Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-B-113 Bezlotoxumab

Stand: August 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Bezlotoxumab
[Prävention der *Clostridium-difficile*-Infektion]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Arzneimittel zur Prävention: keine Arzneimittel zur Behandlung einer *Clostridium-difficile*-Infektion: siehe unter *II. Zugelassene Arzneimittel im Anwendungsgebiet*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Stuhltransplantation („Applikation einer Spenderstuhlsuspension“)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) Anlage XII: Fidaxomicin vom 04.07.2013
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Bezlotoxumab J06BB21 Zinplava®	Zinplava ist indiziert zur Prävention der Rekurrenz einer *Clostridium-difficile*-Infektion (CDI) bei Erwachsenen mit einem hohen Rekurrenzrisiko einer CDI (siehe Abschnitte 4.2, 4.4, und 5.1 der Fachinformation).
Fidaxomicin A07AA12 Dificlir®	DIFICLIR ist indiziert bei Erwachsenen zur Behandlung von *Clostridium-difficile*-Infektionen (CDI), auch bekannt unter der Bezeichnung *Clostridium-difficile*-assoziierte Diarrhö (CDAD) (siehe Abschnitt 5.1). Offizielle Leitlinien zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden.
Metronidazol P01AB01 Arilin®	Arilin 500 mg wird angewendet bei Erwachsenen und Kindern über 6 Jahren. Arilin 500 mg ist angezeigt zur Behandlung von: […] - Infektionen mit Beteiligung von Anaerobiern, besonders Infektionen, die vom weiblichen Genitale, Magen-Darm-Trakt, Hals-Nasen-Ohren- und Zahn-Mund-Kiefer-Bereich ausgehen […] Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Metronidazol zu berücksichtigen. 5.1 Pharmakodynamische Eigenschaften (Ausschnitt):

Üblicherweise empfindliche Spezies
Anaerobe Mikroorganismen
Bacteroides fragilis
Clostridium difficile
Clostridium perfringens°Δ
Fusobacterium spp.°
Peptoniphilus spp.°
Peptostreptococcus spp.°
Porphyromonas spp.°
Prevotella spp.°
Veillonella spp.°

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Teicoplanin J01XA02 Targocid®	[…] Targocid ist auch angezeigt zur oralen Anwendung als Alternativbehandlung von durch Infektion mit *Clostridium difficile* verursachter Diarrhö und Kolitis. Targocid sollte falls erforderlich in Kombination mit anderen antibakteriellen Arzneimitteln eingesetzt werden. Offizielle Empfehlungen zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden.
Vancomycin A07AA09 Vanco-saar®	Bei oraler Anwendung: Vancomycin-Pulver kann nach Auflösen eingenommen werden zur Behandlung bestimmter Darmentzündungen: - antibiotikabedingter pseudomembranöser Enterokolitis (z. B. durch *Clostridium difficile*) […] Parenteral angewandt ist Vancomycin bei diesen Erkrankungen nicht wirksam. […]

Quellen: AMIS-Datenbank, Fachinformationen. Stand Juni 2017.

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Clostridium-difficile* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 22.06.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 344 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 8 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

ZINPLAVA ist indiziert zur Prävention der Rekurrenz einer *Clostridium-difficile*-Infektion (CDI) bei Erwachsenen mit einem hohen Rekurrenzrisiko einer CDI.

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDI	Clostridium difficile infection
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
ESMO	European Society for Medical Oncology
FMT	Fecal microbiota transplantation
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PMC	pseudomembranous colitis
RCDI	Recurrent or relapsing CDI
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2013 [4]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Fidaxomicin vom 4. Juli 2013 **IQWiG, 2013 [6] und IQWiG, 2013 [5].**	**Zugelassenes Anwendungsgebiet[1] (Stand Januar 2013):** DIFICLIR® ist indiziert bei Erwachsenen zur Behandlung von Clostridium-difficile-Infektionen (CDI), auch bekannt unter der Bezeichnung Clostridium-difficile-assoziierte Diarrhö (CDAD). Offizielle Leitlinien zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden. b) Patienten mit schweren und/ oder rekurrenten Krankheitsverläufen von Clostridium-difficile-assoziierten Diarrhöen **Zweckmäßige Vergleichstherapie:** Vancomycin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Vancomycin:** Beleg für einen beträchtlichen Zusatznutzen

Cochrane Reviews

Es konnten keine Quellen identifiziert warden.

Systematische Reviews

<table>
<tr><td rowspan="2">Butler M et al., 2016 [1].
Agency for Healthcare Research and Quality (AHRQ)

Early diagnosis, prevention, and treatment of Clostridium difficile: update</td><td>1. Fragestellung:
KQ3: What are the comparative effectiveness and harms of different antibiotic treatments?

a. Does effectiveness vary by disease severity?

KQ4: What are the effectiveness and harms of other interventions?

a. How do they differ overall?

b. In patients with relapse/recurrent CDI?</td></tr>
<tr><td>2. Methodik

Population:
• Adults with clinical signs consistent with CDI
• Adjunctive to prevent CDI: Adults at risk for CDI
• Adjunctive to prevent recurrence: Adults with clinical signs consistent with CDI
Intervention:
• Standard antibiotic treatments:
o Metronidazole
o Rifaxamin
o Vancomycin
o Fidaxomicin
• Nonantibiotic adjunctive treatments:
o Fecal transplant
o Immunoglobulin
o Pre/probiotics
o Toxin binding agents
o Rifampicin
• Other new treatments available in the U.S.
Komparator:
• Standard antibiotic treatments: active treatments such as metronidazole or vancomycin
• Nonantibiotic adjunctive treatments: placebo, active controls, usual care.
Endpunkte:
• Mortality
• Recurrence (study author defined)
• Clearance (study author defined)</td></tr>
</table>

	• Complications • CDI-related colectomy rate • Symptom resolution (study author defined) • Harms, such as delayed treatment response Suchzeitraum (Aktualität der Recherche): Ovid MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) from 2011 to April 2015 to update CER No. 3. We conducted additional grey literature searching Anzahl eingeschlossene Studien/Patienten (Gesamt): KQ3 = 3 original research, KQ4: 38 original research Qualitätsbewertung der Studien: modified AMSTAR criteria für SR, Cochrane Risk of Bias tool für RCTs, development of an instrument for assessing risk of bias for observational studies based on the RTI Observational Studies Risk of Bias and Precision Item Bank Qualitätsbewertung erfolgte durch zwei unabhängige Personen und bei Dissens wurde eine dritte Person herangezogen. Einschätzung Aussagesicherheit: overall strength of evidence for select outcomes within each comparison were evaluated based on four required domains: (1) study limitations (internal validity); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate).[32] A fifth domain, reporting bias,was assessed when strength of evidence based upon the first four domains was moderate or high
	3. Ergebnisdarstellung Qualitätsbewertung: siehe Anhang 1 **KQ3: What are the comparative effectiveness and harms of different antibiotic treatments?**

Table 6. Summary of standard treatment findings using pooled RCT data from original report and update

Intervention	Study Information	Findings	Strength of Evidence
Vancomycin vs. metronidazole	4 RCTs N=872	Initial Cure: favors vancomycin 83.9% vs. 75.7%; RR 1.08, 95% CI 1.02 – 1.15	High (moderate study limitation, consistent, precise)
	N=705	Recurrent CDI: not significantly different 16.5% vs. 18.7%; RR 0.89, 95% CI 0.65 – 1.23	Moderate (moderate study limitation, imprecise, consistent)
Fidaxomicin vs. vancomycin	2 RCTs N=1,111	Initial Cure: not significantly different 87.6% vs. 85.6%; RR 1.02, 95% CI 0.98-1.07	Moderate (low study limitation, consistent, imprecise)
	N=962	Recurrent CDI: favors fidaxomicin 14.1% vs. 26.1% RR 0.55, 95% CI 0.42-0.71	High (low study limitation, consistent, precise)
Any intervention: Treatment effect by disease severity	3 RCTs	Treatment results did not differ by disease severity	Low (moderate to high study limitation, inconsistent, imprecise)

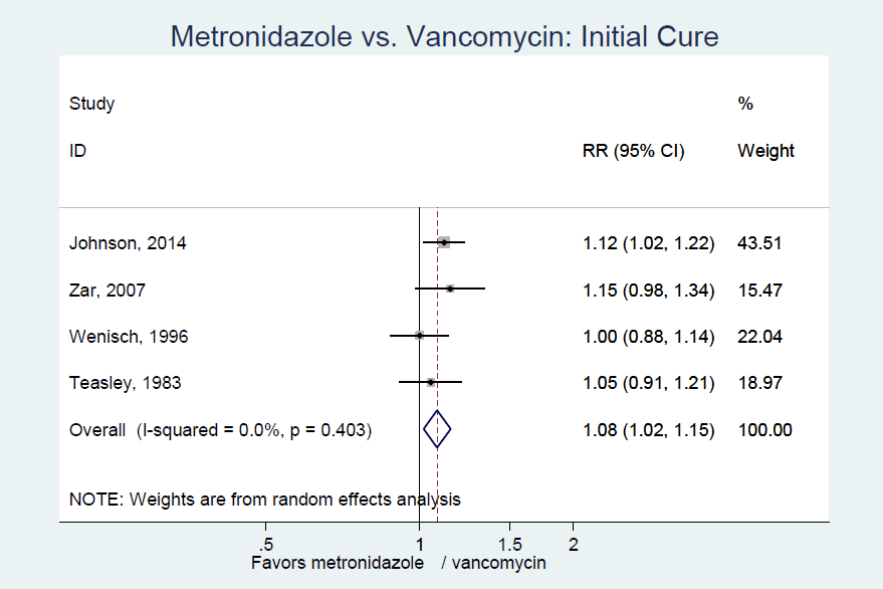
CDI = *Clostridium difficile* infection; CI = confidence interval; RCT = randomized controlled trial; RR = relative risk

Benefits:

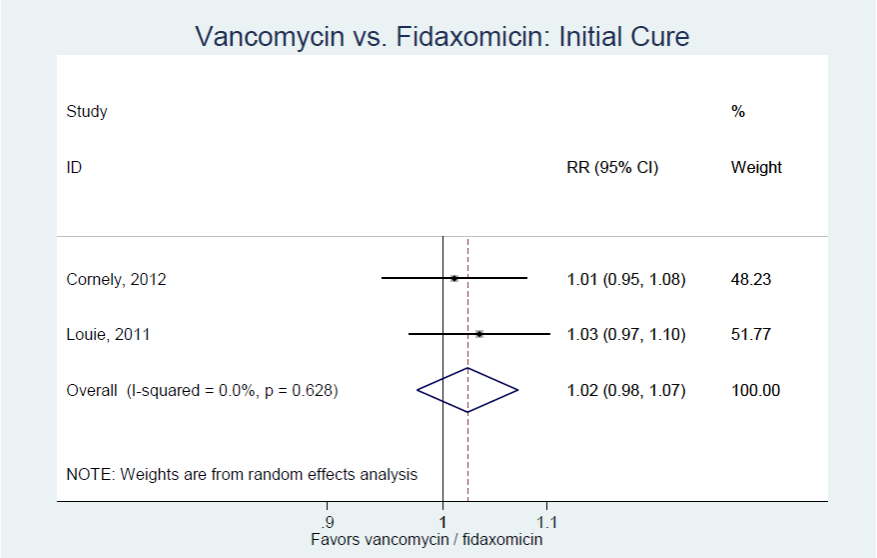
The findings that vancomycin is more effective for initial cure of CDI in adults is new to this update because of improved precision. While the results for fidaxomicin versus vancomycin are consistent with the original review, the strength of the evidence improved. […] Initial cure was comparable for oral vancomycin (81 percent) and oral metronidazole (82.6 percent), but was significantly lower for intravenous metronidazole (52.4 percent; P <.001). Intravenous metronidazole performed significantly worse than either oral drug.

Endpunkt: Initial Cure:

Appendix Figure G16. Initial clinical cure: vancomycin versus metronidazole

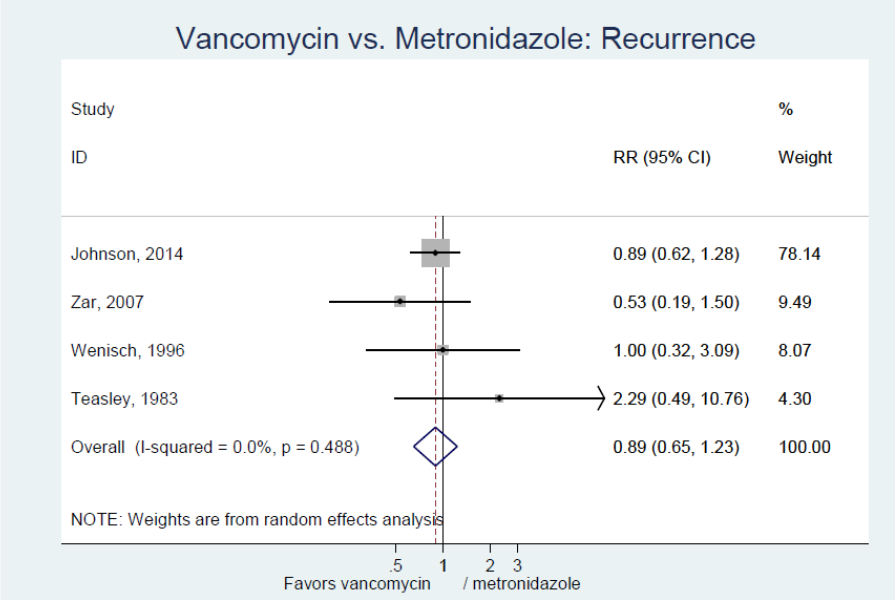


Appendix Figure G17. Initial clinical cure: vancomycin versus fidaxomicin

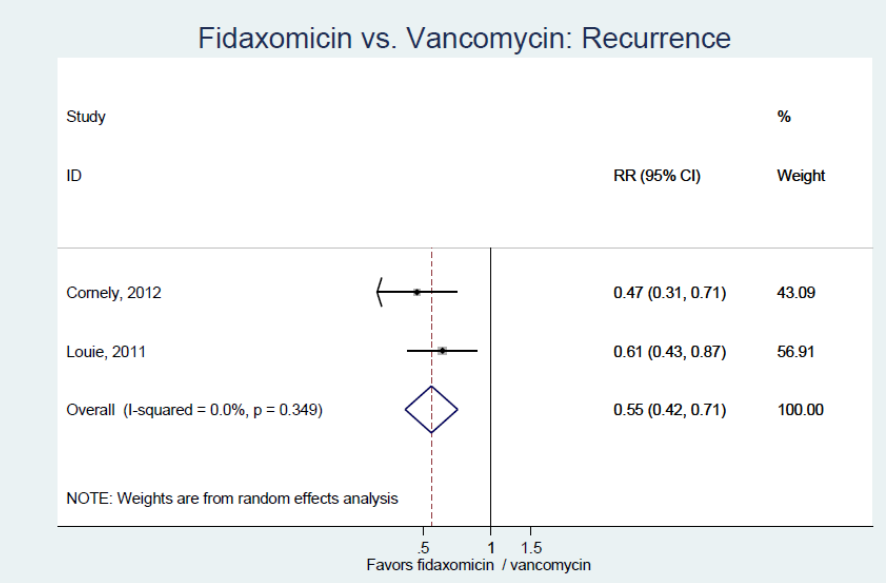


Endpunkt: Recurrence:

Appendix Figure G18. Recurrence of CDI: metronidazole versus vancomycin



Appendix Figure G19. Recurrence of CDI: vancomycin versus fidaxomicin



Harms:

Only a slight change was observed based on the newly included studies. Similar to the original report, in the trial of metronidazole versus vancomycin, a similar percentage of subjects in each treatment arm experienced one or more serious adverse events. However, more subjects in the metronidazole group discontinued study medication because of an adverse event (11.2 percent versus. 6.5 percent; P = .06), whereas more subjects in the vancomycin group had evidence of nephrotoxicity (4.6 percent versus 1.0 percent, P = .02). Other harms, such as antimicrobial resistance, were not reported.

KQ4: What are the effectiveness and harms of other interventions?

(Hinweis: Dies ist eine ergänzende Darstellung, da Verfahren/Wirkstoffe nicht als zVT qualifizieren)

Table 7. Summary of nonstandard treatment findings using data from original report and update

Intervention	Study Information	Findings	Strength of Evidence
FMT	3 RCTs, 23 case series N=751	Resolves diarrhea and prevents relapse in patients with recurrent CDI FMT given both for prevention of recurrence and for symptom resolution; often not clearly stated in studies.	Low (high study limitation, consistent, precise)
	3 contributing case series on refractory CDI N=19	Mixed findings on small number of patients	Insufficient (high study limitation, imprecise, unknown)
Lactobacillus vs. placebo	6 RCTs N=1251	Prevent CDI: favors lactobacillus RR 0.27, 95% CI 0.15-0.49	Low (moderate to high study limitation, consistent, imprecise)
S. boulardii vs. placebo	6 RCTs N=1244	Prevent CDI: not significant RR 0.77, 95% CI 0.38-1.54	Low (high study limitation, consistent, imprecise)
Multiorganism probiotics vs. placebo	5 RCT N=3960	Prevent CDI: favors multiorganism RR 0.50, 95%, CI 0.28-0.88	Low (high study limitation, consistent, imprecise)

CDI = *Clostridium difficile* infection; CI = confidence interval; FMT = fecal microbiota transplantation; RCTs = randomized controlled trials; RR = relative risk

	Zusammenfassung der Ergebnisse: siehe Anhang 2
	4. Anmerkungen/Fazit der Autoren A second important finding is continuing moderate-strength evidence that fidaxomicin is similar to vancomycin for the initial cure of CDI, and increased strength of evidence for **fidaxomicin is superior for the prevention of recurrent CDI**. Since the desired outcome with CDI treatment is cure of the initial illness without subsequent recurrence, this finding ought to prompt consideration of fidaxomicin for the initial treatment of CDI. This is especially relevant to the treatment of CDI since each episode of recurrence increases the likelihood of further episodes. Low-strength evidence supports FMT as a promising therapy for recurrent CDI. Our findings are consistent with another recent systematic review which provided greater detail regarding method and route of FMT, as well as donor characteristics. […]The data from the RCTs comparing FMT to vancomycin are encouraging, demonstrating a significant benefit for FMT, although the study risk of bias is high. […] Additionally, followup was limited in most studies; thus, the long-term consequences of FMT treatment are unknown.
Di X et al., 2015 [3]. **A meta-analysis of metronidazole and vancomycin for the treatment of Clostridium difficile infection, stratified by disease severity**	1. Fragestellung investigate the efficacy of metronidazole compared to vancomycin, and to investigate which agent was superior for treating either mild or severe disease
	2. Methodik Population: adult patients withCDI including mild and/or severe disease Intervention/Komparator: metronidazole and vancomycin Endpunkt: safety or efficacy (clinical and microbiological cure, mortality) Suchzeitraum (Aktualität der Recherche): MEDLINE via Pubmed(1978 to Oct 31, 2014), Embase (1978 to Oct 31, 2014) and the Cochrane Central Register of Controlled Trials (Cochrane library) Anzahl eingeschlossene Studien/Patienten (Gesamt): RCT oder prospketive Kohortenstudien: 6 Studien Qualitätsbewertung der Studien: checklist developed by Downs and Black.(This tool assessed both randomized and nonrandomized studies providing for both an overall score of study quality and a profile of scores for assessing the quality of reporting, external validity,internal validity (bias, confounding), and power. High-quality studies scored 15 or more points, whereas low-quality studiesscored 14 or fewer points.)
	3. Ergebnisdarstellung

Studienübersicht, Risk of Bias:

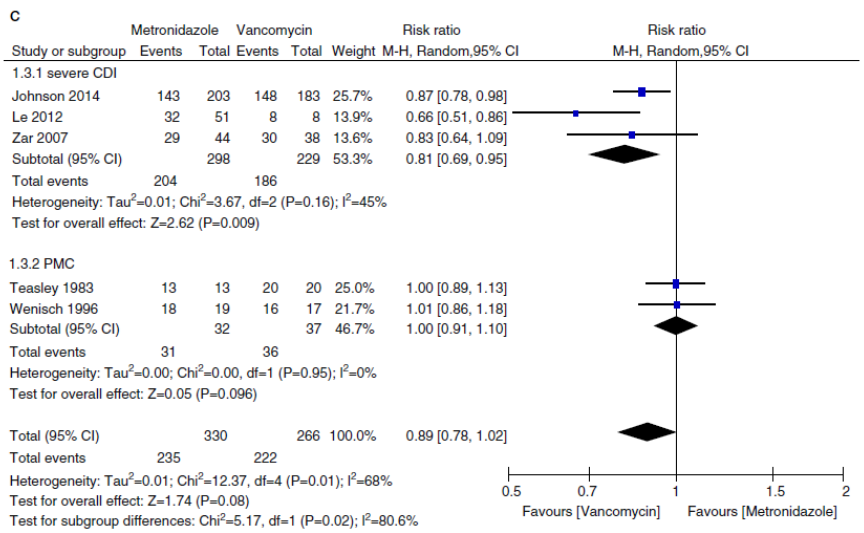
Table 1 – characteristics of 6 identified prospective studies.

Study	Design of study	Country	Duration of study	Drug regimen		Duration of treatment	Duration of follow up	Intention to treat	Study quality score
				Metronidazole	Vancomycin				
Teasley et al. (1983)[4]	RCT	United State	1982.1–1983.1	250 mg, q.i.d, p.o	500 mg, q.i.d, p.o	10 days	21 days	43 vs. 56	20
Wenisch et al. (1996)[5]	RCT	Austria/Europe	1993.1–1995.4	500 mg, t.i.d, p.o	500 mg, t.i.d, p.o	10 days	30 days	31 vs. 31	20
Zar et al. (2007)[9]	RCT	United State	1994.10–2002.6	250 mg, q.i.d, p.o	125 mg, q.i.d, p.o	10 days	21 days	90 vs. 82	23
Le et al. (2012)[15]	CS	United State	2006–2008	500 mg, q6h p.o or iv	125 mg, q.i.d, p.o	NA	21 days	128 vs. 16	17
Wenisch et al. (2012)[24]	CS	Austria/Europe	2008.12–2010.3	500 mg, t.i.d p.o or iv	250 mg, q.i.d, p.o	10 days	30 days	163 vs. 42	17
Johnson et al. (2014)[16]	RCT	United State, Canada; Europe	2005–2007	375 mg, q6h, p.o	125 mg, q6h, p.o	10 days	28 days	278 vs. 258	23

RCT, randomized controlled trial; CS, cohort study; NA, not available.

Initial Cure:

The initial clinical cure rates were significantly higher with vancomycin (81%) versus metronidazole (68%) in those with severe CDI (527 patients, REM, RR = 0.81, 95% CI = 0.69–0.95, p = 0.009, Fig. 2c). However, when the patients with PMC in two studies 4,5 were considered as severe CDI, no significant difference was found (596 patients, FEM, RR = 0.89, 95%CI = 0.78–1.02, p = 0.08, Fig. 2c).

	 **Sustained Cure:** No statistical significant difference between the treatments in patients with severe CDI: 527 patients, REM, RR = 0.86, 95%CI = 0.72–1.02, p = 0.08 or PMC: 69 patients, REM,RR = 1.07, 95% CI = 0.88–1.29, p = 0.51 **Recurrence rate:** No statistical difference between treatments for severe CDI patients (399 patients, FEM, RR = 1.27, 95% CI = 0.85–1.91, p = 0.25), andfor PMC (67 patients, FEM, RR = 0.64, 95% CI = 0.13–3.19, p = 0.59 **All-cause death rate** There was no statistically significant difference between patients treated with metronidazole and those treated with vancomycin
	4. Anmerkungen/Fazit der Autoren In conclusion, vancomycin provides improved initial clinical and sustained cure rates in patients with C. difficile infection compared with metronidazole, especially in patients with severe C. difficile infection. 5. *Kommentar zu Review /LL: The authors declare no conflicts of interest.*
Li R et al., 2015 [7]. **Efficacy and Safety of Metronidazole Monotherapy versus Vancomycin Monotherapy or Combination Therapy in**	1. Fragestellung to compare the efficacy and safety of metronidazole monotherapy with vancomycin monotherapy and combination therapy in CDI patients
	2. Methodik Population: persons with CDI Intervention/Komparator: metronidazole or vancomycin and combination of metronidazole and vancomycin Endpunkte: clinical therapeutic outcomes or AEs (clinical Cure, rate of CDI recurrence) Suchzeitraum (Aktualität der Recherche): before November 2014:

Patients with Clostridium difficile Infection: A Systematic Review and Meta-Analysis	PubMed, Embase, Web of Science, and Cochrane Library. Three Chinese language databases—China National Knowledge Infrastructure (CNKI; available at www.cnki.net), Chinese Scientific Journals Database (VIP; available at www.cqvip.com), and WANFANG DATA (available at www. wanfangdata.com.cn) Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 RCTs Qualitätsbewertung der Studien: modified Jadad score

3. Ergebnisdarstellung:

Studiencharakteristika:

Table 1. Main characteristics of the studies included in the meta-analysis.

Study	Disease Severity	MeanAge	Male (%)	Follow-up (weeks)	Enrolled Patients		Drug Regimen		Case Definitions	AssessmentIndex	EvidenceQuality	Risk of Bias
					T	C	T	C				
Met vs. Van												
Stuart,2014 [13]	Mild/ Severe	65.0	47.0	4	278	258	Met	Van	Method 1	(1)(3)	High	Low
Fred,2007[26]	Mild/ Severe	58.5	54.7	3	90	82	Met	Van	Method 1	(1)(2)(3)	High	Low
Wafa,2008[27]	Mild	71.0	NA	12	34	18	Met	Van	Method 1	(2)(3)	High	Unclear
Frank,2012 [20]	Mild/ Severe	60.5	49.0	12	128	16	Met	Van	Method 1	(1)(2)(3)	Moderate	Unclear
Jacques-a,2006[28]	Severe	NA	44.1	8	115	171	Met	Van	Method 2	(2)(3)	Moderate	Unclear
Enrico,2010 [29]	Severe	53.0	50.0	4	19	7	Met	Van	Method 1	(1)(2)(3)	Moderate	Unclear
Wenisch,1996 [30]	NA	41.0	53.2	4	31	31	Met	Van	Method 1	(3)	Moderate	Unclear
Ethan,2011 [31]	Mild	12.1	48.7	8	37	37	Met	Van	Method 1	(1)	Moderate	Unclear
Sahil,2013[32]	Mild	2.3	54.3	12	69	6	Met	Van	Method 1	(1)(2)	Moderate	Unclear
Mono vs. Combi												
Danny,2006 [10]	NA	69.0	41.0	4	20	19	Met	Met +Rif	Method 1	(1)(2)(3)	High	Low
Bass,2013[33]	Severe	65.8	NA	4	35	43	Van	Met +Van	Method 1	(1)(2)(3)	High	Unclear
Jacques-b,2006[28]	Severe	NA	44.1	8	115	36	Met	Met +Van	Method 2	(2)(3)	Moderate	Unclear
Jacques-c,2006[28]	Severe	NA	44.1	8	171	36	Van	Met +Van	Method 2	(2)(3)	Moderate	Unclear
Mihaela-a,2013[34]	NA	67.1	41.7	8	132	98	Met	Met +Van	Method 1	(2)	Moderate	Unclear
Mihaela-b,2013[34]	NA	67.1	41.7	8	76	98	Van	Met +Van	Method 1	(2)	Moderate	Unclear
Sapna-a,2014 [35]	NA	60.0	57.5	6	54	13	Met	Met +Van	Method 1	(1)(2)	Moderate	Unclear
Sapna-b,2014 [35]	NA	60.0	57.5	6	6	13	Van	Met +Van	Method 1	(1)(2)	Moderate	Unclear

Abbreviations: T: Treatment (Met or Mono); C: Control (Van or Combi); Met: Metronidazole; Van: Vancomycin; Rif: Rifampin; Mono: Monotherapy group; Combi: Combination therapy group; NA: Not available. Method 1: *C. difficile* toxin assay and/or a clinical diagnosis; Method 2: *C. difficile* toxin assay; (1): Rate of clinical cure; (2): Rate of CDI recurrence; (3): AEs.

Qualitätsbewertung:

S2 Table. Quality appraisal of studies included in the meta-analysis.

Study	Random allocation	Concealment schemes	Blinding	Drop-out	Integrity of the results	Selective report	Jadad scale
Danny 2006[10]	Yes	UA	S-B	Yes	Yes	UA	6
Stuart 2014[13]	Yes	UA	D-B	Yes	Yes	UA	6
Fred 2007[26]	Yes	UA	D-B	Yes	Yes	UA	6
Wafa 2008[27]	Yes	UA	UA	Yes	Yes	UA	5
Bass 2013[33]	Yes	UA	UA	Yes	Yes	UA	5
Frank 2012[20]	UA	UA	UA	UA	Yes	UA	3
Jacques 2006[28]	UA	UA	UA	UA	Yes	UA	3
Enrico 2010[29]	Yes	UA	UA	UA	Yes	UA	3
Wenisch 1996[30]	Yes	UA	UA	UA	Yes	UA	3
Ethan 2011[31]	UA	UA	UA	UA	Yes	UA	3
Sahil 2013[32]	UA	UA	UA	Yes	Yes	UA	3
Mihaela 2013[34]	UA	UA	UA	UA	Yes	UA	3
Sapna 2014[35]	UA	UA	UA	UA	Yes	UA	3

Abbreviations: UA:Unclear; S-B:single-blinded; D-B: double-blind.

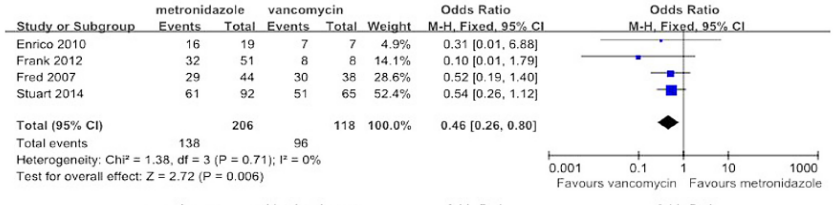
Jadad scale: Points were determined as follows, I. generation of allocation sequence (computer-generated random numbers, 2 points; not described, 1 point; inappropriate method,0 point); II. allocation concealment (central randomization, sealed envelopes or similar, 2 points; not described, 1 point; inappropriate or unused, 0 point); III. blindness (identical placebo tablets or similar, 2 point; inadequate or not described, 1 point; inappropriate or no double blinding, 0 point); IV. withdrawals and drop-outs (numbers and reasons are described, 1 point; not described, 0 point). The Jadad scale score ranges from 1 to 7; higher score indicates better RCT quality. If a study had a modified Jadad score >4 points, it was considered to be of high quality; if the score was 3-4 points, it was of moderate quality; and if the score was <3 points, it was of low quality.

Publikationsbias anhand Begg's funnel plot and the Egger's test untersucht: kein Hinweis auf Verzerrung.

Rate of clinical cure

the rate of clinical cure was lower for metronidazole than for vancomycin for the treatment of severe CDI (4 studies[13,20,26,29], 324 patients, OR = 0.46, 95% CI (0.26, 0.80), p = 0.006, I2 = 0%)

b)



results did not show a significant difference in the rate of clinical cure between monotherapy and combination therapy (4 studies (one article included two separate studies[35]), 190 patients, OR = 1.07, 95% CI (0.58, 1.96), p = 0.83, I2 = 0%)

Rate of CDI recurrence

the comparison of metronidazole with vancomycin, the meta-analysis results did not show any significant difference in the rate of CDI recurrence for the treatment of severe CDI (4 studies [20,26,28,29], 430 patients, OR = 0.98, 95% CI (0.63, 1.53), p = 0.94, I2 = 0%)

The meta-analysis results did not show any significant difference in the rate of CDI recurrence between monotherapy and combination therapy

	(8 studies (three articles each included two separate studies [28,34,35]), 804 patients, OR = 0.91, 95% CI (0.66, 1.26), p = 0.56, I2 = 0%) **Adverse Events:** The reported AEs from the included studies consisted of death, colectomy, diarrhea, any complication, ileus, colonic perforation, nausea and vomiting, pseudomembranous colitis, toxic megacolon, rash and severe enterocolitis. We performed subgroup analysis according to the AEs. The meta-analysis results did not show any significant difference in the rate of AEs between metronidazole and vancomycin However, the rate of AEs was significantly lower for monotherapy than for combination therapy (the results from 3 studies were separated into eight subgroups [10,28,33], 439 patients, OR = 0.30, 95% CI (0.17, 0.51), p<0.0001, I2 = 0%)
	4. Anmerkung/Fazit der Autoren: Metronidazole and vancomycin are equally effective for the treatment of mild CDI, but vancomycin is superior for the treatment of severe CDI. Combination therapy is not superior to monotherapy because it appears to be associated with an increase in the rate of AEs. 5. *Kommentar zu Review /LL: In der vorliegenden Metaanalyse wurden Odds Ratios als Effektmaße gewählt. Vor dem Hintergrund der Häufigkeit des Auftretens der Endpunkte erscheint dies nicht plausibel und könnte zu einer Verzerrung geführt haben. Risk Ratios wären in diesem Fall die bevorzugten Effektmaße.*
O'Horo JC et al., 2014 [8]. **Treatment of recurrent Clostridium difficile infection: a systematic review**	1. Fragestellung: We undertook a systematic review to critically evaluate the efficacy of therapeutic interventions in RCDI
	2. Methodik Population: Patients with RCDI Intervention: k. A. Komparator: k. A. Suchzeitraum (Aktualität der Recherche): MEDLINE, CINAHL, EMBASE, and the Cochrane Review Database were searched in September of 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 105 studies analyzing eight major treatments strategies for RCDI were identified and included in this review, 7 studies included in quantitative meta-analysis Qualitätsbewertung der Studien: risk of bias was

assessed according to the instrument developed by Downs and Black. This tool encompasses six sections which assess reporting, external validity, internal validity/bias, internal validity/confounding, and power. Disagreements were resolved by a third author. Studies with scores ≥12 were considered to be high-quality studies.

3. Ergebnisdarstellung:

Qualitätsbewertung: siehe Anhang 3-5

Wirksamkeit:

Antibiotics:

Examining high-quality trials using vancomycin, three studied a metronidazole comparator [15–17] and two fidaxomicin [19, 20]. The metronidazole comparator studies included 179 patients given metronidazole compared to 310 receiving vancomycin. Using sustained response (e.g., no recurrence), vancomycin was as efficacious as metronidazole [relative risk (RR) 1.08, 95 % confidence interval (CI) 0.85–1.35, I2 = 0 %, p = 0.53). Studies comparing fidaxomicin to vancomycin, discussed further below, included a total of 79 patients in each arm, and appeared slightly more efficacious than vancomycin (RR 1.86, 95 % CI 1.04–3.31, I2 = 0 %, p = 0.04) (Fig. 2).

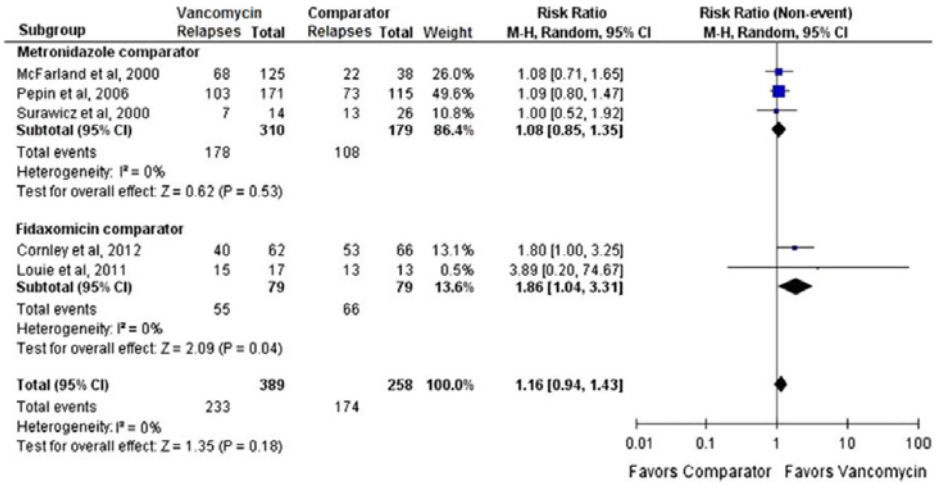


Fig. 2.
Forest plot of vancomycin versus metronidazole and fidaxomicin. Risk ratio of not having further relapses with vancomycin versus comparators in listed studies

Evidence supporting the use of vancomycin is moderate. There is considerable variability in dosing and duration for RCDI, but it is currently the standard of care in treating RCDI.

Fidaxomicin:

Both studies of fidaxomicin were prospective trials in a mixed inpatient–out-patient population [19, 20], totaling 116 patients. Clinical resolution was the endpoint of both studies. Initial response rates were high at 93 %, with sustained response occurring in 82 % of patients. One study indicated a clear reduction in recurrence after treating primary CDI, and

	evaluated RCDI as a subset. In that secondary analysis, fidaxomicin was superior to vancomycin in preventing a second recurrence in 28 days [19]. Both of the existing studies on fidaxomicin compared the drug to vancomycin and found non-inferiority [19, 20], with pooled results showing the slight superiority of vancomycin (see Fig. 2). Evidence for fidaxomicin is moderate in light of two positive, high-quality studies. *(Hinweise zum Review: Vergleiche zu Immunglobulinen, Probiotika und Stuhltransplantation wurden nicht dargestellt.)*
	4. Anmerkung/Fazit der Autoren: Metronidazole and vancomycin have good evidence for use in RCDI but heterogeneity in treatment duration and dose precludes robust conclusions. Fidaxomicin may have a role in treatment, but evidence is limited to subgroup analyses. Fecal bacteriotherapy was the most efficacious. Saccharomyces boulardii may have a role as adjunctive treatment.

Leitlinien

Debast SB et al., 2014 [2]. **European Society of Clinical Microbiology and Infection (ESCMID)** European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection	Fragestellung/Zielsetzung: The objectives of this document are to: 1. Provide an overview of currently available CDI treatment options 2. Develop an evidence-based update of treatment recommendations
	Methodik Grundlage der Leitlinie • Computerized literature search of PUBMED and Google Scholar using the terms 'Clostridium difficile AND (treatment OR trial)'. • All randomized and non-randomized trials investigating the effect of an intervention on the clinical outcome (resolution or recurrence of diarrhoea; incidence of complications) of CDI published in any language were included. • The resulting literature from 1978 was reviewed and analysed. Furthermore, systematic reviews from the most recent Cochrane analysis [2] and the up-dated guidelines …were evaluated • Recommendations were based on a systematic assessment of the quality of evidence. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was used to grade the strength of our recommendations and the quality of the evidence • Draft versions of the guideline were written by the executive committee (consisting of: S. Debast, M. Bauer and E. Kuijper) and criticized by the Executive Committee and advisors. After this, consensus was reached, resulting in the final version. • methods to evaluate the quality of evidence and to reach group consensus recommendations were based on the method described by Ullmann et al • Authors: The authors declare that they have no conflicts of interest. • Expert Panel: All members of the expert group completed a Conflict of Interest Disclosure Form (COI). LoE

TABLE 2. Definition of the Quality of Evidence (QoE) ESCMID. Adapted from ref. [8]

Quality of evidence	Definition
2a: Level	
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.
2b: Index	
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 or poster of a study published at an international meeting.

GoR

TABLE 1. Definition of the Strength of Recommendation Grade (SoR) ESCMID (adapted from ref. [8])

Strength	Definition
A	Strongly supports a recommendation for use
B	Moderately supports a recommendation for use
C	Marginally supports a recommendation for use
D	Supports a recommendation AGAINST use

Sonstige methodische Hinweise: Zusammensetzung der LL-Gruppe unklar

Freitext/Empfehlungen/Hinweise

B: Severe Clostridium difficile Infection

Oral antibiotic therapy:

Recommendations. Based on its pharmacokinetic properties vancomycin is considered superior to metronidazole in severe C. difficile disease [22,88]. The use of high doses of vancomycin (500 mg orally four times daily) was included in the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America treatment guidelines [3] for management of severe complicated CDI as defined by the treating physician. However, there is insufficient evidence to support the use of doses >125 mg four times daily in the absence of ileus [80].

Fidaxomicin was not inferior to vancomycin for initial cure of CDI, but there are no data available on the efficacy of this drug in severe life-threatening disease [70,91].

TABLE 16. Recommendations on oral antibiotic treatment of initial *Clostridium difficile* infection (CDI): severe disease

Treatment	SoR	QoE	Ref(s)	Comment(s)
Vancomycin, 125 mg four times daily for 10 days	A	I	[70, 88, 90, 91]	Cure rate higher as compared with metronidazole in severe CDI [88][a]
Vancomycin 500 mg four times daily for 10 days	B	III ([a])	[80]	Randomized controlled trial on dose effectiveness: no significant differences in measurable responses of high-dose compared to low-dose regimens. However: results not stratified for severity of illness [80][a].
Fidaxomicin 200 mg twice daily for 10 days	B	I	[70,89,91]	Evidence limited to two Phase III studies [70,91]. Fewer recurrences compared with vancomycin 125 mg four times daily in severe disease (except for PCR ribotype 027). No data on the efficacy in severe life-threatening disease and/or toxic megacolon: excluded from both studies.
Metronidazole, 500 mg three times daily for 10 days	D	I	[88]	Cure rate lower as compared with vancomycin in severe CDI [88]. Intention to treat analysis not reported. Extremely severe CDI excluded[a]. Differences in symptomatic cure of metronidazole versus vancomycin not statistically significant in a pooled analysis [2]. ICU admission and hypoalbuminaemia (= disease severity) predictors of metronidazole failure [119].

[a]Two studies reported in abstract form confirm the superiority of vancomycin over metronidazole for treatment of (severe) CDI [92,124,125].

C: First Recurrence or (Risk of) recurrent Clostridium difficile Infection

Oral antibiotic therapy

Recommendations. The incidence of a second recurrence after treatment of a first recurrence with oral metronidazole or vancomycin is similar. Fewer secondary recurrences with oral fidaxomicin as compared with vancomycin after treatment of a first recurrence are reported [70,91,144]. However, the evidence on fidaxomicin for this specific subgroup of CDI patients is limited to two phase III studies and based on a retrospective subset analysis of data and a limited number of patients (number of patients in the modified intention-to-treat analysis: fidaxomicin n = 79 and vancomycin n = 80) [144]. There are no prospective randomized controlled trials performed with metronidazole, vancomycin or fidaxomicin in this specific patient group. In addition, fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027 in one of the randomized controlled trials [70]. Therefore, based on the evidence currently available, the Strength of Recommendation for treating a first recurrence of CDI with oral vancomycin or oral fidaxomicin is considered equal (B-I), unless disease has progressed from non-severe to severe.

TABLE 18. Recommendations on oral antibiotic treatment of mild/moderate initial *Clostridium difficile* infection (CDI) with risk for recurrent CDI or first recurrence

Treatment	SoR	QoE	Ref(s)	Comment(s)
Vancomycin, 125 mg four times daily for 10 days	B	I	[70,82,90,91]	No statistically significant difference in recurrence rate between vancomycin and teicoplanin [2,82,84].
Fidaxomicin, 200 mg twice daily for 10 days	B	I	[70,89,91]	Evidence limited to two Phase III studies [70,91]. Retrospective subset analysis: fewer secondary recurrences with fidaxomicin (n = 16/79 patients) as compared with vancomycin (n = 26/80 patients) after treatment of a first recurrence [144]. Fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027 [70].
Metronidazole, 500 mg three times daily for 10 days	C	I	[27,88]	Recurrence rate: metronidazole not inferior to vancomycin for treatment of mild primary CDI [2,82,88] or after a first recurrence [27]. Vancomycin significantly more effective in bacteriological cure than metronidazole in recurrent CDI [69].
Vancomycin, 500 mg four times daily for 10 days	C	III	[80]	One randomized controlled trial on dose effectiveness in primary CDI: no significant differences in responses of high-dose compared with low-dose regimens vancomycin. However, results not stratified for recurrent CDI [80].

D: Multiple recurrent Clostridium difficile Infection

Recommendations. In non-severe second (or later) recurrences of CDI oral vancomycin or fidaxomicin is recommended. Vancomycin and

fidaxomicin are equally effective in resolving CDI symptoms, but fidaxomicin has been shown to be associated with a lower likelihood of CDI recurrence after a first recurrence [104,144]. However, there are no prospective randomized controlled trials investigating the efficacy of fidaxomicin in patients with multiple recurrences of CDI.

Recently the first randomized controlled trial on faecal enteric instillation has been published: faecal transplantation following antibiotic treatment with an oral glycopeptide is reported to be highly effective in treating multiple recurrent CDI [145].

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TABLE 21. Recommendations on oral antibiotic treatment of multiple recurrent *Clostridium difficile* infection (CDI) (more than one relapse)

Treatment	SoR	QoE	Ref(s)	Comment(s)
Vancomycin, 125 mg four times daily for 10 days, followed by pulse regimen (125–500 mg/day every 2–3 days) for at least 3 weeks.	B	IIt	[69,150]	Retrospective case cohort of two placebo/antibiotic trials [69]: [126,146]. Observational study: [150]. Expert opinion [3].
Vancomycin, 125 mg four times daily for 10 days, followed by taper regimen: gradually decreasing the dose to 125 mg per day.	B	IIt	[69,150]	Retrospective case cohort of two placebo/antibiotic trials [69]: [125,146]. Observational study: [150]. Expert opinion [3].
Fidaxomicin, 200 mg twice daily for 10 days	B	IIrt	[75,144]	Evidence limited to two Phase III studies [70,91]. Retrospective subset analysis: fewer recurrences as compared to vancomycin treatment after first recurrence [144]. Systematic review: [75]. Efficacy after multiple recurrences was not investigated [144].
Vancomycin, 500 mg four times daily for 10 days	C	IIrt	[69,75]	Retrospective case cohort of two placebo/antibiotic trials: [126,146]. Trend for lower recurrence frequency for high-dose vancomycin [69]. Systematic review: [75].
Metronidazole, 500 mg three times daily for 10 days	D	IIrt	[69,75]	Retrospective case cohort of two placebo/antibiotic trials: [126,146]. Trend for lower recurrence frequency for high-dose vancomycin and low-dose metronidazole [69]. Systematic review: [75].

Empfehlungen für Interventionen in Kombination mit Antibiose: off-label

TABLE 22. **Recommendations on non-antibiotic treatment (in combination with antibiotic treatment) of recurrent *Clostridium difficile* infection (CDI) (more than one relapse)**

Type of intervention	Treatment	SoR	QoE	Ref(s)	Comment(s)
Faecal or bacterial instillation	Vancomycin, 500 mg four times daily, 4 days + bowel lavage + nasoduodenal infusion donor faeces	A	I	[145]	Also many observational studies and meta-analyses. [164,186,189–191].
Probiotics	Vancomycin or metronidazole + *Saccharomyces boulardii*	D	I	[126]	Comparison of relapse rates: in subgroup analysis efficacy in recurrent CDI, but *not* in initial CDI. Evidence-based review: [137].
	Vancomycin or metronidazole + *Lactobacillus* spp.	D	I	[147,148]	Evidence-based review: [137].
Passive immunotherapy with immune whey	Colostral immune whey	D	I	[149]	Study interrupted early.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 21.06.2017

#	Suchfrage
1	MeSH descriptor: [Clostridium difficile] explode all trees
2	Clostridium next (infection* or difficile*):ti,ab,kw
3	#1 or #2
4	#3 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 22.06.2017

#	Suchfrage
1	Clostridium difficile[mh]
2	Clostridium[tiab] AND (Infection*[tiab] OR difficile*[tiab])
3	#1 OR #2
4	(#3) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
5	((#) AND ("2012/06/01"[PDAT] : "2017/06/30"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 22.06.2017

#	**Suchfrage**
1	Clostridium difficile[mh]
2	Clostridium[tiab] AND (Infection*[tiab] OR difficile*[tiab])
3	#1 OR #2
4	(#3) AND((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
5	(((#6) AND ("2012/06/01"[PDAT] : "2017/06/30"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]) NOT ("The Cochrane database of systematic reviews"[Journal]))

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Anhang:

Anhang 1: Risk of Bias für Studien zu Fragestellungen 3 und 4 aus Butler et al. 2016 [1]

KQ3 – Standard Treatment

Appendix Table F4. Standard treatment study risk of bias

Study ID	Design	Funding source	Overall Summary	Comments
Johnson, 2014[37]	RCT- 3 arms, tolevamer vs.metronidazole vs. vancomycin	Genzyme (tolevamer maker)	Low risk of bias	No reason to downgrade.
Cornely, 2012[38]	RCT- Vancomycin vs. fidaxomicin	Optimer pharmaceutical (fidaxomicin maker)	Low risk of bias	No reason to downgrade.
Wenisch, 2012[39]	Prospective Cohort – oral metronidazole vs. IV metronidazole vs. oral vancomycin	"No financial support was received for this study"	High risk of bias	Downgraded for: "no" answers to sequence generation, allocation concealment, blinding, and other (non-RCT). Unclear for incomplete outcome data

KQ4 – Nonstandard Treatment

Appendix Table F5. FMT adjunctive treatments study risk of bias

Study Country Funding	Type of Study	Overall Risk of Bias Assessment	Rationale
Newly identified studies			
Cammarota, 2015[44] Italy Nongovernmental	Open-label RCT	High	Unblinded, stopped early, inadequate sample size, change of FMT protocol during study (decided to give multiple infusions after first 2 patients had recurrence after 1 infusion)
Satokari, 2015[45] Finland	Retrospective review	High	Retrospective, case series
Zainah, 2015[46] United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size
Dutta, 2014[47] United States Health organization, University	Prospective	High	Case series, inadequate sample size
Khan, 2014[48] United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size, CDI assessed based on symptoms only, population inclusion criteria ("recurrent CDI") not defined
Lee, 2014[91] Canada University	Retrospective review	High	Retrospective, case series
Ray, 2014[50] United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size, lack of systematic followup (n=10/20 with 0-1 months followup)
Seekatz, 2014[51] United States Government, foundation	Prospective	High	Case series, inadequate sample size
Weingarden, 2014[52] United States Government, University	Observational	High	Case series, inadequate sample size, population inclusion criteria ("recurrent CDI") not defined, adverse events not reported
Youngster, 2014[54] United Sates Health organization	Open-label feasibility study	High	Inadequate sample size, no comparison group
Youngster, 2014[53] United States Government, University	Open-label RCT	High	Inadequate sample size, no non-FMT comparison group, attrition
Emanuelsson, 2013[55] Sweden No funding	Retrospective review	High	Retrospective, case series, inadequate sample size, lack of systematic followup (n=5 patients with 0-1 months follow-up)
Patel, 2013[56] United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size, attrition
Pathak, 2013[57] United States Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size
Rubin, 2013[58] United States Health organization	Retrospective review	High	Retrospective, case series

Study Country Funding	Type of Study	Overall Risk of Bias Assessment	Rationale
van Nood, 2013[59] The Netherlands Government	Open-label randomized trial	High	Unblinded, inadequate sample size (n=43 randomized, n=13-17 per arm), stopped early
Brandt, 2012[107] United States No funding	Survey	High	Retrospective, survey design
Hamilton, 2012[60] United States Foundation, government	Case series	High	Case series, followup not reported
Jorup-Ronstrom, 2012[61] Sweden Funding NR	Observational	High	Retrospective, case series, inadequate sample size, outcomes not clearly defined
Kelly, 2012[62] United States Funding NR	Case series	High	Case series, inadequate sample size, adverse events not reported
Mattila, 2012[63] Finland Foundation	Retrospective review	High	Retrospective, case series
Mellow, 2011[64] United States Funding NR	Observational	High	Case series, inadequate sample size, selective CDI testing
Garborg, [65]2010[65] Norway Funding NR	Retrospective review	High	Retrospective, case series, heterogeneous sample (confirmed or suspected CDI), lack of systematic followup
Aas, 2003[66] United States Health organization	Retrospective review	High	Retrospective, case series, inadequate sample size, selective CDI testing
Previously identified studies			
Rohlke, 2010[67] United States No funding	Retrospective review	High	Retrospective, case series, inadequate sample size, population inclusion criteria ("recurrent CDI") not defined, adverse events not reported
Yoon, 2010[68] United States No funding	Case series	High	Retrospective, case series, inadequate sample size
MacConnachie, 2009[69] United Kingdom Funding NR	Retrospective review	High	Retrospective, case series, inadequate sample size

Appendix Table F6. Probiotic adjunctive treatments study risk of bias

Study Country Funding	Overall Risk of Bias Assessment	Rationale
Newly identified randomized trials		
Ouwehand, 2014[70] China Industry	Moderate	Outcomes not clearly reported for CDI
Allen, 2013[71] United Kingdom Government	High	Underpowered for event rate, limited followup duration
Selinger, 2013[72] United Kingdom Industry, government	High	Underpowered for event rate, 45% did not complete study, trial stopped early due to low incidence of CDI
Pozzoni, 2012[73] Italy Hospital	High	Possible attrition bias, selective CDI testing, underpowered for event rate
Gao, 2010[74] China Industry	Moderate	Selective CDI testing.
Lonnermark, 2010[75] Sweden Funding NR	High	Possible attrition bias, selective CDI testing, limited followup duration, underpowered for event rate
Psaradellis, 2010[76] Canada Industry	High	Unclear randomization process and allocation concealment, possible attrition bias, selective CDI testing, underpowered for event rate, outcomes not reported by recurrence (heterogeneous population)
Safdar, 2008[77] United States Industry, NR	High	Underpowered for event rate
Beausoleil, 2007[78] Canada Industry	High	Unclear randomization process and allocation concealment, selective CDI testing, underpowered for event rate
Duman, 2005[79] Turkey Funding NR	High	Unclear randomization process and allocation concealment, open label, possible attrition bias, underpowered for event rate
Newly identified observational study		
Bakken, 2014[81] United States Case series None	High	No comparison group.
Maziade, 2013[80] Canada Open prospective Hospital	High	Observational design, unclear details of treatment/comparison groups
Previously identified trials		
Hickson, 2007[82] United Kingdom Foundation	High	Possible attrition bias, selective CDI testing, underpowered for event rate
Can, 2006[83] Turkey Funding NR	High	Unclear randomization process and allocation concealment, blinding patient or assessors; possible attrition bias, underpowered for event rate
Plummer, 2004[84] United Kingdom Funding NR	High	Unclear randomization process and allocation concealment, selective CDI testing, underpowered for event rate, outcomes not reported by carrier status (heterogeneous population)

Study Country Funding	Overall Risk of Bias Assessment	Rationale
Thomas, 2001[85] United States Industry	High	Possible attrition bias, selective CDI testing, CDI assessment by retrospective chart review, underpowered for event rate
Lewis, 1998[86] United Kingdom Health organization	High	Unclear randomization process and allocation concealment, unclear followup duration, underpowered for event rate
McFarland, 1995[87] United States	High	Unclear randomization process and allocation concealment, attrition bias, underpowered for event rate
Surawicz, 1989[88] United States Industry	High	Unclear allocation concealment, attrition bias, underpowered for event rate, outcomes not reported by carrier status (heterogeneous population)

Anhang 2: Zusammenfassung der Ergebnisse zu Fragestellungen 3 und 4 aus Butler et al. 2016 [1]

Key Questions	Level of Evidence Update	Level of Evidence Original Report	Summary/Conclusion/Comments
KQ3 – Standard Treatment			
Vancomycin versus Metronidazole	High level	Moderate level	Vancomycin more effective in achieving initial cure
	Moderate level	Low level	No difference between groups for recurrent CDI
Fidaxomicin versus Vancomycin	Moderate level	Moderate level	No significant differences in initial cure.
	High level	Moderate level	Decreased recurrence among those receiving fidaxomicin
Effect by disease severity	Low level	Insufficient level	Reported results by treatment arm are present regardless of severity
All other comparisons of standard treatments	NA	Low level for all comparisons	Vancomycin versus bacitracin, vancomycin versus nitazoxanide, vancomycin high versus low dose, metronidazole versus nitazoxanide, and metronidazole versus metronidazole plus rifampin. No differences
Strain of organism	NA	Low level	One RCT (fidaxomicin versus vancomycin) demonstrated decreased recurrence among those receiving fidaxomicin when the infecting organism was a non-NAP1 strain
Patient characteristics	NA	Insufficient level	No comparative data were available
Resistance of other pathogens	NA	Insufficient level	No data were available
KQ4 – Other Treatment			
Treating CDI, active control	NA	Low level	Probiotics, prebiotics, *C. difficile* immune whey, and colestipol, are not more effective in treating CDI than standard antibiotic treatment with oral vancomycin or metronidazole
Treating CDI, placebo	NA	Low level	Administration of a probiotic with live bacteria to treat CDI in critically ill patients increases risk for greater morbidity and mortality from fungemia without any known benefit
Treating recurrent CDI	Low level	Low level	Fecal microbiota treatment is effective in treating recurrent CDI
	Insufficient level	NA	Data insufficient for patients with refractory CDI
Preventing CDI	NA	Low level	Prebiotics and monoclonal antibodies are not more effective than placebo for primary prevention of CDI
Preventing recurrent CDI	Low level	Low level	Probiotics using lactobacillus or multiorganism strains are more effective than placebo for reducing recurrent CDI
	Low level	Low level	Probiotics using *S. boulardii* are not more effective than placebo for reducing recurrent CDI
	NA	Moderate level	Monoclonal antibodies are effective in preventing recurrence of CDI

CDI = *Clostridium difficile* infection; NA = not applicable

Vancomycin in recurrent *Clostridium difficile* infection (RCDI)

Study	Design	Inclusion criteria	Definition of CDI	Duration of follow up	Mean age	Adjunctive/preparatory treatments	No. treated with vancomycin	Initial response rate	Sustained response rate	Comparator	Comparator initial response	Comparator sustained response rate	Study quality[a]
Tedesco et al. [13]	Case series	Patients with recurrent PMC treated with vancomycin taper and pulse	Histologic evidence of PMC	60 days	59	None	21	100 %	100 %	None	N/A	N/A	Low
Surawicz et al. [17]	RCT	Symptomatic RCDI	3 or more loose stools/day for at least 2 days with positive EIA, culture, or toxin assay	8 weeks		None	14[b] 38[c]	NR	50 %[b] 55 %[c]	Metro	NR	50 %	High
						S. boulardii	18[b] 45[c]	NR	83 %[b] 49 %[c]	Metro		52 %	
Shetler et al. [14]	Case series	Recurrent PMC treated with colonic decompression and intracolonic vancomycin	Histologic evidence of PMC	NR	70	Rectal tube	7	57 %	NR	None	N/A	N/A	Low
McFarland et al. [15]	Case series	Active diarrhea with positive toxin assay	Positive EIA, at least 3 loose stools in 24 h, and one of the following findings: abdominal pain, fever, and/or leukocytosis	1 year	NR	None	125	NR	54 %	Metro	NR	58 %	High
Pépin et al. [16]	Case series	Positive toxin assay or clinical diagnosis of PMC	Positive cytotoxin assay or endoscopic evidence of PMC	60 days	NR	None	171	NR	60 %	Metro	NR	79 %	High
Musher et al. [21]	RCT	Two recurrences after 14-day treatment with metronidazole or vancomycin recurrences	Positive EIA, at least 3 loose stools in 24 h, and one of the following findings: abdominal pain, fever, and/or leukocytosis	60 days	66	None	27	74 %	66 %	Nita	77 %	72 %	Low
Basu et al. [18]	RCT	Failure of vancomycin and/or metronidazole	Positive PCR assay with 5–10 stools/day while not meeting sepsis criteria	28 days	NR	None	15	73 %	73 %	Nita	67 %	67 %	Low
Louie et al. [19]	RCT	Lack of response to metronidazole	Positive toxin assay with at least 3 loose stools in preceding 24 h	90 days	63	None	43	94 %	72 %	Fidax	95 %	88 %	High
Cornely et al. [20]	RCT	First time RCDI occurring within 90 days of index case	Positive toxin assay with at least 3 loose stools in preceding 24 h	28 days	65	None	62	73 %	65 %	Fidax	92 %	80 %	High
van Nood et al. [22]	RCT	Adults with RCDI refractory to metronidazole and/or vancomycin	Positive PCR assay with >8 stools/48 h or >3 stools in 24 h for 2 days	10 weeks	66	None	13	NR	30.8 %	Fecal transplant	NR	81.3 %	Low
					69	Bowel lavage	13	NR	23.1 %				

PMC pseudomembranous colitis, *NR* not reported, *Metro* metronidazole, *RCT* randomized controlled trial, *Nita* nitazoxanide, *Fidax* fidaxomicin, *PCR* polymerase chain reaction

Metronidazole in RCDI

Study	Design	Inclusion criteria	Definition of CDI	Duration of follow up	Mean age	Adjunctive/preparatory treatments	No. treated with metronidazole	Initial response rate	Sustained response rate (%)	Comparator	Comparator initial response rate	Comparator sustained response rate	Study quality[a]
Surawicz et al. [17]	RCT	Adults with symptomatic RCDI	3 or more loose stools/day for at least 2 days with positive EIA, culture or toxin assay	8 weeks	66[b]	None	26	87.5 %[b]	50	Vanco[c]	NR	84 %	High
						S. boulardii	27		52	Vanco[c]		50 %	High
McFarland et al. [15]	Case series	Adults with symptomatic RCDI	Active diarrhea with positive toxin assay	1 year	NR		38	NR	58	Vanco	NR	54 %	High
Wullt et al. [26]	RCT	Adults with toxin-positive CDI with recurrence	3 or more loose stools/day for at least 2 days with positive EIA	70 days	65	*Lactobacillus plantarum* 299v	12	92 %	66	None	N/A	N/A	High
					63	Placebo	9	77 %	56	NR	N/A	N/A	High
Pépin et al. [16]	Case series	RCDI with positive toxin assay or clinical diagnosis of pseudomembranous colitis	Positive cytotoxin assay or endoscopic evidence of PMC	2 months	NR	None	115	NR	79	Vanco	NR	60 %	High
Mattila et al. [25][a]	RCT	Adult patients with at least two episodes of toxin-positive symptomatic CDI within 3 months	Active diarrhea with positive toxin assay	28 days	66	*Clostridium difficile* immune whey	20	100 %	60	CDIW	83 %	61 %	High

NR not reported, *RCT* randomized controlled trial, *Vanco* vancomycin, *CDIW Clostridium difficile* immune whey, *EIA* enzyme immunoassay, *PMC* pseudomembranous colitis

[a] High quality indicates a Downs and Black score greater than or equal to 12

[b] Combined for with adjunctive *S. boulardii* and without

[c] From "High dose vancomycin" comparator arm

Fidaxomicin in RCDI

Study	Design	Inclusion criteria	Definition of recurrence	Duration of follow up	Mean age	Adjunctive/preparatory treatments	No. treated with fidaxomicin	Initial response rate (%)	Sustained response rate (%)	Comparator	Comparator initial response rate (%)	Comparator sustained response rate (%)	Study quality[a]
Louie et al. [19]	RCT	Lack of response to metronidazole	Positive toxin assay with at least 3 loose stools in preceding 24 h	90 days	63	None	48	95	88	Vanco	95	72	High
Cornely et al. [20]	RCT	First time RCDI occurring within 90 days of index case	Positive toxin assay with at least 3 loose stools in preceding 24 h	28 days	65	None	66	92	80	Vanco	92	65	High

RCT randomized controlled trial, *vanco* vancomycin

[a] High quality indicates a Downs and Black score more than 12