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 [komplizierte Harnwegsinfektionen]	
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 Harnwegsinfektionen
Doxycyclin J01AA02 Doxy-CT®	Doxycyclin ist angezeigt bei Infektionen, die durch gegen Doxycyclin-empfindliche Krankheitserreger verursacht sind, insbesondere bei: […] • Infektionen des Urogenitaltrakts […] – Harnwegsinfektionen (nur bei nachgewiesener Empfindlichkeit der Erreger) […] Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Doxycyclin zu berücksichtigen.
Tetracyclin J01AA07 Tetracyclin Wolff®	Durch Tetracyclin-empfindliche Erreger ausgelöste Infektionen […] – des Urogenitaltraktes (z. B. Harnwegsinfektionen, nichtgonorrhoische Urethritis durch Chlamydia trachomatis oder Ureaplasma urealyticum, Granuloma inguinale sowie bei Kontraindikation von Penicillin unkomplizierte Gonorrhöe und Syphilis), […] National und international anerkannte Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Tetracyclin Wolff 250 zu berücksichtigen.
Ampicillin J01CA01 Ampicillin-ratiopharm®	Behandlung von Infektionen, die durch Ampicillin-empfindliche Erreger (siehe Abschnitt 5.1) verursacht werden und einer oralen Therapie zugänglich sind. Infektionen […] • der Nieren und ableitenden Harnwege […] Bei schweren Krankheitsbildern ist die parenterale der oralen Therapie vorzuziehen. Die allgemein anerkannten Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Ampicillin zu berücksichtigen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Amoxicillin J01CA04 Amoxicillin Heumann®	Zur Behandlung von akuten und chronischen Infektionen unterschiedlicher Lokalisation und Intensität, die durch Betalaktamasenegative, Amoxicillin-empfindliche (bzw. Ampicillin-empfindliche), Gram-positive und Gram-negative Krankheitserreger verursacht werden und einer oralen Therapie zugänglich sind: […] • Infektionen der Nieren und der ableitenden Harnwege […] National und international anerkannte Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Amoxicillin Heumann 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 Harnwegsinfektionen (einschließlich Pyelonephritis) […] Die offiziellen Leitlinien für den angemessenen Gebrauch von antibakteriellen Wirkstoffen sind zu berücksichtigen.
Sultamicillin J01CR04 Sultamicillin-ratiopharm®	Sultamicillin-ratiopharm® 375 mg Filmtabletten sind geeignet zur Behandlung von Infektionen, die durch Sultamicillin-empfindliche Erreger verursacht werden, z. B. […] — Infektionen der Nieren und der ableitenden Harnwege wie Urozystitis und Pyelonephritis […] Ferner ist Sultamicillin-ratiopharm® 375 mg Filmtabletten bei Patienten, die einer Nachbehandlung mit Sultamicillin im Anschluss an eine intravenöse oder intramuskuläre Therapie mit Sulbactam/Ampicillin bedürfen, indiziert. Die offiziellen Richtlinien für den angemessenen Gebrauch von Antibiotika sind zu beachten.
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 Harnwegsinfektionen (einschließlich Pyelonephritis) […] Offizielle Empfehlungen für den angemessenen Gebrauch von antibakteriellen Wirkstoffen sollten berücksichtigt werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ampicillin/ Sulbactam J01CR21 Unacid®	[…] Unacid ist geeignet zur Behandlung von Infektionen, die durch Sulbactam-/ Ampicillin-empfindliche Erreger verursacht sind, z. B. Infektionen […] – der Nieren und der ableitenden Harnwege, […]
Cefadroxil J01DB05 GrünCef®	GRÜNCEF ist angezeigt bei Erwachsenen und Kindern ab 6 Jahren zur Behandlung durch cefadroxilempfindliche Keime verursachter Infektionen […] – der Harn- und Geschlechtsorgane […] Die offiziellen Richtlinien für den angemessenen Gebrauch von Antibiotika sind zu berücksichtigen.
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). […] • Komplizierte Harnwegsinfektionen einschließlich Pyelonephritis. […] 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 der Niere und ableitenden Harnwege, […] Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Claforan zu berücksichtigen.
Ceftazidim J01DD02 Ceftazidim Kabi®	Ceftazidim wird angewendet bei Erwachsenen und Kindern inklusive Neugeborenen (von Geburt an) bei Infektionen die untenstehend aufgelistet sind. […] – Komplizierte Harnwegsinfektionen […] 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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ceftriaxon J01DD04 Rocephin®	Rocephin wird angewendet zur Behandlung der nachfolgend genannten Infektionen bei Erwachsenen und Kindern, einschließlich Neugeborenen (ab der Geburt): […] Komplizierte Harnwegsinfektionen (einschließlich Pyelonephritis) […] 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.
Cefixim J01DD08 Cefixdura®	Zur Behandlung von akuten und chronischen Infektionen unterschiedlichen Schweregrades, die durch Cefixim-empfindliche Krankheitserreger verursacht werden und einer oralen Therapie zugänglich sind: […] Infektionen der Niere und der ableitenden Harnwege […] Die allgemein anerkannten Empfehlungen für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Cefixdura zu berücksichtigen.
Cefpodoxim J01DD13 Cefpodoxim-ratiopharm®	Cefpodoxim-ratiopharm® ist angezeigt zur Behandlung von Infektionen, die durch Cefpodoxim-empfindliche Erreger verursacht werden und einer oralen Therapie zugänglich sind. […] Infektionen der Harnwege: — Infektionen der oberen Harnwege (Nierenbeckenentzündung) — Infektionen der unteren Harnwege (unkomplizierte Blasenentzündung der Frau) […] Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Cefpodoxim-ratiopharm® zu berücksichtigen.
Ceftazidim/ Avibactam J01DD52 Zavicefta®	Zavicefta wird angewendet bei Erwachsenen zur Behandlung der folgenden Infektionen (siehe Abschnitte 4.4 und 5.1): […] • Komplizierte Harnwegsinfektionen (cUTI), einschließlich Pyelonephritis […] 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: […] – schwere Infektionen der Harnwege; […]

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 Infektionen der Nieren und ableitenden Harnwege, […] Für den angemessenen Gebrauch von Antibiotika sollten die offiziellen Leitlinien 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 Infektionen der Harnwege […] Die offiziellen nationalen Leitlinien zur adäquaten Anwendung von Antibiotika sind zu beachten.
Cotrimoxazol J01EE01 Cotrim-ratiopharm®	Infektionen mit Krankheitserregern, die gegen Cotrimoxazol empfindlich sind: […] – Infektionen der Nieren und der ableitenden Harnwege […] Cotrim-ratiopharm® [Ampullen SF 480 mg/ 5 ml] ist indiziert bei Erwachsenen, Jugendlichen, Kindern und Säuglingen ab 6 Wochen. Die allgemein anerkannten Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind zu berücksichtigen.
Roxithromycin J01FA06 Roxithromycin Heumann®	Zur Behandlung von Infektionen durch Roxithromycin-empfindliche Krankheitserreger, die einer oralen Therapie zugänglich sind (siehe Abschnitt 5.1). […] – Infektionen des Urogenitaltraktes: Urethritis, Cervicitis, Cervicovaginitis, verursacht durch Chlamydien und Mycoplasmen. Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Roxithromycin Heumann zu berücksichtigen.

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:[…] • komplizierten und rezidivierenden Infektionen der Nieren und der ableitenden Harnwege […] 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: […] – Infektionen der Harn- und Geschlechtsorgane (Gonorrhoe und Syphilis gehören nicht zum Anwendungsbereich)
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: […] – komplizierte und rezidivierende Harnwegsinfektionen, […] 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 der unteren und oberen Harnwege […] 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 […] • Harnwegsinfektionen […]
Norfloxacin J01MA06 Norfloxacin AL	Norfloxacin AL 400 mg ist zur Therapie folgender Infektionen indiziert, die durch Norfloxacin-empfindliche Bakterien hervorgerufen werden (siehe Abschnitte 4.2 und 5.1): • Komplizierte als auch unkomplizierte, akute oder chronische Infektionen der oberen und unteren Harnwege (außer komplizierte Pyelonephritis), • Harnwegsinfektionen im Zusammenhang mit chirurgischen urologischen Eingriffen oder Nephrolithiasis. Zu beachten sind die jeweils geltenden Richtlinien, z.B. die Empfehlungen der nationalen Fachgesellschaften hinsichtlich der sachgerechten Anwendung und Verordnung von Antibiotika.
Levofloxacin J01MA12 Tavanic®	Tavanic ist angezeigt bei Erwachsenen zur Behandlung der folgenden Infektionen (siehe Abschnitte 4.4 und 5.1): […] – Pyelonephritis und komplizierte Harnwegsinfektionen (siehe Abschnitt 4.4), […] Die offiziellen Empfehlungen zum angemessenen Gebrauch von Antibiotika sollten beachtet werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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): […] • komplizierte Harnwegsinfektionen, […] 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.
Nitrofurantoin J01XE01 Nifurantin®	Nifurantin® 50 mg ist zur Behandlung der folgenden Infektion, die durch Nitrofurantoin-empfindliche Erreger verursacht werden, angezeigt (siehe Abschnitte 4.3, 4.4 und 5.1): […] Für die folgenden Anwendungen darf Nifurantin ® 50 mg nur verabreicht werden, wenn risikoärmere Antibiotika oder Chemotherapeutika nicht einsetzbar sind (siehe Abschnitte 4.3 und 4.4): – Suppressivtherapie chronisch-obstruktiver Harnwegsinfektionen bei Patienten mit angeborener oder erworbener Abflussbehinderung der Harnwege. – Reinfektionsprophylaxe chronisch rezidivierender aszendierender Harnwegsinfektionen. Die offiziellen Richtlinien zum angemessenen Einsatz antibakteriell wirksamer Substanzen sind zu beachten.
Fosfomycin J01XX01 Infectofos®	INFECTOFOS ist zur Behandlung der folgenden akuten und chronischen Infektionen indiziert, wenn diese durch Fosfomycin-empfindliche Erreger verursacht werden (s. Abschnitt 5.1). INFECTOFOS ist insbesondere dann indiziert, wenn Penicilline und Cephalosporine nicht gegeben werden können bzw. deren Wirksamkeit auf Grund der Lokalisation der Infektion und der Empfindlichkeit der Erreger nicht ausreicht. INFECTOFOS wird in der Regel im Rahmen einer Kombinationstherapie, insbesondere bei der Behandlung multiresistenter Keime, verabreicht (s. Abschnitt 4.5). […] • Infektionen der Harnwege […] Die allgemein anerkannten Empfehlungen für den angemessenen Gebrauch von antibakteriellen Substanzen sind bei der Anwendung von INFECTOFOS zu berücksichtigen.

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-233c (Ceftolozan/Tazobactam)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	18. Dezember 2018

Inhaltsverzeichnis

Abkürzungsverzeichnis 3
1 Indikation 4
2 Systematische Recherche....4
3 Ergebnisse....5
3.1 G-BA Beschlüsse/IQWiG Berichte 5
3.2 Cochrane Reviews 5
3.3 Systematische Reviews....5
3.4 Leitlinien....17
4 Detaillierte Darstellung der Recherchestrategie 29
Referenzen 30

Abkürzungsverzeichnis

3GCs	Third-generation cephalosporins
APN	Acute pyelonephritis
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BL/ BLIs	Novel β-lactam/β-lactamase inhibitors
CE	Clinically evaluable population,
cIAI	Complicated intraabdominal infections
cUTI	Complicated urinary tract infections
EME	Extended microbiologically evaluable population
EOT	End of Treatment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
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
OR	Odds Ratio
RR	Relative Risk
TMP	Trimethoprim
TOC	Test-of-cure
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zur Behandlung komplizierter Harnwegsinfektionen bei Erwachsenen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *komplizierter Harnwegsinfekt* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 16.11.2018 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 353 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 6 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten G-BA Beschlüsse/IQWiG Berichte identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Chen M et al., 2018 [3].

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 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 included patients with cIAI, and novel BL/BLIs were compared with meropenem in all patients.
- 3 studies 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.

Studienergebnisse:

- Clinical treatment success
  - the cUTI subgroup revealed that patients treated with novel BL/BLIs appeared to have better clinical treatment success (2 RCTs, OR = 2.14, 95% CI = (1.06, 4.31), p = 0.03) (Figure 3).
- Microbiological treatment success
  - In another subgroup analysis including patients with cUTI, there was significantly higher microbiological treatment success detected in novel BL/BLIs group (3 RCTs, 1340 patients, OR = 1.70, 95%CI = (1.29, 2.25), p = 0.0002) (Figure 5).
- Mortality
  - Subgroup analysis - patients with cUTI: no significant difference detected between novel BL/BLIs and comparator regimens
- Adverse events and serious adverse events
  - Keine Subgruppenanalyse

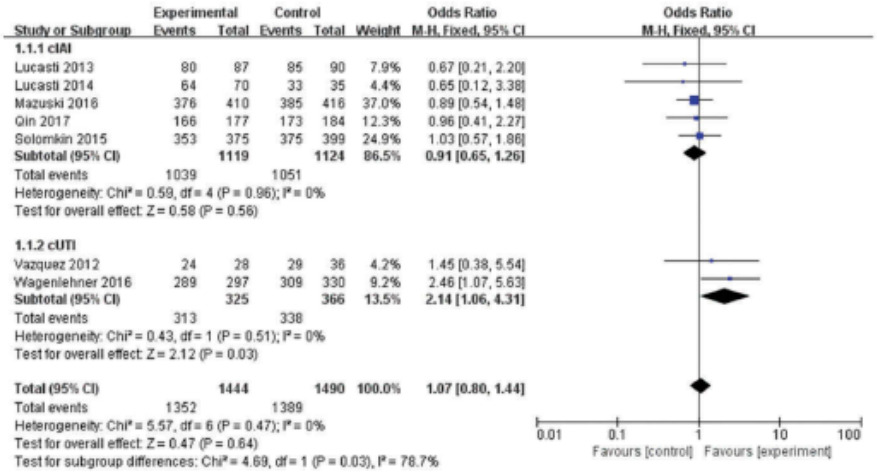


Figure 3. Forest plot of clinical treatment success at the TOC visit for the clinically evaluable (CE) population.

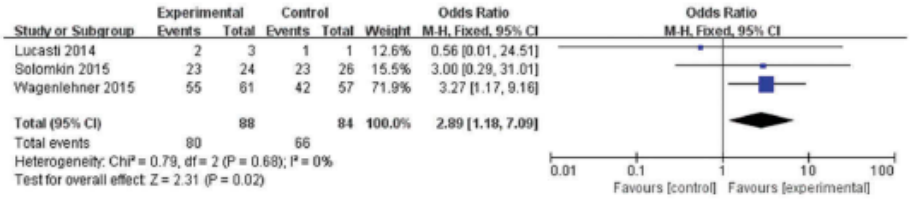


Figure 4. Forest plot of clinical treatment success at the TOC visit for patients with baseline ESBL-producing *Enterobacteriaceae* infection.

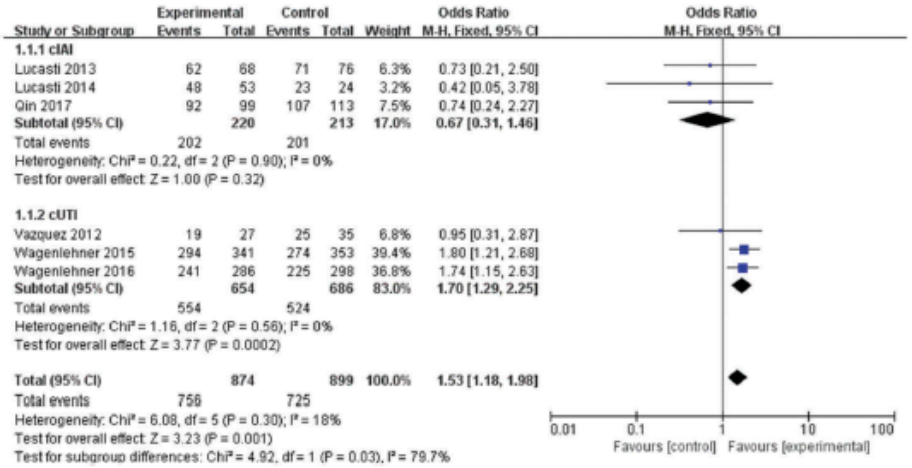


Figure 5. Forest plot of microbiological treatment success at the TOC visit for the microbiologically evaluable (ME) population.

Anmerkung/Fazit der Autoren

- we found that novBL/BLIs achieved a significant success for the treatment of cUTI in comparison with other antibiotics.

Zhang Y et al., 2018 [5].

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

to assess the efficacy and safety of ceftazidime-avibactam in the treatment of complicated intra-abdominal infections (CIAIs) and complicated urinary tract infections (CUTIs).

Methodik

Population:

- Patients with CIAIs and CUTIs

Intervention:

- ceftazidime-avibactam

Komparator:

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

Endpunkte:

- The efficacy outcomes:
  - 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
  - Analyses were 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. The MITT population consisted of patients who received at least one dose of the study drug and followed intention-to-treat principles. The mMITT population consisted of patients who met the clinical disease criteria and had ≥ 1 pathogen identified at baseline. The CE population consisted of patients who met the disease definition and had received the scheduled study drug, with sufficient information to determine clinical outcome. The ME population was a subset of the CE population who also had microbiologically documented infections. The EME population was a subset of ME population.
  - 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.[19]	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.[18]	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 (range 3-5) and four trials had a high score of 5

Studienergebnisse:

- Clinical cure success for the treatment of CUTIs (see table 2 for results)
  - Clinical cure success rate for the treatment of CUTIs on the mMITT sample was provided only in one trial. The ceftazidime-avibactam group was associated with lower rate of clinical cure success, but the difference was not significant at TOC visit, EOT visit or LFU visit (Table 2). In our meta-analysis, the study of Carmeli et al. was split because in this study the LFU visit was divided into FU1 visit (21-25 days post-therapy) and FU2 visit (28-32 days post-therapy).

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	Patients	Analysis model	Odds ratio (95CI)	Heterogeneity
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.

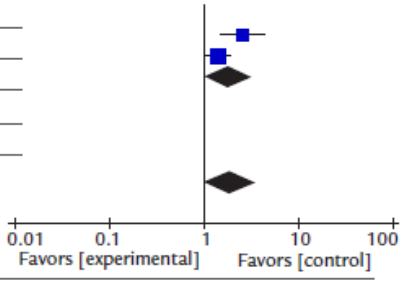
CIAIs: complicated intra-abdominal infections; CUTIs: complicated urinary tract infections; MITT: modified intent-to-treat; mMITT: microbiologically modified intent-to-treat; TOC: test-of-cure; LFU: late-follow-up; EOT: end-of-treatment; ME: microbiological evaluable; CE: clinically evaluable; EME: extended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

- Microbiological response success for the treatment of CUTIs (see Figure 1 A-I for results)
  - mMITT population: Data on the microbiological response success for the treatment of CUTIs were provided in two of the included RCTs with mMITT patients. The ceftazidime-avibactam group was associated with higher rate of microbiological response success, but the difference was not significant at TOC visit and EOT visit (Figure 1B). In total, 470 (69.0%) of the 681 patients in the ceftazidime-avibactam therapy group and 405 (58.6%) of the 691 patients in the comparison therapy group achieved microbiological response success at LFU visit. The ceftazidime-avibactam therapy group was associated with significantly more patients achieving microbiological response success at LFU visit (OR = 1.58, 95CI 1.26-1.97, p<0.0001, Figure 1C).
  - MITT population: Data on the microbiological response success for the treatment of CUTIs were provided in one of the included RCTs on MITT patients. In both comparisons, ceftazidime-avibactam shows higher success rate than comparison group at TOC visit (data not shown in the figure) and LFU visit (data not shown in the figure), but at EOT visit shows lower success rate than comparison group (data not shown in the figure) and the difference was not significant.
  - ME Population: Data on the microbiological response success for the treatment of CUTIs were provided in two of the included RCTs on ME patients. In all, 260 (83.1%) of the 313 patients in the ceftazidime-avibactam therapy group and 250 (75.1%) of the 333 patients in the comparison therapy group achieved microbiological response success at TOC visit. The ceftazidime-avibactam therapy group was associated with significantly more patients achieving microbiological response success at TOC visit (OR = 1.61, 95CI 1.10-2.38, p=0.02, Figure 1D). In all, 197 (72.7%) of the 271 patients in the ceftazidime-avibactam therapy group and 184 (63.0%) of the 292 patients in the comparison therapy group achieved microbiological response success at LFU visit. The ceftazidime-avibactam therapy group was associated with significantly more patients achieving microbiological response success at LFU visit (OR = 1.56, 95CI 1.09-2.23, p=0.02, Figure 1F). The ceftazidime-avibactam group was associated with a lower rate of microbiological response success and the difference was no significant at EOT visit (Figure 1E).
  - EME population: The treatment success of two RCTs was based on EME populations. There was no significant difference in treatment success at EOT visit between patients treated with ceftazidime-avibactam and those treated with comparisons (Figure 1H). However, in EME populations, the success of ceftazidime-avibactam treatment in the CUTIs subgroup was significantly higher than that in the comparison groups at the TOC visit and LFU visit (for TOC visit, 858 patients, OR = 2.15, 95CI 1.08-4.27, p=0.03,

Figure 1G; for the LFU visit, 1,001 patients, OR = 1.75, 95CI 1.33-2.29, p<0.0001, Figure 1I).

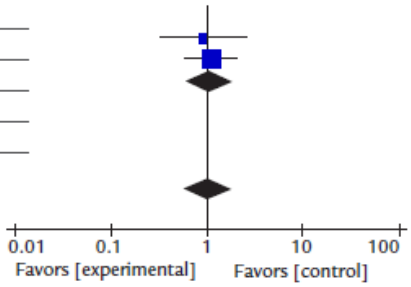
Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95CI
A mMITT-TOC						
Carmeli et al.[20]	118	144	88	137	42.8%	2.53 [1.46, 4.38]
Wagenlehner et al.[22]	299	393	291	417	57.2%	1.38 [1.01, 1.88]
Subtotal (95CI)		537		554	100.0%	1.79 [0.99, 3.22]
Total events	417		379			

Heterogeneity: Tau² = 0.13; Chi² = 3.54, df = 1 (p=0.06); I² = 72%
Test for overall effect: Z = 1.93 (p=0.05)



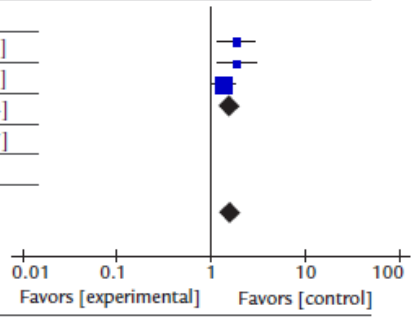
Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95CI
B mMITT-EOT						
Carmeli et al.[20]	136	144	130	137	28.5%	0.92 [0.32, 2.60]
Wagenlehner et al.[22]	374	393	395	417	71.5%	1.10 [0.58, 2.06]
Subtotal (95CI)		537		554	100.0%	1.04 [0.61, 1.79]
Total events	510		525			

Heterogeneity: Chi² = 0.08, df = 1 (p=0.77); I² = 0%
Test for overall effect: Z = 0.16 (p=0.87)



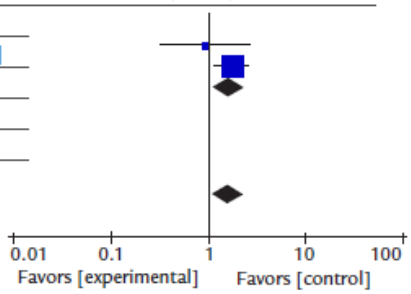
Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95CI
C mMITT-LFU						
Carmeli et al.[20]	99	144	73	137	18.8%	1.93 [1.19, 3.14]
Carmeli et al.[20]	103	144	78	137	18.3%	1.90 [1.16, 3.12]
Wagenlehner et al.[22]	268	393	254	417	62.9%	1.38 [1.03, 1.84]
Subtotal (95CI)		681		691	100.0%	1.58 [1.26, 1.97]
Total events	470		405			

Heterogeneity: Chi² = 2.06, df = 2 (p=0.36); I² = 3%
Test for overall effect: Z = 4.01 (p<0.0001)

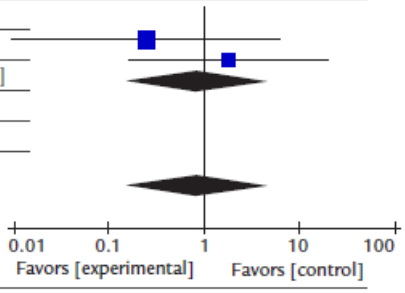


Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95CI
D ME-TOC						
Vazquez et al.[14]	19	27	25	35	15.7%	0.95 [0.31, 2.87]
Wagenlehner et al.[22]	241	286	225	298	84.3%	1.74 [1.15, 2.63]
Subtotal (95CI)		313		333	100.0%	1.61 [1.10, 2.38]
Total events	260		250			

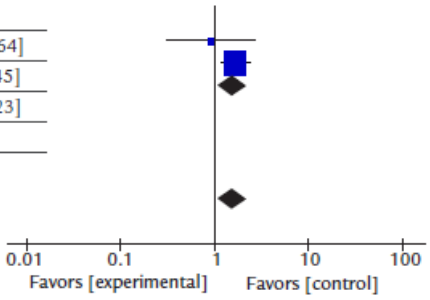
Heterogeneity: Chi² = 1.01, df = 1 (p=0.32); I² = 1%
Test for overall effect: Z = 2.43 (p=0.02)



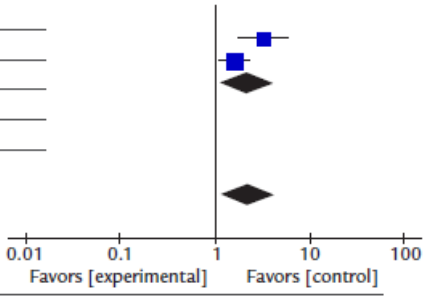
Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
E ME-EOT							
Vazquez et al.[14]	25	26	34	34	61.5%	0.25 [0.01, 6.30]	
Wagenlehner et al.[22]	324	325	359	361	38.5%	1.81 [0.16, 20.00]	
Subtotal (95CI)		351		395	100.0%	0.85 [0.15, 4.87]	
Total events	349		393				
Heterogeneity: Chi² = 0.94, df = 1 (p=0.33); I² = 0%							
Test for overall effect: Z = 0.19 (p=0.85)							



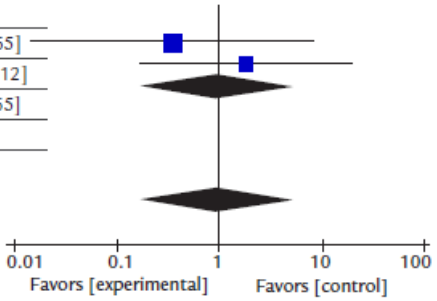
Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
F ME-LFU							
Vazquez et al.[14]	15	26	18	30	14.6%	0.91 [0.31, 2.64]	
Wagenlehner et al.[22]	182	245	166	262	85.4%	1.67 [1.14, 2.45]	
Subtotal (95CI)		271		292	100.0%	1.56 [1.09, 2.23]	
Total events	197		184				
Heterogeneity: Chi² = 1.11, df = 1 (p=0.29); I² = 10%							
Test for overall effect: Z = 2.43 (p=0.02)							



Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, random, 95CI	M-H, random, 95CI
G EME-TOC							
Carmeli et al.[20]	114	131	84	124	43.7%	3.19 [1.69, 6.02]	
Wagenlehner et al.[22]	243	292	236	311	56.3%	1.58 [1.05, 2.36]	
Subtotal (95CI)		423		435	100.0%	2.15 [1.08, 4.27]	
Total events	357		320				
Heterogeneity: Tau² = 0.18, Chi² = 3.40, df = 1 (p=0.07); I² = 71%							
Test for overall effect: Z = 2.18 (p=0.03)							



Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
H EME-EOT							
Carmeli et al.[20]	133	134	127	127	58.2%	0.35 [0.01, 8.65]	
Wagenlehner et al.[22]	335	336	369	371	41.8%	1.82 [0.16, 20.12]	
Subtotal (95CI)		470		498	100.0%	0.96 [0.16, 5.65]	
Total events	468		496				
Heterogeneity: Chi² = 0.65, df = 1 (p=0.42); I² = 0%							
Test for overall effect: Z = 0.04 (p=0.97)							



Study or subgroup	Experimental		Control			Odds ratio	Odds ratio
	Events	Total	Events	Total	Weight	M-H, fixed, 95CI	M-H, fixed, 95CI
I EME-LFU							
Carmeli et al.[20]	85	117	68	115	23.4%	1.84 [1.06, 3.18]	
Carmeli et al.[20]	98	126	75	120	21.3%	2.10 [1.20, 3.67]	
Wagenlehner et al.[22]	184	251	173	272	55.3%	1.57 [1.08, 2.28]	
Subtotal (95CI)		494		507	100.0%	1.75 [1.33, 2.29]	
Total events	367		316				
Heterogeneity: Chi² = 0.76, df = 2 (p=0.69); I² = 0%							
Test for overall effect: Z = 4.04 (p<0.0001)							

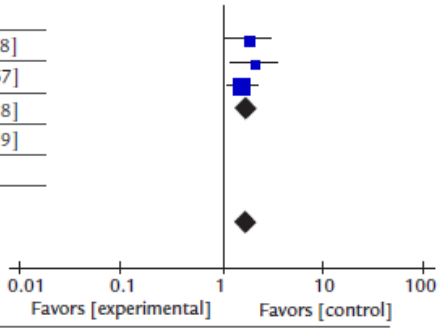


FIGURE 1 Meta-analysis of microbiological response success for the treatment of CUTIs based on mMITT populations, ME populations and EME populations: (A) microbiological response success at test-of-cure visit on mMITT populations; (B) microbiological response success at end-of-treatment visit on mMITT populations; (C) microbiological response success at late-follow-up visit on mMITT populations; (D) microbiological response success at test-of-cure visit on ME populations; (E) microbiological response success at end-of-treatment visit on ME populations; (F) microbiological response success at late-follow-up visit on ME populations; (G) microbiological response success at test-of-cure visit on EME populations; (H) microbiological response success at end-of-treatment visit on EME populations; (I) microbiological response success at late-follow-up visit on EME populations. Vertical line indicates no difference between linezolid and vancomycin. The size of each square denotes the proportion of information given by each trial. CI: confidence interval.

- Adverse effects (6 trials)
  - Keine Ergebnisse für cUTIs
- Mortality (4 trials)
  - Keine Ergebnisse für cUTIs

Anmerkung/Fazit der Autoren

- results suggest that ceftazidime-avibactam is as effective as comparison antibiotics for the treatment of patients with CUTIs and CIAIs
  - there was no significant difference in the numbers of clinical cure success between patients treated with ceftazidime-avibactam and the imipenem-cilastatin, doripenem or best available therapy for CUTIs based on mMITT populations at the TOC visit, EOT visit and LFU visit in these RCTs.
  - Ceftazidime-avibactam versus active comparison drugs demonstrated a statistically significant higher rate of microbiological response success in ME and EME populations at the TOC visit and LFU visit for the treatment of CUTIs. Similar results are presented at the LFU visit on mMITT populations for the treatment of CUTIs.

Kommentare zum Review

- In den Review von Zhong et al. [6] wurden die gleichen Studien eingeschlossen, daher wurde auf eine separate Extraktion verzichtet.

Sternbach N et al., 2018 [4].

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

Fragestellung

to assess 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 search was 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

Study ID	Type of infection	Comparator drug	Patients randomized (*n*)	Randomization[a] generation	Randomization[a] 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)
  - Among subcategories of type of infection, no statistically significant difference in mortality was demonstrated (Figure 2).

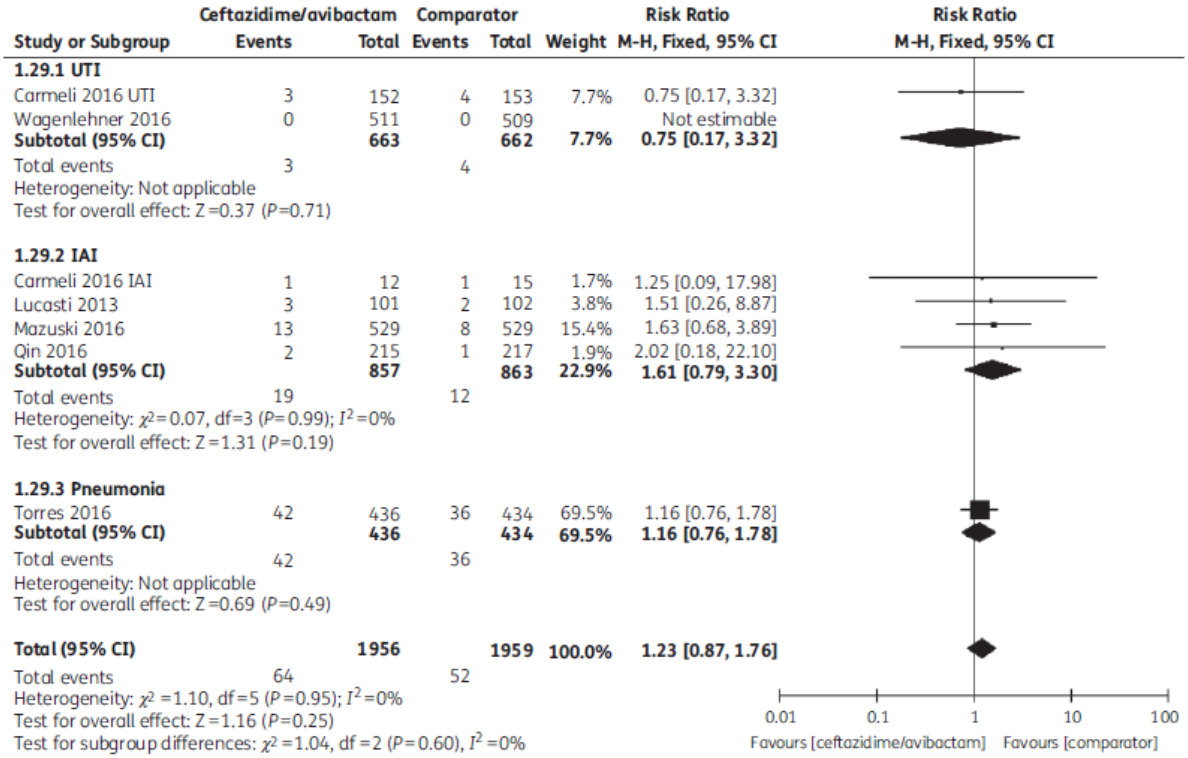


Figure 2. All-cause mortality at late follow-up. M-H, Mantel–Haenszel.

- Clinical response (table 2)
  - Keine Subgruppenanalyse für cUTIs
- Microbiological response
  - Per patient at TOC: Compiling only trials including patients with UTI, a significantly higher rate of microbiological response was demonstrated among the ceftazidime/avibactam arm (three trials, 1153 patients, RR 1.14, 95% CI 1.0–1.29, p=0.05, I_2=51%). The significant heterogeneity was eliminated by excluding the study of Carmeli et al. without changing the results.
  - Per patient at LFU: three UTI trials (1147 patients) also demonstrated a statistically significant advantage of ceftazidime/avibactam in terms of microbiological response (RR 1.15, 95%CI 1.05–1.26, P=0.002, I2=12%).

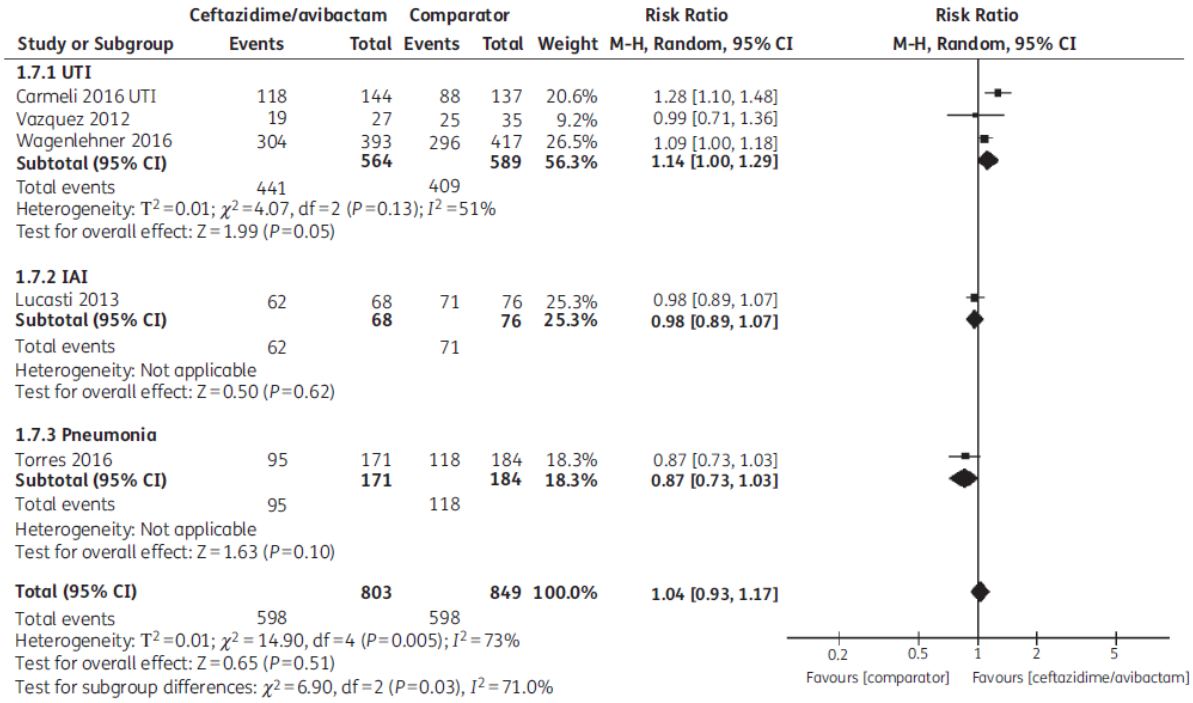


Figure 3. Microbiological response per patient at test of cure. M-H, Mantel–Haenszel.

- Adverse events
  - Kein signifikanter Effekt in der Subgruppe cUTI

Anmerkung/Fazit der Autoren

- Microbiological response in patients with cUTI is superior with ceftazidime/avibactam.
- In conclusion, ceftazidime/avibactam is 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.

Kommentare zum Review

- Es wurden die gleichen Studien eingeschlossen wie im Review von Zhang et al. [5]. Hier wird jedoch das Ergebnis gepoolt über alle Populationen hinweg dargestellt.

3.4 Leitlinien

Caron et al., 2018 [2].

Practice guidelines for the management of adult community-acquired urinary tract infections

Leitlinienorganisation/Fragestellung

Management of adult community-acquired urinary tract infections (UTI)

Methodik

Grundlage der Leitlinie

- The present updates to the guidelines on the management of adult community-acquired urinary tract infections (UTI) was performed under the aegis of the French Infectious Diseases Society (French acronym SPILF), by experts from the following specialties: infectious diseases, microbiology, urology, primary care medicine, geriatrics, and radiology.
- As per the French National Authority for Health (HAS) method, each recommendation was attributed a grade (A, B, or C) based on the level of scientific evidence provided by related studies. When literature data was lacking, the recommendations were drafted on the basis of a consensus achieved by healthcare professionals taking into consideration current practices and experts' opinion.

LoE/GoR

Table 1
Level of scientific evidence and strength of the recommendations.

Level I	Grade A
Well-powered randomized and comparative study	
Meta-analysis	
Level II	Grade B
Low-power randomized and comparative study	
Level III	Grade C
Recent non-randomized comparative study	
Cohort study	
Level IV	Grade C
Comparative trial with a historical cohort	
Case series	

Sonstige methodische Hinweise

- The guidelines were posted on the SPILF website in 2014 (cystitis, pyelonephritis, male UTI) and were then updated in 2015 (UTI in pregnancy, use of temocillin and trimethoprim [TMP]). The present document provides an overview of the main recommendations, and includes changes decided in 2017 to take into account updates related to the bacterial resistance to antibiotics as well as the most recent publications.

Empfehlungen:

Terminology

- The term "UTI at risk of complication" is preferred to the former term "complicated UTI" because it refers to patients presenting with at least one risk factor, which may lead to a

more severe or a more difficult-to-treat infection, but the complication does not necessarily develop.

- Risk factors for complication include organ or functional abnormalities of the urinary tract (post-void residual urine, vesicoureteral reflux, lithiasis, tumor, recent urological procedure, etc.) and some underlying patients' characteristics (male gender, pregnancy, elderly patients with frailty criteria, severe chronic renal failure [creatinine clearance< 30 mL/min], and severe immunodeficiency [although precise "levels of at-risk immunodeficiency" cannot be defined]).

General principles of antibiotic treatment and epidemiology of the resistance among Escherichia coli strains: Three criteria must be taken into consideration when choosing the antibiotic treatment:

- efficacy, i.e. the causative agent must be susceptible to the pre-scribed antibiotic and the molecule must adequately diffuse in the infected site;
- tolerability, which must be in line with the natural history of the treated pathology (a good prognosis for uncomplicated cystitis – which can be cured with a simple hyperdiuresis – means that adverse events are unacceptable, even though uncommon);
- the ecological impact on the gut microbiota must be as limited as possible. The currently used hierarchy is as follows: very small impact for fosfomycin, nitrofurantoin, and pivmecillinam; high impact for third-generation cephalosporins (3GCs), fluoroquinolones, and to a lesser extent amoxicillin-clavulanic acid and co-trimoxazole; carbapenem sparing strategies are mandatory.

(…) Resistance levels significantly vary by patients' characteristics. Physicians must therefore always refer to the resistance level of the patient group concerned. Besides, resistance levels depend on "breakpoints" (cut-off values distinguishing susceptible strains from resistant strains when only one breakpoint is available, or susceptible strains from strains with an intermediate or resistant pattern when two breakpoints are available).Treatment may sometimes be delayed until antimicrobial susceptibility test results are available. The antimicrobial agent with the narrowest spectrum can thus be prescribed right away. Most often, an empirical antibiotic treatment is required. Treatment must therefore cover many potential causative agents according to an antibiotic resistance risk level adapted to the clinical criteria:

- ≤ 10% risk for APN, male UTI, cystitis in pregnancy, and other cystitis presentations at risk of complication. (…)

Cystitis at risk of complication

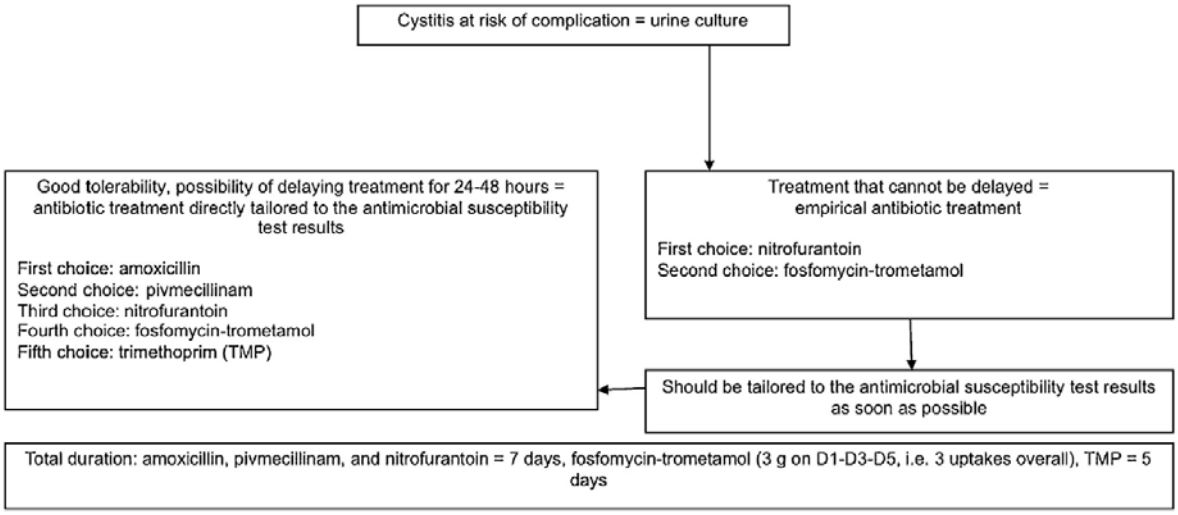


Fig. 3. Cystitis at risk of complication.

- Treatment should be delayed to directly prescribe an appropriate agent on the basis of the antimicrobial susceptibility test results;
  - A urine culture must always be performed (II-B). The etiology of the infection will be investigated on a case-by-case basis depending on the risk factor for complication. When acute urinary retention is suspected, a simplified examination of post-void residual urine using ultrasound (e.g., Bladder-scan) must be performed. If this examination cannot be performed, a urinary tract ultrasonography must be performed. This type of investigation is particularly useful in elderly patients. The key recommendation is to delay the antibiotic treatment, whenever possible, to directly prescribe a treatment tailored to the antimicrobial susceptibility test results (Fig. 3) (healthcare professional agreement).
  - On the basis of the antimicrobial susceptibility test results, the agent with the best proven efficacy and the lowest selection pressure on the microbiota (IV-C*)* should be chosen: i.e.,
    - amoxicillin (7days) for the first-line treatment,
    - pivmecillinam (7 days) for the second-line treatment,
    - nitrofurantoin (7 days) for the third-line treatment,
    - fosfomycin-trometamol for the fourth-line treatment (3 doses each administered 48h apart),
    - and TMP for the fifth-line treatment (5 days).
- For the rare cases requiring an empirical treatment: first-line nitrofurantoin (except for patients presenting with a known renal failure with creatinine clearance <40 mL/min) and second-line fosfomycin-trometamol;
  - Nitrofurantoin and fosfomycin-trometamol may be used when treatment initiation cannot be delayed (highly symptomatic female patient, etc.) – this must remain rare though:
    - nitrofurantoin (III-B) (except in patients presenting with a known renal failure [creatinine clearance < 40 mL/min]),because of the associated low risk of resistance and well-established efficacy, including against ESBL-E;

        - fosfomycin-trometamol (III-B), because it is still active against more than 95% of *E. coli* strains isolated from patients presenting with cystitis at risk of complication, without any real difference with the prevalence of resistance in uncomplicated cystitis, and because of its excellent tolerability profile. However, its efficacy is not well established in patients presenting with cystitis at risk of complication, and the three-dose regimen is still administered off-label.
- Fluoroquinolones and cefixime should no longer be used for the empirical treatment of cystitis at risk of complication.
    - Cefixime and fluoroquinolones (suggested for the second-line empirical treatment until 2015) are no longer recommended (healthcare professional agreement) because of their substantial ecological impact and of a much higher resistance level than nitrofurantoin and fosfomycin-trometamol in these patients.

Recurrent cystitis

- Treatment of recurrent cystitis in patients presenting with risk factors for complication is based on a multidisciplinary decision including an infectious disease specialist, a urologist, a gynecologist, and a radiologist. These case-by-case strategies cannot fall under standardized recommendations.

Pyelonephritis

Siehe Evidenzsynopse zur „akuten Pyelonephritis“

Urinary tract infections in pregnancy

a) Cystitis in pregnancy

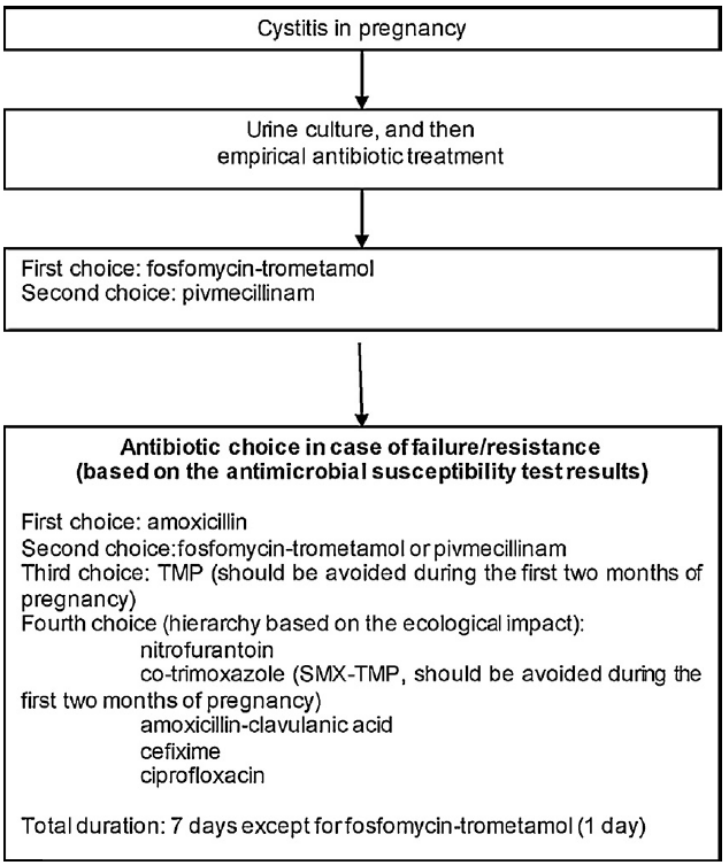


Fig. 9. Treatment of cystitis in pregnancy.

- Mandatory urine culture, followed by an empirical antibiotic treatment.
- Treatment of cystitis in pregnancy is similar to that of uncomplicated cystitis: fosfomycin-trometamol for the first-line treatment and pivmecillinam for the second-line treatment.
  - The only recommended first-line treatment (Fig. 9) is a single dose of fosfomycin-trometamol (II-B) as recent studies con-firmed that single dose regimens are effective in the treatment of cystitis in pregnancy. The molecule is also associated with alow prevalence of resistance to antibiotics, an excellent maternal and fetal tolerability, and a minor impact on the gut microbiota. The use of pivmecillinam is suggested for the second-line treatment (IV-C). Although very rare, the third-line treatment must rely on nitrofurantoin, cefixime, or ciprofloxacin (the only fluoroquinolone indicated during pregnancy because of a well-established and reassuring pharmacovigilance).
  - When a treatment switch is required, the strategy used for colonization in pregnancy applies:
    - amoxicillin for the first-line treatment,
    - fosfomycin-trometamol or pivmecillinam for the second-line treatment (depending on the prior treatment),
    - TMP for the third-line treatment (should be avoided during the first two months of pregnancy), and nitrofurantoin (very good pharma-covigilance for the fetal risk, but

same rare severe adverse events for the mother as the ones observed in the general popultion),

- co-trimoxazole (SMX-TMP, should be avoided during the first two months of pregnancy), amoxicillin-clavulanic acid, cefixime, or ciprofloxacin for the fourth-line treatment (health-care professional agreement).

- The recommended treatment duration is a single dose for fosfomycin-trometamol and 7 days for the other treatment regimens (healthcare professional agreement).

b) Pyelonephritis in pregnancy

- Mandatory obstetrical examination and common initial hospitalization.
  - A urine culture is mandatory. Blood cultures are required for severe presentations or diagnostic uncertainties (fever in patients presenting with urinary tract colonization for instance). A urinary tract ultrasound is required and must be urgently performed when confronted with severe or hyperalgesic presentations. A gynecology consultation is mandatory, irrespective of the pregnancy stage.
  - Initial hospitalization is quite common. Outpatient treatment may be prescribed upon initial examination at the hospital when the following criteria are met: good clinical tolerability, non-hyperalgesic presentation, no vomiting, normal obstetrical examination, possibility of home surveillance by close relatives, absence of immunodeficiency, no recurrent UTI, and no under-lying urological disorder.
- Similar treatment as the one for APN at risk of complications.
  - The empirical antibiotic treatment for APN in pregnancy without severity criteria relies on a parenteral 3GC [81].
  - Ciprofloxacin may be used as an alternative in patients presenting with β-lactam allergy, with a treatment switch aiming at avoiding co-trimoxazole (SMX-TMP) during the first two months of pregnancy (IV-C).
  - The antibiotic treatment for APN in pregnancy without severity criteria or for ESBL-E documented APN is similar to that prescribed to the general population (healthcare professional agreement).

Male urinary tract infections

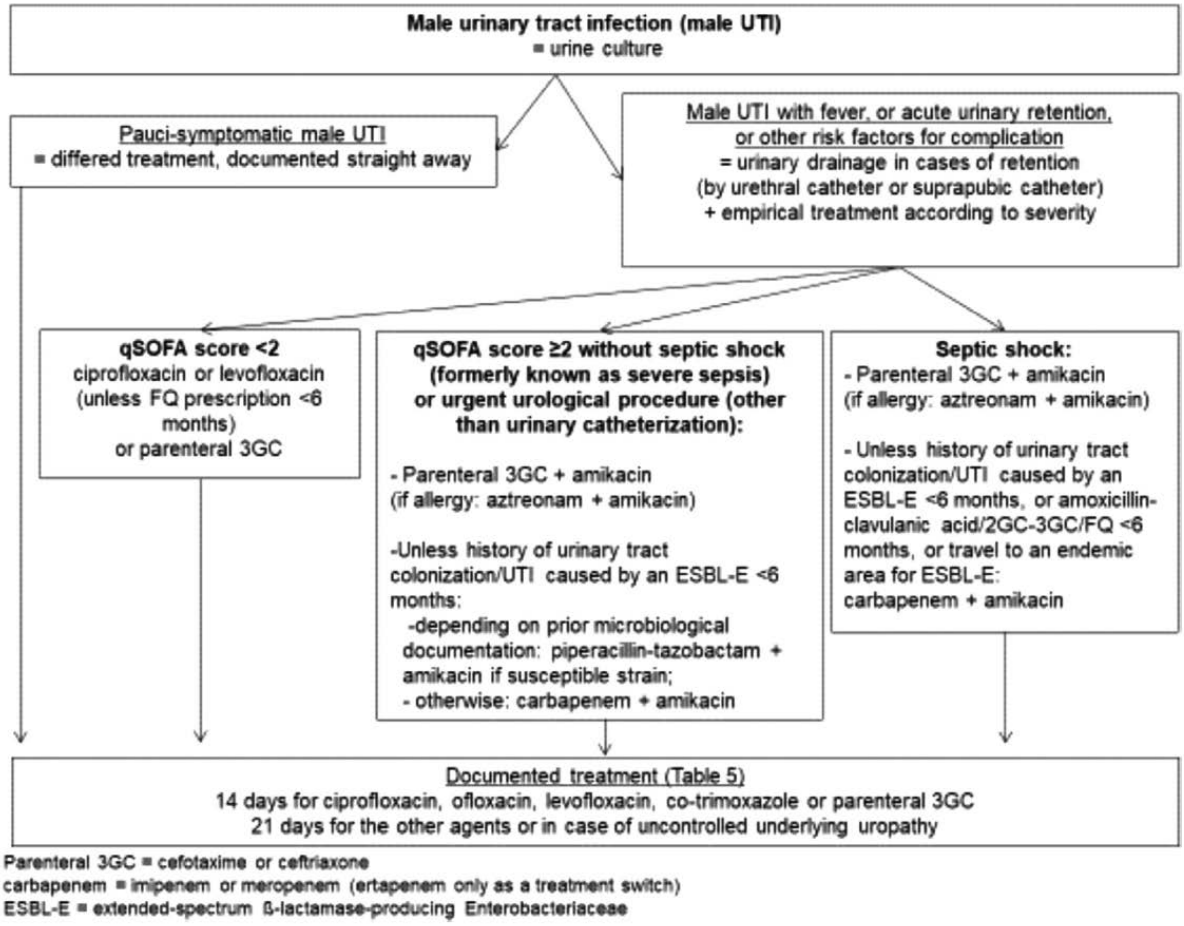


Fig. 10. Management of male urinary tract infections.

- Mandatory urine culture.
  - A negative urine test strip in male patients presenting with urinary functional signs cannot rule out the UTI diagnosis (low negative predictive value), while a positive urine test strip reinforces the diagnostic suspicion (high positive predictive value). The urine culture contributes to the infection documentation and to guiding treatment prescription. A urine test strip is therefore recommended in male patients, and the urine culture is mandatory. A blood culture is indicated when fever is observed.
- Possibility of differing the treatment of pauci-symptomatic male UTIs.
  - The antibiotic treatment for pauci-symptomatic male UTI may be differed until the antimicrobial susceptibility test results are available, so as to directly prescribe the best treatment; an empirical antibiotic treatment is indicated in case of fever or poor tolerability of urinary tract symptoms, and it must initially be similar to that of APN at risk of complication but without severity criteria. Ciprofloxacin and levofloxacin can thus be widely used (IV-C).
  - Patients presenting with acute urinary retention or severe immunodeficiency but no other concerning clinical symptoms, must be hospitalized and the same empirical antibiotic treatment as the one prescribed for APN without severity criteria but at risk of complication, must be prescribed. Parenteral 3GCs are therefore most frequently favored (healthcare professional agreement).

- Patients presenting with severity criteria must be treated with a β-lactam + amikacin combination. The β-lactam choice must take into consideration the presence of risk factors for ESBL-E infection.

- The use of fluoroquinolones and co-trimoxazole (SMX-TMP) must be preferred, even with multidrug-resistant bacteria – for prostate diffusion purposes.
  - In light of current data, the antibiotic treatment switch must always favormolecules with a good prostate diffusion (healthcare professional agreement).
  - Fluoroquinolones (ciprofloxacin, levofloxacin, or ofloxacin when the strain has been documented as susceptible) are the reference molecules for the treatment of male UTIs (II-B):their prostate diffusion is excellent and their efficacy against susceptible strains has already been proven.
  - Co-trimoxazole (SMX-TMP) can be used as an alternative in the treatment of male UTIs caused by susceptible strains: good prostate diffusion, but little clinical efficacy data is available (III-C).
  - TMP can no longer be used in this indication as clinical data is lacking.
  - Various alternative strategies (Table 5) are suggested when neither fluoroquinolones nor co-trimoxazole (SMX-TMP) can be used, especially for ESBL-E UTIs. The alternative strategies are based on diffusion data and on small clinical studies (III-C).

Table 5
Treatment of documented male urinary tract infections.

	Non-ESBL-producing Enterobacteriaceae	ESBL-producing Enterobacteriaceae
First choice	Ciprofloxacin, levofloxacin Or ofloxacin	Ciprofloxacin, levofloxacin or ofloxacin
Second choice	Co-trimoxazole (TMP-SMX)	Co-trimoxazole (TMP-SMX)
Third choice	Cefotaxime or ceftriaxone	Cefoxitin Or Piperacillin-tazobactam Or Temocillin
Fourth choice		Imipenem Meropenem Ertapenem (if ≥ 80 kg: 1 g twice a day)

  - Treatment of enterococcal UTI and UTI caused by other uncommon microbial species cannot be standardized in light of the available scientific literature data.
  - Treatment failure may be triggered by an untreated underlying urological disorder (IV-C).

- 14 days of treatment in most cases.
  - There is currently no data available to adjust treatment duration on the basis of the initial clinical presentation.
  - A 14-daytreatment duration is recommended for infections treated with fluoroquinolones or co-trimoxazole (SMX-TMP), except for the uncommon cases of abscess that may require a prolonged treatment (IV-C).
  - A prolonged 21-day treatment must be discussed for patients presenting with uncontrolled underlying urological disorder or when treatment requires molecules other

than fluoroquinolones, co-trimoxazole, or parenteral β-lactams (healthcare professional agreement).

- Importance of urological investigations.
  - Urinary drainage by urethral catheter or suprapubic catheter must be performed in patients presenting with acute urinary retention (IV-C).
  - Antibiotic treatment alone is usually enough in case of prostate abscesses. Surgical or instrumental drainage may be required in case of unfavorable outcome, and despite the administration of an adequate antibiotic treatment. In case of favorable outcome, a control urine culture per-formed during treatment or after treatment discontinuation is not recommended as persistent colonization would not be treated (healthcare professional agreement).
  - Male patients presenting with an initial episode of UTI must have a detailed anamnesis and clinical examination performed to screen for anatomical and/or functional abnormality of the urinary tract (e.g., bladder or prostate abnormality): pollakiuria, urge urination, reduced urine flow, nycturia, dysuria, or abnormality at digital rectal examination (IV-C).
  - For patients presenting with a second UTI episode or if a urinary tract abnormality is suspected (especially in patients aged > 50 years), a urinary tract ultrasound with post-void residual measurement, a urology consultation, and depending on cases a uroflowmetry are recommended (healthcare professional agreement).

Bonkat et al., 2018 [1].

European Association of Urology (EAU)

Urological Infections; Guideline

Leitlinienorganisation/Fragestellung

To provide medical professionals with evidence-based information and recommendations for the prevention and treatment of urinary tract infections (UTIs) and male accessory gland infections.

Methodik

Grundlage der Leitlinie

- Panel composition: The EAU Urological Infections Guidelines Panel consists of a multi-disciplinary group of urologists, with particular expertise in this area, and an infectious disease specialist. All experts involved in the production of this document have submitted potential conflict of interest statements
- independent peer review

Recherche/Suchzeitraum:

- The Urological Infections Guidelines were first published in 2001. This 2018 document presents a limited update of the 2017 publication.
- Broad and comprehensive literature searches. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 1980 and February 1st 2017.

LoE/GoR

- For the 2018 edition of the EAU Guidelines the Guidelines Office have transitioned to a modified GRADE methodology across all 20 guidelines. For each recommendation within the guidelines there is an accompanying online strength rating form which addresses a number of key elements namely:
  - the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence
  - the magnitude of the effect (individual or combined effects);
  - the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
  - the balance between desirable and undesirable outcomes;
  - the impact of patient values and preferences on the intervention;
  - the certainty of those patient values and preferences.
- These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak'. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Empfehlungen

(…) The underlying factors that are generally accepted to result in a cUTI are outlined in Table 5. The designation of cUTI encompasses a wide variety of underlying conditions that result in a remarkably heterogeneous patient population. Therefore, it is readily apparent that a universal approach to the evaluation and treatment of cUTIs is not sufficient, although there are general principles of management that can be applied to the majority of patients with cUTIs.

Table 5: Common factors associated with complicated UTIs [154-156]

Obstruction at any site in the urinary tract	UTI in males
Foreign body	Pregnancy
Incomplete voiding	Diabetes
Vesicoureteral reflux	Immunosupression
Recent history of instrumentation	Healthcare-associated infections

A cUTI is associated with clinical symptoms (e.g. dysuria, urgency, frequency, flank pain, costovertebral angle tenderness, suprapubic pain and fever), although in some clinical situations the symptoms may be atypical for example, in neuropathic bladder disturbances or catheter-associated UTI (CA-UTI). Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a post-operative CA-UTI, which might disappear spontaneously as soon as the catheter is removed. (…) Concomitant medical conditions, such as diabetes mellitus and renal failure, which can be related to urological abnormalities, are often also present in a cUTI.

General principles of cUTI treatment

Appropriate management of the urological abnormality or the underlying complicating factor is mandatory. Optimal antimicrobial therapy for cUTI depends on the severity of illness at presentation, as well as local resistance patterns and specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by (oral) administration of an appropriate antimicrobial agent on the basis of the isolated uropathogen.

Choice of antimicrobials:

- In the IDSA guidelines for the treatment of uncomplicated UTI, it is recommended that the resistance percentages of causative micro-organisms must be < 20% to consider an agent suitable for empirical treatment of a lower UTI and must be < 10% for treatment of an upper UTI. Considering the current resistance percentages of amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulphamethoxazole, it can be concluded that these agents are not suitable for the empirical treatment of pyelonephritis in a normal host and, therefore, also not for treatment of all cUTIs. The same applies to ciprofloxacin and other fluoroquinolones in urological patients.
- Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside with or without amoxicillin or a second or third generation cephalosporin or an extended-spectrum penicillin with or without an aminoglycoside. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results. These recommendations are not only suitable for pyelonephritis but for all other cUTIs.
- In view of the high degree of resistance, particularly among patients admitted to the department of urology, fluoroquinolones are not automatically suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last six months. Fluoroquinolones can only be recommended as empirical treatment when the patient is not seriously ill and it is considered safe to start initial oral treatment or if the patient has had an anaphylactic reaction to beta-lactam antimicrobials.

Summary of Evidence	LE
Patients with a UTI with systemic symptoms requiring hospitalisation should be initially treated with an intravenous antimicrobial regimen chosen based on local resistance data, and the regimen should be tailored on the basis of susceptibility result.	1b
If the prevalence of fluoroquinolone resistance is thought to be > 10% and the patient has contraindications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with uncomplicated pyelonephritis.	2
In the event of hypersensitivity to penicillin, a third generation cephalosporin can still be prescribed, with the exception of systemic anaphylaxis in the past.	2
In patients with a UTI with systemic symptoms empirical treatment should cover ESBL in the initial treatment only in patients who are colonised with ESBL-producing micro-organisms.	2

ESBL=Extended-spectrum beta-lactamase.

Recommendations	Strength rating
Use the combination of: • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms.	Strong
Only use ciprofloxacin provided that the local resistance percentages are < 10% when; • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials.	Strong
Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from the urology department or when patients have used fluoroquinolones in the last six months.	Strong
Manage any urological abnormality and/or underlying complicating factors.	Strong

Duration of antimicrobial therapy

Treatment for seven to fourteen days is generally recommended, but the duration should be closely related to the treatment of the underlying abnormality.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 15.11.2018

#	Suchfrage
1	[mh “urinary tract infections“]
2	urinary next tract* and (infection* or inflammator*):ti,ab,kw and (recurren* OR complicate*)
3	(bacteriuria OR pyria):ti,ab,kw
4	{OR #1-#3}
5	#3 with Cochrane Library publication date from Nov 2013 to Nov 2018, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 15.11.2018

#	Suchfrage
1	urinary tract infections[mh]
2	(infection*[tiab] OR inflammator*[tiab]) AND (urinary[tiab] AND tract*[tiab])
3	(urinary tract* inflammator*[tiab]) OR urinary tract* infection*[tiab]
4	bacteriuria[tiab] OR pyria[tiab]
5	(#1 OR #2 OR #3) AND (recurren[tiab] OR complicate*[tiab])
6	#5 OR #4
7	(#6) 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]))))
8	((#7) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 15.11.2018

#	Suchfrage
1	urinary tract infections[mh]
2	(infection*[tiab] OR inflammator*[tiab]) AND (urinary[tiab] AND tract*[tiab])
3	(urinary tract* inflammator*[tiab]) OR urinary tract* infection*[tiab]
4	bacteriuria[tiab] OR pyria[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2013/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

Referenzen

1. **Bonkat G, Pickard R, Bartoletti T, Cai T, Bruyère F, Geerlings S, et al.** Urological Infections; Guideline [online]. Arnhem (NED): European Association of Urology (EAU); 2018. [Zugriff: 16.11.2018]. URL: http://uroweb.org/guideline/urological-infections/.

2. **Caron F, Galperine T, Flateau C, Azria R, Bonacorsi S, Bruyere F, et al.** Practice guidelines for the management of adult community-acquired urinary tract infections. Med Mal Infect 2018;48(5):327-358.

3. **Chen M, Zhang M, Huang P, Lin Q, Sun C, Zeng H, et al.** Novel beta-lactam/beta-lactamase inhibitors versus alternative antibiotics for the treatment of complicated intra-abdominal infection and complicated urinary tract infection: a meta-analysis of randomized controlled trials. Expert Rev Anti Infect Ther 2018;16(2):111-120.

4. **Sternbach N, Leibovici Weissman Y, Avni T, Yahav D.** Efficacy and safety of ceftazidime/avibactam: a systematic review and meta-analysis. J Antimicrob Chemother 2018;73(8):2021-2029.

5. **Zhang Y, Tao LN, Qu XY, Niu JQ, Ding YH, Zhang SX.** 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. Rev Assoc Med Bras (1992) 2018;64(3):253-263.

6. **Zhong H, Zhao XY, Zhang ZL, Gu ZC, Zhang C, Gao Y, et al.** Evaluation of the efficacy and safety of ceftazidime/avibactam in the treatment of Gram-negative bacterial infections: a systematic review and meta-analysis. Int J Antimicrob Agents 2018;52(4):443-450.