Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-233 Ceftolozan/Tazobactam

Stand: Dezember 2018

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

Ceftolozan/Tazobactam [intraabdominelle Infektionen]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*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.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor
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:	
Ceftolozan/ Tazobactam J01DI54 Zerbaxa®	Anwendungsgebiet: Komplizierte intraabdominelle Infektionen
Tigecyclin J01AA12 Tigecyclin-ratiopharm®	Tigecyclin ist zur Behandlung folgender Infektionen bei Erwachsenen und Kindern ab 8 Jahren angezeigt (siehe Abschnitte 4.4 und 5.1): […] — komplizierte intraabdominelle Infektionen (cIAI). Tigecyclin sollte nur in solchen Situationen angewendet werden, bei denen andere alternative Antibiotika nicht geeignet sind (siehe Abschnitte 4.4, 4.8 und 5.1). Die allgemein anerkannten Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind zu berücksichtigen.
Piperacillin J01CA12 Piperacillin Eberth®	Piperacillin ist angezeigt zur Behandlung der folgenden Infektionen bei Erwachsenen und Kindern (siehe Abschnitte 4.2, 4.4 und 5.1): Erwachsene und Jugendliche: […] - Komplizierte intraabdominelle Infektionen […] Die offiziellen Leitlinien für den angemessenen Gebrauch von antibakteriellen Wirkstoffen sind zu berücksichtigen.
Amoxicillin/ Clavulansäure J01C R02 AmoxClav HEXAL®	AmoxClav HEXAL i. v. ist zur Behandlung folgender Infektionen bei Erwachsenen und Kindern indiziert (siehe Abschnitte 4.2, 4.4 und 5.1): […] •• intraabdominelle Infektionen […] •• in der Beckenhöhle […] Die offiziellen Richtlinien für den angemessenen Gebrauch von Antibiotika sind zu beachten.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Piperacillin/ Tazobactam J01CR05 Piperacillin/ Tazobactam Stragen®	Piperacillin/Tazobactam ist angezeigt zur Behandlung der folgenden Infektionen bei Erwachsenen und Kindern über 2 Jahren (siehe Abschnitt 4.2 und 5.1): Erwachsene und Jugendliche […] – Komplizierte intra-abdominale Infektionen […] Offizielle Empfehlungen für den angemessenen Gebrauch von antibakteriellen Wirkstoffen sollten berücksichtigt werden.
Ampicillin/ Sulbactam J01CR21 Unacid®	[…] Unacid ist geeignet zur Behandlung von Infektionen, die durch Sulbactam-/ Ampicillin-empfindliche Erreger verursacht sind, z. B. Infektionen […] – des Bauchraumes, […]
Cefuroxim J01DC02 Cefuroxim Fresenius®	Cefuroxim Fresenius 750 mg Pulver zur Herstellung einer Injektionslösung wird angewendet zur Behandlung der nachfolgend genannten Infektionen bei Erwachsenen und Kindern einschließlich Neugeborenen (von Geburt an) (siehe Abschnitte 4.4 und 5.1). […] • Intraabdominelle Infektionen […] Zur Behandlung und Prävention von Infektionen, die mit hoher Wahrscheinlichkeit durch anaerobe Organismen verursacht wurden, sollte Cefuroxim zusammen mit zusätzlichen geeigneten antibakteriellen Substanzen angewendet werden. Die offiziellen Richtlinien für den angemessenen Gebrauch von antibakteriellen Wirkstoffen sind zu berücksichtigen.
Cefotaxim J01DD01 Claforan®	Schwere Infektionen, wenn diese durch Cefotaxim-empfindliche Erreger (siehe Abschnitt 5.1) verursacht sind: […] – Infektionen des Bauchraumes (einschließlich Peritonitis), […] Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Claforan zu berücksichtigen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ceftazidim J01DD02 Ceftazidim Kabi®	Ceftazidim wird angewendet bei Erwachsenen und Kindern inklusive Neugeborenen (von Geburt an) bei Infektionen die untenstehend aufgelistet sind. […] – Komplizierte intraabdominale Infektionen […] Bei der Wahl von Ceftazidim sollte sein antibakterielles Spektrum berücksichtigt werden, welches hauptsächlich auf aerobe Gram-negative Bakterien limitiert ist (siehe Abschnitt 4.4 und 5.1). Ceftazidim sollte gemeinsam mit anderen antibakteriellen Substanzen angewendet werden, wenn die mögliche Bandbreite der verursachenden Bakterien nicht vom Wirkspektrum von Ceftazidim abgedeckt wird. Offizielle Richtlinien zum angemessenen Gebrauch von antibakteriellen Arzneimitteln sollten berücksichtigt werden.
Ceftriaxon J01DD04 Rocephin®	Rocephin wird angewendet zur Behandlung der nachfolgend genannten Infektionen bei Erwachsenen und Kindern, einschließlich Neugeborenen (ab der Geburt): […] Infektionen im Bauchraum […] Rocephin sollte zusammen mit anderen Antibiotika verabreicht werden, wann immer das mögliche Erregerspektrum nicht von seinem Anwendungsbereich abgedeckt wird (siehe Abschnitt 4.4). Offizielle Richtlinien für den sachgemäßen Gebrauch von Antibiotika sollten berücksichtigt werden.
Ceftazidim/ Avibactam J01DD52 Zavicefta®	Zavicefta wird angewendet bei Erwachsenen zur Behandlung der folgenden Infektionen (siehe Abschnitte 4.4 und 5.1): […] • Komplizierte intraabdominelle Infektionen (cIAI) […] Die offiziellen Richtlinien für den angemessenen Gebrauch von antibakteriellen Wirkstoffen sind zu berücksichtigen.
Cefepim J01DE01 Maxipime®	Zur Behandlung von Infektionen, die durch Cefepim-empfindliche Erreger verursacht werden: […] – Infektionen des Bauchraumes, einschließlich Peritonitis; Eine Kombinationstherapie mit einem weiteren Antibiotikum ist unter Berücksichtigung des individuellen Risikoprofils des Patienten und der zu erwartenden bzw. nachgewiesenen Erreger gegebenenfalls zu empfehlen. […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Meropenem J01DH02 Meropenem Kabi®	Meropenem Kabi ist angezeigt zur Behandlung der folgenden Infektionen bei Erwachsenen und Kindern älter als 3 Monate (siehe Abschnitt 4.4 und 5.1): – komplizierte intraabdominelle Infektionen, […] Für den angemessenen Gebrauch von Antibiotika sollten die offiziellen Leitlinien beachtet werden.
Ertapenem J01DH03 Invanz®	Behandlung INVANZ ist indiziert bei Kindern und Jugendlichen (im Alter von 3 Monaten bis 17 Jahren) und bei Erwachsenen zur Behandlung folgender Infektionen, wenn diese durch sicher oder wahrscheinlich Ertapenem-empfindliche Bakterien verursacht sind und eine parenterale Therapie erfordern (siehe Abschnitte 4.4 und 5.1): • Intraabdominelle Infektionen […] Die offiziellen Therapieempfehlungen zum angemessenen Einsatz von Antibiotika sollten beachtet werden.
Imipenem/ Cilastatin J01DH51 Zienam®	ZIENAM* ist zur Behandlung der folgenden Infektionen bei Erwachsenen und Kindern ab 1 Jahr angezeigt (siehe Abschnitte 4.4 und 5.1): […] • Komplizierte intraabdominelle Infektionen […] Die offiziellen nationalen Leitlinien zur adäquaten Anwendung von Antibiotika sind zu beachten.
Clindamycin J01FF01 Clindamycin Heumann®	Akute und chronische bakterielle Infektionen (Erkrankungen durch Ansteckung) durch Clindamycin-empfindliche Erreger, wie […] – Infektionen des Becken- und Bauchraumes, […] Bei schweren Krankheitsbildern sollte einleitend eine Behandlung mit Clindamycinhaltigen Arzneimitteln vorgenommen werden, die langsam in ein Blutgefäß verabreicht werden (Infusionen).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Tobramycin J01GB01 Gernebcin®	Zur Behandlung von schweren Infektionen, die durch Tobramycin-empfindliche Erreger verursacht sind (siehe dazu auch 5.1), wenn weniger toxische Antibiotika nicht wirksam sind. Unter diesen Voraussetzungen kann Gernebcin angewendet werden bei:[…] • intraabdominellen Infektionen […] Bei der systemischen Anwendung (i.v. und i.m.) wird Gernebcin üblicherweise im Rahmen einer Kombinationsbehandlung verabreicht, vorwiegend zusammen mit einem Betalaktam-Antibiotikum oder mit einem gegen anaerobe Bakterien wirksamen Antibiotikum, vor allem bei lebensbedrohlichen Infektionen durch einen (zunächst noch) unbekannten Erreger, bei gemischten anaeroben/aeroben Infektionen, bei systemischen Pseudomonas-Infektionen sowie bei abwehrgeschwächten, vorwiegend neutropenischen Patienten. Die üblichen und allgemein anerkannten Richtlinien für den angemessenen Gebrauch von Antibiotika sind bei der Anwendung von Gernebcin zu beachten.
Gentamicin J01GB03 Refobacin®	Die allgemein anerkannten Richtlinien für den angemessenen Gebrauch von antibakteriellen Wirkstoffen sind bei der Anwendung von Refobacin zu berücksichtigen. Zur Behandlung von schweren Infektionen, die durch Gentamicin-empfindliche Erreger verursacht sind. Grundsätzliche Indikationen für Aminoglykoside sind Infektionen durch Erreger, die gegenüber anderen, weniger toxischen Arzneimitteln resistent sind, sowie schwere Infektionen mit gramnegativen Erregern, im Krankenhaus erworbene Infektionen sowie Infektionen bei abwehrgeschwächten und neutropenischen Patienten. Unter diesen Voraussetzungen kann Refobacin angewandt werden bei: […] – intraabdominellen Infektionen
Amikacin J01GB06 Amikacin B. Braun	Zur Behandlung der folgenden schwerwiegenden Infektionen durch Amikacin-empfindlichen Erregern (siehe Abschnitt 5.1), wenn weniger toxische Antibiotika nicht wirksam sind: […] – intraabdominale Infektionen, einschließlich Peritonitis, […] Amikacin B. Braun 2,5 mg/ml, 5 mg/ml und 10 mg/ml Infusionslösung wird häufig mit anderen geeigneten Antibiotika kombiniert, um das Bakterienspektrum der entsprechenden Infektion abzudecken. Die offiziellen Richtlinien für die angemessene Anwendung von Antibiotika sind zu beachten.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ofloxacin J01MA01 Ofloxacin-ratiopharm®	Ofloxacin-ratiopharm® Filmtabletten sind zur Behandlung folgender bakterieller Infektionen indiziert, wenn sie durch Ofloxacinempfindliche Erreger verursacht worden sind: […] – Infektionen des Bauchraumes, z. B. Infektionen des kleinen Beckens […] Zur Behandlung schwerer und/oder lebensbedrohlicher Infektionen ist die parenterale Behandlung indiziert. Es sind die jeweils geltenden offiziellen/nationalen Richtlinien zur antibakteriellen Resistenz sowie zur sachgerechten Anwendung von Antibiotika zu beachten (siehe auch Abschnitt 5.1).
Ciprofloxacin J01MA02 Ciprofloxacin Kabi®	Ciprofloxacin Kabi ist zur Behandlung der folgenden Infektionen angezeigt (siehe Abschnitte 4.4 und 5.1). Vor Behandlungsbeginn sollten besonders die verfügbaren Informationen zu Resistenzen beachtet werden. Offizielle Empfehlungen zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden. Erwachsene […] • Intraabdominale Infektionen […]
Teicoplanin J01XA02 Targocid®	Targocid ist bei Erwachsenen und Kindern ab der Geburt indiziert zur parenteralen Behandlung von folgenden Infektionen (siehe Abschnitte 4.2, 4.4 und 5.1): […] • Peritonitis, assoziiert mit kontinuierlicher ambulanter Peritonealdialyse (CAPD), […] Targocid sollte falls erforderlich in Kombination mit anderen antibakteriellen Arzneimitteln eingesetzt werden. Offizielle Empfehlungen zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden.
Colistin J01XB01 Colist-Infusion®	Colist-Infusion 2 Millionen I.E. ist bei Erwachsenen und Kindern, einschließlich Neugeborener, zur Behandlung schwerer, durch bestimmte aerobe gramnegative Erreger verursachter Infektionen indiziert, sofern für die Patienten nur begrenzte Therapieoptionen zur Verfügung stehen (siehe Abschnitte 4.2, 4.4, 4.8 und 5.1). Die offiziellen Richtlinien zur sachgemäßen Anwendung von Antibiotika sind zu beachten.

Quellen: AMIS-Datenbank, Fachinformationen (Stand: 11/2018)

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-233a (Ceftolozan/Tazobactam)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. Dezember 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis

AEs	Adverse events
APD	Automated PD
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BL/ BLIs	Novel β-lactam/β-lactamase inhibitors
CA-IAI	Community-acquired IAI
CAPD	Continuous ambulatory PD
CE	Clinically evaluable population,
cIAI	Complicated intraabdominal infections
c-mITT	clinical modified intent-to-treat population,
CRP	Cardiopulmonary resuscitation
cUTI	Complicated urinary tract infection
EME	Extended microbiologically valuablepopulation
EOT	End-of-treatment visit
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HA-IAI	Hospital-associated IAI
HR	Hazard Ratio
IP	Intraperitoneal
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	Intravenous
KI	Konfidenzintervall
LFU	Late follow-up
LoE	Level of Evidence
ME	Microbiologically evaluable population
mITT	Modified intent-to-treat) population,
m-mITT	Microbiological mITTpopulation
NICE	National Institute for Health and Care Excellence

OR	Odds Ratio
PD	Peritoneal Dialysis
RR	Relatives Risiko
SAEs	Serious AEs
SIGN	Scottish Intercollegiate Guidelines Network
TOC	Test-of-cure
TRIP	Turn Research into Practice Database
VER	Vancomycin-resistant Enterococcus spp.
WHO	World Health Organization

1 Indikation

a) Komplizierte intraabdominelle Infektionen bei Erwachsenen

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Intraabdominelle Infektionen durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 28.11.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, 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 876 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 9 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es liegen keine Berichte vom G-BA oder vom IQWiG vor.

3.2 Cochrane Reviews

Ballinger AE et al., 2014 [1].

Treatment for peritoneal dialysis-associated peritonitis

Fragestellung

To evaluate the benefits and harms of treatments for PD-associated peritonitis

Methodik

Population:

- Adult and paediatric patients who were receiving PD (CAPD or APD) and developed PD-associated peritonitis

Intervention:

- antimicrobial agent, fibrinolytic agent, peritoneal lavage, IP immunoglobulin

Komparator:

- Interventions could be tested directly against each other or compared to placebo/no treatment
  - Studies of the same antibiotic agent administered by different routes (e.g. IP versus oral, IP versus IV).
  - Studies comparing the same antibiotic agent administered at different doses.
  - Studies comparing different schedules of administration of antimicrobial agents (in particular regimens involving single daily dosing versus more than one daily dose).
  - Comparisons of different regimens of antimicrobial agents.
  - Studies comparing different treatment durations with the same antimicrobial agents.
  - Studies comparing any other intervention including fibrinolytic agents, peritoneal lavage, IP immunoglobulin administration, and early catheter removal.

Endpunkte:

- Primary outcomes

  1. Primary peritonitis treatment failure (failure to achieve a clinical response, defined as resolution of symptoms and signs, by day 4 to 6)

  2. Complete cure (clinical or microbiological improvement or both with no subsequent relapse)

  3. Peritonitis relapse (reoccurrence of peritonitis due to the same organism with the same antibiotic sensitivities within 28 days of completing treatment)

  4. Death due to peritonitis (all-cause mortality data were also collected)

  5. Toxicity of antibiotic treatments (ototoxicity, decline in residual kidney function, rash, nausea and vomiting, convulsions, other).

- Secondary outcomes

  1. Time to peritonitis relapse

  2. Need to change antibiotic following culture results

3. Catheter removal or replacement or both

4. Hospitalisation (duration of hospital stay) and hospitalisation rate (number of patients hospitalised)

5. Technique failure (transfer from PD to haemodialysis or transplantation due to peritonitis).

Recherche/Suchzeitraum:

- Cochrane Renal Group's Specialised Register and EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE OVID SP, Handsearching of renal-related journals and the proceedings of major renal conferences, Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.
- to 5 March 2014 without language restriction.

Qualitätsbewertung der Studien:

- Cochrane risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien & Charakteristika der Population:

- in total: 42 studies (58 reports, 2433 participants)
- 36 studies (1949 patients) that considered the use of antimicrobial agents.
- 14 studies that compared different routes of antibiotic administration - IP versus IV (3 studies, 156 participants) and IP versus oral (11 studies, 601 participants)
- 17 studies: different IP antibiotic classes or combinations or both were tested head-to-head, these included
  - 3 studies (234 participants) that compared glycopeptides to first generation cephalosporins (Flanigan 1991; Khairullah 2002; Lupo 1997);
  - 5 studies (421 participants) that compared intermittent and continuous IP antibiotic dosing (Boyce 1988; Choy 2001; Lye 1995; Klaus 1995a; Velasquez-Jones 1995)
  - 6 studies that investigated adjunctive therapies: urokinase versus placebo (Gadallah 2000c; Innes 1994; Tong 2005a); catheter removal or replacement or both (Williams 1989), peritoneal lavage (Ejlersen 1991), IP immunoglobulin (Coban 2004).
  - Data for automated PD were absent.

Qualität der Studien:

- risks of bias were in high in most studies - overall, both blinding and selective reporting were assessed at high risk of bias

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

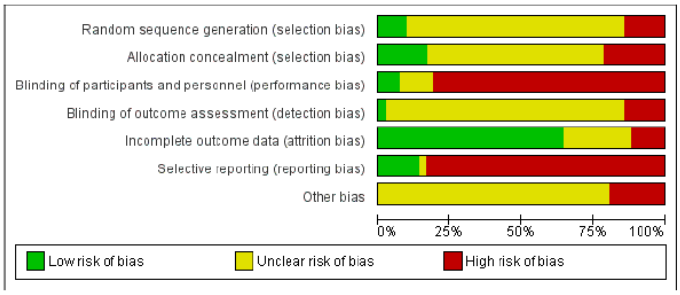
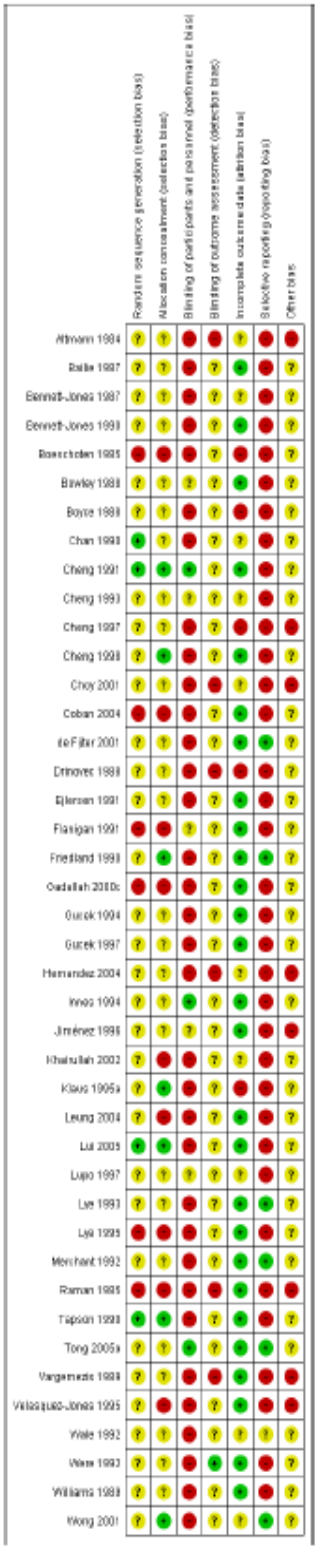


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Studienergebnisse: (extraction only for comparisons of different regimens of antimicrobial agents)

- First generation cephalosporin versus glycopeptide based regimens
  - Complete cure was significantly more likely with a glycopeptide-based regimen than one based on cephalosporins (3 studies, 370 participants): RR 1.66, 95% CI 1.01 to 2.72; P = 0.04; I^2 = 41%).
    - This was true for both vancomycin (2 studies, 305 participants): RR 1.51, 95% CI 1.03 to 2.22; P = 0.26; I^2 = 20%) and teicoplanin-based regimens (Analysis 7.1.2 (1 study, 65 participants):RR 9.65, 95%CI 1.04 to 20.58).
  - Uncertain effects due to the lack of power within the meta-analysis of glycopeptides on:
    - primary treatment failure (2 studies, 305 participants): RR 1.14, 95% CI 0.69 to 1.87; P = 0.38; I^2 = 0%),
    - relapse (Analysis 7.3 (3 studies, 350 participants): RR 1.68, 95%CI 0.84 to 3.36; P = 0.14; I^2 = 0%),
    - catheter removal (2 studies, 305 participants): RR 0.95, 95% CI 0.41 to 2.19; P = 0.90; I^2 = 52%) and
    - microbiological eradication (1 study, 45 participants): RR 0.83, 95% CI 0.62 to 1.13)
- Teicoplanin versus vancomycin-based IP antibiotic regimens
  - Primary treatment failure was less likely with teicoplanin than vancomycin (2 studies, 178 participants): RR 0.36, 95% CI 0.13 to 0.96; P = 0.04),
  - Effects on complete cure were uncertain (2 studies, 178 participants): RR 0.67, 95% CI 0.40 to 1.15; P = 0.14; I^2 = 0%).
  - risk of relapse rates was also similar for both agents (2 studies, 178 participants): RR 1.01, 95% CI 0.49 to 2.11; P = 0.97; I^2 = 0%)
- Different regimens of oral antibiotics
  - Uncertain effects of oral rifampicin and ofloxacin (regimen 2) compared with oral ofloxacin alone (regimen 1) (Chan 1990) in achieving a complete cure (74 participants): RR 0.88, 95% CI 0.35 to 2.17) and catheter removal (74 participants): RR 2.00, 95% CI 0.19 to 21.11)
  - No differences in the need to change antibiotics following culture results (74 participants): RR 0.33, 95% CI 0.04 to 3.06), nausea and vomiting (74 participants): RR 3.00, 95% CI 0.13 to 71.34) and rash (74 participants): RR 3.00, 95% CI 0.13 to 71.34) between the two regimens. (Chan 1990)
- Head-to-head studies
  - 12 studies in which different regimens of IP antibiotics were compared head-to-head
  - Only one statistically significant outcome (de Fijter 2001): rifampicin/ciprofloxacin was better than cephradine in reducing treatment failure (98 participants; RR 0.50, 95% CI 0.28 to 0.89).

Anmerkung/Fazit der Autoren

- review found that in generally low-quality evidence

- IP antibiotic therapy may lower risks of primary treatment failure compared with IV antibiotics in two small studies
- Insufficient data available to determine if specific antibiotic classes are most effective for reducing treatment failure and relapse, although glycopeptides may improve complete cure rates compared with first generation cephalosporins.
- Oral antibiotics were associated with increased risk of nausea and vomiting compared with IP administration

Conclusion

- currently available evidence from RCTs is not robust and does not identify an optimal antibiotic regimen for the treatment of PD-associated peritonitis
- Available studies are small, and generally at high risk of bias, lowering the certainty of treatment effects for all available treatments.

Kommentare zum Review

High risk of bias, no trustworthy evidence

3.3 Systematische Reviews

Chen M et al., 2018 [2].

Novel β-lactam/β-lactamase inhibitors versus alternative antibiotics for the treatment of complicated intra-abdominal infection and complicated urinary tract infection: a metaanalysis of randomized controlled trials

Fragestellung

we conduct a meta-analysis of all published RCTs to conclusively appraise the efficacy and safety of novel BL/ BLIs in comparison with other available antibiotics for the treatment of cIAI and cUTI.

Methodik

Population:

- adult patients (over 18 years old) with cIAI and cUTI

Intervention:

- ceftazidime/avibactam or ceftolozane/tazobactam

Komparator:

- any other antibiotics for the treatment of cIAI and cUTI

Endpunkte:

- Primary outcome: efficacy of novel BL/BLIs including clinical treatment success in CE population and microbiological treatment success in ME population at the TOC visit.
- Secondary outcome: the safety of novel BL/BLIs and this included mortality and adverse events in safety population at the LFU visit.

Recherche/Suchzeitraum:

- Pubmed, Embase, Web of Science and the Cochrane Central Register of Controlled Trials
- retrieval was updated to September 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration ‘Risk of bias’ tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 studies, 5348 patients

Charakteristika der Population:

- 1 study [18] covered patients with a diagnosis of cIAI or cUTI, and ceftazidime/avibactam was used to compare with best available therapy option which was determined by the investigators according to local recommendations.
- 5 studies [19–23] included patients with cIAI, and novel BL/BLIs were compared with meropenem in all patients.

- 3 studies [24–26] included patients with cUTI, and three different drugs (doripenem, levofloxacin and imipenem/cilastin) in each trial were used to compare with novel BL/BLIs.

Qualität der Studien:

- All studies had low risk for sequence generation and allocation concealment.
- Only one trial was performed in open label model, with a high risk for performance bias and detection bias.
- The remaining eight trials were all designed in double-blind, double-dummy model, with low risk for performance bias and detection bias.
- As for attrition bias, two studies possessed high risk with relatively great amount of missing data, another two studies had unclear risk with insufficient details for patient dropouts
- Five trials were assessed as low risk.
- All studies had available protocols with consistent primary outcomes and secondary outcomes reported in the protocols and publications.

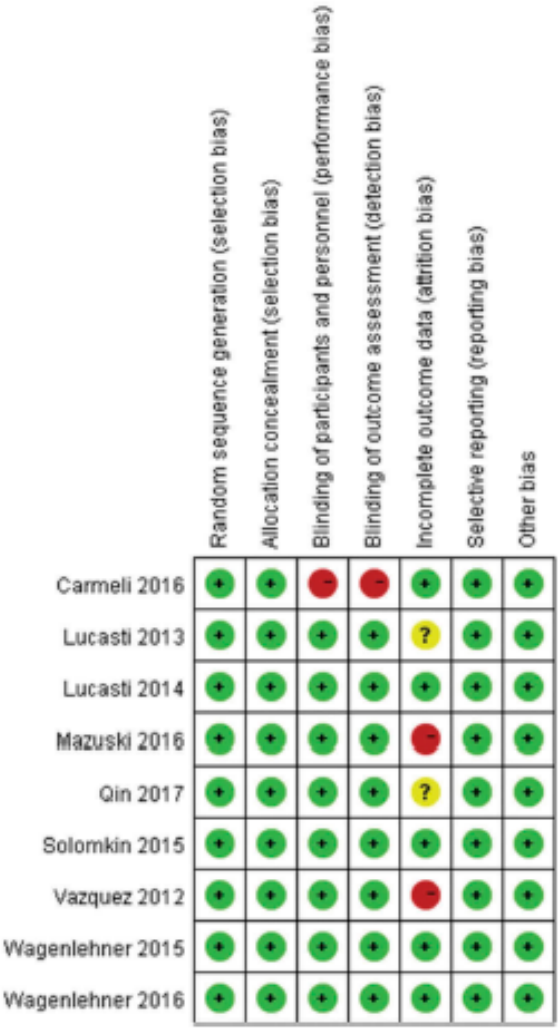


Figure 2. Risk of bias summary. Red circles indicate high risk, green circles indicate low risk, and yellow circles indicate unclear risk. Full color available online.

Studienergebnisse:

- Clinical treatment success
  - Regarding the cIAI subgroup - no significant difference between patients treated with novel BL/BLIs, and those treated with meropenem (5 RCTs, OR = 0.91, 95%CI = (0.65, 1.26), p = 0.56)
  - novel BL/BLI was superior to doripenem, and was similar to meropenem and imipenem/cilastin
  - studies in patients infected with ESBL-producing Enterobacteriaceae (172 patients), showed that the efficacy of ceftolozane/tazobactam was significantly higher than comparators (OR = 2.89, 95%CI = (1.18, 7.09), p = 0.02)
- Microbiological treatment success
  - Subgroup analysis - patients with cIAI: no difference detected regarding microbiological treatment success between novel BL/BLIs and meropenem treatment groups in ME population (3 RCTs, 433 patients, OR = 0.67, 95%CI = (0.31, 1.46), p = 0.32)
  - treatment with novel BL/BLIs was associated with significantly higher eradication rates for Gram-negative pathogens (OR = 1.82, 95%CI = (1.26, 2.64), p = 0.001)
  - For E.coli and K.pneumoniae, the eradication rates were significantly higher in the novel BL/BLIs group (OR = 1.74, 95%CI = (1.26, 2.64), p = 0.001 and OR = 2.41, 95% CI = (1.03, 5.69), p = 0.04, respectively)
  - For P.aeruginosa, no statistically significant differences in bacterial eradication were detected between groups (OR = 2.40, 95%CI = (0.54, 10.69), p = 0.25)
- Mortality
  - Subgroup analysis - patients with cIAI: no significant difference detected between novel BL/BLIs and comparator regimens
- Adverse events and serious adverse events
  - No differences were found regarding AEs (OR = 1.07, 95%CI = (0.95, 1.19), p = 0.26) (Figure 8) and SAEs (OR = 1.14, 95% CI = (0.90, 1.44), p = 0.27) (Figure 9) between novel BL/BLIs and controlled treatments

Anmerkung/Fazit der Autoren

- no significant difference detected in the cases of cIAI between novel BL/BLIs and carbapenems
- As for the safety endpoints, there were no significant differences in mortality, adverse events and serious adverse events.
- Novel BL/BLIs were more sensitive to Gram-negative pathogens, special for E.coli and K.pneumoniae.

Kommentare zum Review

Gute Studienqualität

Novel BL/BLIs are not inferior to other available antibiotics for the treatment of cIAI

Shen F et al., 2015 [6].

Efficacy and safety of tigecycline for the treatment of severe infectious diseases: an updated meta-analysis of RCTs

Fragestellung

to re-evaluate the efficacy and safety of tigecycline in comparison with other antimicrobial regimens for infectious diseases

we carried out an updated meta-analysis to reexamine the efficacy and safety of tigecycline using all available data from RCTs published before 2015 Feb.

Methodik

Population:

- Infectious diseases in patients of more than 18 years old (including cIAIs)

Intervention:

- tigecycline

Komparator:

- with any antimicrobial regimens

Endpunkte:

- Primary outcomes: clinical treatment success and microbiological treatment success
- Secondary outcomes: adverse events, all-cause mortality

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library
- through 2015 Feb

Qualitätsbewertung der Studien:

- Cochrane collaboration's tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 studies including 7689 cases (3909 cases for tigecycline and 3780 cases for comparator drugs)

Charakteristika der Population:

- 5 studies listed examined cIAI
  - comparators: Imipinem/cilastatin & Ceftriaxone/metronidazole

Qualität der Studien:

- Eight studies had low risk for sequence generation, while the other seven studies did not describe randomization method.
- Five studies had low risk of bias for allocation concealment, while the rest of studies did not mention the method of allocation concealment.

- Eleven trials were double-blind and four were open-label.
- Only eight trials had available protocols with consistent primary outcomes and secondary outcomes reported in the protocols and publications.
- 5 studies examining cIAI – moderate to high risk of bias

Table 1
Characteristics of included studies

Study	Design	mITT population	Indications	Comparator drug	Treatment duration	Test of Cure	Risk of bias
Fomin 2005[12]	MC, DB	817	cIAI	Imipenem/cilastatin	5-14	14-35	MR
Oliva 2005[13]	MC, DB	825	cIAI	Imipenem/cilastatin	5-14	14-35	MR
Chen 2010[14]	MC, OL	199	cIAI	Imipenem/cilastatin	2-14	12-37	HR
Towfigh 2010[15]	MC, OL	467	cIAI	Ceftriaxone/metronidazole	4-14	10-21	HR
Qvist 2012[16]	MC, OL	467	cIAI	Ceftriaxone/metronidazole	4-14	8–44	HR
Breedt 2005[17]	MC, DB	543	cSSSI	Vancomycin/aztreonam	14	12-92	MR
Sacchidanand[18] 2005	MC, DB	573	cSSSI	Vancomycin/aztreonam	14	12-92	MR
Matthews 2012[19]	MC, OL	531	cSSSI	Ampicillin-sulbactam or amoxicillin-clavulanate	7-14	8-50	HR
O'Riordan 2015[20]	MC, DB	150	cSSSI	Delafloxacin or tigecycline	5–14	14–21	HR
Tanaseanu 2009[21]	MC, DB	428	CAP	Levofloxacin	7-14	10-21	LR
Bergallo 2009[22]	MC, DB	418	CAP	Levofloxacin	3-14	7-23	MR
Freire 2010[23]	MC, DB	934	HAP	Imipenem/cilastatin	7-14	10-21	MR
Ramirez 2013[24]	MC, DB	105	HAP	Imipenem/cilastatin	14	10-21	MR
Florescu 2008[25]	MC, DB	171	MRSA VRE	Vancomycin linezolid	7–28	12-37	MR
Lauf 2014[26]	MC, DB	1061	DFI	Ertapenem	28- 42	12-92	LR

MC = multicenter; DB = double-blind; OL = open-lable; cIAI = complicated intra-abdominal infection; cSSSI = complicated skin and skin-structure infection; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; MRSA = methicillin-resistant staphylococcus aureus; VRE = vancomycin-resistant enterococci; DFI = diabetic foot infection; LR = low risk of bias; MR = moderate risk of bias; HR = high risk of bias.

<u>Studienergebnisse:</u>

Primary outcomes

- Clinical treatment success
  - Pooling the data from fourteen studies that assessed clinical treatment success in clinical evaluable (CE) population (5663 patients) showed significantly lower cure rate in tigecycline than in comparator drugs (OR = 0.83, 95% CI = 0.73 to 0.96, P=0.01) → figure 2
  - efficacy of tigecycline was significantly lower than that of comparator regimens (OR = 0.81, 95% CI = 0.72 to 0.92, P=0.001) → figure 3
- Microbiological treatment success
  - 8 studies reported microbiological treatment success in microbiological mITT (m-mITT) populations of 2704 patients, and showed no significant differences between groups (OR = 0.91, 95% CI = 0.74 to 1.11, P=0.35) → figure 4
  - microbiologically assessable (ME) populations reported in 12 studies (2876 patients), the microbiological treatment success for tigecycline was numerically lower than that for the comparator group with no significant difference (OR = 0.94, 95% CI = 0.77 to 1.16, P=0.56) → figure 5
  - Treatment with tigecycline was associated with numerically lower eradication rates for Bacteroides fragilis, Escherichia coli, Klebsiella pneumonia and MRSA with no significance difference.
  - Treatment with tigecycline was associated with numerically higher eradication rates for Enterococcus faecalis with no significant difference.
  - For MSSA, the eradication rate is significantly lower in the tigecycline group
  - for Streptococcus spp., the eradication rate is significantly higher in the tigecycline group

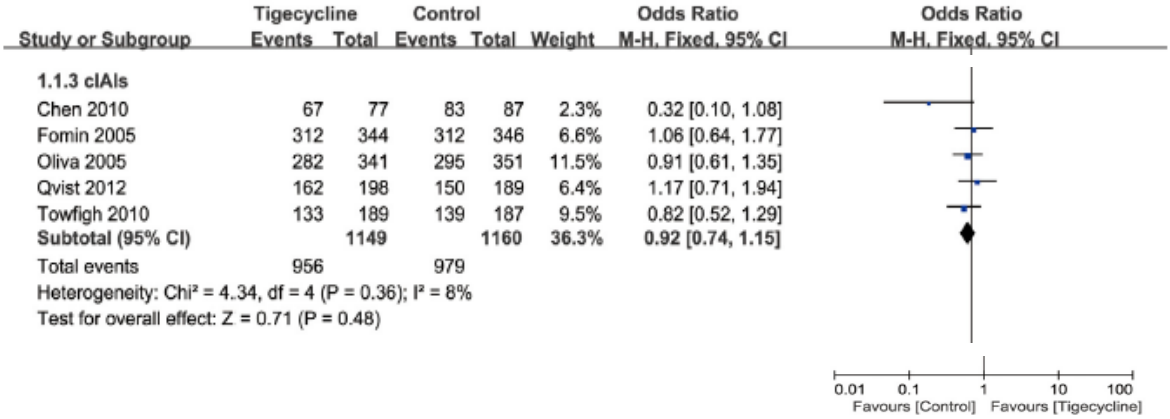


Figure 2. Forest plot and meta-analysis of clinical cure rate for clinically evaluable [CE] population. M-H=Mantel-Haenszel method.

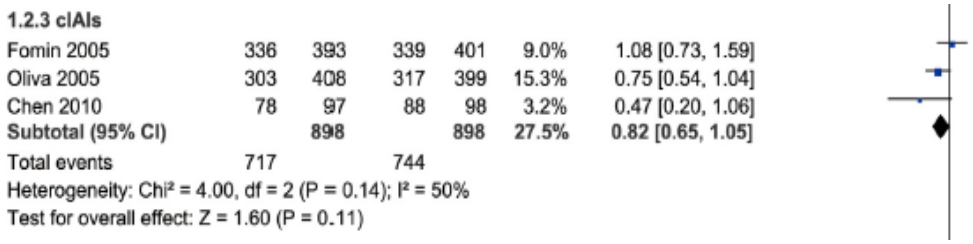


Figure 3. Forest plot and meta-analysis of clinical cure rate for clinical modified intent-to-treat [c-mITT] population. M-H=Mantel-Haenszel method.

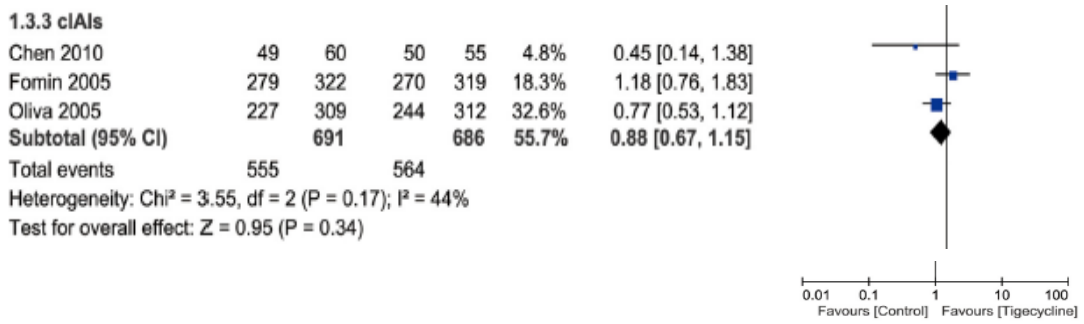


Figure 4. Forest plot and meta-analysis of microbiological cure rate for microbiological modified intent-to-treat [m-mITT] population. M-H=Mantel-Haenszel method.

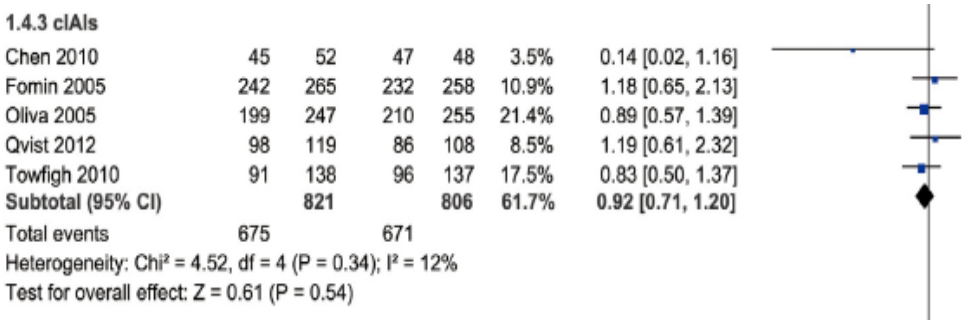


Figure 5. Forest plot and meta-analysis of microbiological cure rate for microbiological evaluable [ME] population. M-H=Mantel-Haenszel method.

Secondary outcomes

- Adverse events
  - Twelve studies including 6292 patients reported different adverse events (AEs). The AEs rate is significantly higher in the tigecycline group than in the comparator drug group (OR =1.49, 95% CI = 1.23 to 1.80, P <0.0001)
  - severe adverse events (SAEs) reported in thirteen studies including 6663 patients, the incidence rate is also significantly higher in the tigecycline group than in the control group (OR = 1.18, 95% CI = 1.03 to 1.35, P = 0.02)
  - Statistical significance of higher AEs in the tigecycline group when evaluating the digestive system (OR = 2.08, 95% CI = 1.53 to 2.83, P<0.00001) and body as a whole (OR = 1.21, 95% CI = 1.01 to 1.45, P = 0.04).
  - No statistical significance of higher AEs in the hemic and lymphatic system (OR = 1.24, 95% CI = 0.99 to 1.55, P = 0.06).
  - No statistical significance of lower AEs in the metabolism and nutrition (OR = 0.96, 95% CI = 0.79 to 1.16, P = 0.66) and respiratory system (OR = 0.70, 95% CI = 0.43 to 1.14, P = 0.15).
  - Cardiovascular AEs were significantly lower in the tigecycline group than in the control group (OR = 0.68, 95% CI = 0.52 to 0.88, P = 0.004)
- All-cause mortality
  - Pooling the data from 14 studies that assessed all-cause mortality in 7504 patients showed significantly higher mortality rate in the tigecycline group than in the control group (4.05% and 3.07%, OR = 1.33, 95% CI = 1.03 to 1.72, P = 0.03)
- Publication bias
  - Non found

Anmerkung/Fazit der Autoren

- tigecycline was not as effective as the comparator drugs with more frequency of adverse effects and all-cause mortality
- no significant differences of efficacy between tigecycline and control groups
- We found a significant decrease in clinical treatment success of tigecycline compared with other antibiotics with significant difference
- Tigecyline is not as effective as standard antibiotic regimens for infectious diseases.
- Tigecycline is associated with more frequency of adverse events and higher mortality rate.

Kommentare zum Review

Keine Auflistung der Cochrane risk of Bias Bewertung pro Studie in der Publikation

Sternbach N et al., 2018 [7].

Efficacy and safety of ceftazidime/avibactam: a systematic review and meta-analysis

Fragestellung

performed a systemic review and meta-analysis assessing the efficacy and safety of ceftazidime/avibactam for the treatment of various bacterial infections.

to assess the efficacy of this drug for the treatment of complicated infections and specifically for subgroups of patients infected with resistant pathogens.

Methodik

Population:

- treatment of any infection among adult patients

Intervention:

- ceftazidime/avibactam, with or without metronidazole

Komparator:

- any other antibiotic regimen

Endpunkte:

- Primary outcome: 30 day all-cause mortality and if that was unavailable, mortality at the end of follow-up
- Secondary outcomes included: clinical response, as defined in individual studies; microbiological response (per patient and per pathogen, as available); superinfections; development of resistance; any adverse events (AEs) and serious AEs (SAEs), AEs requiring discontinuation, renal and liver AEs, and Clostridium difficile-associated diarrhoea

Recherche/Suchzeitraum:

- PubMed, Cochrane Central Register of Controlled Trials (Central) and LILACS databases
- last searchwas conducted in December 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien und Charakteristika der Population:

- 7 publications representing 8 trials (4093 patients) that compared ceftazidime/avibactam +metronidazole versus any other antibiotic regimen for treatment of cUTI (3), cIAI (4) and nosocomial pneumonia (1)
- The main comparator was a carbapenem
- Place of infection acquisition was explicitly described as hospital-acquired in only one trial

Qualität der Studien:

- All trials had low risk of bias for allocation generation, allocation concealment, selective outcome reporting and incomplete outcome assessment.
- One publication was open-label whereas all others were double-blinded.

Table 1. Characteristics of included trials

				Randomization[a]				
Study ID	Type of infection	Comparator drug	Patients randomized (*n*)	generation	concealment	Blinding	MTZ added to CAZ/AVI?	Additional antibiotic coverage allowed
Vazquez *et al.*[20]	cUTI	IPM/cilastatin	137	A	A	double-blind		
Qin *et al.*[18]	cIAI	MEM	441	A	A	double-blind	yes	Gram-positive
Carmeli *et al.*[15]	cUTI, cIAI	best available therapy, mostly carbapenem[b]	333	A	A	open-label	yes for cIAI	
Torres *et al.*[19]	nosocomial pneumonia	MEM	879	A	A	double-blind		Gram-positive and amikacin[c]
Lucasti *et al.*[16]	cIAI	MEM	204	A	A	double-blind	yes	Gram-positive
Mazuski *et al.*[17]	cIAI	MEM	1066	A	A	double-blind	yes	Gram-positive
Wagenlehner *et al.*[21]	cUTI	DOR	1033	A	A	double-blind		

CAZ/AVI, ceftazidime/avibactam; DOR, doripenem; MEM, meropenem; IPM, imipenem; MTZ, metronidazole.
[a]Randomization generation and concealment: 'A' represents low risk of bias.
[b]Only 7/168 patients assigned to best available therapy in this publication were reported to receive a regimen other than carbapenem monotherapy.
[c]80% of patients in the CAZ/AVI arm and 82% in the comparator arm were given amikacin.

Studienergebnisse:

- Primary outcome: 30 day all-cause mortality (Figure 2)
  - Overall, 36/610 (5.9%) patients died within 30 days in the ceftazidime/avibactam arm and 34/629 (5.4%) in the comparator arm.
  - Mortality for long-term follow-up was 64/1956 (3.3%) in the ceftazidime/avibactam arm and 52/1957 (2.7%) in the comparator arm.
  - All-cause 30 day mortality was reported in four trials including 1239 patients (one UTI, two IAI and one pneumonia trial).
  - No significant difference in mortality was demonstrated between ceftazidime/avibactam and the comparator (RR 1.1, 95% CI 0.7–1.72, P=0.69, I^2=0).
  - Seven trials including 3915 patients reported all-cause mortality at LFU with no significant difference between study arms (RR 1.23, 95% CI 0.87–1.76, P=0.25, I^2=0).
  - Among subcategories of type of infection, no statistically significant difference in mortality was demonstrated (Figure 2).

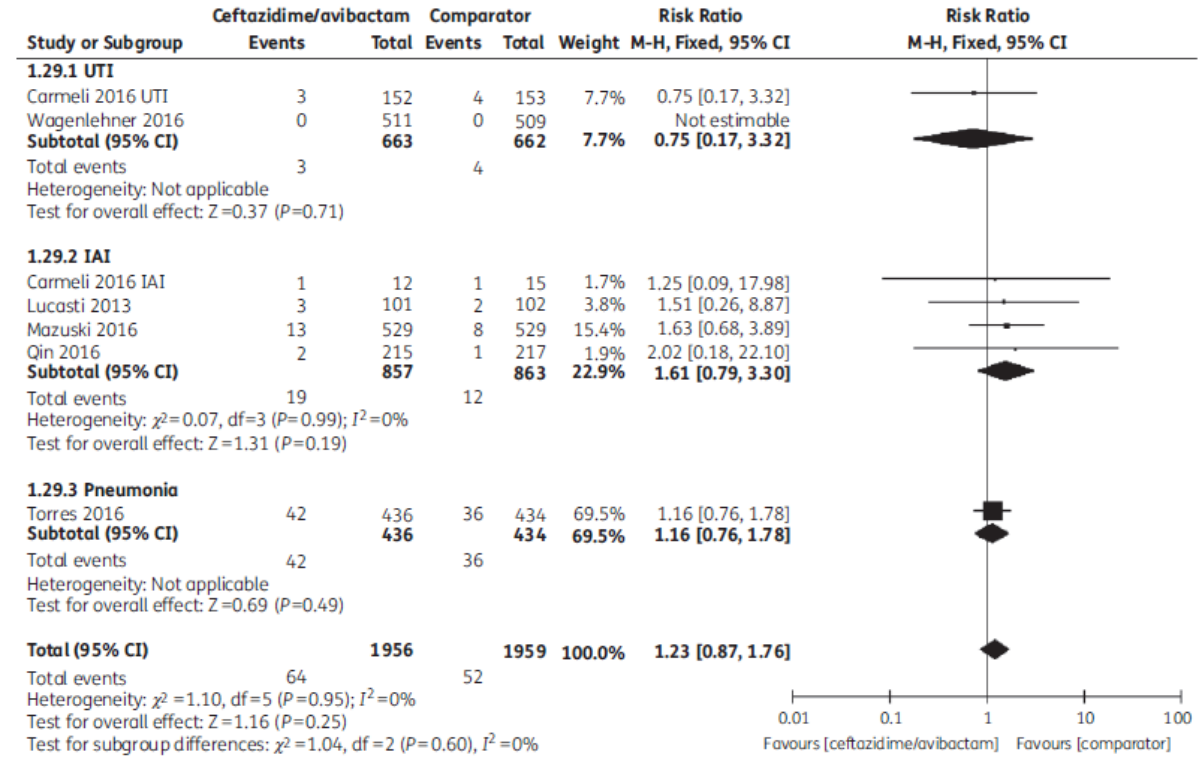


Figure 2. All-cause mortality at late follow-up. M-H, Mantel–Haenszel.

- Clinical response (table 2)
  - Clinical response in the included trials was evaluated at EOT, TOC and LFU - At all of these timepoints no significant difference was demonstrated between study arms.
  - Eight trials reported clinical response at the TOC visit (3292 patients) with no difference between study arms (RR 0.98, 95% CI 0.96–1.01, P=0.21, I^2=0)

Table 2. Clinical response[a]

					Response rate	
Time of follow-up	No. of trials	No. of patients	RR	95% CI	CAZ/AVI	comparator
EOT	7	2591	0.99	0.98–1.01	1214/1276 (95%)	1261/1315 (96%)
UTI	3	1155	0.99	0.97–1.01		
IAI	4	1436	1.00	0.97–1.02		
TOC	8	3292	0.98	0.96–1.01	1390/1619 (86%)	1460/1673 (87%)
UTI	3	1155	1.00	0.96–1.03		
IAI	4	1411	0.99	0.96–1.02		
pneumonia	1	726	0.94	0.86–1.04		
LFU	7	2551	1.00	0.97–1.03	1096/1253 (87%)	1131/1298 (87%)
UTI	3	1154	1.01	0.96–1.07		
IAI	4	1397	0.99	0.96–1.03		

CAZ/AVI, ceftazidime/avibactam.
[a]There was no heterogeneity (I^2 = 0%) for all these outcomes.

- Microbiological response
  - Microbiological response per patient at the EOT was reported in four trials (1506 patients, 1151 of them cUTI) with no significant difference between study arms (RR 0.99, 95% CI 0.96–1.02, P=0.36, I^2=0).

- Similar results were reported at the TOC visit (5 trials, 1652 patients, RR 1.04, 95% CI 0.93–1.17, P=0.51, I^2=73%)

- Adverse events
  - Any AEs were reported in 8 trials including 3988 patients.
  - These included 974/1993 (49%) AEs in the ceftazidime/avibactam group and 943/1995 (47%) in the comparator group (RR 1.03, 95% CI 0.97–1.10, P=0.28, I^2=14%).
  - Among two trials evaluating cIAI a significantly higher rate of discontinuation was demonstrated for the ceftazidime/avibactam group (RR 2.11, 95% CI 1.00–4.44, P=0.05, I^2=0%).
  - SAEs were statistically significantly more common in the ceftazidime/avibactam arm (RR 1.24, 95% CI 1.00–1.54, P=0.05, I^2=0%)
  - Gastrointestinal AEs were significantly more common in the ceftazidime/avibactam group in trials evaluating cIAI (RR 1.61, 95%CI 1.31–1.97, P=0.01, I^2=31%).
  - C. difficile-associated diarrhoea was reported in three trials with rates of 3/1255 patients in the ceftazidime/avibactam group and 1/1255 patients in the comparator group.
  - Creatinine increase was significantly more common in the ceftazidime/avibactam group (RR 3.00, 95% CI 1.09–8.20, P=0.03, I^2=0%), though this result stemmed from one study.
  - Other AEs had no significant difference between study arms, including liver function abnormalities, pyrexia, peripheral oedema, hypersensitivity reactions and neurological AEs.

Anmerkung/Fazit der Autoren

- We found no significant difference in 30 day mortality and mortality at the end of follow-up between study arms.
- Clinical response rates were also similar between ceftazidime/avibactam and comparators.
- Microbiological response was significantly higher for the ceftazidime/avibactam arm in cUTI trials
- In trials assessing patients with cIAIs, gastrointestinal AEs and AEs requiring drug discontinuation were significantly more common in the ceftazidime/avibactam arm.
- SAEs were significantly more common with ceftazidime/avibactam.
- In conclusion, ceftazidime/avibactamis clinically as effective as carbapenems for the treatment of cUTI, cIAI and nosocomial pneumonia in a setting in which ~25% of Enterobacteriaceae are ESBL positive.
- Microbiological response in patients with cUTI is superior with ceftazidime/avibactam.

Kommentare zum Review

4 studies with cIAI, low risk of bias

Tsai CC et al., 2018 [8].

Comparison of topical mupirocin and gentamicin in the prevention of peritoneal dialysis-related infections: A systematic review and meta-analysis

Fragestellung

we performed a systematic review and meta-analysis to compare the effect of topical gentamicin with that of mupirocin on infection rates in patients on peritoneal dialysis

Methodik

Population:

- patients on peritoneal dialysis

Intervention:

- topical gentamicin

Komparator:

- mupirocin

Endpunkte:

- infection rates (exit-site infection, peritonitis)

Recherche/Suchzeitraum:

- MEDLINE/Pubmed, Cochrane Library, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- from the earliest records to June 2016

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias for RCTs
- checklist proposed by Wells and colleagues for non-RCTs & observational studies

Ergebnisse

Anzahl eingeschlossener Studien und Charakteristika der Population:

- Nine studies - two randomized trials (including one conference abstract), two prospective non-randomized studies, and five retrospective studies.
- Five studies specifically indicated that only adults patients were included.
- the average age of participants of all studies was in the fifties

Table 1
Characteristics of the included studies comparing topical mupirocin (M) and gentamicin (G) in patients on peritoneal dialysis.

Study	Country	Study type	Patients (n) M/G	Mean age (years) M/G	Male (%) M/G	Diabetes (%) M/G
Bernardini 2005[9]	USA	Randomized, double-blind	66/67	51/54	58%/51%	41%/40%
Chu 2008[10]	Hong Kong	Prospective	38/43	61/58	82%/63%	29%/42%
Mahaldar 2009[20]	USA	Retrospective	50/50		50%/46%	40%/38%
Mortazavi 2011[18]	Iran	Randomized	61/60	51/59	53%/30%	
Davenport 2012[21]	UK	Retrospective	1270/502	56/58	58%/58%	29%/22%
Pierce 2012[11]	USA	Retrospective	79/93	52/52	48%/58%	43%/41%
Al-Hwiesh 2013[19]	Saudi Arabia	Prospective	105/98	56/53	58%/52%	38%/37%
Wu 2013[22]	Canada	Retrospective	59/37	58/58	61%/54%	42%/46%
Chen 2016[23]	USA	Retrospective	265/179	49/51	44%/46%	37%/36%

Qualität der Studien:

- A RCT published as a conference abstract was excluded from quality assessment

  The other randomized, double-blind trial had a low risk of bias for all key domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias).

  Quality assessment of two prospective non-randomized studies and three retrospective studies showed that none of these studies had a high risk of bias.

Studienergebnisse:

- Exit-site infection
  - 7 studies were considered for the analysis of exit-site infection (458 patients in the mupirocin group, 448 patients in the gentamicin group)
  - no difference between the two groups in overall (RR = 1.064, 95% CI 0.606 to 1.868, P = 0.829) and gram-positive (RR = 0.915, 95% CI 0.451 to 1.856, P = 0.806) exit-site infection rates; heterogeneity was substantial (I^2 = 76.0% and 59.7%, respectively)
  - The mupirocin group tended to have fewer Staphylococcus aureus exit-site infections (RR = 0.553, 95% CI 0.297 to 1.029, P = 0.062, I^2 = 0.0%), but the difference not statistical significant
  - gram-negative exit-site infection rate was significantly lower in the gentamicin group (RR = 2.125, 95% CI 1.046 to 4.319, P = 0.037, I^2 = 41.7%)
  - no difference in Pseudomonas exit-site infection rate (RR = 1.925, 95% CI 0.687 to 5.392, P = 0.213, I^2 = 37.2%).
- Peritonitis
  - 6 studies were included in the analysis of peritonitis infection (397 patients in the mupirocin group and 388 patients in the gentamicin group)
  - The two groups had no difference in overall (RR = 1.028, 95% CI 0.720 to 1.469, P = 0.878, I^2 = 74.4%), gram-positive (RR = 0.830, 95% CI 0.581 to 1.186, P = 0.307, I^2 = 42.6%), S. aureus (RR = 0.761, 95% CI 0.379 to 1.531, P = 0.444, I^2 = 0.0%), and gram-negative (RR = 1.446, 95% CI 0.743 to 2.814, P = 0.278, I^2 = 51.8%) peritonitis rates.
  - Moderate-to-high heterogeneity in the overall analysis.
  - The mupirocin group tended to have more Pseudomonas peritonitis (RR = 2.498, 95% CI 0.871 to 7.160, P = 0.089) though not statistically significant; no heterogeneity
- Sensitivity analysis
  - including only robust randomized and prospective studies; the overall estimated RRs were fairly stable
  - the difference in gram-negative exit-site infection was of marginal significance (RR = 2.862, 95% CI 0.984 to 8.320, P = 0.053, I^2 = 61.4%).
- Additional analysis
  - the between-group difference appeared to be negatively associated with the incidence of the mupirocin group in regard to gram-positive exit-site infection and gram-negative peritonitis

- This implies that when the use of mupirocin ointment was associated with a relatively high incidence of gram-positive exit-site infection or gram-negative peritonitis, a switch to topical gentamicin would have a better chance to reduce the infection rate

Anmerkung/Fazit der Autoren

- topical gentamicin is superior to mupirocin in reducing the incidence of gram-negative exit-site infection.
- Gentamicin has comparable efficacy to mupirocin for gram-positive and -negative peritonitis as well as gram- positive exit-site infection

Kommentare zum Review

Hohes Verzerrungspotential der Studien

Nur ein RCT vertreten

Zhang Y et al., 2018 [9].

Efficacy and safety of ceftazidime-avibactam in the treatment of complicated intra-abdominal infections (CIAIs) and complicated urinary tract infections (CUTIs): A meta-analysis of randomized controlled trials

Fragestellung

aim of this study was to assess the efficacy and safety of ceftazidime-avibactam in the treatment of complicated intra-abdominal infections (CIAIs) and complicated urinary tract infections (CUTIs) with meta-analysis method

Methodik

Population:

- Patients with CIAIs and CUTIs

Intervention:

- ceftazidime-avibactam

Komparator:

- other antibiotics (meropenem, doripenem, imipenem; best available therapy)

Endpunkte:

- The efficacy outcomes of this meta-analysis were:
  - clinical treatment success (defined as “clinical cure”)
  - clinical response and
  - microbiological response
  - respectively assessed at the test-of-cure (TOC) visit, late-follow-up (LFU) visit and end-of-treatment (EOT) visit based on modified intent-to-treat (MITT) population, microbiologically modified intent-to-treat (mMITT) population, clinically evaluable (CE) population, microbiological evaluable (ME) population or extended microbiologically valuable (EME) population in each individual study
  - incidence of adverse events (AEs), mortality

Recherche/Suchzeitraum:

- PubMed, Embase and Cochrane Library; To identify relevant unpublished studies, we searched “ISRCTN Register” and “ClinicalTrials.gov”; handsearch
- up to 30 June 2016

Qualitätsbewertung der Studien:

- Jadad scoring system (high-quality RCTs scored 3 or more points.)

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 randomized studies were included in the meta-analysis: 5 published trials and 1 unpublished trial1, 3,259 subjects aged 18-90 years.

Charakteristika der Population:

TABLE 1 The main characteristics of the trials included.

Authors (reference)	RCT study design	Type of infection	Drug regimen		Treatment duration (days)	Time to test of cure visit (days)	Time to end of treatment visit (hours)	Time to late follow-up visit (days)	No. of patients enrolled	Study quality score
			Ceftazidime-avibactam	Comparison						
Mazuski et al.[21]	Multicentre, double-blind, phase III	CIAIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. over 2 h, plus metronidazole at 500 mg i.v. over 60 min q8h	Meropenem at 1,000 mg i.v. over 30 min q8h	8 vs. 8.3	28-35	24	42-49	1,066	5
Lucasti et al.[13]	Multicentre, double-blind, phase II	CIAIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. over 30 min, plus metronidazole at 500 mg i.v. over 1 h q8h	Meropenem at 1,000 mg i.v. q8h	5-14	14	–	28-42	204	5
Vazquez et al.[14]	Multicentre, single-blind*, phase II	CUTIs	Ceftazidime-avibactam at 500 mg/125 mg i.v. over 30 min q8h	Imipenem-cilastatin 500 mg i.v. over 30 min q6h	5 vs. 6	5-9	–	28-42	137	5
Wagenlehner et al.[22]	Multicentre, double-blind, phase III	CUTIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. over 1 h q8h	Doripenem 500 mg i.v. over 1 h q8h	7 vs. 8	21-25	–	45-52	1,033	5
Carmeli et al.[20]	Multicentre, open-label, phase III	CIAIs, CUTIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v. for CUTI, plus metronidazole at 500 mg i.v. for CIAI q8h	Best available therapy	5-21	7-10	28	FU1: 21-25 FU2: 28-32	333	3
NCT01726023	Multicentre, double-blind, phase III	CIAIs	Ceftazidime-avibactam at 2,000 mg/500 mg i.v., plus metronidazole at 500 mg i.v. q8h	Meropenem at 1,000 mg i.v. q8h	14	28-35	24	42-49	486	–

*This study was investigator and patient-blind.
CIAIs: complicated intra-abdominal infections; CUTIs: complicated urinary tract infections.

- Most subjects in ceftazidime-avibactam groups (for CIAIs in combination with metronidazole) received ceftazidime-avibactam 2,000 mg of ceftazidime and 500 mg of avibactam as intravenous infusion every 8 hours, followed by metronidazole (500 mg as intravenous infusion every 8 hours) for CIAIs.

Qualität der Studien:

- mean Jadad score of the five publication RCTs was 4.6 (rang 3-5) and four trials had a high score of 5

Studienergebnisse:

- Clinical cure success for the treatment of CIAIs (see table 2 for results)
  - Clinical cure success rate for the treatment of CIAIs in the mMITT sample (3 trials totaling 1,139 subjects): ceftazidime-avibactam group was associated with lower rate of clinical cure success, but the difference was not significant at TOC visit (p=0.11), EOT visit (p=0.44) and LFU visit (p=0.23)
  - Data on MITT patients for the treatment of CIAIs (1 trial): the clinical cure success rate of ceftazidime-avibactam group was also lower than that of the comparison group at TOC visit (1,043 patients, OR = 0.84, 95CI 0.60-1.17, p=0.30), EOT visit (1,043 patients, OR = 0.64, 95CI 0.42-0.97, p=0.04) and LFU visit (1,043 patients, OR = 0.94, 95CI 0.68-1.30, p=0.71), but the difference was not significant at TOC visit and LFU visit.
  - Significant in EOT visit in which comparison therapy group achieved more clinical cure treatment success
  - Clinical cure success rate for the treatment of CIAIs in the CE sample (2 trials): ceftazidime-avibactam group was associated with lower rate of clinical cure success, but

the difference was not significant at TOC visit (p=0.66, Table 2), EOT visit (p=0.33) and LFU visit (p=0.81)

- Data on ME patients for the treatment of CIAIs (1 trial): In both comparisons, ceftazidime-avibactam shows lower success rate than comparison group at TOC visit (212 patients, OR = 0.74, 95CI 0.24-2.27, p=0.60) and LFU visit (202 patients, OR = 0.76, 95CI 0.25-2.35, p=0.64), but at EOT visit shows higher success rate than comparison group (224 patients, OR = 1.52, 95CI 0.35-6.52, p=0.57), difference was not significant.
- Data on EME patients (1 trial): the clinical cure success rate of the ceftazidime-avibactam group was also lower than that of the comparison group at TOC visit (219 patients, OR = 0.71, 95CI 0.23-2.17, p=0.54), EOT visit (232 patients, OR = 1.44, 95CI 0.34-6.19, p=0.62) and LFU visit (209 patients, OR = 0.73, 95CI 0.24-2.24, p=0.58), but again the difference was not significant at TOC visit, EOT visit and LFU visit

- Microbiological response success for the treatment of CIAIs
  - two of the included RCTs with mMITT and EME patients
  - For mMITT patients, in total, 127 (83.0%) of the 153 patients in the ceftazidime-avibactam therapy group and 141 (86.5%) of the 163 patients in the comparison therapy group achieved microbiological response success - the ceftazidime-avibactam therapy group failed to produce a significant difference in the number of patients achieving microbiological response success at TOC visit (OR = 1.11, 95CI 0.23-5.29), EOT visit (OR = 1.68, 95CI 0.16-18.03) and LFU visit (OR = 1.12, 95CI 0.25-5.08).
  - Similar results in the EME analysis with patients with lower rate of microbiological response success in the ceftazidime-avibactam therapy group (at TOC visit, 232 patients, OR = 0.71, 95CI 0.23-2.17; at EOT visit, 246 patients, OR = 1.44, 95CI 0.34-6.19; at LFU visit, 221 patients, OR = 0.73, 95CI 0.24-2.24).
  - ME patients (1 trial): In both comparisons, ceftazidime-avibactam shows lower success rate than comparison group at TOC visit (p=0.60) and LFU visit (p=0.64), but at EOT visit shows higher success rate than comparison group (p=0.57) and the difference was not significant.
- Adverse effects (6 trials)
  - ceftazidime-avibactam was numerically higher than comparisons on incidence of AEs, but the difference was not significant (3,180 subjects, OR = 1.09, 95CI 0.94-1.25, p=0.26)
  - no significant difference in the proportions of patients who developed serious adverse events (SAEs) in the ceftazidime-avibactam groups and comparison groups (six RCTs, 3,180 subjects, OR = 1.14, 95CI 0.84- 1.54, p=0.40)
- Mortality (4 trials)
  - numerically higher mortality was found in the ceftazidime-avibactam groups, there was no significant difference in mortality between the ceftazidime-avibactam and comparison groups (2,029 patients, FEM, OR = 1.36, 95CI 0.70-2.65, p=0.37)

TABLE 2 Effect of study/patient characteristics for the treatment of CIAIs of clinical cure success and microbiological response success and for the treatment of CUTIs of clinical cure success.

	Type of infection	Treatment success by population	Patients	Analysis model	Odds ratio (95CI)	Heterogeneity (I^2, p-value)
Clinical cure success	CIAIs	mMITT-TOC	1,139	FEM	0.77 (0.56-1.06)	21%, 0.11
		mMITT-EOT	1,139	REM	0.74 (0.35-1.58)	54%, 0.44
		mMITT-LFU	1,139	FEM	0.82 (0.60-1.13)	21%, 0.23
		MITT-TOC	1,043	–	0.84 (0.60-1.17)	–, 0.30
		MITT-EOT	1,043	–	0.64 (0.42-0.97)	–, 0.04
		MITT-LFU	1,043	–	0.94 (0.68-1.30)	–, 0.71
		CE-TOC	1,187	FEM	0.91 (0.59-1.41)	0%, 0.66
		CE-EOT	1,212	FEM	0.78 (0.47-1.29)	13%, 0.33
		CE-LFU	1,173	FEM	0.95 (0.64-1.43)	0%, 0.81
		ME-TOC	212	–	0.74 (0.24-2.27)	–, 0.60
		ME-EOT	224	–	1.52 (0.35-6.52)	–, 0.57
		ME-LFU	202	–	0.76 (0.25-2.35)	–, 0.64
		EME-TOC	219	–	0.71 (0.23-2.17)	–, 0.54
		EME-EOT	232	–	1.44 (0.34-6.19)	–, 0.62
		EME-LFU	209	–	0.73 (0.24-2.24)	–, 0.58
Microbiological response success	CIAIs	mMITT-TOC	316	REM	1.11 (0.23-5.29)	61%, 0.89
		mMITT-EOT	316	REM	1.68 (0.16-18.03)	73%, 0.67
		mMITT-LFU	316	REM	1.12 (0.25-5.08)	59%, 0.88
		ME-TOC	212	–	0.74 (0.24-2.27)	–, 0.60
		ME-EOT	224	–	1.52 (0.35-6.52)	–, 0.57
		ME-LFU	202	–	0.76 (0.25-2.35)	–, 0.64
		EME-TOC	232	–	0.71 (0.23-2.17)	–, 0.54
		EME-EOT	246	–	1.44 (0.34-6.19)	–, 0.62
		EME-LFU	221	–	0.73 (0.24-2.24)	–, 0.58
Clinical cure success	CUTIs	mMITT-TOC	281	–	0.68 (0.27-1.72)	–, 0.42
		mMITT-EOT	281	–	0.52 (0.05-5.82)	–, 0.60
		mMITT-LFU	562	REM	0.96 (0.59-1.58)	0%, 0.88

"–" shows that data in this study was provided only in one trial.

CIAIs: complicated intra-abdominal infections; CUTIs: complicated urinary tract infections; MITT: modified intent-to-treat; mMITT: microbiologically modified intent-to-treat; TOC: test-of-cure; LFU: late-follow-up; EOT: end-of-treatment; ME: microbiological evaluable; CE: clinically evaluable; EME: extended microbiologically valuable; FEM: fixed-effect model; REM: random-effects model.

Anmerkung/Fazit der Autoren

- results suggest that ceftazidime-avibactam is as effective as comparison antibiotics for the treatment of patients with CUTIs and CIAIs
- ceftazidime-avibactam shows comparable efficacy in clinical cure and microbiological response compared with meropenem and best available therapy for CIAIs on mMITT, ME and EME populations at the TOC visit, EOT visit and LFU visit
- no significant difference in the numbers of AEs, SAEs and mortality between patients treated with ceftazidime-avibactam and the comparison drugs
- In conclusion, ceftazidime-avibactam as a potential alternative to carbapenems for treating CUTIs and CIAIs was effective and comparable to those of ceftazidime, metronidazole, meropenem and best available therapy

Kommentare zum Review

Gute Studienqualität

3.4 Leitlinien

Leifeld L et al., 2013 [3].

Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) und der Deutschen Gesellschaft für Allgemein- und Viszeralchirurgie (DGAV) ggf. Organisation

S2k Leitlinie Divertikelkrankheit / Divertikulitis (AWMF Registernummer 021/20; gültig bis 31.12.2018)

Leitlinienorganisation/Fragestellung

Ziel der Leitlinie ist eine Zusammenfassung und Bewertung des aktuellen Erkenntnisstands zur Divertikelkrankheit und der Aussprache von Empfehlungen zur Diagnostik und Therapie der Erkrankung.

Methodik

Grundlage der Leitlinie

das aktuelle Wissen zur Divertikelkrankheit / Divertikulitis interdisziplinär zu erarbeiten und zu bewerten und nun erstmals eine Leitlinie zu entwickeln, die die gegenwärtigen Erkenntnisse zusammenfasst und Handlungsvorschläge zum Umgang mit Betroffenen gibt.

Recherche/Suchzeitraum:

- systematische Literatursuche: Pubmed/Medline
- Suchzeitraum vom 1.9.1998 bis zum Tag der Leitlinienkonferenz am 16.März 2013; Literatur bis zum 1.9.1998 war in der EAES Konsensus Konferenz [9] erfasst worden und wurde hiervon übernommen.
- Zusätzlich wurden alle Arbeiten berücksichtigt, die die 2012 erschienene dänische Leitlinie ausgewählt hatte [10], mit deren Leitung bzgl. ihres Suchalgorithmus ebenfalls Kontakt aufgenommen worden war.

LoE/GoR

Starker Konsens	Zustimmung >95% der Teilnehmer
Konsens	Zustimmung >75 – 95% der Teilnehmer
Mehrheitliche Zustimmung	Zustimmung >50 – 75% der Teilnehmer
Kein Konsens	Zustimmung < 50% der Teilnehmer

Tabelle 4 Konsensusstärken

Formulierung	**Empfehlungsstärke**
„Soll“	Starke Empfehlung
„Sollte“	Empfehlung
„Kann“	Offene Empfehlung
„Sollte nicht“	Negativempfehlung
„Soll nicht“	Starke Negativempfehlung

Tabelle 5 Nomenklatur der Empfehlungsstärken

Sonstige methodische Hinweise

- Es gab eine strukturierte Konsensfindung (über Portal Leitlinienentwicklung, DELPHI-Verfahren)

  6 inhaltliche Arbeitsgruppen

Empfehlung 1 (Empfehlungsgrad: Empfehlung)

Statement 5.3

Eine Antibiotikatherapie einer akuten unkomplizierten linksseitigen Divertikulitis sollte bei Patienten mit Risikoindikatoren für einen komplizierten Verlauf durchgeführt werden.

Konsensusstärke: Konsens, Empfehlungsstärke: Empfehlung

Kommentar zu Statements 5.2 und 5.3

Risikoindikatoren für einen komplizierten Verlauf sind arterielle Hypertonie, chronische Nierenerkrankungen, Immunsuppression, allergische Disposition (siehe Kommentar zu Statement 2.10).

Eine randomisierte multizentrische Studie mit 623 Patienten mit CT-gesicherter unkomplizierte linksseitiger Divertikulitis zeigte keine statistisch signifikanten Unterschiede in der Komplikationsrate (Perforation, Notwendigkeit Resektion, Dauer Krankenhausaufenthaltes) während des Krankenhausaufenthaltes sowie der Wiederaufnahme wegen Divertikulitsrezidiv beim 1- Jahres-Follow-up in der Gruppe ohne Antibiotika im Vergleich zur Antibiotika-Gruppe. Die Abszessrate war in der Gruppe ohne Antibiotika im statistischen Trend höher (1% vs. 0%; p=0.08). Die Studie hat einige methodische Schwächen: Die Antibiotikatherapie (Art des Medikamentes, Applikationsweg) war nicht standardisiert. Das CRP bei Aufnahme war in der Antibiotikagruppe im statistischen Trend höher (100 vs. 90 mg%; p=0.07). Die Komorbiditäten wurden nicht mittels eines validierten Komorbiditätsindex erfasst und basierten auf den Daten der chirurgischen Krankenakte. Einige Ausschlusskriterien (z. B. Sepsis) waren unzureichend definiert [296].

Zwei retrospektive Fall-Kontrollstudien mit 191 und 311 Patienten fanden ebenfalls keine Unterschiede in der Häufigkeit von Komplikationen und eines Divertikulitisrezidivs bei Patienten mit milder Divertikulitis (nach Ambrosetti Kriterien), welche mit und ohne Antibiotika behandelt wurden [297,298].

Eine kontrollierte randomisierte Studie mit 123 Patienten zeigte keine Unterschiede zwischen einer 4- und 7-tägigen intravenösen (Ertapenem) Antibiotikatherapie in der Krankenhausverweildauer und der klinischen Erfolgsrate [299].

Die Empfehlung zur Antibiotikatherapie bei Risikogruppen gründet auf Expertenkonsens.

Empfehlung 2 (Empfehlungsgrad: starke Empfehlung)

Statement 5.7

Bei der komplizierten Divertikulitis soll eine Antibiotikatherapie durchgeführt werden.

Konsensusstärke: Starker Konsens, Empfehlungsstärke: Starke Empfehlung

Kommentar zum Statement 5.7

In den aktuellen Studien zur unkomplizierten Divertikulitis der letzten Jahre sind sicher auch Patienten mit dem Stadium Hansen-Stock IIa vertreten und auch in älteren Therapiestudien der akuten Divertikulitis ist diese Patientengruppe als Untergruppe vertreten, die in den Studien jedoch nicht gesondert ausgewertet wird. Aus diesem Grund ist die Therapieempfehlung zur antibiotischen Therapie nicht durch gezielte Studien für diese Patientengruppe belegt, sondern muss aus den genannten älteren Studien [300-302] extrapoliert werden.

Es wird eine Antibiotikatherapie empfohlen, die das zu erwartende polymikrobielle Erregerspektrum erfasst. Es liegen derzeit keine Daten vor, die die Überlegenheit einer Kombinationstherapie gegenüber einer Monotherapie belegen. Bei der Applikationsart (intravenös oder oral) gibt es ebenfalls keine Evidenz, die eindeutige Präferenzen und Empfehlungen erlaubt. Die Auswahl und der Administrationsmodus der Antibiotikatherapie bedürfen einer individuellen Entscheidung, die den Allgemeinzustand und das Risikoprofil des Patienten sowie die lokale Resistenzlage berücksichtigt. In der klinischen Routine verwendete Medikamente sind Cefuroxim oder Ciprofloxacin, jeweils mit Metronidazol, Ampicillin/Sulbaktam, Piperacillin/Tazobaktam sowie Moxifloxacin.

Zu den genannten Medikamenten liegen Wirksamkeitsdaten aus randomisierten Studien zur antimikrobiellen Behandlung von komplizierten intraabdominellen Infektionen (inkl. Patienten mit Divertikulitis) vor. In diesen Studien ist das Stadium der Divertikulitis ist oft nicht genau bezeichnet. Entsprechend sind stadienabhängige Therapieergebnisse für Patienten mit Divertikulitis selten dokumentiert.

Referenzen aus Leitlinien
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Mazuski JE et al., 2017 [4].

The Surgical Infection Society (SIS)

The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection

Leitlinienorganisation/Fragestellung

- The Surgical Infection Society (SIS) developed and disseminated guidelines for the management of these infections in 1992 [1], in 2002 [2,3], and most recently in 2010 as a joint guideline with the Infectious Diseases Society of America (IDSA) [4].
- Aim to update the guidelines for the management of these infections from 2010

Methodik

Grundlage der Leitlinie

- The Surgical Infection Society (SIS) developed and disseminated guidelines for the management of these infections in 1992 [1], in 2002 [2,3], and most recently in 2010 as a joint guideline with the Infectious Diseases Society of America (IDSA) [4].
- To maintain the clinical relevance of the guideline, the SIS appointed a task force to revise the 2010 guideline
- after completion the document was subjected to external review by additional experts from the SIS, modified according to these reviews by consensus of the task force and sent to the Executive Council of the SIS for final approval.

Recherche/Suchzeitraum:

- systematic search of the Medline database using various strategies in an effort to identify all literature related to IAI published between 2007 and mid-2014.
- These publications were combined with literature published between 2000 and 2007, which had been selected from a similar search of the Medline database performed for preparation of the previous guideline
- Secondary searches to supplement the primary search when evidence was found to be lacking for examination of a specific question
- literature relevant to the topic was identified during systematic evaluations of review articles for pertinent references, including those published as part of the Cochrane Database of Systematic Reviews
- Before final review of the guideline, an additional comprehensive Medline search was performed to uncover relevant articles published between 2014 and early 2016 that had not been already identified during the previous or supplementary searches.

LoE

TABLE 1. CLASS OF EVIDENCE

A	High quality evidence	The evidence was primarily obtained from RCTs, meta-analyses of such trials, or methodologically sound epidemiologic studies. If the preponderance of evidence is based on studies that do not directly address the question being posed, the overall grade is downgraded to B or C. If there are conflicts in Class A data, the evidence grade is lowered to B or C, depending on the degree of conflict.
B	Moderate quality evidence	The evidence was obtained from lower quality prospective studies, retrospective case control studies, and large observational, cohort, or prevalence studies, and was based on clearly reliable data. If there are significant conflicts in Class B data, the evidence grade is lowered to C.
C	Weak quality evidence	The evidence was obtained from smaller observational studies, studies relying on retrospective or less reliable data, authoritative opinions expressed in reviews, or expert opinions of task force members.
None	Insufficient evidence	There was little or no relevant evidence to address a question, or the evidence reviewed was highly conflicting.

RCT = randomized controlled trial.

GoR

- based on the

GRADE (Grades of Recommendation Assessment, Development, and Evaluation) system

Table 2. Rating Scale for Recommendations

1	Strong recommendation	The task force concluded that the intervention is a desirable approach for the care of those patients to whom the question applies. This rating is generally based on moderate to high quality evidence. The conclusion is unlikely to be changed with future research. The magnitude of the effect is also sufficient to justify the recommendation. A strong recommendation was also used to describe interventions that are likely to have a significant effect on patient outcome, even if based on weak evidence. These recommendations are prefaced as "We recommend …".
2	Weak recommendation	The task force concluded that the intervention is a reasonable approach for the care of patients. Not all patients and clinicians, however, would necessarily want to follow the recommendation. A decision not to follow the recommendation is unlikely to result in a major adverse outcome. This rating was generally based on weak to moderate quality evidence. Both the magnitude of the treatment effect and its direction might be altered by future research. These recommendations are prefaced as "We suggest …".
None	No recommendation	The evidence was considered inadequate or too inconsistent to allow any meaningful conclusion to be reached.

Sonstige methodische Hinweise

- Because of the limited quantity of methodologically rigorous studies investigating key questions in the management of IAI, the task force did not undertake a detailed statistical analysis for most of these recommendations, but relied on a process of iterative consensus among task force members to develop the recommendations and their final grading.
- RCTs were selected; Quality was graded on a scale of 0–5 based on adequacy of randomization, blinding, and description of patients excluded from the study, according to the system of Jadad et al. [11].
- Quality was also assessed based on whether or not patients enrolled in the trial met the criteria for complicated IAI, as specified by IDSA criteria [12]. Discrepancies between the two reviewers were resolved by a third reviewer.

Empfehlung 1 (Empfehlungsgrad)

4. Intravenous antimicrobial agents

Many IV antimicrobial agents are potentially useful in the treatment of patients with IAI, as a supplement to source control. Specific recommendations regarding antimicrobial agents for the management of IAI include:

A. General principles

- Use antimicrobial regimens that have activity against the typical gram-negative Enterobacteriaceae, grampositive cocci, and obligate anaerobes involved in these infections (Grade 1-A).

B. Aminoglycoside-based regimens

- Do not use aminoglycoside-based regimens routinely for empiric therapy (Grade 1-B). Consider use of these agents for treatment of neonatal patients and for management of IAI because of resistant gram-negative organisms in all patients, if other agents are not suitable (Grade 2-B).

F. Carbapenems

- Use ertapenem for empiric therapy of lower-risk adults and children (Grade 1-A).
- Use doripenem for empiric therapy of adults (Grade 1-A), but reserve this agent primarily for higher-risk patients because of its broader-spectrum antimicrobial activity (Grade 2-C). Do not use doripenem for empiric therapy of children unless no other options are available (Grade 1-C).

- Use imipenem-cilastatin or meropenem for the empiric therapy of adults and children (Grade 1-A), but reserve these agents primarily for higher-risk patients because of their broader-spectrum antimicrobial activity (Grade 2-C).

H. Tigecycline

- Do not use tigecycline for empiric therapy under most circumstances (Grade 1-B). Consider use of this agent for therapy of adult patients with resistant pathogens, particularly as a component of a combination regimen, if other agents are not suitable (Grade 2-B).

I. Anti-anaerobic agents

- Use metronidazole as the preferred anti-anaerobic agent in combination regimens for empiric therapy in adults and children (Grade 1-B).
- Do not use clindamycin as an anti-anaerobic agent in combination regimens for the empiric treatment in adults and children unless metronidazole cannot be used (Grade 2-B).

J. Anti-enterococcal and anti-staphylococcal agents

- Consider use of ampicillin for empiric or pathogendirected therapy of susceptible enterococcal strains in higher-risk adults and children (Grade 2-B).

Empfehlung 2 (Empfehlungsgrad)

6. Selection of empiric antimicrobial therapy for adult patients with CA-IAI

A. Lower-risk patients with CA-IAI

- Use cefotaxime or ceftriaxone plus metronidazole or ertapenem as the preferred agents for initial empiric therapy of lower-risk patients (Grade 1-A). Consider use of cefuroxime plus metronidazole or cefoperazonesulbactam, where available, as alternatives (Grade 2-B). Use ciprofloxacin plus metronidazole or moxifloxacin monotherapy for patients who have serious blactam allergies (Grade 1-A).

B. Higher-risk patients with CA-IAI

- Treat higher-risk patients with broader-spectrum empiric antimicrobial agents to ensure coverage of less common gram-negative pathogens potentially involved in these infections (Grade 2-C).
- Use piperacillin-tazobactam, doripenem, imipenemcilastatin, meropenem, or cefepime plus metronidazole as the preferred agents for initial empiric therapy of higher-risk patients (Grade 2-A). Consider use of ceftazidime plus metronidazole as an alternative regimen for these patients (Grade 2-B).
- Consider use of added ampicillin or vancomycin for empiric anti-enterococcal treatment in higher-risk patients if the patient is not being treated with piperacillintazobactam or imipenem-cilastatin (Grade 2-B).
- Do not use antifungal agents routinely for empiric therapy of higher-risk patients (Grade 1-B). Consider use of antifungal agents for empiric therapy of critically ill patients with an upper gastrointestinal source (Grade 2-B).

Empfehlung 3 (Empfehlungsgrad)

7. Selection of empiric antimicrobial therapy for adult patients with HA-IAI

Because patients with HA-IAI are at risk for infection from resistant organisms, additional antimicrobial agents may lessen the risk of inadequate initial therapy and subsequent treatment failure. The recommendations include:

A. General approach

- Assess patients with respect to their separate risks of infection from Enterococcus spp., MRSA, resistant gram-negative bacilli, and Candida spp. (Grade 2-B).
- Use the broader-spectrum agents recommended for higher-risk patients with CA-IAI for initial empiric therapy of patients with HA-IAI. Consider addition of other empiric agents based on the patient's risk for an infection from Enterococcus spp., MRSA, resistant gram-negative bacilli, and Candida spp. (Grade 2-B).

B. Anti-enterococcal therapy

- Identify patients with HA-IAI who have post-operative infections, recent exposure to broad-spectrum antimicrobial therapy, signs of severe sepsis or septic shock, or known to be colonized with VRE as at risk for infection with Enterococcus spp. (Grade 2-B).
- Consider use of vancomycin or teicoplanin for empiric therapy of HA-IAI in patients at risk for infection from Enterococcus spp. Consider use of linezolid or daptomycin for empiric therapy of patients known to be colonized with or at high risk for infection with VRE (Grade 2-B).

C. Anti-staphylococcal therapy

- Identify patients with HA-IAI with multiple healthcare associated risk factors for MRSA colonization, including advanced age, co-morbid medical conditions, previous hospitalization or surgery, and significant recent exposure to antibiotic agents, or known to be colonized with MRSA at risk for infection due to MRSA (Grade 2-B).
- Consider use of vancomycin or teicoplanin, where available, or linezolid or daptomycin as alternatives, for empiric therapy of patients known to be colonized or at high risk for infection with MRSA (Grade 2-B).

D. Antibacterial therapy for resistant gram-negative organisms

- Identify patients who have received substantial previous broad-spectrum antimicrobial therapy, had prolonged hospitalizations, undergone multiple invasive interventions, or known to have been colonized or infected with a resistant gram-negative organism at risk for infection from a resistant gram-negative pathogen (Grade 2-B). Consult local epidemiologic data and antibiograms for assistance in selecting empiric antimicrobial therapy in patients considered at risk for infection with resistant gram-negative pathogens (Grade 2-B).
- Consider use of a broad-spectrum carbapenem, or ceftolozane-tazobactam or ceftazidime-avibactam as alternatives, for empiric therapy of patients at risk for infection with ESBL-producing Enterobacteriaceae (Grade 2-B).
- Consider use of a broad-spectrum carbapenem, with ceftazidime-avibactam as an alternative, for empiric therapy of patients at risk for infection with Amp C-β-lactamase–producing Enterobacteriaceae (Grade 2-B).
- Consider use of combinations of a carbapenem or ceftazidime-avibactam as an alternative, an aminoglycoside, a polymyxin, and/or tigecycline for empiric therapy of patients at risk for infection with carbapenem-resistant Enterobacteriaceae (Grade 2-B).

- Consider use of combinations of a b-lactam antibiotic, including ceftolozane-tazobactam, an aminoglycoside, and/or a polymyxin, for empiric therapy of patients at risk for infection with multi-drug resistant (MDR)-, extensively drug resistant (XDR)-, or pandrug resistant (PDR)-strains of P. aeruginosa (Grade 2-B). Consider use of combinations of a carbapenem, an aminoglycoside, a polymyxin, and/or tigecycline for empiric therapy of patients at risk for infection with MDR-, XDR-, or PDR-strains of Acinetobacter spp. (Grade 2-B).

Backgroundinfos aus Leitlinien: Aufgrund der Vielzahl der Literaturangaben können keine konkreten Angaben pro Empfehlung gemacht werden. Es erfolgt hiermit der Verweis auf die Originalpublikation.

Bodmann K-F et al., 2017 [5].

Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. (PEG)

S2k Leitlinie: Kalkulierte parenterale Initialtherapie bakterieller Erkrankungen bei Erwachsenen – Update 2018 (AWMF-Registernummer 082-006, gültig bis 12/2021)

Leitlinienorganisation/Fragestellung

Ziel der Leitlinie ist es, den aktuellen Kenntnisstand zu den wichtigsten Antibiotika für die kalkulierte parenterale Initialtherapie, zur Epidemiologie von Erregern und Resistenz, einschließlich medizinischer Maßnahmen zur Vermeidung einer weiteren Resistenzentwicklung, zur Pharmakokinetik und Pharmakodynamik von Antibiotika, einschließlich des therapeutischen Drug-Monitorings, zur Sicherheit und Verträglichkeit von Antibiotika und zur kalkulierten Antibiotika-Therapie bei allen wichtigen Infektionsentitäten, von den respiratorischen Infektionen über die Hals-Nasen-Ohreninfektionen, die intrabdominellen Infektionen, die gastrointestinalen Infektionen, die Infektionen der Niere und des Urogenitaltrakts, Haut-und Weichgewebeinfektionen, Knochen- und Gelenkinfektionen bis zur Sepsis, zur bakteriellen Endokarditis und der bakteriellen Meningitis sowie zu speziellen Situationen wie der Antibiotikatherapie des alten Menschen und der Therapie von Infektionen durch multiresistente Gramnegative Erreger auf Basis der wissenschaftlichen Evidenz zusammenzufassen, im Experten-Konsens zu bewerten und daraus Therapieempfehlungen für die Praxis zu geben.

Methodik

Grundlage der Leitlinie

- Bei der vorliegenden Leitlinie handelt es sich um eine Aktualisierung der „Empfehlungen zur kalkulierten parenteralen Initialtherapie bakterieller Erkrankungen bei Erwachsenen“ aus dem Jahr 2010.
- Im Auftrag des Vorstands der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. (PEG), die als Herausgeber der Leitlinie fungiert, wurde im Jahr 2014 die Aktualisierung der „PEG-Empfehlungen“ aus dem Jahr 2010 begonnen.
- Erstellt 12/2017; gülitg bis 12/2021

Recherche/Suchzeitraum:

- Die relevante Literatur wurde von den Arbeitsgruppen in den medizinischen Datenbanken Pubmed und Embase sowie im Leitlinienportal der AWMF recherchiert.
- Ursprünglich war festgelegt worden, bis April 2016 veröffentlichte Literatur zu berücksichtigen. In wichtigen Fällen wurde auch Literatur bis Anfang 2017 einbezogen.
- Eine systematische Literaturrecherche nach festgelegten Schlüsselwörtern fand nicht statt, ebenso keine strukturierte Bewertung der Evidenz.

LoE / GoR

Tab. 1.1 Empfehlungsgrade

A Hoher Empfehlungsgrad, gilt als allgemein akzeptierte Empfehlung
B Mittlerer Empfehlungsgrad
C Niedriger Empfehlungsgrad

Sonstige methodische Hinweise

- Keine Bewertung des Level of evidence (Qualität der Evidenz)

Empfehlung 1 (Empfehlungsgrad EG)

- Primäre Peritonits

Tab. 7.1: Therapieempfehlungen zur Initialtherapie der verschiedenen Formen der primären Peritonitis

Diagnose	Häufige Erreger	Therapie-Empfehlung	Tagesdosis	Therapiedauer	EG
Juvenile Peritonitis	A-Streptokokken Pneumokokken *H. influenzae*	Ampicillin/Sulbactam Amoxicillin/Clavulansäure Cefuroxim	3 x 3 g 3 x 2,2 g 3 x 1,5 g	7 Tage	B B B
Peritonitis bei Leberzirrhose	*Escherichia coli* Enterokokken *Klebsiella* spp. ESBL-Bildner	Ceftriaxon Cefotaxim Piperacillin/Tazobactam s. **Tabelle 7.6**	1 x 2 g 3 x 2 g 3 x 4,5 g	7 Tage	B B B
Peritonitis bei Tbc	Mykobakterien	Kombinationstherapie nach Testung		> 6 Monate	C
Peritonitis bei CAPD	Staphylokokken *Escherichia coli* Enterokokken Andere Streptokokken Andere *Enterobacteriaceae* *Pseudomonas* spp. *Acinetobacter* spp. MRSA, VRE ESBL-Bildner *Candida* spp.	Cefuroxim Cefotaxim Ceftriaxon +/- Ciprofloxacin s. **Tabelle 7.6**	3 x 1,5 g 3 x 2 g 1 x 2 g +- 2 x 0,4 g	7-10 Tage	B B C

Empfehlung 2 (Empfehlungsgrad EG)

- Sekundäre und Teriäre Peritonitis

Tab. 7.3: Empfehlungen zur Initialtherapie der verschiedenen Formen der sekundären und tertiären Peritonitis

Diagnose	Häufige Erreger	Therapie-Empfehlung	Tagesdosis	Therapiedauer	EG
Ambulant erworben	*Enterobacteriaceae*	Cefuroxim + Metronidazol	3x1,5g + 3x0,5g	1 Tag	A
keine Perforation	Anaerobier	Cefotaxim + Metronidazol	3x2g + 3x0,5g	(Stufe 1)	A
minimale Peritonitis	Enterokokken	Ceftriaxon + Metronidazol	1x2g + 3x0,5g		A
kreislaufstabil		Ciprofloxacin + Metronidazol	2x0,4g+3x0,5g		A
kein MRE-Risiko		Levofloxacin + Metronidazol	1x0,5g+3x0,5g		A
Bsp.: Phlegmonöse		Ampicillin/Sulbactam	3 x 3 g		A
Appendizitis		Amoxicillin/Clavulansäure	3 x 2,2 g		A
		Moxifloxacin	1 x 0,4 g		A
Ambulant erworben	*Enterobacteriaceae*	Cefuroxim + Metronidazol	3x1,5g + 3x0,5g	3 Tage	A
frische Perforation	Anaerobier	Cefotaxim + Metronidazol	3x2g + 3x0,5g	(Stufe 2)	A
lokalisierte Peritonitis	Enterokokken	Ceftriaxon + Metronidazol	1x2g + 3x0,5g		A
kreislaufstabil		Ciprofloxacin + Metronidazol	2x0,4g+3x0,5g		A
kein MRE-Risiko (Bsp.: Perforierte Cholezystitis)		Levofloxacin + Metronidazol	1x0,5g+3x0,5g		A
		Ampicillin/Sulbactam	3 x 3 g		A
		Amoxicillin/Clavulansäure	3 x 2,2 g		A
		Moxifloxacin	1 x 0,4 g		A
Ambulant erworben	*Enterobacteriaceae*	Piperacillin/Tazobactam	3 x 4,5 g	5 Tage	A
ältere Perforation	Anaerobier	Ertapenem	1 x 1-2 g	(Stufe 3)	A
diffuse Peritonitis	Enterokokken	Tigecyclin	2 x 0,05 g*		A
kreislaufstabil		Moxifloxacin	1 x 0,4 g		A
individuelles MRE-Risiko		Ceftolozan/Tazobactam + Metronidazol	3 x1,5 g + 3 x 0,5 g		B
(Bsp.: frei					

perforierte Sigamdivertikulitis)					
Nosokomial (postoperativ/ tertiär) diffuse Peritonitis kreislaufinstabil hohes MRE-Risiko (Bsp.: Nahtleckage nach Rektumresektion)	*Enterobacteriaceae* (inkl. ESBL-Bildner) Enterokokken (inkl. VRE) Anaerobier *Pseudomonas* spp. Staphylokokken (inkl. MRSA)	Tigecyclin* Meropenem (+ Linezolid) Imipenem (+ Linezolid) Ceftolozan/Tazobactam + Metronidazol (+ Linezolid) Ceftazidim/Avibactam + Metronidazol (+ Linezolid) Fosfomycin (keine Monotherapie)	2 x 0,05-0,1 g* 3x2g(+2x0,6g) 3x1g(+2x0,6g) 3 x 1,5 -3 g + 3x0,5g (+2x0,6g) 3 x 2,5 g.+ 3x0,5g (+ 2x0,6 g) 3 x 4-8 g	7-10 Tage (Stufe 4)	A A A B A B

* Aufladungsdosis erforderlich, keine Monotherapie im septischen Schock

Empfehlung 3 (Empfehlungsgrad EG)

- Nekrotisierende Pankreatitis und intraabdominelle Mykosen

Tab. 7.4: Kalkulierte Antibiotika-Therapie bei nekrotisierender Pankreatitis und intraabdominellen Mykosen

Diagnose	Häufige Erreger	Therapie-Empfehlung	Tagesdosis	Therapiedauer	EG
Nekrotisierende Pankreatitis mit infizierten Nekrosen	*Enterobacteriaceae* (inkl. ESBL-Bildner) Enterokokken (inkl. VRE) Staphylokokken Anaerobier	Imipenem Meropenem Ertapenem Tigecyclin* Piperacillin/Tazobactam Moxifloxacin	3 x 1 g 3 x 1 g 1 x 1-2 g 2 x 0,05 g* 3 x 4,5 g 1 x 0,4 g	7-10 Tage	A A A B B C
Intraabdominelle Mykose	*Candida* spp.	Anidulafungin§ Caspofungin§ Micafungin Fluconazol§ Voriconazol§ liposomales Amphotericin B	1 x 0,1 g§ 1 x 0,05 g§ 1 x 0,1 g 1 x 0,4-0,8 g§ 2 x 0,2 g§ 1-3 mg/kg KG	≥14 Tage	A A A B B B

* Aufladungsdosis erforderlich, keine Monotherapie im septischen Schock

§ Aufladungsdosis erforderlich

Empfehlung 4 (Empfehlungsgrad)

- Intraabdominelle Infektionen mit v.a. resistenten Erregern

Tab. 7.6: Kalkulierte Antibiotika-Therapie bei intraabdomineller Infektion mit V. a. resistentem Erreger

Erreger	Antibiotikum	Empfehlungsgrad
MRSA	Tigecyclin	A
	Linezolid+	A
	Vancomycin+	A
VRE	Tigecyclin	A
	Linezolid+	A
ESBL-Bildner	Tigecyclin	A
(*E. coli*, *Klebsiella* spp.)	Ceftolozan/Tazobactam	A
	Ceftazidim/Avibactam	A
	Imipenem	A
	Meropenem	A
	Ertapenem	A
	Fosfomycin (keine Monotherapie)	B
Acinetobacter spp.	Colistin	A
	Tigecyclin	A
	Sulbactam	A
Carbapenem-resistente	Tigecyclin	A
Enterobacteriaceae	Colistin	A
	Ceftazidim/Avibactam	A
	Meropenem (Hochdosis)	A
Pseudomonas spp.	Imipenem, Meropenem	A
	Piperacillin/Tazobactam	A
	Cefepim	A
	Gentamicin, Amikacin ◊	B
	Ciprofloxacin*, Levofloxacin*	A
	Ceftolozan/Tazobactam	A
	Ceftazidim/Avibactam	B

MRSA=Methicillin resistenter *S. aureus*, VRE= Vancomycin-resistenter *E. faecium* bzw. *E. faecalis*, ESBL= „Extended-Spektrum" Beta-Lactamase-bildende Spezies, + = Kombination mit Antibiotikum zur Erfassung gramnegativer und anaerober Spezies erforderlich ◊=keine Monotherapie;*Einsatz nur sinnvoll bei lokalen Empfindlichkeitsraten > 90 %

Referenzen aus Leitlinien: Aufgrund der zahlreichen Literaturangaben wird auf die Orginal AWMF Leitlinie S. 203-209 verwiesen

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Es liegen keine ergänzenden Dokumente anderer Organisationen zu möglichen Komparatoren vor.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 23.11.2018

#	Suchfrage
#1	[mh “Intraabdominal Infections”]
#2	[mh “Abdominal abscess”]
#3	[mh “Enterocolitis, Neutropenic“]
#4	((intra-abdominal or intraabdominal) NEAR infection*):ti,ab,kw
#5	((Subdiaphragmatic OR subphrenic OR abdominal OR intraabdominal OR intra-abdominal) AND (abscess)):ti,ab,kw
#6	peritonitis:ti,ab,kw
#7	Appendicitis:ti,ab,kw
#8	(diverticulitis or (diverticular disease*)):ti,ab,kw
#9	(Typhlitis or (Neutropenic Enterocolitis)):ti,ab,kw
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	#10 with Cochrane Library publication date from Nov 2013 to Nov 2018, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 23.11.2018

#	Suchfrage
#1	Intraabdominal Infections[mh]
#2	Abdominal abscess[mh]
#3	Enterocolitis, Neutropenic[mh]
#4	(intra-abdominal[tiab] OR intraabdominal[tiab]) AND infection*[tiab]
#5	((Subdiaphragmatic[tiab] OR subphrenic[tiab] OR abdominal[tiab] OR intraabdominal[tiab] OR intra-abdominal[tiab]) AND (abscess[tiab]))
#6	Peritonitis[tiab]
#7	Appendicitis[tiab]
#8	diverticulitis[tiab] OR "diverticular disease*"[tiab] OR sigmadiverticulitis[tiab]
#9	Typhlitis[tiab] OR "Neutropenic Enterocolitis"[tiab]
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	(#10) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
#12	(#10) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR

#	Suchfrage
	(((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))) Filters: Publication date from 2013/11/01

Leitlinien in Medline (PubMed) am 23.11.2018

#	Suchfrage
#1	Intraabdominal Infections[mh]
#2	Abdominal abscess[mh]
#3	Enterocolitis, Neutropenic[mh]
#4	(intra-abdominal[tiab] OR intraabdominal[tiab]) AND infection*[tiab]
#5	((Subdiaphragmatic[tiab] OR subphrenic[tiab] OR abdominal[tiab] OR intraabdominal[tiab] OR intra-abdominal[tiab]) AND (abscess[tiab]))
#6	Peritonitis[tiab]
#7	Appendicitis[tiab]
#8	diverticulitis[tiab] OR "diverticular disease*"[tiab] OR sigmadiverticulitis[tiab]
#9	Typhlitis[tiab] OR "Neutropenic Enterocolitis"[tiab]
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
#12	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti]) Filters: Publication date from 2013/11/01

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