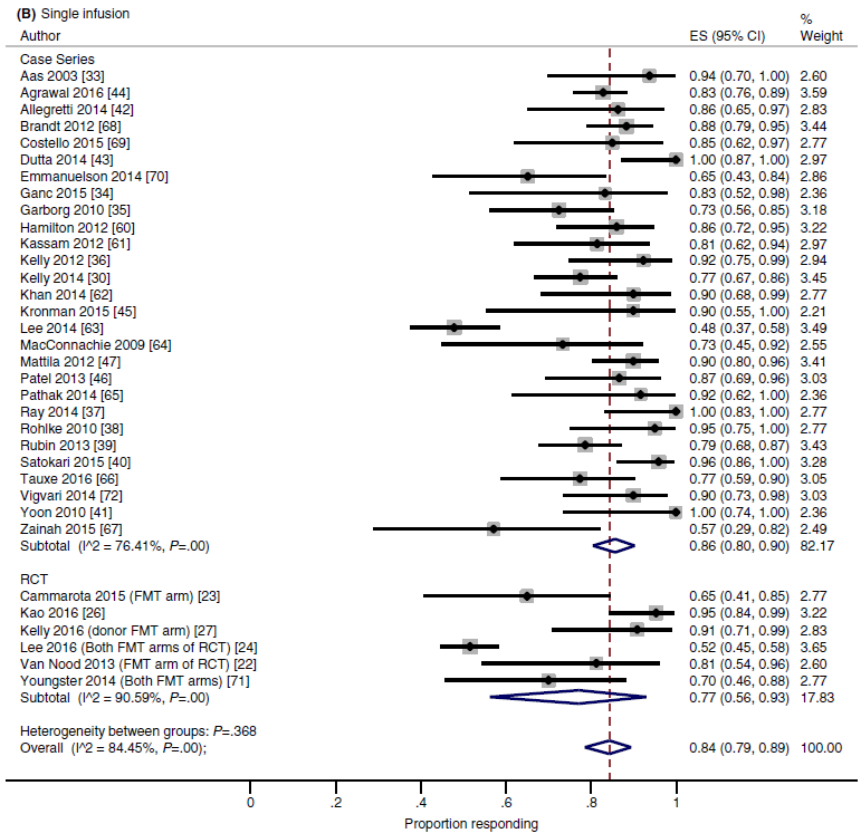
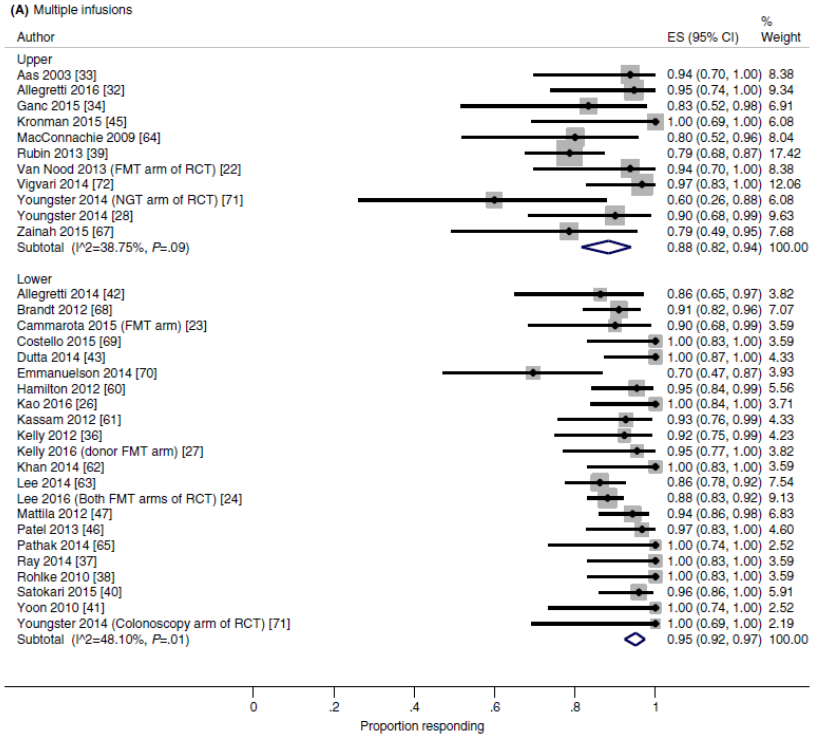
Mikrobiotatransfer





Quraishi et al. Aliment Pharmacol Ther. 2017 Sep;46(5):479-493.

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Mikrobiotatransfer beim immunsupprimierten Patienten

Table 1a. Study patient demographics and pre-FMT data

Total number of study patients	80
Adults	75 (94%)
Women	38 (48%)
Men	42 (52%)
Mean adult age (years)	53 (range 20–88)
Mean pediatric age (years)	10.9 (range 6.5–16)
Mean follow-up (months)	11 (range 3–46)
CDI Classification before FMT	
Recurrent	44 (55%)
Refractory	9 (11%)
Severe/complicated	1 (1%)
Overlap (severe/complicated and recurrent or refractory)	26 (33%)
Reason for immunocompromise	
Immunosuppressive agents for IBD	36
Solid organ transplant recipients	19
HIV/AIDS	3
Cancer and treatment with antineoplastic agents	7
Other chronic medical conditions[a]	15

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease.

[a]Conditions included: rheumatoid arthritis (4), adrenal insufficiency, cirrhosis/end-stage liver disease (6), end-stage renal disease (ESRD) on hemodialysis (HD) and panhypopituitarism, end-stage chronic obstructive pulmonary disease on chronic steroids, ESRD on HD and allograft failure, Sjogren's disease.

Table 2. Adverse events

Adverse event	Number of patients sustaining this AE	Reason for Immuno-compromise	Day post-FMT event occurred
Deaths[a]			
Pneumonia	1	SOT	13
Aspiration	1	SOT and esopha-geal cancer	1
Hospitalizations[a]			
Fever, diarrhea, encephalopathy and pancytopenia	1	Cirrhosis and non-Hodgkin's lymphoma	4
Abdominal pain post FMT colonoscopy	1	SOT	0
IBD flare: Crohn's (2), UC (1)	3	IBD	<84
Cerebrovascular ac-cident; nausea and vomiting	1	ESRD and panhy-popituitarism	21
Colectomy	1	IBD	<28
Fall and sustained hip fracture	1	End-stage COPD	84
Influenza B and diarrhea (non-CDI)	1	SOT	3
Catheter infection	1	Cancer	14

Kelly et al. Am J Gastroenterol. 2014 Jul;109(7):1065-71.

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Clostridium difficile Infektion

Gezielte Therapie – schwere Infektion

Clinical situation	Intention	Intervention	SoR	QoE	Reference
CDI – severe	Cure	Vancomycin 125 mg qid po for 10 days or	A	II_t	Cornely TLID 2012, Louie NEJM 2011, Zar CID 2007
		Fidaxomicin 200 mg bid po for 10 days			
		Metronidazole	D	I	Johnson CID 2014
CDI – sever and oral administration not possible	Cure	Metronidazole 500 mg tid iv for 10 days	A	II_u	Bolton Gut 1986, Friedenberg Dys Colon Rectum 2001
		plus vancomycin 500 mg intracolonic every 4 - 12 h and/or vancomycin 500 mg qid by nasogastric tube	C	III	Apisarnthanarak CID 2002

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Clostridium difficile Infektion

Refraktäre und rekurrente Situation

Clinical situation	Intention	Intervention	SoR	QoE	Reference
CDI – refractory	Cure	Combination treatment with vancomycin po plus metronidazole any route or	C	II_h	Rokas CID 2015, Li PlosOne 2015
		Teicoplanin 100 mg bid po or		II_u	Popovic J Infect Dev Ctries 2015
		Tigecyclin 100 mg loading, followed by 50 mg bid for 3-21d or		II_h	Thomas Int J Infect Dis 2014, Metan J Chemother 2015, Britt Infect Dis Ther 2014
		Fecal microbiota transfer		II_t	Quraishi Aliment Pharmacol Ther 2017
CDI - 1st recurrence	Cure	Repeat strategy from 1st episode or	C	III	Fischer Am J Gastroenterol 2016, Waye J Clin Gastroenterol 2016
		Vancomycin 125 mg qid po for 10 days or	A	II_t	Cornely TLID 2012, Louie NEJM 2011
		Fidaxomicin 200 mg bid po for 10 days or			
		Vancomycin pulsed/taper strategy†			Hota CID 2016
CDI - multiple recurrences	Cure	Fidaxomicin 200 mg bid po for 10 days or	A	II_t	Cornely TLID 2012, Louie NEJM 2011
		Vancomycin pulsed/taper strategy†			Hota CID 2016

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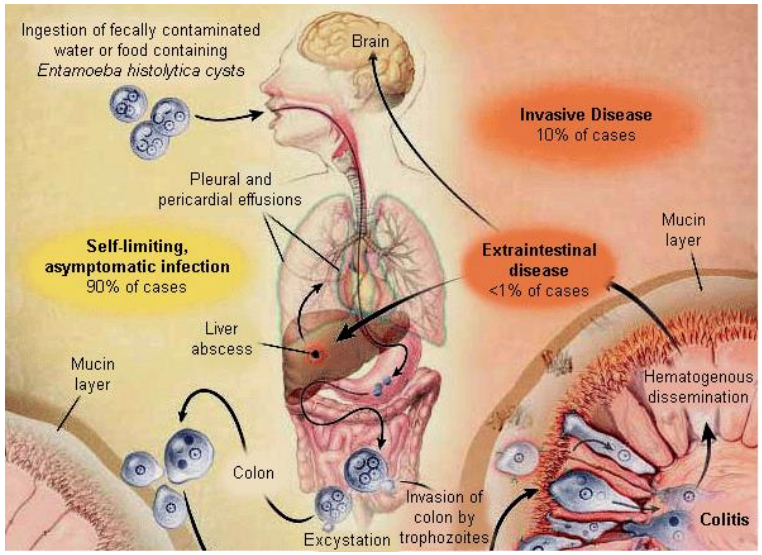
Infektionen mit Parasiten



Box 1: Diagnostic workup of diarrhea (≥3 unformed bowel movements/24h)	
Hospital-acquired diarrhea (≥72h of hospitalization)	**Initial workup:** - *Clostridium difficile* - Norovirus **Extended workup:** - SSYC - Adenovirus, astrovirus, CMV, rotavirus - Parasites - Lactose breath test - Consider alternative causes (treatment-associated, paraneoplastic)
Community-acquired diarrhea (<72h of hospitalization)	**Initial workup:** - SSYC - Norovirus - If recent chemotherapy or antibiotic treatment: *Clostridium difficile* - Obtain travel history **Extended workup:** - *Clostridium difficile* (if not yet analyzed) - Adenovirus, astrovirus, CMV, rotavirus - Parasites - Lactose breath test - Consider alternative causes (treatment-associated, paraneoplastic)
All cases	Consider local infectious diarrhea outbreaks

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Infektionen mit Parasiten

- *Blastocystis* spp.
- Cryptosporidium
- *Cyclospora cayetanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*
- *Isospora belli*
- *Sarcocystis hominis, S. suihominis*
- *Strongyloides stercoralis*

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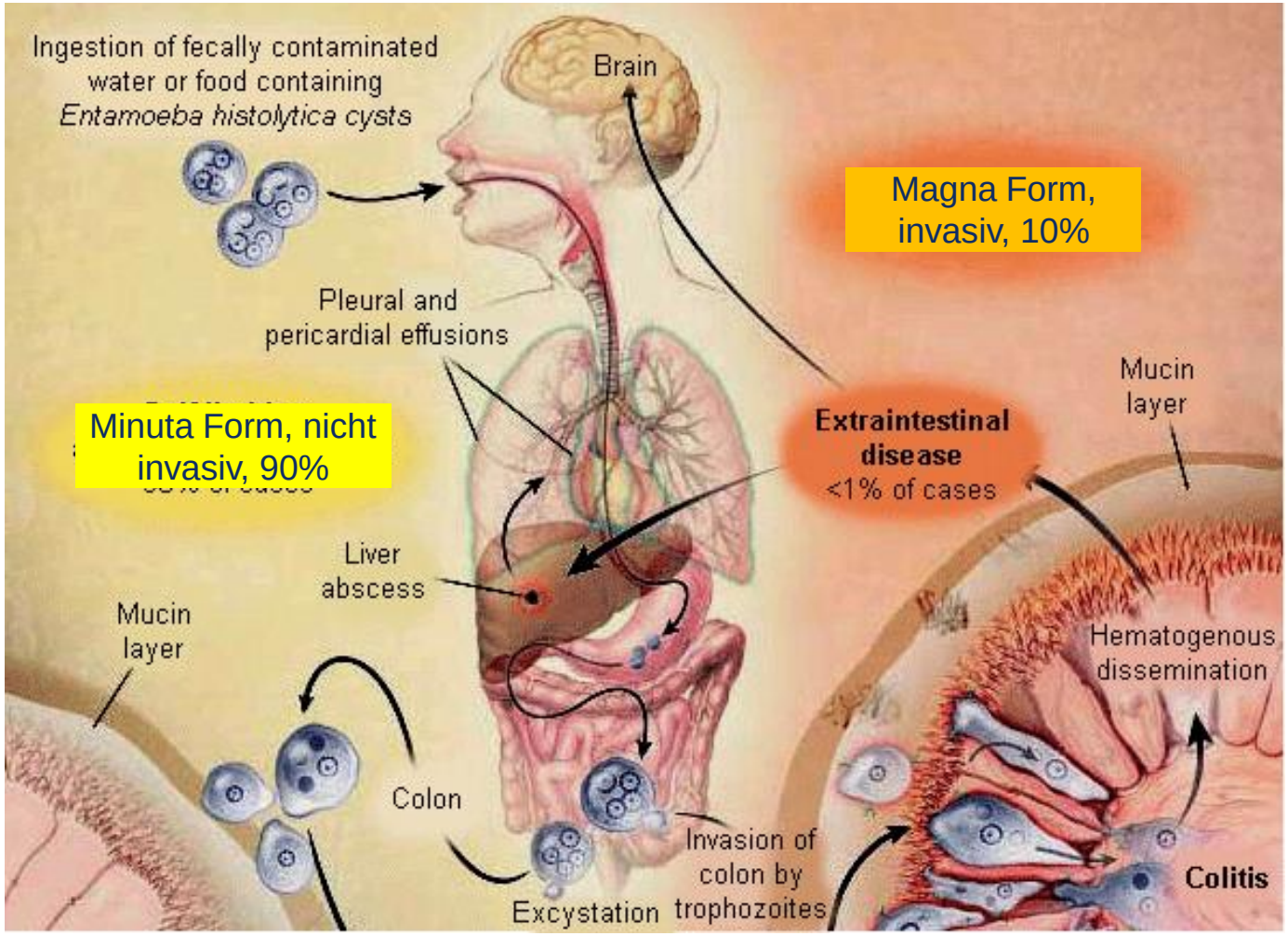
Entamoeba histolytica



www.bmj.com

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Entamoeba histolytica

Clinical situation	Intention	Intervention	SoR	QoE	References
Entamoeba histolytica infection, non-invasive	Cure	Paromomycin 30 mg/kg qd po in three divided doses for 7 days	B	IIt	Kikuchi Parasitol Int 2013
Entamoeba histolytica, invasive colitis	Cure	Tinidazole 2 g qd po for 3 days or	A	IIr,t	Gonzales Cochrane 2009
		Metronidazole 500 mg tid po for 10 days followed by:	B	IIr,t	
		Paromomycin 30 mg/kg qd po in three divided doses for 7 days or	B	III	
		Diiodohydroxyquin 650 mg tid po for 20 days or			
		Diloxanide furoate 500 mg tid po for 10 days			

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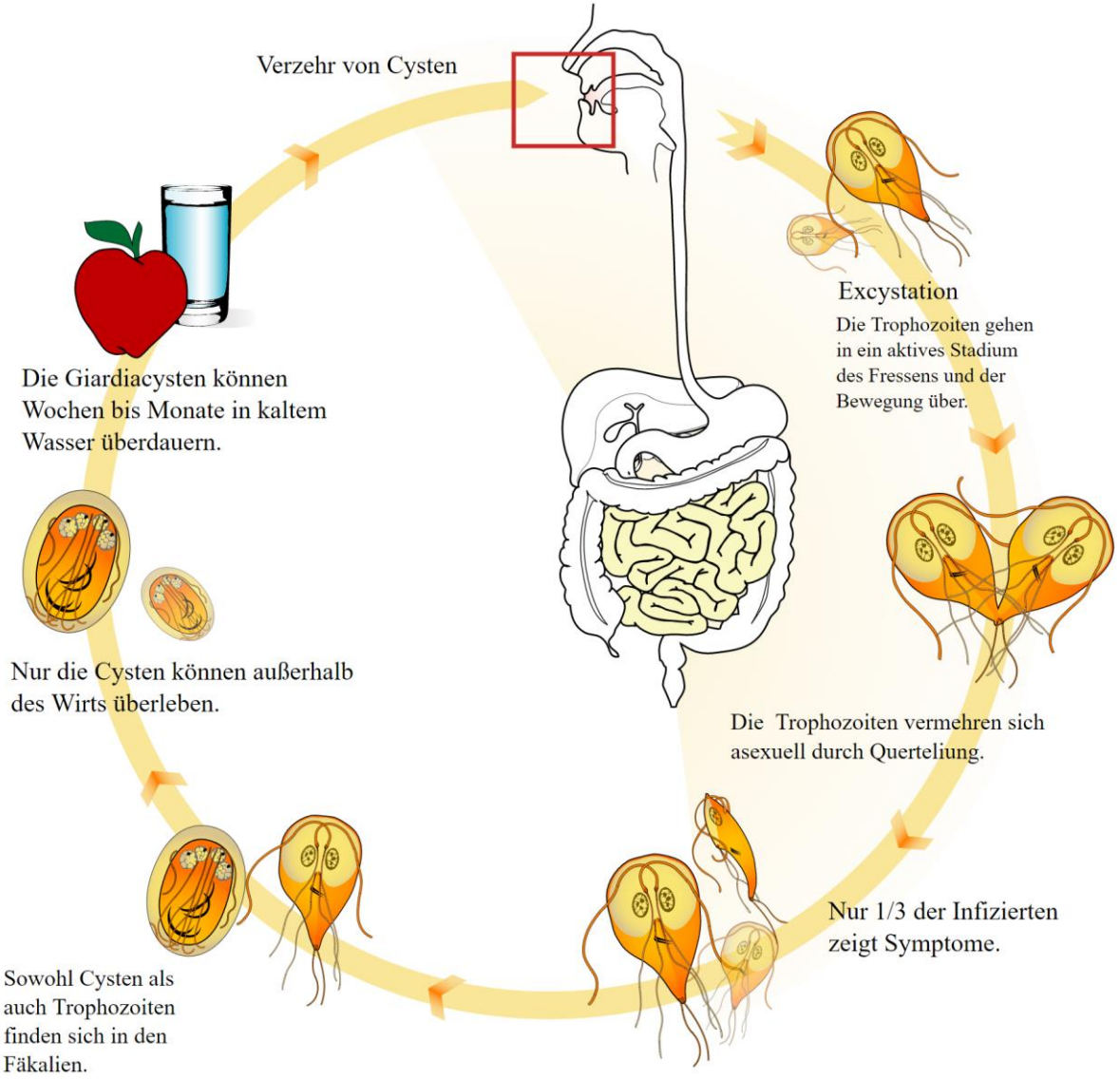
Giardia lamblia



Wikimedia Commons, the free media repository

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Giardia lamblia

Clinical situation	Intention	Intervention	SoR	QoE	References	Comment
Giardia spp. Infection	Cure	Metronidazole 250 mg tid po for 5-10 days or Tinidazole 2 g po as a single dose or	A	$II_{r,t}$	Canete Curr Med Res Opin 2006, Granados Cochrane 2012	
		Albendazole 400 mg qd po for 5-10 days or Mebendazole 200 mg tid po for 3-7 days or	A	$II_{r,t}$	Granados Cochrane 2012	
		Nitazoxanide 500 mg bid for 3 days	B	II_{t}	Escobedo Ann Trop Med Parasitol 2008	Higher dosages (e.g. 1000 mg bid for up to 14 days) might be required in severely immunocompromised patients

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Zusammenfassung I

Update *Clostridium difficile* Infektion:

- Zweischrittiges diagnostisches Verfahren empfohlen (hohe Sensitivität → hohe Spezifität)
- Klassifikation von Patienten mit hämatologischen/onkologischen Erkrankungen in der Regel als “severe disease”
- Vancomycin und Fidaxomicin in der Situation der initialen schweren Infektion gleichwertig (**AII$_t$**)
- Bezlotoxumab in der Sekundärprophylaxe **(1. Episode AII$_t$, Rezidiv BII$_t$)** aktuell noch ohne Refinanzierung
- Fäkaler Mikrobiotatransfer in der Sekundärprophylaxe nach multiplen Rezidiven (**AII$_t$**) oder in der refraktären Situation (**CII$_{t,u}$**)
- Vancomycin+Metronidazol, Teicoplanin und Tigecyclin als Alternativen mit begrenzter Evidenz in der refraktären Situation (**CII$_{t,u,h}$**)

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Zusammenfassung II

Update parasitäre Infektionen

- Diagnostik erst in der 2. Linie bei persistierender Diarrhoe
- 3 sehr frische Stuhlproben
- Therapeutische Empfehlungen zu *Blastocystis* spp., Cryptosporidium, *Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia, Isospora belli, Sarcocystis hominis, S. suihominis, Strongyloides stercoralis*

AGIHO INFEKTIONEN IN DER HÄMATOLOGIE UND ONKOLOGIE
FACHGRUPPE DER DGHO

UNIKLINIK KÖLN SSYC

Clinical situation	Intention	Intervention	SoR	QoE	Reference	Comments
Neutropenia or immunosuppression	Prevention	Antimicrobial prophylaxis against Salmonella, Shigella, Yersinia or Campylobacter spp.	D	$II_{t,u}$	[4, 136, 138]	
Diarrhea caused by nontyphoidal Salmonella spp.	Cure	Ciprofloxacin 500 mg bid po or 400 mg bid iv or Ceftriaxon 2g qd iv	B	III		-Treat only if patient currently immunocompromised or severly ill -Consider local resistance patterns -Treatment duration recommended for immunocompetent patients is 5-7 days and should be extended to 14 days in immunocompromised individuals
Bacteremia caused by nontyphoidal Salmonella spp.	Cure	Ceftriaxone 2 g qd iv plus ciprofloxacin 400 mg bid iv	B	III		Start with combination therapy and de-escalate once resistance data becomes available
Diarrhea caused by Shigella spp.	Cure	Fluoroquinolone, e.g. ciprofloxacin 400 mg bid iv or 500 mg bid po or Azithromycin 500 mg qd iv/po	B	II_t	[142, 143]	Treatment duration recommended for immunocompetent patients is 3-5 days and may be extended to 5-7 days in immunocompromised individuals

Clinical situation	Intention	Intervention	SoR	QoE	Reference	Comments
Diarrhea caused by Campylobacter spp.	Cure	Azithromycin 500 mg qd iv/po or Ciprofloxacin 400 mg bid iv or 500 mg bid po	A B	II_t	[143]	-Treat only if patient currently immunocompromised or severely ill -Treatment duration recommended for immunocompetent patients is 3 days and may be extended in immunocompromised individuals -High fluorquinolone resistance
Bacteremia caused by Yersinia spp.	Cure	Ceftriaxone 2 g qd iv plus gentamicin 5 mg/kg qd iv	B	III	[146]	-Treat only if patient currently immunocompromised or severely ill -Treatment duration recommended for immunocompetent patients is 7-14 days and may be extended in immunocompromised individuals
Diarrhea caused by Shigatoxin producing Escherichia coli	Cure	Carbapenem iv or Azithromycin po	C	III	[147, 148]	-Limited data in immunocompromised patients -If possible, restrict to supportive treatment, as antibiotics may be deleterious

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Virale Infektionen

Clinical situation	Intention	Intervention	SoR	QoE	Reference	Comments
Rotavirus enteritis	Cure	Nitazoxanide 7.5 mg/kg bid po	C	II_t	[159, 160]	Mainly assessed in immunocompetent pediatric patients.
		Oral immunoglobulin	C	III	[162]	No sufficient evidence to recommend dosage
Adenovirus enteritis	Cure	Cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every other week	B	II_u	[163, 165]	To reduce cidofovir toxicity, add at least 2L of iv prehydration and probenecid 2 g po 3h prior and 1 g 2 and 8 h following cidofovir

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Virale Infektionen

Clinical situation	Intention	Intervention	SoR	QoE	Reference	Comments
CMV enteritis	Cure	Ganciclovir 5 mg/kg bid iv for 2-3 weeks followed by several weeks of 5 mg/kg qd iv on 5 days per week	A	I	[170]	
		Foscarnet 90 mg/kg bid iv over 2h or 60 mg/kg tid iv over 1h or	B	II_t	[181]	Used in a pre-emptive setting
		Cidofovir 5 mg/kg iv once weekly for 2 weeks, then once every other week or	B	II_u	[182-184]	To reduce cidofovir toxicity, add at least 2L of iv prehydration and probenecid 2 g po 3h prior and 1 g 2 and 8 h following cidofovir
		Foscarnet 90 mg/kg bid iv over 2h or 60 mg/kg tid iv over 1h plus ganciclovir 5 mg/kg bid iv for 2-3 weeks followed by several weeks of 5 mg/kg qd iv on 5 days per week	B	II_t	[185-187]	Alternatively, the dosage of both combination partners may be reduced by 50%

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

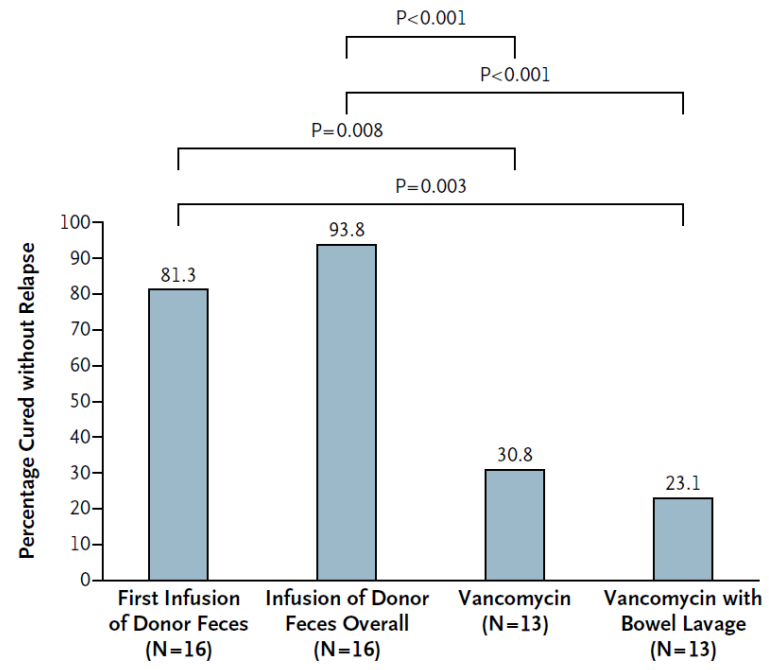

Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

Van Nood et al. NEJM 2013; 368(5):407-15.

UNIKLINIK KÖLN

Clostridium difficile Infektion

Empirische Therapie

Clinical situation	Intention	Intervention	SoR	QoE	Reference	Comments
Diarrhea with CDI suspected – non-severe disease	Cure	Empirical therapy	D	II_u	Vasa Am J Gastroenterol 2003	
Diarrhea with CDI suspected -Severe or complicated clinical disease	Cure	Empirical therapy	B	III		Only if patient instable and high suspicion of CDI

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Testmethoden

Test	Sens	Spec	Time to Result	Comments
ELISA for GDH Ag	High	Low	Rapid	Does not distinguish toxigenic and non-toxigenic strains
ELISA for toxin A/B	Low	High	Rapid	Only 70-85% sensitive
PCR for toxin genes	High	High	Rapid	Expensive; Cannot distinguish active infection from carriage
Toxigenic culture	High	High	Very slow	Gold std but slow and labor intense
Cytotoxin assay	High	High	Slow	Similar limitations to Cx

Current preferred testing strategies include either 1) PCR or 2) two-step testing with ELISA for GDH Ag and Toxin

Solomon D, et al. Open Forum ID (Spring 2014); E-pub 4/2/2014.